

Bidirectional association of autoimmune diseases and pregnancy complications

By

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Abstract

Background Given the global rise of autoimmune conditions, particularly in women of reproductive age, there is a need to better understand their burden during pregnancy and their impact on pregnancy outcomes. Despite extensive research, certain autoimmune conditions and pregnancy complications have been more thoroughly examined than others. Also, how the pregnancy complications might lead to the development of the autoimmune condition need to be examined further.

Methods- An epidemiological study using the UK primary care database, and the associated pregnancy register was using to describe the annual prevalence of 17 autoimmune diseases in pregnant women (15-49 years) from 2000-2021. Logistic regression estimated odds ratios for the relationship between women's characteristics and autoimmune disease during pregnancy. The umbrella review summarised evidence on the association between these diseases and adverse pregnancy outcomes, using data from Medline, Embase, and Cochrane (up to December 2023). A population-based cohort study linked CPRD and HES data to assess the association between autoimmune diseases and pregnancy outcomes, using modified Poisson regression to estimate adjusted relative risks. Lastly, a systematic review explored the link between pregnancy complications and development of autoimmune diseases in women, with searches in Medline, CINAHL, and Cochrane (up to January 2024).

Results- The prevalence of 17 autoimmune diseases increased from 3.5% in 2000 to 4.7% in 2021, with psoriasis the most common (1.8% to 2.0%). The steepest increases were in Hashimoto thyroiditis (0.05% to 0.12%), coeliac disease (0.11% to 0.27%), Grave's disease (0.17% to 0.35%), and T1DM (0.14% to 0.49%). In the umbrella review including thirty-two

reviews. Higher risk of miscarriage is reported in women with Sjögren's syndrome RR 8.85 (95% CI 3.10-25.26). Pre-eclampsia was higher in women with T1DM OR 4.19 (3.08-5.71), GDM reported with IBD OR 2.96 (1.47-5.98). Increased risk of intrauterine growth restriction in women with systemic sclerosis OR 3.20 (2.21-4.53), preterm birth with T1DM OR 4.36 (3.72-5.12) or SLE OR 2.79 (2.07-3.77). Low birth weight babies in women with women with SLE or systemic sclerosis OR 5.95 (4.54-7.80) and higher risk of stillbirth in women with T1DM OR 3.97 (3.44-4.58). The cohort study (5,239,383 pregnancies, 2,057,150 birth) found hyperemesis in Addison's disease aRR (3.72, 95% CI 2.48–5.59), ectopic pregnancy in rheumatoid arthritis (1.50, 1.21–1.86), miscarriage in Sjogren syndrome (1.36, 1.09–1.70), pre-eclampsia in T1DM (3.56, 3.32–3.82), GDM in Addison's disease (2.52, 1.35-4.68) caesarean birth in IBD (1.27, 1.22–1.31), small for gestational age in SLE (2.45, 1.65–3.62), preterm birth in rheumatoid arthritis (1.47, 1.29–1.67), and stillbirth in SLE (1.93, 1.10–3.39). Mental health outcomes were linked with most conditions. The systematic review including 30 studies reported that pregnancy complications increased the risk of autoimmune diseases RR 3.20 (2.90-3.51), and stillbirth was associated with composite autoimmune conditions RR 5.82 (4.87-6.81). Postpartum psychosis was linked to autoimmune thyroid disease IRR 2.26 (1.61-2.90).

Conclusion- The burden of pregnancies affected by autoimmune diseases is rising, with greater risk of adverse pregnancy outcomes. Women with pregnancy complications also face a higher risk of later autoimmune diagnoses. Further research is needed to improve care from preconception to postnatal stages and to investigate the links between autoimmune diseases and pregnancy outcomes.

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Structure and Repetition

In this thesis, some repetition of sentences and references may occur due to the overlap of key concepts and findings across different sections. This is intentional to maintain clarity and coherence when discussing interconnected themes. Additionally, chapter introductions might need to readdress these points to provide appropriate context and rationale for the discussions that follow.

List of manuscripts arising from PhD thesis

Singh, M., Wambua, S., Lee, S.I. *et al.* Autoimmune diseases and adverse pregnancy outcomes: an umbrella review. *BMC Med* 22, 94 (2024). <https://doi.org/10.1186/s12916-024-03309-y>

Singh, M., Fayaz, F.F.A., Wang, J. *et al.* Pregnancy complications and autoimmune diseases in women: systematic review and meta-analysis. *BMC Med* 22, 339 (2024). <https://doi.org/10.1186/s12916-024-03550-5>

Manuscript in submission to peer reviewed journal (under review)

Singh, M et al Trends in the prevalence of autoimmune diseases in pregnancy in the UK 2000-2021: findings from the Clinical Practice Research Datalink (CPRD), *Lancet rheumatology*

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Other related manuscripts published during this PhD

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Subramanian, A., Nirantharakumar, K., Hughes, S. *et al*. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat Med* **28**, 1706–1714 (2022).

<https://doi.org/10.1038/s41591-022-01909-w>

Tyldesley-Marshall, N., Grove, A., Ghosh, I. *et al*. Investigating informed choice in screening programmes: a mixed methods analysis. *BMC Public Health* **22**, 2319 (2022).

<https://doi.org/10.1186/s12889-022-14685-6>

Lee SI, Hope H, O'Reilly D, *et al* Maternal and child outcomes for pregnant women with pre-existing multiple long-term conditions: protocol for an observational study in the UK

BMJ Open 2023;13:e068718. doi: 10.1136/bmjopen-2022-068718

Ayorinde A, Ghosh I, Ali I, *et al* Health inequalities in infectious diseases: a systematic overview of reviews *BMJ Open* 2023;13:e067429. doi: 10.1136/bmjopen-2022-067429

Subramanian A, Lee SI, Hemali Sudasinghe SPB, Wambua S, Phillips K, Singh M, Azcoaga-Lorenzo A, Cockburn N, Wang J, Fagbamigbe A, Usman M, Damase-Michel C, Yau C, Kent L, McCowan C, O'Reilly D, Santorelli G, Hope H, Kennedy J, Mhereeg M, Abel KM, Eastwood KA, Black M, Loane M, Moss N, Brophy S, Brocklehurst P, Dolk H, Nelson-Piercy C, Nirantharakumar K; MuM-PreDiCT Group. Detection and evaluation of signals associated with exposure to individual and combination of medications in pregnancy: a signal detection

study protocol. *BMJ Open*. 2023 Oct 9;13(10):e073162. doi: 10.1136/bmjopen-2023-073162.

PMID: 37813531; PMCID: PMC10565241.

Lee, S.I., Hanley, S., Vowles, Z. *et al*. The development of a core outcome set for studies of pregnant women with multimorbidity. *BMC Med* **21**, 314 (2023).

<https://doi.org/10.1186/s12916-023-03013-3>

Wambua, S., Singh, M., Okoth, K. *et al*. Association between pregnancy-related complications and development of type 2 diabetes and hypertension in women: an umbrella review. *BMC Med* **22**, 66 (2024). <https://doi.org/10.1186/s12916-024-03284-4>

Wang J, Nirantharakumar K, Sainsbury C, Moore DJ, Sinclair A, Thomas GN, Hanif W, Singh M, Tan L, Wang Z, Simms-Williams N, Yao M, Gunathilaka MN, Singh P, Toulis K, Tsapas A, Coomar D, Price MJ. The optimal second-line therapy for older adults with type 2 diabetes mellitus: protocol for a systematic review and network meta-analysis using individual participant data (IPD). *Syst Rev*. 2024 Jun 13;13(1):155. doi: 10.1186/s13643-024-02558-5. PMID: 38872216; PMCID: PMC11170882.

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List of abbreviations

aHR	Adjusted hazard ratio
95% CI	95% confidence intervals
AAPC	Average annual percent change
ACPAs	Anti-citrullinated protein antibodies
ACTH	Adrenocorticotropin
aIRR	Adjusted Incidence Risk ratio
AMSTAR 2	Assessment of multiple systematic reviews version 2
ANA	Antinuclear antibodies
anti-dsDNA	Anti-double-stranded DNA
aOR	Adjusted Odds ratio
APH	Antepartum haemorrhage
APS	Antiphospholipid syndrome
aRR	Adjusted Risk ratio
AxSpA	Axial spondyloarthritis
BAFF	B-cell activating factor
BMI	Body mass index
CCA	Corrected covered area
CD	Clusters of differentiation
CNS	Central nervous system
CPRD	Clinical practice research datalink
CS	Caesarean section
CTD	Connective tissue diseases
DALY	Disability-adjusted life year
DMARDs	Disease-modifying antirheumatic drugs
DMTs	Disease-modifying therapies
DNA	Deoxyribonucleic acid
ESP2013	European standard population 2013
ETS2	ETS proto-oncogene 2
FMC	Fetal microchimerism
GBD	Global Burden of Disease
GDM	Gestational diabetes mellitus
GEE	Generalized estimating equations
GHT or PE	Gestational hypertension OR Pre-eclampsia
GTD	Gestational trophoblastic disease
hCG	Human chorionic gonadotropin
HELLP	Haemolysis, elevated liver enzymes and low platelet syndrome
HES	Hospital episode statistics
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
IIMD	Immune-mediated inflammatory diseases
IL-17A	Interleukin-17A

imd	Index of multiple deprivation
IRF5	Interferon regulatory factor 5
IUGR	Intrauterine growth retardation
JAK	Janus kinase
JBI	Joanna briggs institute
LBW	Low birth weight
MESH	Medical subject headings
MHC	Major histocompatibility complex
MOOSE	Meta-analyses of Observational Studies
MS	Multiple sclerosis
Mtor	Mammalian target of rapamycin
MuSK	Muscle-specific kinase
NA	Not applicable
NHS	National health service
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PPH	Postpartum haemorrhage
PPIE	Patient and public involvement and engagement
PRIOR	Preferred Reporting Items for Overviews of Reviews
PRISMA	Preferred reporting items for systematic review and meta-analysis
PUVA	Psoralen + ultraviolet a
RA/PSA/ANK S	Rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis
RNA	Ribonucleic acid
RR	Risk ratio
SGA	Small for gestational age
SLE	Systemic lupus erythematosus
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T1DM	Type 1 diabetes mellitus
TgAb	Thyroglobulin antibody
TLR	Toll-like receptors
TNF- α	Tumour Necrosis Factor alpha
TPO	Thyroid peroxidase antibody
TSAb	Thyroid-stimulating antibodies
UCTD	Undifferentiated connective tissue disease
UK	United Kingdom
US	United states
UVB	Ultraviolet B

Chapter 1 Introduction

Chapter overview

This chapter first provides an overview of autoimmune diseases, including their definition, clinical features, pathophysiology, management, and epidemiology. It then examines what is the prevalence and presentation of these conditions in women. The chapter also discusses the interplay between pregnancy complications and autoimmune diseases, highlighting the potential impact on maternal health. Additionally, it defines and outlines the epidemiology of the pregnancy outcomes studied in this thesis. A justification for the thesis is presented, followed by a statement of its aims and objectives.

1.1 Introduction

Autoimmune disease occurs when the body's natural defence system cannot differentiate between its own cells and foreign cells often triggered by T or B cell activation without external stimuli, which causes the body to attack its own normal cells. Autoimmune diseases encompass over 80 distinct conditions [1-5]. Though research has advanced, the exact mechanisms remain elusive, and treatment is often lifelong due to the chronic nature of these diseases [6, 7]. Considerable progress in understanding autoimmunity over the years has led to improvements in diagnosing, classifying, and treating autoimmune diseases. Macfarlane Burnett's pioneering "forbidden clone" theory played a crucial role in uncovering immune system processes like thymic education, cell death, and the elimination of self-reactive immune cells [8].

Today, it is widely accepted that autoimmune diseases arise from a mix of genetic susceptibility and environmental influences, though no clinical genetic tests can reliably predict disease risk. Twin studies show only 12–67% concordance, underscoring the importance of the interplay between genetic and environmental factors [9-11]. The identification of cytokines, chemokines, and their receptors has enabled the development of treatments that block damaging inflammatory responses, particularly benefiting conditions such as rheumatoid arthritis [12]. Autoimmune diseases, now affect 3–5% of the population, with almost 80 known types. These include both organ-specific diseases like autoimmune thyroid disease and type 1 diabetes (T1DM), as well as systemic conditions such as systemic lupus erythematosus (SLE) [13]. Recent advancements in molecular immunology and laboratory testing have enhanced disease diagnosis, classification, and prognosis [14].

The concept of Immune-mediated inflammatory diseases (IMIDs) has recently been introduced that includes autoimmune diseases as well as other conditions that share similar inflammatory pathways, leading to disruptions in immune regulation or abnormal immune responses to specific antigens. While some IMIDs result from a general malfunction of immune cells, others are more targeted, with antigen-specific responses, influencing the choice of treatment. In recent years, certain autoimmune diseases, such as Coeliac disease and inflammatory bowel diseases (IBD) like Crohn's disease and ulcerative colitis, have been increasingly classified as IMIDs. This distinction highlights that while all autoimmune diseases are IMIDs, not all IMIDs are autoimmune, as the term refers to a wider spectrum of immune system dysfunction [15-18].

While the exact cause of autoimmune diseases is not fully understood, several risk factors have been identified that contribute to their development.

1.2 Aetiology

1.2.1 Genetic Factors

A family history of autoimmune diseases significantly increases the risk of developing such conditions. Certain genetic markers, such as specific human leukocyte antigen (HLA) types, have been linked to various autoimmune diseases. Genome-wide research highlights shared susceptibility genes across autoimmune diseases, particularly in MHC and non-MHC regions in disease development particularly multiple sclerosis or SLE [19] . Another study highlighted individuals with the HLA-DR4 allele are at a higher risk for rheumatoid arthritis [20]. Recent study using genetic association data discovered 305 causal loci for autoimmune diseases that operate through gene expression changes in specific immune cell types and provided further insight into genetic mechanisms underlying immune function and autoimmune disease risk [21]. Another study identified an enhancer in non-coding DNA that activates ETS2 in immune cells, driving inflammation in IBD and positioning ETS2 as a potential treatment target[22].

1.2.2 Environmental factors/triggers

Environmental factors, including infections, toxins, can trigger autoimmune responses in genetically predisposed individuals. For instance, viral infections (like Epstein-Barr virus) have been implicated in the onset of multiple sclerosis [23]. Chemicals such as heavy metals and solvents (silica, mercury, pristane, pesticides) can also contribute to the risk of autoimmune disorders like SLE or systemic sclerosis [24]. And bacteria (*Helicobacter pylori* - cagA-positive strains) has been linked to autoimmune disease development through

mechanisms like molecular mimicry and immune response dysregulation particularly rheumatoid arthritis and SLE [25].

1.2.3 Hormonal factors

Autoimmune diseases are significantly more prevalent in women than in men, suggesting that hormonal differences play a role in immune system regulation and disease susceptibility. Sex hormones, particularly oestrogen, progesterone, and androgens, influence various immune pathways, including the activity of immunoregulatory T cells, cytokine production, and antibody responses. Oestrogen has been shown to enhance immune activation by promoting the survival and function of B cells and T cells, which may contribute to the increased risk of autoimmune diseases in women. Conversely, androgens and progesterone tend to have immunosuppressive effects, which may explain why men generally have a lower prevalence of autoimmune conditions [26, 27]. The impact of sex hormones on immune function is particularly evident in diseases such as SLE and autoimmune thyroid disorders, both of which predominantly affect women and often manifest during reproductive years. Oestrogen is thought to play a key role in the pathogenesis of SLE by increasing B cell activity and promoting the production of autoantibodies, which drive inflammation and tissue damage. Similarly, thyroid disorders such as Hashimoto's thyroiditis and Graves' disease, which are more common in women, are linked to hormonal fluctuations that influence immune system activity [28]. Overall, the interplay between sex hormones and immune function is a crucial factor in the higher prevalence of autoimmune diseases among women.

1.2.4 Diet and lifestyle factors

Dietary habits and lifestyle choices can also affect the risk of autoimmune diseases. Diets high in processed foods [29] and sugars have been associated with increased inflammation, while obesity is linked to a higher risk of conditions like rheumatoid arthritis and T1DM. Conversely, diets rich in omega-3 fatty acids, antioxidants, and vitamins may have a protective effect [30, 31]. A recent study reported that vitamin D supplementation or omega 3 fatty acids for five years, reduced autoimmune disease by 22% or 15% respectively [32].

1.2.5 Other factors

Additional risk factors include stress, and microbiome imbalances. Chronic stress (adverse childhood experiences, post-traumatic stress disorder, or major life stress) can dysregulate immune function have been associated with an increased risk of autoimmune diseases like multiple sclerosis, rheumatoid arthritis and SLE [33]. Emerging research suggests that gut health and the microbiome also play crucial roles in autoimmune disease susceptibility [34, 35]. For example, multiple sclerosis patients have reduced levels of anti-inflammatory bacteria (*Prevotella* and *Parabacteroides*) while increased bacteria (*Akkermansia muciniphila*) associated with pro-inflammatory T cells whereas in patients with rheumatoid arthritis have abundant *Prevotella copri*, inducing pro-inflammatory responses, while anti-inflammatory SCFA-producing bacteria are reduced. These require further research to confirm the role in pathogenesis of these diseases [36].

Recent study identifies that unusual self-antigens, or neoself-antigens, presented on MHC class II (MHC-II) without the invariant chain, are key triggers for autoimmune responses in systemic lupus erythematosus (SLE). These neoself-antigens lead to clonal expansion of autoreactive T cells, contributing to lupus-like disease. In SLE patients, these T cells are

notably expanded, and Epstein-Barr virus (EBV) reactivation appears to exacerbate this by downregulating the invariant chain, increasing neoself-antigen presentation. This suggests that neoself-antigen presentation by MHC-II plays a crucial role in SLE's pathogenesis [37].

1.3 Definitions, epidemiology, pathophysiology, clinical features, and management of the autoimmune diseases

1.3.1 Addison's disease

Addison's disease, identified by Thomas Addison in 1855, is a rare form of primary adrenal insufficiency. It occurs when the adrenal cortex fails to produce enough cortisol and aldosterone, leading to metabolic and electrolyte imbalances [38].. This results in elevated ACTH levels, causing skin hyperpigmentation and symptoms like low blood pressure, muscle weakness, and abdominal pain [39, 40].. The global prevalence is estimated at 4 to 6 cases per 100,000 people, with a higher frequency in women and a typical onset between 30 and 50 years [41]. Symptoms can be acute, such as hypotension, confusion, abdominal pain, fever, and adrenal crisis, or chronic, including fatigue, weight loss, hyperpigmentation, and electrolyte imbalances. Treatment involves hormone replacement therapy, including glucocorticoids (hydrocortisone), mineralocorticoids (fludrocortisone), and sometimes androgen replacement (DHEA) [42-44].

1.3.2 Alopecia areata

Alopecia areata is a common, non-scarring, inflammatory hair loss disorder. It manifests as patchy hair loss but can progress to complete loss of hair on the scalp and body. The exact cause of alopecia areata remains unclear, but it involves immune system disruptions that are triggered by genetic and environmental factors, resulting in inflammation around the hair

follicles [45]. It affects about 7.51 per 100,000 people with higher prevalence rates especially in North America and Asia [46]. There was a female predominance of the disease with (female to male ratio 2.3:1) [47]. Diagnosis is upon clinical examination, supported by dermoscopy or biopsy in uncertain cases. Management primarily involves corticosteroids (intralesional, topical, or systemic) to reduce inflammation and stimulate hair regrowth. [48, 49].

1.3.3 Ankylosing spondylitis/Axial spondylarthritis

Ankylosing spondylitis is a chronic inflammatory condition primarily affecting the axial skeleton, including the spine and sacroiliac joints. [50]. Non-radiographic axial spondylarthritis (nr-axSpA) and ankylosing spondylitis share similar epidemiological, genetic, and clinical characteristics, suggesting they are part of the same disease spectrum. The pathophysiology of ankylosing spondylitis involves a complex interaction of genetic factors, particularly the HLA-B27 antigen, and environmental influences, leading to immune dysregulation and inflammation affecting the axial skeleton and surrounding structure [51]. Both conditions have a prevalence of 0.3–0.6%, with equal numbers of nr-axSpA to ankylosing spondylitis in newly diagnosed cases [52]. Systemically, it is characterised by inflammatory back pain, which can progress to spinal stiffness and fusion. Inflammation may also extend to extra-articular structures, most notably the eyes... First-line treatments for ocular symptoms include topical corticosteroids and cycloplegic agents. For systemic manifestations, nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), methotrexate, and biologics such as TNF- α inhibitors and anti-IL-17A monoclonal antibodies have proven effective in controlling both joint and ocular inflammation [53, 54].

1.3.4 Coeliac disease

Coeliac disease is a chronic autoimmune disorder triggered by the ingestion of gluten in genetically predisposed individuals. It primarily affects the small intestine, causing inflammation and damage due to an inappropriate immune response to gluten, mediated by T cells that recognise gluten peptides presented by HLA-DQ2 or HLA-DQ8 (human leukocyte antigens) [55]. Common gastrointestinal symptoms include diarrhoea, abdominal pain, bloating, and weight loss. Extra-intestinal symptoms, such as fatigue, iron-deficiency anaemia, osteopenia, and skin conditions like dermatitis herpetiformis, may also occur. The global prevalence of coeliac disease is approximately 1.4% [56] with women being two to three times higher than men. Current research shows that women make up 60% to 70% of those diagnosed with the condition[57]. Management of coeliac disease is a strict, lifelong gluten-free diet along with nutritional counselling. [58, 59].

1.3.5 Inflammatory bowel disease

Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis, with aetiology linked to a complex interaction of genetic, environmental, and immunological factors, resulting in immune system dysregulation in response to intestinal microbiota.. The global prevalence of IBD is 0.3% to 0.5%, with higher rates in high-income regions such as North America and Europe, where it can exceed 1%. The male-to-female ratio for Crohn's disease is approximately 1:1.5, and for ulcerative colitis, it is 1:1.2. [60]. [61, 62]. Symptoms include abdominal pain, diarrhoea (often bloody), weight loss, and fatigue, with extra-intestinal manifestations like joint pain, skin rashes, and ocular inflammation. Management focuses on reducing inflammation, controlling symptoms, and maintaining remission

through medications such as corticosteroids, amino salicylates, immunomodulators, and biologics (e.g., TNF- α inhibitors) or surgery in severe cases. [63-65].

1.3.6 Grave's disease

Grave's disease, first described in 1835, involves thyroid-stimulating antibodies (TSAb) that activate the thyrotropin receptor, causing hyperthyroidism. It primarily affects the thyroid but can extend to the eyes (Grave's ophthalmopathy) and skin (myxoedema). Grave's disease is characterised by the activation of the thyrotropin receptor via TSAb, leading to excess thyroid hormone production, thyroid hypertrophy, and goiter. [66]. Grave's disease is the most common cause of hyperthyroidism in high-income countries, mainly affecting individuals aged 30 to 60 years. Women are 5 to 10 times more likely to be diagnosed, with prevalence rates ranging from 0.2% to 1% [67]. Grave's disease causes weight loss, heat intolerance, fatigue, heart palpitations, and goiter. Ophthalmopathy affects about 50% of cases, leading to bulging eyes, double vision, and rarely optic nerve compression. Treatment includes antithyroid medications, radioiodine therapy, thyroidectomy, beta-blockers, and, for severe cases, corticosteroids, orbital decompression, and smoking cessation. [68, 69].

1.3.7 Hashimoto's thyroiditis

Hashimoto's thyroiditis is a common autoimmune disorder where the immune system attacks the thyroid, causing hypothyroidism. It is marked by lymphocytic infiltration and thyroid-specific autoantibodies (anti-TPO and anti-thyroglobulin), which disrupt thyroid hormone production... [70]. The global prevalence is estimated to range between 0.3% and 1.5% of the population and the risk women is approximately 4 times than that of men [71]. Patients typically present with symptoms associated with hypothyroidism, such as fatigue,

weight gain, cold intolerance, dry skin, and constipation. The primary treatment for Hashimoto's disease is levothyroxine, a synthetic thyroid hormone that compensates for hormone deficiency and restores normal thyroid function. [72].

1.3.8 Multiple sclerosis

Multiple sclerosis (MS) is a central nervous system disorder characterized by inflammation, demyelination, and neurodegeneration, driven by an autoimmune [73]. The global prevalence of multiple sclerosis is estimated to be around 0.3% to 0.5% of the population approximately 2.8 million individuals living with the condition worldwide being more prevalent in women [74, 75]. Symptoms are variable and include fatigue, sensory disturbances, motor impairments, visual deficits, and cognitive dysfunction, with relapsing episodes followed by periods of remission. Management includes disease-modifying therapies (DMTs) to reduce relapses and slow progression, corticosteroids for acute relapses, and symptomatic treatments for fatigue, spasticity, and pain. [76, 77].

1.3.9 Myasthenia gravis

Myasthenia gravis is a chronic autoimmune neuromuscular disorder causing muscle weakness and rapid fatigue. It occurs when the immune system produces antibodies that block or destroy acetylcholine receptors at the neuromuscular junction, impairing nerve-to-muscle communication [78]. The global prevalence of myasthenia gravis is estimated to be 12.4 cases per 100,000 people and is more prevalent in women [79]. Symptoms include muscle weakness that worsens with activity and improves with rest, ptosis, diplopia, dysphagia, and dysarthria. Treatment focuses on enhancing muscle function and reducing

autoimmune activity, using anticholinesterase inhibitors (e.g., pyridostigmine) and immunosuppressive therapies like corticosteroids and azathioprine. [78, 80].

1.3.10 Psoriasis

Psoriasis is a chronic autoimmune skin disorder causing rapid keratinocyte proliferation, resulting in thick, red, scaly plaques. It arises from genetic, environmental, and immune factors, with abnormal T-cell activation leading to increased pro-inflammatory cytokines (TNF- α , IL-17, IL-23). [81]. Psoriasis has a prevalence of 2% to 3% in the global population with a similar prevalence in men and women. Rates in Northern Europe can reach 8% to 11% [82]. The clinical manifestations of psoriasis vary in severity and can include well-defined erythematous plaques covered with silvery-white scales, typically found on the elbows, knees, scalp, and lower back. Treatment options are tailored to disease severity and can include topical therapies (such as corticosteroids and vitamin D analogs), phototherapy (e.g., UVB and PUVA), and systemic treatments [83-85].

1.3.11 Psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis causing joint inflammation, pain, and potential joint damage. It results from genetic predisposition, environmental factors, and immune dysregulation, with HLA alleles increasing susceptibility. T-cell activation and pro-inflammatory cytokines (TNF- α , IL-17, IL-23) drive inflammation, leading to synovitis and enthesitis, affecting joint function. [86]. [87]. Global prevalence ranges from 0.1% to 0.25% in the general population with similar prevalence rates in men and women. Among people with psoriasis, approximately 30% to 40% develop this condition [88]. PsA causes joint pain, stiffness, and swelling, often affecting the fingers, toes, and spine. Key features include

dactylitis, enthesitis, and nail changes like pitting and onycholysis. Management aims to reduce symptoms and prevent joint damage, using NSAIDs for pain relief and DMARDs like methotrexate to slow disease progression [89-91].

1.3.12 Rheumatoid arthritis

Rheumatoid arthritis is a chronic autoimmune disorder causing joint inflammation, pain, swelling, and potential deformities. It can also affect organs like the lungs, heart, and eyes. RA develops from genetic and environmental factors, leading to immune dysfunction and autoantibody production (rheumatoid factor, ACPAs) that attack the synovium. [92].

Prevalence varies widely, with estimates ranging from 0.25% to 0.69%. with average prevalence was approximately 0.54% [93]. Studies report women are about three times more likely to have the disease [94]. Disease presents as symmetric joint pain, stiffness (especially morning stiffness >1 hour), and swelling, primarily in the hands and feet. Larger joints may be affected as the disease progresses. Systemic symptoms include fatigue, weight loss, and fever. Treatment focuses on controlling inflammation and preventing joint damage, with DMARDs like methotrexate as the main therapy. Biologic DMARDs (TNF inhibitors) and JAK inhibitors offer targeted immune pathway treatment. [94-96].

1.3.13 Sjögren's syndrome

Sjögren's syndrome is an autoimmune disease affecting exocrine glands, causing dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca). The disease results from immune dysfunction, with genetic factors (HLA-DR, IRF5) and B-cell hyperactivity (elevated BAFF) leading to autoantibody production (anti-Ro, anti-La) and glandular damage. [97]. The global prevalence is estimated to be between 1 to 4 per 1,000 individuals with mostly affecting

women. [98]. Disease cause difficulty swallowing, increased risk of dental cavities, and a gritty eye sensation. Systemic symptoms include fatigue, joint pain, and potential organ involvement. Management focuses on symptomatic relief with artificial tears and saliva substitutes, while systemic treatments like hydroxychloroquine, corticosteroids, and biologic therapies (e.g., rituximab) help control inflammation and immune-mediated damage. [99, 100].

1.3.14 Systemic lupus erythematosus

SLE causes chronic inflammation and multi-organ damage. It results from immune dysregulation driven by genetic, environmental, and hormonal factors. Key features include autoantibody production (ANA, anti-dsDNA), increased B-cell activation, and elevated type I interferons, leading to tissue damage in the skin, joints, kidneys, heart, and central nervous system.[101]. Prevalence estimates range from 20 to 150 per 100,000 people, with significant variations based on geographic location, ethnicity, and sex, being more common in women, especially those of African, Hispanic, and Asian descent. Prevalence rates are higher in North America (40 to 150 per 100,000) compared to Europe and Asia [102]. SLE presents with varied symptoms, from fatigue and joint pain to severe complications like lupus nephritis. Classic signs include a malar rash, photosensitivity, oral ulcers, and arthralgia. Severe cases may involve pleuritis, pericarditis, neurological issues, and blood disorders. Management ranges from NSAIDs and hydroxychloroquine for mild cases to glucocorticoids and immunosuppressants for severe disease, with biologics like belimumab and rituximab used for refractory [103].

1.3.15 Systemic sclerosis

Systemic sclerosis, or scleroderma, is an autoimmune disease marked by widespread fibrosis in the skin and internal organs, along with vascular and immune system abnormalities. Its pathophysiology involves immune dysregulation, vascular damage, and fibrosis. Research has highlighted various autoantibodies, such as anti-Scl-70 and anticentromere antibodies, as well as T cell activation, suggesting an autoimmune process is central to the disease.

[104]. Prevalence of systemic sclerosis is approximately 17.6 cases per 100,000 people globally with mostly being in women [105, 106].. Common symptoms include skin thickening, tightness, and pigmentation changes, especially on the fingers and face.

Treatment is personalised, focusing on symptom relief, complication prevention, and disease modification. Immunosuppressive therapies like mycophenolate mofetil or cyclophosphamide are used for interstitial lung disease, while pulmonary arterial hypertension is managed with vasodilators. [107, 108].

1.3.16 Type 1 Diabetes Mellitus

T1DM is an autoimmune disorder characterised by the destruction of insulin-producing β -cells in the pancreas, leading to absolute insulin deficiency. The pathogenesis involves a complex interplay of genetic susceptibility and environmental factors that trigger an autoimmune response, culminating in the loss of β -cells [109]. Global prevalence range between 0.5% to 1.0% with some regions, particularly Nordic countries, report much higher incidence rates, reaching around 30 to 40 cases per 100,000 individuals [110]. T1DM typically presents with classic symptoms such as polyuria, polydipsia, polyphagia, and unexplained weight loss. In some cases, individuals may present with diabetic ketoacidosis, a critical acute complication characterised by severe hyperglycaemia, ketonuria, and metabolic

acidosis with many long-term complications. Management involves exogenous insulin administration through multiple daily injections or continuous subcutaneous insulin infusion via insulin pumps. Patient education on carbohydrate counting and lifestyle modifications is essential for effective self-management [111, 112].

1.3.17 Vitiligo

Vitiligo is skin disorder characterised by the loss of pigmentation due to the destruction of melanocytes, leading to well-defined white patches on the skin. The aetiology of vitiligo is multifactorial, involving genetic, autoimmune, and environmental components [113]. Global prevalence ranges from approximately 0.5% to 2% with equal prevalence in both men and women [114]. The condition involves an autoimmune attack on melanocytes. Treatment focuses on restoring skin pigmentation and improving quality of life, with options like topical corticosteroids, calcineurin inhibitors, and narrowband UVB therapy showing effectiveness. Psychological support, including counselling and support groups, is essential for addressing the emotional impact. [115, 116].

1.4 Women and autoimmune diseases

Autoimmune diseases disproportionately affect women, accounting for nearly 80% of cases [117]. The higher prevalence in women, with some conditions showing a female-to-male ratio of 9:1 [118] is believed to be due to a combination of genetic, hormonal, and other factors. This significant gender disparity raises few hypothesis about the mechanisms driving the increased susceptibility in women.

1.4.1 Genetic factors (X chromosome)

Women have two X chromosomes that carry genes related to immune function, increasing their susceptibility to autoimmune diseases. Abnormalities like skewed X-chromosome inactivation can lead to overexpression of immune-related genes, affecting T cell responses and antigen presentation. During X-chromosome inactivation, one X is silenced, but some genes, such as TLR7 and TLR8 (Toll-like receptors), may escape this process, resulting in increased activity in certain immune cells [119]. This dysregulation of TLR expression contributes to women's heightened vulnerability to autoimmune diseases. The inactivation process involves RNA strands called XIST (X-inactive-specific transcript) that coil around the chromosome, attracting proteins to silence the genes [120].

1.4.2 Oestrogen

Female hormones like oestrogen enhance immune responses, contributing to autoimmune risk. Significant hormonal changes occur during puberty, menopause, and pregnancy, which influence the immune system and modify women's susceptibility to these diseases [121]. These endocrine transitions interact with various hormones and cytokines, impacting immune responses and the balance between defence and autoimmunity. Understanding how these hormonal changes affect autoimmune disease development can enhance prediction, prevention, and treatment strategies for women [122].

1.4.3 Stronger immune response

Women typically have more robust immune systems, which can sometimes lead to immune overactivation. They demonstrate stronger immune responses than men, resulting in quicker pathogen clearance but also a higher risk of developing autoimmune diseases [123]. These

differences arise from a combination of hormonal, genetic, and environmental factors that can change throughout life. For instance, females have a higher expression of TLR7 (Toll Like Receptor 7-protein playing role in the immune system) which boosts cytokine production, along with notable differences in innate immunity characteristics, such as increased natural killer cell frequencies and phagocytic activity. In contrast, men usually exhibit lower immune responses, might face higher risks of infections but potentially lower susceptibility to autoimmune diseases, balancing the demands of survival and reproduction in different ways than women [124].

1.4.4 Epigenetic differences

Epigenetic mechanisms create a dynamic interplay between genetics and the environment, contributing to the predisposition to autoimmune diseases in women [125]. These factors include DNA methylation, which alters gene expression by adding methyl groups to cytosine bases, and histone modifications that can either promote or repress transcription.

Chromatin remodelling facilitates changes in the accessibility of DNA for transcription factors, impacting immune gene expression, while non-coding RNAs like microRNAs can regulate gene expression post-transcriptionally [126].

1.4.5 Microbiome differences

Microbiota may influence immune responses through various mechanisms, including the modulation of inflammatory pathways and the development of immune cells [127].

Research shows that gut microbiota composition differs significantly between men and women, which affects immune gene expression. Larger studies have emphasised the interplay between sex and genotype in determining these variations, suggesting that sex-specific microbiota profiles could influence health outcome[128].

1.5 Interplay between pregnancy/pregnancy complications and autoimmune diseases

The relationship between pregnancy and autoimmune diseases is intricate and multifaceted, encompassing the effects of autoimmune conditions on pregnancy outcomes and the potential for pregnancy/pregnancy complications itself to contribute to the onset of autoimmune diseases in women. Understanding how these conditions influence pregnancy and vice versa is crucial for optimising maternal and fetal health outcomes.

1.5.1 Pre-existing autoimmune diseases in women and pregnancy/pregnancy complications

Pregnancy involves profound immunological adaptations, making it a unique immunological state [129]. The maternal immune system must tolerate the foetus, which is genetically distinct from the mother, while still protecting the body from infections. For women with autoimmune diseases, these changes can have varied effects, sometimes improving disease activity and at other times exacerbating symptoms or triggering complications [130].

1.5.1.1 The effect of pregnancy on autoimmune Disease

During pregnancy, the maternal immune system undergoes significant changes to support the growth of the foetus. It shifts toward an anti-inflammatory profile, especially during the second and third trimesters, creating an immunosuppressive state that prevents the maternal body from rejecting the foetus, which carries paternal antigens. However, this shift can have varying effects for women with autoimmune disease [131]. For some, such as those with rheumatoid arthritis, pregnancy may bring symptom relief, as pregnancy hormones like progesterone and estriol suppress the inflammatory response driving the disease [132]. On the other hand, conditions like SLE can worsen during pregnancy, particularly in women with

kidney involvement or a history of high disease activity due to increased blood volume in pregnancy. Research has shown that pregnant women with SLE are at higher risk of disease flares, complicating pregnancy management and increasing the likelihood of adverse outcomes for both mother and foetus [133]. In such cases, careful medication management is essential to balance maternal health and fetal safety. Furthermore, autoimmune conditions like SLE and Sjögren's syndrome can affect the foetus through autoantibodies, which may lead to congenital heart block or neonatal lupus [134, 135]. Close monitoring and individualised treatment are crucial for minimising these risks.

1.5.1.2 Effect of autoimmune Diseases on pregnancy outcomes

Women with autoimmune diseases, particularly those with poorly controlled disease activity, face heightened risks of complications during pregnancy, including preterm birth, intrauterine growth restriction (IUGR), and preeclampsia [136]. These complications arise from both the disease's direct impact on placental function and the effects of medications used to manage the conditions. Fluctuations in autoimmune activity can lead to exacerbations that complicate treatment. Medications like corticosteroids and DMARDs, while effective in controlling symptoms, pose potential risks during pregnancy, requiring healthcare providers to carefully weigh the benefits of disease control against any adverse effects on fetal development [137]. Diseases like SLE and antiphospholipid syndrome (APS) increase the risk of placental insufficiency, resulting in fetal growth issues and maternal complications like hypertension. Preeclampsia is also more common in these pregnancies, posing significant risks of maternal organ dysfunction and fetal distress [138].

1.5.2 Pregnancy as a trigger for autoimmune Diseases

While much attention has been given to how autoimmune diseases affect pregnancy, the reverse relationship of how pregnancy can influence the development or exacerbation of autoimmune diseases is also a key area of study. Several hypotheses have been proposed to explain how pregnancy and its complications might serve as a trigger for autoimmune diseases in women.

1.5.2.1 Pregnancy as a “Stress Test” for the immune system

One hypothesis is that pregnancy acts as a stress test for the maternal immune system, revealing underlying susceptibilities to long term health conditions that may not have been evident before [139]. This has been explored for the cardiovascular or kidney disease in later life earlier [140]. However, the profound hormonal changes and immunological adaptations that occur during pregnancy can unmask or exacerbate autoimmune diseases in women who are genetically predisposed. For example, the postpartum period is a time of significant immune system reactivation, which can lead to the onset of autoimmune diseases such as postpartum thyroiditis or rheumatoid arthritis [141, 142]. This hypothesis is supported by the observation that the postpartum period is a time of increased risk for the development of autoimmune diseases. The return of the immune system to its pre-pregnancy state after delivery can trigger a flare of autoimmune conditions, or in some cases, the first manifestation of an autoimmune disease. Hormonal shifts, including the drop in oestrogen and progesterone levels, are thought to play a role in this process [143].

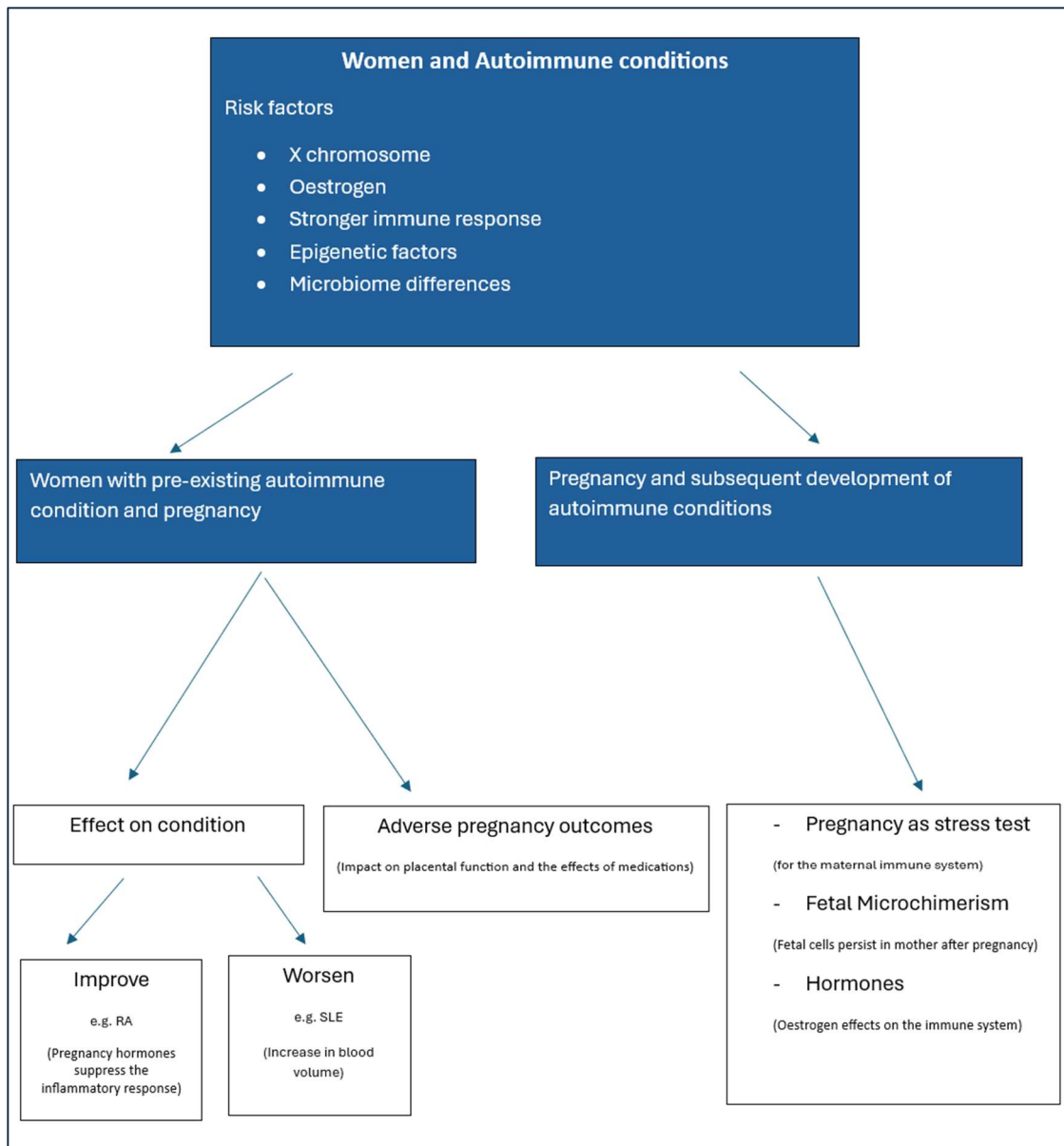
1.5.2.2 Fetal Microchimerism as a trigger for autoimmune Diseases

Another hypothesis in the development of autoimmune diseases is the role of foetal microchimerism (FMC). FMC refers to the presence of a small number of foetal cells that persist in the mother's body long after pregnancy has ended. These foetal cells, which are genetically distinct from maternal cells, can remain in maternal tissues for decades after delivery. Some researchers suggest that these cells might provoke an immune response in certain women, potentially leading to the development of autoimmune diseases. Elevated levels of foetal cells have been found in the blood of women with autoimmune conditions such as systemic lupus erythematosus (SLE), suggesting a potential link between FMC and autoimmunity. However, while the theory has gained traction, the evidence remains inconclusive, and more research is needed to fully understand the role of FMC in autoimmune disease pathogenesis [144, 145]. Supporting this theory, the study by Keelin O'Donoghue et al provides evidence that foetal mesenchymal stem cells persist in maternal bone and bone marrow for decades following pregnancy [146]. This supports the allograft host hypothesis, suggesting that pregnancy functions as a form of natural transplantation, where foetal cells integrate into maternal tissues, particularly within stem cell niches. These foetal-derived cells may contribute to maternal tissue repair and immune modulation, potentially aiding in bone regeneration and haematopoiesis. However, their long-term persistence also raises important questions regarding their role in autoimmune diseases and immune dysregulation. In genetically predisposed individuals, these foetal cells may either promote immune tolerance or trigger autoimmune responses, contributing to conditions like systemic sclerosis and thyroid disorders [147]. Understanding the long-term effects of these cells on maternal health could provide valuable insights into pregnancy-related immune

adaptations, bone health, and the increased susceptibility of some women to autoimmune diseases.

1.5.2.3 Hormonal Influences.

Oestrogen has well-documented effects on the immune system, and levels fluctuate dramatically during pregnancy with high oestrogen levels thought to have immunosuppressive effects, helping to modulate the immune response. However, the sudden drop in oestrogen after childbirth may reactivate the immune system, increasing the risk of autoimmune diseases [148]. Hormonal fluctuations during pregnancy can also affect disease susceptibility by influencing processes like autophagy, which causes cells to breakdown. Elevated oestrogen and progesterone during pregnancy enhance autophagy by inhibiting the apoptosis pathways, such as the mTOR (Mammalian target of rapamycin) pathway. Additionally, dihydrotestosterone may promote T cell death through mechanisms that overlap with autophagy [149, 150]. This hormonal influence is thought to be particularly relevant in diseases like SLE, which disproportionately affect women and are often associated with hormonal changes. For example, women with SLE frequently experience disease flares during periods of hormonal fluctuation, such as pregnancy, menstruation, or menopause, suggesting a link between oestrogen levels and disease activity.



SLE=systemic lupus erythematosus, RA=Rheumatoid arthritis

Figure 1.1 Women and autoimmune conditions

1.5.3 Conclusion

Understanding this interplay is essential for optimising the care of women with autoimmune diseases during pregnancy and for identifying those at risk of developing autoimmune diseases postpartum. While this is not the part of the thesis further research is needed to clarify the mechanisms underlying these interactions and to develop targeted strategies for preventing and managing autoimmune diseases in pregnant and postpartum women.

Through careful monitoring, multidisciplinary care, and a nuanced understanding of the immune system's response to pregnancy, healthcare providers can improve outcomes for both mothers and their children.

1.6 Definitions and epidemiology of adverse pregnancy outcomes/pregnancy complications

1.6.1 Hyperemesis gravidarum

Severe, protracted nausea and vomiting associated with weight loss of more than 5% of pre pregnancy weight, dehydration, and electrolyte imbalances [151]. This condition is caused by elevated hormone levels, particularly hCG, along with genetic and gastrointestinal factors. It leads to dehydration, weight loss, and requires medical treatment in severe cases.

Affecting about 0.3% to 3% of pregnancies, it is more common in women with multiple pregnancies or a history of the condition [152].

1.6.2 Ectopic pregnancy

If the fertilised egg fails to move from the fallopian tube into the uterus, where the pregnancy grows and develops, and the fertilised egg may implant and start to develop outside the uterus [153]. Conditions like tubal scarring from previous infections (e.g., pelvic inflammatory disease), surgeries, or congenital abnormalities can impair the egg's passage

to the uterus. Other risk factors include hormonal imbalances, smoking, and the use of assisted reproductive technologies. Ectopic pregnancies affect approximately 1-2% of all pregnancies and are more common in women with a history of pelvic infections or previous ectopic pregnancies [154, 155].

1.6.3 Miscarriage/ recurrent miscarriage/ spontaneous pregnancy loss.

Spontaneous loss of a pregnancy before 24 weeks of gestation. Early miscarriage occurs before 13 weeks of gestation. Late miscarriage, between 13 and 24 weeks of gestation and recurrent miscarriage is loss of three or more consecutive pregnancies before 24 weeks of gestation [156]. It is the most common complication of pregnancy, with approximately 23 million miscarriages occurring worldwide each year. Most miscarriages happen early, during the first trimester. The causes of miscarriage include chromosomal abnormalities, endometrial defects, demographic factors such as maternal age, body mass index, and ethnicity, lifestyle factors like smoking and high alcohol consumption, and clinical factors such as antiphospholipid antibodies, subclinical hypothyroidism, thyroid autoantibodies, uterine anomalies, and sexually transmitted infections [157].

1.6.4 Gestational hypertension/Pre-eclampsia/Eclampsia

Gestational hypertension is new hypertension presenting after 20 weeks of pregnancy without significant proteinuria. Pre-eclampsia can be classified as early and late onset. Recurrent pre-eclampsia is the new onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy and the coexistence of 1 or more of the following new-onset conditions, proteinuria, other maternal organ dysfunction (renal insufficiency, liver involvement, neurological complications, haematological complications) - uteroplacental dysfunction. Eclampsia HELLP (Haemolysis, Elevated Liver enzymes and Low

Platelets). The new onset of seizures or coma in a pregnant woman with pre-eclampsia HELLP syndrome is a life-threatening pregnancy complication usually considered to be a variant of pre-eclampsia [158]. About 10% of pregnancies are complicated by hypertension during pregnancy worldwide and is major cause of maternal morbidity and mortality [159]. Risk factors include advanced maternal age, obesity, multiple pregnancies, and pre-existing conditions like diabetes. It is more common in low- and middle-income countries, with racial and ethnic disparities also observed[160]. If unmanaged, gestational hypertension can lead to complications such as preeclampsia, fetal growth restriction, and preterm birth [161]. The pathogenesis of hypertensive disorders of pregnancy are not clearly understood. These disorders are characterised by aberrant spiral artery remodelling, abnormal placentation, placental ischaemia, and oxidative stress resulting in endothelial dysfunction and end organ damage[162].

1.6.5 Gestational diabetes mellitus

GDM is hyperglycaemia in pregnancy that is above diagnostic thresholds for diabetes such as a fasting plasma glucose level of 5.6 mmol/litre or above or a 2-hour plasma glucose level of 7.8 mmol/litre or above [163]. Globally, GDM affects about 14% of all pregnancies, equating to approximately 18 million deliveries each year [164]. Risk factors for GDM include genetic predisposition, family history, demographic factors such as advanced maternal age, ethnicity, and shorter stature, lifestyle factors like high pre-pregnancy BMI, physical inactivity, and poor diet, as well as clinical factors like vitamin D deficiency, polycystic ovary syndrome, and twin pregnancies. GDM develops due to impaired glucose tolerance resulting from β -cell dysfunction combined with chronic insulin resistance. The reduced insulin resistance

observed during the second or third trimester typically reflects a pre-existing state of insulin resistance before pregnancy [165].

1.6.6 Placental abnormalities

Placenta previa is low lying placenta after 20 weeks of pregnancy. Placenta accrete is where placenta is stuck to the uterine muscle. Placenta percreta is a condition where placenta attaches itself and grows through the uterus and potentially to the nearby organs (such as the bladder) [166]. Placenta accreta typically occurs due to a failure of the decidualisation process (development of the uterine lining to allow normal placental attachment), often in areas of the uterus that have been scarred from previous surgeries, such as caesarean sections, uterine curettage, or other uterine procedures. Globally, placenta accreta occurs in approximately 1 in 533 to 1 in 2,500 pregnancies, its incidence is increasing due to the rising number of caesarean births [167, 168]. Placental abruption is the early separation of a placenta from the lining of the uterus before completion of the second stage of labour. It is one of the causes of bleeding during the second half of pregnancy. Placental abruption is also called abruptio placentae [169, 170]. Risk factors for this condition include demographic factors such as advanced maternal age, lifestyle factors like smoking and cocaine use, and clinical factors such as hypertension and a prior history of placental abruption. The placenta plays a critical role in supplying oxygen and nutrients to the foetus, while also removing waste products. Placental abruption occurs when maternal blood vessels detach from the placenta, causing bleeding between the uterine lining and the placenta. The accumulation of blood further separates the placenta from the uterine wall [171].

1.6.7 Molar pregnancy/Choriocarcinoma

Abnormal cells or tumours that start growing in the womb from cells that would normally develop into the placenta are called gestational trophoblastic disease that forms a group of disorders spanning the conditions of complete and partial molar pregnancies through to the malignant conditions of invasive mole (choriocarcinoma) [172, 173]. These conditions may lead to excessive production of hCG (human chorionic gonadotropin) and can cause complications such as bleeding, high blood pressure, and potential progression to invasive disease or cancer if not managed appropriately. Molar pregnancies are rare, occurring in about 1 in 1,000 to 1 in 1,500 pregnancies, and are more common in certain populations, particularly women of Asian descent or those with a history of molar pregnancy [174].

1.6.8 Obstetric /postpartum haemorrhage

Heavy bleeding after birth postpartum haemorrhage (PPH) can be primary or secondary. Primary PPH is blood loss of 500 ml (a pint) or more within the first 24 hours after the birth of the baby. Secondary PPH occurs when there is abnormal or heavy vaginal bleeding between 24 hours and 12 weeks after the birth [175]. It is a significant global health concern, with prevalence estimates ranging from 3% to 15% of deliveries, and accounting for approximately 25% of maternal deaths, particularly in low- and middle-income countries. Major risk factors include multiple pregnancies, prolonged labour, uterine atony, and inadequate healthcare access [176].

1.6.9 Stillbirth

Stillbirth occurs when baby born after the 24th week of pregnancy who did not show any signs of life after being born [177]. Around 2 million stillbirths occur globally each year (13.9

stillbirths per 1,000 total births). Stillbirths are classified as antepartum when they happen before labour begins, and intrapartum when they occur during labour. The causes of stillbirth include demographic factors such as advanced maternal age and Black ethnicity, lifestyle factors like smoking and high alcohol consumption, and clinical factors such as multiple gestations and the use of assisted reproductive technology [178].

1.6.10 Mode of birth

Instrumental birth of a singleton/multiple baby/babies between 37+0 and 42+6 weeks of gestation, who give birth vaginally with the assistance of instruments (ventouse and forceps births). Caesarean birth of a singleton/ multiple babies' baby between 37+0 and 42+6 weeks of gestation, by caesarean birth (elective or emergency) [179]. 29.7 million births (21.1%) occurred via caesarean section, nearly double the number in 2000. Caesarean birth rates vary significantly by region, with the highest use in Latin America (44.3%) and the lowest in West and Central Africa (4.1%). Disparities were also noted within countries, with higher Caesarean birth use among wealthier populations and in private healthcare facilities [180].

1.6.11 Low birth weight

Low birth weight (LBW) is defined when the baby born at full term and the weight at birth < 2500 grams (5.5 pounds), Low birth weight is further classified as very low (< 1500g) or extremely low (< 1000g) [181]. The prevalence of LBW varies globally, ranging from about 5% to 20% of live births, with higher rates typically found in low- and middle-income countries. Small for gestational age are babies with a birth weight below the 10th centile [182].

1.6.12 Pre-term birth

Babies born alive before 37 weeks of pregnancy are completed are considered pre-term., extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), moderate to late preterm (32 to 37 weeks) [183]. Each year, approximately 15 million preterm deliveries occur worldwide, with rates ranging from 5% to 18%. Risk factors for preterm delivery include demographic factors such as advanced maternal age and Black ethnicity, lifestyle factors like extreme BMI, smoking, and stress, as well as clinical factors such as a history of preterm delivery, uterine curettage, cervical surgery, uterine malformations, and antepartum haemorrhage. Although the biological mechanisms behind preterm delivery are not fully understood, proposed explanations include genetic predisposition, maternal vascular under perfusion, increases in cell-free fetal DNA during the mid-trimester, and the presence of inflammation or infection [184].

1.6.13 Obstetric cholestasis

This disorder affects the liver during pregnancy causing build-up of bile acids in the body. The main symptom is itching of the skin with no rash. The symptoms get better after delivery [185]. The condition is thought to result from hormonal changes, genetic predisposition, and impaired bile flow, with symptoms typically appearing in the third trimester. It affects approximately 0.1% to 2% of pregnancies, with a higher prevalence in certain populations (Hispanic and Swedish) and increased risk for women with a history of the condition [186, 187].

1.6.14 Perinatal mental health

Perinatal mental health encompasses the emotional, psychological, and social well-being of women during pregnancy and the first year after childbirth, including conditions such as perinatal depression and anxiety disorders [188]. The pathophysiology of these disorders involves a combination of hormonal changes, genetic predisposition, psychosocial stressors, and physical health issues that can affect mood regulation. Hormonal fluctuations during and after pregnancy can increase susceptibility to mental health challenges, while a family history of such disorders can further heighten risk. Perinatal mental health disorders are prevalent, affecting approximately 10% to 20% of women during pregnancy and about 15% to 20% in the postpartum period [189].

1.7 Sociodemographic factors and autoimmune diseases

Age has an important role in the onset, progression, and severity of autoimmune diseases and certain autoimmune conditions have a distinct pattern of onset over the life course. For example, T1DM typically manifests in childhood or adolescence, whereas rheumatoid arthritis, SLE, and multiple sclerosis are more likely to develop in young adulthood or middle age [190].

The severity and progression of autoimmune diseases can also be influenced by age.

Conditions such as polymyalgia rheumatica and Hashimoto's thyroiditis are more common in older adults. However, the presence of other age-related comorbidities, such as cardiovascular or metabolic diseases, can exacerbate the severity of autoimmune diseases in the elderly. Additionally, older individuals often experience interactions between autoimmune diseases and other chronic health issues, requiring specialised management strategies [191].

The aging process can, in itself, contribute to a decline in immune function a process known as immunosenescence [192]. This leads to dysregulation in both the innate and adaptive immune responses, influencing the risk of developing autoimmune diseases and how these diseases progress. This decline in immune function also affects how patients respond to treatments, potentially altering the disease course and requiring adjustments in therapeutic approaches [190, 192, 193].

A study examining the relationship between reproductive history and autoimmune disease risk in 4.6 million Danish women showed that, overall, women with children had a slightly higher risk of autoimmune diseases compared to nulliparous women including Hashimoto's thyroiditis, Graves' disease, erythema nodosum, psoriasis, sarcoidosis, and systemic lupus erythematosus, with the postpartum period showing the most significant association [194]. Another community-based study found that a higher number of pregnancies was associated with an increased risk of developing conditions such as Hashimoto's thyroiditis and Graves' disease. These findings indicate that immune adaptations during pregnancy may play a role in autoimmunity, . Further research is needed to clarify the immunological mechanisms underlying these associations [195].

Higher body mass index is associated with an increased risk [(HR, 1.27; 95% CI, 1.11 to 1.46) compared with normal weight women ($18.5 \leq 25 \text{ kg/m}^2$)] of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease. Obesity contributes to autoimmune disease development through chronic low-grade inflammation, immune system alterations, and hormonal imbalances, with fat tissue secreting pro-inflammatory cytokines that trigger autoimmune responses [196]. The rising global prevalence of obesity, linked to numerous comorbidities, also increases autoimmune disease

incidence. Chronic inflammation, driven by factors like leptin, platelet activation, gut dysbiosis, and aging, links obesity to autoimmunity chronic inflammation, a key factor in obesity-related diseases [197, 198].

Ethnicity plays a significant role in the onset, prevalence, and risk of autoimmune diseases, with notable differences observed across racial and ethnic groups due to genetic, environmental, and healthcare access factors. In the UK, individuals from South Asian, African-Caribbean, and Mixed-ethnicity/Other backgrounds are diagnosed with autoimmune diseases earlier than White individuals, with differences ranging from 2 to 30 years. For example, rheumatoid arthritis is diagnosed at an average age of 49 years in African-Caribbean individuals, compared to 56 years in White individuals [199]. In the US, diseases like SLE, IBD, and multiple sclerosis show varying prevalence across ethnic groups. SLE is more common in Hispanic and non-Hispanic Black adults, while multiple sclerosis is more prevalent in Black women under 60 years of age when compared to other ethnic groups. Conversely, conditions like IBD and psoriasis are less common in non-White populations [200].

The relationship between socioeconomic status and autoimmune diseases is complex, with varying impacts on the prevalence and severity of conditions such as rheumatoid arthritis, multiple sclerosis, and asthma, influenced by factors such as income, occupation, and access to healthcare. In 2021 Global Burden of Diseases study shows that the impact of autoimmune diseases varies according to socioeconomic status, as measured by the Socio-Demographic Index (SDI). Countries with a high SDI had the highest age-standardised rates for rheumatoid arthritis and multiple sclerosis. In contrast, low to middle SDI countries exhibited higher rates of type 1 diabetes (T1DM) and asthma [201]. Geographically, high-

income North America had the highest rates of rheumatoid arthritis and multiple sclerosis. A Swedish prospective cohort study found that individuals in socioeconomically disadvantaged neighbourhoods were at higher risk of developing autoimmune diseases, likely due to factors such as chronic stress, limited healthcare access, and lifestyle exposures [202]. Similarly, a UK study showed that people in deprived areas had higher rates of autoimmune conditions [203].

1.8 Rationale of the thesis

With the rising prevalence of autoimmune conditions during pregnancy, it is crucial to understand the associated adverse pregnancy outcomes and whether these outcomes are unique to specific conditions or shared across various autoimmune disorders. The symptoms of autoimmune conditions can improve, worsen, or remain unchanged during pregnancy, depending on the specific disorder, and their episodic nature complicates the assessment of pregnancy's role in triggering or exacerbating these conditions, as well as its impact on pregnancy outcomes. Effective management of pregnancies complicated by autoimmune disorders requires interdisciplinary care, clear preconception protocols, and a thorough understanding of the associated risks for adverse outcomes.

Certain events during pregnancy including the interactions between hormonal and immunological factors may contribute to the development of autoimmune diseases in women, similar to that of other long-term health conditions such as cardiovascular and renal conditions. Given the growing trend of pregnancy complications influenced by lifestyle factors, older maternal age, and pre-existing health conditions, it is essential to study how these complications may contribute to the development of autoimmune disorders.

Thus, this thesis aims to study this key area as it attempts to understand to clarify the complex relationship between autoimmune conditions and pregnancy outcomes, addressing a critical gap in knowledge that could inform clinical practice and improve maternal health. By examining how specific autoimmune disorders impact pregnancy and how pregnancy complications may contribute to the future development of these conditions, the research aims to enhance interdisciplinary care strategies, develop effective preconception and postpartum protocols.

1.9 Aim and objectives

Aim: To estimate the bidirectional relationship between pregnancy complications and autoimmune diseases.

Research objectives:

- 1) To assess the prevalence of autoimmune diseases in pregnant women by analysing primary care electronic health records (Clinical practice research datalink, CPRD) in the UK over time and by factors such as age, ethnicity, and social deprivation (chapter 3).
- 2) Review existing systematic review evidence of the associations of autoimmune diseases in women with risk of adverse pregnancy outcomes in an umbrella review (chapter 4).
- 3) To carry out epidemiological studies using electronic primary care record databases (CPRD) to describe the association of autoimmune diseases in pregnancy and adverse pregnancy outcomes (chapter 5).
- 4) To investigate the association of pregnancy complications with the development of autoimmune diseases in a systematic review (chapter 6).

Chapter 2: General methods and database overview

Chapter overview

This chapter gives a brief description of methods, datasets and rationale for the methods used in this thesis to address the research objectives. Routinely collected healthcare data was analysed for the studies comprising chapter 3 and 5 of this thesis. I have presented the rationale for using this type of data and described the specific datasets used along with their strengths and limitations. I also describe two of the specific methods used in chapters 4 and 6 umbrella review and systematic review, respectively. Lastly the rationale for using these methods along with their strengths and limitations is described.

2.1 Electronic health records and admin data system (CPRD Gold and CPRD Aurum)

Electronic health records (EHRs) have been utilised in UK primary care since the 1990s. Key software systems such as EMIS Health, Vision, and SystmOne enable clinicians to record patient symptoms, diagnoses, investigations, and prescriptions during consultations. In addition to their clinical and administrative use, these systems provide a valuable data source for research purposes [5, 204]. The data from the Clinical Practice Research Datalink (CPRD), a large electronic health record database that is widely used in the UK has been utilised for this thesis. The CPRD contains extensive anonymised patient-level data, offering detailed information on demographics, symptoms, diagnoses, prescriptions, physical measurements, and laboratory test results. This resource enables the conduct of comprehensive longitudinal analyses, providing valuable insights into patient health across time. CPRD's data are primarily collected for clinical care but have been repurposed for research, making it important resources for population-based health studies globally [205].

The study utilised data from both CPRD Gold and CPRD Aurum. CPRD Gold contains data from 985 general practices that use the Vision software, while CPRD Aurum covers 1,489 practices utilising EMIS software. Together, these databases encompass approximately 5% and 20% of the UK population, respectively [206]. The inclusion of these two databases ensures broad population coverage, representing various geographical regions, social backgrounds, and clinical practices. As the data is longitudinal, it provides a continuous view of patient health records, capturing long-term outcomes and enabling analyses of health trajectories and risks.

2.1.1 CPRD Pregnancy Register

A unique aspect of the CPRD system is its specialised pregnancy register, which is particularly focused on maternal health and pregnancy outcomes. This register is a rich source of anonymised data on antenatal care, maternal medical history, pregnancy complications, and linked maternal-neonatal records [207]. Unlike many pregnancy datasets, which are limited to pregnancies resulting in live births, the CPRD pregnancy register also captures outcomes such as miscarriages, terminations, and ectopic pregnancies [208]. This inclusivity enables the study of early pregnancy losses and their associated factors, an area that is often underrepresented in research. The CPRD pregnancy register allows researchers to follow individuals throughout the entire course of pregnancy, from early antenatal care to delivery and postnatal outcomes. Furthermore, the ability to link the pregnancy register with other national datasets, such as the Hospital Episode Statistics (HES), enhances the robustness of the data. HES provides information on secondary care outcomes, including inpatient and outpatient hospital visits, thus capturing pregnancy-related complications and procedures that occur within NHS hospitals [209]. The inclusion of HES data in this study is crucial, as it

provides diagnostic information (pregnancy outcomes) from secondary care settings, which complements the primary care data available in the CPRD. HES data covers all NHS-funded hospital activity in England, which includes approximately 98-99% of all hospital admissions, making it highly representative of hospital-based care [210].

2.1.2 HES Maternity tail

Linking Hospital Episode Statistics (HES) data with the CPRD provides a comprehensive resource for studying health outcomes related to secondary care. The HES Admitted Patient Care (HES APC) dataset captures data on all admissions to NHS hospitals in England, covering an estimated 98-99% of hospital activity. While this data primarily serves to inform service planning and the Payment by Results (PbR) reimbursement system, its extensive coverage and longitudinal nature make it valuable for research and service evaluation. In maternal health research, HES data include delivery/birth episodes and a "maternity tail" that provides detailed obstetric information, such as the method of onset of labour, live and stillbirth status, length of gestation, and birth weight. With almost 97.5% of births occurring in NHS hospitals, this data is highly representative and crucial for epidemiological studies on a population scale [211, 212].

2.1.3 Justification of using electronic health records

This retrospective cohort study (Chapters 3 and 5) leverages the vast data resources of the CPRD, including its Gold and Aurum databases, the specialized pregnancy register, the HES Maternity Tail, and broader HES datasets, to investigate pregnancy-related health outcomes. CPRD provides comprehensive electronic health records routinely collected from general practices, offering a wealth of data on patient demographics, diagnoses, prescriptions, and

referrals. Its vast sample size, encompassing millions of patients, supports robust statistical analyses and facilitates the study of rare conditions, such as certain autoimmune diseases like myasthenia gravis. The reliance on clinician-documented records in CPRD minimizes recall bias and reduces the risk of misclassification errors, which are more common with self-reported data. This approach enhances the study's efficiency by allowing the analysis of trends and associations in a large and diverse population. Additionally, CPRD enables the exploration of long-term conditions requiring consistent management and real-world clinical outcomes, providing insights critical for healthcare planning. The integration of primary care, secondary care, and socioeconomic data, including ethnicity and the IMD ensures a comprehensive examination of maternal and neonatal health. The high coverage of deliveries (>97%) in the CPRD Aurum linked maternity trail further supports a thorough investigation of health outcomes across the continuum of care, from primary care to hospital-based interventions. These robust data resources provide essential insights for improving health policies and practices related to maternal and neonatal care.

2.1.4 Limitations of using electronic health records

In the CPRD pregnancy register, some pregnancy records overlap, therefore the estimated start and end date of pregnancies using the CPRD pregnancy register Algorithm may not be fully accurate. Around 47% of women in the UK receive pregnancy care directly through midwifery services. While this information is supposed to be shared with general practitioners, it may not always be documented, potentially leading to incomplete pregnancy records in the CPRD dataset. In the pregnancy register, a small proportion of pregnancies have 'unknown outcomes,' this may result in underestimation in some of the pregnancy complications such as miscarriage and to overcome this limitation we have used

linked HES data to increase the capture of outcomes. IMD scores are based on postcode and may not accurately represent deprivation at an individual level but should be broadly representative across the populations studied. As this is an observational study using anonymised routine health records, key limitations include missing data, misclassification bias due to inaccurate clinical coding and residual confounding [213]. The completeness and quality of the data can vary between NHS trusts, as it is not part of a mandatory return. For example, missing data on birth weight and gestational age were issues encountered in this analysis.

2.2 Systematic review

Systematic review methodology is used to compile the available evidence on the associations between pregnancy complications and development of autoimmune diseases in women (Chapter 6). Systematic reviews differ significantly from traditional narrative reviews in their methodology, scope, and reliability. Narrative reviews are typically descriptive and do not involve a systematic search of the literature, often focusing on a selected subset of studies that may be chosen based on availability or the author's preference. This selective approach can lead to bias and may result in conflicting conclusions, especially when similar studies yield divergent results. In contrast, systematic reviews are designed to minimise bias by following a detailed, pre-established plan and search strategy that aims to identify, appraise, and synthesise all relevant studies on a specific topic. This process often includes a meta-analysis, where statistical techniques are applied to combine data from multiple studies, producing a quantitative estimate of the effect size, such as odds ratios or risk ratios. The systematic approach ensures that the review is comprehensive, transparent, and reproducible, providing a more accurate and reliable summary of the evidence.

A systematic review is a rigorous and structured approach to synthesising research evidence on a specific topic or question. Unlike traditional literature reviews, which may be more narrative and subjective, systematic reviews aim to minimise bias by following a predefined and transparent methodology. The process begins with clearly defining the research question, often using the PICO framework (Population, Intervention, Comparison, Outcome), ensuring that the review focuses on a specific, answerable question. Next, a comprehensive literature search is conducted across multiple databases and sources to identify all relevant studies, both published and unpublished. This exhaustive search minimises the risk of selection bias and ensures the inclusion of a comprehensive set of data [214]. Identified studies are then screened against predefined inclusion and exclusion criteria to determine their relevance. This step typically involves multiple reviewers working independently to ensure objectivity. Each included study is critically appraised for its methodological quality, using tools like the Newcastle Ottawa risk [215] of bias tool to assess aspects such as selection, representativeness, comparability and other factors that could influence the results. Relevant data from the included studies are extracted and synthesised. In some systematic reviews, this synthesis is narrative, but it is often combined with a meta-analysis, where statistical techniques are used to quantitatively combine results from multiple studies. Finally, the findings are interpreted in the context of the quality of the evidence and the consistency of the results across studies. The review is reported following guidelines like PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [216] to ensure transparency and reproducibility. Systematic reviews are considered the gold standard for summarising evidence in healthcare and other fields, providing a reliable basis for clinical guidelines, policy decisions, and future research.

2.2.1 Justification for using systematic review methodology

The systematic literature search in Chapter 6 followed the standards of a systematic review for the search strategy and study selection. Three electronic databases were searched. There were numerous observational studies which have studied the association of pregnancy complications with the development of autoimmune diseases in women. There were no existing systematic reviews addressing this question and this was the best way to collate all data in one document to inform communicating risk in clinical practice and future research.

2.2.2 Limitations for using systematic review methodology

Systematic review methodology, while robust, has several limitations. One key challenge is its reliance on the quality and completeness of the included studies. If the primary studies are poorly designed, inconsistently reported, or biased, these issues can weaken the validity of the review's findings. Tools are available to assess the quality of primary studies, but they cannot fully eliminate these challenges.

Systematic reviews also depend on thorough literature searches, yet they may still miss important studies due to publication bias, language barriers, or limited access to grey literature. Another common limitation is the variation, or heterogeneity, between studies, such as differences in populations, interventions, or outcomes. This variability can make it harder to combine results and may limit the applicability of the findings to different settings or groups.

Lastly, systematic reviews can be influenced by reviewer bias during the selection of studies, data extraction, or interpretation of results. While standardized guidelines like PRISMA aim to improve consistency and transparency, subjective decisions by reviewers can still impact

the outcomes. These limitations highlight the importance of critical appraisal when conducting or using systematic reviews.

2.3 Umbrella review

Umbrella review methodology is used to compile the available evidence from systematic reviews on association between autoimmune diseases and adverse pregnancy outcomes (Chapter 4). An umbrella review is a systematic approach to synthesising and comparing the findings from multiple existing systematic reviews on a specific topic [217]. These reviews go by various names in scientific literature, such as overviews of reviews, reviews of reviews, summaries of systematic reviews, and syntheses of reviews. Given the growing number of systematic reviews available [218], umbrella reviews have become increasingly important as they provide a broad examination of the available evidence, offering a comprehensive overview that compares the conclusions of numerous studies [219]. This type of review is particularly valuable for identifying consistent findings across different reviews or highlighting areas where discrepancies or contradictory results exist. In the hierarchy of evidence, systematic reviews are regarded as the highest level of evidence available, providing comprehensive analyses of multiple studies on a given topic [220]. Consequently, umbrella reviews play a crucial role in informing policy decisions and guiding further research by synthesising this high-level evidence. These reviews offer a robust foundation for evidence-based practice by aggregating and analysing the most reliable data available in each field [221, 222]. Umbrella reviews are not limited to analysing evidence for a single intervention or condition; they can also summarise findings from multiple interventions addressing the same problem or different outcomes related to the same intervention. Additionally, these reviews may focus on different conditions, problems, or populations,

depending on the research question. A key aspect of these reviews is that they do not re-synthesise the results of existing reviews but rather summarise and synthesise the findings from those reviews to provide a cohesive overview [223]. To ensure the inclusion of high-quality evidence, the systematic reviews considered for an umbrella review must undergo a rigorous assessment of their methodological quality. Various checklists and tools are available to evaluate the quality of systematic reviews, typically using criteria that assess whether certain standards are met. These assessments are usually performed by multiple independent reviewers to ensure objectivity and reliability. The methodology to conduct Umbrella reviews is similar to the systematic review with a few key differences. The main difference is the overlap between the reviews need to be calculated when two or more reviews studied the association of the same exposure and outcome. For this thesis the corrected covered area (CCA) was used to measure and establish the percentage of overlap (44, 45). CCA less than 5 indicated low overlap and CCA 10 or above indicates moderate/high overlap. Where reviews had a high overlap ($CCA \geq 10\%$), the Cochrane review was selected over a non-Cochrane review. If there were no Cochrane reviews, then a review was selected if: it had a higher AMSTAR (A Measurement Tool to Assess Systematic Reviews) quality rating, was conducted more recently, included a meta-analysis, or had a larger sample size [224-226].

2.2.3 Justification of using umbrella review methodology

For my thesis I utilised umbrella review methodology as there were many systematic reviews published which reported the adverse pregnancy outcomes in women with each individual autoimmune disease. There was more than one review for one specific disease and outcome. With a purpose of bringing all the evidence together, address the conflicting

findings and identify gaps this review was performed. The umbrella review approach helps consolidate the large amounts of evidence on this subject, helping health professionals and policy makers to navigate the research findings, which will be of help where different clinical recommendations may overlap or contradict one another [227]. Also, it has been recently an area of research that autoimmune conditions co-occur, and this umbrella review is useful to understand the effects of various autoimmune conditions in one document making it easy to navigate through pregnancy outcomes in women with more than one condition [228]. The umbrella review pulls together the information from various reviews and often by conduction meta-analysis provide a pooled effect estimate showing the totality of evidence. Identify gaps in the research. The umbrella review compiles the available incidence and also identifies the gaps in the research.

One novel approach that was adapted in addition to the standard umbrella review methodology, in cases where the reviews had a non-overlapping association ($CCA < 10\%$), the reviews were retained and the data from primary studies of the reviews were extracted without double counting of the primary studies, a meta-analysis was conducted to generate pooled effect sizes. This allowed us to get the pooled estimates from the primary studies without conducting a new review. Secondly, conversion of all the effect-estimates of the included reviews was done where possible to facilitate the understanding of the results.

2.2.4 Limitations of using umbrella review methodology

Umbrella reviews encounter several limitations that can affect their reliability and comprehensiveness. A significant challenge is managing overlap between systematic reviews, which arises when multiple reviews address similar research questions and share common primary studies. This redundancy complicates synthesis and may introduce bias.

Approaches to addressing overlap include the full inclusion of all overlapping reviews, which is exhaustive but resource-intensive, and a restricted approach, where only one review is selected based on criteria like quality or recency. While the restricted approach simplifies the process, it risks omitting valuable evidence. A hybrid approach, combining both methods, helps mitigate these issues but still requires careful evaluation using tools such as citation matrices and Corrected Covered Area (CCA) calculations. Even with these measures, some relevant data may still be excluded when overlap is high.

The validity of an umbrella review also depends on the quality of included systematic reviews and the primary studies they summarize. Quality assessments, such as using the AMSTAR 2 tool, rely on the systematic reviews' reporting, limiting the ability to independently verify primary study quality. Additionally, synthesizing data poses challenges when reviews are outdated, as conclusions may no longer reflect current evidence. Efforts to account for overlap or outdated findings can inadvertently exclude some evidence, potentially impacting conclusions.

Chapter 3: Trends in the prevalence of autoimmune diseases in pregnancy in the UK 2000-2021: findings from the Clinical Practice Research Datalink (CPRD)

Chapter overview

This chapter used CPRD pregnancy register to address the research objectives, 1) Using electronic health records calculate the annual prevalence of the group of autoimmune diseases (17) in pregnant women between 2000-2021, 2) Using logistic regression to estimate odds ratios, describing the relationship between women's characteristics (age, ethnicity, deprivation, BMI, smoking status, gravidity, practice and comorbidities) and autoimmune disease during pregnancy.

Manuscript under review (Lancet rheumatology)

Personal contribution

- Compiled lists of Read/SnomedCT codes and drug codes for Clinical Practice Research Datalink (CPRD)
- Developed disease phenomes with co-authors
- Applied for data access from CPRD
- Conducted analysis
- Wrote initial draft of manuscript, submitted for publication and addressed reviewers' comments.

Title-Trends in the prevalence of autoimmune diseases in pregnancy in the UK 2000-2021: findings from the Clinical Practice Research Datalink (CPRD)

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3.1 Abstract

3.1.1 Background

Autoimmune diseases are on the rise globally and are overrepresented in women of reproductive age. Given the association of pregnancy and autoimmune diseases it is important to estimate the burden of autoimmune disease in pregnancy.

3.1.2 Methods

This was a UK population-based retrospective cohort study using routinely collected data from two large databases: Clinical Practice Research Datalink (CPRD) Gold and Aurum and

associated pregnancy registers. Prevalence was calculated annually for 17 autoimmune diseases in pregnancies among women of reproductive age (15-49 years) from 2000 to 2021. Logistic regression was used to estimate odds ratios, describing the relationship between women's characteristics (age, ethnicity, deprivation, BMI, smoking status, gravidity, practice and comorbidities) and autoimmune disease during pregnancy.

3.1.3 Results

There was an increase in prevalence of the combination of 17 autoimmune disease: ranging from 3.5% in 2000 to 4.7% in 2021. Psoriasis had the highest prevalence throughout the study period and increased from 1.8% (2000) to 2.0% in (2021). The prevalence of most of the autoimmune diseases increased from the year 2000-2021 with steepest rise seen in Hashimoto thyroiditis (0.05% in 2000 to 0.12% in 2021) followed by coeliac disease (0.11% to 0.27%), Grave's disease (0.17% to 0.35%) and type 1 diabetes (0.14% to 0.49%). Women in the least deprived areas had higher odds of an autoimmune disease during pregnancy [adjusted odds ratio (aOR) 1.10 (1.07-1.14)], while ethnic minority groups had lower incidence rates compared to White women. Ex smokers had significantly higher risk of autoimmune disease compared to non smokers [1.19 (1.16-1.21)]. When compared to women with a single pregnancy, the odds were significantly higher for women with five or more pregnancies [1.12 (1.10-1.15)]. Women with metabolic and mental health conditions were at a significantly higher odds of having autoimmune disease during pregnancy [type 2 diabetes ((aOR, 1.41 (1.30-1.53)) hypertension ((aOR 1.07 (1.01-1.13)), anxiety ((1.15 (1.12-1.19))), and depression ((1.17 (1.14-1.20)))].

3.1.1 Conclusion

The burden of pregnancies affected by autoimmune diseases is on the rise. There is an imperative for comprehensive studies to further investigate the associations of these diseases and their impact on pregnancy outcomes.

Evidence before this study

- Autoimmune diseases are significantly more prevalent in women, accounting for approximately 80% of all cases, with the overall prevalence increasing over the years.
- Pregnancy can influence disease activity, with some conditions improving and others worsening, potentially leading to complications for both mother and child.
- Despite higher prevalence, women face challenges such as diagnosis delays, and the need for more personalized management approaches during pregnancy.

Added value of this study

- The prevalence of autoimmune diseases in pregnant women in the UK increased by 4.7% over the past two decades, with psoriasis being the most common.
- Higher odds of being diagnosed with an autoimmune disease were associated with white ethnicity, less deprived areas, higher BMI, older maternal age, and smoking, though trends varied across specific diseases.

Implications for practice or policy and future research

- Understanding the prevalence of autoimmune diseases in pregnancy helps healthcare providers assess risks and manage potential complications more effectively.
- Prevalence data supports the development of clinical guidelines and health policies, enhancing maternal and fetal health outcomes and raising awareness for early detection and support.

3.2 Introduction

Autoimmune diseases are characterised by the body's immune system attacking its own cells, typically initiated by T cell or B cell activation, in the absence of external stimuli or infection [229, 230]. Despite extensive research efforts, the precise aetiology of autoimmune diseases remains elusive, and lifelong treatment is often required due to their incurable

nature [6, 7]. Notably, these diseases exhibit a pronounced gender bias, disproportionately affecting women, particularly those in the reproductive age group, with approximately 80% of some type of conditions occurring in women [231-235]. Pregnancy induces significant physiological and immunological changes that can affect the course and management of autoimmune diseases [236]. The immunological adaptations during pregnancy, including the shift towards a Th2-dominant immune response, increased levels of regulatory T cells, and elevated hormone levels such as oestrogen and progesterone, are thought to influence autoimmune disease activity [237, 238]. The interaction between pregnancy and autoimmune diseases is complex and multifaceted. Autoimmune diseases can complicate pregnancy by exacerbating existing immunologic challenges and potentially altering fetal development and placental function. For instance, antibodies produced by the mothers with systemic lupus erythematosus (SLE) can cross the placenta, adversely affecting fetal growth [239]. Extensive research has demonstrated associations between autoimmune disease and adverse pregnancy outcomes, including, but not limited to, miscarriage and gestational hypertension in women with SLE, and preterm birth in women with type 1 diabetes mellitus (T1DM) [136, 240, 241].

Understanding the prevalence and impact of autoimmune diseases in pregnancy is crucial for several reasons. Firstly, it aids in healthcare planning and ensuring that adequate resources and specialised care are available to women with the disease. Secondly, insights into prevalence can inform clinical guidelines and recommendations for managing pregnancies in women with autoimmune diseases, ensuring evidence-based practices are used. A study using Global Burden of Disease (GBD) data [242] reported a high global prevalence of autoimmune disease such as rheumatoid arthritis (226.07 to 337.65) and T1DM 506.37 (386.08 to 646.59) age-standardised DALY (disability-adjusted life year) rate in

women of reproductive age in the European region in 2019. An Australian study reported a 2% prevalence of autoimmune diseases among women receiving primary care during pregnancy [243]. Despite the global rise in autoimmune diseases, with prevalence rates suggesting one in ten individuals affected in the UK, [203, 244, 245] there is a notable gap in research regarding the prevalence of these diseases specifically in pregnant women, and there are no studies reporting trends of autoimmune diseases exclusively in the UK population.

To address this gap in knowledge, this study aims to estimate the prevalence trend of a comprehensive list of autoimmune diseases (17) during pregnancy in the UK and associations with sociodemographic variables. By quantifying the burden of autoimmune diseases during pregnancy, this research will help inform the impact of autoimmune disease in pregnancy and could shape planning and commissioning of future specialised obstetric services.

3.3 Methods

3.3.1 Data source

Clinical Practice Research Datalink (CPRD) contains anonymised patient-level data on demographics, symptoms, diagnoses, drug prescriptions, physical measurements, and laboratory test results. The study utilised data sourced from the CPRD (CPRD Gold and CPRD Aurum) databases [246, 247], associated with general practices utilising VISION and EMIS software, respectively. CPRD Gold encompasses records from 985 general practices, while CPRD Aurum covers 1489 practices. These databases contain longitudinal records, representing approximately 5% and 20% of the population, respectively, and are used for patient care and support [205, 206]. Within the CPRD, there is a specialised database called

the Pregnancy Register, focusing on maternal health and pregnancy outcomes. This resource provides anonymised electronic health records of pregnant individuals, offering detailed information on antenatal care, maternal medical history, and pregnancy complications, as well as linking maternal and neonatal data [248]. We also utilised Hospital Episode Statistics (HES; the administrative database of all care episodes in general NHS hospitals) to capture the outcomes of interest from secondary care. CPRD is linked to pregnancy register, HES, and area-level measure of deprivation. HES provides diagnostic secondary care inpatient and outpatient records for England only thus restricting the analysis to pregnancies in England, and the IMD is a proxy for the socioeconomic status.

While the CPRD datasets aim for representativeness, certain subpopulations may be underrepresented, such as individuals from specific ethnic minorities or those living in rural areas. Given that the database covers a large population, it provides a true representation of national demographics. Primary care data were extracted using the data extraction for epidemiological research (DExtER) tool, which facilitates extraction based on predefined exposures, covariates, and outcomes [249]. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[250].

3.3.2 Study Population

The study population included women of reproductive age (15-49 years) who were registered in the Pregnancy Register (CPRD Gold and CPRD Aurum) between 2000 and 2021. Pregnancies formed the unit of analysis, and all pregnancies were included despite the outcome. Inclusion criteria required women to have acceptable patient flag [246, 247] , minimum 1 year of registration with a practice and minimum 1 year of registered practice

qualifying for up-to-standard date (for CPRD Gold only) at the time of the pregnancy start date. All women who were found eligible were included in the study. Pregnancies formed the unit of analysis, and all pregnancies were included despite the outcome. The pregnancies from the CPRD Gold and Aurum were merged, however it is possible that some of the pregnancy episodes might be overlapping between the two data sources

3.3.3 Case Definition and covariates

The diagnosis of autoimmune diseases occurred before the pregnancy start date using primary care records and relevant diagnostic codes (Read codes in CPRD Gold and SNOMEDCT codes in CPRD Aurum) occurred before the pregnancy start date, ensuring all conditions were identified prior to the onset of pregnancy (supplementary Table 3.1) [251, 252]. We considered a comprehensive set of 17 autoimmune diseases in this study. These include (1) Addison's disease, (2) alopecia areata, (3) ankylosing spondylitis, (4) coeliac disease, (5) inflammatory bowel disease (IBD) (including Crohn's disease and ulcerative colitis (UC)) (6) Grave's disease, (7) Hashimoto's thyroiditis, (8) multiple sclerosis (MS), (9) myasthenia gravis, (10) psoriasis, (11) psoriatic arthritis, (12) rheumatoid arthritis, (13) Sjögren's syndrome, (14) systemic lupus erythematosus (SLE), (15) systemic sclerosis, (16) T1DM and (17) vitiligo. These autoimmune diseases were selected after review of literature and consultation with experts in the subject, as they are [253, 254]. The autoimmune origins of some of these diseases are still under debate, and they might be better classified as immune-mediated inflammatory diseases (IMDs). For the sake of simplicity and readability, we will refer to them as autoimmune diseases throughout this manuscript [18]. The search terms for these autoimmune diseases are added in supplementary file table 3.14.

Demographic variables such as age, ethnicity, and socioeconomic status were included as covariates, along with clinical factors such as smoking status, body mass index (BMI), gravidity and presence of comorbidities (hypertension, type 2 diabetes mellitus, anxiety, depression, psychosis). These co-morbidities were captured only prior to pregnancy start date. The association between all the chosen covariates and the odds of having autoimmune disease during pregnancy were examined.

3.3.4 Statistical Analysis

The annual prevalence of autoimmune diseases during pregnancy was calculated for each year between 2000 and 2021 by dividing the number of women meeting the exposure definition (coded diagnosis of one of the 17 autoimmune diseases before pregnancy start date) whose pregnancy started within the given year by the total number of pregnancies that started within the year. Crude prevalence and age standardised prevalence was calculated using the direct method and the prevalence for each year were applied to the European Standard Population 2013 (ESP2013) [255]. Prevalence of the women with autoimmune conditions was also calculated. Average Annual Percent Change (AAPC) in prevalence over time was calculated for all the autoimmune diseases [246, 256]. The prevalence trends are reported overall (combining all the 17 autoimmune diseases included) and for specific diseases. The test for trend was estimated by including year as a continuous variable in the regression model.

Logistic regression was used to estimate unadjusted and adjusted odds ratios and 95% confidence intervals to describe the relationship between women's characteristics (age, ethnicity, deprivation, BMI, smoking status, gravidity, and key comorbidities such as hypertension, diabetes, anxiety, depression, psychosis) and autoimmune disease during

pregnancy. Further, analysis was also conducted by categorising the diseases by organs systems and calculated the odds ratios for the demographic variables. To account for similarity of outcomes within practices recognising that individuals within the same general practice may exhibit greater similarity due to shared socio-economic and environmental factors, statistical inference from the logistic regression model was based on cluster-robust standard errors. We also accounted for the clustering of multiple pregnancies within the same woman using generalised estimating equations (GEE) for overall autoimmune diseases tabulated in table 3.2. Analysis was performed in Stata IC version 17 (Stata Corp) [9] and R Studio (12.1) [193, 257-259]. The funder was not involved in the data collection, analysis, interpretation, or the writing of the manuscript. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement supplementary file 2.

Post hoc analysis

Differential fertility rates may have contributed to some of the findings presented and could further influence their clinical significance. The fertility trends have been calculated in the reproductive age women (15-49 years). For each analysis year (2000–2021), eligible women were classified as exposed if they had a diagnosis of autoimmune disease at the start of the analysis year and unexposed if there was no diagnosis. For each analysis year, women with the autoimmune disorder were matched to up to four unexposed women (no record of autoimmune disease) by age. Women with target autoimmune condition were followed up until the earliest of any censoring events (transfer date, death, year-end, or collection), while women without target condition were further censored if they develop the target autoimmune condition. The number of pregnancies were counted during follow-up time

within each analysis year, within each outcome category. Incidence rates (IR) were calculated for each year for fertility (number of pregnancies).

3.4 Results

In total, 5,165,960 pregnancies among 2,831,472 women in the CPRD Gold and Aurum pregnancy registers met the data quality criteria. 185,208 pregnancies among 100,655 women had a coded diagnosis of autoimmune disease in the years 2000-2021. Baseline characteristics of the population is shown in Table 3.1. Details of the pregnancies and women in each database, separately is shown in supplementary Table 3.2. The prevalence of autoimmune diseases in women ranged from 3.1% in 2000 to 5.1% in 2021 with crude prevalence of 3.5%. (supplementary Table 3.12).

The mean age of women with autoimmune disease 31.5 [SD (standard deviation 6.5)] years was older compared to women without autoimmune disease 29.7 (6.4) years. Women with autoimmune disease were more likely to live in the least deprived areas (15.8% v 14.6%), be from the white ethnic group (57.0 v 49.3), and have a BMI ≥ 25 kg/m² (36.8% v 33.4%) compared to the women without autoimmune conditions. Women with autoimmune conditions were more likely to have had more pregnancies (gravidity ≥ 4) compared to women without autoimmune conditions (37.4% v 33.9%).

The overall crude prevalence of autoimmune diseases during the entire study period among the eligible cohort of pregnancies was 3.6%. The prevalence ranged from 3.7 % in 2000 to 4.7% in 2021 (Figure 3.1-3.2). The age-adjusted prevalence ranged from 4.2% in 2000 to 4.7% in 2021. The prevalence of autoimmune diseases in women ranged from 3.1% in 2000 to 5.1% in 2021 with crude prevalence of 3.5% (Figure 3.1-3.2 and supplementary tables 3.3-3.55).

Psoriasis had the highest prevalence throughout the study period (1.8% in 2000 and 1.99% in 2021). This was followed by inflammatory bowel disease (IBD) and rheumatoid arthritis in earlier decade (2000-2010) and type 1 diabetes mellitus (T1DM) and inflammatory bowel disease in the later decade (2010-2021) as shown in Figure 3.2 and supplementary Figure 3.1.

The average annual percent change (AAPC) showed that the prevalence for the majority of the autoimmune diseases rose significantly between 2000 and 2021, with steepest rise for Hashimoto thyroiditis (0.05% in 2000 to 0.12% in 2021) followed by coeliac disease (0.11% to 0.27%) and Grave's disease (0.17% to 0.35%). There was also a slight decrease in the prevalence of multiple sclerosis, ankylosing spondylitis, and myasthenia gravis. The AAPC for the prevalence are shown in supplementary Table 3.6. Between 2000 and 2021, 14,547,475 women aged 15–49 years were included. Women with autoimmune conditions had higher fertility rates, with IR 52.34 (51.91–52.78) in CPRD Gold and IR 65.75 (65.40–66.10) in CPRD Aurum, compared to age-matched women without autoimmune conditions (IR 48.54 (48.33–48.75) per 1,000 women in CPRD Gold and 57.07 (56.91–57.23) per 1,000 women in CPRD Aurum) figure 3.3. Higher fertility rates are observed in women with autoimmune conditions compared to those without, across both databases from 2000-2021. However, conditions such as Addison's disease and ankylosing spondylitis are associated with lower fertility rates. Over time, fertility rates have increased in women with dermatological conditions (alopecia areata, vitiligo, psoriasis), Hashimoto's thyroiditis, systemic lupus erythematosus (SLE), myasthenia gravis, rheumatoid arthritis, and multiple sclerosis. In contrast, fertility rates have declined in women with gastrointestinal diseases (coeliac disease, IBD), Graves' disease. Details reported in supplementary table 3.15, 3.16, supplementary figure 3.3 and text 3.2.

With older age at pregnancy, there was a increase in the odds of having an autoimmune disease diagnosis. Compared to those aged 14-20 years, women aged 21-30, 31-40 and 41-50 had a 17%, 49% and 78% increased odds of having an autoimmune disease diagnosis before pregnancy; [aOR: 1.17 (1.14-1.20), 1.50 (1.45-1.55) and 1.75 (1.68-1.82)], respectively (Table 3.2).

Compared to women living in the most deprived areas, women in the least deprived areas had a higher odds of having an autoimmune disease diagnosis before pregnancy [aOR 1.10 (1.07-1.14)]. Women who were smokers and ex-smokers had a significantly higher risk of having an autoimmune disease when compared to non smokers with aOR 1.19 (1.16-1.21) and aOR 1.20 (1.18-1.23), respectively.

Compared to women with a pre-gravid BMI, women who were obese had a significantly higher odds of having autoimmune disease aOR 1.02 (1.00-1.04). Compared with women of white ethnicity, women from all the other ethnic groups had a lower odds of having autoimmune disease, with the lowest odds in women from the black ethnic group aOR 0.48 (0.45-0.51).

Women with more than one pregnancy recorded prior to the index pregnancy were at higher odds of having autoimmune disease compared to women with only one recorded pregnancy and the odds increased with the number of pregnancies aOR 1.05 (1.04-1.06) for 2 pregnancies to aOR 1.12 (1.10-1.15) for more than 5 pregnancies.

Women with a concurrent diagnosis of metabolic and mental health conditions were at significantly higher odds of having autoimmune disease [T2DM: aOR 1.41 (1.30-1.53), hypertension: 1.07 (1.01-1.13), depression: aOR 1.17 (1.14-1.20) and anxiety :aOR 1.15

(1.12-1.19). Results of by categorising the diseases by organs systems is reported in supplementary table 3.13 and supplementary text 3.1.

3.4,1 Demographic differences in individual autoimmune diseases

In older pregnant women, the odds of having the majority of the autoimmune diseases were higher. However, the odds of T1DM decreased with older age, and the odds of vitiligo was highest among pregnant women in the 21-30 years and 31-40 years age groups (Table 3.3 and supplementary Tables 3.7-3.11).

When compared to women of BMI 18.5 to $<25 \text{ kg/m}^2$, there was an increased odds of gastrointestinal conditions (coeliac disease and IBD) and Addison's disease in women with a lower BMI ($<18.5 \text{ kg/m}^2$). Whereas the odds of T1DM, psoriatic disease, and myasthenia gravis increased with a higher BMI ($\geq 25 \text{ kg/m}^2$).

For most autoimmune diseases, women living in the least deprived areas had a higher odds of having the autoimmune disease; however, some diseases such as alopecia areata, myasthenia gravis, psoriasis, and Grave's disease were more prevalent in women living in the most deprived areas.

Compared to women from the white ethnic group, all the other ethnicities had a lower odds of having most of the autoimmune diseases. However, there was a higher odds of having alopecia areata and rheumatoid arthritis in women from the Asian ethnic group and psoriatic arthritis in women from the other ethnic group. There was also a higher odds of having SLE, Grave's disease, and vitiligo in non-white ethnicities compared to white ethnicity.

When compared to non smokers, the odds of having most of the autoimmune diseases were higher in women who were smokers. However, the odds of ulcerative colitis, coeliac disease, myasthenia gravis, Sjögren's syndrome, and T1DM were lower in smokers.

Women with more than two or three pregnancies were at higher odds of having autoimmune diseases overall. However, there was a lower odds of having coeliac disease, Grave's disease, Hashimoto, rheumatoid arthritis, multiple sclerosis, SLE, systemic sclerosis, and T1DM in women who had multiple pregnancies.

The odds of most of the autoimmune diseases were higher among women with comorbidities (hypertension, T2DM, anxiety, depression or psychosis) when compared to women without the comorbidity. However, the the odds of coeliac and IBD were lower in women with hypertension.

After categorising the disease by organ system, it was noted that all autoimmune disorders were more common with increasing age. Lower BMI was linked to higher odds of systemic, gastrointestinal, and neurological disorders, while higher BMI was associated with endocrine and dermatological disorders. Women in the least deprived areas had higher odds for most autoimmune diseases, except endocrine disorders, which were more common in the most deprived areas. Ethnic minorities had lower odds for most autoimmune diseases, except for systemic (Black) and endocrine disorders (Asian) in specific groups. Smoking increased odds for most autoimmune diseases but reduced odds for systemic, endocrine, and gastrointestinal disorders in current smokers.

3.5 Discussion

This study revealed an overall increase in the prevalence of autoimmune diseases (4.7%) among pregnant women in the UK, with psoriasis (2.04%) being the most common. Over the last two decades, Hashimoto's thyroiditis, coeliac disease, and alopecia areata showed the highest annual percent increases. Women of white ethnicity, living in the least deprived areas, with higher BMI, and of older maternal age had an increased odds of being diagnosed with an autoimmune disease. The discussion has also been rewritten for better readability.. The discussion also rephrased for better readability. For most individual autoimmune diseases, the odds of diagnosis increased with older maternal age, except for T1DM and vitiligo. Smokers had higher odds of developing most autoimmune diseases, although exceptions included Addison's disease, coeliac disease, ulcerative colitis, myasthenia gravis, Sjögren's syndrome, SLE, and T1DM. While the overall odds of autoimmune diseases increased with a greater number of pregnancies, trends were inconsistent for specific conditions; dermatological diseases showed higher odds with increasing gravidity, while neurological diseases showed little association. Among co-morbid conditions, T2DM was associated with higher odds of Addison's disease, coeliac disease, IBD, and psoriatic diseases, while hypertension was linked to higher odds of ankylosing spondylitis, rheumatoid arthritis, systemic sclerosis, and T1DM. Anxiety and depression were associated with the majority of autoimmune diseases, with the exceptions of myasthenia gravis and SLE. Overall, the fertility rates of patients with autoimmune diseases were reported to be lower than the national fertility trends for England and Wales. This discrepancy is particularly evident in CPRD Gold, which also includes data from Scotland and Northern Ireland. Additionally, the difference in fertility rates may be partly explained by the age groups considered: national

data focuses on individuals aged 15–45 years, whereas our calculations included the broader age range of 15–49 years [260]

3.5.1 Findings in the context of other literature

While numerous studies have reported the global prevalence of autoimmune diseases in the general population [228, 261], only a few have focused on prevalence in pregnant women or in women of reproductive age. A recent study utilising the GBD data estimated the prevalence of specific autoimmune diseases among women of reproductive age, reported age-standardised DALY rate rates of 215.86 for rheumatoid arthritis 63.54 for IBD, 28.74 for multiple sclerosis and 477.20 for T1DM. Additionally, some studies have provided prevalence data for specific autoimmune diseases in women [228] [262].

An Australian study examining the prevalence of overall autoimmune diseases in pregnant women from 2011 to 2015 reported a prevalence ranging from 0.8% in women under 20 years old to 2.7% in women aged 40–44 years. Another Australian hospital-based study reported a higher prevalence of autoimmune diseases in pregnancy at 4.1% with a particularly high prevalence of Hashimoto’s thyroiditis (2.8%), which differs from the 2021 findings of higher psoriasis prevalence (1.9%) reported in this study. These discrepancies may result from numerous factors, including differences in the source populations used or reliance on hospital records [243, 263].

No other studies have estimated the prevalence of autoimmune disease in pregnancy, but a few have reported the prevalence in women overall or women of reproductive age group. This includes a recent study in the UK using CPRD data which reported the overall prevalence of autoimmune diseases in the general population (no age restriction) years of 10.2%, with 13.1% in women and 7.4% in men [203]. The prevalence of most diseases,

including Grave's disease, coeliac disease, and Hashimoto thyroiditis, was increasing as found in this study, except for Sjögren's syndrome, which showed a variable trend. This concurs with the findings in our study specifically among pregnant women.

Systemic inflammatory disorders

One of the UK studies reported a lower prevalence of Sjögren's syndrome in women compared to this study as it included white women. While an older review also reported a lower prevalence of Sjögren's syndrome in women than we report. They also reported there was a higher prevalence in women from the white ethnic group when compared to non-white ethnic groups contrasting with this study's findings of a higher prevalence in women from the black ethnic group [98, 264]. A UK study indicated an increase in SLE prevalence among reproductive-age women from 2009 to 2014, while our study reported a decline this could be due to the difference in the study population and known fertility issues in women with SLE due to the medications involved for the treatment of the condition [265] [266]. Few other studies noted high SLE prevalence in women from the black ethnic group, which is in line with our study [102, 267]. Globally, a higher prevalence of systemic sclerosis is reported in women from the black ethnic group, but our study found higher odds in white ethnicity women when compared with other ethnicities [261, 268, 269].

Endocrine disorders

A US study reported a rise in the prevalence of endocrine autoimmune conditions during pregnancy from 5.6 per 100,000 person years in 2003 to 9.6 per 100,000 in 2011. The lower prevalence reported in the US study was probably due to the different diagnostic sources used (Healthcare cost and utilisation project-nationwide inpatient sample) [270]. Globally,

autoimmune thyroid diseases have a prevalence of 1.7%, with a prevalence of Grave's disease of 0.2–0.4%, with increasing prevalence over the years similar to our findings [271, 272]. The prevalence of T1DM in women of reproductive age in the US and UK increased from 0.14 to 0.23 between 1996-2004 and from 1.56 to 4.09 per 1000 pregnancies between 1995-2015 respectively, a finding that is similar to our study [273, 274]

Dermatological disorders

The prevalence of alopecia areata in women found in this study [1.25 (1.05-1.47)] is similar to that from earlier studies, but no studies have reported the prevalence of alopecia areata in pregnancy. [275-277]. There was a higher odds of alopecia areata in the Asian population compared to the white ethnic group [275-277]. There were also no studies on the prevalence of psoriasis or vitiligo in pregnancy. One systematic review that included 90 studies from 22 countries reported the prevalence of psoriasis in women to be 3.2% which is higher than the prevalence reported in this study as the systematic review included more studies from the other European countries which have high prevalence of psoriasis [278]. The population-based prevalence of vitiligo was 0.4%, which aligns with this study [279].

Musculoskeletal disorders

A US study noted an increase in the prevalence of ankylosing spondylitis among women from 1995 to 2010 contrasting with our study which reported a decline [280]. In earlier studies psoriatic arthritis was found to be more common in obese women who smoke, consistent with this study's findings [281-283]. A UK study reported a higher prevalence of psoriatic arthritis in women of reproductive age (0.16%-0.28%) like our study [284]. An older

US based study reported a higher prevalence of rheumatoid arthritis (1.2%), than our study as it reported the prevalence in psoriasis cohort [285].

Gastrointestinal disorders

A UK hospital-based study reported a prevalence of 2.1% of coeliac disease in pregnancy which is higher than our study [286]. An Australian study reported a 0.31% prevalence of IBD in pregnancy, with higher odds in older age, Asian ethnicity, and deprived areas, whereas our study found higher odds in least deprived areas and among white women [287]. Lastly, a US study reported a global prevalence of 0.48% for Crohn's disease and 0.62% for ulcerative colitis in women, higher than what was observed in this study [288].

Neurological disorders

A California-based study found that multiple sclerosis (MS) prevalence increased with older maternal age, was higher in women from the white ethnic group compared to other ethnic groups, and those with conditions like hypertension. The current study found depression more likely to co-exist with MS [289]. Sellner et al. reported an increase in global MS prevalence among women, contrary to this study's finding of a decline in prevalence among pregnant women [290]. While global studies report a rise in myasthenia gravis prevalence, the results from this study do not agree with that trend [291, 292].

Although the aetiology of the autoimmune diseases is not fully understood, there are various hypothesis suggested to explain the observed increase in the prevalence of some of these diseases over time [293]. There has been a 3-4% annual increase in autoimmune diseases in last three decades which has been attributed to changes in lifestyle (e.g., diet), environmental and genetic factors [294-298]. Various environmental factors such as

pollution, diet, and exposure to chemicals have been implicated in the rise of autoimmune diseases. Recent studies have shown a correlation between air pollution, smoking, and autoimmune diseases, including rheumatoid arthritis and SLE [299, 300]. Alterations in the composition of gut microbiota due to factors such as diet, antibiotic use, and lifestyle changes have also been linked to autoimmune diseases like IBD. Dysbiosis in the gut microbiota can lead to immune dysregulation and the development of T1DM [301-303]. Genetic factors play a significant role in the development of autoimmune diseases. Certain genetic variations increase susceptibility to autoimmune diseases, and the rising prevalence could partly be attributed to changes in gene-environment interactions over time [304-306]. Psychological stress also has been associated with the onset and exacerbation of autoimmune diseases through mechanisms involving the dysregulation of the immune system. Chronic stressors such as trauma, depression, and anxiety may contribute to the increasing prevalence of autoimmune diseases like psoriasis, SLE, and rheumatoid arthritis [307-309].

3.5.2 Strengths and limitations

One of the main strengths of this study is the inclusion of a wide range of autoimmune diseases which are known to be more prevalent in women of reproductive age. We have used both CPRD Gold and Aurum databases and thus these results include a large sample of 5,165,960 pregnancies. Furthermore, use of these large databases allowed us to examine the associations of age, socioeconomic status, and other demographic variables with autoimmune diseases over the last two decades. This is one of the first studies to describe trends in the prevalence of such wide range of autoimmune diseases in pregnancy. The use

of routinely reported diagnoses also captures the burden of disease and increases the generalisability of findings.

However, there are some limitations to the study. We have included autoimmune diseases which are more prevalent in women of reproductive age group and some of the autoimmune diseases which are rare such as dermatomyositis are not included. Secondly, the diagnosis of autoimmune diseases was captured from primary care records and because most of these conditions are diagnosed and managed in secondary care, this may have underestimated the prevalence. The comorbidities observed in the study may be linked to treatments for autoimmune diseases, such as corticosteroids, but examining the medications used among these women was beyond the scope of this study [310]. Since the unit of analysis was pregnancy, it is important to consider the fertility trends across different groups when interpreting variations in the prevalence of diseases. Another potential limitation of this study is that changes in diagnostic coding systems over time may have influenced the classification and diagnosis of autoimmune diseases, which could affect the consistency of prevalence estimates across different time periods. In the CPRD pregnancy register, some pregnancy records overlap [311], and the estimated start and end date of pregnancies using the CPRD Pregnancy Register Algorithm might therefore be inaccurate also the pregnancies which ended in early miscarriage will not be in the database. However, this will affect only a small percentage of the cohort and will have only a negligible effect on the prevalence estimates. As this is an observational study using anonymised routine health records, key limitations include missing data and the completeness and accuracy of electronic health records, particularly regarding ethnicity, have varied over time due to financial incentives under the Quality and Outcomes Framework, which may impact the

generalisability of the findings [312]. A missing category for other variables has been created to include all available data, while future studies can address potential bias from missing data using appropriate imputation techniques, sensitivity analyses, and methods tailored to the type of missingness.

3.5.3 Implications for research and practice

It was important to estimate the burden of autoimmune diseases in pregnancy as there is increasing evidence for how they might adversely affect pregnancy outcomes [136, 234, 313-318]. While we have explored the prevalence of autoimmune diseases during pregnancy, there is still a need and interest in exploring how pregnancy and pregnancy related factors are associated with the development of autoimmune diseases post pregnancy [319-322]. Healthcare providers should be equipped to discuss reproductive goals with women who have autoimmune diseases and should emphasise preconception planning [323, 324]. Preconception planning should involve evaluation and management of disease-related organ damage and optimising medications to avoid those that are teratogenic, to improve both maternal and pregnancy [325] outcomes. This study gives a clear estimate of the burden of these diseases in UK and the possible association with various demographic factors. Hence this will be a stepping stone in the process of improved maternity care for women with these health conditions.

Future studies should explore several key factors not included in this analysis: perspectives on postponing pregnancy until women attain stable disease remission while on suitable medications; the effects of recurrent pregnancy loss in those with autoimmune diseases; the influence of treat-to-target approaches and new treatments on quality of life and family

planning; and the changing attitudes of healthcare providers, moving from discouraging pregnancy to providing support and management for women with autoimmune conditions.

3.5.4 Conclusion

This study provides evidence of the rising prevalence of autoimmune diseases among pregnant women. While the burden of each disease is relatively small, the overall prevalence of autoimmune disease is important. It underscores the need to establish adaptable health policies and allocate resources effectively to address the diverse needs associated with autoimmune diseases in this population.

Table 3.1: Baseline characteristics

Characteristics	All autoimmune diseases n (%)	No autoimmune diseases n (%)
Number of pregnancies	185,208 (3.59)	4, 980,752 (96.41)
Number of women	100,655 (3.55)	2,730,817 (96.45)
Age categories*		
15-20 years	10,755 (5.81)	425,547 (8.54)
21-30 years	69,971 (37.78)	2,147,224 (43.11)
31-40 years	90,600 (48.92)	2,142,291 (43.01)
41-49 years	13,882 (7.50)	265,690 (5.33)
IMD (Index of Multiple Deprivation)		
1 (Most deprived)	33,219 (17.94)	971,463 (19.50)
2	31,388 (16.95)	892,065 (17.91)
3	29,132 (15.73)	770,831 (15.48)
4	29,696 (16.03)	737,898 (14.81)
5 (Least deprived)	29,335 (15.84)	724,456 (14.55)
Missing	32,438 (17.51)	884,039 (17.75)
Smoking status		
Non-Smoker	88,400 (47.73)	2,524,459 (50.68)
Ex-Smoker	30,822 (16.64)	676,293 (13.58)
Current smoker	52,839 (28.53)	1,286,469 (25.83)
Missing	13,147 (7.10)	493,531 (9.91)
BMI (kg/m²),		
Underweight (<18.5)	6,082 (3.28)	178,459 (3.58)
18.5-<25	79,596 (42.98)	2,057,273 (41.30)
Overweight (25-<30)	38,936 (21.02)	961,636 (19.31)
Obese (≥30)	29,200 (15.77)	699,521 (14.04)
Missing	31,394 (16.95)	1,083,863 (21.76)
Ethnicity		
White	105,625 (57.03)	2,452,228 (49.23)

Mixed	35,601 (19.22)	1,041,160 (20.90)
Black	4,028 (2.17)	208,681 (4.19)
Asian^	10,086 (5.45)	325,781 (6.54)
Other@	1,553 (0.84)	48,943 (0.98)
Missing	28,315 (15.29)	903,959 (18.15)
Gravidity (Total number of pregnancies)		
1	38,266 (20.66)	1,173,249 (23.56)
2	42,350 (22.87)	1,180,456 (23.70)
3	35,334 (19.08)	938,588 (18.84)
4	25,370 (13.70)	645,689 (12.96)
≥5	43,888 (23.70)	1,042,770 (20.94)
Comorbidities		
Hypertension	4,121 (2.23)	72,206 (1.45)
Type 2 diabetes	2,376 (1.28)	25,615 (0.51)
Mental health conditions		
Anxiety	23,106 (12.48)	453,361 (9.10)
Depression	32,956 (17.79)	645,747 (12.96)
Psychotic disorders	988 (0.53)	19,899 (0.40)

*Age is calculated at the pregnancy start date. ^The Asian category includes patents whose origin is from India, Pakistan, China, Cambodia, Thailand, Vietnam, Malaysia, Sri Lanka, Nepal, Bangladesh, Japan or Taiwan. @ The other ethnicity category included patients with native American, Middle Eastern or Polynesian origin.

Table 3.2 -Characteristics associated with autoimmune diseases (overall)

Characteristics	Unadjusted odds ratios (95% CI)	Adjusted odds ratio*	Adjusted odds ratio[#]
Age categories, (years)			
15-20 years	Ref	Ref	Ref
21-30 years	1.33 (1.30-1.35)	1.17 (1.14-1.20)	1.18 (1.15-1.22)
31-40 years	1.76 (1.73-1.80)	1.50 (1.45-1.55)	1.52 (1.48-1.57)
40-50 years	2.27 (2.21-2.32)	1.75 (1.68-1.82)	1.82 (1.75-1.88)
IMD			
1 Most deprived	Ref		
2	1.02 (1.01-1.04)	1.01 (0.98-1.05)	1.01 (0.98-1.04)
3	1.09 (1.07-1.11)	1.05 (1.02-1.08)	1.04 (1.01-1.07)
4	1.15 (1.13-1.17)	1.11 (1.07-1.14)	1.09 (1.06-1.12)
5 Least deprived	1.15 (1.14-1.17)	1.10 (1.07-1.14)	1.09 (1.06-1.12)
Missing	1.22 (1.23-1.24)	1.22 (1.17-1.27)	1.18 (1.15-1.22)
Smoking status			
Non-Smoker	Ref	Ref	Ref
Ex-Smoker	1.27 (1.26-1.29)	1.20 (1.18-1.23)	1.18 (1.16-1.20)
Current smoker	1.16 (1.15-1.17)	1.19 (1.16-1.21)	1.16 (1.14-1.18)
Missing	0.74 (0.73-0.75)	0.90 (0.87-0.93)	0.94 (0.88-0.92)
BMI categories (kg/m²)			
Underweight (<18.5)	0.98 (0.93-0.99)	0.97 (0.93-1.01)	0.97 (0.93-1.01)
(18.5-<25)	Ref	Ref	Ref
Overweight (25-<30)	1.21 (1.18-1.24)	1.01 (0.99-1.03)	1.02 (1.00-1.03)
Obese (≥30)	1.23 (1.20-1.26)	1.02 (1.00-1.05)	1.05 (1.03-1.07)
Missing	0.82 (0.80-0.84)	0.87 (0.85-0.89)	0.87 (0.85-0.89)
Ethnicity			

White	Ref	Ref	Ref
Mixed	0.90 (0.89-0.91)	0.94 (0.91-0.97)	0.90 (0.88-0.92)
Others	0.75 (0.72-0.79)	0.84 (0.74-0.95)	0.82 (0.75-0.90)
Black	0.49 (0.47-0.50)	0.48 (0.45-0.51)	0.47 (0.44-0.49)
Asian	0.75 (0.74-0.77)	0.81 (0.77-0.85)	0.79 (0.76-0.82)
Missing	0.73 (0.72-0.74)	0.80 (0.78-0.82)	0.80 (0.78-0.82)
Gravidity			
1	Ref	Ref	Ref
2	1.12 (1.11-1.14)	1.05 (1.04-1.06)	1.05 (1.04-1.07)
3	1.20 (1.19-1.22)	1.07 (1.05-1.09)	1.08 (1.06-1.10)
4	1.27 (1.25-1.29)	1.10 (1.08-1.12)	1.11 (1.09-1.13)
5+	1.38 (1.36-1.40)	1.12 (1.10-1.15)	1.15 (1.12-1.17)
Co-morbidities			
Hypertension	1.56 (1.52-1.61)	1.07 (1.01-1.13)	1.30 (1.24-1.37)
Type 2 diabetes	2.92 (2.81-3.04)	1.41 (1.30-1.53)	2.07 (1.93-2.23)
Mental health conditions			
Anxiety	1.42 (1.40-1.44)	1.15 (1.12-1.19)	1.13 (1.10-1.16)
Depression	1.45 (1.43-1.47)	1.17 (1.14-1.20)	1.22 (1.19-1.25)
Psychotic disorders	1.39 (1.31-1.47)	1.04 (0.93-1.16)	1.00 (0.93-1.11)

IMD= Index of Multiple Deprivation, BMI=Body mass index, 95%CI=95% confidence interval, *Clustering by general practice, # clustering of pregnancies within same women.

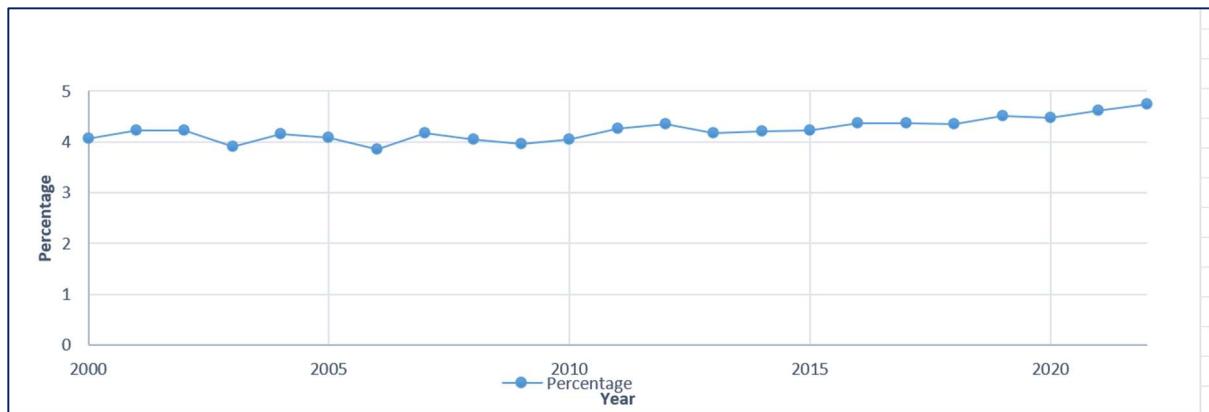
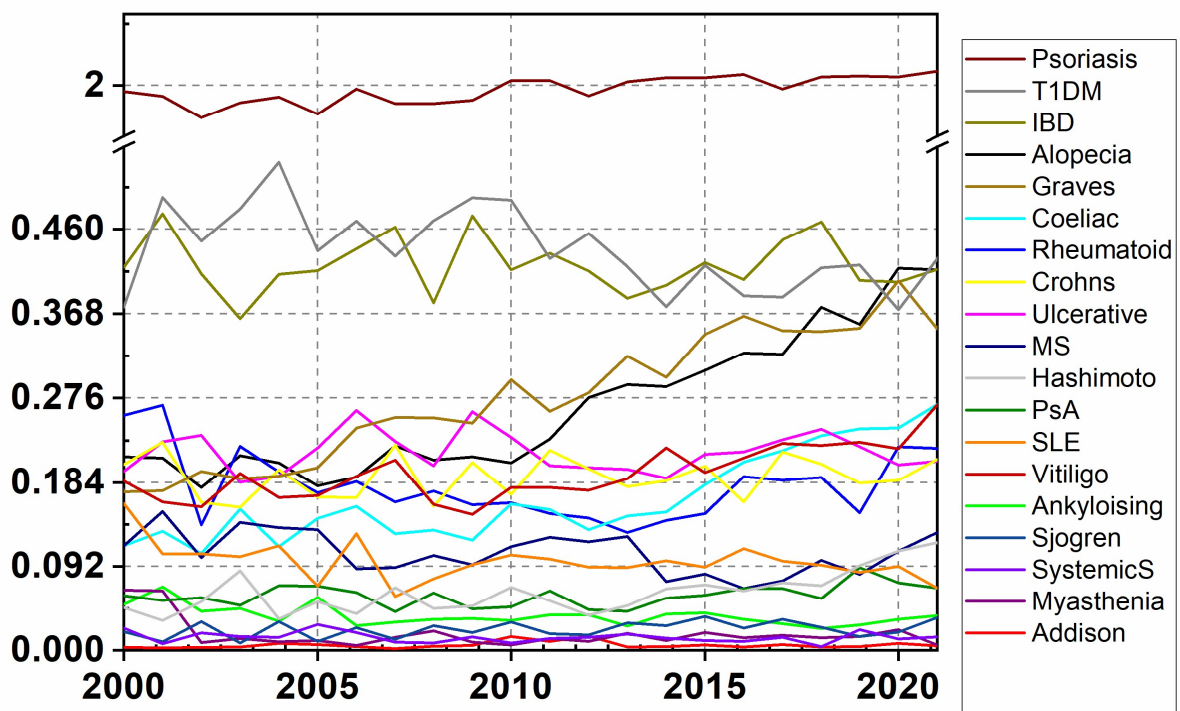


Figure 3.1 Age-standardised prevalence of autoimmune diseases, 2000-2021

Test for trend $P < 0.001$



Y axis is the percentage and x axis are year. T1DM=Type one diabetes mellitus, IBD=Inflammatory bowel disease, MS=Multiple sclerosis, PsA=Psoriatic arthritis, SLE =Systemic lupus erythematosus, SystemicS=Systemic sclerosis

Figure 3.2 Age standardised prevalence of specific autoimmune diseases, 2000-2021

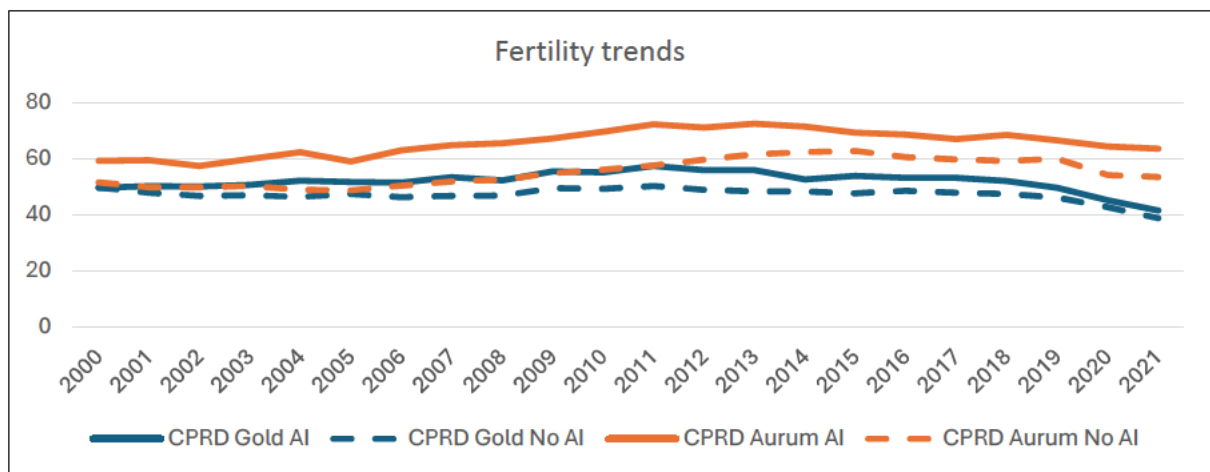


Figure 3.3 Annual rate of fertility/live births of women with autoimmune diseases when compared to matched comparators in CPRD Gold and Aurum

AI=autoimmune disease (any)

Table 3.4: Heat map illustrating the adjusted odds ratios of specific autoimmune disease by certain sociodemographic characteristics of pregnant women

Characteristics	All AID	Systemic inflammatory Disorders				Dermatological Disorders			Endocrine Disorders				Gastrointestinal Disorders				Musculoskeletal Disorders			Neurological disorder	
		Sjogren's	SLE	Systemic		Alopecia	Psoriasis	Vitiligo	Addison	Graves	Hashimoto	T1DM	Coeliac	IBD	Crohn's	Ulcerative	AS	Psoriatic	RA	MS	Myasthenia
AGE																					
15-20 years	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
21-30 years	1.17	1.56	2.95	1.07	1.22	1.04	0.95	0.95	7.96	3.23	1.56	0.84	1.06	3.14	3.19	3.47	8.22	2.62	2.63	8.56	2.94
31-40 years	1.50	6.00	5.60	2.06	1.08	1.14	0.98	0.98	11.26	6.51	2.90	0.66	1.36	5.82	5.53	7.44	23.43	5.56	6.28	26.23	5.40
40-50 years	1.75	15.51	9.57	3.58	1.11	1.12	1.01	1.01	11.88	8.74	4.27	0.71	1.67	7.86	6.79	10.98	33.53	7.73	11.46	47.58	10.91
BMI																					
Underweight (<18.5)	0.97	1.18	0.94	1.50	0.89	0.90	0.99	0.99	2.48	1.07	1.01	0.40	1.29	1.27	1.48	1.20	0.87	0.86	1.18	1.18	1.09
Normal weight (18.5-25)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Overweight (25-30)	1.01	0.88	0.88	1.08	1.01	1.06	0.89	0.89	0.95	0.99	1.04	1.62	0.78	0.85	0.83	0.86	0.96	1.22	1.07	0.94	1.14
Obese (≥30)	1.02	0.63	0.74	0.75	0.98	1.18	0.74	0.74	0.97	0.98	1.29	1.04	0.62	0.71	0.76	0.64	0.87	1.78	1.09	0.84	1.27
Missing	0.87	0.66	0.99	0.89	0.79	0.96	0.80	0.80	1.10	0.73	0.87	0.27	0.78	0.80	0.77	0.82	0.99	1.10	0.99	0.93	1.17
IMD																					
1- Most deprived	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	1.01	1.34	1.13	1.22	1.02	0.96	1.09	1.09	1.40	0.99	1.01	1.04	1.13	1.23	1.18	1.36	1.55	1.06	0.98	1.22	1.01
3	1.05	1.32	1.07	1.32	1.03	0.97	1.24	1.24	1.18	0.98	1.30	1.06	1.22	1.35	1.34	1.38	1.88	1.25	1.04	1.18	0.72
4	1.11	1.23	1.15	1.06	0.98	1.02	1.34	1.34	1.07	0.96	1.24	1.12	1.36	1.54	1.52	1.64	2.10	1.38	1.05	1.38	1.06
5-Least deprived	1.10	1.53	1.30	0.92	0.98	0.98	1.43	1.43	1.79	1.01	1.17	1.07	1.35	1.70	1.65	1.81	1.61	1.23	0.98	1.28	0.88
Missing data	1.22	1.73	1.16	1.39	0.85	1.20	0.91	0.91	1.63	0.95	1.21	1.29	1.46	1.47	1.51	1.40	1.61	1.60	1.04	1.40	0.73
ETHNICITY																					
White	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mixed	0.94	0.54	0.94	1.09	1.05	0.87	1.19	1.19	0.60	0.92	0.74	0.92	0.68	0.82	0.81	0.80	0.75	0.77	0.94	0.99	0.82
Others	0.84	0.95	1.80	1.00	1.26	0.61	1.40	1.40	1.01	1.44	1.99	1.09	0.62	1.01	1.07	0.90	0.74	1.73	0.87	1.21	0.17
Black	0.48	1.00	2.62	0.55	1.00	0.19	1.82	1.82	0.13	1.30	0.42	0.59	0.21	0.35	0.29	0.41	0.25	0.12	0.86	0.59	1.32
Asians	0.81	1.10	1.77	0.74	1.75	0.48	2.86	2.86	0.25	1.58	0.88	0.72	0.74	0.57	0.45	0.66	0.56	0.63	1.34	0.52	0.70
Missing	0.80	0.62	0.92	0.82	0.80	0.78	0.96	0.96	0.80	0.72	0.70	1.03	0.75	0.94	0.95	0.93	1.02	0.85	0.86	0.86	1.13
SMOKING STATUS																					
Non-Smoker	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ex-Smoker	1.20	0.73	1.04	0.87	1.28	1.32	1.06	1.06	0.92	1.16	0.88	0.98	0.83	1.19	1.37	0.98	1.11	1.23	0.92	1.31	0.61
Current Smoker	1.19	0.70	0.99	0.89	1.42	1.41	0.91	0.91	0.59	0.96	0.71	0.82	0.69	0.82	1.11	0.55	0.94	1.11	0.91	1.07	0.85
Missing data	0.90	0.75	1.01	1.07	0.94	0.95	0.76	0.76	0.74	0.95	0.78	0.82	0.60	0.88	0.90	0.86	1.05	1.01	0.94	1.19	0.74
GRAVIDITY																					
One	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Two	1.05	0.90	0.96	0.79	1.06	1.09	0.97	0.97	0.87	1.13	1.03	0.91	0.94	0.96	0.97	0.93	0.98	0.93	0.95	0.95	0.76
Three	1.07	0.77	0.95	0.88	1.13	1.14	0.99	0.99	0.90	1.25	0.88	0.82	0.88	0.93	0.94	0.91	0.93	0.90	0.88	0.85	0.97
Four	1.10	0.65	0.97	0.72	1.21	1.20	1.00	1.00	0.57	1.25	0.89	0.77	0.81	0.92	0.92	0.93	0.91	0.84	0.81	0.83	0.74
Five+	1.12	0.45	1.01	0.61	1.21	1.29	1.03	1.03	0.62	1.23	0.79	0.70	0.84	0.84	0.81	0.87	0.77	0.89	0.74	0.63	0.71
Hypertension																					
No	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Yes	1.07	1.28	3.51	2.53	0.91	1.01	0.97	0.97	1.01	1.14	0.94	2.76	0.76	1.05	1.23	0.79	1.31	1.25	1.74	1.13	1.10
T2DM																					
No	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Yes	1.41	1.94	0.55	1.08	0.96	1.24	1.05	1.05	2.56	1.16	1.15	1.15	1.20	1.32	0.77	1.69	0.59	1.73	1.02	1.15	0.64
Anxiety																					
No	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Yes	1.15	1.36	1.15	0.94	1.34	1.14	1.28	1.28	1.22	1.20	1.24	0.85	1.45	1.08	1.06	1.13	0.86	1.02	1.01	1.07	0.94
Depression																					
No	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Yes	1.17	1.08	1.29	1.03	1.26	1.17	1.14	1.14	1.12	1.13	0.85	1.47	1.18	1.15	1.24	1.01	1.49	1.34	1.32	1.55	0.90
Psychosis																					
No	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Yes	1.04	1.17	0.85	0.99	1.09	0.99	1.41	1.41	3.29	1.33	1.19	0.70	1.48	0.79	0.90	0.66	0.26	0.79	1.10	1.52	1.28

Odds ratios depicted in bold are statistically significant BMI=body mass index, AI=autoimmune diseases, AS= Addison's disease, Alopecia= alopecia areata, AS=ankylosing spondylitis, coeliac= coeliac disease, IBD =Inflammatory bowel disease, Crohn's=Crohn's disease, ulcerative =ulcerative colitis, Graves=Grave's disease, Hashimoto =Hashimoto's thyroiditis, MS=multiple sclerosis (MS), myasthenia =myasthenia gravis, psoriatic A=psoriatic arthritis, rheumatoid =rheumatoid arthritis, Sjögren =Sjögren's syndrome, SLE= Systemic lupus erythematosus, systemic= systemic sclerosis,T1DM= Type1 diabetes mellitus



Increase in odds of having the health condition



Decrease in odds of having the health condition

Chapter end summary

The chapter utilised CPRD pregnancy register to address the research objective, and

identified that the prevalence of autoimmune disease is though small but significant and is increasing over the years. The autoimmune disease are more common in pregnant women of white ethnicity, living in least deprived area when compared to other ethnicities and women living in most deprived area. Prevalence is also higher in women who are smokers compared to non smokers.

Chapter 4: Autoimmune diseases and adverse pregnancy outcomes: an umbrella review

Chapter overview

The study was conducted to address the research objective: to consolidate the available evidence on association of autoimmune diseases and adverse pregnancy outcomes. This review helped to summarise the evidence available in the literature and formed the basis for the chapter 5.

The published manuscript is presented as follows

Published manuscript

Singh, M., Wambua, S., Lee, S.I. *et al.* Autoimmune diseases and adverse pregnancy outcomes: an umbrella review. *BMC Med* 22, 94 (2024). <https://doi.org/10.1186/s12916-024-03309-y>

Personal contribution

- Developed the review question and study design guided by co-authors
- Identified, searched, appraised and extracted data as first reviewer for umbrella review
- Synthesised data and wrote first draft of the manuscript
- Submitted for publication and addressed reviewers' comments

Title- Autoimmune diseases and adverse pregnancy outcomes: an umbrella review

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4.1 Abstract

4.1.1 Background

There is a high prevalence of autoimmune conditions in women specially in the reproductive years, thus the association with adverse pregnancy outcomes has been studied widely.

Hence considerable research has been undertaken to study the association of autoimmune conditions with adverse pregnancy outcomes. However, few autoimmune conditions/adverse outcomes have been studied more than others, and this umbrella review aims to consolidate existing knowledge in this area with aim to provide new knowledge and also identify gaps in this research area.

4.1.2 Methods

Medline, Embase, and Cochrane databases were searched from inception to December 2023. Screening, data extraction, and quality appraisal (AMSTAR 2) were done by two independent reviewers. Data were synthesised narratively and quantitatively. Relative risks (RR)/ odds ratio (OR) with 95% confidence intervals were reported.

4.1.3 Results

Thirty-two reviews were included consisting of 709 primary studies. The review reported the association between 12 autoimmune conditions and 16 adverse pregnancy outcomes. Higher risk of miscarriage is reported in women with Sjögren's syndrome RR 8.85 (95% CI 3.10-25.26) and systemic lupus erythematosus (SLE) OR 4.90 (3.10-7.69). Pre-eclampsia was higher in women with type 1 diabetes mellitus (T1DM) OR 4.19 (3.08-5.71), and SLE OR 3.20 (2.54-4.20). Women reported higher risk of diabetes during pregnancy with inflammatory bowel disease (IBD) OR 2.96 (1.47-5.98). There was an increased risk of intrauterine growth restriction in women with systemic sclerosis OR 3.20 (2.21-4.53) and coeliac disease OR 1.71 (1.36-2.14). Preterm birth was associated with T1DM OR 4.36 (3.72-5.12) and SLE OR 2.79 (2.07-3.77). Low birth weight babies were reported in women with women with SLE or systemic sclerosis OR 5.95 (4.54-7.80) and OR 3.80 (2.16-6.56), respectively. There was a higher risk of stillbirth in women with T1DM OR 3.97 (3.44-4.58), IBD OR 1.57 (1.03-2.38), and coeliac disease OR 1.57 (1.17-2.10). T1DM in women was associated with 32% lower odds of small-for-gestational-age baby OR 0.68 (0.56-0.83).

4.1.4 Conclusion

The umbrella review highlights the impact of autoimmune diseases on maternal and foetal health, with findings suggesting that conditions such as rheumatoid arthritis, SLE, and thyroid disorders are associated with a greater risk of developing adverse pregnancy outcomes, including preterm birth, gestational hypertension, and foetal growth restriction. Creating targeted care plans from preconception to postnatal care is essential for reducing the risk of these adverse outcomes in women with autoimmune conditions. This would involve early identification and management of autoimmune diseases and tailored interventions to mitigate risks during pregnancy and enhance maternal and neonatal health.

4.2 Background

There are over 80 different types of autoimmune conditions with about 80% of those diagnosed with these conditions being women [1-3]. The prevalence of autoimmune conditions is higher in women by almost twofold and is often associated with the X chromosome [326-329]. For many individual autoimmune conditions, there is a higher female-to-male ratio e.g., systemic lupus erythematosus (SLE) 7:1, Sjögren's syndrome 9:1, and rheumatoid arthritis or systemic sclerosis 3:1 [330-332]. Women undergo various hormonal changes throughout their life; during puberty, pregnancy, and then in menopause [333]. These endocrine transitions in women may increase their susceptibility to autoimmune conditions and many autoimmune conditions such as SLE, systemic sclerosis, rheumatoid arthritis, and psoriasis develop during the female reproductive age influenced by the T cell cytokine-mediated response and hormonal, immunological and bodily changes [333, 334]. Earlier literature also reported autoimmune conditions as the seventh most

frequent underlying cause of death among females in age groups below 75 years in the UK and US [327, 335].

There has been an increasing trend of autoimmune conditions worldwide. Lerner et al estimated the net % increase per year for the incidence and prevalence of autoimmune conditions are 19.1% and 12.5%, respectively in the last 30 years [4, 336]. This increasing trend is due to many environmental factors like lifestyle changes, changes in diet, and exposure to certain infections and drugs [337-344]. With this increase in the prevalence and thereby an increased number of pregnancies presenting with autoimmune conditions, it is pertinent to have a clear idea of the adverse pregnancy outcomes associated with the specific autoimmune conditions and to identify whether these outcomes are unique to specific conditions or are shared across the spectrum of autoimmunity.

Symptoms of autoimmune conditions could improve, worsen, or remain unchanged when a woman becomes pregnant depending upon her specific autoimmune condition. For example, improvement in the symptoms of rheumatoid arthritis during pregnancy has been observed in some women whereas worsening of symptoms is a common feature in SLE [130, 345]. Autoimmune conditions may complicate pregnancy as antibodies that the mother produces can enter the foetus's system e.g. anti-Ro/SSA antibodies crossing the placenta and impacting development of the fetal heart [346]. These conditions have variable course and are episodic in nature, making it harder to determine the impact of pregnancy in triggering and/or progressing the condition and thereafter its impact on the pregnancy outcome [345]. Clinical management of pregnancies with autoimmune condition requires interdisciplinary care with clear preconception care protocol/recommendations and clear understanding of the risk of adverse pregnancy outcomes [347, 348].

Many systematic reviews have examined the role of autoimmune conditions on both maternal and fetal outcomes [314, 349, 350]. It has been well established that autoimmune conditions like SLE, and inflammatory bowel disease (IBD) may have adverse pregnancy outcomes like miscarriage and preterm birth [351-354]. Whereas conditions like multiple sclerosis are known to have an adverse effect on pregnancy outcomes but evidence is sparse to support this [349, 355]. Some autoimmune conditions have been studied more than others with inconsistent findings [356, 357]. This umbrella review aims to consolidate evidence from systematic reviews of the association of common autoimmune conditions with pregnancy outcomes in order to identify the strength and precision of these associations. Also, if fetal or maternal outcomes are shared between autoimmune disease this might suggest a common pathological process which could be targeted across conditions. Which will help identify the potential gaps in current research to help prioritise the future research in autoimmune conditions with limited evidence in this area [358]

4.3 Methods

This umbrella review aims to summarise the evidence available in the form of systematic reviews studying the adverse pregnancy outcomes in women with autoimmune conditions. This umbrella review has been conducted in accordance with Joanna Briggs Institute (JBI) umbrella review methodology [359] and the PRIOR (Preferred Reporting Items for Overviews of Reviews) checklist were used to report the review [360]. The protocol has been registered to Prospero (registration number CRD4202233499). Deviations from the protocol are listed in the supplementary: table 4.2.

4.3.1 Inclusion and exclusion criteria

Systematic reviews reporting the associations between autoimmune conditions and adverse pregnancy outcomes were included. No language restriction was applied. The population considered were pregnant women without any age restriction. We did not include reviews where all women who were pregnant were because of assisted reproductive treatment because this presents with its own set of risks. The autoimmune conditions that were selected were those that were more common in women of reproductive age and after consultation with experts in the subject [1, 361]. Furthermore, a scoping search was conducted before finalising the list of exposures and outcomes. Autoimmune conditions included Addison's disease, alopecia areata, axial spondyloarthritis (AxSpA), coeliac disease, IBD including Crohn's disease and ulcerative colitis, multiple sclerosis, myasthenia gravis, psoriatic diseases (including psoriasis and psoriatic arthritis), rheumatoid arthritis, Sjögren's syndrome, SLE, systemic sclerosis, and thyroid autoimmunity (including Grave's disease and Hashimoto's thyroiditis) and Type 1 diabetes mellitus (T1DM) and vitiligo.

The outcomes included were adverse pregnancy outcomes which were considered after consultations with experts (obstetricians and epidemiologists) and after input from patient public involvement and engagement (PPIE) group members. The outcomes definitions were defined prior, [362] and definitions were compared between the reviews. The outcomes are listed in Table 4.1.

Systematic reviews were included with or without a meta-analysis. The identified reviews were carefully examined to determine whether the review qualified as systematic review [363]. The reviews were excluded 1) if the review was not qualified as systematic review e.g. scoping reviews, reviews, protocols, conference abstracts, 2) if they did not report the

associations of the specified autoimmune conditions and adverse pregnancy outcome/s, 3) if studying the association of drugs for autoimmune conditions and the pregnancy outcome/s, 4) if comparing the effects of one autoimmune condition to another, and 5) duplicates.

4.3.2 Search strategy

Medline, Embase and Cochrane database were systematically searched from the inception to 15th December 2023. A robust search strategy was used, and the systematic review filter was used to limit the searches. The search was repeated periodically to identify the latest published reviews. The Medical Subject Headings and free text search for autoimmune conditions (exposure) and pregnancy outcomes were used. The detailed search strategy for Medline is presented in supplementary table 4.2. This search strategy was adapted for use in other databases.

4.3.3 Study selection

Once the literature search was completed, a reference management software (EndnoteV.X9) was used to manage the studies. After removing duplicate studies, two independent reviewers (MS, SW) conducted the title and abstract screening, and ineligible studies were excluded. Full-text screening of eligible studies was conducted by two independent reviewers (MS, SW) and a third senior reviewer (FC, KN) were consulted to resolve any discrepancy. The list of excluded studies with reasons for excluding them are shown in supplementary table 4.4 [314, 316, 364-421] We found four non-English reviews. One was in Spanish and three were in Mandarin. Fellow researchers with expertise in these languages were consulted. They translated the reviews and performed the data extraction and quality

assessment for these reviews. The review in Spanish was excluded after the full text screening but the three reviews in Mandarin were included.

4.3.4 Data extraction

Two independent reviewers (MS, SW) extracted the data from the reviews and in the case of discrepancy, a third reviewer (FC, KN) was consulted. Data was extracted under the following headings: aim of the review; database searched; search period; exposures; comparator; outcomes; study design(s); definition of exposure; definition of outcome; data synthesis method; quality assessment tool; quality of the included primary studies as assessed by review authors; various characteristics for example year of publication, geographical area, type of studies included etc. of the included reviews; effect sizes; and conclusion of the review. The authors of the reviews were contacted where further information was required. The data extraction form used is shown in supplementary table 4.4.

4.3.5 Quality assessment

Assessment of multiple systematic reviews version 2 (AMSTAR 2) checklist was completed by two reviewers independently (MS, SW) to assess the methodological quality of the included reviews [422]. In case of any disagreements, a third reviewer (FC, KN) was consulted to resolve these. The reviews were rated in four categories: high, moderate, low, and critically low. Out of the 16 items on the AMSTAR 2 checklist, seven were considered critical. These were: registration of the protocol before starting the reviews; conduct of an adequate search of the literature; providing justification for the exclusion of individual studies; satisfactory assessment of risk of bias in the studies included in the reviews; use of appropriate statistical methods in performing a meta-analysis; accounting for risk of bias when interpreting the

results. If any of these critical domains were not fulfilled, then the review was rated as low quality. The reviews rated as critically low quality were excluded. Details of quality assessment are presented in supplementary table 4.5.

4.3.6 Reviews with overlapping primary studies and update of reviews

When two or more reviews studied the association of the same exposure and outcome it is important to measure the extent of overlap in the primary studies included in the reviews. We used the corrected covered area (CCA) measure to establish the percentage of overlap [224, 225]. CCA less than 5 indicates low overlap and CCA 10 or above indicates moderate/high overlap. Where reviews had a high overlap. Cochrane review was selected over a non-Cochrane review. If there were no Cochrane reviews, then a review was selected if: it had higher AMSTAR quality rating, was conducted recently, included a meta-analysis, or had a larger sample size [224-226]. Further detailed information on dealing with overlapping reviews and update of reviews is provided in supplementary file.

Box 1: Formula for corrected cover area

$$CCA (\%) = N - r / rc - r$$

CCA: corrected covered area, N = number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic reviews).

4.3.7 Data synthesis

We firstly categorised the outcomes as maternal and fetal/neonatal outcomes. We reported the basic characteristics of the included reviews in tables and indicated which outcomes the

review reported, and which were retained for the umbrella review after estimating the overlap. The overlap of the reviews was quantified through CCA, and the percentage was calculated. (a) $CCA > 10\%$ = Two reviews with high overlap ($CCA > 10\%$). One review was selected to present the results based on the criteria mentioned earlier. The effect estimates from that review were presented as it is or meta-analysed where it was presented separately for cohort and case control studies to get a pooled effect of that outcome. (b) $CCA < 10\%$ = (few overlapping primary studies between the reviews) Data from the unique primary studies of the overlapping reviews is extracted and meta-analysis (random effect) is performed. Data were then extracted (number of exposed, unexposed and total numbers or odds ratio or risk ratio) from these primary studies. Using random effect model, meta-analysis was conducted to obtain a pooled effect estimate of the outcome in question. (c) $CCA = 0\%$ = (no overlapping primary studies between the reviews) Data from the primary studies of these reviews is extracted and meta-analysis (random effect) is performed to get the combined effect estimate. The results were synthesised in narrative form, forest plots and tables. For consistency, the effect sizes were converted to odds ratio where possible. [423]. For certain outcomes, the summary estimates could not be converted to odds ratio due to missing data. R and STATA were used for the analysis.

4.4 Results

Literature search

The literature search from Medline, Embase and Cochrane library of systematic reviews identified 2743 potential reviews. We excluded 392 duplicates. After screening 2351 titles and abstracts, 92 full texts were screened, of which 43 were excluded, with reason for exclusion documented. Forty-nine reviews were initially included for appraisal of the study

quality and study overlap. A further 17 reviews were excluded due to critically low study quality and overlaps in the included primary studies. Finally, 32 reviews were included in this umbrella review [313, 315, 318, 349-357, 424-443]. Figure 4.1 shows the selection process in accordance with the PRISMA flow diagram.

Quality assessment

Of the 49 reviews that were initially included, five reviews were excluded due to being critically low in quality (assessed using the AMSTAR2 tool). The critical domains – meaning that a review would be rated as high quality review, were: protocol registered before commencement of the review (item 2), adequacy of the literature search (item 4), justification for excluding individual studies (item 7), risk of bias from individual studies being included in the review (item 9), appropriateness of meta-analytical methods (item 11), consideration of risk of bias when interpreting the results of the review (item 13), and assessment of presence and likely impact of publication bias (item 15) [215]. The five reviews which were excluded did not qualify on at least three of these critical domains.[364, 376, 406, 412, 414]. The five reviews which were excluded did not qualify on at least three of these critical domains. In the included systematic reviews, the quality of the primary studies was assessed through Newcastle-Ottawa scale [215]. The majority of reviews reported moderate to high quality rating of studies.

Overlapping and non-overlapping association and update of review

The overlapping association was noted with most autoimmune conditions reporting various pregnancy outcomes except for myasthenia gravis, multiple sclerosis, and systemic sclerosis, as only one review for each of these conditions was identified. The degree of overlap (CCA) ranged from 0% to 66%. Out of 41 overlapping associations calculated, 34 high overlapping

associations with CCA ranging from 12%-66%. Review was selected in these cases to report the results based on the above-mentioned criteria. Eleven reviews were excluded owing to high overlap [314, 316, 367, 372, 374, 382, 397, 407, 415, 419, 421]. For six associations the CCA was between 0-7%. Random effect meta-analysis was conducted to obtain the pooled estimate from the primary studies from these reviews without double counting. Details of how the citation matrix was created and the CCA calculated is given in supplementary text 1[5, 215, 224, 316, 349, 350, 352-354, 357, 360, 364, 367, 372, 374, 382, 385, 397, 407, 415, 421, 423-430, 432-437, 439-442, 444-452] and supplementary table 4.6 and 4.7. After consultation with experts, we decided that none of the reviews required an update. More information in supplementary text 1 and supplementary table 4.9.

Summary of the results

Of the 32 systematic reviews included, 30 had completed a meta-analysis and two synthesised the findings narratively. The characteristics of the included systematic reviews are presented in table 4.2 and details in supplementary table 4.10-4.12. Figure 4.3 presents the heatmap of the association of each autoimmune conditions with pregnancy outcomes, highlighting areas with evidence gap, especially for multiple sclerosis and Sjögren's syndrome. More information about heterogeneity and publication bias is reported in supplementary text 4.1 and supplementary table 4.8.

The effect sizes (odds ratios/risk ratios) of the included meta-analysis are shown in supplementary table 4.11 and the narrative synthesis conducted by the included reviews are in supplementary table 4.12.

4.4.1 Maternal outcomes

Figure 4.8 presents the forest plots of effect sizes from the included systematic reviews for maternal outcomes. Ectopic Pregnancy: Significant risk of ectopic pregnancy was reported in women with IBD; odds ratio (OR) 1.26 (95% confidence intervals 1.11-1.44). It was also reported that the risk is similar for women with Crohn's disease OR 1.51 (1.21-1.88) and ulcerative colitis OR 1.50 (1.00-2.23) [435]. No significant association was observed in women with coeliac disease; OR 1.21(0.85-1.71) or in women with SLE; OR 1.79 (0.57-5.59) [424].

Miscarriage- Higher risk of miscarriage was reported in women with Sjögren's syndrome relative risk (RR) 8.85(3.10-25.26) or SLE; OR 4.90(3.10-7.69) respectively [313, 351]. In the presence of thyroid autoimmunity (all antibodies) the risk was almost three-fold; OR 2.77 (2.10-3.65) [425]. Similar risk was reported with only thyroid peroxidase antibody; OR 2.74 (2.12-3.54) [437]. Significant association of miscarriage was also observed with coeliac disease; OR 1.38 (1.12-1.69), rheumatoid arthritis; OR 1.32 (1.21, 1.43) psoriasis; OR 1.10 (1.01-1.20), and systemic sclerosis; OR 1.60 (1.29-2.22) [314, 315, 349, 440]. No significant association was reported for miscarriage in women with IBD; OR 1.63 (0.49-5.43) or psoriatic arthritis; OR 1.35 (0.79-2.32)[353, 440, 443]. One of the studies reported composite outcome of abortion (spontaneous and therapeutic) in pregnant women with SLE; OR 1.40 (1.20-1.60) [424].

Recurrent pregnancy loss- Women with coeliac disease had almost six-fold higher odds of recurrent pregnancy loss; OR 5.82 (2.3-14.74). The risk was also reported as almost two-fold higher in the presence of thyroid autoimmunity (all) OR 1.94 (1.43-2.86) [427, 436].

Gestational hypertension-The odds of gestational hypertension in women with T1DM was more than two-fold; OR 2.68 (1.85-3.89) [441]. There were also almost 20-50% higher odds of gestational hypertension in women with psoriatic diseases (psoriasis OR 1.29 (1.15-1.45), Psoriatic arthritis OR 1.49 (1.09-2.06), and presence of thyroid autoimmunity (TPO); OR 1.29 (1.00 -1.45) [440, 442].

Pre-eclampsia-The odds of developing pre-eclampsia were more than four times greater in women with T1DM; OR 4.19 (3.08-5.71) [441]. High risk was also reported in women with SLE; OR 3.20 (2.54-4.20) or systemic sclerosis; OR 2.20 (2.21-4.53) [349, 350]. Some association was observed in women with rheumatoid arthritis; OR 1.65 (1.53, 1.78) or psoriatic diseases (psoriasis OR; 1.25 (1.09-1.42), psoriatic arthritis; OR 1.45 (1.13-1.85) [314, 440, 443]. No significant association was noted in women with AxSpA; OR 1.74 (0.85-3.54), coeliac disease; OR 1.04 (0.87-1.21), or IBD; OR 4.65 (0.76-28.35) [315, 353, 357, 434].

Another review which collectively evaluated the outcome as the risk of eclampsia and pre-eclampsia reported an increased risk in women with psoriatic diseases (psoriasis OR 1.25 (1.09-1.42), psoriatic arthritis; OR 1.45 (1.13-1.85) [440]. No association was seen between women with multiple sclerosis and occurrence of pre-eclampsia; OR 0.99 (0.89-1.09) [318].

Gestational diabetes mellitus (GDM) The risk of women developing GDM was almost three-fold in women with IBD; OR 2.96 (1.47-5.98) [353]. Some association was also reported in women with thyroid autoimmunity (all); OR 1.49 (1.07-2.07) or psoriasis; OR 1.19 (1.09-1.30), [432, 440]. Lou et al reported similar risk of GDM in both women with only thyroglobulin antibodies; OR 1.88 (1.13-3.12) and only thyroid peroxidase antibodies OR 1.65 (1.13-2.40). No significant association was reported for developing GDM in women

with AxSpA; OR 0.88 (0.24-3.21), psoriatic arthritis; OR 1.26 (0.90-1.77), rheumatoid arthritis; OR 1.61 (1.25, 2.07) and SLE OR 0.97 (0.57-1.60) [314, 351, 357, 440, 443].

Placenta previa and placental abruption. No risk of placenta previa and placental abruption was reported in women with thyroid autoimmunity; OR 0.42 (0.12-1.43) [442].

Antepartum haemorrhage /Postpartum haemorrhage (APH/PPH)- No significant association reported for APH/PPH in women with coeliac disease; OR 1.11(0.96-1.28) or psoriatic diseases (psoriasis; OR 1.22(0.74-01), psoriatic arthritis; OR 0.82(0.37-1.82) when compared to women without psoriatic diseases [315, 440].

Caesarean section (CS) Risk of delivering via CS is almost two to three-fold greater in the presence of T1DM; OR 3.97 (3.31-4.77), SLE; OR 2.11 (1.57-2.83) [441]. Women with all other reported autoimmune conditions were reported to have increased chances of delivering via CS compared to women without the autoimmune conditions. The odds are as follows AxSpA; OR 1.85 (1.46-2.30), coeliac disease; OR 1.10 (1.03-1.16), IBD; OR 1.67 (1.15-2.41), psoriasis; OR 1.26 (1.05-1.51), psoriatic arthritis; OR 1.45 (1.27-1.66), rheumatoid arthritis; OR 1.62 (1.43, 1.84) [314, 315, 353, 357, 424, 426, 440, 443]. It was further reported that there was a significant risk of women delivering through CS with Crohn's disease; OR 1.65 (1.19-2.29) but not as much with ulcerative colitis; OR 1.30 (0.86 to 1.96) [352, 353, 426]. One of the reviews conducted a narrative analysis and reported women with myasthenia gravis are at increased risk of requiring assisted vaginal delivery or CS compared to women without the condition (population size=854)[356].

Postpartum depression Almost a two-fold increased risk of developing postpartum depression in the presence of thyroid autoimmunity (TPO); OR 2.00 (1.62 to 2.66) was reported [433].

4.4.2 Fetal/Neonatal outcomes

It has been observed that there is a higher risk of IUGR, stillbirth, preterm birth or low birth weight in women with SLE and women with T1DM associated with 32% lower odds of small-for-gestational-age baby as shown in figure 4.3

Intrauterine growth restriction (IUGR) -The evidence is suggestive of almost two and three-fold risk of IUGR in women with systemic sclerosis or coeliac disease; OR 3.20 (2.21-4.53) OR 1.71 (1.36-2.14) respectively [315, 349, 434]. Whereas no significant association was observed in women with AxSpA; OR 1.05 (0.24-4.49), SLE; OR 7.67 (0.32-161.50), thyroid autoimmunity (TPO); OR 1.61 (0.23-11.12) [351, 357, 442]. Tong et al reported composite outcome IUGR (including IUGR, foetal growth restriction, and low birth weight) in women with thyroid autoimmunity (TPO) which was reported as OR 1.57 (0.77-3.18) [438] when compared to women without thyroid autoimmunity[438].

Small for gestational age (SGA) -There is an increased risk of small for gestational age in women with SLE; OR 2.49 (1.88-3.31) [351, 424]. A significant association is reported with rheumatoid arthritis; OR 1.48 (1.25, 1.75) [443]. No significant association was reported in women with AxSpA; OR 1.66 (0.93-2.25), coeliac disease; OR 2.62 (0.47-14.61), IBD; OR 1.61 (0.93-2.79), psoriatic diseases (psoriasis; OR 1.01 (0.92-1.11), psoriatic arthritis; OR 0.99 (0.72-1.36) [357, 434, 436, 440]. Whereas women with T1DM have a lower effect with OR 0.68 (0.56-0.83) [441].

Stillbirth-There was a very high risk of stillbirth in women with SLE, although with wide confidence intervals; OR 16.90 (3.02-94.40) [351] and almost a four-fold higher risk of stillbirth for women with T1DM; OR 3.97 (3.44-4.58) [441]. There was a significantly higher odds for women with rheumatoid arthritis OR 1.99 1.55 (1.17, 2.06), coeliac disease; OR 1.57

(1.17-2.10), IBD; OR 1.57 (1.03-2.38), [315, 316, 352, 443]. There was no significant association with stillbirth in women with and AxSpA; OR 0.70 (0.26-1.85), psoriatic diseases (psoriasis; OR 1.17 (0.84-1.63), psoriatic arthritis; OR 1.06 (0.46- 2.46), or Sjögren's syndrome; OR 1.05 (0.37-2.97) [357, 439, 440]. Two separate reviews reported significantly higher odds of stillborn/neonatal/perinatal death as a composite outcome in women with SLE; OR 1.75 (1.47-2.37) and in women with rheumatoid arthritis; OR 1.38 (1.09-1.74) [314, 424].

Preterm birth- There was more than four-fold higher odds of preterm birth for women with T1DM; OR 4.36 (3.72-5.12). The odds of preterm birth were also higher in women with SLE; OR 2.79 (2.07-3.77), and in women with Sjögren's syndrome; RR 2.27 (1.46-3.52) [313, 351, 424, 441]. There was a significant association for preterm birth in women with coeliac disease; OR 1.30 (1.13-1.50), IBD; OR 1.81 (1.37-2.38), psoriatic diseases (psoriasis; OR 1.22 (1.04-1.42), psoriatic arthritis; OR 1.48 (1.24- 1.78), rheumatoid arthritis; OR 1.57 (1.00, 2.48), systemic sclerosis; OR 2.40 (1.14-4.86) and for thyroid autoimmunity (all); OR 1.88 (1.32-2.67), thyroid autoimmunity (TPO); OR 1.33(1.15-1.56) when compared to women without these conditions [314-316, 349, 351, 354, 424, 430, 440, 443]. Korevar et al further reported higher odds of preterm birth for thyroid autoimmunity (TPO) positive women OR; 1.33 (1.15-1.56) and no significant association with thyroid autoimmunity (TgAb) positive women; OR 0.88 (0.64 to 1.20) when studied separately[429] .Two separate reviews analysed the odds of preterm birth with multiple sclerosis (sample size n=6230) and myasthenia gravis (n=854) in a narrative analysis and did not find any significant association [318, 356].

Low birth weight -The odds of giving birth to a baby with a low birth weight (< 2500 g) was 4-6 times higher in women with SLE or systemic sclerosis; OR 5.95 (4.54- 7.80) and OR 3.80 (2.16-6.56), respectively [349, 351]. There was a significant association for women with IBD; OR 2.25 (1.37-3.69), coeliac disease; OR 1.63 (1.06-2.51), rheumatoid arthritis OR; 1.73 (1.46, 2.06) or Sjögren's syndrome RR 1.99 (1.34-2.97) [313, 314, 430, 434, 443]. There was a higher odd of having a low-birth-weight infant for women with Crohn's disease OR 2.82 (1.42-5.60) but the association was not significant for women with ulcerative colitis OR 1.66 (0.48 - 5.66) [352, 353, 426]. The association for women with AxSpA; OR 1.47 (0.98-2.21) or psoriatic diseases (psoriasis; OR 1.14 (0.87-1.49), psoriatic arthritis; OR 1.15 (0.84-1.58) [357, 440] and low birth weight was not significant. Another review reported the odds of low birth weight with multiple sclerosis in a narrative analysis (n=635) and only one study reported a higher risk of low birth weight in women with multiple sclerosis [318].

Neonatal mortality SLE was associated with a much greater odds of neonatal mortality; OR 8.32 (5.23-13.22). There was also a significantly higher odds of neonatal mortality for women with T1DM OR 2.26 (1.74-2.95) or Sjögren's syndrome OR 1.77 (1.28-2.46). Psoriasis was not significantly related to neonatal mortality OR 1.13 (0.90-1.43) (5, 42, 43).

4.5 Discussion

Results from this umbrella review agree with the previous literature and showed that women with SLE, T1DM and systemic sclerosis have a higher risk for a number of adverse pregnancy outcomes and also that women with T1DM were less likely to have a baby that was small for gestational age. Women with SLE had a greater risk of miscarriage, pre-eclampsia, small for gestational age, preterm birth, stillbirth and low birth weight. Women with T1DM were more likely to develop pre-eclampsia, caesarean section, preterm birth,

and still birth, and women with systemic sclerosis had a higher risk of pre-eclampsia, IUGR, low birth weight and preterm birth. There was also a greater risk of miscarriage for women with thyroid autoimmunity, and for women with Sjögren's syndrome. Women with IBD had a higher risk of GDM and low birth weight babies. The associations of AxSPa, coeliac disease, psoriatic diseases, multiple sclerosis and myasthenia gravis with certain adverse pregnancy outcomes were not clearly evident. There was no evidence of significant association of multiple sclerosis with risk of pre-eclampsia and low birth weight, for SLE with risk of GDM, and for AxSPa with preterm birth, stillbirth or GDM. There are various knowledge gaps identified. No systematic reviews identified for few autoimmune conditions (Grave's disease, Hashimoto's thyroiditis, vitiligo, Addison's disease, alopecia areata). Further few adverse pregnancy outcomes like ectopic pregnancy, obstetric haemorrhage, perineal tears, postpartum depression or psychosis are not widely studied.

4.5.1 Strengths and limitations

The main strength of this umbrella review is the comprehensive search strategy with no language or time restrictions. Searches that were repeated periodically to include newly published systematic reviews. Secondly, we included a wide range of autoimmune conditions and adverse pregnancy outcomes which were identified by scoping searches of the literature and after consultation with subject experts, making this review more relevant and useful. Definitions of the outcomes for inclusion were predefined so that these were uniform across the systematic reviews[362]. The summary estimates have been converted to odds ratios where possible to facilitate the interpretation of the results.

The main limitation of this umbrella review was that we were not able to include certain autoimmune conditions and their effects on pregnancy outcomes if there were no

systematic reviews. For example, there were primary studies reporting the association of vitiligo with adverse pregnancy outcome, but no systematic review has been conducted on this topic [453]. None of the included reviews were rated high quality following the AMSTAR2 checklist and were all either moderate or low quality, which affected the overall certainty of the evidence in this umbrella review. There was high heterogeneity between the reviews. Most of the included reviews had multiple outcomes and in many instances the sample size of the primary studies used for measuring the outcome in the systematic review was small thus providing large variation in the effect size. Some reviews restricted the search strategy (e.g., time period or type of study) and the number of studies included in the meta-analysis was small meaning there could be some publication bias. Even though we attempted to include the majority of common autoimmune conditions, not all of them could be included (i.e., antiphospholipid syndrome and dermatomyositis) [454, 455]. Another limitation is that this review cannot address the effects of co-morbidities on outcomes for example, increased risk of antiphospholipid syndrome (APS) in SLE which might be the cause of the outcomes rather than SLE directly [456]. For the outcome caesarean delivery, the reviews did not specify or analysed the indications and therefore remains unclear if the increased risk was caused by the disease activity, medications or other factors including patient or physician preference. This umbrella review provides comprehensive evidence on the adverse pregnancy outcomes in women with autoimmune conditions. No systematic reviews identified for thyroid diseases Grave's disease or Hashimoto's thyroiditis, however there was extensive research for thyroid autoimmunity and effects on pregnancy outcome. Hence this review has incorporated thyroid autoimmunity as a whole and consolidate the findings in this area. Other diseases not included are vitiligo, Addison's disease or alopecia areata for which there are no prior systematic reviews. Two of the retrospective cohort

studies identified exploring the association of vitiligo with spontaneous miscarriage reported significant association with OR 1.25 (1.14-1.36) and aHR 1.16 (1.09-1.25) when compared with women without vitiligo [457, 458]. Other studies showed no significant association of vitiligo with risk of preterm birth, GDM, or stillbirth [453, 457, 458]. Two different studies reported Addison's disease was associated with almost two-fold increase in the risk of preterm birth and caesarean section compared to women without the condition [459, 460]. One of the cohort studies showed that women with alopecia areata had a greater risk of adverse pregnancy outcomes including spontaneous miscarriage or ectopic pregnancy with OR 1.09 (1.00- 1.18) and OR 1.28 (1.13- 1.46) respectively [461]. There are also other rare autoimmune conditions that were beyond the scope of this review (e.g. myositis, vasculitis) which may be associated with increased risk of adverse pregnancy outcomes [462]. Small for gestational age, pregnancy loss, IUGR, preeclampsia, and preterm birth and miscarriage has been associated with the connective tissue diseases [463-465]. The drugs used for the treatment of these autoimmune conditions such as biological and conventional synthetic disease-modifying antirheumatic drugs (DMARDs), oral glucocorticoids and non-steroidal anti-inflammatory drugs can also affect the pregnancy outcomes and various studies have been conducted to estimate which medication pose higher risk than others [466-468]. However active inflammatory disease has been shown to increase the risk of miscarriage, preterm delivery, small for gestational age babies and preterm delivery [469]. Understanding the contribution of disease activity and the effect of pregnancy on the disease and vice versa has not been addressed in this review and will require further research [470]. Similarly understanding the risk of these medications and how they contribute towards adverse pregnancy outcomes need to be researched and guidelines need to be formulated [471]. Furthermore, the effect of the autoimmunity in women during pregnancy also might affect

the offspring, and they have been linked with learning disabilities, dyslexia and autism [472-474]. Further research of the associations of these conditions with pregnancy outcomes is therefore warranted.

4.5.2 Clinical and research implications

The primary objective of this review is to consolidate the findings from the systematic reviews, present what is known, and to identify gaps in the research. This review is aimed primarily at a range of health professionals who are directly involved with managing women with these autoimmune conditions who are planning a pregnancy or are pregnant. This includes specialists like rheumatologists, endocrinologists, gynaecologists, obstetricians, rheumatology nurses/allied health professionals, general practitioners as well as the patients themselves. This document may also be a useful resource for policymakers to evaluate the present guidelines and propose further recommendations and help to service provider to risk stratify women and decide on the referral threshold or best care pathway. Since many adverse pregnancy outcomes are shared across conditions than this provides argument for i) research to identify if there is a common mechanism which could lead to newer treatments and ii) guidelines which are relevant across different conditions. This review not only identify gaps in the research but is especially of value to non-specialist obstetricians who might see a number of different autoimmune diseases within the same clinic.

There are currently limited guidelines for preconception and pregnancy care for a limited number of autoimmune conditions. For example, there is a best practice guideline from a UK multispecialty working group for myasthenia in pregnancy [475] and the National Institute for Health and Care Excellence (NICE) guidelines for T1DM in pregnancy, UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines [476, 477].

There are few guidelines on prescribing medication in pregnancy for women with rheumatic diseases and other musculoskeletal diseases like SLE or antiphospholipid syndrome [478-480]. there are guidelines around prescribing in pregnancy but less so around other aspects of autoimmune disease. Most guidelines focus on safety of medication (which is applicable to all diseases), but the unmet need is in management of these patients in general. But there is a need for the development of more evidence-based standardised guidelines for a wider range of autoimmune conditions t since they have shared outcomes o help clinicians and women with decision making for managing these conditions before planning a pregnancy and while pregnant [334, 345, 348, 481-483]. It has been established that preconception care for chronic disease can help improve pregnancy outcome such as miscarriages in women with autoimmune rheumatic conditions and low birth weight in women with IBD [484]. Preconception counselling and risk stratification are possible tools that may help reduce the risk of complications during pregnancy by ensuring disease stability / control prior to conception. antenatal care, for example use of low dose aspirin to prevent and predictive / diagnostic biomarkers for pre-eclampsia in women with SLE or T1DM for example predictive biomarkers for pre-eclampsia in women with SLE or T1DM and identification of placental insufficiency with fetal growth restriction in order to decide the best timing for delivery may also lead to improved outcomes [317, 481, 485]. Many autoimmune conditions like Addison's disease, alopecia areata, vitiligo could not be reported due to no systematic reviews conducted is reported as a gap in research. Future research should address the evidence gaps identified in this umbrella review, for example for women with multiple sclerosis and Sjögren's syndrome.

4.6 Conclusions

This review has provided comprehensive summary of the current evidence of the association of pregnancy outcomes in women with autoimmune conditions and identified gaps that need further research. Given the potential adverse outcomes, more clinical guidelines need to be developed to guide the preconception and maternity care for pregnant women with autoimmune conditions.

Patient and public involvement-Patient and public involvement and engagement (PPIE) representatives (RP and NM) were involved in formulating the research question. They have also played key role in collaboration with clinicians and researchers to identify and consider the list of pregnancy complications and autoimmune conditions in the study. They will also play a key role in disseminating the results once the reviews have been undertaken.

Table 4.1 Outcomes- Adverse pregnancy outcomes

Maternal Outcomes
1-Miscarriage/ recurrent miscarriage/ spontaneous pregnancy loss
2-Hypertensive disorders of pregnancy (gestational hypertension pre-eclampsia- early or late onset, recurrent pre-eclampsia, HELLP (haemolysis, elevated liver enzymes and low platelet) syndrome)
3-Placental disorders (placenta previa, placental abruption, placenta accreta, placenta percreta)
4-Hyperemesis gravidarum
5-Gestational diabetes mellitus (GDM)
6-Ectopic pregnancy
7-Molar pregnancy/ Choriocarcinoma
8- Obstetric cholestasis
9-Obstetric haemorrhage
10-Mode of birth: Caesarean, Instrumental
11- Perineal trauma-3 rd and 4 th degree tear
12- Postpartum depression
13- Puerperal psychosis
Fetal/Neonatal outcomes
1-- Intrauterine growth restriction (IUGR)
2- Small for gestational age (SGA)
3- Stillbirth
4- Preterm birth/ Recurrent preterm birth
5- Low birth weight
6-Neonatal death

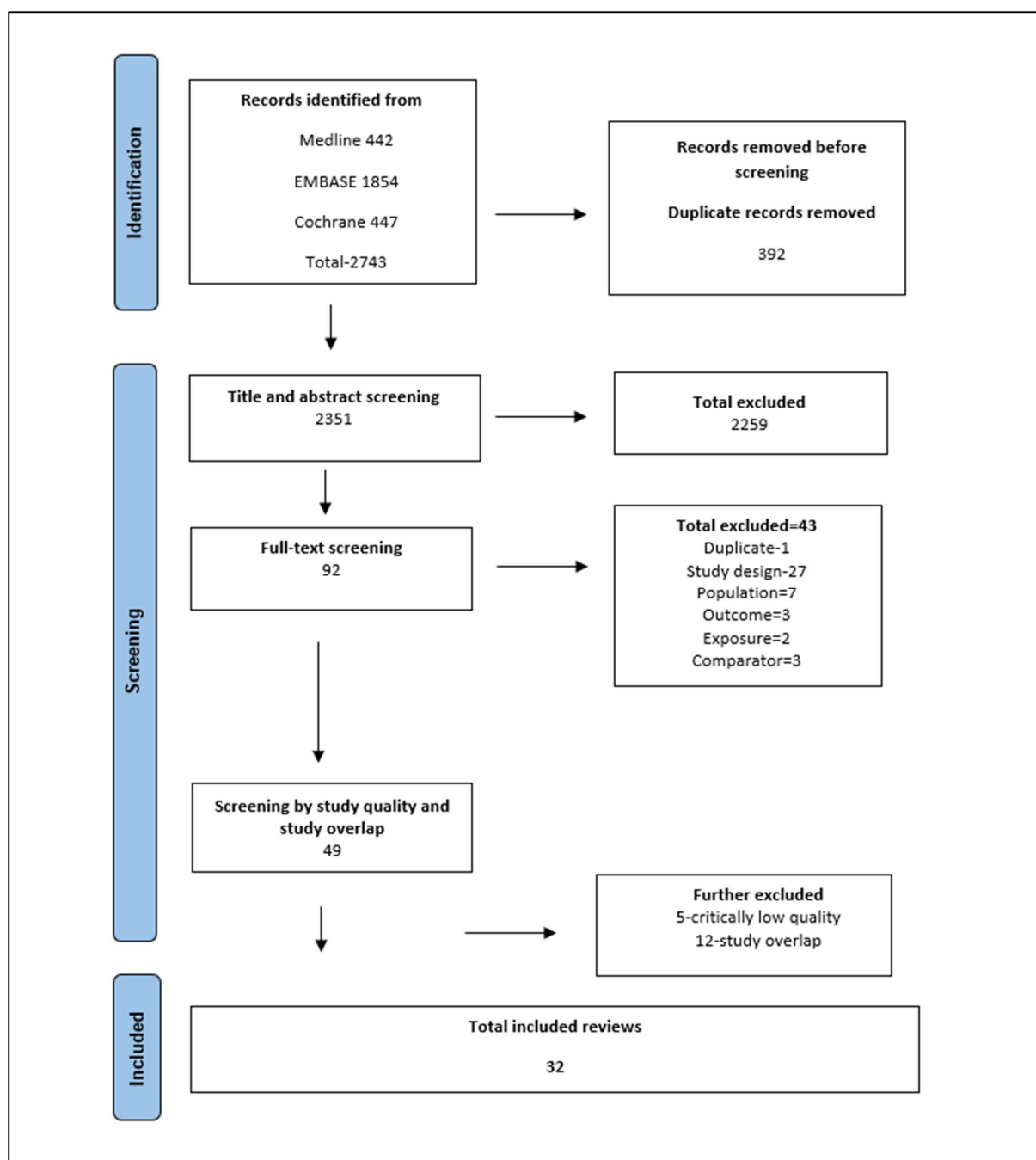


Figure 4.1 Preferred reporting items for systematic review and meta-analysis (PRISMA) flow diagram

Table 4.2: Characteristics of the included systematic reviews reporting the association of autoimmune conditions and adverse pregnancy outcomes

Exposure	Author & Year	Outcomes	Number of included primary studies	Quality assessment AMSTAR 2
Axial spondyloarthropathy	Maguire 2020	Pre-eclampsia, gestational diabetes mellitus, caesarean section, small for gestational age, intrauterine growth restriction, preterm birth, low birth weight	18	Moderate
Coeliac disease	Saccone 2016	Small for gestational age, low birth weight	10	Low
	Tersigni 2014	Recurrent miscarriage, small for gestational age	24	Low
	Arvanitakis 2022	Miscarriage, pre-eclampsia caesarean section, postpartum haemorrhage, stillbirth, intrauterine growth restriction, preterm birth	18	Moderate
Inflammatory bowel disease	Cornish 2007	Caesarean section, small for gestational age, stillbirth, preterm birth	13	Moderate
	O'Toole 2015	Caesarean section, small for gestational age, preterm birth, low birth weight	23	Moderate
	Leung 2021	Preterm birth, small for gestational age, low birth weight	72	Moderate
	Talavera 2021	Ectopic pregnancy	5	Moderate
	Tandon 2020	Ectopic pregnancy, miscarriage, caesarean section, gestational	53	Moderate

		hypertension, pre-eclampsia, placenta previa, placental abruption, termination of pregnancy		
Rheumatoid arthritis	Jiamin 2023	Miscarriage, pre-eclampsia, gestational diabetes mellitus, caesarean section, small for gestational age, intrauterine growth restriction, preterm birth, low birth weight, stillbirth	41	Moderate
Multiple sclerosis	Arafa 2021	Pre-eclampsia	8	Moderate
	*Modrego 2021	Preterm birth, low birth weight	17	Low
Myasthenia gravis	*Banner 2021	Caesarean section, preterm birth	32	Low
Psoriasis and psoriatic arthritis	Xie 2021	Psoriasis-Pre-eclampsia or eclampsia, gestational hypertension, gestational diabetes mellitus, caesarean section, small for gestational age, intrauterine growth restriction, preterm birth, low birth weight antepartum and postpartum haemorrhage, neonatal mortality Psoriatic arthritis- Ectopic pregnancy, pre-eclampsia or eclampsia, gestational hypertension, gestational diabetes mellitus, caesarean section, preterm birth	16	Moderate
Sjögren's syndrome	Upala 2015	Miscarriage, preterm birth, stillbirth, small for gestational age,	7	Moderate

		intrauterine growth restriction, fetal loss		
	Geng 2022	Miscarriage, preterm birth, low birth weight	9	Moderate
Systemic lupus erythematosus	Bundhun 2017	Ectopic pregnancy, miscarriage, pre-eclampsia, caesarean section, low birth weight, small for gestational age, preterm birth	11	Low
	Dong 2020	Pre-eclampsia	10	Moderate
	He W 2020	Miscarriage, pre-eclampsia, gestational diabetes mellitus, caesarean section, small for gestational age, intrauterine growth restriction, stillbirth, preterm birth, low birth weight, fetal loss	6	Moderate
	Wei 2017	Preterm birth	24	Moderate
Systemic sclerosis	Blagojevic 2020	Miscarriage, pre-eclampsia, intrauterine growth restriction, preterm birth, low birth weight	16	Low
Thyroid autoimmunity (both thyroid peroxidase antibody, and thyroglobulin antibody)	Chen 2011	Miscarriage	22	Low
	HeX 2012	Preterm birth	11	Moderate
	Li M 2016	Preterm birth	18	Low
	Lou 2020	Gestational diabetes mellitus	44	Low
	Dong 2020	Recurrent miscarriage, miscarriage	17	Low
Thyroid peroxidase antibody	Korevaar 2020	Preterm birth	19	Moderate
	Milandi 2020	Postpartum depression	5	Low
	Thangaratinam 2011	Miscarriage, preterm birth	36	Moderate
	Tong 2016	Intrauterine growth restriction, small for gestational age, low birth weight	7	Moderate
	Zhang, 2016	Adverse obstetric outcomes, miscarriage, preterm birth, gestational hypertension, placental	7	Low

		abruption, intrauterine growth restriction		
Type 1 diabetes mellitus	Yu 2017	Pre-eclampsia or eclampsia, gestational hypertension, caesarean section, small for gestational age, intrauterine growth restriction, preterm birth, low birth weight	100	Low

All the studies conducted a meta-analysis except the studies marked (*) are narrative analysis

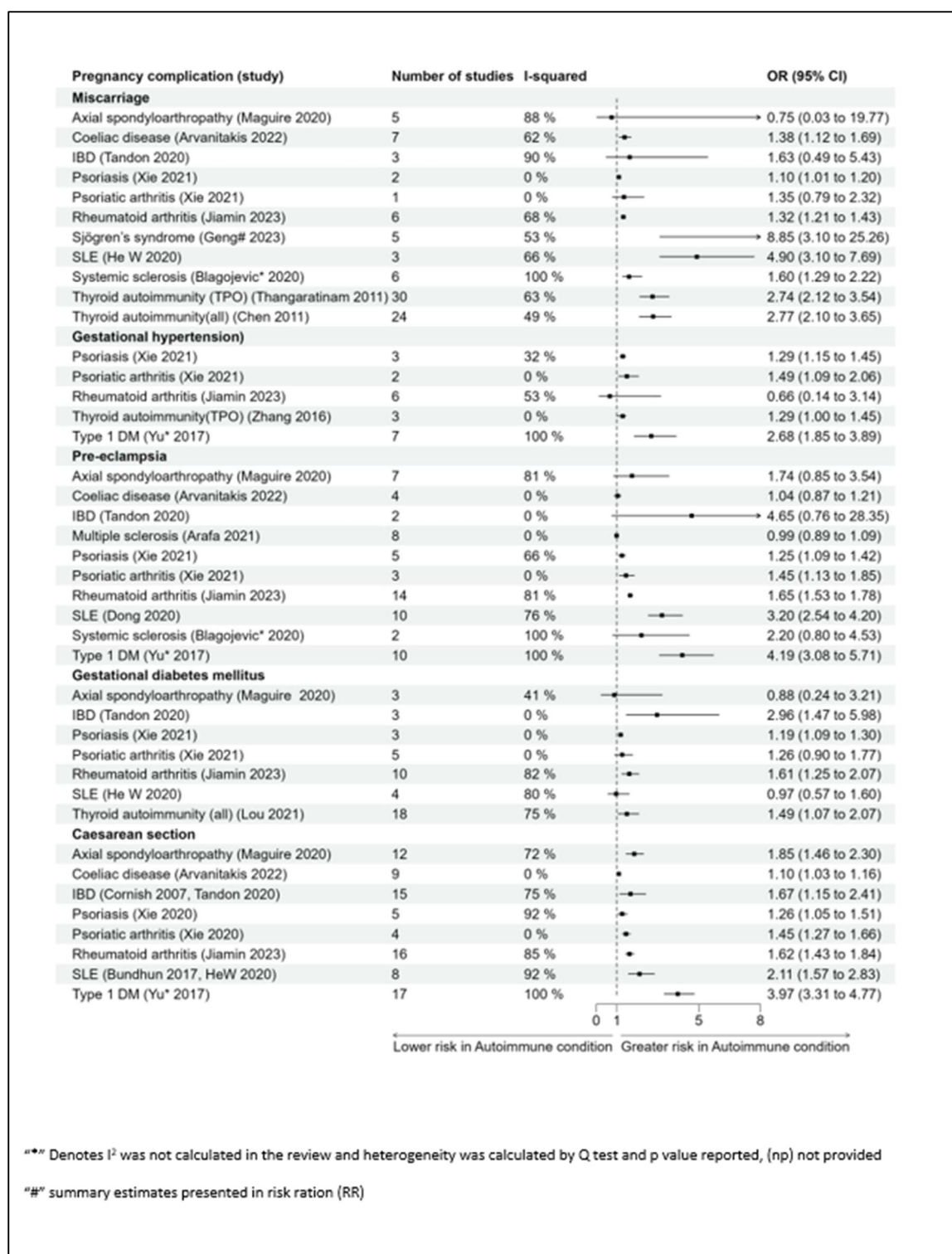
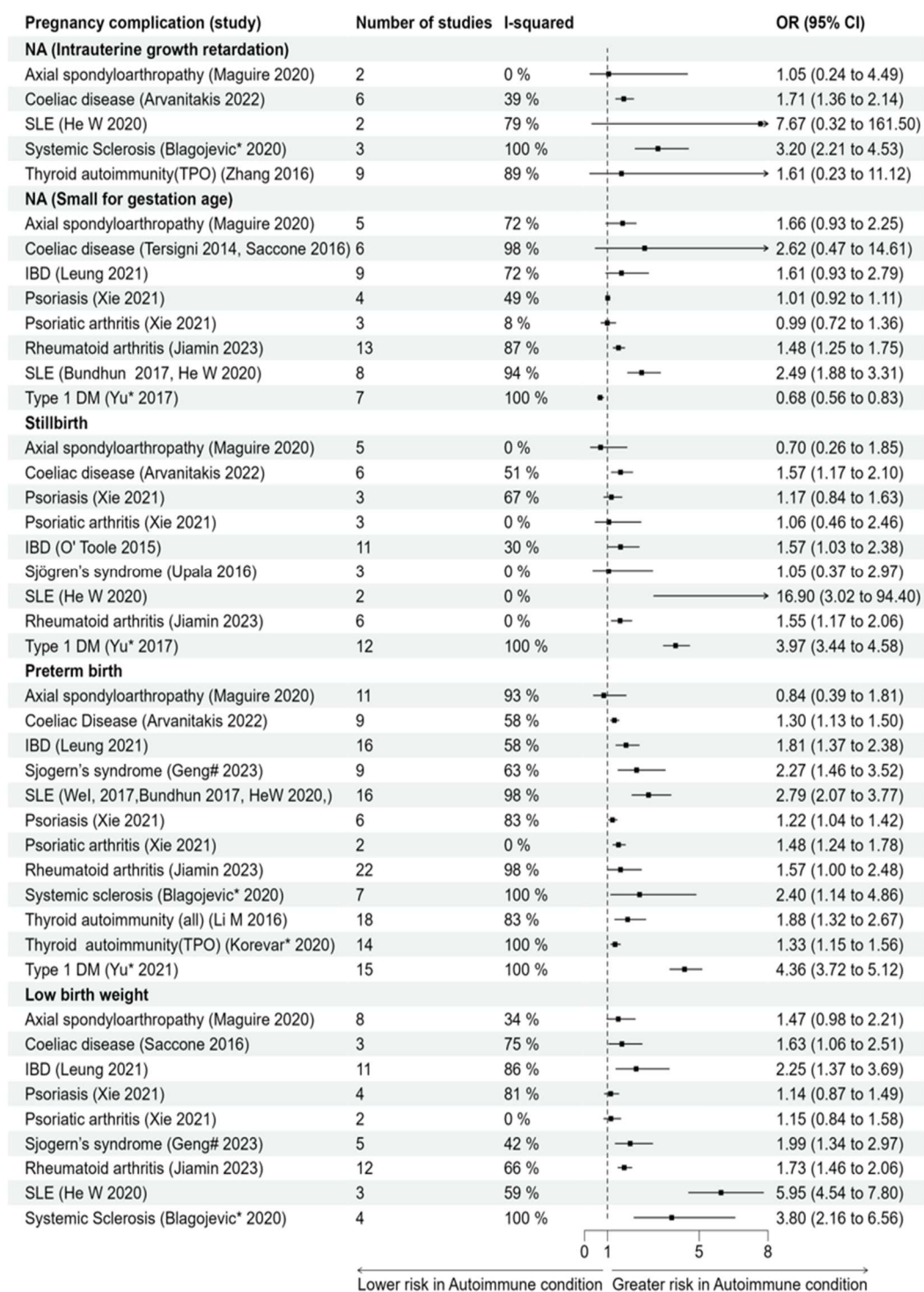


Figure 4.2 Forest plot for association of pregnancy complications and fetal/neonatal outcomes



“*” Denotes I^2 was not calculated in the review and heterogeneity was calculated by Q test and p value reported, (np) not provided

“#” summary estimates presented in risk ratio (RR)

Figure 4.3-Forest plot for association of pregnancy complications and maternal outcomes

Table 4.3: Heat map of the association of autoimmune conditions and adverse pregnancy outcomes

	AxSPa	Coeliac disease	IBD	Multiple sclerosis	Psoriasis	Psoriatic arthritis	Rheumatoid arthritis	Sjögren's syndrome	Systemic sclerosis	SLE	Thyroid autoimmunity	Type 1 DM
Miscarriage												
GHT												
Pre-eclampsia												
GDM												
CS												
IUGR												
SGA												
Stillbirth												
PTB												
LBW												
	Protective association with OR less than 1 and confidence intervals not crossing null											
	No association OR less than 1 and confidence interval crossing null											
	Association suggestive of adverse effect but not significant association – confidence interval crossing null											
	Clear association with OR greater than 1 but less than 2, confidence intervals not crossing null											
	Significant association OR above 2 and confidence interval on right side											
	Not reported in any of the included reviews											

GHT-gestational hypertension, GDM gestational diabetes mellitus, CS-Caesarean section, IUGR-intrauterine growth restriction, SGA-small for gestational age, PTB-preterm birth, LBW-low birth weight, AxSPa-axial spondyloarthritis, IBD-inflammatory bowel disease, SLE-systemic lupus erythematosus, T1DM-type 1 diabetes mellitus

Chapter end summary

This study was conducted to address the objective of compiling all the existing evidence on the association of autoimmune diseases and adverse pregnancy outcomes. The findings suggest that few of the autoimmune conditions like T1DM, SLE are strongly associated with the adverse pregnancy outcomes than others. Also identified gaps in the research with some inconsistent findings across systematic reviews and no existing evidence for few of the autoimmune disease risk in pregnancy like alopecia areata, vitiligo etc.

Chapter 5 Autoimmune diseases and risk of adverse pregnancy outcomes: a population-based cohort study of five million pregnancies in the UK

Chapter overview

The study reported in this chapter was conducted to address the objective: To carry out epidemiological studies using electronic primary care record databases (CPRD) to describe the association of autoimmune diseases in pregnancy and adverse pregnancy outcomes. The manuscript for this paper is submitted to Annals of rheumatic disease journal.

Title: Autoimmune diseases and risk of adverse pregnancy outcomes: a population-based cohort study of five million pregnancies in the UK

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5.1 Abstract

5.1.1 Introduction

With an increasing trend in the prevalence of maternal autoimmune diseases in pregnancy, there is need for evidence on the association between autoimmune diseases and pregnancy outcomes.

5.1.2 Methods

This population-based cohort study used data on pregnancies from primary care practices that contributed to the UK Clinical Practice Research Datalink (CPRD) database (Gold and Aurum) between 2000 and 2022, linked to Hospital Episode Statistics (HES). Modified Poisson regression with robust standard errors estimated adjusted relative risks (RR) and 95% confidence intervals (95% CI) assessing the association between 17 autoimmune diseases and 12 pregnancy outcomes, selected following literature review and expert consultation. Models were adjusted for demographic and comorbidity variables.

5.1.3 Results

5,239,383 pregnancies (2,863,863 women) in the CPRD pregnancy register and 2,057,150 births for obstetric outcomes (1,513,278 women) in the HES maternity tail were eligible for analysis. There was a higher risk of following antenatal outcomes- hyperemesis in Addison's disease aRR 3.72 (95% confidence interval 2.48-5.59), ectopic pregnancy in rheumatoid arthritis 1.50 (1.21-1.86), miscarriage in Sjogren syndrome 1.36 (1.09-1.70), gestational hypertension in type 1 diabetes mellitus (T1DM) 2.95 (2.77-3.15), pre-eclampsia/eclampsia in T1DM 3.56 (3.32-3.82) and GDM in Addison's disease (2.52,1.35-4.68),or systemic sclerosis (1.72,1.02-2.91). Among obstetric outcomes caesarean birth in women with

inflammatory bowel disease (IBD) 1.27 (1.22-1.31), small for gestational age in systemic lupus erythematosus (SLE) 2.45 (1.65-3.62), preterm birth in rheumatoid arthritis 1.47 (1.29-1.67), and stillbirth in SLE 1.93 (1.10-3.39) were increased. Mental health outcomes were also associated with most of the diseases studied but more profoundly in myasthenia gravis [(anxiety 3.05 (1.89-4.92), depression 1.77 (1.37-2.28)], SLE [anxiety 2.11 (1.67-2.67), depression 1.36 (1.22-1.53)] and in multiple sclerosis, [anxiety 1.76 (1.38-2.23), depression 1.94 (1.77-2.12)]. Several inverse associations were identified: for hyperemesis in systemic sclerosis 0.25 (0.08-0.78), SLE 0.74(0.58-0.95), myasthenia gravis 0.41 (0.17-0.98) and ectopic pregnancy in T1DM 0.53 (0.43-0.65). Multiple sclerosis was inversely associated with gestational hypertension and pre-eclampsia/eclampsia as well, 0.68 (0.52-0.89) and 0.65 (0.47-0.90) respectively.

5.1.4 Interpretation

Customised care protocols are likely to improve health outcomes for women with autoimmune diseases in maternity care by addressing the unique needs of each individual. Firstly, autoimmune diseases vary in their presentation and progression, making individualised management essential. Tailoring care plans ensures that treatments and interventions are specific to each woman's condition, severity, and health profile, helping to mitigate risks and improve both maternal and foetal outcomes. Secondly, women with autoimmune diseases are at increased risk for complications such as preterm birth, preeclampsia, and foetal growth restrictions. Customised care allows for early identification of high-risk pregnancies and the implementation of preventative measures or more frequent monitoring, reducing the likelihood of adverse outcomes. Thirdly, many women with autoimmune diseases require medication that may not always be safe during pregnancy. A

personalised care plan can adjust medications and closely monitor side effects, ensuring that both the mother's health and the safety of the foetal are prioritised. Autoimmune diseases can affect not only physical health, but also psychological well-being so mental health support is a crucial component of customised care. Offering tailored mental health support, including counselling, stress management, and peer support, can help women cope with the challenges of managing both pregnancy and chronic illness, fostering better overall well-being and improved health outcomes.

What is already known on this topic

- Women have higher susceptibility of autoimmune diseases which is influenced by genetic, hormonal, and environmental factors, indicating a critical need for deeper understanding of their specific health impacts.
- Autoimmune diseases, including SLE and rheumatoid arthritis, elevate the risk of pregnancy complications in women, such as miscarriage, preterm birth, gestational hypertension, and pre-eclampsia.

What this study adds

- This study aims to explore associations between wide range of autoimmune diseases (17) and various pregnancy complications (12), leveraging CPRD data to improve clinical management and maternal-foetal outcomes.
- Women with autoimmune conditions face significantly higher risks of adverse pregnancy outcomes, including hyperemesis gravidarum, ectopic pregnancy, miscarriage, gestational hypertension, PE/eclampsia, GDM, caesarean birth, SGA, preterm birth, stillbirth as well as adverse perinatal mental health, which was less studied.

- This study helps fill an evidence gap on pregnancy complications in women with less commonly studied autoimmune conditions, such as myasthenia gravis and Addison's disease.

How this study might affect research, practice, or policy

- Guidelines for managing pregnancy in women with autoimmune diseases focus primarily on medication, overlooking broader pregnancy risks. Expanding these guidelines to include comprehensive risk assessments and mental health considerations could improve antenatal care.
- This study underscores the need for mental health support in prenatal care for women with autoimmune conditions, as these diseases are linked to higher rates of anxiety and depression.

5.2 Background

Autoimmune diseases encompass a diverse range of conditions, typically associated with autoantibody development, chronic inflammation, and tissue damage [486]. Common autoimmune conditions include type 1 diabetes mellitus (T1DM), rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus (SLE), [135, 136, 487, 488]. Most autoimmune diseases disproportionately affect women with a higher incidence compared to men although the female: male ratio varies between conditions. For instance, when compared to men, women are nine times more likely to develop SLE and three times more likely to develop rheumatoid arthritis [487, 489]. The increasing trend in autoimmune diseases among women has been attributed to a combination of factors including genetic susceptibility, hormonal influences, and environmental factors, underscoring the need for a greater understanding of their impact on women's health [262, 490].

In an umbrella review, we investigated the relationship between autoimmune diseases and pregnancy complications [136]. For example, women with SLE are at a higher risk of miscarriage and preterm birth [351, 354, 368, 416]. Similarly, rheumatoid arthritis has been associated with an increased incidence of gestational hypertension and pre-eclampsia [314, 316], and T1DM are linked to the development of anxiety and depression during pregnancy [441, 491]. In the UK context, a study using the Clinical Practice Research Datalink (CPRD) found that women with psoriasis or T1DM had higher rates of miscarriage or preterm birth and women with coeliac disease or inflammatory bowel disease (IBD) are at higher risk of postpartum haemorrhage compared to women without these health conditions [492-496]. Furthermore, women with autoimmune diseases are at a 30% higher risk of developing a mental health condition [34, 497, 498]. We have identified an important knowledge gap in our understanding of pregnancy complications in women with less common autoimmune diseases such as myasthenia gravis or Addison's disease and rarer outcomes in common autoimmune diseases.

This study aims to comprehensively analyse the association between a range of autoimmune diseases and key pregnancy complications, including hyperemesis gravidarum, ectopic pregnancy, miscarriage, gestational hypertension, pre-eclampsia/eclampsia (PE/eclampsia), gestational diabetes mellitus (GDM), preterm birth, and newly developed mental health conditions during pregnancy (anxiety or depression). Utilising the large and diverse UK CPRD database [246, 247], this research will offer novel insights into the specific risks posed by different autoimmune conditions during pregnancy. It is expected that the findings will enhance our understanding of how autoimmune diseases impact pregnancy, thereby informing clinical management practices to improve maternal and foetal health outcomes.

5.3 Methods

Ethical approval for this study was approved by Independent Scientific Advisory Committee for research involving CPRD data (protocol no. 23_002650) [499, 500]. The study results are reported as per the STROBE (Strengthening the reporting of observational studies in epidemiology) statement [250] .

5.3.1 Study design and data sources

This is a retrospective cohort study utilising data from the CPRD, a large UK-based primary care database. The CPRD contains anonymised patient-level data, including demographics, symptoms, diagnoses, drug prescriptions, physical measurements, and laboratory test results [246, 247]. The study combines data from two CPRD databases: CPRD Gold and CPRD Aurum, which are linked to general practices using VISION and EMIS software, respectively. CPRD Gold includes records from 985 general practices, while CPRD Aurum covers 1,489 practices, representing approximately 5% and 20% of the UK population respectively. Both CPRD Gold and CPRD Aurum maintain Pregnancy Registers derived from electronic health records (EHRs) in primary care, consolidating information on pregnancy dates, related covariates, and outcomes. For this study, maternal primary care records from these databases, along with their respective Pregnancy Registers, were used to gather data on exposure to pre-existing autoimmune diseases, relevant covariates before pregnancy, and pregnancy outcomes [205, 206, 248].

We utilised CPRD linked births recorded in the Hospital Episodes Statistics (HES) maternity tail dataset to accurately capture obstetric outcomes. Additionally, secondary care outcomes were obtained using linked HES Admitted Patient Care data, which captures inpatient records from general National Health Service hospitals [205, 206, 246-248]. HES Admitted

Patient Care data provides diagnostic records for secondary care inpatient admissions, but is only available for England, thus restricting the analysis to pregnancies within England. Data on exposure, outcomes and covariates were extracted using the data extraction for epidemiological research (DExtER) tool, which facilitates extraction based on predefined parameters [249].

5.3.2 Study Population

There were two study cohorts based on the types of outcomes studied.

(i) Pregnancy cohort

This cohort included pregnant women aged 15 to 49 from the Pregnancy Register between 2000 to 2022. It was used to study antenatal outcomes and mental health outcomes, which were ascertained in both primary care and linked HES secondary care records. This cohort included pregnant women who were not eligible for HES linkage. Pregnancies were the unit of analysis.

(ii) Birth cohort

This cohort included pregnant women aged 15 to 49, who had a birth recorded in the HES maternity tail dataset between 2000 to 2022. It was used to study obstetric outcomes including preterm birth, small for gestational age (SGA), caesarean birth and stillbirth. These outcomes were ascertained from HES records. Births were the unit of analysis. Women identified in the HES maternity tail were linked back to primary care data to ascertain their autoimmune disease exposure status. This cohort is limited to England.

5.3.3 Data quality

Pregnancies and births were the units of analysis, to capture key obstetric outcomes such as preterm birth, SGA, caesarean section, and stillbirth. To ensure data quality, pregnancies were included after the mother's record received an acceptable patient flag from CPRD and after a minimum of one year of registration with a practice. All eligible women meeting these criteria were included in the study [246, 247]. The cohort selection criteria are detailed in Figure 5.1 and 5.2 and supplementary figure 5.1-5.4.

5.3.4 Exposure Definition

Autoimmune diseases were identified using primary care records based on diagnostic codes (Read and SNOMED CT in CPRD Gold and Aurum, respectively) [251, 252]. The study encompassed 17 autoimmune conditions; (1) Addison's disease, (2) alopecia areata, (3) Ankylosing spondylitis (4) coeliac disease, (5) inflammatory bowel diseases (IBD) including Crohn's disease and ulcerative colitis, (6) Grave's disease, (7) Hashimoto's thyroiditis, (8) multiple sclerosis, (9) myasthenia gravis, (10) psoriasis, (11) psoriatic arthritis (12) rheumatoid arthritis, (13) Sjögren's syndrome, (14) SLE, (15) systemic sclerosis, (16) T1DM and (17) vitiligo. Selection of these conditions was based on their prevalence in women of reproductive age, informed by literature review and expert consultation [501]. For the ease of description, these diseases are grouped according to the organ system namely systemic inflammatory disorders, dermatological disorders, endocrine disorders, gastrointestinal disorders, musculoskeletal disorders and neurological disorders.

5.3.5 Outcomes

Data from both CPRD and HES were used to ascertain the outcomes of interest. Pregnancy complications were identified using ICD-10 codes from HES records, as well as Read codes and SNOMED CT from CPRD clinical files. Additionally, the prescription of relevant medications was used to capture outcomes such as gestational hypertension, PE/eclampsia, GDM, and perinatal anxiety and depression. Pregnancy episodes in women with pre-existing diagnoses of hypertension, type 1 or 2 diabetes, anxiety, or depression recorded in CPRD at the start of pregnancy were excluded from the analysis of corresponding gestational outcomes (e.g., gestational hypertension, PE/eclampsia, GDM, perinatal anxiety, and perinatal depression). Other key outcomes included preterm birth, SGA, caesarean section, and stillbirth. Selection of Read, ICD-10 code lists was performed using an inhouse software platform called Code Builder [249], with systematic searching of existing code lists, and through clinical knowledge and discussion methods used in our previous publications. The definitions and list of codes used for outcome ascertainment are provided in supplementary table 5.1-5.15.

5.3.6 Covariates

Covariates considered for adjustment include maternal age at the start of pregnancy (categorised into 5-year age bands), year of pregnancy, ethnicity, Index of Multiple Deprivation (IMD) in quintiles, latest BMI (Body mass index) prior to conception (or up to 16 weeks from the booking date if available), preconception smoking status (categorised as non-smoker, ex-smoker and current smoker), gravidity and a list of key comorbidities (hypertension, type 2 diabetes mellitus, anxiety, depression, psychosis). Ethnicity was identified using relevant Read codes from primary care records and was categorised as (1)

White, (2) Asian, (3) Black and (4) mixed or multiple ethnic groups or (5) other ethnic groups.

Primary care linked English IMD data provided a relative measure of deprivation based on seven different domains [502]. Pre-gravid BMI was identified as the latest BMI measured in primary care at least a year before the pregnancy start date and was categorised according to WHO (World health organisation) standards as underweight ($< 18.5 \text{ kg/m}^2$), BMI $< 25 \text{ kg/m}^2$, overweight ($25\text{--}30 \text{ kg/m}^2$) and obese ($>30 \text{ kg/m}^2$).

A separate missing category was created for those with missing data on ethnicity, deprivation, number of babies born within the delivery and pre-gravid BMI. The comorbidities were identified from primary care through relevant Read codes or Snomed CT codes.

5.3.7 Statistical analysis

Baseline characteristics were described using median and interquartile range were for non-normally distributed continuous variables, and frequency and percentage for categorical variables, stratified by exposure of any autoimmune disease. Modified Poisson regression models with the log link function and robust standard errors to account for repeat pregnancies was used to estimate relative risks (RR) and 95% confidence intervals (95% CI) for the association between autoimmune disease and out-comes of interest. Models were fitted for each autoimmune disease and for any autoimmune disease, for each outcome. Models were adjusted for potential confounders, demographic variables (age, ethnicity, socioeconomic status), clinical factors (smoking status, BMI, comorbidities), and gravidity. Analysis was performed in Stata IC version 17 (StataCorp) [9] and R studio (12.1) [257].

5.4 Results

Total of 5,239,383 pregnancies in the CPRD pregnancy register and 2,485,366 births in the HES maternity tail met the data quality criteria. Among them 188,682 pregnancies of 106,024 women in pregnancy cohort and 84,221 births of 63,972 women had a diagnosis of autoimmune diseases. The cohort selection is enumerated in flowchart 5.1 and 5.2. Baseline characteristic tabulated in table 5.1.

Women with autoimmune disease were older at the time of pregnancy compared to women without autoimmune disease; median 31.1 vs 29.7 years. Women with autoimmune diseases were more likely to be affluent (IMD 5 (least deprived quintile): 15.8% vs 14.5%), white (57.1% vs 49.8%) have a higher BMI and gravidity. All the comorbidities studied were higher in the cohort of pregnancies of women with autoimmune diseases.

Exposure to any of the autoimmune conditions and risk of pregnancy outcomes:

Women with at least one autoimmune disease had a statistically significant higher risk of all antenatal pregnancy complications studied. Autoimmune disease was strongly associated with the following outcomes: PE/eclampsia aRR (adjusted relative risk) 1.30 (95% confidence intervals 1.26-1.34), gestational hypertension aRR 1.24 (1.20-1.28), GDM 1.08 (1.04-1.12), hyperemesis gravidarum aRR 1.08 (1.05-1.11), miscarriage aRR 1.06 (1.05-1.08) and ectopic pregnancy aRR 1.04 (1.00-1.09).

For obstetric outcomes, women with autoimmune diseases were more likely to have caesarean birth aRR 1.20 (1.18-1.21), preterm birth aRR 1.45 (1.41-1.48), stillbirth aRR 1.11 (1.00-1.23) and SGA 1.15 (1.08-1.22).

Women with autoimmune disease had a higher risk of adverse mental health conditions during pregnancy; anxiety aRR 1.25 (1.21-1.31) and depression aRR 1.20 (1.19-1.22).

Individual autoimmune diseases are explored as risk factors for pregnancy complications, and the results are shown in the forest plot stratified by outcomes of interest in Figure 3 and supplementary file figure 5-22 and table 17.

Systemic inflammatory disorders

Sjogren's syndrome was associated with a higher risk of miscarriage aRR 1.66 (1.02-2.70) and depression during pregnancy aRR 1.43 (1.10-1.85). SLE was associated with an increased risk of gestational hypertension aRR 1.51 (1.21-1.87) and PE/eclampsia aRR 1.48 (1.15-1.90).

Women with SLE also had an increased risk of total caesarean birth aRR 1.22 (1.13-1.33), including emergency aRR 1.24 (1.09-1.39) and elective [1.20 (1.04-1.38)], nearly twice the risk for preterm birth aRR 2.12 (1.86-2.43), SGA aRR 2.45 (1.65-3.62) and stillbirth aRR 1.82 (1.12-1.84). Risk of anxiety and depression during pregnancy was also higher in women with SLE aRR 2.11 (1.67-2.67) and aRR 1.36 (1.22-1.53)], respectively. However, women with SLE had a 25% lower risk of hyperemesis gravidarum aRR 0.74 (0.58-0.95).

Women with systemic sclerosis had approximately two times greater risk of preterm birth aRR 2.34 (1.67-3.27) and GDM aRR 1.72 (1.02 -2.91). Women with systemic sclerosis were at a 75% reduced risk of hyperemesis gravidarum aRR 0.25 (0.08-0.78) compared to women without systemic sclerosis.

Dermatological diseases

Women with alopecia areata had a higher risk of hyperemesis gravidarum aRR 1.32 (1.20-1.45), miscarriage, aRR 1.06 (1.00-1.13) gestational hypertension aRR 1.12 (1.00-1.27), GDM

aRR 1.16 (1.02-1.31), depression in pregnancy aRR 1.12 (1.00-1.27), aRR SGA 1.36 (1.22-1.53) and preterm birth aRR 1.25 (1.14-1.38).

Psoriasis in pregnancy was associated with a slightly higher risk of developing most of the outcomes studied; hyperemesis gravidarum aRR 1.04 (1.00-1.08), ectopic pregnancy aRR 1.08 (1.02-1.15), miscarriage aRR 1.04 (1.02-1.06), gestational hypertension, aRR 1.08 (1.03-1.13), PE/eclampsia aRR 1.07 (1.02-1.13), GDM aRR 1.05 (1.00-1.10), and SGA babies aRR 1.12 (1.03-1.22). Women with psoriasis were more likely to have a caesarean birth 1.02 (1.00-1.05) and preterm birth aRR 1.04 (1.00-1.08). Women with psoriasis also had a higher risk of perinatal mental health conditions; anxiety aRR 1.11 (1.05-1.18) and depression aRR 1.14 (1.11-1.16).

Women with vitiligo were more likely to develop hyperemesis gravidarum aRR 1.15 (1.03-1.29), miscarriage aRR 1.07 (1.00-1.14), gestational hypertension aRR 1.19 (1.04-1.35) and GDM aRR 1.16 (1.01-1.34).

Endocrine disorders

Women with Addison's disease had a four-fold higher risk of having SGA baby aRR 4.29 (1.93-9.57) and had two to three times higher risk of hyperemesis gravidarum aRR 3.72 (2.48-5.59), gestational hypertension aRR 2.21 (1.28-3.80), PE/eclampsia 2.20 (1.16-4.17), aRR GDM 2.52 (1.35-4.68) and preterm birth aRR 2.44 (1.58-3.75). They were also at higher risk of caesarean birth aRR 1.50 (1.16-1.94).

Women with Grave's disease had an increased risk of hyperemesis gravidarum aRR 1.33 [1.21-1.47], miscarriage aRR 1.09 (1.03-1.15), gestational hypertension aRR 1.26 (1.12-1.41), PE/eclampsia 1.19 (1.04-1.37), GDM aRR 1.34 (1.20-1.50), caesarean birth aRR 1.12 (1.07-

1.18), and preterm birth aRR 1.23 (1.11-1.36). Grave's disease was also associated with increased anxiety aRR 2.04 [1.80-2.32) and depression aRR 1.64 (1.46-1.83) during pregnancy. Hashimoto's thyroiditis was linked to a higher risk of mental health conditions during pregnancy, anxiety aRR 1.26 [0.90-1.77) and depression aRR 1.16 [1.01-1.32).

There was more than fivefold higher risk of preterm birth in mothers with T1DM, aRR 5.18 (5.00-5.36). There was also higher risk of caesarean birth aRR 2.50 (2.45-2.56) including both elective aRR 2.62 (2.52-2.74) and emergency aRR 2.39 (2.30-2.49). Pregnancies of women with T1DM were also around three times more likely to develop gestational hypertension, PE/eclampsia, and stillbirth aRR 2.95 (2.77-3.15), aRR 3.56 (3.32-3.82) and aRR 2.64 (2.09-3.33), respectively. Risk of miscarriage aRR 1.25 (1.20-1.31) hyperemesis gravidarum aRR 1.16 (1.07-1.26), anxiety aRR 1.16 (1.02-1.32) and depression aRR 1.46 (1.40-1.53) in pregnancy were also higher in women with T1DM. Risk of ectopic pregnancy was almost 50% lower in pregnancies of women with T1DM aRR 0.53 (0.43-0.65).

Gastrointestinal diseases

Women with coeliac disease had a higher risk of developing hyperemesis gravidarum, anxiety and depression in pregnancy as compared to women without coeliac disease with aRR 1.14 (1.00-1.31), aRR 1.65 (1.38-1.97), and aRR 1.21 (1.12-1.31), respectively. The risk of caesarean birth aRR 1.11 (1.04-1.18) was higher in pregnancies of women with coeliac disease, and this was significantly higher for elective caesarean section aRR 1.16 (1.05-1.28) but not for emergency caesarean birth aRR 1.08 (0.99-1.17). There was also a twenty percent higher risk of preterm birth for women with coeliac disease compared to women without coeliac disease aRR 1.26 (1.12-1.42).

Women with IBD had an increased risk of ectopic pregnancy, with aRR of 1.17 (1.02-1.34), and of PE/eclampsia, aRR 1.12 (1.00-1.26). These risks were notably higher in women with Crohn's disease; ectopic pregnancy aRR 1.33 (1.11-1.60), and PE/eclampsia aRR 1.23 (1.05-1.45). However, for women with ulcerative colitis, the associations were not statistically significant; ectopic pregnancy aRR 0.92 (0.73-1.15) and PE/eclampsia aRR 1.03 (0.86-1.22). Pregnancies in women with IBD also had a higher likelihood of caesarean birth, particularly elective, and were more likely to result in preterm birth, with aRR of 1.27 (1.22-1.31) and aRR 1.26 (1.17-1.36), respectively. The risk of anxiety or depression was elevated in women with IBD, with aRR 1.29 (1.13-1.46) and aRR 1.22 (1.16-1.28) respectively, and was similarly increased in both Crohn's disease and ulcerative colitis. Interestingly, women with Crohn's disease had 30% lower risk of GDM aRR 0.68 (0.55-0.84), although no significant associations with GDM were observed in women with ulcerative colitis or IBD overall compared to those without these conditions.

Musculoskeletal disorders

There was almost a two-fold higher risk of developing anxiety in pregnancy aRR 1.78 (1.39-2.27) in women with ankylosing spondylitis. Risk of ectopic pregnancy and caesarean birth were also slightly higher in women with ankylosing spondylitis aRR 1.17 (1.00-1.37) and aRR 1.27 [1.13-1.42], respectively.

Women with psoriatic arthritis had a 30% greater risk of developing GDM aRR 1.33 (1.03-1.71). Higher risk for preterm birth aRR 1.37 (1.12-1.69) and caesarean birth aRR 1.19 (1.08-1.32), with a higher likelihood of emergency caesarean aRR 1.27 [1.11-1.46) was also observed.

Women with rheumatoid arthritis had a higher risk of hyperemesis gravidarum aRR 1.50 (1.21-1.86) and preterm birth aRR 1.53 [1.33-1.76]. They were also more likely to develop PE/eclampsia aRR 1.24 [1.03-1.51], have a caesarean birth aRR 1.23 (1.16-1.31), have SGA babies aRR 1.42 (1.00-2.02) and develop depression during pregnancy aRR 1.21 (1.11-1.32).

Neurological disorders

Women with multiple sclerosis had nearly double the risk of mental health conditions during pregnancy, depression aRR 1.94 (1.77-2.12) and anxiety aRR 1.76 (1.38-2.23). They also have higher risk of elective caesarean birth aRR 1.21 (1.06-1.39) and preterm birth aRR 1.25 (1.06-1.48). On the other hand, multiple sclerosis was inversely associated with gestational hypertension aRR (0.68 [0.52-0.89) and PE/eclampsia aRR 0.65 [0.47-0.90).

Women with myasthenia gravis had a markedly higher risk of anxiety aRR 3.05 (1.89–4.92) and depression aRR 1.77 (1.37–2.28) during pregnancy. They also experienced a 30% to 60% increased risk of miscarriage aRR 1.30 (1.00–1.69) and a 60% higher risk of preterm birth aRR 1.60, (1.04–2.46). In contrast, pregnancies in women with myasthenia gravis were less likely to be affected by hyperemesis gravidarum aRR 0.41 (0.17-0.98).

5.5 Discussion

Our study provides evidence of a significantly higher risk of all adverse pregnancy outcomes (12) hyperemesis gravidarum, ectopic pregnancy, miscarriage, gestational hypertension, PE/eclampsia, GDM, caesarean birth, SGA, preterm birth, stillbirth, perinatal anxiety, and depression in women with autoimmune conditions.

Hyperemesis has been associated with all dermatological disorders, endocrine disorders, and coeliac disease. Ectopic pregnancy risk is elevated in women with psoriasis, IBD and

rheumatoid arthritis. Miscarriage is linked to all dermatological conditions, Sjögren's syndrome, IBD, and myasthenia gravis. Gestational hypertension and PE/eclampsia is more common in women with dermatological and endocrine disorders, systemic sclerosis, IBD, and rheumatoid arthritis. GDM is primarily linked Addison's disease, Grave's disease, psoriasis and psoriatic arthritis.

Preterm birth occurs more frequently across most conditions studied, except for Sjögren's syndrome, vitiligo, Hashimoto's thyroiditis, and multiple sclerosis. Women with SLE, alopecia areata, psoriasis, Addison's disease, and rheumatoid arthritis have an increased risk of having SGA babies. caesarean section rates are higher for most conditions except Sjögren's syndrome, systemic sclerosis, alopecia areata, vitiligo, and neurological disorders. Stillbirth risk is only notably elevated in women with T1DM.

Mental health conditions, perinatal anxiety and depression are more prevalent in women with multiple sclerosis and myasthenia gravis. Inversely, systemic sclerosis, SLE, and myasthenia gravis are linked to a lower risk of hyperemesis gravidarum. T1DM is associated with a reduced risk of ectopic pregnancy, while Crohn's disease (a form of IBD) lowers the risk of GDM. Additionally, multiple sclerosis appears to offer some protection against gestational hypertension and PE/eclampsia.

This study addressed the evidence gap particularly for less commonly studied autoimmune conditions such as myasthenia gravis and Addison's disease, in the context of pregnancy complications [136].

5.5.1 Findings in the context of other literature

Our findings align with previous research indicating increased risks of adverse pregnancy outcomes among women with autoimmune diseases. This is the first study to report associations for less common autoimmune diseases including Addison's disease, myasthenia gravis and ankylosing spondylitis. Sjögren's syndrome, which predominantly affects women [503], has not been extensively studied but is associated with miscarriage [504]. SLE has known associations with miscarriage and hypertension during pregnancy [351, 354, 368, 416] that were confirmed in this study. This study confirms the associations of psoriasis, widely studied in relation to pregnancy complications, with miscarriage and gestational hypertension or pre-eclampsia in this study, although it did not confirm a previously suggested link to GDM [367, 424, 440]. Less commonly studied, alopecia areata and vitiligo have also been associated with miscarriage and gestational hypertension, which supports the results of previous observational studies [453, 457, 458, 461]. Systemic sclerosis, SLE and myasthenia gravis were associated with reduced risk of hyperemesis in pregnancy, a novel finding, that requires further research.

Among endocrine autoimmune diseases, T1DM has been extensively studied, particularly regarding its association with adverse pregnancy outcomes. This study aligns with previous research indicating an increased risk of gestational hypertension in women with T1DM. However, this study suggests an inverse association between T1DM and ectopic pregnancy, a finding that warrants further investigation [365, 441]. Grave's disease and Hashimoto's thyroiditis have been less studied, but existing literature suggests that thyroid autoimmunity can lead to pregnancy complications such as miscarriage and gestational hypertension [369]. This study presents the pregnancy outcomes of these two autoimmune conditions

separately. Research on the association between Addison's disease and pregnancy complications is limited. However, few studies indicate an increased risk of adverse obstetric outcomes in women with Addison's disease [425, 437, 460]. This study reports a strong association of Addison's disease with hyperemesis gravidarum, gestational hypertension, GDM, and depression along with known adverse obstetric outcomes.

Rheumatoid arthritis is the most extensively studied musculoskeletal disease and the association with miscarriage, gestational hypertension, and GDM was also reported in earlier literature [314, 316]. Previous limited studies on ankylosing spondylitis and pregnancy complications have found no significant associations [505, 506] but this study reports association with miscarriage and anxiety in pregnancy. Earlier reviews suggested a higher risk of hypertension in pregnancy for women with psoriatic arthritis with no conclusive findings on GDM [400, 440], however this study reports an increased risk of developing GDM and no association with hypertension in women with psoriatic arthritis., this difference could be due to difference in cohort characteristics.

Previous studies have reported an association of coeliac disease with miscarriage and GDM with IBD [507]. Results from this study offer concordance with the miscarriage association but not with GDM. In this study, significant effects on mental health during pregnancy were observed across all autoimmune gastrointestinal diseases studied which is consistent with recent research [508, 509].

Few studies have explored the effect of multiple sclerosis on pregnancy complications, but only for selected complications and with inconclusive results [355, 376]. Our study explores the association with 12 adverse pregnancy outcomes and reported higher risk of adverse perinatal mental health and a novel finding of reduced risk of hypertension in pregnancy.

Whereas limited literature exists for association with myasthenia gravis which suggests association with PE/eclampsia which was not observed in this study [356]. Our study extends these findings by also identifying significant associations with anxiety, and depression, particularly in myasthenia gravis and multiple sclerosis; areas that have been underexplored in previous research. In the current study higher risk of mental health outcomes is also reported in diseases like coeliac disease, IBD and T1DM.

5.5.2 Possible Mechanism

The mechanisms behind adverse pregnancy outcomes are complex, involving physiological changes, treatment regimens, and immune responses. Chronic inflammation and immune dysregulation can impair placental function, increasing the risks of PE/eclampsia, fetal growth restriction, premature birth, and low birth weight. Effective management of inflammation is essential to prevent these complications [510, 511].

Conditions such as IBD, coeliac disease, and multiple sclerosis further disrupt placental function through cytokine imbalances and inflammation, with nutritional deficiencies exacerbating these risks [512-516]. Increased proinflammatory cytokines in autoimmune conditions like psoriasis and vitiligo disrupt immune balance during pregnancy, leading to higher rates of miscarriage and lower live birth rates [350, 354, 424].

Hyperglycaemia in T1DM induces oxidative stress and immune dysregulation, heightening the likelihood of PE/eclampsia and miscarriage [517-519]. Thyroid autoimmunity negatively impacts the fetal-maternal interface, resulting in miscarriage and premature birth due to altered cytokine expression and thyroid hormone levels. Additionally, Addison's disease is associated with preterm birth due to insufficient cortisol replacement therapy [519, 520].

Certain autoantibodies can directly lead to pregnancy complications. For instance, anti-Ro/SSA and anti-La/SSB antibodies are linked to neonatal lupus syndrome and congenital heart block, potentially causing intrauterine death in severe cases [521-523]. Anti-phospholipid antibodies, which impair placental function, increase the risk of pre-eclampsia, fetal growth restriction, and pregnancy loss [523-530].

Women with Addison's disease are at higher risk of hyperemesis gravidarum due to adrenal insufficiency, hormonal fluctuations, and metabolic stress during pregnancy. Addison's disease causes cortisol and aldosterone deficiencies, vital for blood pressure, glucose, and electrolyte balance. During pregnancy, increased cortisol production is needed to manage stress, but women with Addison's disease lack this response, making them more vulnerable to severe nausea and vomiting [531]. Aldosterone deficiency also leads to sodium loss, dehydration, and hypotension, worsening hyperemesis gravidarum symptoms. Hormonal changes, particularly elevated human chorionic gonadotropin (hCG) levels, may exacerbate nausea in those with adrenal insufficiency due to altered hypothalamic-pituitary-adrenal (HPA) axis function. Rising progesterone levels, which antagonise glucocorticoid receptors, further impair cortisol effectiveness [531, 532].

The treatment of autoimmune conditions during pregnancy requires balancing inflammation control with potential risks to both mother and foetus. Corticosteroids, while effective at managing inflammation, can increase the risk of GDM, hypertension, pre-eclampsia, and intrauterine growth restriction (IUGR) [533]. Some immunosuppressive drugs such as methotrexate or mycophenolate mofetil are contraindicated in pregnancy and may increase the risk including preterm birth, low birth weight, congenital abnormalities, and neonatal complications such as immunosuppression or infections [511, 534-536]. Therefore, careful

consideration of treatment options is essential, with a thorough risk-benefit analysis weighing medication exposure against the consequences of untreated inflammation. Involving the healthcare team, the patient, and their support network in discussions ensures that both maternal and fetal risks are properly addressed [537].

5.5.3 Implications for research and practice

Despite updated guidelines for managing pregnant patients with autoimmune diseases, most guidelines for systemic inflammatory disorders and musculoskeletal diseases [135, 480, 538, 539] focus on medication management. The existing guidelines need to have their scope extended to ensure evidence on each of the conditions is incorporated into antenatal risk that includes risk assessment for preventing adverse pregnancy outcomes in women with these conditions. Existing guidelines for thyroid related autoimmune diseases like Grave's disease and Hashimoto disease describe approaches to reducing the risk of miscarriage and preterm birth with little focus on associated complications like gestational hypertension. On the other hand, the guidelines for T1DM [540-542] focus mainly on management of the disease in pregnancy which can be expanded to potential risk mitigation for all the related complications. Similarly, recommendations are in place for mode of birth and medication use for women with IBD but not for other possible adverse outcomes [543]. Existing guidelines on multiple sclerosis and myasthenia gravis need to add the effect of the disease on mental health in pregnancy which is evident from this study [544, 545]. No pregnancy specific guidelines exist for diseases like coeliac diseases, alopecia areata, vitiligo and Addison's disease. While guidelines for specific autoimmune diseases exist, they often fail to reflect the full range of potential adverse pregnancy outcomes. Rather than focusing

solely on management, these guidelines should alert clinicians to the increased risks associated with these conditions and provide more comprehensive risk assessments.

Our study also highlights the importance of considering the psychosocial aspects of autoimmune diseases during pregnancy. The significant associations we found with anxiety and depression underscore the need for comprehensive prenatal care that includes mental health support. Autoimmune diseases can be exacerbated by stress, and pregnancy itself is a period of heightened emotional vulnerability [546]. Thus, integrating mental health support into routine prenatal care for women with autoimmune diseases could mitigate some of these adverse outcomes.

Our study significantly advances the understanding of the impact of autoimmune diseases on pregnancy outcomes and extends these findings by also identifying significant associations with anxiety and depression, particularly in conditions like Coeliac disease, IBD, T1DM and myasthenia gravis, areas that have been underexplored in previous research. The associations identified between a range of autoimmune conditions and pregnancy complications emphasize the need for targeted management strategies to improve maternal and fetal health. Clinicians should be aware of these risks and adopt a multidisciplinary approach to care that includes monitoring for both physical and mental health complications. Further research is needed to explore the biological mechanisms driving these associations and to develop interventions that can mitigate the risks for this vulnerable population.

5.5.4 Strengths and limitations

The strengths of our study include the use of a large, representative cohort (106,024 women with autoimmune diseases) within the robust CPRD dataset and pregnancy register, which

provided detailed longitudinal health data. The nature of the available data allowed us to control for a wide range of potential confounders, including age, socioeconomic status, and comorbidities. However, our study is not without limitations. The observational nature of the study prevents any definitive conclusions regarding causality. Additionally, the use of electronic health records creates potential variability in the accuracy of diagnoses and completeness of data. Further, sample sizes for few of the diseases (myasthenia gravis, Addison's disease) are small, hence the associations reported might be significantly high, but the absolute risk may be lower. Another limitation is that the study is unable to ascertain the effects of either disease activity or medication on the outcome. Future research should aim to corroborate these findings through prospective cohort studies and further explore the underlying the effect of disease activity, drugs and understand underlying mechanisms. Investigations into the potential effect of medications used for the management of autoimmune diseases on outcomes should also be completed. The use of standard BMI categories based on the WHO classification rather than ethnicity-specific BMI categories may influence the observed associations by potentially overlooking differences in body composition and health risks across ethnic groups, yet it ensures consistency, comparability, and generalisability [547].

5.6 Conclusion

The complex interplay of immune, inflammatory, hormonal, and nutritional factors in autoimmune diseases underscores the importance of tailored prenatal care for affected women. Overall, the management of autoimmune diseases during pregnancy requires a balanced approach that considers both disease control and fetal safety. Close collaboration between rheumatologists, obstetricians, and other specialists is crucial for optimizing

maternal and fetal outcomes. Enhanced prenatal care and a thorough understanding of medication risks can help mitigate complications and improve the prognosis for both mother and child.

Authors' Contributions

MS was responsible for analysis and drafting of the manuscript. SW, NC, AG provided support with statistical analysis. FC, AS and KN provided their input and guidance at each step of the study. MB, JAK, SH and SIL were responsible for revising the manuscript critically and for important intellectual content. All authors read and approved the final manuscript.

Declaration of interest

Co-author AS was employed by the University of Birmingham when this study was initiated but moved to work with AstraZeneca. She currently holds an honorary contract with the University of Birmingham. All the other authors declare that they have no competing interests.

Ethics Approval

Ethical approval for this study has been approved by Independent Scientific Advisory Committee for research involving CPRD data (protocol no. 23_002650).

Data availability statement

Access to anonymized patient data from CPRD is subject to a data sharing agreement containing detailed terms and conditions of use following protocol approval from the MHRA Independent Scientific Advisory Committee. This study-specific analysable dataset is therefore not publicly available but can be requested from the corresponding author at

██████████ subject to research data governance approvals. Details about

Independent Scientific Advisory Committee applications and data costs are available on the CPRD website (cprd.com).

Table 5.1: Baseline characteristics of women aged 15-49 years in the UK (pregnancy cohort and birth cohort from CPRD Gold and CPRD Aurum)

	Pregnancy cohort		Birth cohort	
Characteristics	Autoimmune conditions (any)	No autoimmune conditions	Autoimmune conditions (any)	No autoimmune conditions
Number of pregnancies n (%)	188,602 (3.60)	5,050,781 (96.40)	84,221 (3.39)	2,401,145 (96.61)
Number of women n (%)	106,024 (3.70)	2,757,839 (96.30)	63,972 (3.50)	1,766,322 (96.50)
Maternal Age, median (IQR) years	31.11 (26.88-35.11)	29.70 (25.29-29.70)	30.68 (26.9-34.71)	29.73 (25.7-33.93)
Age categories n (%)				
>=15- <20 years	8,243 (4.36)	328,023 (6.49)	2,086 (2.48)	85,439 (3.56)
>=20- <25 years	22,985 (12.19)	812,828 (16.09)	8,061 (9.57)	298,453 (12.43)
>=25- <30 years	41,474 (21.99)	1,215,461 (24.06)	16,621 (19.73)	514,120 (21.41)
>=30- <35 years	56,965 (30.20)	1,429,576 (28.25)	23,859 (28.33)	627,939 (26.15)
>=35- <40 years	41,222 (21.86)	916,457 (18.14)	15,804 (18.76)	366,763 (15.27)
>=40- <45 years	14,323 (7.59)	292,880 (5.80)	3,413 (4.05)	79,270 (3.30)
>=45-49 years	3,390 (1.80)	55,556 (1.10)	14,375 (17.07)	428,825 (17.86)
Index of multiple deprivation, n (%)				
1-Most deprived	33,851 (17.95)	985,446 (19.51)	17,610 (20.91)	549,792 (22.90)
2	31,982 (16.96)	904,674 (17.91)	16,955 (20.13)	505,506 (21.05)
3	29,680 (15.74)	781,574 (15.47)	16,120 (19.14)	447,408 (18.63)
4	30,270 (16.05)	747,569 (14.80)	16,280 (19.33)	436,762 (18.19)
5-Least deprived	29,825 (15.81)	732,911 (14.51)	16,684 (19.181)	441,146 (18.37)

Missing	32,994 (17.49)	898,607 (17.79)	100 (0.12)	3,251 (0.14)
Smoking status				
Non-Smoker	90,434 (47.95)	2,567,029 (50.82)	41,150 (48.86)	1,221,622 (50.88)
Ex-Smoker	31,371 (16.63)	685,995 (13.58)	14,224 (16.98)	326,868 (13.61)
Current smoker	53,584 (28.41)	1,301,219 (25.76)	22,719 (26.84)	589,261 (24.54)
Missing	13,213 (7.01)	496,538 (9.83)	6,128 (7.28)	263,394 (10.97)
Body mass index (kg/m²), n (%)				
Median (IQR)	24.30 (21.60- 28.39)	24.00 (21.36-28.10)	21.9 (4.76)	21.79 (4.73)
Underweight (<18.5)	6,204 (3.29)	181,028 (3.58)	2,824 (3.35)	87,447 (3.64)
(18.5-<25)	80,989 (42.94)	2,085,036 (41.28)	37,461 (44.48)	1,022,709 (42.59)
Overweight (25-<30)	39,794 (21.10)	977,645 (19.36)	17,617 (20.92)	458,452 (19.09)
Obese (≥30)	29,918 (15.86)	713,881 (14.13)	12,370 (14.69)	313,019 (13.04)
Missing	31,697 (16.81)	1,093,191 (21.64)	14,029 (17.12)	519,518 (22.39)
Ethnicity n (%)				
White	107,842 (57.18)	2,491,247 (49.32)	72,265 (85.88)	1,895,715 (78.95)
Mixed	36,111 (19.15)	1,054,579 (20.88)	1,095 (1.30)	34,972 (1.46)
Others*	1,592 (0.84)	50,163 (0.99)	2,645 (3.14)	108,989 (4.54)
Black	4,100 (2.17)	211,540 (4.19)	1,840 (2.18)	121,533 (5.06)
Asian^	10,392 (5.51)	332,553 (6.58)	4,481 (5.37)	157,763 (6.57)
Missing	28,565 (15.15)	910,699 (18.03)	1,895 (2.25)	82,173 (3.42)
Gravidity[#] n (%)				
1	38,963 (20.66)	1,189,134 (23.54)	34,146 (40.54)	1,024,635 (42.67)
2	43,139 (22.87)	1,198,035 (23.72)	28,001 (33.26)	771,875 (32.15)
3	36,029 (19.10)	952,115 (18.85)	9,137 (10.85)	251,911 (10.49)
4	25,825 (13.69)	654,587 (12.96)	2,835 (3.37)	76,748 (3.20)
5+	44,646 (23.67)	1,056,910 (20.93)	6,173 (7.73)	163,695 (6.82)
Comorbidities n (%)				
Hypertension	4,219 (2.24)	73,319 (1.45)	1,546 (2.24)	31,999 (1.60)

Type 2 diabetes mellitus	2,433 (1.29)	26,191 (0.52)	720 (0.85)	6,751 (0.28)
Mental health conditions				
Depression	33,833 (17.94)	659,928 (13.07)	3,911 (25.61)	82,748 (20.04)
Anxiety	24,010 (12.73)	468,689 (9.28)	46 (0.30)	818 (0.20)
Psychosis	1,024 (0.54)	20,526 (0.41)	32 (0.21)	955 (0.23)

Numbers of pregnancies form the unit of analysis. ^The Asian category consisted of participants with origin from all over Asia, including India, Pakistan, China, Cambodia, Thailand, Vietnam, Malaysia, Sri Lanka, Nepal, Bangladesh, Japan or Taiwan. *The 'other' ethnicity category consisted of patients with native American, Middle Eastern or Polynesian origin. # Total number of pregnancies

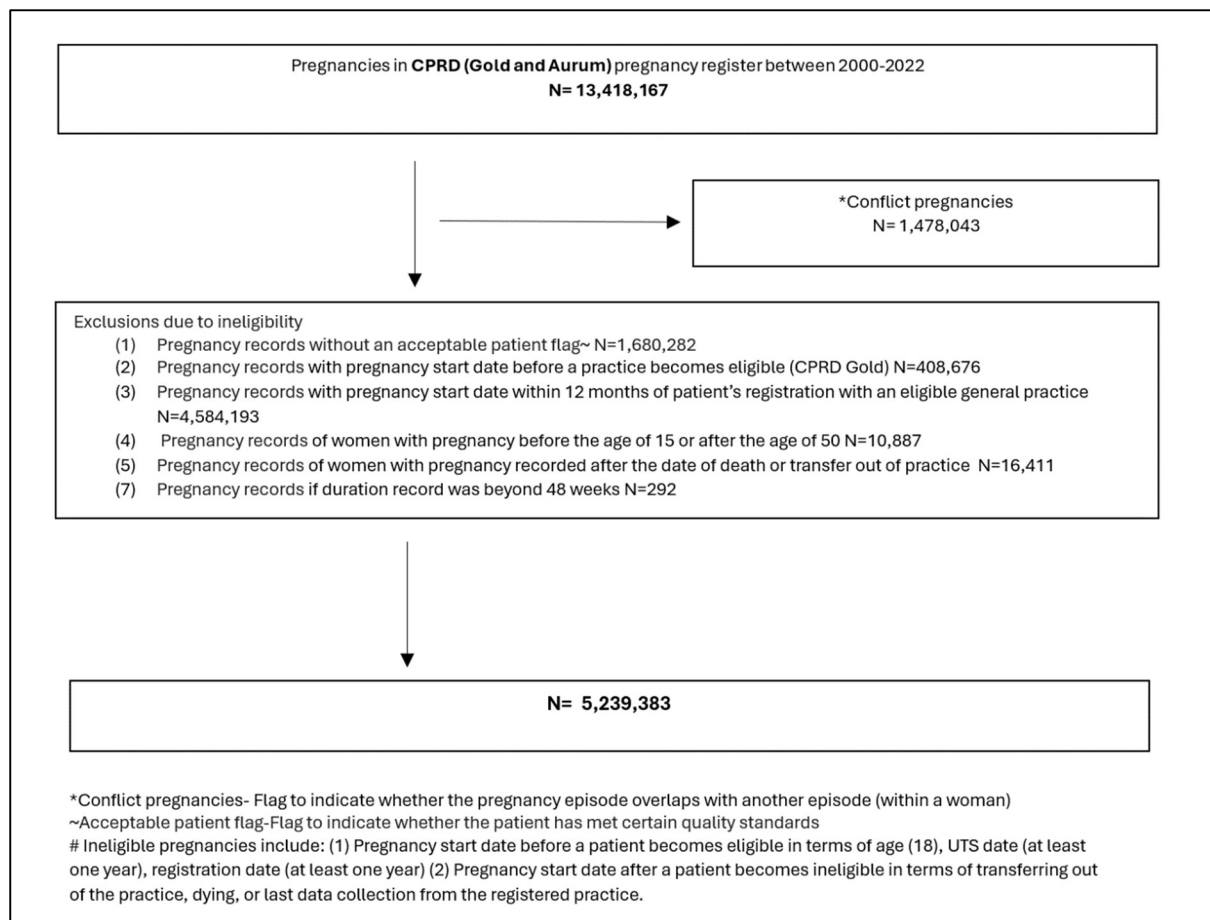
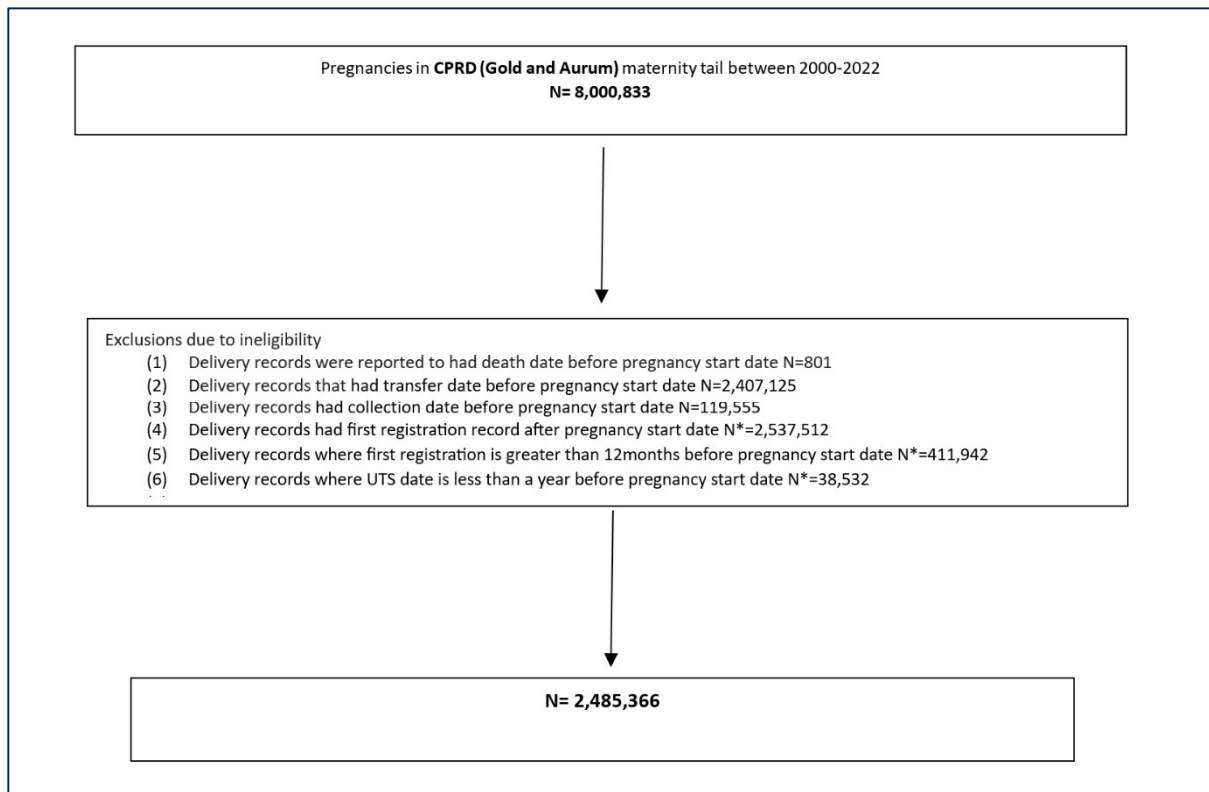
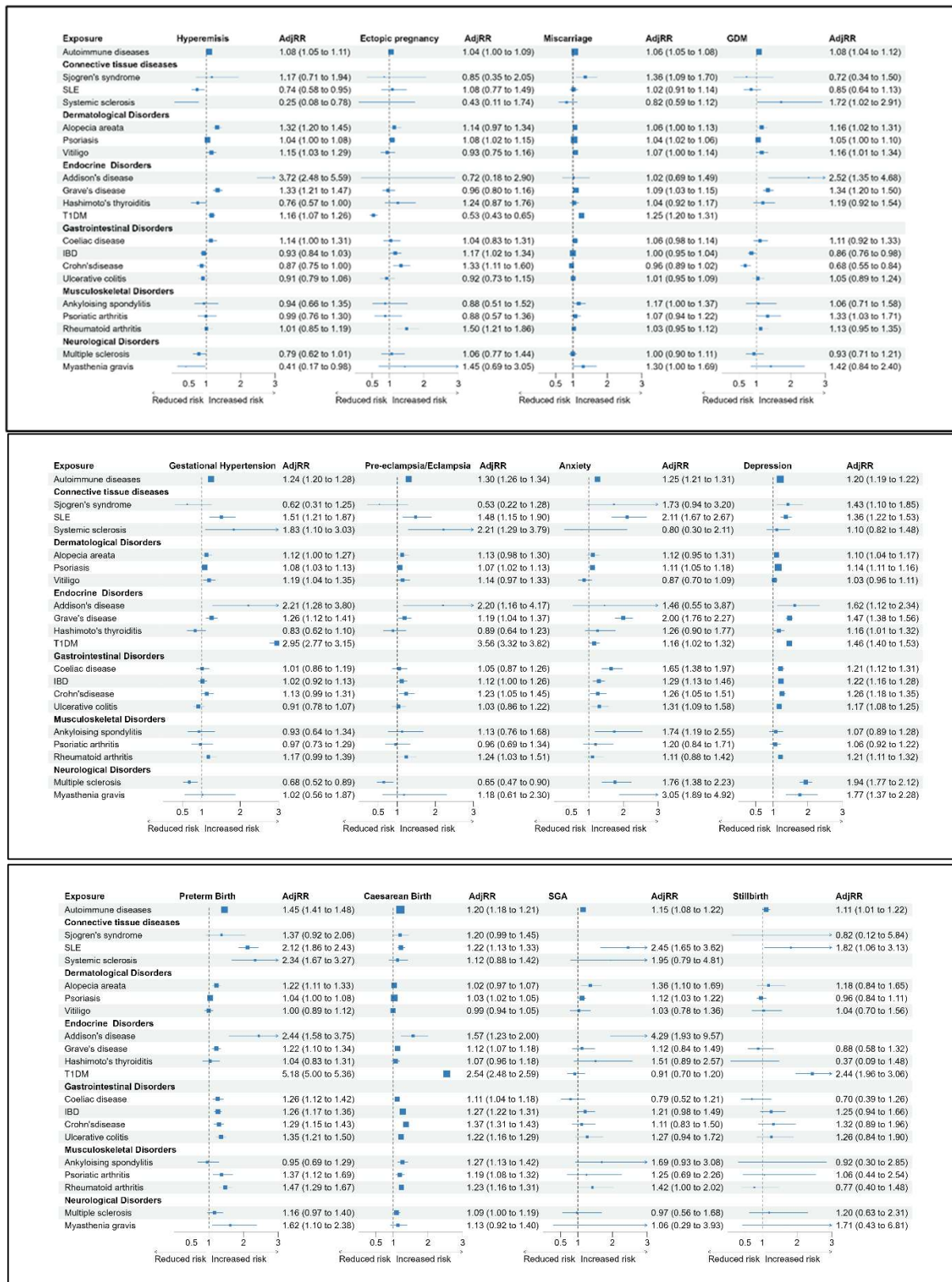


Figure 5.1 Flowchart describing pregnancy cohort selection



*Data quality check, UTS=Up to standard date

Figure 5.2 Flowchart describing birth cohort (HES maternity tail) selection



GDM= Gestational diabetes mellitus, SGA =small for gestational age, AdjRR=adjusted risk ratio

Figure 5.3-Forestplots reporting association of the autoimmune diseases and the adverse pregnancy outcomes

Chapter end summary

The chapter used CPRD data to carry out epidemiological studies to describe the association of autoimmune diseases in pregnancy and adverse pregnancy outcomes. A wide range of autoimmune diseases were included as exposures and range of pregnancy complications including mental health were analysed. Association between many of the autoimmune diseases like SLE, T1DM were reported to have been associated with pregnancy complications. Most of the findings from chapter 4 have been confirmed in this study with new findings specially for less common autoimmune diseases like myasthenia gravis.

Chapter 6: Pregnancy complications and autoimmune diseases in women: systematic review and meta-analysis

Chapter overview

The study was conducted to address the research objective: To investigate the association of pregnancy complications with the development of autoimmune diseases in a systematic review.

The published manuscript is presented as follows

Singh, M., Fayaz, F.F.A., Wang, J. et al. Pregnancy complications and autoimmune diseases in women: systematic review and meta-analysis. BMC Med 22, 339 (2024).

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Personal contribution

- Developed the search strategy
- Conducted the literature search in the electronic databases
- Screened title and abstracts and full texts and compared findings with second reviewer
- Extracted data and compared findings with second reviewer
- Written the manuscript

Title: Pregnancy complications and autoimmune diseases in women: systematic review and meta-analysis

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6.1 Abstract

6.1.1 Background

Pregnancy complications might lead to the development of autoimmune diseases in women.

This review aims to summarise studies evaluating association between pregnancy complications and development of autoimmune diseases in women.

6.1.2 Methods

Medline, CINAHL, and Cochrane databases were searched up to January 2024. Nineteen pregnancy complications and fifteen autoimmune conditions included. Title, abstract, full-text screening, data extraction, quality assessment was performed by two reviewers independently. Data synthesised using narrative and quantitative methods. Results presented using odds ratios (OR), relative risks (RR), incidence rate ratios (IRR) 95% confidence intervals (CI).

6.1.3 Results

Thirty studies included. One study reported composite exposure of pregnancy complications had risk of any autoimmune disease RR 3.20 (2.90-3.51) compared to women without pregnancy complications. Women with hyperemesis gravidarum had a higher risk of developing coeliac disease (n=1) IRR 1.98 (1.27-2.94), Crohn's disease (n=1) IRR 1.61 (1.25-2.04), psoriasis (n=1) IRR 1.33 (1.01-1.71) and rheumatoid arthritis (n=2) IRR 1.35 (1.09-1.64). Miscarriage associated with subsequent diagnosis of Sjogren syndrome (n=2) IRR 1.33 (1.06-2.81) and rheumatoid arthritis (n=4) OR 1.11(1.04-1.20). Gestational hypertension / preeclampsia was linked with development of systemic sclerosis (n=2) IRR 2.60 (1.10-4.60) and T1DM (n=2) IRR 2.37 (2.09-2.68). Stillbirth associated with composite autoimmune conditions (n=2) RR 5.82 (95% CI 4.87-6.81) and aIRR 1.25 (1.12-1.40). Postpartum psychosis was associated with autoimmune thyroid disease (n=1) aIRR2.26 (1.61-2.90).

6.1.4 Conclusions

Women with pregnancy complications subsequently had higher risk of being diagnosed with autoimmune conditions. Whether this is due to pre-existing undiagnosed health conditions or being causally linked to pregnancy complications is not known.

What is already known about this subject?

- The prevalence of autoimmune conditions and pregnancy complications has increased globally.
- Women with pregnancy complications are at higher risk of cardiometabolic conditions in later life.

What does this study add?

- This systematic review consolidate evidence from studies which have studied the association of the pregnancy complications and later development of autoimmune diseases in women.
- This review provides new knowledge to help establish the association of the pregnancy complications and autoimmune diseases and identifies the need for further research to establish true association between few conditions like development of SLE or rheumatoid arthritis followed by miscarriage.

How might this impact on clinical practice?

- This study will be useful for health professionals and policymakers to navigate the research findings and identify the need for clinical guidelines beyond postnatal care for women with pregnancy complications

6.2 Background

The prevalence of autoimmune diseases has been increasing globally over the last decade [13] and in the UK, 1 in 10 people have an autoimmune disease [13, 293, 548]. The majority of autoimmune diseases are more common in women than men [549] and are a leading cause of death in women between the age of 65 to 75 in US and UK [327, 550]. Although the aetiology of autoimmunity is still not fully understood, the increased prevalence of autoimmune disease has been linked to defective X chromosome inactivation [551, 552] and the effects of female hormones [553].

During pregnancy, there are significant fluctuations in hormone levels and increased physiological stress. Women with pre-existing autoimmune diseases may experience flare-ups or a decrease in their symptoms. For example, rheumatoid arthritis, Grave's disease or

psoriasis may improve during pregnancy [554-556], whilst patients with systemic lupus erythematosus (SLE) or multiple sclerosis are at an increased risk of disease exacerbations [557, 558]. With an increasing trend in pregnancy complications due to factors such as older age at pregnancy and women entering pregnancy with pre-existing long-term health conditions [559-567] it is important to study the role of pregnancy complications in the development of autoimmune diseases. Whilst it is well-established that women with autoimmune diseases have an increased risk of fertility problems and adverse pregnancy outcomes such as miscarriage and foetal growth restriction [354, 376, 416, 568-571], less is known about the risk of developing autoimmunity in women who experience pregnancy complications [572]. Some studies have shown an association between parity and increased risk of Hashimoto thyroiditis, Sjögren's syndrome, Grave's disease and rheumatoid arthritis [194, 573]. Moreover, the association between gestational diabetes mellitus (GDM) and development of type 1 diabetes (T1DM) is well established [574]. Some pregnancy complications such as hyperemesis gravidarum and gestational hypertension have been associated with development of rheumatoid arthritis [319, 575], while other studies have reported that pregnancy loss and gestational hypertension are associated with the development of SLE and systemic sclerosis [576, 577]. But other studies conducted on these associations have reported contradictory/inconsistent findings [578, 579].

This systematic review aims to determine the association between a wide range of pregnancy complications and the development of autoimmune diseases in women.

6.3 Methods

This systematic review and meta-analysis have been conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and

Reporting Guidelines for Meta-analyses of Observational Studies (MOOSE) (supplementary table 6.1 table 6.2) [580]. The protocol for this review was registered with Prospero CRD42023412549.

6.3.1 Inclusion and exclusion criteria

Cohort, cross-sectional, or case-control studies reporting on the associations between pregnancy complications and the risk of autoimmune diseases were included (table 1 and table 6.2). No language restrictions were applied. The population considered were pregnant women without any age restriction. The pregnancy complications (19) and autoimmune diseases (15) selected for inclusion were those that were more common in women, after consultation with experts in the subject (obstetricians, obstetric physician, rheumatologists, and epidemiologists), and after input from patient and public involvement and engagement (PPIE) group members.

The pregnancy complications included are listed in Table 6.1 and autoimmune diseases in table 6.2.

6.3.2 Search strategy

Medline, CINAHL, and Cochrane Library were searched for studies from 2010 till January 2024. The search strategies used pre-defined keywords of the exposures (pregnancy complications) and outcomes (autoimmune disease). Terms/keywords for each of the pregnancy complications ((early adj3 pregnancy loss*, mp.miscarriage.mp, GDM) and autoimmune diseases (exp Arthritis, Rheumatoid systemic lupus or SLE) were used in the search strategy. Google scholar was searched to identify other grey literature. In addition, the reference list of the included studies, systematic reviews, scoping reviews, were searched manually to

minimise the possibility of missing any relevant studies. Letters, commentaries, or editorials were excluded and studies that did not involve humans were also excluded. The searches were repeated periodically to identify newly published studies. The detailed search strategy for Medline is presented in the supplementary table 6.1. This search strategy was adapted for use in other databases (CINAHL and Cochrane library). Pragmatic approach was taken given there were substantial number of studies that needed screening (n=24,340) and the study period was limited from 2010-2023 (n=13,234). But this was complimented by secondary search strategy looking at references of included studies, systematic reviews, scoping reviews and by discussing with topic experts (KN, FC) to minimise the possibility of missing any study before 2010.

6.3.3 Study selection

EndNote reference manager [581] was used for the title and abstract screening by two researchers independently (MS, JW). Full text of the eligible reviews was screened by two researchers independently (MS, FF). Covidence software [582] was used for full text screening and data extraction. A third senior researcher was consulted to resolve any discrepancies in the selection of the studies (FC, KN).

6.3.4 Data extraction

Two reviewers extracted data from the included studies. The data extraction form was adapted from JBI (Joanna Briggs Institute) data extraction form [583]. A standardised data extraction form was used and was piloted before use. The data were extracted for the following fields: author/s, year of publication, geographical area, aim of the study, population, exposures, comparator, outcomes, covariates, study design, definition of exposure, risk of bias

assessment tool and result, number of participants included in the study, summary estimates, authors' conclusion, and study limitations. The data extraction form is enclosed in supplementary table 6.11.

6.3.5 Quality assessment

The quality of included cohort, cross-sectional and case-control studies was assessed using the Newcastle-Ottawa scale that measures study quality based on selection, comparability of the exposure and comparator groups, and the ascertainment of outcomes and exposures [584]. The scale has an overall score of 8 points for cohort or case-control studies, and 7 for cross-sectional studies with a maximum of one point for each numbered item within the selection and outcome/exposure categories and a maximum of two points for the comparability category. We defined studies with a score of ≥ 7 points as low-risk of bias studies (very good), studies with a score of 6 points as moderate-risk of bias studies (good), and those with a score of ≤ 5 points as high-risk of bias studies (satisfactory).

6.3.6 Data synthesis

The effect estimates were reported as adjusted incidence rate ratios (aIRR), adjusted hazards ratios a(HR), adjusted odds ratios (aOR), or adjusted relative risks (aRR) and 95% confidence intervals (CI). We converted these effect estimates using appropriate methods (where possible) to maintain uniformity across studies [423]. Where more than one study reported the same exposure and outcome, a meta-analysis was conducted using a random effects model to generate a summary estimate. Statistical heterogeneity was estimated using the I^2 statistic. To deal with potentially missing data (sample size, number exposed and unexposed), the supplementary table 6.7 of each included study were checked thoroughly, and the authors

of the studies were contacted to request the data. If the data was not available and a meta-analysis could not be conducted, then effect estimates were reported as they were published. Where statistical pooling was not possible, the findings were presented in a narrative form including tables and figures to aid data presentation. R (3.3.0) and R Studio (12.1) were used to conduct statistical analysis [257, 585, 586].

Patient and public involvement

Patient and public involvement and engagement (PPIE) representatives (RP and NM) participated in formulating the research question. They have also played key role in collaboration with clinicians and researchers to identify and consider the list of pregnancy complications and autoimmune diseases in the study. They will play a key role in disseminating the results.

6.4 Results

Out of the 13,234 records identified from the search and after full text screening of 85 studies, 30 studies were included [319-322, 572, 574, 575, 578, 579, 587-607]. Studies were excluded if they did not qualify in the study inclusion criteria based on the study design (n=22), population (n=5), intervention (2), outcome (23) and comparator (3). The selection process is shown in the PRISMA diagram (Figure 1) [580]. The list of excluded studies is provided in supplementary table 6.3.

Characteristics of the included studies are reported in Table 6.2. Out of the 30 studies, the majority were prospective cohort studies (n=21), eight were retrospective case-control studies, and one was a cross-sectional study. There were 23 studies conducted in Europe, the remainder were in Taiwan (2), China (2), South Korea (1), and the United States (2). In

most cohort studies (n=14), information about the pregnancy complications and autoimmune diseases was collected through medical records. Medical records were used to establish the autoimmune diseases in case-control studies and questionnaires were used to determine the pregnancy complications. The follow-up period of the cohort studies varied from 9 months to 26 years with a median of 12 years. Out of the 21 cohort studies, nine used the data from the same cohort (Danish national registry) [322, 572, 575, 578, 590, 591, 598, 603]. In the instance of two studies reporting the same exposure and outcome, the most recent study was used to avoid duplication. We have done this in accordance with the Cochrane handbook for systematic reviews [608]. For instance, two studies Mikkelsen et al (2022) and Nielsen et al (2011) were both reporting the association of pregnancy complications and future development of multiple sclerosis in women using Danish Civil Registration System. Mikkelsen et al was used to report the findings in this review. Details have been added in the supplementary table 6.3 and 6.10 [609, 610]. A total of eighteen different pregnancy complications and 12 autoimmune diseases (including an overall “all autoimmune diseases”) were investigated across the studies. Rheumatoid arthritis (8 studies) and SLE (5 studies) were two of the most included outcomes. The meta-analysis performed in this systematic review are included in the supplementary figure 6.7.

Quality assessment

Results of the quality assessment of the studies using the Newcastle-Ottawa scale is shown in Figure 6.2 and supplementary table 6.4-6.6 [215]. Eighteen out of thirty studies had a low risk of bias with an overall “very good” rating. The principal areas of concern were comparability of cohorts and adequacy of follow up.

All autoimmune diseases

There was more than a three-fold higher risk of developing autoimmune diseases (n=7) in women with pregnancy complications (n=6) RR 3.20 (95% CI 2.90-3.51) when compared with women without pregnancy complications [595]. Out of the pregnancy complications studied individually, two studies reported, women with previous miscarriage RR 3.41 (3.03-3.85) and aIRR 1.10 (1.07-1.14) was reported to have higher risk [595]. One cohort and one case control study reported a higher risk of autoimmune diseases in women with gestational hypertension or pre-eclampsia RR 2.05 (1.70-2.48) and aIRR 1.21 (1.16-1.26) [591, 595] respectively. Women with stillbirth was reported to have higher chances to have autoimmune disease in later life reported by two studies RR 5.82 (4.97-6.81) [595] and aIRR 1.25 (1.12-1.40) [591]. There was a significantly higher risk of developing autoimmune diseases for women with preterm birth RR 2.35 (1.89-2.92) [595]. There was little association reported with caesarean section, induced abortion, or postpartum depression with the development of autoimmune diseases [572, 591, 597]. However, a study reported a higher risk of developing autoimmune diseases in women with perinatal depression aHR 1.52 (1.46-1.58), with antenatal depression aHR 1.50 (1.43-1.58) and postpartum depression aHR 1.55 (1.45-1.65) [607].

Autoimmune thyroid diseases

Hyperemesis gravidarum aIRR 1.49 (1.28-1.72), gestational hypertension or pre-eclampsia aIRR 1.20 (1.10-1.30), and postpartum depression aHR 1.57 (1.05-2.33) [591, 596] were all associated with a higher risk of Grave's disease but there was no significant association between ectopic pregnancy and Grave's disease aIRR 1.04 (0.93- 1.17) [591]. Gestational hypertension/pre-eclampsia aIRR 1.41 (1.17-1.68) were associated with a higher risk of Hashimoto's thyroiditis but there was little association of hyperemesis gravidarum or ectopic pregnancy with Hashimoto's thyroiditis; aIRR 1.38 (0.95-1.92) and aIRR 0.92 (0.68- 1.21),

respectively [591]. Two cohort studies reported a greater risk of autoimmune thyroid disease in women with postpartum psychosis aOR 2.78 (1.08-7.17) at 9 months and aIRR 2.26 (1.61-2.90) with two years follow up postpartum when compared with women without postpartum psychosis [587, 588].

Coeliac disease

Women who experienced hyperemesis gravidarum had almost a two-fold risk of coeliac disease compared to women without aIRR 1.98 (1.27-2.94) [591]. None of the other pregnancy complications were significantly associated with coeliac disease ectopic pregnancy aIRR 1.12 (0.75-1.61), gestational hypertension, pre-eclampsia aIRR 1.19 (0.89-1.56), and intrahepatic cholestasis of pregnancy aHR 1.20 (0.82-1.74 [591, 606].

Inflammatory bowel disease (Crohn's disease and ulcerative colitis)

Out of the five pregnancy complications reported for IBD (hyperemesis gravidarum, missed abortion, gestational hypertension, pre-eclampsia, and caesarean section) none of these associations were statistically significant. However, studies reporting ulcerative colitis and Crohn's disease separately found significant associations. Hyperemesis was significantly associated with the development of both ulcerative colitis and Crohn's disease, aIRR 1.34 (1.09-1.62) and aIRR 1.61 (1.25-2.04), respectively [591]. Furthermore, a higher risk of Crohn's disease was also observed in women with intrahepatic cholestasis of pregnancy, HR 1.55 (1.14-2.10) [606]. No other pregnancy complications were associated with the development of IBD as reported in Figure 6.4.

Ankylosing spondylitis

Out of the three pregnancy complications studied with the development of ankylosing spondylitis in women, there was no significant association for hyperemesis gravidarum IRR 1.63 (0.96-2.25) or ectopic pregnancy IRR 1.02 (0.66-1.50), a significant association was noted with gestational hypertension and pre-eclampsia IRR 1.40 (1.06-1.82) [591] Figure 6.5.

Rheumatoid arthritis

Out of the five studies reporting the association of miscarriage and rheumatoid arthritis, four were meta-analysed to estimate 11% higher odds: pooled OR 1.11 (1.04-1.20) with the other study showing a slightly elevated risk that was not statistically significant aIRR 1.06 (0.97-1.15) [319, 575, 591, 594, 600, 601]. A significant association also reported with hyperemesis, gestational hypertension, and pre-eclampsia with aIRR 1.35 (1.09-1.64), aIRR 1.18 (1.05-1.31) respectively [591] [319, 575, 591, 594, 600, 601]. While three studies were pooled to derive a significant association between rheumatoid arthritis and induced abortion 1.46 OR (1.01-2.12). Women with any pregnancy loss were reported to be at higher risk of developing the disease in one study aIRR 1.12 (1.06-1.12) and other reported no association aIRR 1.01 (0.67-1.44) and this will require further research to establish the true association. The association for induced abortion or any pregnancy loss with rheumatoid arthritis reported mixed findings with significant association reported by few studies and insignificant by others as shown in figure 5 [319, 572, 575, 591, 594, 600, 601]. A higher risk of developing rheumatoid arthritis was observed in women who delivered “extremely low birth weight” babies (<1,000 gm) with RR 3.70 (1.00-13.20) or “low birth weight” babies (<2,500 gm) with RR 1.40 (1.00-2.10) when compared to women who delivered normal birth weight babies [579]. An increased risk of rheumatoid arthritis was also reported for women

with postpartum depression with aHR 2.62 (1.28-5.39) [596]. No other pregnancy complication studied in relation with development of rheumatoid arthritis were statistically significant (Figure 5). There was also no significant association with development of rheumatoid arthritis as reported in women who delivered very low birth weight babies (<1,500 g) in a study with a small sample size (n=20) [579].

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis (composite outcome)

There were no other significant associations with rheumatoid arthritis or the composite outcome with other pregnancy complications studied (gestational hypertension or pre-eclampsia, caesarean section, postpartum haemorrhage, or mothers delivering preterm births or low birth weight babies) (Figure 5) [605]. Women who delivered small for gestational age babies were more likely to have the composite outcome of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis aOR 1.60 (1.00-2.56) when compared to women with normal for gestational age babies.

Connective tissue diseases (Systemic lupus erythematosus, Sjogren syndrome, systemic sclerosis)

Connective tissue disease

Seven pregnancy complications were reported in association with connective tissue disease (CTD). Women with placental abruption or preterm birth had significantly higher risk of CTD; RR 3.39 (1.96-5.89) and RR 1.78 (1.12-2.82), respectively [595] in figure 6.6. The associations of gestational hypertension, intrauterine growth restriction (IUGR), miscarriage, stillbirth, and composite pregnancy complications with CTD were not statistically significant [595].

Systemic lupus erythematosus (SLE)

Results for an association between miscarriage and SLE were mixed with one study reporting aIRR of 1.43 (1.08-1.88) and a pooled RR for two smaller studies showing no significant association 0.94 (0.37-2.40) [591, 595, 600, 603]. However, there was a significant association reported with any pregnancy loss and future development of the disease with OR 1.87 (1.31-2.67) [589, 592]. Missed abortions were associated with a higher risk of SLE IRR 2.13 (1.48-2.98) [591, 603]. Women with history of IUGR had almost a five-fold higher risk of SLE RR 4.80 (1.60-14.50) when compared with women with no IUGR [592]. Results from three studies showed that a history of stillbirth was associated with a four times higher risk of SLE pooled RR 4.01 (3.11-5.17) and pooled IRR 3.29 (3.22-4.88) [591, 595, 600, 603].

Systemic sclerosis

There was an association between gestational hypertension or pre-eclampsia and systemic sclerosis in two studies: OR 2.60 (1.10-4.60). Kamper et al, 2018 reported a significant association with development of localised scleroderma in women with pre-eclampsia with IRR 1.69 (1.02–2.80) but a nonsignificant association with subset of systemic disease aIRR 1.46 (0.75-2.80) [593, 604]. There was a three to four-fold higher risk of systemic sclerosis for women with IUGR compared with women with normal fetal growth OR 3.90 (1.20-12.30) [604] and caesarean birth compared to vaginal birth RR 3.09 (1.96-4.63) [320].

Sjögren's syndrome

There were seven pregnancy complications examined in relation to Sjögren's syndrome with results showing a greater risk with hyperemesis gravidarum aIRR 1.79 (1.06-2.81), miscarriage aIRR 1.33 (1.08-1.63) and induced abortion; aIRR 1.18 (1.01-1.38), gestational hypertension or pre-eclampsia; aIRR 1.43 (1.09-1.85) [591]. The associations for ectopic pregnancy, missed abortion or preterm birth; aIRR 1.18 (0.79-1.68), aIRR 1.12 (0.80-1.51), and RR 0.09 (0.04-18.09), respectively] [591, 595, 600] were not statistically significant.

Type 1 Diabetes Mellitus (T1DM)

Hyperemesis gravidarum aIRR 1.05 (0.74-1.45), ectopic pregnancy aIRR 1.06 (0.58-1.77) were not significantly associated with T1DM [574, 591, 599, 602] in figure 7. Results from one cohort study showed that gestational hypertension or pre-eclampsia was associated with a two-fold higher risk of T1DM aIRR 2.37 (2.09-2.68) [602], whereas in the other study the association was higher but not statistically significant OR 1.80 (0.80-3.80) [599]. Results from two studies showed the risk of T1DM for women with gestational diabetes was considerably higher pooled OR 40.89 (24.31-68.78) [574, 599]. There was almost a four-fold higher risk of T1DM in women who delivered large for gestational age babies compared to women delivering normal weight for gestational age babies aHR 3.60 (3.23-4.01) [602]. There was no significant association for women who delivered small for gestational age babies and T1DM aHR 1.11 (0.94-1.30) [321, 605].

Psoriasis

Out of the seven pregnancy complications, five complications were associated with a higher risk of psoriasis; hyperemesis gravidarum HR 1.33 (1.01-1.71), ectopic pregnancy aIRR 1.28

(1.07-1.53), induced abortions aIRR 1.33 (1.24-1.42), gestational hypertension or pre-eclampsia aIRR 1.22 (1.06-1.40) and intrahepatic cholestasis of pregnancy aIRR 1.27 (1.07-1.51) [591, 597, 606]. Missed abortion and postpartum depression were not significantly associated with the risk of psoriasis (Figure 6.7) [591, 597].

Associations of pregnancy complications with other miscellaneous autoimmune conditions

No significant association was reported with pregnancy complications studied (Hyperemesis, ectopic pregnancy, miscarriage, or gestational hypertension) and development of multiple sclerosis as mentioned in figure 6.7 [598]. The association of postpartum depression and alopecia areata (HR 1.97 (0.72-5.37) [596], and recurrent pregnancy loss and myasthenia gravis (RR 0.85 0.54-1.31) were not statistically significant [322].

Timing of developing autoimmune diseases following pregnancy/pregnancy complications

Four studies reported the occurrence of autoimmune diseases following pregnancy over different follow-up times [572, 588, 591, 603]. Following a pregnancy complication, a woman's risk of developing Grave's disease or SLE was higher in the early years after childbirth in comparison to later in life [319, 322, 578, 591, 603]. For instance, there was a higher risk of SLE in women with pregnancy loss in the first year postpartum IRR 2.64 (1.18-6.29), whereas there was no significant association noted after two or more years postpartum IRR 1.90 (0.87-4.48) [603]. Conversely, the risk of developing rheumatoid arthritis (RR 1.05; 0.98-1.13, 5+ years: RR 2.24; 1.58-3.05, and multiple sclerosis) (RR 1.00; 0.91-1.09, 5+ years: RR 2.20; 1.72-2.77) was greater after 5 or more years postpartum. Also, women with hyperemesis gravidarum were at a greater risk of developing rheumatoid arthritis in first four years post birth, this reduced after five years, IRR 1.40 (1.09-1.76) and IRR 1.02 (0.59-1.11) respectively [591, 603].

6.5 Discussion

This systematic review provides an overview of the associations of eighteen pregnancy complications with risk of developing 15 autoimmune diseases. This review compiles all the available evidence on pregnancy complications linked to development of autoimmune diseases in women in later life (Fig 2-7). Generates new evidence by quantitative or qualitative analysis of the studies studying same exposure and outcomes (supplementary figure 6.1.10). Further also points out on the differences in the results observed in two or more studies analysing the association of same pregnancy complication and autoimmune disease (supplementary fig 6.9).

Studies reported associations for gestational hypertension/preeclampsia followed by preterm birth, hyperemesis gravidarum and ectopic pregnancy and future autoimmunity. However, there was little or no research for some complications such as molar pregnancy or placental disorders. From the perspective of autoimmune disease outcomes, most studies examined the associations with rheumatoid arthritis followed by autoimmune thyroid diseases, Sjögren's syndrome, and psoriasis. In contrast, there were very few studies that included vitiligo or myasthenia gravis.

Many of the pregnancy complications increased the risk of overall autoimmune diseases almost three-fold, particularly hyperemesis gravidarum, miscarriage, gestational hypertension, stillbirth, and antenatal/postpartum depression. Apart from the known association of gestational diabetes and T1DM, results from this review showed that IUGR or stillbirth were associated with almost three to four-fold increased risk systemic sclerosis or systemic lupus erythematosus. There was a higher risk of rheumatoid arthritis with preterm birth and low birth weight babies.

There are findings which require further research, for example the association of miscarriage and development of SLE [595, 599, 603] and association of gestational hypertension with T1DM [591, 599]. The difference in the findings could be due to the varying study designs or difference in the sample size of the studies. There had been mixed findings among the studies included and these may be due to the varying sample size or the study designs.

6.5.1 Implications in research and policy

Earlier studies focused on the association of pregnancy complications with child outcomes such as caesarean birth or pre-eclampsia and the association with long-term health conditions in babies [611-617]. However, more recently, studies have reported the association of pregnancy complications and the development of long-term conditions in the mother [572, 618]. Reproductive factors and pregnancy complications were found to be associated with later development of metabolic conditions [619-621]. An association between pregnancy itself, irrespective of pregnancy complications, and the development of autoimmune diseases have been reported [572]. Some studies identified the association between parity and the development of systemic sclerosis; however, the findings have been conflicting [622-625].

It is not clear whether the observed pregnancy complications occur in women with preclinical autoimmune disease or whether these events directly pre-dispose to the development of autoimmune disease [626]. In terms of the former, women with undifferentiated connective tissue disease (UCTD), who have features compatible with a CTD but do not have a defined CTD [627], have an increased risk of pregnancy complications including premature delivery, pre-eclampsia, and stillbirth [628]. As approximately 30% of UCTD may progress to CTD, typically SLE, it is possible that some of the pregnancy

complications occurred in women who were in the initial stages of UCTD, i.e. the pregnancy complications were due to a subclinical autoimmune disease.

On the other hand, pregnancy/pregnancy complications bring about fluctuations in female sex hormones accompanied by physiological stress [629]. Blood levels of both oestrogen and progesterone increase rapidly from the middle of the second trimester, peaking at term.

Oestrogen and progesterone have broad effects on the function of both innate and adaptive immune cells (including monocytes/macrophages, neutrophils, dendritic cells and T and B lymphocytes) [630]. In pregnancy, placental production of oestriol (E3) increases dramatically. Oestriol has potent anti-inflammatory effects including reducing pro-inflammatory cytokine production, increasing anti-inflammatory cytokines and reducing CD4+ and CD8+ T cells [631]. Similarly, progesterone increases regulatory T cells and reduces natural killer cell function systemically and within the placenta [631]. It is possible, therefore, that hormonal fluctuations and the loss of this anti-inflammatory state post-partum could accelerate the development of autoimmune disease. Furthermore, oestrogens reduce B cells apoptosis which, whilst contributing to maternal humoral immunity, may promote autoreactive B cell survival and drive the immune system toward autoimmunity [632].

A key driver of future autoimmune disease may be fetal microchimerism [633]. Fetal cells are present at a low frequency in the maternal circulation post-partum and may persist for decades. [594, 634-636]. Fetal origin microchimerism is observed at increased rates during pregnancy complications such as miscarriage, pre-eclampsia, fetal growth restriction [637] or premature labour [635, 638]. The mechanisms by which fetal microchimeric cells mediate an increased risk of autoimmunity is not understood although an increased number of these cells is observed in the thyroid gland of women with autoimmune thyroid disease [639]. To

date a pathogenic role for fetal microchimeric cells has not been demonstrated and these cells may induce maternal tolerance to fetal antigens, and via a bystander effect reduce the severity of some autoimmune diseases such as rheumatoid arthritis during pregnancy [639].

6.5.2 Strengths and Limitations

Our study has several strengths. The scope of our review was broad and summarises the association of pregnancy complications and the subsequent development of a wide range of autoimmune diseases and we were able to perform a meta-analysis of studies reporting the same exposure and outcome where possible. We employed rigorous methodology with pre-specified protocol and our systematic search was conducted without language restriction and two reviewers screened, extracted data, and appraised the quality of the studies.

There are, however, some limitations. A meta-analysis could not be performed for some of the studies due to missing data such as the sample size, or number of exposed/unexposed. Some of the results reported therefore are as reported in one study. Also, nine studies were conducted using the same cohort (Danish birth cohort) this may have a disproportionate effect on our findings; however, efforts were made to avoid duplication in reporting of results. This study is not able to determine causality and there is a possibility that the women already have undiagnosed preclinical autoimmune diseases, which increased their risk of pregnancy complications in studies, especially those with shorter follow up time.

Additional research is required that incorporate a comprehensive analysis of pregnancy complications and characterize the phenotype and functionality of persistent fetal origin cells in women with autoimmune diseases compared with healthy women. The exact pathophysiology behind the development of these conditions remains unclear and we do not know why some pregnancy complications have a larger effect than others. To address

these questions, prospective longitudinal studies following up women who experienced pregnancy complications is needed, observing when autoantibodies are first detected [640]. Furthermore, larger epidemiological studies would be required to define whether autoimmune disease is more prevalent in women who have experienced pregnancy complications and if there is a clear underlying association.

6.6 Conclusions

This review has reported that there is an association between pregnancy complications and the subsequent development of autoimmune diseases in women. To further address this question prospective longitudinal studies following up women who experienced pregnancy complications is needed, observing when autoantibodies are first detected. Meanwhile clinicians should be vigilant and detect autoimmune conditions early in women with history of pregnancy complications.

Availability of Data and Materials-All data generated or analysed during this study are included in this published article and its additional information files.

Authors' Contributions- MS was responsible for analysis and drafting of the manuscript. FF/JW were the second reviewer for study selection; data extraction checks and the quality appraisal. FC and KN were the third reviewer and provided their inputs and guidance at each step of the review. KN, JR, AS, FC, SW were responsible for revising the manuscript critically and for important intellectual content. All authors read and approved the final manuscript.

Competing interests- Co-author AS was part of university of Birmingham when this review was initiated but moved to work with AstraZeneca. She currently holds an honorary contract

with the university of Birmingham. All the other authors declare that they have no competing interests.

Ethics Approval- Since this review analysis the data from the prior systematic reviews, no ethical approval is required.

Table 6.1 – List of pregnancy complications (exposures) included in the systematic review

1. Hyperemesis Gravidarum
2. Miscarriage – missed abortion, recurrent miscarriage, spontaneous pregnancy loss or induced abortion
3. Ectopic pregnancy
4. Molar pregnancy/Choriocarcinoma
5. Hypertensive disorders of pregnancy, pre-eclampsia – early or late onset, recurrent pre-eclampsia, eclampsia, HELLP (haemolysis, elevated liver enzymes, and low platelets)
6. Gestational diabetes mellitus
7. Intrahepatic cholestasis of pregnancy
8. Pelvic girdle pain
9. Placental disorders – placenta previa, placental abruption, placenta accrete, placenta percreta
10. Gestational diabetes mellitus
11. intra-uterine growth restriction
12. Obstetric haemorrhage (postpartum)
13. Perineal trauma - 3 rd and 4 th degree
14. Caesarean birth, instrumental birth
15. Postpartum depression
16. Puerperal psychosis
17. Pre-term birth, recurrent pre-term birth
18. Low birth weight
19. Small for gestational age

Table 6.2- List of autoimmune diseases (outcomes) included in the systematic review

1. Alopecia areata
2. Ankylosing spondylitis or axial spondyloarthritis.
3. Autoimmune thyroid disease (Grave's disease, Hashimoto's disease)
4. Coeliac disease
5. Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
6. Multiple sclerosis
7. Myasthenia gravis
8. Psoriasis
9. Psoriatic arthritis
10. Rheumatoid arthritis
11. Sjögren's syndrome
12. Systemic lupus erythematosus (SLE)
13. Systemic sclerosis
14. T1DM
15. Vitiligo

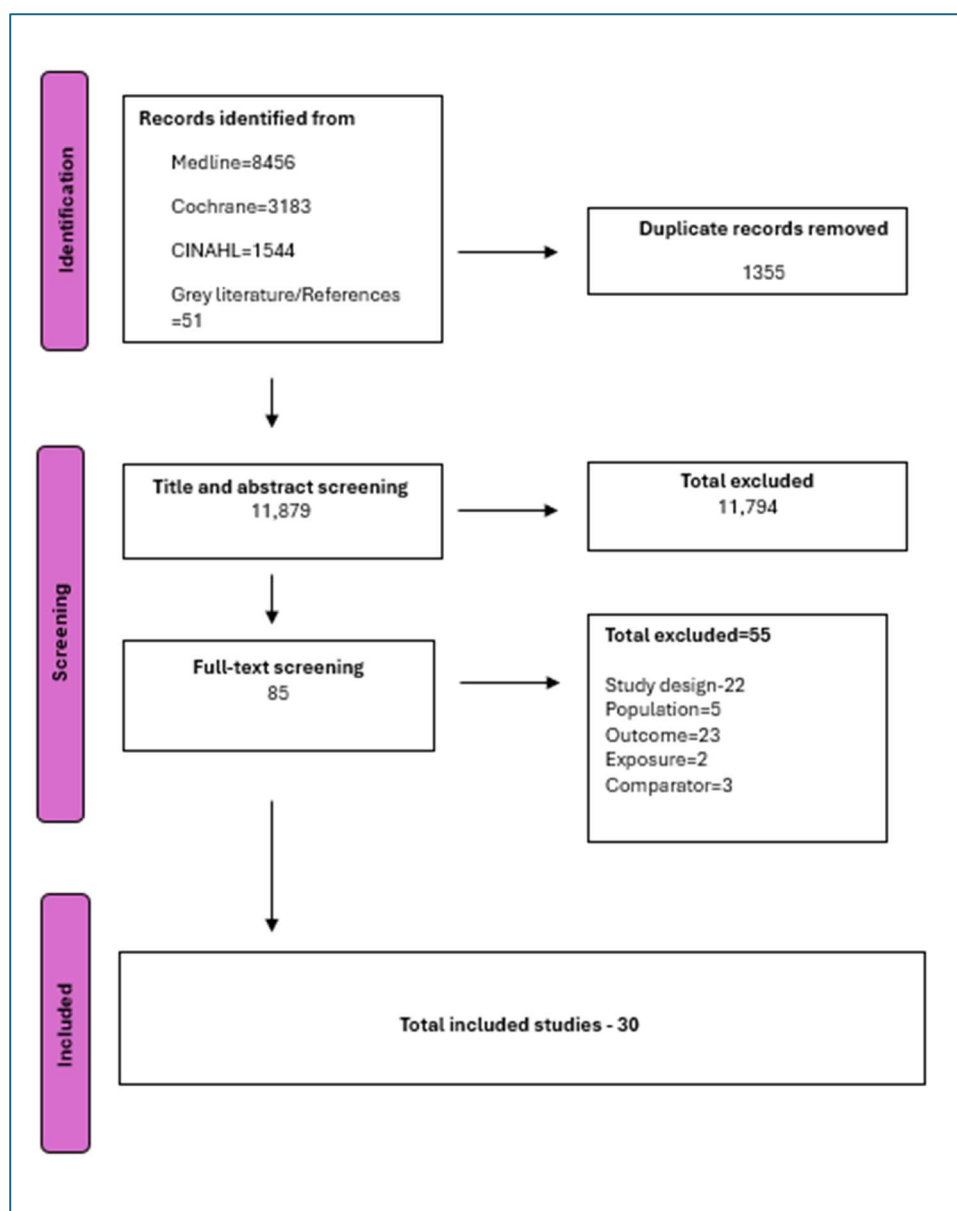


Figure 6.1: Preferred reporting items for systematic review and meta-analysis (PRISMA) flow diagram

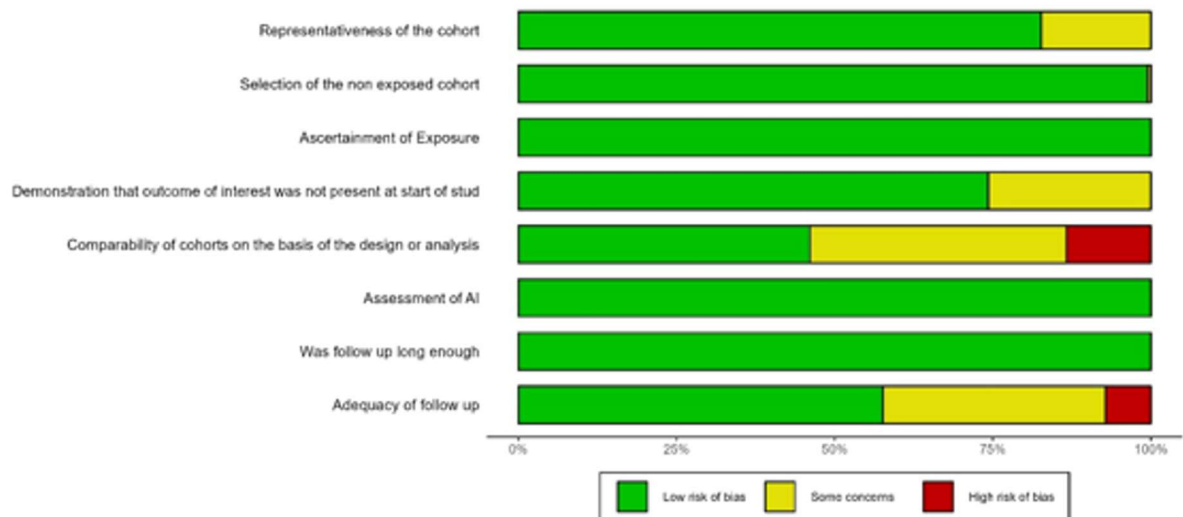


Figure 2A Cohort studies (21)

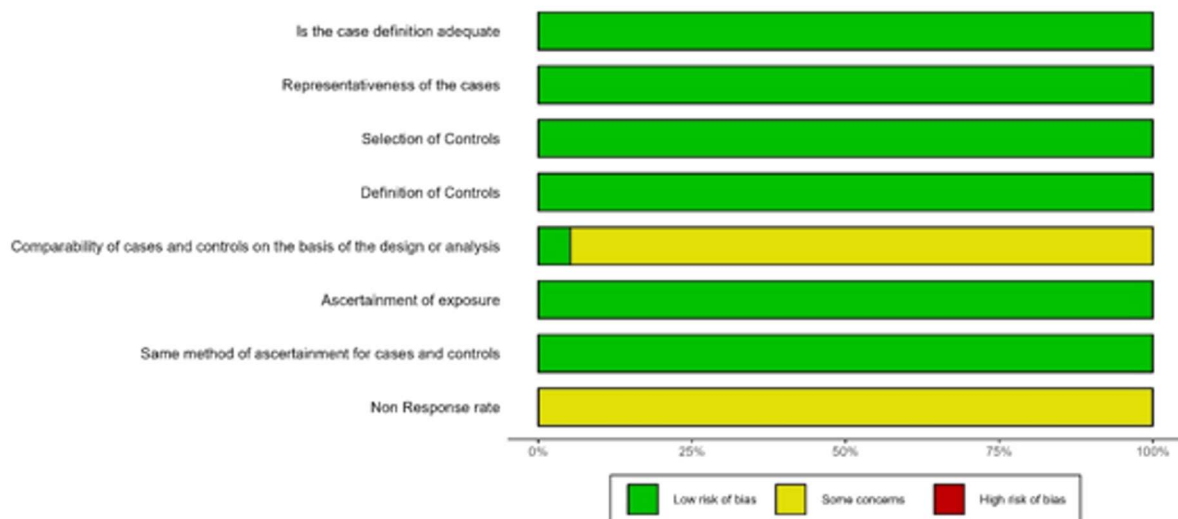


Figure 2B Case-control studies (8)

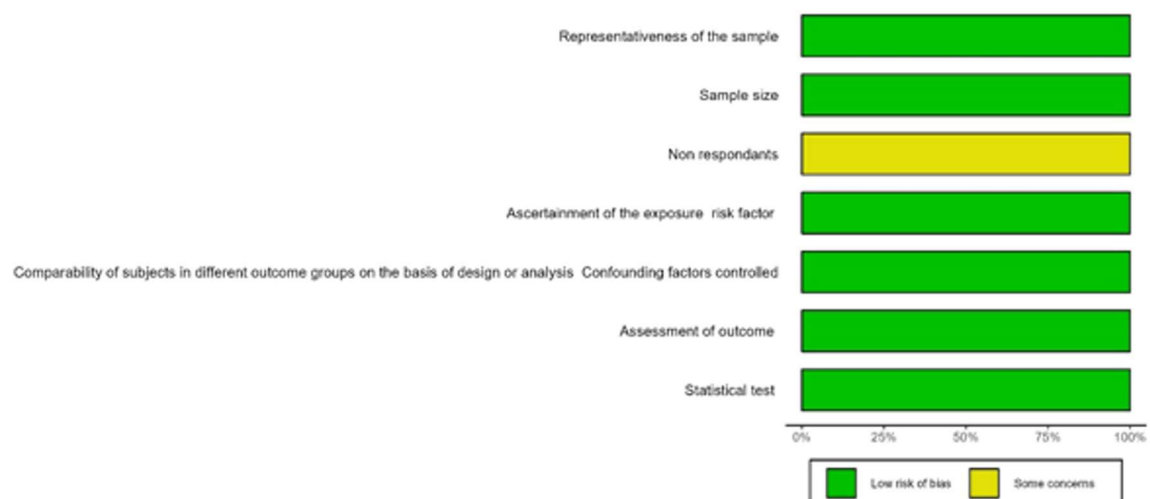


Figure 2C Cross-sectional study (1)

Figure 6.2-Quality assessment of included studies (New Castle Ottawa scale)

Table 6.3-Basic characteristics of included thirty studies

Serial Number	Author, year	Geographical area	Database/health care setting	Sample Size	Pregnancy complication(s) considered (exposure)	Autoimmune disease(s) considered (outcome)
Prospective cohort studies						
1.	Auvinen 2020	Finland	University hospital	782	Gestational diabetes mellitus	Type 1 diabetes mellitus
2.	Bergink, 2011 [587]	The Netherlands	Department of psychiatry at the Erasmus Medical Centre for evidence of postpartum psychosis	148	Postpartum psychosis	Autoimmune thyroid dysfunction
3.	Bergink 2018 [588]	Denmark	Danish national registry	312,779	Postpartum psychosis	Autoimmune thyroid dysfunction
4.	Bränn 2023 [607]	Sweden	Swedish National Medical Birth Register	530,397	Perinatal depression	Autoimmune diseases
5.	Hardy 1999 [589]	UK	Patients from Nottingham	314	Pregnancy loss (spontaneous abortion, stillbirth, miscarriage, or ectopic pregnancy), Induced abortion	Systemic lupus erythematosus
6.	Harpsoe 2013 [590]	Denmark	Danish National Birth Cohort	56,108	Hyperemesis gravidarum, gestational hypertension, pre-eclampsia	Inflammatory bowel disease

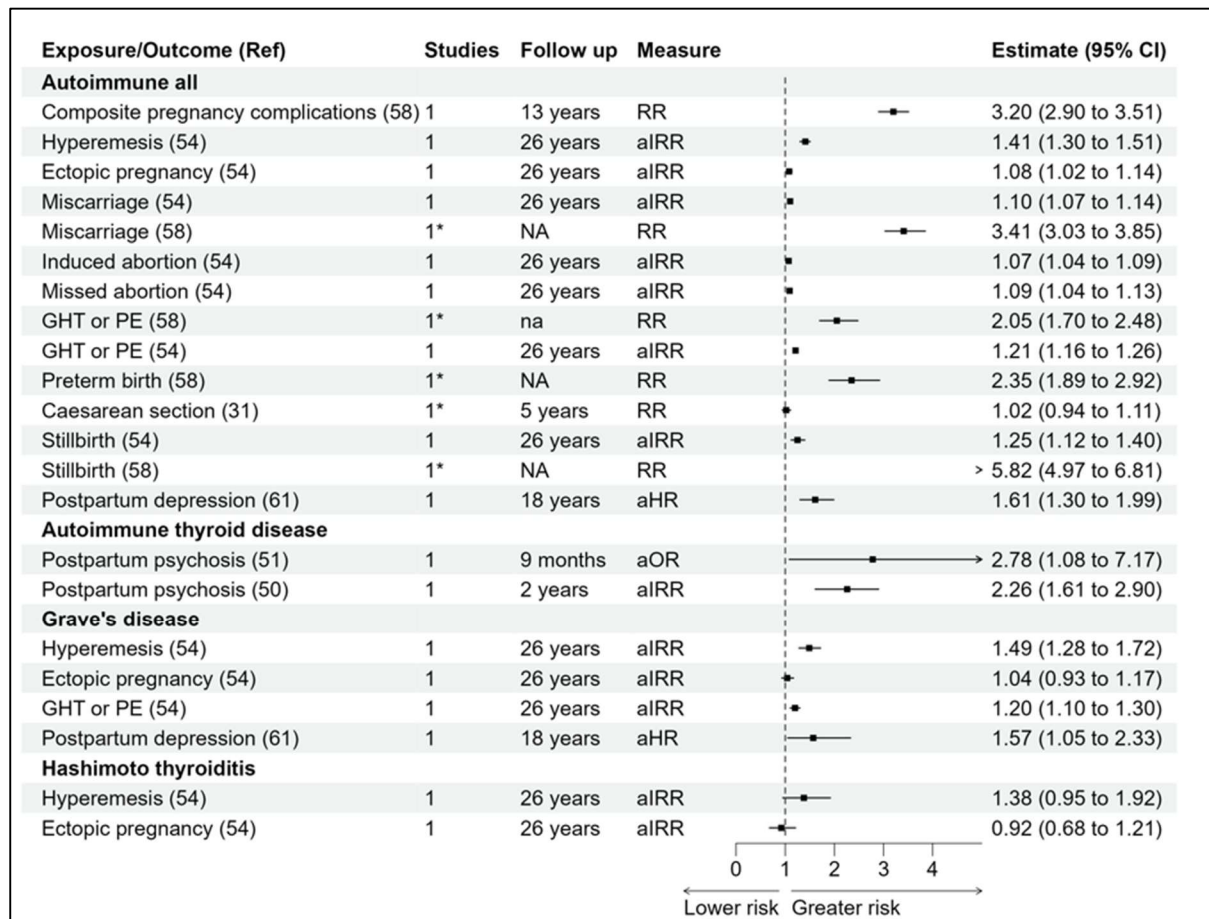
7.	Jørgensen 2010 [575]	Denmark	Danish civil Registration System	7017	Hyperemesis gravidarum, ectopic pregnancies, miscarriage, induced abortions missed abortions, hydatidiform moles, gestational hypertension, and pre- eclampsia	Rheumatoid arthritis
8.	Jørgensen 2012 [591]	Denmark	Danish women born between 1955 and 1993.	1,564,567	Hyperemesis gravidarum, gestational hypertension, preeclampsia, spontaneous abortions, missed abortions, ectopic pregnancies	Autoimmune diseases
9.	Jørgensen 2014 [578]	Denmark	Danish National Birth Cohort	97,077	Gestational hypertension, pre-eclampsia, hyperemesis gravidarum	Rheumatoid arthritis
10.	Kamper 2018 [593]	Denmark	Danish Medical Birth Register	778, 758	Pre-eclampsia	Systemic sclerosis
11.	Khashan 2011 [572]	Denmark	Danish Civil Registration System, the Danish National Hospital Register [28] and the Danish	1,035,639	Caesarean section, induced abortion	Any autoimmune disease

			Medical Birth Register			
12.	Lee 2022 [320]	South Korea	National health insurance corporation	2,260,952	Caesarean section	Systemic sclerosis
13.	Lin 2018 [596]	Taiwan	National Health Insurance Research Database	45,451	Postpartum depression	Autoimmune diseases
14.	Lin 2016 [597]	Taiwan	National Health Insurance program	145,455	Gestational hypertension	Systemic lupus erythematosus
15.	Mao 2022 [321]	China	National Health and Nutrition Examination Survey cohort	11,997	Gestational diabetes mellitus	Rheumatoid arthritis
16.	Mikkelsen 2022 [322]	Denmark	Danish Civil Registration System	1,513,560	Miscarriage	Myasthenia gravis
17.	Nielsen 2011 [598]	Denmark	Danish Civil Registration System	6,332	Miscarriage, ectopic pregnancy, hyperemesis gravidarum, gestational hypertension, pre-eclampsia, stillbirth,	Multiple sclerosis
18.	Savitz 2014 [599]	USA	Data on all births in hospitals in New York City, New York	849,639	Gestational hypertension	Type 1 diabetes mellitus
19.	Stuart 2018 [602]	Sweden	Swedish National Board of Health and the data	1,873,440	Low birth weight	Type 1 diabetes mellitus

20.	Ulf-Møller 2009 [603]	Denmark	Civil Registration System	2,140,000	Abortion (spontaneous, missed, induced), ectopic pregnancy, molar pregnancy	Systemic lupus erythematosus
21.	Wikstrom 2015 [606]	Sweden	Swedish Medical Birth Register	125,281	Intrahepatic cholestasis of pregnancy	Inflammatory bowel disease
Retrospective case control studies						
1.	Julkunen 1993 [592]	Finland	Fourth and Second Departments of Medicine and the Department of Dermatology of the Helsinki University Central Hospital	659	Spontaneous abortion, stillbirth, preterm birth, intrauterine growth restriction	Systemic lupus erythematosus
2.	Kay 1965 [594]	UK	American Rheumatism Association	418	miscarriage, stillbirth	Rheumatoid arthritis
3.	Kither 2020 [595]	UK	Clinical Practice Research Datalink	117,446	miscarriage, gestational hypertension, intrauterine growth restriction, placental complications Stillbirth	Connective tissue disease, Systemic lupus erythematosus
4.	Ma 2014 [579]	USA	Group Health Cooperative, a large Seattle-	1,304	Low birth weight, small	Rheumatoid arthritis

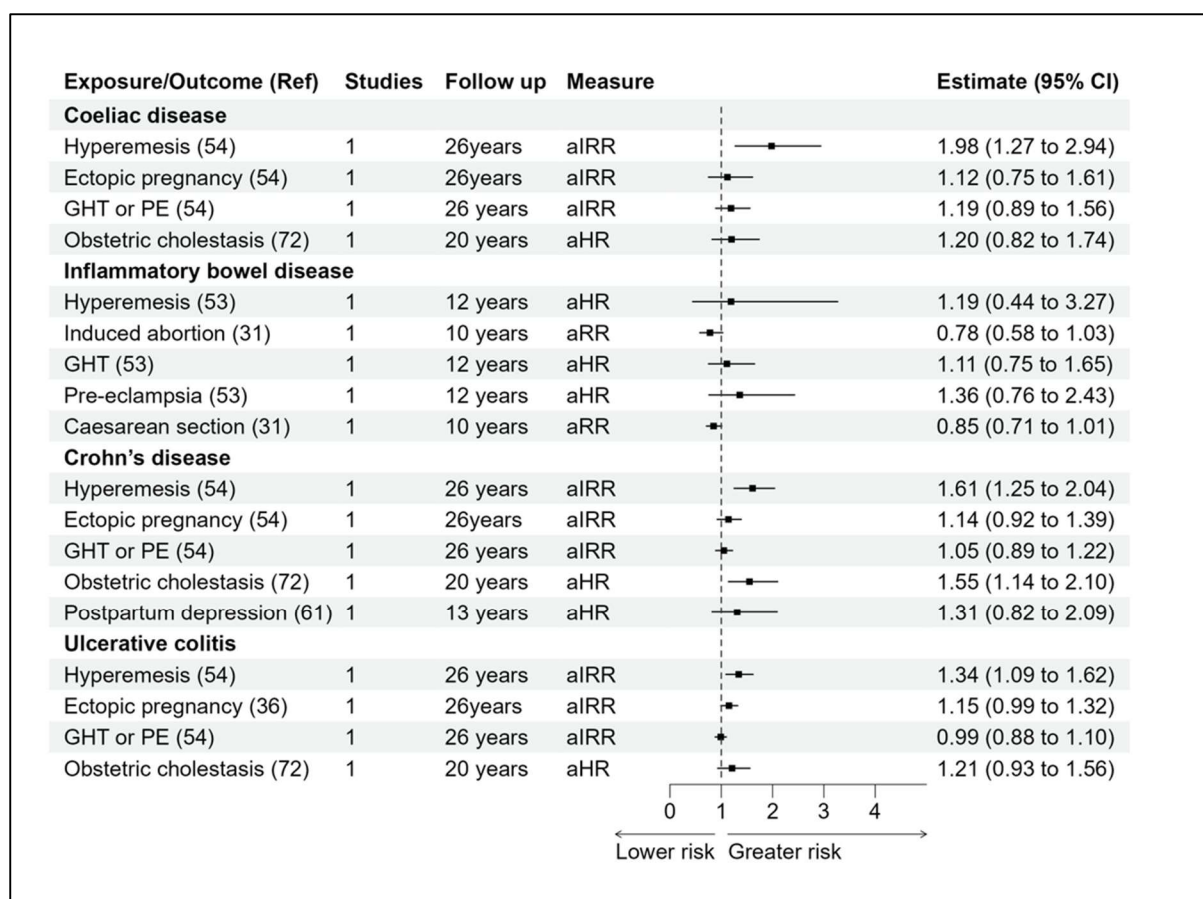
			based consumer- governed non- profit health care system		for gestational age	
5.	Siamopoulou 1988 [600]	Greece	Greek married women	573	miscarriage, preterm birth, stillbirth,	Systemic lupus erythematosus, Rheumatoid arthritis
6.	Spector 1990 [601]	UK	American Rheumatism Association criteria	657	miscarriage induced abortion, stillbirth	Rheumatoid arthritis
7.	Van Wyk 2011 [604]	The Netherlands	Leiden University Medical Centre (LUMC) and the VU Medical Centre of Amsterdam (VUMC) in the Netherlands.	206	miscarriage, gestational hypertension, intrauterine growth restriction	Systemic sclerosis
8.	Wallenius 2011 [605]	Norway	Medical Birth Registry of Norway	335,377	Pre-eclampsia, Caesarean section, Postpartum haemorrhage, Low birth weight, Preterm delivery, small for gestational age,	Chronic inflammatory arthritis RA/PSA/ANK S
Cross-sectional study						
1.	Hee 2022 [319]	China	China Kadoorie Biobank (CKB)	302,510	Miscarriage	Rheumatic arthritis

NOS (Newcastle Ottawa's scale for quality assessment of the cohort, cross-sectional or case control studies), RA/PSA/ANK S (Rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis), T1DM (Type 1 diabetes mellitus)



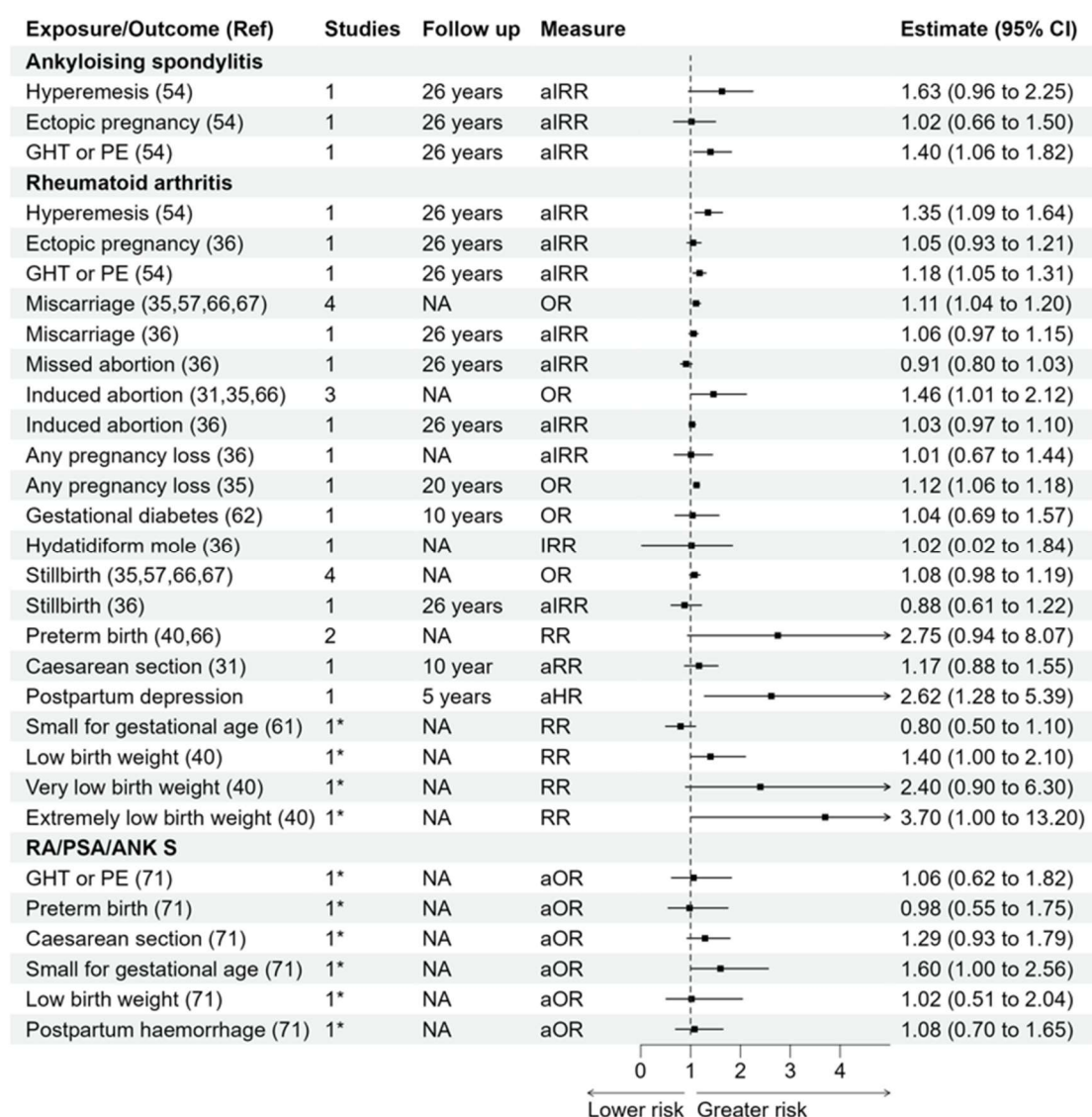
GHT or PE=Gestational hypertension or pre-eclampsia, HR=hazard ratio, RR=risk ratio, IRR=incidence rate ratio, OR=odds ratio, NA=not available, '*'=Case control study

Figure 6.3 Forest plot-association of pregnancy complications and autoimmune diseases (overall) and autoimmune thyroid diseases



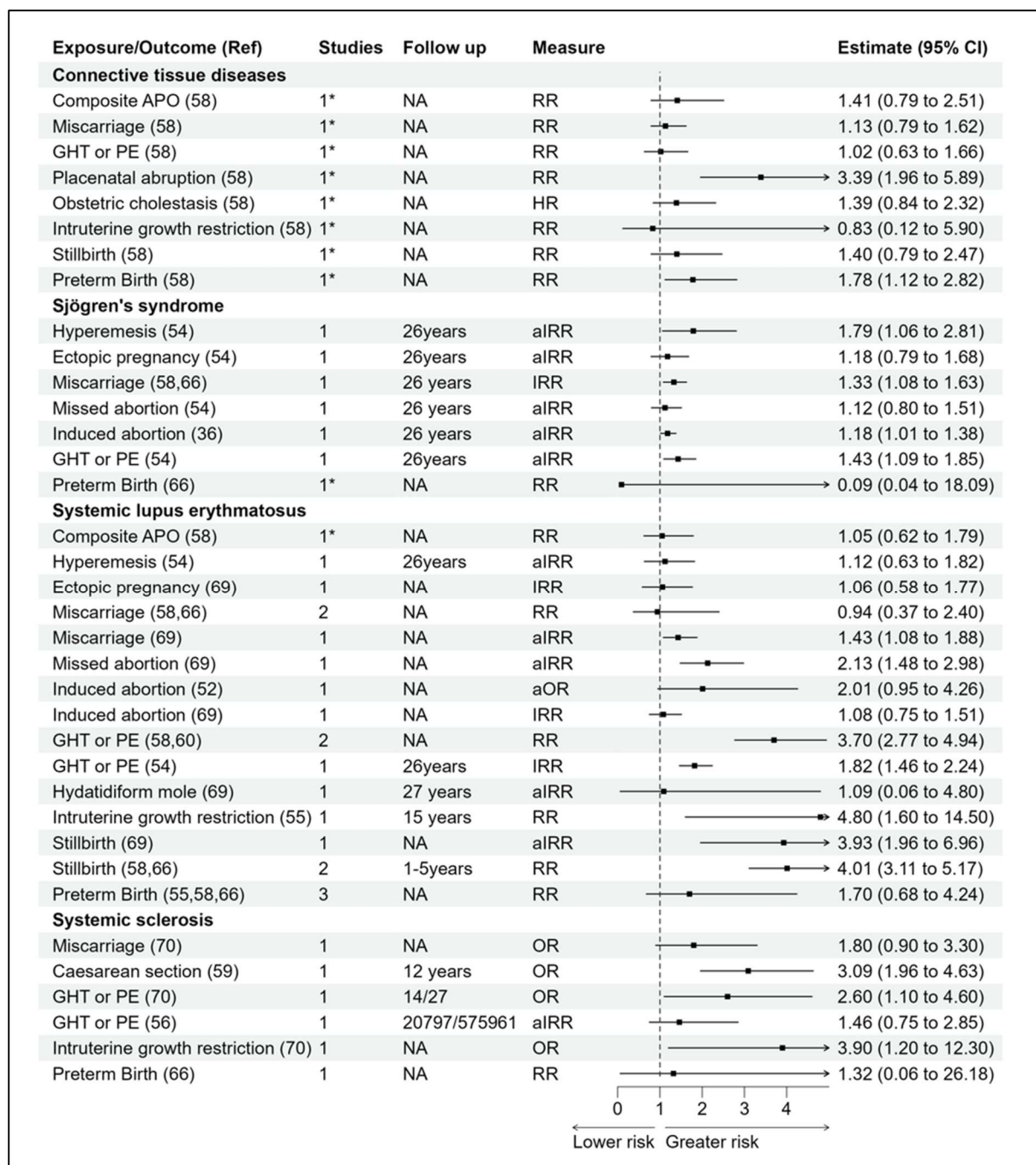
GHT or PE=Gestational hypertension or pre-eclampsia, HR=hazard ratio, RR=risk ratio, IRR=incidence rate ratio, OR=odds ratio, NA=not available, '*'=Case control study

Figure 6.4 Forest plot-association of pregnancy complications and coeliac disease or inflammatory bowel disease (Crohn's disease and ulcerative colitis)



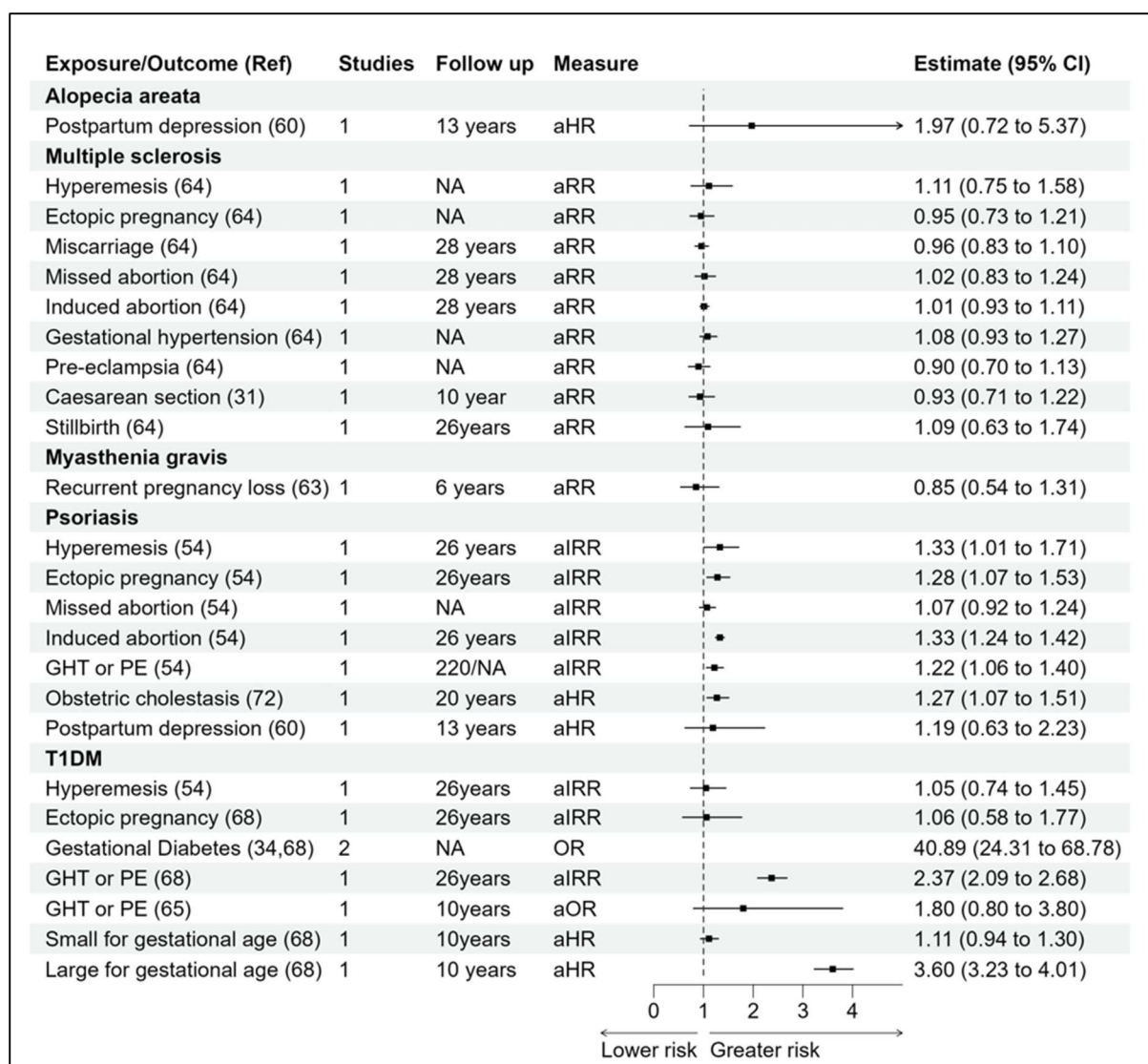
GHT or PE=Gestational hypertension or pre-eclampsia, RA/PSA/ANK S (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis) HR=hazard ratio, RR=risk ratio, IRR=incidence rate ratio, OR=odds ratio, NA=not available, '*'=Case control study

Figure 6.5 Forest plot- association of pregnancy complications and Ankylosing spondylitis, rheumatoid arthritis, or RA/PSA/ANK S



GHT or PE=Gestational hypertension or pre-eclampsia, HR=hazard ratio, RR=risk ratio, IRR=incidence rate ratio, OR=odds ratio, NA=not available, '*'=Case control study

Figure 6.6 Forest plot showing the association of pregnancy complications and connective tissue diseases



GHT or PE=Gestational hypertension or pre-eclampsia, T1DM (Type 1 diabetes mellitus), RPL= Recurrent pregnancy loss, HR=hazard ratio, RR=risk ratio, IRR=incidence rate ratio, OR=odds ratio, na=not available, '*'=Case control study

Figure 6.7 Forest plot showing the association of pregnancy complications and alopecia areata, multiple sclerosis, myasthenia gravis, psoriasis or T1DM

Chapter end Summary

The study was conducted to address the research objective: To investigate the association of pregnancy complications with the development of autoimmune diseases in a systematic review. This review compiled all the available evidence on the association of pregnancy complications and future development of autoimmune diseases in women.

Chapter 7: Discussion

7.1 Thesis overview

The aims of this thesis were 1) to carry out epidemiological studies using electronic primary care record databases to describe the prevalence of 17 autoimmune diseases in pregnancy and describe the characteristics of the women (Chapter 3); 2) to conduct an umbrella review of the literature to consolidate the evidence on the association of the autoimmune diseases in women and adverse pregnancy outcomes (Chapter 4); 3) to undertake analysis of electronic health record data to describe the risk of adverse pregnancy outcomes in women with autoimmune diseases (Chapters 5); and 4) to conduct a systematic review consolidate the evidence on the effect of pregnancy complications on subsequent development of autoimmune diseases in women (Chapter 6).

7.2 Chapter overview

This chapter will summarise findings, discuss strengths and limitations of the studies, discuss implications of findings for policy, practice, and future research recommendations. Finally, I will reflect on the impact it has had on my career.

7.3 Summary of the main findings

Chapter 3

An increase in the prevalence of the overall and individual autoimmune disease was observed: ranging from 3.5% in 2000 to 4.7% in 2021. Psoriasis had the highest prevalence throughout the study period from 1.8% (2000) to 2.0% in (2021). Prevalence of most of the autoimmune diseases increased from the year 2000-2021 with steepest rise seen in

Hashimoto thyroiditis (0.05% in 2000 to 0.12% in 2021) followed by coeliac disease (0.11% to 0.27%), Grave's disease (0.17% to 0.35%) and T1DM (0.14% to 0.49%). White women living in the least deprived areas ((aOR 1.16 (1.15-1.18)) were at significantly higher odds of having autoimmune disease during pregnancy. Ex smokers had significantly higher risk of autoimmune disease compared to non smokers (aOR 1.17 (1.16-1.18)).

Chapter 4

In the umbrella review thirty-two reviews were included consisting of 709 primary studies.

The review reported the association between 12 autoimmune conditions and 16 adverse pregnancy outcomes. Higher risk of miscarriage is reported in women with Sjögren's syndrome RR 8.85 (95% CI 3.10-25.26) and SLE OR 4.90 (3.10-7.69). Pre-eclampsia was higher in women with T1DM OR 4.19 (3.08-5.71), and SLE OR 3.20 (2.54-4.20). Women reported higher risk of GDM with inflammatory bowel disease (IBD) OR 2.96 (1.47-5.98).

There was an increased risk of intrauterine growth restriction in women with systemic sclerosis OR 3.20 (2.21-4.53) and coeliac disease OR 1.71 (1.36-2.14). Preterm birth was associated with T1DM OR 4.36 (3.72-5.12) and SLE OR 2.79 (2.07-3.77). Low birth weight babies were reported in women with SLE OR 5.95 (4.54-7.80) and systemic sclerosis OR 3.80 (2.16-6.56). There was a higher risk of stillbirth in women with T1DM OR 3.97 (3.44-4.58), IBD OR 1.57 (1.03-2.38), and coeliac disease OR 1.57 (1.17-2.10). T1DM in women was associated with 32% lower odds of small-for-gestational-age baby OR 0.68 (0.56-0.83)

Chapter 5

In the cohort study 5,239,383 pregnancies (2,863,863 women) in CPRD pregnancy register and 2,057,150 deliveries for obstetric outcomes (1,513,278 women) in HES maternity tail were eligible for analysis. There was a higher risk of hyperemesis in Addison's disease aRR

3.72 (95% confidence interval 2.48-5.59), ectopic pregnancy in rheumatoid arthritis aRR 1.50 (1.21-1.86), miscarriage in Sjogren syndrome aRR 1.36 (1.09-1.70), gestational hypertension in T1DM aRR 2.95 (2.77-3.15) and Addison's disease aRR 2.21 (1.29-3.80), pre-eclampsia/eclampsia in T1DM aRR 3.56 (3.32-3.82), GDM in Grave's disease aRR 1.37 (1.21-1.55), caesarean birth in women with T1DM aRR 2.50 (2.45-2.56) and inflammatory bowel disease aRR 1.27 (1.22-1.31), small for gestational age in SLE aRR 2.45 (1.65-3.62), preterm birth in T1DM aRR 5.21 (5.01-5.41) and rheumatoid arthritis aRR 1.47 (1.29-1.67) and stillbirth in SLE aRR 1.93 (1.10-3.39). Mental health outcomes were also associated with most of the diseases studied: multiple sclerosis, [anxiety aRR 1.76 (1.38-2.23), depression aRR 1.94 (1.77-2.12)], myasthenia gravis [(anxiety aRR 3.05 (1.89-4.92), depression aRR 1.77 (1.37-2.28)] and SLE [anxiety aRR 2.11 (1.67-2.67), depression aRR 1.36 (1.22-1.53)]. Several inverse associations were identified: for hyperemesis in systemic sclerosis aRR 0.25 (0.08-0.78), aRR SLE 0.74(0.58-0.95), myasthenia gravis aRR 0.41 (0.17-0.98) and ectopic pregnancy in T1DM aRR 0.53 (0.43-0.65). Multiple sclerosis was inversely associated with gestational hypertension aRR 0.68 (0.52-0.89) and pre-eclampsia/eclampsia aRR 0.65 (0.47-0.90).

Chapter 6

In the systematic review studying association of pregnancy complications and future risk of autoimmune conditions, thirty studies were included, and 80 associations reported. One study reported composite exposure of pregnancy complications had risk of any autoimmune disease RR 3.20 (2.90-3.51) compared to women without pregnancy complications. Women with hyperemesis gravidarum had a higher risk of developing coeliac disease (n=1) IRR 1.98 (1.27-2.94), Crohn's disease (n=1) IRR 1.61 (1.25-2.04), psoriasis (n=1) IRR 1.33 (1.01-1.71)

and rheumatoid arthritis (n=2) IRR 1.35 (1.09-1.64). Miscarriage was associated with subsequent diagnosis of Sjogren syndrome (n=2) IRR 1.33 (1.06-2.81) and rheumatoid arthritis (n=4) OR 1.11(1.04-1.20). Gestational hypertension / preeclampsia was linked with development of systemic sclerosis (n=2) IRR 2.60 (1.10-4.60) and T1DM (n=2) IRR 2.37 (2.09-2.68). Stillbirth was associated with composite autoimmune conditions (n=2) RR 5.82 (95% CI 4.87-6.81) and aIRR 1.25 (1.12-1.40). Postpartum psychosis was associated with autoimmune thyroid disease (n=1) aIRR2.26 (1.61-2.90).

Table 7.1 Summary of thesis

	Prevalence 2000-2021 Cohort study (Chapter 3)	Associated Socio demographic factors Cohort study (Chapter 3)	Adverse pregnancy outcomes Umbrella review* (Significant associations identified) (Chapter 4)	Adverse pregnancy outcomes Cohort Study* (Significant associations identified) (Chapter 5)	Pregnancy complications leading to Autoimmune diseases Systematic review** (Significant associations identified) (Chapter 6)
Autoimmune diseases					
Any Autoimmune diseases	Increase	Older age, obese, least deprived, smoker, White, higher gravidity	No systematic reviews identified	Hyperemesis gravidarum, ectopic pregnancy, miscarriage, GDM, gestational hypertension, pre-eclampsia/eclampsia, anxiety, depression, preterm birth, Caesarean birth, SGA, stillbirth	Any pregnancy complications, hyperemesis gravidarum, ectopic, miscarriage, abortions, gestational hypertension/ pre-eclampsia/eclampsia, stillbirth postpartum depression
Connective tissue diseases					
Sjogren's syndrome	Increase	Increasing age, underweight, nonsmoker, least deprived, Black and Asian, lower gravidity	Miscarriage, preterm birth, low birth weight	GDM, miscarriage, depression	Hyperemesis gravidarum, miscarriage, abortion, gestational hypertension/pre-eclampsia/eclampsia

SLE	Increase	Increasing age, underweight, smoker, least deprived Black/Asian, higher gravidity	Miscarriage, pre-eclampsia, Caesarean birth, SGA, stillbirth, preterm birth, low birth weight	Gestational hypertension, pre-eclampsia/eclampsia, anxiety, depression, preterm birth, caesarean birth, SGA Inverse association= hyperemesis gravidarum	Miscarriage, gestational hypertension/pre-eclampsia/eclampsia, IUGR, stillbirth
Systemic sclerosis	Increase	Increasing age, overweight, smoker, least deprived White, lower gravidity	Miscarriage, Preterm birth, Low birth weight	Gestational hypertension, pre-eclampsia/eclampsia, GDM, preterm birth Inverse association- Hyperemesis gravidarum	Caesarean birth, gestational hypertension/pre-eclampsia/eclampsia, IUGR
Dermatological Disorders					
Alopecia areata	Increase	Increasing age, overweight, smoker, most deprived, Asian, higher gravidity	No reviews identified	Hyperemesis gravidarum, miscarriage, GDM, gestational hypertension, pre-eclampsia/eclampsia, depression, preterm birth, SGA	No significant association identified
Psoriasis	Increase	Increasing age, overweight, Smoker, most deprived, White, higher gravidity	Miscarriage, gestational hypertension, pre-eclampsia/eclampsia, GDM, caesarean birth, IUGR, preterm birth	Hyperemesis gravidarum, ectopic pregnancy, miscarriage, GDM, gestational hypertension, pre-eclampsia/eclampsia, anxiety, depression, preterm birth, caesarean birth, SGA	Hyperemesis gravidarum, ectopic pregnancy, abortion, gestational hypertension, pre-eclampsia/eclampsia, obstetric cholestasis
Vitiligo	Increase	Younger age, underweight, Smoker, least deprived, White, higher gravidity	No reviews identified	Hyperemesis gravidarum, miscarriage, GDM, gestational hypertension	No studies identified

Endocrine Disorders					
Addison's disease	Increase	Increasing age, underweight, nonsmoker, most deprived, other ethnicities, lower gravidity	No reviews identified	Hyperemesis gravidarum, GDM, gestational hypertension, pre-eclampsia/eclampsia, depression, preterm birth, caesarean birth, SGA	No studies identified
Grave's disease	Increase	Increasing age, underweight, nonsmoker, least deprived, Asian ethnicity, higher gravidity	Thyroid autoimmunity-miscarriage, gestational hypertension, GDM, preterm birth	Hyperemesis gravidarum, miscarriage, GDM, gestational hypertension, pre-eclampsia/eclampsia, anxiety, depression, preterm birth, caesarean birth.	Hyperemesis gravidarum, postpartum depression, gestational hypertension, pre-eclampsia/eclampsia.
Hashimoto's thyroiditis	Increase	Increasing age, overweight, nonsmoker, most deprived, other ethnicities, lower gravidity		Depression	No significant association identified
T1DM		Younger age, underweight, nonsmoker, least deprived, White, lower gravidity	Gestational hypertension, pre-eclampsia, caesarean birth, stillbirth, preterm birth Inverse association -SGA	Hyperemesis gravidarum, miscarriage, gestational hypertension, pre-eclampsia/eclampsia, anxiety, depression, preterm birth, caesarean birth, stillbirth Inverse association-ectopic pregnancy	Gestational hypertension/pre-eclampsia/eclampsia, Large for gestational age
Gastrointestinal Disorders					
Coeliac disease	Increase	Increasing age, underweight, nonsmoker, least deprived, White, lower gravidity	Miscarriage, Caesarean birth, IUGR, stillbirth, preterm birth, low birth weight	Hyperemesis gravidarum, preterm birth, caesarean birth, anxiety, depression	Hyperemesis gravidarum

IBD	Increase	Increasing age, underweight, smoker, least deprived, White, lower gravidity	GDM, caesarean birth, stillbirth, preterm birth, low birth weight	Ectopic, pre-eclampsia/eclampsia, anxiety, depression, preterm birth, caesarean birth.	No significant association identified
Crohn's disease	Increase	Increasing age, underweight, smoker, least deprived, White, lower gravidity	Ectopic pregnancy, caesarean birth, low birth weight	Ectopic pregnancy, pre-eclampsia/eclampsia, anxiety, depression, preterm birth, caesarean birth	Hyperemesis gravidarum, obstructive cholestasis
Ulcerative colitis	Increase	Increasing age, underweight, nonsmoker, least deprived, White, lower gravidity	Ectopic pregnancy	Anxiety, depression, preterm birth, caesarean birth	Hyperemesis gravidarum
Musculoskeletal Disorders					
Ankylosing spondylitis	Decrease	Increasing age, underweight, smoker, least deprived, White, lower gravidity	Caesarean birth	Miscarriage, anxiety, Caesarean birth	Gestational hypertension/pre-eclampsia/eclampsia
Psoriatic arthritis	Increase	1. Increasing age, obese, smoker, least deprived, White and Other, increasing gravidity	Gestational hypertension, pre-eclampsia, caesarean birth, preterm birth	GDM, preterm birth, Caesarean birth	No studies identified
Rheumatoid arthritis	Increase	Increasing age, underweight, nonsmoker, most deprived, Asian, lower gravidity	Miscarriage, pre-eclampsia, caesarean section, SGA, stillbirth, preterm birth, low birth weight	Ectopic pregnancy, pre-eclampsia, depression, preterm birth, caesarean birth, SGA	Hyperemesis gravidarum, ectopic pregnancy, Gestational hypertension/pre-eclampsia/eclampsia, miscarriage, abortion, stillbirth, caesarean birth, postpartum

					depression, stillbirth
Neurological Disorders					
Multiple sclerosis	Decrease	Increasing age, underweight, smoker, least deprived, White/other, lower gravidity	No significant association identified	Ectopic pregnancy, anxiety, depression, caesarean birth Inverse association- Gestational hypertension, pre-eclampsia/eclampsia	No significant association identified
Myasthenia gravis	Decrease	Increasing age, obese, nonsmoker, least deprived, Black, lower gravidity	Caesarean birth	Miscarriage, preterm birth, anxiety, depression Inverse association- Hyperemesis gravidarum	No significant association identified

GDM=Gestational hypertension, IBD= Inflammatory bowel disease, IUGR= intra uterine growth restriction, SGA= Small for gestational age, SLE=Systemic lupus erythematosus, T1DM= type one diabetes mellitus, anxiety/depression in table refers to perinatal anxiety, depression

*Association of women with autoimmune conditions leading to adverse pregnancy outcomes

**Association of pregnancy complications leading to development of autoimmune diseases in women.

7.4 Strengths and Limitations

A key strength of this thesis is the inclusion of a range of autoimmune condition and pregnancy outcomes. The autoimmune diseases included are notably more prevalent in women of reproductive age. The selection of these conditions was carefully determined through an extensive review of the existing literature [262, 641, 642], consultations with experts in the field and engaged with public patient group (MuM-PreDiCT) ensuring both clinical significance and patient priorities. This rigorous selection process enhances the relevance and depth of our study, providing a comprehensive exploration of autoimmune diseases in a critical life stage for women. Similarly wide range of pregnancy complications have been included after literature review and consultation with experts and patient public

engagement. Moreover the definitions of the outcomes were predefined so that these were uniform across the study [362]. Since some of the autoimmune conditions we studied are relatively rare, we incorporated data from both databases (CPRD GOLD and Aurum; chapter 3 and 5), we were able to increase the likelihood of identifying these less prevalent diseases, thereby enhancing the sample size. This dual-database approach also allowed us to mitigate potential biases associated with underreporting in any one source, providing a more comprehensive view of autoimmune disease occurrence and capture the effect on the pregnancy outcome. The large dataset enabled a comprehensive examination of how various factors, including age, sex, socioeconomic status, and other demographic characteristics, influence the prevalence and distribution of autoimmune diseases. As a result, the generalisability of our findings is enhanced, making them more applicable to broader healthcare populations. The reviews conducted in the thesis follow robust methodology (chapter 4 and 6). Use of comprehensive search strategy, which was designed to ensure inclusivity and thoroughness. By imposing no restrictions on language, the search effectively captured a wide array of studies from diverse contexts and backgrounds. Additionally, the search strategy included periodic updates to account for newly published studies, ensuring that the review remained current and reflective of the latest research advancements. This iterative process of searching and including recent literature contributes to the rigor and relevance of the review, however, it was hampered by the quality of included studies. The thesis has identified critical associations with adverse pregnancy outcomes but have also uncovered noteworthy links to mental health issues such as anxiety and depression, which have received limited attention in previous research.

However, limitations exist. There were challenges related to data quality, including missing data and misclassification bias stemming from inaccurate clinical coding. (chapter 3 and 5)

The IMD scores utilised in our analysis are based on postcode data, which may not accurately reflect individual-level deprivation. While these scores are expected to be broadly representative of the populations studied, they may not capture the nuanced socioeconomic factors affecting individual patients. Furthermore, residual confounding remains a concern, as unmeasured factors could influence the observed associations between autoimmune diseases and pregnancy outcomes. Recognising these limitations is crucial for interpreting our findings and for guiding future research efforts aimed at addressing these gaps. The primary limitations of the reviews is that we were unable to include certain autoimmune or pregnancy outcomes due to the absence of existing literature on these topics (chapter 4 and 6). Moreover, the reviews did not adequately address the role of disease activity during pregnancy and how pregnancy itself may influence the course of these autoimmune conditions. Similarly understanding the risk of these medications and how they contribute towards adverse pregnancy outcomes were not considered [471]. Another limitation is that this thesis is unable to establish a direct cause-and-effect relationship between autoimmune diseases and pregnancy complications.

7.5 Implications for policy and clinical practice

The findings emphasise the urgent need for comprehensive, evidence-based guidelines for preconception and pregnancy care across a wide range of autoimmune conditions. Healthcare professionals, including rheumatologists, endocrinologists, gynaecologists, obstetricians, nurses, and general practitioners involved in the care of women with autoimmune conditions, as well as policymakers responsible for evaluating existing guidelines. While specific guidelines exist for diseases like T1DM, and multiple sclerosis, they largely focus on medication safety rather than on broader management strategies. Given

that many adverse pregnancy outcomes are shared across different autoimmune conditions, there is a strong rationale for research to uncover common mechanisms and develop universal guidelines to support clinicians in practice.

Preconception care and risk stratification are essential for improving pregnancy outcomes [643], including reducing risks like miscarriage and low birth weight. Implementing antenatal care measures such as administering low-dose aspirin, where indicated and using predictive biomarkers for conditions like pre-eclampsia [644, 645] can significantly improve outcomes for women with autoimmune diseases. By prioritising these areas, healthcare providers can better support women's reproductive health, ultimately leading to improved outcomes for mothers and their children.

Our review has shown links between miscarriage and SLE, as well as gestational hypertension and T1DM, but variations in study designs and sample sizes have led to mixed results. While earlier research focused on the impact of pregnancy complications, such as caesarean births and pre-eclampsia, on child outcomes, recent studies suggest that pregnancy complications may also contribute to the development of long-term conditions in mothers. Additionally, reproductive factors and pregnancy itself may be linked to the later onset of autoimmune diseases, though findings remain inconsistent [646]. Further research, particularly through prospective longitudinal studies and larger epidemiological analyses, is crucial to elucidate the mechanisms linking pregnancy complications with subsequent autoimmune disease development. By following individuals over time, prospective studies can capture temporal relationships and help distinguish between causal associations and correlations. In addition, larger epidemiological studies with diverse populations are needed to identify genetic, environmental, and lifestyle factors that modulate these risks. Such

studies would also help to quantify how different types and severities of pregnancy complications, such as preeclampsia, gestational diabetes, or preterm birth, may differentially impact autoimmune risk. These insights would not only improve our understanding of underlying mechanisms but could also inform early interventions for women identified as high risk for autoimmune diseases post-pregnancy.

Health economic evaluation plays a crucial role in translating research into healthcare policy and practice, particularly within the NHS, where resource allocation must be evidence-based and meet cost-effective thresholds to be considered for adoption. In the context of maternity care (based on the implications arising from this thesis), evaluating the economic case for implementing customised care protocols for pregnant women with autoimmune diseases will ensure that new interventions are both clinically beneficial and financially sustainable. A relevant health economic study should assess the cost-effectiveness of a risk-based maternity care model compared to standard NHS care, focusing on whether additional antenatal monitoring, specialist input, and tailored interventions can reduce adverse pregnancy outcomes and long-term healthcare costs. This is particularly important for pregnancies affected by autoimmune diseases, where the risk of complications such as preterm birth, pre-eclampsia, and fetal growth restriction is elevated. By targeting resources towards those at highest risk, such models may improve maternal and neonatal outcomes while optimising healthcare utilisation. Key components would include a cost-effectiveness analysis to compare intervention costs against potential savings from reduced complications, a budget impact analysis to assess financial feasibility within NHS maternity services, and an implementation feasibility assessment to ensure scalability and integration into existing pathways [647]. Additionally, considerations of health equity are vital to determine whether high-risk groups, such as ethnic minorities and socioeconomically disadvantaged women,

experience greater benefits. By providing clear economic justification, such evaluations support policy change, inform NHS commissioning decisions, and promote equitable access to high-quality maternity care, improving maternal and neonatal health outcomes.

7.6 Recommendations on existing guidelines

The current guidelines for most autoimmune diseases emphasise drug management to maintain remission or low disease activity before and during pregnancy to minimise the risk of adverse pregnancy outcomes. The guidelines specify which medications are safe to use during the pre-conception period, each trimester, and breastfeeding. However, limitations exist, particularly due to insufficient evidence for the use of certain antirheumatic drugs, such as interleukin-17 inhibitors and rituximab. Although antenatal counselling is advised, it mainly centres around medication use and associated risks [478].

7.6.1 Systemic inflammatory disorders

General guidelines for the management of SLE [265] exist, and our study identifies SLE as a condition associated with several adverse pregnancy outcomes. This underscores the need for a dedicated set of recommendations, particularly focused on timely interventions to prevent complications such as miscarriage, pre-eclampsia, small-for-gestational-age infants, and preterm birth. Additionally, recommendations addressing perinatal mental health need to be included given the high risk of adverse mental health outcomes observed in our study.

While guidelines for systemic sclerosis [648], are available, they offer limited guidance on pregnancy management. For women with the disease planning a pregnancy, the guidelines suggest assessing for significant renal, cardiac, or lung complications and discontinuing harmful medications in favour of safer alternatives, such as azathioprine where appropriate.

Our studies highlight an increased risk of pre-eclampsia and preterm birth in these patients, indicating that the guidelines could be enhanced by recommending low-dose aspirin [649] or developing individualised birth management plan.

For pregnant women with Sjögren's syndrome, guidelines [650] recommend low-dose aspirin for high-risk pregnancies to improve placental implantation and reduce miscarriage risk. However, previous studies have shown no significant difference in pregnancy outcomes with aspirin use [651, 652]. Our research identified a higher risk of preterm birth and mental health disorders, which should be integrated into antenatal management and counselling for these women.

7.6.2 Dermatological disorders

Guidelines exist for the management of vitiligo [653], but they lack specific recommendations for pregnant women or those planning conception. Our studies have reported an increased risk of hyperemesis, miscarriage, and gestational hypertension associated with vitiligo. Additionally, vitiligo is linked to conditions such as pernicious anaemia, Addison's disease, atopic dermatitis, and diabetes [653, 654], further increasing the risk of adverse pregnancy outcomes.

The guidelines for managing alopecia areata [655] mention women of childbearing age, recommending close monitoring of treatments like ciclosporin and advising caution with corticosteroids due to their associated risks, including cleft lip and preterm delivery.

Treatments to avoid during pregnancy include contact immunotherapy, methotrexate, mycophenolate mofetil, JAK inhibitors, and minoxidil, with recommendations to avoid pregnancy during and up to 6 months post-treatment. Our studies observed a higher risk of

hyperemesis, miscarriage, gestational hypertension, preterm birth, and small-for-gestational-age infants, which should be addressed in the guidelines.

Recommendations for the use of biologics in psoriasis exist [656] and a review [657] has discussed psoriasis management during pregnancy, focusing on reducing risks such as miscarriage, preterm birth, depression, and birth defects. Our studies indicate that psoriasis is associated with various adverse pregnancy outcomes, highlighting the need for a dedicated national guideline for managing psoriasis in pregnancy.

7.6.3 Endocrine disorders

The NICE guidelines for Addison's disease recommend pre-pregnancy counselling, specialist monitoring during pregnancy, and steroid dose management for all women with adrenal insufficiency [658, 659]. The treatment of hyperemesis gravidarum is also detailed in these guidelines, aligning with our study, which reports a high risk of hyperemesis. However, the guidelines should incorporate other observed outcomes associated with Addison's disease, such as gestational hypertension, pre-eclampsia/eclampsia, preterm birth, and depression.

For thyroid disorders, the 2017 guidelines from the American Thyroid Association [660] discuss the treatment of pregnant women with thyroid disease, with an emphasis on miscarriage and preterm birth. However, there is a lack of specific guidance for Grave's disease or Hashimoto's thyroiditis, even though our study indicates these conditions have risk of adverse pregnancy outcomes. Grave's disease is associated with higher risks of gestational hypertension, GDM, preterm birth, and mental health issues during pregnancy, which are not as prevalent in Hashimoto's thyroiditis. These conditions should be treated separately, with tailored recommendations.

Regarding T1DM, existing guidelines primarily focus on diabetes management during pregnancy [661]. Our study shows an increased risk of almost all adverse pregnancy outcomes in women with T1DM. Therefore, guidelines should be expanded to include information on these risks and interventions to prevent them, including the development of individualised birth plans for women with T1DM.

7.6.4 Gastrointestinal disorders

Generic guidelines for management of coeliac disease in adults are available with no special recommendation for pregnant women [662, 663]. Our studies report higher risk of miscarriage, preterm birth, caesarean section, and adverse mental health during pregnancy and there is a need or pregnancy focused guideline.

Also, generic guidelines on management of IBD in adults suggest careful monitoring of drugs like methotrexate, Anti-tnF, vedolizumab, ustekinumab and tofacitinib therapy and caesation of these drugs second trimester onwards [664]. British Society of Gastroenterology and the British Maternal and Fetal Medicine Society guidance [664] report for pregnant women focuses on antenatal care, effect of Biologics and planning of mode of birth. However, our study also reports increase in the mental health disorders which need to be addressed.

7.6.5 Musculoskeletal disorders

For ankylosing spondylitis, there is no specific guideline for disease management during pregnancy [665, 666]. However, the ACR (American college of rheumatology) and BSR (British society of Rheumatology) guidelines provide recommendations on the use of medications such as NSAIDs, biologics, and corticosteroids. Our studies indicate a higher risk

of miscarriage, preterm birth, caesarean section, and mental health issues in women with ankylosing spondylitis, which should be incorporated into pregnancy-specific guidelines.

Similarly, no specific guidelines exist for the management of psoriatic arthritis during pregnancy [667], although general drug guidelines cover most treatments used for the condition. Our studies report an increased risk of preterm birth and caesarean section, underscoring the need for dedicated recommendations.

For rheumatoid arthritis, there is also no specific pregnancy management guideline [668], though broader guidelines address drug use in treatment. Our studies suggest an elevated risk of pre-eclampsia, preterm birth, and caesarean section in women with rheumatoid arthritis, highlighting the importance of including specific interventions to prevent these outcomes in future guidelines.

7.6.6 Neurological disorders

For myasthenia gravis, best practice guidelines from a UK multispecialty working group provide recommendations on managing medications during pregnancy, along with guidance on antenatal care and planning the mode of birth [669]. However, our study identifies a higher risk of miscarriage, preterm birth, and mental health disorders in women with myasthenia gravis, which should be addressed in the guidelines to ensure comprehensive care.

For multiple sclerosis, the UK consensus on pregnancy covers various aspects, including contraception, conception, disease management during pregnancy, delivery, anaesthetic options, and breastfeeding recommendations [670]. However, our research highlights the

need to incorporate mental health considerations into these guidelines, as women with multiple sclerosis may face increased risks of mental health disorders during pregnancy.

Despite the existing guidelines, there is a notable gap in the comprehensive management of autoimmune conditions during pregnancy. Most current guidelines primarily focus on medication management. Recommendations for future guidelines include disease specific guidelines that account for the unique risks and management strategies associated with each autoimmune condition. Risk assessment tools for adverse pregnancy outcomes based on specific autoimmune conditions will aid in tailoring care for women. Intervention strategies should aim at preventing adverse pregnancy outcomes.

7.7 Future research

7.7.1 Autoimmune diseases and offspring outcomes

Emerging research suggests that autoimmune conditions in pregnant women may contribute to birth defects and have long-term effects on their offspring. Studies have linked maternal autoimmune diseases to developmental challenges in children, such as learning disabilities, dyslexia, and autism spectrum disorders [474, 671]. These findings highlight the importance of further research into how maternal autoimmunity and related factors influence pregnancy outcomes and the health of children over time. This understanding is crucial for improving clinical practices and enhancing maternal and child health. Additionally, recent registry studies report a higher risk of mental health disorders in children born to women with autoimmune diseases [672]. This thesis emphasizes the need to evaluate the mental health of these mothers, given the potential intergenerational impact. Another area of concern involves the effects of medications used to manage autoimmune conditions on the

fetal microbiome, which increasingly appears to play a significant role in long-term health outcomes [673]..

These findings underscore the need for targeted management strategies to support both maternal and fetal health. By understanding these complex associations, clinical practices can be improved to better address risks and promote long-term well-being for mothers and their children. Further research into the scope of these intergenerational effects could guide the development of preventative measures and targeted interventions to optimise outcomes across generations.

7.7.2 Further pharmaco-epidemiological studies on drugs used in autoimmune diseases and adverse pregnancy outcomes

Women with autoimmune diseases, such as rheumatoid arthritis, SLE, and multiple sclerosis, require continuous treatment to manage their conditions. However, many medications used to treat these diseases can potentially impact pregnancy outcomes, fetal development, and lactation. The most prescribed drugs include immunosuppressants, biologics, antimetabolites, corticosteroids, anti-TNF therapies, DMARDs, and NSAIDs. While intermittent (due to low risk of miscarriage involved) rather than regular use of all non-selective NSAIDs is recommended throughout pregnancy, they should be avoided in the third trimester (26 week onwards) due to fetal risks [674]. Despite the critical need for safe treatment options, few studies investigate the effects of these drugs during pregnancy, and guidelines are limited for many autoimmune diseases. For instance, research on the safety of biologics in pregnant women with psoriasis and IBD has yielded contradictory findings [675-678]. Some studies indicate that anti-TNF α medications are associated with a higher risk of preterm births and newborn infections, particularly in IBD patients, who are already at

increased risk for these outcomes. Conversely, no significant risk of adverse pregnancy outcomes has been identified in women with rheumatoid arthritis or psoriasis [679, 680]. Evidence regarding corticosteroid use during pregnancy and its effects on outcomes such as preterm birth, birth weight, preeclampsia, and gestational diabetes remains limited and inconsistent. While some data suggest a slight risk of oral clefts [681], the overall findings are conflicting. Corticosteroids, particularly prednisolone, are generally considered safe with careful monitoring; however, long-term use may increase complications. Some DMARDs are deemed safe during pregnancy, but methotrexate, leflunomide, and certain biologics are contraindicated due to potential harm to the foetus [682, 683]. Research on the safety of medications used for autoimmune diseases during pregnancy and lactation is still lacking. Although drugs like corticosteroids are known to transfer into breast milk in small amounts, the clinical significance of this exposure for infants remains uncertain. For biologics, their large molecular size suggests limited transfer into breast milk, but data on this topic are sparse [684, 685]. Another crucial area that requires further investigation is the timing and dosing of medications. While some drugs may be safe during specific trimesters, much of the existing data stems from observational studies, case reports, and small cohort studies. Clinical trials often exclude pregnant women, resulting in a significant knowledge gap. A deeper understanding of these risks would enable clinicians to better balance the management of the mother's autoimmune condition with minimising potential harm to the foetus [686].

7.7.3 Further research into potential mechanisms behind associations between autoimmune disease and pregnancy complications

Several potential mechanisms have been suggested; how maternal autoimmune diseases and their related chronic inflammation can impact pregnancy outcomes. Chronic inflammation associated with autoimmune diseases elevates pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), which may disrupt placental development and function, leading to adverse pregnancy outcomes [687, 688].. This inflammatory response can interfere with fetal development, increasing risks of complications like congenital malformations, neurodevelopmental disorders, and other adverse outcomes in offspring. Furthermore, the impact of autoantibodies is a mechanism of interest in this direction. Identifying specific autoantibody profiles that predict pregnancy complications could enhance prenatal monitoring and management, improving outcomes for both mother and child [346]. Additionally, maternal factors such as age, comorbidities, and medication use also influence pregnancy outcomes, shaping the maternal environment and its effects on fetal development. Future research should focus on the interactions between maternal and fetal microbiomes to better understand their roles in these associations [689].

Conversely, pregnancy itself may predispose women to autoimmune diseases later in life, a second direction of association. Heightened immune activation during pregnancy can leave lasting effects on maternal immune responses, as the immunological changes that induce a state of tolerance during pregnancy may persist beyond pregnancy, increasing susceptibility to autoimmune conditions [690]. Hormonal influences, particularly the roles of oestrogen and progesterone, can modulate immune responses and affect disease activity, with some

conditions experiencing remission during pregnancy while others may flare postpartum due to stress or hormonal shifts [691]. Genetic factors may also play a role in this direction, as women who experience pregnancy complications might carry genetic predispositions—such as specific single nucleotide polymorphisms (SNPs), that elevate their risk for autoimmune diseases [692]. To explore these mechanisms further, a multi-faceted research approach is necessary, involving longitudinal cohort studies to monitor inflammatory markers, genetic studies to identify SNPs linked to autoimmune conditions, microbiome analyses to assess maternal and fetal microbiota, and interventional trials to evaluate safe medication adjustments during pregnancy.

7.7.4 Conclusion

There is rising prevalence of autoimmune diseases among pregnant women. While the burden of each individual disease may be small, collectively, they pose a significant public health concern. The findings emphasise the necessity for adaptable health policies and resource allocation to meet the diverse needs of this population. There is clear association of adverse pregnancy outcomes in women with autoimmune conditions and identifies research gaps. To mitigate potential adverse outcomes, it advocates for the development of comprehensive clinical guidelines to improve preconception and maternity care for these women. The management of autoimmune diseases during pregnancy requires a balanced approach that considers both disease control and fetal safety. Close collaboration between rheumatologists, obstetricians, and other specialists is crucial for optimising maternal and fetal outcomes. Additionally, there is link between pregnancy complications and the later development of autoimmune diseases, calling for prospective longitudinal studies to track

women with pregnancy complications and the early detection of autoantibodies. Clinicians are urged to identify autoimmune conditions promptly in women with such histories.

7.8 Personal reflection

I developed a passion for maternal health during my undergraduate studies, especially after observing hospital rounds in India. I noticed that while most wards were filled with pain and suffering, the obstetric ward was the only one that had an atmosphere of hope and joy. However, as I progressed in my work to improve maternity care, I came to realise that there are significant challenges around maternity care and a great need for improvement, both in developed and developing nations. This realisation motivated me to pursue this research, aiming to gain an in-depth understanding of one aspect of this vast field.

The journey of completing my PhD has been both challenging and rewarding. Reflecting on the process, I recognise the hurdles I faced, including handling large datasets, learning statistical methods, learning new research methodologies, and managing the complexities of presenting multiple exposures and outcomes.

When I first embarked on my research journey, I had doubts about whether I could fully commit to the rigorous demands of pursuing a PhD. To manage this uncertainty, I decided to start with an MSc by Research, allowing me to gain experience and assess my capabilities before committing to a longer-term path. My initial project involved conducting an umbrella review, a methodology I had not worked with before. While the learning curve was steep, I successfully completed this major piece of research by the time of my first-year Annual Progress Review (APR). This achievement gave me the confidence I needed to move forward, and with the support and encouragement of my supervisors, I applied to upgrade my degree

to a PhD. The transition marked a pivotal moment in my academic journey, confirming that I was ready to take on the challenges and opportunities that a PhD would offer.

New Methodologies and adaptations

Conducting the umbrella review proved to be particularly challenging due to the steep learning curve involved in mastering an unfamiliar methodology. The literature offered various approaches, making it difficult to determine which would be the most rigorous and yield high-quality research. While the existing literature clearly outlined how to calculate the overlap in the included reviews and provided guidelines for handling cases of high overlap, there was little guidance on how to proceed when the overlap between reviews was low or non-existent. After thoroughly studying the available methodologies, I made the decision to include the low-overlap or non-overlapping reviews and perform a meta-analysis on the primary studies within these reviews. To avoid double-counting, I carefully ensured that the studies were not duplicated in the analysis, allowing me to present the results with clarity and precision. Although I was already familiar with systematic review methodologies, the overwhelming number of search results created an additional hurdle. This forced me to limit my search to studies published after 2010 to make the process more manageable. To mitigate missing important studies before 2010, I had to employ a snowballing approach to ensure that I didn't miss any key studies, which significantly increased my workload. When I reached the data extraction stage, I encountered another challenge: missing data in many of the studies. I thoroughly examined supplementary materials and even reached out to the authors for clarification. Unfortunately, my attempts were largely unsuccessful, preventing me from conducting a meta-analysis for many of the outcomes. Like the umbrella review, this project also involved reporting on many associations: around 80 in total, which required

significant time and strategic planning to present the findings in a meaningful and accessible way.

Project manager MuM-PreDiCT

Key aspect that contributed to my growth during this PhD was my role as project manager for MuM-PreDiCT, a project focusing on long term health conditions in pregnant women.

This role expanded my skill set beyond research, allowing me to develop leadership and organisational skills by coordinating meetings, managing timelines and resources. I gained experience in coordinating different teams, overseeing project timelines, and ensuring the successful implementation of research aims.

Working closely with MuM-PreDiCT Patient and Public Involvement and Engagement (PPIE) group was a transformative experience. It made me acutely aware of the importance of using desexed language in research and communication, ensuring that my work was inclusive and respectful of diverse populations. This awareness profoundly shaped my approach to communicating research outcomes, encouraging me to adopt a more compassionate and empathetic perspective when working with vulnerable populations.

The insights from the PPIE group were invaluable in reminding me that research impacts real people, and sensitivity to the language and framing used is essential for both inclusivity and patient-centred care.

Statistical Methods and big datasets

One of the most formidable challenges I encountered during my PhD was learning and applying advanced statistical techniques. While I had a foundation in basic statistics, the intricate methods required for my research demanded a deeper understanding of complex

statistical concepts. For instance, working with large datasets like the CPRD pregnancy register and Hospital Episode Statistics required me to develop proficiency in statistical techniques. The need for precision in selecting the right statistical approach for each aspect of my work pushed me to seek additional resources and collaborations with statisticians. Through persistent effort and countless revisions, I was able to overcome these challenges and apply these methods confidently to my research.

Presenting Multiple Exposures and Outcomes

One of the most conceptually difficult aspects of my PhD research was managing and presenting multiple exposures and outcomes. The thesis involved presenting intricate relationships between various diseases and outcomes, requiring careful consideration of confounding variables and interactions. The challenge lay not only in the analysis but also in effectively communicating these complex relationships. Balancing statistical rigor with clarity in presenting my findings was difficult, as I needed to ensure that my results were interpretable and actionable. I found it challenging to structure my research so that the multiple dimensions of exposure and outcome could be presented in a cohesive and digestible format for different audiences, from clinicians to researchers.

Summary of reflection

Overall, the process of completing my PhD has been an intense learning experience that has tested my perseverance, adaptability, and critical thinking. The hurdles I faced with mastering statistical methods, adapting to new research methodologies, and managing the complexities of multiple exposures and outcomes have all contributed to my growth as a researcher. While the path was fraught with challenges, each obstacle helped to sharpen my skills and deepen my understanding of my field. I now feel better equipped to conduct

rigorous research and contribute meaningfully to the academic and clinical communities, particularly around maternal health. Additionally, working with patient involvement groups like MuM-PreDiCT has taught me the importance of collaboration, communication, and compassionate language in health research. Ultimately, this thesis has equipped me with the skills, knowledge, and empathy to make meaningful contributions to women's healthcare in the future.

References

1. Invernizzi, P., et al., *Female predominance and X chromosome defects in autoimmune diseases*. Journal of autoimmunity, 2009. **33**(1): p. 12-16.
2. Jacobson, D.L., et al., *Epidemiology and estimated population burden of selected autoimmune diseases in the United States*. Clin Immunol Immunopathol, 1997. **84**(3): p. 223-43.
3. Eaton, W.W., et al., *Epidemiology of autoimmune diseases in Denmark*. J Autoimmun, 2007. **29**(1): p. 1-9.
4. Davidson, A. and B. Diamond, *Autoimmune diseases*. N Engl J Med, 2001. **345**(5): p. 340-50.
5. Wang, L., F.-S. Wang, and M.E. Gershwin, *Human autoimmune diseases: a comprehensive update*. Journal of Internal Medicine, 2015. **278**(4): p. 369-395.
6. Marmont, A.M., *Stem cell transplantation for severe autoimmune diseases: progress and problems*. Haematologica, 1998. **83**(8): p. 733-743.
7. Hawsawi, Y.M., et al., *Stem cell applications for treatment of cancer and autoimmune diseases: its promises, obstacles, and future perspectives*. Technology in cancer research & treatment, 2018. **17**: p. 1533033818806910.
8. Roberts-Thomson, P.J., M.W. Jackson, and T.P. Gordon, *A seminal monograph: Mackay and Burnet's Autoimmune diseases*. Med J Aust, 2012. **196**(1): p. 74-6.
9. Klareskog, L., et al., *Genes, environment and immunity in the development of rheumatoid arthritis*. Current opinion in immunology, 2006. **18**(6): p. 650-655.
10. Greco, L., et al., *The first large population based twin study of coeliac disease*. Gut, 2002. **50**(5): p. 624-8.
11. Hervonen, K., et al., *Concordance of dermatitis herpetiformis and celiac disease in monozygous twins*. J Invest Dermatol, 2000. **115**(6): p. 990-3.
12. McInnes, I.B. and G. Schett, *Cytokines in the pathogenesis of rheumatoid arthritis*. Nat Rev Immunol, 2007. **7**(6): p. 429-42.
13. Miller, F.W., *The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention*. Current Opinion in Immunology, 2023. **80**: p. 102266.
14. Goodnow, C.C., et al., *Cellular and genetic mechanisms of self tolerance and autoimmunity*. Nature, 2005. **435**(7042): p. 590-597.
15. Wu, D., et al., *Global, regional, and national incidence of six major immune-mediated inflammatory diseases: findings from the global burden of disease study 2019*. eClinicalMedicine, 2023. **64**.
16. McInnes, I.B. and E.M. Gravallese, *Immune-mediated inflammatory disease therapeutics: past, present and future*. Nature Reviews Immunology, 2021. **21**(10): p. 680-686.
17. Monteleone, G., et al., *Immune-mediated inflammatory diseases: common and different pathogenic and clinical features*. Autoimmunity Reviews, 2023: p. 103410.
18. Bezzio, C., et al., *Inflammatory bowel disease and immune-mediated inflammatory diseases: looking at the less frequent associations*. Therapeutic Advances in Gastroenterology, 2022. **15**: p. 17562848221115312.
19. Cooper, G.S., F.W. Miller, and J.P. Pandey, *The role of genetic factors in autoimmune disease: implications for environmental research*. Environmental Health Perspectives, 1999. **107**(suppl 5): p. 693-700.
20. Costenbader, K.H., et al., *Genes, epigenetic regulation and environmental factors: which is the most relevant in developing autoimmune diseases?* Autoimmunity reviews, 2012. **11**(8): p. 604-609.
21. Yazar, S., et al., *Single-cell eQTL mapping identifies cell type-specific genetic control of autoimmune disease*. Science, 2022. **376**(6589): p. eabf3041.
22. Stankey, C.T., et al., *A disease-associated gene desert directs macrophage inflammation through ETS2*. Nature, 2024. **630**(8016): p. 447-456.
23. Jörg, S., et al., *Environmental factors in autoimmune diseases and their role in multiple sclerosis*. Cellular and Molecular Life Sciences, 2016. **73**: p. 4611-4622.
24. Dooley, M. and S. Hogan, *Environmental epidemiology and risk factors for autoimmune disease*. Current opinion in rheumatology, 2003. **15**(2): p. 99-103.
25. Youssefi, M., et al., *Helicobacter pylori infection and autoimmune diseases; Is there an association with systemic lupus erythematosus, rheumatoid arthritis, autoimmune atrophy gastritis and autoimmune pancreatitis? A systematic review and meta-analysis study*. Journal of Microbiology, Immunology and Infection, 2021. **54**(3): p. 359-369.

26. Ansar Ahmed, S., W.J. Penhale, and N. Talal, *Sex hormones, immune responses, and autoimmune diseases. Mechanisms of sex hormone action*. The American journal of pathology, 1985. **121**(3): p. 531-551.
27. Cutolo, M. and R.H. Straub, *Sex steroids and autoimmune rheumatic diseases: state of the art*. Nature Reviews Rheumatology, 2020. **16**(11): p. 628-644.
28. Shoenfeld, Y., et al., *The mosaic of autoimmunity: hormonal and environmental factors involved in autoimmune diseases--2008*. The Israel Medical Association Journal, 2008. **10**(1): p. 8.
29. Ross, F.C., et al., *The interplay between diet and the gut microbiome: implications for health and disease*. Nature Reviews Microbiology, 2024. **22**(11): p. 671-686.
30. Scrivo, R., et al., *Dietary habits bursting into the complex pathogenesis of autoimmune diseases: the emerging role of salt from experimental and clinical studies*. Nutrients, 2019. **11**(5): p. 1013.
31. Manzel, A., et al., *Role of "Western diet" in inflammatory autoimmune diseases*. Current allergy and asthma reports, 2014. **14**: p. 1-8.
32. Hahn, J., et al., *Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial*. BMJ, 2022. **376**: p. e066452.
33. Ploesser, M., et al., *The link between traumatic stress and autoimmune rheumatic diseases: A systematic scoping review*. Seminars in Arthritis and Rheumatism, 2024. **69**: p. 152558.
34. Song, H., et al., *Association of Stress-Related Disorders With Subsequent Autoimmune Disease*. JAMA, 2018. **319**(23): p. 2388-2400.
35. Yang, C.-Y., et al., *The implication of vitamin D and autoimmunity: a comprehensive review*. Clinical reviews in allergy & immunology, 2013. **45**: p. 217-226.
36. Miyauchi, E., et al., *The impact of the gut microbiome on extra-intestinal autoimmune diseases*. Nature Reviews Immunology, 2023. **23**(1): p. 9-23.
37. Mori, S., et al., *Neoself-antigens are the primary target for autoreactive T cells in human lupus*. Cell, 2024. **187**(21): p. 6071-6087.e20.
38. Brooke, A.M. and J.P. Monson, *Addison's disease*. Medicine, 2017. **45**(8): p. 492-496.
39. Charmandari, E., N.C. Nicolaides, and G.P. Chrousos, *Adrenal insufficiency*. The Lancet, 2014. **383**(9935): p. 2152-2167.
40. Dalin, F., et al., *Clinical and immunological characteristics of autoimmune Addison disease: a nationwide Swedish multicenter study*. The Journal of Clinical Endocrinology & Metabolism, 2017. **102**(2): p. 379-389.
41. Murray, C.J., *The global burden of disease study at 30 years*. Nature medicine, 2022. **28**(10): p. 2019-2026.
42. Nieman, L.K. and M.L.C. Turner, *Addison's disease*. Clinics in Dermatology, 2006. **24**(4): p. 276-280.
43. Mason, A.S., et al., *Epidemiological and clinical picture of Addison's disease*. The Lancet, 1968. **292**(7571): p. 744-747.
44. Ten, S., M. New, and N. Maclaren, *Addison's disease 2001*. The Journal of Clinical Endocrinology & Metabolism, 2001. **86**(7): p. 2909-2922.
45. Pratt, C.H., et al., *Alopecia areata*. Nature Reviews Disease Primers, 2017. **3**(1): p. 17011.
46. Jeon, J.J., et al., *Global, regional and national epidemiology of alopecia areata: a systematic review and modelling study*. British Journal of Dermatology, 2024. **191**(3): p. 325-335.
47. Lundin, M., et al., *Gender differences in alopecia areata*. Journal of drugs in dermatology: JDD, 2014. **13**(4): p. 409-413.
48. Wasserman, D., et al., *Alopecia areata*. International Journal of Dermatology, 2007. **46**(2): p. 121-131.
49. Zhou, C., et al., *Alopecia areata: an update on etiopathogenesis, diagnosis, and management*. Clinical Reviews in Allergy & Immunology, 2021. **61**(3): p. 403-423.
50. Ebrahimiadib, N., et al., *Ankylosing spondylitis*. Journal of ophthalmic & vision research, 2021. **16**(3): p. 462.
51. Poddubnyy, D. and J. Sieper, *Similarities and differences between nonradiographic and radiographic axial spondyloarthritis: a clinical, epidemiological and therapeutic assessment*. Curr Opin Rheumatol, 2014. **26**(4): p. 377-83.
52. Strand, V., et al., *Prevalence of axial spondyloarthritis in United States rheumatology practices: Assessment of SpondyloArthritis International Society criteria versus rheumatology expert clinical diagnosis*. Arthritis care & research, 2013. **65**(8): p. 1299-1306.
53. Mauro, D., et al., *Ankylosing spondylitis: an autoimmune or autoinflammatory disease?* Nature Reviews Rheumatology, 2021. **17**(7): p. 387-404.

54. Hwang, M.C., L. Ridley, and J.D. Reveille, *Ankylosing spondylitis risk factors: a systematic literature review*. Clinical rheumatology, 2021. **40**: p. 3079-3093.
55. Lindfors, K., et al., *Coeliac disease*. Nature Reviews Disease Primers, 2019. **5**(1): p. 3.
56. Roberts, S.E., et al., *Systematic review and meta-analysis: the incidence and prevalence of paediatric coeliac disease across Europe*. Alimentary Pharmacology & Therapeutics, 2021. **54**(2): p. 109-128.
57. Lenti, M.V. and A. Di Sabatino, *Disease-and gender-related characteristics of coeliac disease influence diagnostic delay*. European Journal of Internal Medicine, 2021. **83**: p. 12-13.
58. Green, P.H. and B. Jabri, *Coeliac disease*. The Lancet, 2003. **362**(9381): p. 383-391.
59. Lebowitz, B., D.S. Sanders, and P.H. Green, *Coeliac disease*. The Lancet, 2018. **391**(10115): p. 70-81.
60. Alatab, S., et al., *The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017*. The Lancet Gastroenterology & Hepatology, 2020. **5**(1): p. 17-30.
61. Wagtmans, M., et al., *Gender-related differences in the clinical course of Crohn's disease*. Official journal of the American College of Gastroenterology | ACG, 2001. **96**(5): p. 1541-1546.
62. Ozin, Y., et al., *Clinical features of ulcerative colitis and Crohn's disease in Turkey*. J Gastrointest Liver Dis, 2009. **18**(2): p. 157-62.
63. Kaplan, G.G. and J.W. Windsor, *The four epidemiological stages in the global evolution of inflammatory bowel disease*. Nature reviews Gastroenterology & hepatology, 2021. **18**(1): p. 56-66.
64. Baumgart, D.C. and S.R. Carding, *Inflammatory bowel disease: cause and immunobiology*. The Lancet, 2007. **369**(9573): p. 1627-1640.
65. Zhao, M., et al., *The burden of inflammatory bowel disease in Europe in 2020*. Journal of Crohn's and Colitis, 2021. **15**(9): p. 1573-1587.
66. Weetman, A.P., *Graves' disease*. New England Journal of Medicine, 2000. **343**(17): p. 1236-1248.
67. Antonelli, A., et al., *Graves' disease: Epidemiology, genetic and environmental risk factors and viruses*. Best Practice & Research Clinical Endocrinology & Metabolism, 2020. **34**(1): p. 101387.
68. Brent, G.A., *Graves' disease*. New England Journal of Medicine, 2008. **358**(24): p. 2594-2605.
69. Davies, T.F., et al., *Graves' disease*. Nature reviews Disease primers, 2020. **6**(1): p. 1-23.
70. Caturegli, P., A. De Remigis, and N. Rose, *Hashimoto thyroiditis: clinical and diagnostic criteria*. Autoimmunity reviews, 2014. **13**(4-5): p. 391-397.
71. Hu, X., et al., *Global prevalence and epidemiological trends of Hashimoto's thyroiditis in adults: A systematic review and meta-analysis*. Frontiers in Public Health, 2022. **10**.
72. Ragusa, F., et al., *Hashimoto's thyroiditis: Epidemiology, pathogenesis, clinic and therapy*. Best Practice & Research Clinical Endocrinology & Metabolism, 2019. **33**(6): p. 101367.
73. Dobson, R. and G. Giovannoni, *Multiple sclerosis—a review*. European journal of neurology, 2019. **26**(1): p. 27-40.
74. Ehteshami, N., M.Z. Rafie, and M. Mosallaei, *The global prevalence of familial multiple sclerosis: an updated systematic review and meta-analysis*. BMC Neurology, 2021. **21**(1): p. 246.
75. Alonso, A. and M.A. Hernán, *Temporal trends in the incidence of multiple sclerosis: a systematic review*. Neurology, 2008. **71**(2): p. 129-135.
76. Attfield, K.E., et al., *The immunology of multiple sclerosis*. Nature Reviews Immunology, 2022. **22**(12): p. 734-750.
77. McGinley, M.P., C.H. Goldschmidt, and A.D. Rae-Grant, *Diagnosis and treatment of multiple sclerosis: a review*. Jama, 2021. **325**(8): p. 765-779.
78. Jayam Trouth, A., et al., *Myasthenia gravis: a review*. Autoimmune diseases, 2012. **2012**(1): p. 874680.
79. Salari, N., et al., *Global prevalence of myasthenia gravis and the effectiveness of common drugs in its treatment: a systematic review and meta-analysis*. J Transl Med, 2021. **19**(1): p. 516.
80. Bubuioc, A.-M., et al., *The epidemiology of myasthenia gravis*. Journal of medicine and life, 2021. **14**(1): p. 7.
81. Raharja, A., S.K. Mahil, and J.N. Barker, *Psoriasis: a brief overview*. Clinical Medicine, 2021. **21**(3): p. 170-173.
82. Parisi, R., et al., *Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence*. Journal of Investigative Dermatology, 2013. **133**(2): p. 377-385.
83. Yamanaka, K., O. Yamamoto, and T. Honda, *Pathophysiology of psoriasis: A review*. The Journal of dermatology, 2021. **48**(6): p. 722-731.
84. Bu, J., et al., *Epidemiology of psoriasis and comorbid diseases: a narrative review*. Frontiers in immunology, 2022. **13**: p. 880201.

85. Reid, C. and C.E. Griffiths, *Psoriasis and treatment: past, present and future aspects*. Acta dermatovenereologica, 2020. **100**(3): p. 69-79.
86. Chandran, V., et al., *Human leukocyte antigen alleles and susceptibility to psoriatic arthritis*. Human immunology, 2013. **74**(10): p. 1333-1338.
87. López-Ferrer, A., A. Laiz, and L. Puig, *Psoriatic arthritis*. Medicina Clínica (English Edition), 2022. **159**(1): p. 40-46.
88. Scotti, L., et al., *Prevalence and incidence of psoriatic arthritis: A systematic review and meta-analysis*. Semin Arthritis Rheum, 2018. **48**(1): p. 28-34.
89. Ocampo, V. and D. Gladman, *Psoriatic arthritis*. F1000Research, 2019. **8**.
90. Umezawa, Y., *Psoriatic arthritis*. The Journal of Dermatology, 2021. **48**(6): p. 741-749.
91. Karmacharya, P., R. Chakradhar, and A. Ogdie, *The epidemiology of psoriatic arthritis: A literature review*. Best Practice & Research Clinical Rheumatology, 2021. **35**(2): p. 101692.
92. Smith, J.B. and M.K. Haynes, *Rheumatoid arthritis—a molecular understanding*. Annals of internal medicine, 2002. **136**(12): p. 908-922.
93. Almutairi, K.B., et al., *The prevalence of rheumatoid arthritis: a systematic review of population-based studies*. The Journal of rheumatology, 2021. **48**(5): p. 669-676.
94. Finckh, A., et al., *Global epidemiology of rheumatoid arthritis*. Nature Reviews Rheumatology, 2022. **18**(10): p. 591-602.
95. Alivernini, S., G.S. Firestein, and I.B. McInnes, *The pathogenesis of rheumatoid arthritis*. Immunity, 2022. **55**(12): p. 2255-2270.
96. Weyand, C.M. and J.J. Goronzy, *The immunology of rheumatoid arthritis*. Nature immunology, 2021. **22**(1): p. 10-18.
97. Negrini, S., et al., *Sjögren's syndrome: a systemic autoimmune disease*. Clinical and experimental medicine, 2022. **22**(1): p. 9-25.
98. Qin, B., et al., *Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis*. Annals of the rheumatic diseases, 2015. **74**(11): p. 1983-1989.
99. Vivino, F.B., *Sjogren's syndrome: Clinical aspects*. Clinical Immunology, 2017. **182**: p. 48-54.
100. Jonsson, R., *Disease mechanisms in Sjögren's syndrome: What do we know?* Scandinavian Journal of Immunology, 2022. **95**(3): p. e13145.
101. Mok, C. and C. Lau, *Pathogenesis of systemic lupus erythematosus*. Journal of clinical pathology, 2003. **56**(7): p. 481-490.
102. Rees, F., et al., *The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies*. Rheumatology, 2017. **56**(11): p. 1945-1961.
103. Tian, J., et al., *Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study*. Annals of the rheumatic diseases, 2023. **82**(3): p. 351-356.
104. Volkmann, E.R., K. Andréasson, and V. Smith, *Systemic sclerosis*. The Lancet, 2023. **401**(10373): p. 304-318.
105. Zhong, L., et al., *Prevalence and incidence of systemic sclerosis: a systematic review and meta-analysis*. International journal of rheumatic diseases, 2019. **22**(12): p. 2096-2107.
106. Hughes, M., et al., *Gender-related differences in systemic sclerosis*. Autoimmunity reviews, 2020. **19**(4): p. 102494.
107. Denton, C.P. and D. Khanna, *Systemic sclerosis*. The Lancet, 2017. **390**(10103): p. 1685-1699.
108. Allanore, Y., et al., *Systemic sclerosis*. Nature Reviews Disease Primers, 2015. **1**(1): p. 15002.
109. Katsarou, A., et al., *Type 1 diabetes mellitus*. Nature Reviews Disease Primers, 2017. **3**(1): p. 17016.
110. Mobasser, M., et al., *Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis*. Health promotion perspectives, 2020. **10**(2): p. 98.
111. *Type 1 Diabetes Mellitus*. Annals of Internal Medicine, 2022. **175**(3): p. ITC33-ITC48.
112. Atkinson, M.A., G.S. Eisenbarth, and A.W. Michels, *Type 1 diabetes*. The Lancet, 2014. **383**(9911): p. 69-82.
113. Wang, Y., S. Li, and C. Li, *Clinical Features, Immunopathogenesis, and Therapeutic Strategies in Vitiligo*. Clinical Reviews in Allergy & Immunology, 2021. **61**(3): p. 299-323.
114. Haulrig, M.B., et al., *The global epidemiology of vitiligo: A systematic review and meta-analysis of the incidence and prevalence*. JEADV Clinical Practice, 2024.
115. Lerner, A.B. and J.J. Nordlund, *Vitiligo: What Is It? Is It Important?* JAMA, 1978. **239**(12): p. 1183-1187.
116. Seneschal, J., et al., *An update on Vitiligo pathogenesis*. Pigment Cell & Melanoma Research, 2021. **34**(2): p. 236-243.
117. Voskuhl, R., *Sex differences in autoimmune diseases*. Biology of sex differences, 2011. **2**: p. 1-21.

118. Kivity, S. and M. Ehrenfeld, *Can we explain the higher prevalence of autoimmune disease in women?* Expert review of clinical immunology, 2010. **6**(5): p. 691-694.
119. Dolgin, E., *Why autoimmune disease is more common in women: X chromosome holds clues.* Nature, 2024. **626**(7999): p. 466-466.
120. Miquel, C.-H., B. Faz-Lopez, and J.-C. Guéry, *Influence of X chromosome in sex-biased autoimmune diseases.* Journal of Autoimmunity, 2023. **137**: p. 102992.
121. Desai, M.K. and R.D. Brinton, *Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan.* Front Endocrinol (Lausanne), 2019. **10**: p. 265.
122. Lasrado, N., et al., *Mechanisms of sex hormones in autoimmunity: focus on EAE.* Biology of Sex Differences, 2020. **11**(1): p. 50.
123. Klein, S.L. and K.L. Flanagan, *Sex differences in immune responses.* Nature Reviews Immunology, 2016. **16**(10): p. 626-638.
124. Dupuis, M.L., et al., *Immune response and autoimmune diseases: a matter of sex.* Journal of Sex-and Gender-Specific Medicine, 2019. **5**(1): p. 11-20.
125. Hewagama, A. and B. Richardson, *The genetics and epigenetics of autoimmune diseases.* J Autoimmun, 2009. **33**(1): p. 3-11.
126. Mazzone, R., et al., *The emerging role of epigenetics in human autoimmune disorders.* Clinical Epigenetics, 2019. **11**(1): p. 34.
127. Zheng, D., T. Liwinski, and E. Elinav, *Interaction between microbiota and immunity in health and disease.* Cell Research, 2020. **30**(6): p. 492-506.
128. Rosser, E.C., N.M. de Gruijter, and D.E. Matei, *Mini-Review: Gut-Microbiota and the Sex-Bias in Autoimmunity—Lessons Learnt From Animal Models.* Frontiers in Medicine, 2022. **9**: p. 910561.
129. Abu-Raya, B., et al., *Maternal immunological adaptation during normal pregnancy.* Frontiers in immunology, 2020. **11**: p. 575197.
130. Piccinni, M.-P., et al., *How pregnancy can affect autoimmune diseases progression?* Clinical and Molecular Allergy, 2016. **14**(1): p. 11.
131. Mor, G. and I. Cardenas, *The immune system in pregnancy: a unique complexity.* Am J Reprod Immunol, 2010. **63**(6): p. 425-33.
132. Jethwa, H., et al., *Does rheumatoid arthritis really improve during pregnancy? A systematic review and metaanalysis.* The Journal of rheumatology, 2019. **46**(3): p. 245-250.
133. Clowse, M.E., et al., *Predictors of preterm birth in patients with mild systemic lupus erythematosus.* Annals of the rheumatic diseases, 2013. **72**(9): p. 1536-1539.
134. Wainwright, B., et al., *Autoimmune-mediated congenital heart block.* Best Practice & Research Clinical Obstetrics & Gynaecology, 2020. **64**: p. 41-51.
135. Andreoli, L., et al., *EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome.* Annals of the rheumatic diseases, 2017. **76**(3): p. 476-485.
136. Singh, M., et al., *Autoimmune diseases and adverse pregnancy outcomes: an umbrella review.* BMC Medicine, 2024. **22**(1): p. 94.
137. Bharti, B., et al., *Disease severity and pregnancy outcomes in women with rheumatoid arthritis: results from the organization of teratology information specialists autoimmune diseases in pregnancy project.* The Journal of rheumatology, 2015. **42**(8): p. 1376-1382.
138. Walter, I.J., et al., *Pregnancy outcome predictors in antiphospholipid syndrome: A systematic review and meta-analysis.* Autoimmunity Reviews, 2021. **20**(10): p. 102901.
139. Williams, D., *Pregnancy: a stress test for life.* Curr Opin Obstet Gynecol, 2003. **15**(6): p. 465-71.
140. Okoth, K., et al., *Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review.* bmj, 2020. **371**.
141. Ostensen, M. and P.M. Villiger, *The remission of rheumatoid arthritis during pregnancy.* Semin Immunopathol, 2007. **29**(2): p. 185-91.
142. Muller, A.F., H.A. Drexhage, and A. Berghout, *Postpartum thyroiditis and autoimmune thyroiditis in women of childbearing age: recent insights and consequences for antenatal and postnatal care.* Endocrine reviews, 2001. **22**(5): p. 605-630.
143. Tincani, A., et al., *Autoimmune diseases and pregnancy.* Best Practice & Research Clinical Endocrinology & Metabolism, 2019. **33**(6): p. 101322.
144. Fugazzola, L., V. Cirello, and P. Beck-Peccoz, *Fetal microchimerism as an explanation of disease.* Nature Reviews Endocrinology, 2011. **7**(2): p. 89-97.

145. Johnson, B.N., et al., *Chimerism in health and potential implications on behavior: A systematic review*. American Journal of Medical Genetics Part A, 2020. **182**(6): p. 1513-1529.
146. O'Donoghue, K., et al., *Microchimerism in female bone marrow and bone decades after fetal mesenchymal stem-cell trafficking in pregnancy*. Lancet, 2004. **364**(9429): p. 179-82.
147. Kekow, M., et al., *Long-term persistence and effects of fetal microchimerisms on disease onset and status in a cohort of women with rheumatoid arthritis and systemic lupus erythematosus*. BMC musculoskeletal disorders, 2013. **14**: p. 1-8.
148. Khan, D. and S. Ansar Ahmed, *The immune system is a natural target for estrogen action: opposing effects of estrogen in two prototypical autoimmune diseases*. Frontiers in immunology, 2016. **6**: p. 635.
149. Zhao, X., et al., *Physiological and pathological regulation of autophagy in pregnancy*. Archives of Gynecology and Obstetrics, 2020. **302**(2): p. 293-303.
150. Straub, R.H., *The complex role of estrogens in inflammation*. Endocrine reviews, 2007. **28**(5): p. 521-574.
151. Royal college of obstetrician and gynaecologists, *The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum*
Green-top Guideline No. 69, 2016
<https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg69-hyperemesis.pdf>.
152. Fejzo, M.S., et al., *Nausea and vomiting of pregnancy and hyperemesis gravidarum*. Nature reviews Disease primers, 2019. **5**(1): p. 62.
153. Royal college of obstetrician and gynaecologists, *Ectopic pregnancy, 2016*
<https://www.rcog.org.uk/en/patients/patient-leaflets/ectopic-pregnancy/>.
154. Marion, L.L. and G.R. Meeks, *Ectopic pregnancy: history, incidence, epidemiology, and risk factors*. Clinical obstetrics and gynecology, 2012. **55**(2): p. 376-386.
155. Moussa, B., et al., *Ectopic pregnancy: epidemiological, clinical, therapeutical, anatomopathological aspects and prognosis at the Department of Obstetrics and Gynecology of the Teaching Hospital Sourou Sanou of Bobo-Dioulasso: about 79 cases and literature review*. Open Journal of Obstetrics and Gynecology, 2022. **12**(1): p. 1-10.
156. Quenby, S., et al., *Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss*. The Lancet, 2021. **397**(10285): p. 1658-1667.
157. Quenby, S., et al., *Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss*. The Lancet, 2021. **397**(10285): p. 1658-1667.
158. National Institute for Health and Care Excellence. *NICE Guideline [NG133]: Hypertension in pregnancy: diagnosis and management*. 2019.
<https://www.nice.org.uk/guidance/ng133/chapter/Recommendations#management-of-gestationalhypertension>.
159. Wang, W., et al., *Epidemiological trends of maternal hypertensive disorders of pregnancy at the global, regional, and national levels: a population-based study*. BMC Pregnancy and Childbirth, 2021. **21**(1): p. 364.
160. Bilano, V.L., et al., *Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low-and middle-income countries: a WHO secondary analysis*. PloS one, 2014. **9**(3): p. e91198.
161. Bramham, K., et al., *Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis*. Bmj, 2014. **348**.
162. Agrawal, A. and N.K. Wenger, *Hypertension during pregnancy*. Current hypertension reports, 2020. **22**(9): p. 64.
163. *BMJ-Best practice, Gestational diabetes mellitus, 2021*
<https://bestpractice.bmj.com/topics/en-qb/665>.
164. Sweeting, A., et al., *Epidemiology and management of gestational diabetes*. The Lancet, 2024. **404**(10448): p. 175-192.

165. Gajera, D., et al., *Detailed review on gestational diabetes mellitus with emphasis on pathophysiology, epidemiology, related risk factors, and its subsequent conversion to type 2 diabetes mellitus*. Hormone and Metabolic Research, 2023. **55**(05): p. 295-303.
166. Royal college of obstetrician and gynaecologists, *Placenta praevia, placenta accreta and vasa praevia*, 2018
<https://www.rcog.org.uk/globalassets/documents/patients/patient-informationleaflets/pregnancy/pi-placenta-praevia-placenta-accreta-and-vasa-praevia.pdf>.
167. Matsuzaki, S., et al., *Trends, characteristics, and outcomes of placenta accreta spectrum: a national study in the United States*. American journal of obstetrics and gynecology, 2021. **225**(5): p. 534. e1-534. e38.
168. Fitzpatrick, K.E., et al., *Incidence and risk factors for placenta accreta/increta/percreta in the UK: a national case-control study*. PLoS One, 2012. **7**(12): p. e52893.
169. Workalemahu T, Enquobahrie DA, Gelaye B, Thornton TA, Tekola-Ayele F, Sanchez SE, et al. *Abruptio placentae risk and genetic variations in mitochondrial biogenesis and oxidative phosphorylation: replication of a candidate gene association study*. American journal of obstetrics and gynecology. 2018;219(6):617. e1-. e17. .
170. Martinelli KG, Garcia ÉM, Santos Neto ETd, Gama SGNd. *Advanced maternal age and its association with placenta praevia and placental abruption: a meta-analysis*. Cadernos de saude publica. 2018;34. .
171. Tikkanen, M., *Placental abruption: epidemiology, risk factors and consequences*. Acta obstetrica et gynecologica Scandinavica, 2011. **90**(2): p. 140-149.
172. Royal college of obstetrician and gynaecologists, *Molar pregnancy and gestational trophoblastic disease*, 2019
[https://www.rcog.org.uk/en/patients/patient-leaflets/gestational-trophoblastic-diseaseqtd/#:~:text=Molar%20pregnancy%20is%20an%20abnormal,from%20your%20uterus%20\(womb\)](https://www.rcog.org.uk/en/patients/patient-leaflets/gestational-trophoblastic-diseaseqtd/#:~:text=Molar%20pregnancy%20is%20an%20abnormal,from%20your%20uterus%20(womb)).
173. *Gestational trophoblastic disease*, Cancer research UK
<https://www.cancerresearchuk.org/about-cancer/gestational-trophoblastic-disease-qtd> accessed in Feb, 2022. .
174. Darling, A.J., et al., *Molar pregnancy: Epidemiology, diagnosis, management, surveillance*. Current Obstetrics and Gynecology Reports, 2022. **11**(2): p. 133-141.
175. Royal college of obstetrician and gynaecologists, *Heavy bleeding after birth (postpartum haemorrhage)*, 2016
<https://www.rcog.org.uk/en/patients/patient-leaflets/heavy-bleeding-after-birth-postpartumhaemorrhage/>. .
176. Carroli, G., et al., *Epidemiology of postpartum haemorrhage: a systematic review*. Best practice & research Clinical obstetrics & gynaecology, 2008. **22**(6): p. 999-1012.
177. *Legislation UK* <https://www.legislation.gov.uk/ukpga/1992/29/section/1>.
178. Hug, L., et al., *Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment*. The Lancet, 2021. **398**(10302): p. 772-785.
179. *National maternal and Perinatal Audit* <https://maternityaudit.org.uk/Audit/Charting/ClinicalByMeasure>. 2017/2018. .
180. Boerma, T., et al., *Global epidemiology of use of and disparities in caesarean sections*. The Lancet, 2018. **392**(10155): p. 1341-1348.
181. World health organisation
Low birth weight, 2019
<https://www.who.int/data/nutrition/nlis/info/low-birth>.
182. Royal college of obstetrician and gynaecologists, *Small-for-Gestational-Age Foetus*,

183. World health organisation

Preterm birth,2018

184. Walani, S.R., *Global burden of preterm birth*. International Journal of Gynecology & Obstetrics, 2020. **150**(1): p. 31-33.

185. Royal college of obstetrician and gynaecologists ,*Obstetric Cholestasis,(Green-top Guideline No. 43),2014*

186. Odutola, P.O., et al., *Intrahepatic cholestasis of pregnancy is associated with increased risk of hepatobiliary disease and adverse fetal outcomes: A systematic review and meta-analysis*. iLIVER, 2023.

187. Odabaş, R.K., et al., *The Incidence of Intrahepatic Cholestasis of Pregnancy and its Maternal, Fetal, and Neonatal Adverse Outcomes: A Systematic Review and Meta-Analysis*. Journal of Midwifery & Women's Health, 2024.

188. National institute of health and care excellence,*Antenatal and postnatal mental health:*

clinical management and service guidance,2020,

189. Howard, L.M. and H. Khalifeh, *Perinatal mental health: a review of progress and challenges*. World Psychiatry, 2020. **19**(3): p. 313-327.

190. Zhao, M., et al., *Age-standardized incidence, prevalence, and mortality rates of autoimmune diseases in adolescents and young adults (15-39 years): an analysis based on the global burden of disease study 2021*. BMC Public Health, 2024. **24**(1): p. 1800.

191. Amador-Patarroyo, M.J., A. Rodriguez-Rodriguez, and G. Montoya-Ortiz, *How does age at onset influence the outcome of autoimmune diseases?* Autoimmune diseases, 2012. **2012**(1): p. 251730.

192. Beeson, P.B., *Age and sex associations of 40 autoimmune diseases*. The American Journal of Medicine, 1994. **96**(5): p. 457-462.

193. Balduzzi S, Rücker G, Schwarzer G. *How to perform a meta-analysis with R: a practical tutorial*. *BMJ Ment Health*. 2019;22(4):153–60.

194. Jørgensen, K.T., et al., *Childbirths and risk of female predominant and other autoimmune diseases in a population-based Danish cohort*. J Autoimmun, 2012. **38**(2-3): p. J81-7.

195. Walsh, J.P., et al., *Parity and the Risk of Autoimmune Thyroid Disease: A Community-Based Study*. The Journal of Clinical Endocrinology & Metabolism, 2005. **90**(9): p. 5309-5312.

196. Harpsøe, M.C., et al., *Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort*. Int J Epidemiol, 2014. **43**(3): p. 843-55.

197. Kwiat, V.R., et al., *Autoimmunity as a sequela to obesity and systemic inflammation*. Front Physiol, 2022. **13**: p. 887702.

198. Li, X., et al., *The Causal Effect of Obesity on the Risk of 15 Autoimmune Diseases: A Mendelian Randomization Study*. Obesity Facts, 2023. **16**(6): p. 598-605.

199. Subramanian, A., et al., *Ethnicity-based differences in the incident risk of allergic diseases and autoimmune disorders: A UK-based retrospective cohort study of 4.4 million participants*. Clin Exp Allergy, 2021. **51**(1): p. 144-147.

200. Goonesekera, S.D., et al., *Racial/ethnic differences in autoimmune disease prevalence in US claims/EHR data*. Am J Manag Care, 2024. **30**(1): p. e4-e10.

201. Guan, S.-Y., et al., *Global burden due to modifiable risk factors for autoimmune diseases, 1990–2021: Temporal trends and socio-demographic inequalities*. Autoimmunity Reviews, 2024. **23**(12): p. 103674.

202. Li, X., et al., *Neighborhood Deprivation and Risks of Autoimmune Disorders: A National Cohort Study in Sweden*. International Journal of Environmental Research and Public Health, 2019. **16**(20): p. 3798.

203. Conrad N, Misra S, Verbakel JY, Verbeke G, Molenberghs G, Taylor PN, et al. *Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a*

- population-based cohort study of 22 million individuals in the UK. *The Lancet*. 2023;401(10391):1878-90.
204. Hiam, L., M. Orcutt, and R. Yates, *Universal health coverage in the UK*. *BMJ*, 2019. **367**: p. l7054.
 205. Herrett, E., et al., *Data Resource Profile: Clinical Practice Research Datalink (CPRD)*. *International Journal of Epidemiology*, 2015. **44**(3): p. 827-836.
 206. Wolf, A., et al., *Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum*. *International Journal of Epidemiology*, 2019. **48**(6): p. 1740-1740g.
 207. Minassian, C., et al., *Methods to generate and validate a Pregnancy Register in the UK Clinical Practice Research Datalink primary care database*. *Pharmacoepidemiol Drug Saf*, 2019. **28**(7): p. 923-933.
 208. Campbell, J., et al., *Investigating the optimal handling of uncertain pregnancy episodes in the CPRD GOLD Pregnancy Register: a methodological study using UK primary care data*. *BMJ Open*, 2022. **12**(2): p. e055773.
 209. Williams, T., et al., *Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource*. *Ther Adv Drug Saf*, 2012. **3**(2): p. 89-99.
 210. Thorn, J.C., et al., *Validation of the Hospital Episode Statistics Outpatient Dataset in England*. *PharmacoEconomics*, 2016. **34**(2): p. 161-168.
 211. *Birth characteristics in England and Wales: 2019*<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthcharacteristicsinenglandandwales/2019> assessed on Sep,2024.
 212. Murray, J., et al., *Quality of routine hospital birth records and the feasibility of their use for creating birth cohorts*. *Journal of Public Health*, 2012. **35**(2): p. 298-307.
 213. Jick, S., et al., *Use of the CPRD Aurum Database: Insights Gained from New Data Quality Assessments*. *Clin Epidemiol*, 2023. **15**: p. 1219-1222.
 214. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions*.
 215. Wells, G.A., et al., *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. 2000, Oxford.
 216. Stewart, L.A., et al., *Preferred reporting items for a systematic review and meta-analysis of individual participant data: the PRISMA-IPD statement*. *Jama*, 2015. **313**(16): p. 1657-1665.
 217. Brown, H.K., A. McKnight, and A. Aker, *Association between pre-pregnancy multimorbidity and adverse maternal outcomes: A systematic review*. *J Multimorb Comorb*, 2022. **12**: p. 26335565221096584.
 218. Page, M.J., et al., *Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional study*. *PLoS medicine*, 2016. **13**(5): p. e1002028.
 219. Smith, V., D.B. Devane, and C. Begley, *CM and Clarke, M.(2011) Methodology in conducting a systematic review of systematic reviews of healthcare interventions*. *BMC Medical Research Methodology*. **11**: p. 15.
 220. Aromataris, E., et al., *Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach*. *JBIC Evidence Implementation*, 2015. **13**(3): p. 132-140.
 221. Lunny, C., et al., *Evidence map of studies evaluating methods for conducting, interpreting and reporting overviews of systematic reviews of interventions: rationale and design*. *Systematic reviews*, 2016. **5**: p. 1-8.
 222. Caird, J., et al., *Mediating policy-relevant evidence at speed: are systematic reviews of systematic reviews a useful approach?* *Evidence & Policy*, 2015. **11**(1): p. 81-97.
 223. Pollock, A., et al. *Cochrane overviews of reviews: exploring the methods and challenges*. in *Birmingham: UK and Ireland Cochrane Symposium*. 2016.
 224. Lunny, C., et al., *Managing Overlap of Primary Studies Results Across Systematic Reviews: Practical Considerations for Authors of Overviews of Reviews*.
 225. Hennessy, E.A. and B.T. Johnson, *Examining overlap of included studies in meta-reviews: Guidance for using the corrected covered area index*. *Research synthesis methods*, 2020. **11**(1): p. 134-145.
 226. Pollock, M., et al., *A decision tool to help researchers make decisions about including systematic reviews in overviews of reviews of healthcare interventions*. *Systematic Reviews*, 2019. **8**(1): p. 29.
 227. Cant, R., C. Ryan, and M.A. Kelly, *A nine-step pathway to conduct an umbrella review of literature*. *Nurse Author & Editor*.
 228. Conrad, N., et al., *Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK*. *The Lancet*, 2023. **401**(10391): p. 1878-1890.

229. Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. *J Intern Med*. 2015;278(4):369-95.
230. Davidson A, Diamond B. Autoimmune diseases. *N Engl J Med*. 2001;345(5):340-50.
231. Invernizzi P, Pasini S, Selmi C, Gershwin ME, Podda M. Female predominance and X chromosome defects in autoimmune diseases. *Journal of autoimmunity*. 2009;33(1):12-6.
232. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol*. 1997;84(3):223-43.
233. Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. *J Autoimmun*. 2007;29(1):1-9.
234. Borchers, A.T., et al., *The implications of autoimmunity and pregnancy*. *Journal of autoimmunity*, 2010. **34**(3): p. J287-J299.
235. Dou, D.R., et al., *Xist ribonucleoproteins promote female sex-biased autoimmunity*. *Cell*, 2024. **187**(3): p. 733-749. e16.
236. Piccinni, M.-P., et al., *How pregnancy can affect autoimmune diseases progression?* *Clinical and Molecular Allergy*, 2016. **14**: p. 1-9.
237. Graham, J.J., M.S. Longhi, and M.A. Heneghan, *T helper cell immunity in pregnancy and influence on autoimmune disease progression*. *Journal of autoimmunity*, 2021. **121**: p. 102651.
238. Doria, A., et al., *Th2 immune deviation induced by pregnancy: The two faces of autoimmune rheumatic diseases*. *Reproductive toxicology* (Elmsford, N.Y.), 2006. **22**: p. 234-41.
239. Adams Waldorf KM, Nelson JL. Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy. *Immunol Invest*. 2008;37(5):631-44.
240. Munoz Munoz C, Ahmed K, Thomas M, Cohen H, Alijotas-Reig J, Giles I. Comparing pregnancy outcomes in patients with criteria and non-criteria autoimmune disease: A systematic review. *Lupus*. 2022;31(1):5-18.
241. Johansen CB, Egeberg A, Jimenez-Solem E, Skov L, Thomsen SF. Psoriasis and adverse pregnancy outcomes: A nationwide case-control study in 491,274 women in Denmark. *JAAD International*. 2022;7:146-55.
242. Wu, D., et al., *Global, regional, and national incidence of six major immune-mediated inflammatory diseases: findings from the global burden of disease study 2019*. *EClinicalMedicine*, 2023. **64**.
243. Lim, J.R., et al., *Prevalence of autoimmune conditions in pregnant women in a tertiary maternity hospital: a cross-sectional survey and maternity database review*. *Obstetric Medicine*, 2021. **14**(3): p. 158-163.
244. Lerner A, Jeremias P, Matthias T. The world incidence and prevalence of autoimmune diseases is increasing. *Int J Celiac Dis*. 2015;3(4):151-5.
245. EL-GABALAWY, H., L.C. GUENTHER, and C.N. BERNSTEIN, *Epidemiology of Immune-Mediated Inflammatory Diseases: Incidence, Prevalence, Natural History, and Comorbidities*. *The Journal of Rheumatology*, 2010. **85**: p. 2-10.
246. CPRD GOLD July 2022 Dataset. 2022. Available: <https://cprd.com/cprd-gold-july-2022-dataset>.
247. CPRD Aurum Dataset March, 2024 <https://www.cprd.com/cprd-aurum-march-2022-dataset>.
248. Minassian, C., et al., *Methods to generate and validate a Pregnancy Register in the UK Clinical Practice Research Datalink primary care database*. *Pharmacoepidemiology and drug safety*, 2019. **28**(7): p. 923-933.
249. Gokhale, K.M., et al., *Data extraction for epidemiological research (DExtER): a novel tool for automated clinical epidemiology studies*. *European journal of epidemiology*, 2021. **36**(2): p. 165-178.
250. Skrivankova, V.W., et al., *Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement*. *Jama*, 2021. **326**(16): p. 1614-1621.
251. Chisholm, J., *The Read clinical classification*. *BMJ: British Medical Journal*, 1990. **300**(6732): p. 1092.
252. Digital, N., SNOMED CT, <https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct>. 2021.
253. National stem cell foundation, <https://nationalstemcellfoundation.org/glossary/autoimmune-disease/assessed> March, 2024.
254. Invernizzi, P., et al., *Female predominance and X chromosome defects in autoimmune diseases*. *J Autoimmun*, 2009. **33**(1): p. 12-6.
255. Pace M, Lanzieri G, Glickman M, Zupanič T. Revision of the European Standard Population: report of Eurostat's task force: Publications Office of the European Union; 2013.

256. Clegg, L.X., et al., *Estimating average annual per cent change in trend analysis*. Stat Med, 2009. **28**(29): p. 3670-82.
257. StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC.
258. RStudio Team. *RStudio: integrated development environment for R*; 2022. Available from: <http://www.rstudio.com/>.
259. R Core Team. *R: a language and environment for statistical computing*; 2022. Available from: <https://www.R-project.org/>.
260. *Conceptions in England and Wales: 2021*<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/conceptionandfertilityrates/bulletins/conceptionstatistics/2021>.
261. Bairkdar, M., et al., *Incidence and prevalence of systemic sclerosis globally: a comprehensive systematic review and meta-analysis*. Rheumatology, 2021. **60**(7): p. 3121-3133.
262. Angum, F., et al., *The Prevalence of Autoimmune Disorders in Women: A Narrative Review*. Cureus, 2020. **12**(5): p. e8094.
263. Nielsen, T.C., et al., *Prevalence of autoimmune disease among pregnant women and women of reproductive age in New South Wales, Australia: a population-based study*. The Journal of Maternal-Fetal & Neonatal Medicine, 2022. **35**(17): p. 3229-3237.
264. Bowman, S., et al., *Estimating the prevalence among Caucasian women of primary Sjögren's syndrome in two general practices in Birmingham, UK*. Scandinavian journal of rheumatology, 2004. **33**(1): p. 39-43.
265. Fanouriakis, A., et al., *EULAR recommendations for the management of systemic lupus erythematosus: 2023 update*. Annals of the Rheumatic Diseases, 2024. **83**(1): p. 15-29.
266. Rees, F., et al., *The incidence and prevalence of systemic lupus erythematosus in the UK, 1999–2012*. Annals of the rheumatic diseases, 2016. **75**(1): p. 136-141.
267. Izmirly, P.M., et al., *Prevalence of systemic lupus erythematosus in the United States: estimates from a meta-analysis of the Centers for Disease Control and Prevention National Lupus Registries*. Arthritis & Rheumatology, 2021. **73**(6): p. 991-996.
268. Chiffot, H., et al. *Incidence and prevalence of systemic sclerosis: a systematic literature review*. in *Seminars in arthritis and rheumatism*. 2008. Elsevier.
269. Nikpour, M., et al., *Epidemiology of systemic sclerosis*. Best Practice & Research Clinical Rheumatology, 2010. **24**(6): p. 857-869.
270. Schneiderman, M., et al., *Maternal and neonatal outcomes of pregnancies in women with Addison's disease: a population-based cohort study on 7.7 million births*. BJOG: An International Journal of Obstetrics & Gynaecology, 2017. **124**(11): p. 1772-1779.
271. Cooper, D.S. and P. Laurberg, *Hyperthyroidism in pregnancy*. Lancet Diabetes Endocrinol, 2013. **1**(3): p. 238-49.
272. De Leo, S. and E.N. Pearce, *Autoimmune thyroid disease during pregnancy*. The Lancet Diabetes & Endocrinology, 2018. **6**(7): p. 575-586.
273. Peng, T.Y., et al., *Trends and racial and ethnic disparities in the prevalence of pregestational type 1 and type 2 diabetes in Northern California: 1996–2014*. American Journal of Obstetrics and Gynecology, 2017. **216**(2): p. 177.e1-177.e8.
274. Coton, S.J., I. Nazareth, and I. Petersen, *A cohort study of trends in the prevalence of pregestational diabetes in pregnancy recorded in UK general practice between 1995 and 2012*. BMJ Open, 2016. **6**(1): p. e009494.
275. Benigno, M., et al., *A Large Cross-Sectional Survey Study of the Prevalence of Alopecia Areata in the United States*. Clinical, Cosmetic and Investigational Dermatology, 2020. **13**(null): p. 259-266.
276. Lee, H.H., et al., *Epidemiology of alopecia areata, ophiasis, totalis, and universalis: A systematic review and meta-analysis*. Journal of the American Academy of Dermatology, 2020. **82**(3): p. 675-682.
277. Mostaghimi, A., et al., *Trends in Prevalence and Incidence of Alopecia Areata, Alopecia Totalis, and Alopecia Universalis Among Adults and Children in a US Employer-Sponsored Insured Population*. JAMA Dermatology, 2023. **159**(4): p. 411-418.
278. Iskandar, I., et al., *Systematic review examining changes over time and variation in the incidence and prevalence of psoriasis by age and gender*. British Journal of Dermatology, 2021. **184**(2): p. 243-258.
279. Zhang, Y., et al., *The prevalence of vitiligo: a meta-analysis*. PloS one, 2016. **11**(9): p. e0163806.
280. Walsh, J., et al., *Trends in diagnostic prevalence and treatment patterns of male and female ankylosing spondylitis patients in the United States, 2006–2016*. BMC Rheumatology, 2019. **3**(1): p. 39.

281. Remaeus, K., et al., *Maternal and infant pregnancy outcomes in women with psoriatic arthritis: a Swedish nationwide cohort study*. BJOG: An International Journal of Obstetrics & Gynaecology, 2019. **126**(10): p. 1213-1222.
282. Karmacharya, P., et al., *The epidemiology of psoriatic arthritis over five decades: a Population-Based study*. Arthritis & Rheumatology, 2021. **73**(10): p. 1878-1885.
283. Eder, L., et al., *Trends in the prevalence and incidence of psoriasis and psoriatic arthritis in Ontario, Canada: a population-based study*. Arthritis care & research, 2019. **71**(8): p. 1084-1091.
284. Ogdie, A., et al., *Prevalence and treatment patterns of psoriatic arthritis in the UK*. Rheumatology, 2013. **52**(3): p. 568-575.
285. Aljary, H., et al., *Pregnancy outcomes in women with rheumatoid arthritis: a retrospective population-based cohort study*. The Journal of Maternal-Fetal & Neonatal Medicine, 2020. **33**(4): p. 618-624.
286. Norouzinia, M., et al., *Coeliac disease; Prevalence and Outcome in Pregnancy*. HealthMED, 2011. **12**: p. 1537.
287. Shand, A., et al., *Inflammatory bowel disease in pregnancy: a population-based study of prevalence and pregnancy outcomes*. BJOG: An International Journal of Obstetrics & Gynaecology, 2016. **123**(11): p. 1862-1870.
288. Khalili, H., et al., *Geographical variation and incidence of inflammatory bowel disease among US women*. Gut, 2012. **61**(12): p. 1686-1692.
289. Fong, A., et al., *Multiple sclerosis in pregnancy: prevalence, sociodemographic features, and obstetrical outcomes*. The Journal of Maternal-Fetal & Neonatal Medicine, 2018. **31**(3): p. 382-387.
290. Sellner, J., et al., *The increasing incidence and prevalence of female multiple sclerosis—a critical analysis of potential environmental factors*. Autoimmunity reviews, 2011. **10**(8): p. 495-502.
291. Carr, A.S., et al., *A systematic review of population based epidemiological studies in Myasthenia Gravis*. BMC neurology, 2010. **10**: p. 1-9.
292. Salari, N., et al., *Global prevalence of myasthenia gravis and the effectiveness of common drugs in its treatment: a systematic review and meta-analysis*. Journal of translational medicine, 2021. **19**: p. 1-23.
293. Lerner, A., P. Jeremias, and T. Matthias, *The world incidence and prevalence of autoimmune diseases is increasing*. Int J Celiac Dis, 2015. **3**(4): p. 151-5.
294. Luppi, P., et al., *Genetic background and environment contribute synergistically to the onset of autoimmune diseases*. Journal of molecular medicine, 1995. **73**(8): p. 381-393.
295. Ellis, J.A., A.S. Kemp, and A.-L. Ponsonby, *Gene–environment interaction in autoimmune disease*. Expert Reviews in Molecular Medicine, 2014. **16**: p. e4.
296. Slight-Webb, S., et al., *Shared and unique immune alterations in pre-clinical autoimmunity*. Current opinion in immunology, 2019. **61**: p. 60-68.
297. Miller, F.W., *Environmental agents and autoimmune diseases*. Epigenetic Contributions in Autoimmune Disease, 2011: p. 61-81.
298. Miller, F.W., *The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention*. Curr Opin Immunol, 2023. **80**: p. 102266.
299. Miller, F.W., et al., *Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop*. Journal of autoimmunity, 2012. **39**(4): p. 259-271.
300. Cooper, G.S. and B.C. Stroehla, *The epidemiology of autoimmune diseases*. Autoimmunity reviews, 2003. **2**(3): p. 119-125.
301. Honda, K. and D.R. Littman, *The microbiome in infectious disease and inflammation*. Annual review of immunology, 2012. **30**: p. 759-795.
302. Manfredo Vieira, S., et al., *Translocation of a gut pathobiont drives autoimmunity in mice and humans*. Science, 2018. **359**(6380): p. 1156-1161.
303. Belkaid, Y. and T.W. Hand, *Role of the microbiota in immunity and inflammation*. Cell, 2014. **157**(1): p. 121-141.
304. Cho, J.H. and P.K. Gregersen, *Genomics and the multifactorial nature of human autoimmune disease*. New England Journal of Medicine, 2011. **365**(17): p. 1612-1623.
305. Sokratous, M., et al., *Deciphering the role of DNA methylation in multiple sclerosis: emerging issues*. Autoimmunity Highlights, 2016. **7**: p. 1-9.
306. Cooper, G.S., M.L. Bynum, and E.C. Somers, *Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases*. Journal of autoimmunity, 2009. **33**(3-4): p. 197-207.

307. Li, M., C. D'Arcy, and X. Meng, *Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions*. *Psychological medicine*, 2016. **46**(4): p. 717-730.
308. Picardi, A., et al., *Psychiatric morbidity in dermatological outpatients: an issue to be recognized*. *British Journal of dermatology*, 2000. **143**(5): p. 983-991.
309. Dhabhar, F.S., *Effects of stress on immune function: the good, the bad, and the beautiful*. *Immunologic research*, 2014. **58**: p. 193-210.
310. Costello, R.E., et al., *Glucocorticoid use is associated with an increased risk of hypertension*. *Rheumatology (Oxford)*, 2021. **60**(1): p. 132-139.
311. Campbell, J., et al., *Methods to refine and extend a Pregnancy Register in the UK Clinical Practice Research Datalink primary care databases*. *Pharmacoepidemiology and Drug Safety*, 2023. **32**(6): p. 617-624.
312. Shiekh, S.I., et al., *Completeness, agreement, and representativeness of ethnicity recording in the United Kingdom's Clinical Practice Research Datalink (CPRD) and linked Hospital Episode Statistics (HES)*. *Population Health Metrics*, 2023. **21**(1): p. 3.
313. Geng, B., et al., *A meta-analysis of the effect of Sjögren's syndrome on adverse pregnancy outcomes*. *Clinics*, 2022. **77**: p. 100140.
314. Huang, W., et al., *Maternal and fetal outcomes in pregnant women with rheumatoid arthritis: a systematic review and meta-analysis*. *Clinical Rheumatology*, 2022: p. 1-16.
315. Arvanitakis, K., et al., *Adverse pregnancy outcomes in women with celiac disease: a systematic review and meta-analysis*. *Annals of Gastroenterology*, 2023: p. 12-12.
316. Sim, B.L., et al., *Pregnancy Outcomes in Women With Rheumatoid Arthritis: A Systematic Review and Meta-analysis*. *JCR: Journal of Clinical Rheumatology*, 2023. **29**(1): p. 36-42.
317. de Lima, A., et al., *Preconception Care Reduces Relapse of Inflammatory Bowel Disease During Pregnancy*. *Clinical Gastroenterology & Hepatology*, 2016. **14**(9): p. 1285-1292.e1.
318. Modrego, P.J., M.A. Urrea, and L.D. De Cerio, *The effects of pregnancy on relapse rates, disability and peripartum outcomes in women with multiple sclerosis: A systematic review and meta-Analysis*. *Journal of Comparative Effectiveness Research*, 2021. **10**(3): p. 175-186.
319. Hee, J.Y., et al., *Pregnancy loss and the risk of rheumatoid arthritis in Chinese women: findings from the China Kadoorie biobank*. *BMC Public Health*, 2022. **22**(1): p. 1768.
320. Lee, K.A., et al., *Pregnancy-associated risk factors and incidence of systemic sclerosis in primiparous women: A nationwide population-based cohort study*. *Modern Rheumatology*, 2022. **32**(1): p. 149-154.
321. Mao, Y., et al., *Association Between History of Gestational Diabetes Mellitus and the Risk of Arthritis in Women*. *Frontiers in Public Health*, 2022. **10**: p. 878845.
322. Mikkelsen, A.P., et al., *Pregnancy loss and risk of multiple sclerosis and autoimmune neurological disorder: A nationwide cohort study*. *PLoS ONE [Electronic Resource]*, 2022. **17**(3): p. e0266203.
323. Santos, C.S., et al., *AB0630 PREGNANCY IN AUTOIMMUNE DISEASES: THE IMPACT OF PREGNANCY PLANNING ON REPRODUCTIVE OUTCOMES IN A MULTIDISCIPLINARY PRECONCEPTION OUTPATIENT CLINIC*. 2023, BMJ Publishing Group Ltd.
324. Tincani, A., et al., *Pregnancy in patients with autoimmune disease: a reality in 2016*. *Autoimmunity reviews*, 2016. **15**(10): p. 975-977.
325. Sammaritano, L.R., *Contraception and preconception counseling in women with autoimmune disease*. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 2020. **64**: p. 11-23.
326. Angum, F., et al., *The prevalence of autoimmune disorders in women: a narrative review*. *Cureus*, 2020. **12**(5).
327. Thomas, S.L., et al., *Burden of mortality associated with autoimmune diseases among females in the United Kingdom*. *American journal of public health*, 2010. **100**(11): p. 2279-2287.
328. Gleicher, N. and D.H. Barad, *Gender as risk factor for autoimmune diseases*. *Journal of autoimmunity*, 2007. **28**(1): p. 1-6.
329. Ngo, S.T., F.J. Steyn, and P.A. McCombe, *Gender differences in autoimmune disease*. *Frontiers in neuroendocrinology*, 2014. **35**(3): p. 347-369.
330. Smith-Bouvier, D.L., et al., *A role for sex chromosome complement in the female bias in autoimmune disease*. *The Journal of experimental medicine*, 2008. **205**(5): p. 1099-1108.
331. Talal, N., *Sjögren's syndrome: historical overview and clinical spectrum of disease*. *Rheumatic diseases clinics of North America*, 1992. **18**(3): p. 507-515.

332. Van Den Hoogen, F., et al., *2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative*. Arthritis & Rheumatism, 2013. **65**(11): p. 2737-2747.
333. Desai, M.K. and R.D. Brinton, *Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan*. Frontiers in Endocrinology, 2019. **10**.
334. De Carolis, S., et al., *Autoimmunity in obstetrics and autoimmune diseases in pregnancy*. Best Practice & Research Clinical Obstetrics & Gynaecology, 2019. **60**: p. 66-76.
335. Walsh, S.J. and L.M. Rau, *Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States*. American journal of public health, 2000. **90**(9): p. 1463.
336. Wang, L., F.S. Wang, and M.E. Gershwin, *Human autoimmune diseases: a comprehensive update*. J Intern Med, 2015. **278**(4): p. 369-95.
337. Persson, L., et al., *Outside the safe operating space of the planetary boundary for novel entities*. Environmental science & technology, 2022. **56**(3): p. 1510-1521.
338. Arnaud, L., et al., *Drug-induced systemic lupus: revisiting the ever-changing spectrum of the disease using the WHO pharmacovigilance database*. Annals of the Rheumatic Diseases, 2019. **78**(4): p. 504-508.
339. Thorburn, A.N., L. Macia, and C.R. Mackay, *Diet, metabolites, and "western-lifestyle" inflammatory diseases*. Immunity, 2014. **40**(6): p. 833-842.
340. Immunotoxicology, W.H.O.C.C.f., et al., *Principles and methods for assessing autoimmunity associated with exposure to chemicals*. Vol. 236. 2006: World Health Organization.
341. Sener, A.G. and I. Afsar, *Infection and autoimmune disease*. Rheumatology international, 2012. **32**(11): p. 3331-3338.
342. Garbarino, S., et al., *Role of sleep deprivation in immune-related disease risk and outcomes*. Communications biology, 2021. **4**(1): p. 1-17.
343. Dellaripa, P.F., et al., *The Climate Emergency and the Health of Our Patients: The Role of the Rheumatologist*. Arthritis & Rheumatology, 2022.
344. Vojdani, A., *A Potential Link between Environmental Triggers and Autoimmunity*. Autoimmune Diseases, 2014. **2014**: p. 437231.
345. Adams Waldorf, K.M. and J.L. Nelson, *Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy*. Immunol Invest, 2008. **37**(5): p. 631-44.
346. Popescu, M.R., et al., *A Broader Perspective on Anti-Ro Antibodies and Their Fetal Consequences-A Case Report and Literature Review*. Diagnostics (Basel), 2020. **10**(7).
347. Bove, R.M. and M.K. Houtchens, *Pregnancy Management in Multiple Sclerosis and Other Demyelinating Diseases*. Continuum (Minneap Minn), 2022. **28**(1): p. 12-33.
348. Stransky, O.M., et al., *Contraception decision-making and care among reproductive-aged women with autoimmune diseases*. Contraception, 2021. **103**(2): p. 86-91.
349. Blagojevic, J., et al., *Pregnancy in Systemic Sclerosis: Results of a Systematic Review and Metaanalysis*. Journal of Rheumatology, 2020. **47**(6): p. 881-887.
350. Dong, Y., et al., *Preeclampsia in systemic lupus erythematosus pregnancy: a systematic review and meta-analysis*. Clinical Rheumatology, 2020. **39**(2): p. 319-325.
351. He, W.R. and H. Wei, *Maternal and fetal complications associated with systemic lupus erythematosus: An updated meta-analysis of the most recent studies (2017-2019)*. Medicine, 2020. **99**(16): p. e19797.
352. O'Toole, A., O. Nwanne, and T. Tomlinson, *Inflammatory Bowel Disease Increases Risk of Adverse Pregnancy Outcomes: A Meta-Analysis*. Digestive Diseases & Sciences, 2015. **60**(9): p. 2750-61.
353. Tandon, P., et al., *Systematic review with meta-analysis: risk of adverse pregnancy-related outcomes in inflammatory bowel disease*. Alimentary Pharmacology & Therapeutics, 2020. **51**(3): p. 320-333.
354. Wei, S., et al., *Systemic lupus erythematosus and risk of preterm birth: a systematic review and meta-analysis of observational studies*. Lupus, 2017. **26**(6): p. 563-571.
355. Arafa, A., et al., *Does multiple sclerosis increase the risk of preeclampsia? A systematic review and meta-analysis*. Hypertension in Pregnancy, 2021. **40**(3): p. 180-185.
356. Banner, H., et al., *Myasthenia Gravis in pregnancy: Systematic review and case series*. Obstetric Medicine., 2022.
357. Maguire, S., et al., *Pregnancy in axial spondyloarthritis: A systematic review & meta-analysis*. Seminars in Arthritis & Rheumatism, 2020. **50**(6): p. 1269-1279.
358. Papatheodorou, S., *Umbrella reviews: what they are and why we need them*. European journal of epidemiology, 2019. **34**(6): p. 543-546.
359. Institute, T.J.B., *Joanna Briggs Institute Reviewers' Manual: 2014 edition / Supplement*. 2014.

360. Gates, M., et al., *Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement*. BMJ, 2022. **378**: p. e070849.
361. National stem cell foundation, <https://nationalstemcellfoundation.org/glossary/autoimmune-disease/assessed> Nov,2022.
362. Singh, M., et al., *Association of pregnancy complications/risk factors with the development of future long-term health conditions in women: overarching protocol for umbrella reviews*. BMJ Open, 2022. **12**(12): p. e066476.
363. Haddaway, N.R., M. Land, and B. Macura, "A little learning is a dangerous thing": A call for better understanding of the term 'systematic review'. Environment International, 2017. **99**: p. 356-360.
364. Andersen, M.L., et al., *Maternal Multiple Sclerosis and Health Outcomes Among the Children: A Systematic Review*. Clin Epidemiol, 2023. **15**: p. 375-389.
365. Balsells, M., et al., *Maternal and fetal outcome in women with type 2 versus type 1 diabetes mellitus: a systematic review and metaanalysis*. Journal of Clinical Endocrinology & Metabolism, 2009. **94**(11): p. 4284-91.
366. Bansal, S., O. Okoye, and N. Rajora, *Pregnancy and lupus nephritis in developing countries: A systematic review*. Saudi Journal of Kidney Diseases & Transplantation, 2020. **31**(1): p. 10-20.
367. Bobotsis, R., et al., *Psoriasis and adverse pregnancy outcomes: a systematic review of observational studies*. British Journal of Dermatology, 2016. **175**(3): p. 464-472.
368. Bundhun, P.K., M.Z.S. Soogund, and F. Huang, *Arterial/venous thrombosis, fetal loss and stillbirth in pregnant women with systemic lupus erythematosus versus primary and secondary antiphospholipid syndrome: a systematic review and meta-analysis*. BMC Pregnancy & Childbirth, 2018. **18**(1): p. 212.
369. Cellini, M., et al., *Recurrent Pregnancy Loss in Women with Hashimoto's Thyroiditis with Concurrent Non-Endocrine Autoimmune Disorders*. Thyroid, 2020. **30**(3): p. 457-462.
370. Chaudhary, H., et al., *Pregnancy outcomes in a long-term follow-up cohort of pediatric onset systemic lupus erythematosus (PSLE) at a tertiary care center in North-West India*. Annals of the Rheumatic Diseases, 2019. **78**(Supplement 2): p. 793.
371. Crawford, N.M. and A.Z. Steiner, *Thyroid Autoimmunity and Reproductive Function*. Seminars in Reproductive Medicine, 2016. **34**(6): p. 343-350.
372. Dama, M., M. Steiner, and R.V. Lieshout, *Thyroid peroxidase autoantibodies and perinatal depression risk: A systematic review*. Journal of Affective Disorders, 2016. **198**: p. 108-21.
373. Derakhshan, A., et al., *Association of maternal thyroid function with birthweight: a systematic review and individual-participant data meta-analysis*. The Lancet Diabetes and Endocrinology, 2020. **8**(6): p. 501-510.
374. Dong, Y., et al., *Risk of gestational diabetes mellitus in systemic lupus erythematosus pregnancy: a systematic review and meta-analysis*. BMC Pregnancy & Childbirth, 2019. **19**(1): p. 179.
375. Essouma, M., et al., *Outcomes of systemic lupus erythematosus pregnancies and associated factors in sub-Saharan Africa: A systematic scoping review*. Lupus Science and Medicine, 2020. **7**(SUPPL 1): p. A66-A67.
376. Finkelsztejn, A., et al., *What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature*. BJOG: An International Journal of Obstetrics & Gynaecology, 2011. **118**(7): p. 790-7.
377. Foulon, A., et al., *Defining the Most Appropriate Delivery Mode in Women with Inflammatory Bowel Disease: A Systematic Review*. Inflammatory Bowel Diseases, 2017. **23**(5): p. 712-720.
378. Gizzo, S., et al., *An update on diabetic women obstetrical outcomes linked to preconception and pregnancy glycemic profile: a systematic literature review*. Thescientificworldjournal, 2013. **2013**: p. 254901.
379. Gonzalez-Blanco, C., et al., *Glycaemic control and pregnancy outcomes in women with type 1 diabetes: A systematic review and meta-analysis comparison between lispro and regular insulin*. Diabetologia, 2010. **1**: p. S433-S434.
380. Grygiel-Gorniak, B., et al., *Rheumatic Diseases in Reproductive Age-the Possibilities and the Risks*. Reproductive Sciences., 2022.
381. Hage, M.P. and S.T. Azar, *The link between thyroid function and depression*. Journal of Thyroid Research, 2012. **2012** (no pagination).
382. Hamroun, S., et al., *Fertility and pregnancy outcomes in women with spondyloarthritis: A systematic review and meta-analysis*. Annals of the Rheumatic Diseases, 2020. **79**(SUPPL 1): p. 742-743.
383. Hashash, J.G. and S. Kane, *Pregnancy and inflammatory bowel disease*. Gastroenterology and Hepatology, 2015. **11**(2): p. 96-102.

384. Hayslett, J.P., *The effect of systemic lupus erythematosus on pregnancy and pregnancy outcome*. American Journal of Reproductive Immunology, 1992. **28**(3-4): p. 199-204.
385. He, H., et al., *Effect of thyroid autoimmunity per se on assisted reproduction treatment outcomes: A meta-analysis*. Taiwanese Journal of Obstetrics & Gynecology, 2016. **55**(2): p. 159-65.
386. He, H., et al., *Effect of thyroid autoantibodies per se on pregnancy outcomes in euthyroid women undergoing IVF/ICSI*. Human Reproduction, 2015. **1**: p. i190.
387. Houtchens, M.K., N.C. Edwards, and A.L. Phillips, *A review of observational studies of women with MS and pregnancy*. Multiple Sclerosis, 2016. **22**(Supplement 3): p. 435-436.
388. Ideguchi, H., et al., *Pregnancy outcomes in Japanese patients with SLE: retrospective review of 55 pregnancies at a university hospital*. Clinical Reviews in Allergy & Immunology, 2013. **44**(1): p. 57-64.
389. Jaffar, F., K. Laycock, and M.S.B. Huda, *Type 1 Diabetes in Pregnancy: A Review of Complications and Management*. Current diabetes reviews., 2021. **05**.
390. Jia, M., et al., *Meta-analysis of the association between maternal subclinical hypothyroidism and gestational diabetes mellitus*. International Journal of Gynaecology & Obstetrics, 2019. **144**(3): p. 239-247.
391. Kane, S., *Inflammatory bowel disease in pregnancy*. Gastroenterology Clinics of North America, 2003. **32**(1): p. 323-340.
392. Kent, N.L., et al., *Is the link between elevated TSH and gestational diabetes mellitus dependant on diagnostic criteria and thyroid antibody status: a systematic review and meta-analysis*. Endocrine, 2021. **74**(1): p. 38-49.
393. Kim, M.A., et al., *The Influence of Disease Activity on Pregnancy Outcomes in Women With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis*. Journal of Crohn's & colitis, 2021. **15**(5): p. 719-732.
394. Lamah, M. and H.J. Scott, *Inflammatory bowel disease and pregnancy*. International Journal of Colorectal Disease, 2002. **17**(4): p. 216-22.
395. Laube, R., et al., *Assisted Reproductive Technology in Crohn's Disease and Ulcerative Colitis: A Systematic Review and Meta-Analysis*. American Journal of Gastroenterology, 2021. **116**(12): p. 2334-2344.
396. Leiva, P., et al., *There is no association between the presence of anti-thyroid antibodies and increased reproductive loss in pregnant women after ART: a systematic review and meta-analysis*. JBRA Assisted Reproduction, 2017. **21**(4): p. 361-365.
397. Li, M., et al., *Relationship between the thyroid autoimmunity and the risk of preterm birth in pregnant women: a meta-analysis. [Chinese]*. Zhonghua fu chan ke za zhi, 2016. **51**(5): p. 339-344.
398. Lopez-Leon, S., et al., *A systematic review and meta-analyses of pregnancy and fetal outcomes in women with multiple sclerosis. IMI2 conception*. Multiple Sclerosis Journal, 2020. **26**(3 SUPPL): p. 255.
399. McDonald, E.G., et al., *Monitoring of Systemic Lupus Erythematosus Pregnancies: A Systematic Literature Review*. Journal of Rheumatology, 2018. **45**(10): p. 1477-1490.
400. Meissner, Y., et al., *Pregnancy in women with psoriatic arthritis: A systematic literature review of disease activity and adverse pregnancy outcomes*. Seminars in Arthritis & Rheumatism, 2021. **51**(3): p. 530-538.
401. Mintziori, G., et al., *Thyroid diseases and female reproduction*. Minerva Medica, 2012. **103**(1): p. 47-62.
402. Mintziori, G., B.C. Tarlatzis, and D.G. Goulis, *The impact of thyroid autoimmunity on IVF/ICSI outcome: Re-evaluation of the findings*. Human Reproduction Update, 2016. **22**(6): p. 791.
403. Mokbel, A., D.O. Lawson, and F. Farrokhyar, *Pregnancy outcomes in women with ankylosing spondylitis: a scoping literature and methodological review*. Clinical Rheumatology, 2021. **40**(9): p. 3465-3480.
404. Moroni, G., M. Calatroni, and C. Ponticelli, *The impact of preeclampsia in lupus nephritis*. Expert review of clinical immunology., 2022. **05**.
405. Munoz Munoz, C., et al., *Comparing pregnancy outcomes in patients with criteria and non-criteria autoimmune disease: A systematic review*. Lupus, 2022. **31**(1): p. 5-18.
406. Nazarpour, S., et al., *Thyroid autoantibodies and the effect on pregnancy outcomes*. Journal of Obstetrics & Gynaecology, 2016. **36**(1): p. 3-9.
407. Negro, R., *Thyroid autoimmunity and pre-term delivery: Brief review and meta-analysis*. Journal of Endocrinological Investigation, 2011. **34**(2): p. 155-158.
408. Ogallar, M.A.D., N. Cortes-Garcia, and M. Linares-Abad, *Myasthenia gravis and pregnancy. [Spanish]*. Matronas Profesion, 2018. **19**(1): p. 28-34.

409. Pacu, I., et al., *Thyroid antibodies and risk of Preterm delivery: A meta-analysis of prospective cohort studies*. Archives of the Balkan Medical Union, 2013. **48(4)**: p. 400-403.
410. Park, J.J., H.J. Kim, and M.A. Kim, *The influence of disease activity on birth outcomes in patients with inflammatory bowel disease: Meta-analysis*. Journal of Crohn's and Colitis, 2016. **10(Supplement 1)**: p. S201.
411. Petri, M., *Pregnancy in SLE*. Bailliere's Clinical Rheumatology, 1998. **12(3)**: p. 449-476.
412. Piccioni, M.G., et al., *Myasthenia gravis in pregnancy, delivery and newborn*. Minerva Ginecologica, 2020. **72(1)**: p. 30-35.
413. Piccoli, G.B., et al., *Type 1 diabetes, diabetic nephropathy, and pregnancy: a systematic review and meta-study*. The Review of Diabetic Studies, 2013. **10(1)**: p. 6-26.
414. Prummel, M.F. and W.M. Wiersinga, *Thyroid autoimmunity and miscarriage*. European Journal of Endocrinology, 2004. **150(6)**: p. 751-5.
415. Schmidt, P.M.S., et al., *Postpartum depression in maternal thyroidal changes*. Thyroid Research, 2022. **15(1)** (no pagination).
416. Smyth, A., et al., *A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis*. Clinical Journal of The American Society of Nephrology: CJASN, 2010. **5(11)**: p. 2060-8.
417. Tian, L., et al., *Association between pregnant women with rheumatoid arthritis and preeclampsia: A systematic review and meta-analysis*. Medicine (Baltimore), 2023. **102(26)**: p. e34131.
418. Toulis, K.A., et al., *Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: a meta-analysis*. European Journal of Endocrinology, 2010. **162(4)**: p. 643-52.
419. Wang, P., et al., *Thyroid antibodies and risk of preterm delivery: A meta-analysis of prospective cohort studies*. European Journal of Endocrinology, 2012. **167(4)**: p. 455-464.
420. Wu, H., et al., *[Effects of thyroid autoimmunity on pregnancy outcomes in euthyroid women receiving in vitro fertilization: a meta-analysis]*. Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal], 2015. **95(46)**: p. 3770-4.
421. Yang, Y., et al., *Thyroid antibodies and gestational diabetes mellitus: a meta-analysis*. Fertility & Sterility, 2015. **104(3)**: p. 665-71.e3.
422. Shea, B.J., et al., *AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both*. Bmj, 2017. **358**: p. j4008.
423. Fusar-Poli, P. and J. Radua, *Ten simple rules for conducting umbrella reviews*. Evidence Based Mental Health, 2018. **21(3)**: p. 95-100.
424. Bundhun, P.K., M.Z. Soogund, and F. Huang, *Impact of systemic lupus erythematosus on maternal and fetal outcomes following pregnancy: A meta-analysis of studies published between years 2001-2016*. Journal of Autoimmunity, 2017. **79**: p. 17-27.
425. Chen, L. and R. Hu, *Thyroid autoimmunity and miscarriage: a meta-analysis*. Clinical Endocrinology, 2011. **74(4)**: p. 513-9.
426. Cornish, J., et al., *A meta-analysis on the influence of inflammatory bowel disease on pregnancy*. Gut, 2007. **56(6)**: p. 830-7.
427. Dong, A.C., et al., *Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis*. Fertility & Sterility, 2020. **113(3)**: p. 587-600.e1.
428. He, X., et al., *Thyroid antibodies and risk of preterm delivery: a meta-analysis of prospective cohort studies*. Eur J Endocrinol, 2012. **167(4)**: p. 455-464.
429. Korevaar, T.I.M., et al., *Association of Thyroid Function Test Abnormalities and Thyroid Autoimmunity With Preterm Birth: A Systematic Review and Meta-analysis*. Obstetrical and Gynecological Survey, 2020. **75(1)**: p. 10-12.
430. Leung, K.K., et al., *The Risk of Adverse Neonatal Outcomes With Maternal Inflammatory Bowel Disease: A Systematic Review and Meta-analysis*. Inflammatory Bowel Diseases, 2021. **27(4)**: p. 550-562.
431. Li, M., et al., *Ethnic Differences in Preterm Birth Risks for Pregnant Women with Thyroid Dysfunction or Autoimmunity: A Meta-analysis*. Biomedical & Environmental Sciences, 2016. **29(10)**: p. 724-733.
432. Luo, J., et al., *Association of thyroid disorders with gestational diabetes mellitus: a meta-analysis*. Endocrine, 2021. **73(3)**: p. 550-560.
433. Minaldi, E., et al., *Thyroid autoimmunity and risk of post-partum depression: a systematic review and meta-analysis of longitudinal studies*. Journal of Endocrinological Investigation, 2020. **43(3)**: p. 271-277.

434. Saccone, G., et al., *Celiac disease and obstetric complications: a systematic review and metaanalysis*. American Journal of Obstetrics & Gynecology, 2016. **214**(2): p. 225-234.
435. Talavera, J.I., et al., *The association between ectopic pregnancy and inflammatory bowel disease, irritable bowel syndrome, and celiac disease: A systematic review*. Journal of Obstetrics and Gynaecology Research, 2021. **47**(5): p. 1601-1609.
436. Tersigni, C., et al., *Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms*. Human Reproduction Update, 2014. **20**(4): p. 582-93.
437. Thangaratinam, S., et al., *Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence*. Bmj, 2011. **342**.
438. Tong, Z., et al., *The Effect of Subclinical Maternal Thyroid Dysfunction and Autoimmunity on Intrauterine Growth Restriction: A Systematic Review and Meta-Analysis*. Medicine, 2016. **95**(19): p. e3677.
439. Upala, S. and A. Sanguankeo, *Association between primary sjogren's syndrome and pregnancy outcome: A systematic review and meta-analysis*. Arthritis and Rheumatology. Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP, 2015. **67**(SUPPL. 10).
440. Xie, W., et al., *Maternal and neonatal outcomes in pregnant women with psoriasis and psoriatic arthritis: a systematic review and meta-analysis*. Rheumatology, 2021. **60**(9): p. 4018-4028.
441. Yu, L., et al., *Quantitative assessment of the effect of pre-gestational diabetes and risk of adverse maternal, perinatal and neonatal outcomes*. Oncotarget, 2017. **8**(37): p. 61048-61056.
442. Zhang, S.C., et al., *Obstetrical complications of thyroid peroxidase antibody positive during pregnancy and effects of intervention: a meta-analysis*. [Chinese]. Zhonghua fu chan ke za zhi, 2016. **51**(4): p. 250-257.
443. Lv, J., L. Xu, and S. Mao, *Association between disease activity of rheumatoid arthritis and maternal and fetal outcomes in pregnant women: a systematic review and meta-analysis*. BMC Pregnancy & Childbirth, 2023. **23**(1): p. 724.
444. Ahmadzai, N., et al., *A surveillance system to assess the need for updating systematic reviews*. Systematic Reviews, 2013. **2**(1): p. 104.
445. Begg, C.B. and M. Mazumdar, *Operating characteristics of a rank correlation test for publication bias*. Biometrics, 1994: p. 1088-1101.
446. Dalton, J.E., S.D. Bolen, and E.J. Mascha, *Publication bias: the elephant in the review*. Anesthesia and analgesia, 2016. **123**(4): p. 812.
447. Egger, M., et al., *Bias in meta-analysis detected by a simple, graphical test*. Bmj, 1997. **315**(7109): p. 629-634.
448. Garner, P., et al., *When and how to update systematic reviews: consensus and checklist*. BMJ, 2016. **354**: p. i3507.
449. Hennessy, E.A. and B.T. Johnson, *Examining overlap of included studies in meta-reviews: Guidance for using the corrected covered area index*. Research Synthesis Methods, 2020. **11**(1): p. 134-145.
450. Page, M.J., et al., *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews*. Bmj, 2021. **372**: p. n71.
451. Smith, G.D. and K.H.M. Ho, *Systematic reviews: When should they be updated?* Journal of Clinical Nursing. **n/a**(n/a).
452. van den Boogaard, E., et al., *Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: A systematic review*. Human Reproduction Update, 2011. **17**(5): p. 605-619.
453. Horev, A., et al., *Pregnancy outcome in women with vitiligo*. International journal of dermatology, 2011. **50**(9): p. 1083-1085.
454. Kolstad, K.D., et al., *Pregnancy outcomes in adult patients with dermatomyositis and polymyositis*. Seminars in Arthritis and Rheumatism, 2018. **47**(6): p. 865-869.
455. Deguchi, M., et al., *Factors associated with adverse pregnancy outcomes in women with antiphospholipid syndrome: A multicenter study*. Journal of Reproductive Immunology, 2017. **122**: p. 21-27.
456. ALARCÓN-SEGOVIA, D., et al., *Antiphospholipid Antibodies and the Antiphospholipid Syndrome in Systemic Lupus Erythematosus A Prospective Analysis of 500 Consecutive Patients*. Medicine, 1989. **68**(6): p. 353-365.

457. Hung, C.-T., et al., *Pregnancy outcomes in women with vitiligo: A Taiwanese nationwide cohort study*. Plos one, 2021. **16**(3): p. e0248651.
458. Park, K.Y., et al., *Pregnancy outcomes in patients with vitiligo: A nationwide population-based cohort study from Korea*. Journal of the American Academy of Dermatology, 2018. **79**(5): p. 836-842.
459. Schneiderman, M., et al., *Maternal and neonatal outcomes of pregnancies in women with Addison's disease: a population-based cohort study on 7.7 million births*. BJOG: An International Journal of Obstetrics & Gynaecology, 2017. **124**(11): p. 1772-1779.
460. Bjornsdottir, S., et al., *Addison's disease in women is a risk factor for an adverse pregnancy outcome*. The Journal of Clinical Endocrinology & Metabolism, 2010. **95**(12): p. 5249-5257.
461. Cho, S.I., et al., *Pregnancy Outcomes in Female Patients with Alopecia Areata: A Nationwide Population-Based Study*. Journal of Investigative Dermatology, 2021. **141**(7): p. 1844-1847.e4.
462. Chen, J.S., et al., *Pregnancy outcomes in women with rare autoimmune diseases*. Arthritis & Rheumatology, 2015. **67**(12): p. 3314-3323.
463. Spinillo, A., et al., *The effect of newly diagnosed undifferentiated connective tissue disease on pregnancy outcome*. American journal of obstetrics and gynecology, 2008. **199**(6): p. 632. e1-632. e6.
464. Spinillo, A., et al., *Undifferentiated connective tissue diseases and adverse pregnancy outcomes. An undervalued association?* American Journal of Reproductive Immunology, 2017. **78**(6): p. e12762.
465. Mosca, M., et al., *Pregnancy outcome in patients with undifferentiated connective tissue disease: a preliminary study on 25 pregnancies*. Lupus, 2002. **11**(5): p. 304-307.
466. Sperber, K., et al., *Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases*. Pediatric Rheumatology, 2009. **7**(1): p. 1-9.
467. Mecacci, F., et al. *The impact of autoimmune disorders and adverse pregnancy outcome*. in *Seminars in perinatology*. 2007. Elsevier.
468. Tsao, N.W., et al., *Patterns of biologics utilization and discontinuation before and during pregnancy in women with autoimmune diseases: a population-based cohort study*. Arthritis care & research, 2018. **70**(7): p. 979-986.
469. Götestam Skorpen, C., et al., *Women with systemic lupus erythematosus get pregnant more easily than women with rheumatoid arthritis*. Rheumatology (Oxford), 2018. **57**(6): p. 1072-1079.
470. Suci, N., et al., *Fetal and neonatal outcome in celiac disease*. Journal of Maternal-Fetal and Neonatal Medicine, 2014. **27**(8): p. 851-855.
471. Lopez-Leon, S., et al., *A systematic review and meta-analyses of pregnancy and fetal outcomes in women with multiple sclerosis. IMI2 conception*. Multiple Sclerosis Journal, 2020. **26**(3 SUPPL): p. 255.
472. Ross, G., et al., *Effects of mothers' autoimmune disease during pregnancy on learning disabilities and hand preference in their children*. Archives of pediatrics & adolescent medicine, 2003. **157**(4): p. 397-402.
473. Nielsen, T.C., et al., *Association of maternal autoimmune disease with attention-deficit/hyperactivity disorder in children*. JAMA pediatrics, 2021. **175**(3): p. e205487-e205487.
474. Chen, S.-w., et al., *Maternal autoimmune diseases and the risk of autism spectrum disorders in offspring: a systematic review and meta-analysis*. Behavioural brain research, 2016. **296**: p. 61-69.
475. Norwood, F., et al., *Myasthenia in pregnancy: best practice guidelines from a U.K. multispecialty working group*. Journal of Neurology, Neurosurgery & Psychiatry, 2014. **85**(5): p. 538-43.
476. Murphy, H.R., *2020 NICE guideline update: Good news for pregnant women with type 1 diabetes and past or current gestational diabetes*. Diabetic Medicine, 2021. **38**(6): p. e14576.
477. Dobson, R., et al., *UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines*. Pract Neurol, 2019. **19**(2): p. 106-114.
478. Russell, M.D., et al., *Executive Summary: British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids*. Rheumatology, 2022. **62**(4): p. 1370-1387.
479. Skorpen, C.G., et al., *The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation*. Annals of the Rheumatic Diseases, 2016. **75**(5): p. 795-810.
480. Sammaritano, L.R., et al., *2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases*. Arthritis & rheumatology, 2020. **72**(4): p. 529-556.
481. Gordon, C., *Pregnancy and autoimmune diseases*. Best Practice & Research Clinical Rheumatology, 2004. **18**(3): p. 359-379.
482. Keestra, S.M., V. Male, and G.D. Salali, *Out of balance: the role of evolutionary mismatches in the sex disparity in autoimmune disease*. Medical hypotheses, 2021. **151**: p. 110558.

483. Furer, V., et al., *2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases*. *Annals of the rheumatic diseases*, 2020. **79**(1): p. 39-52.
484. Nana, M., et al., *The impact of preconception counselling on maternal and fetal outcomes in women with chronic medical conditions: A systematic review*. *Eur J Intern Med*, 2023. **108**: p. 52-59.
485. Wotherspoon, A.C., et al., *Evaluation of biomarkers for the prediction of pre-eclampsia in women with type 1 diabetes mellitus: A systematic review*. *Journal of Diabetes & its Complications*, 2016. **30**(5): p. 958-66.
486. Davidson, A. and B. Diamond, *Autoimmune diseases*. *New England Journal of Medicine*, 2001. **345**(5): p. 340-350.
487. Fairweather, D. and N.R. Rose, *Women and autoimmune diseases*. *Emerging infectious diseases*, 2004. **10**(11): p. 2005.
488. Wang, L., F.S. Wang, and M.E. Gershwin, *Human autoimmune diseases: a comprehensive update*. *Journal of internal medicine*, 2015. **278**(4): p. 369-395.
489. Fairweather, D., S. Frischno-Kiss, and N.R. Rose, *Sex differences in autoimmune disease from a pathological perspective*. *The American journal of pathology*, 2008. **173**(3): p. 600-609.
490. Rubtsova, K., P. Marrack, and A.V. Rubtsov, *Sexual dimorphism in autoimmunity*. *The Journal of clinical investigation*, 2015. **125**(6): p. 2187-2193.
491. Salimi, H.R., M.D. Griffiths, and Z. Alimoradi, *Prevalence of anxiety and depression among pregnant women with diabetes and their predictors*. *Diabetes Epidemiology and Management*, 2024. **14**: p. 100198.
492. Chen, T.-C., et al., *Fertility Trends and Adverse Pregnancy Outcomes in Female Patients With Psoriasis in the UK*. *JAMA Dermatology*, 2023. **159**(7): p. 736-744.
493. McGrogan, A., J. Snowball, and C.S. de Vries, *Pregnancy losses in women with Type 1 or Type 2 diabetes in the UK: an investigation using primary care records*. *Diabetic Medicine*, 2014. **31**(3): p. 357-365.
494. Sultan, A.A., et al., *Pregnancy Complications and Adverse Birth Outcomes Among Women With Celiac Disease: A Population-Based Study From England*. *Official journal of the American College of Gastroenterology | ACG*, 2014. **109**(10).
495. Abdul Sultan, A., et al., *Adverse Pregnancy Outcomes Among Women with Inflammatory Bowel Disease: A Population-Based Study from England*. *Inflammatory Bowel Diseases*, 2016. **22**(7): p. 1621-1630.
496. Howard, L.M., et al., *Non-psychotic mental disorders in the perinatal period*. *The Lancet*, 2014. **384**(9956): p. 1775-1788.
497. Song, H., et al., *Association of stress-related disorders with subsequent autoimmune disease*. *Jama*, 2018. **319**(23): p. 2388-2400.
498. Bränn, E., et al., *Bidirectional association between autoimmune disease and perinatal depression: a nationwide study with sibling comparison*. *Molecular Psychiatry*, 2024.
499. *Ethical approval CPRD* <https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/clinical-practice-research-datalink-cprd-research-database/> assessed on 15th August 2024.
500. *Research governance approval* [https://www.cprd.com/research-applications#:~:text=Access%20to%20CPRD%20data%2C%20including,Central%20Advisory%20Committee%20\(CAC\).](https://www.cprd.com/research-applications#:~:text=Access%20to%20CPRD%20data%2C%20including,Central%20Advisory%20Committee%20(CAC).) assessed on 15th August 2024.
501. Lee, S.I., et al., *Epidemiology of pre-existing multimorbidity in pregnant women in the UK in 2018: a population-based cross-sectional study*. *BMC Pregnancy Childbirth*, 2022. **22**(1): p. 120.
502. *The English Indices of Deprivation 2019 (IoD2019)*. 2019. <https://www.gov.uk/government/publications/english-indices-of-deprivation-2019-technical-report>. Accessed 8May,2024.
503. Mavragani, C.P. and H.M. Moutsopoulos, *The geoepidemiology of Sjögren's syndrome*. *Autoimmunity reviews*, 2010. **9**(5): p. A305-A310.
504. Therneau, T.M. *Extending the Cox model*. in *Proceedings of the first Seattle symposium in biostatistics: survival analysis*. 1997. Springer.
505. Timur, H., et al., *Pregnancy outcome in patients with ankylosing spondylitis*. *The Journal of Maternal-Fetal & Neonatal Medicine*, 2016. **29**(15): p. 2470-2474.
506. Park, E.H., et al., *Pregnancy outcomes in Korean women with ankylosing spondylitis*. *The Korean Journal of Internal Medicine*, 2021. **36**(3): p. 721.

507. Vigod, S.N., et al., *Inflammatory bowel disease and new-onset psychiatric disorders in pregnancy and post partum: a population-based cohort study*. Gut, 2019. **68**(9): p. 1597-1605.
508. Gray, M.A., et al., *Anti-TNF α therapy in IBD alters brain activity reflecting visceral sensory function and cognitive-affective biases*. PLoS One, 2018. **13**(3): p. e0193542.
509. Lotrich, F.E., et al., *The role of inflammation in the pathophysiology of depression: different treatments and their effects*. The Journal of Rheumatology Supplement, 2011. **88**: p. 48-54.
510. Lehman, H.K., *Autoimmunity and Immune Dysregulation in Primary Immune Deficiency Disorders*. Curr Allergy Asthma Rep, 2015. **15**(9): p. 53.
511. *Correction to: British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids*. Rheumatology, 2022. **62**(5): p. 2021-2021.
512. Ali, M.F., H. He, and D. Friedel, *Inflammatory bowel disease and pregnancy: fertility, complications and treatment*. Annals of gastroenterology, 2020. **33**(6): p. 579.
513. Neurath, M.F., *Strategies for targeting cytokines in inflammatory bowel disease*. Nature Reviews Immunology, 2024.
514. Dudrick, S.J., R. Latifi, and R. Schragar, *Nutritional Management of Inflammatory Bowel Disease*. Surgical Clinics of North America, 1991. **71**(3): p. 609-623.
515. Somerset, D.A., et al., *Normal human pregnancy is associated with an elevation in the immune suppressive CD25⁺ CD4⁺ regulatory T-cell subset*. Immunology, 2004. **112**(1): p. 38-43.
516. Förger, F., P.M. Villiger, and M. Østensen, *Pregnancy in patients with ankylosing spondylitis: do regulatory T cells play a role?* Arthritis Care & Research, 2009. **61**(2): p. 279-283.
517. Djordjevic, A., et al., *Oxidative stress in diabetic pregnancy: SOD, CAT and GSH-Px activity and lipid peroxidation products*. J Matern Fetal Neonatal Med, 2004. **16**(6): p. 367-72.
518. Leach, L., A. Taylor, and F. Sciota, *Vascular dysfunction in the diabetic placenta: causes and consequences*. J Anat, 2009. **215**(1): p. 69-76.
519. Nakamura, H., et al., *Prevalence of interrelated autoantibodies in thyroid diseases and autoimmune disorders*. Journal of endocrinological investigation, 2008. **31**: p. 861-865.
520. Colin, I., et al., *Functional lymphocyte subset assessment of the Th1/Th2 profile in patients with autoimmune thyroiditis by flowcytometric analysis of peripheral lymphocytes*. Journal of biological regulators and homeostatic agents, 2004. **18**(1): p. 72-76.
521. Feist, E., et al., *Autoantibodies in primary Sjogren's syndrome are directed against proteasomal subunits of the α and β type*. Arthritis and Rheumatism, 1999. **42**(4): p. 697-702.
522. Chen, L., L.X. Shang, and Y. Huang, *Immune infertility and immune-related recurrent miscarriage*. People's Army Medical, 2019. **62**(7): p. 665-669.
523. Birru Talabi, M., K.P. Himes, and M.E.B. Clowse, *Optimizing reproductive health management in lupus and Sjogren's syndrome*. Current Opinion in Rheumatology, 2021. **33**(6).
524. Pons-Estel, G.J., et al., *The antiphospholipid syndrome in patients with systemic lupus erythematosus*. Journal of Autoimmunity, 2017. **76**: p. 10-20.
525. Chung, W.-S., et al., *Increased risks of deep vein thrombosis and pulmonary embolism in Sjögren syndrome: a nationwide cohort study*. The Journal of Rheumatology, 2014. **41**(5): p. 909-915.
526. Ramos-Casals, M., et al. *Atypical autoantibodies in patients with primary Sjögren syndrome: clinical characteristics and follow-up of 82 cases*. in *Seminars in arthritis and rheumatism*. 2006. Elsevier.
527. Asherson, R.A., et al., *Antiphospholipid antibodies and HLA associations in primary Sjögren's syndrome*. Annals of the rheumatic diseases, 1992. **51**(4): p. 495-498.
528. Jedryka-Goral, A., et al., *Isotype profile and clinical relevance of anticardiolipin antibodies in Sjögren's syndrome*. Annals of the rheumatic diseases, 1992. **51**(7): p. 889-891.
529. Yang H, Liu H, Xu D, Zhao L, Wang Q, Leng X, et al. (2014) *Pregnancy-Related Systemic Lupus Erythematosus: Clinical Features, Outcome and Risk Factors of Disease Flares — A Case Control Study*. PLoS ONE 9(8): e104375. <https://doi.org/10.1371/journal.pone.0104375>.
530. Teh, C., et al., *Systemic lupus erythematosus pregnancies: ten-year data from a single centre in Malaysia*. Lupus, 2017. **26**(2): p. 218-223.
531. Lewandowski, K., et al., *New onset Addison's disease presenting as prolonged hyperemesis in early pregnancy*. Ginekologia Polska, 2010. **81**(7).
532. Gabra, A., H. Habib, and M. Gabra, *Hyperemesis gravidarum, diagnosis, and pathogenesis*. Crit Care Obstet Gynecol, 2019. **5**(01): p. 1-5.
533. Bandoli, G., et al., *A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes*. Rheumatic Disease Clinics, 2017. **43**(3): p. 489-502.

534. Elliott, A.B. and E.F. Chakravarty, *Immunosuppressive medications during pregnancy and lactation in women with autoimmune diseases*. Women's Health, 2010. **6**(3): p. 431-442.
535. Kim, S.C. and S. Hernandez-Diaz, *Safety of immunosuppressive drugs in pregnant women with systemic inflammatory diseases*. 2014, Wiley Online Library. p. 246-249.
536. Gerosa, M., P.L. Meroni, and R. Cimaz, *Safety considerations when prescribing immunosuppression medication to pregnant women*. Expert opinion on drug safety, 2014. **13**(12): p. 1591-1599.
537. Ghalandari, N., et al., *Intrauterine exposure to biologics in inflammatory autoimmune diseases: a systematic review*. Drugs, 2020. **80**: p. 1699-1722.
538. Flint, J., et al., *BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids*. Rheumatology, 2016. **55**(9): p. 1693-1697.
539. Flint, J., et al., *BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part II: analgesics and other drugs used in rheumatology practice*. Rheumatology, 2016. **55**(9): p. 1698-1702.
540. Group, G.D., *Management of diabetes from preconception to the postnatal period: summary of NICE guidance*. Bmj, 2008. **336**(7646): p. 714-717.
541. Murphy, H.R., *2020 NICE guideline update: good news for pregnant women with type 1 diabetes and past or current gestational diabetes*. Diabetic Medicine, 2021. **38**(6).
542. Greuter, M.J., et al., *Quality of guidelines on the management of diabetes in pregnancy: a systematic review*. BMC pregnancy and childbirth, 2012. **12**: p. 1-7.
543. Selinger, C., et al., *Standards for the provision of antenatal care for patients with inflammatory bowel disease: guidance endorsed by the British Society of Gastroenterology and the British Maternal and Fetal Medicine Society*. Frontline Gastroenterology, 2021. **12**(3): p. 182-187.
544. Norwood, F., et al., *Myasthenia in pregnancy: best practice guidelines from a UK multispecialty working group*. Journal of Neurology, Neurosurgery & Psychiatry, 2014. **85**(5): p. 538-543.
545. Dobson, R., et al., *UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines*. Practical neurology, 2019. **19**(2): p. 106-114.
546. Cataudella, S., et al., *A Pilot Study of the Relationship Between Pregnancy and Autoimmune Disease: Exploring the Mother's Psychological Process*. Frontiers in Psychology, 2019. **10**: p. 478069.
547. *Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies*. The Lancet, 2004. **363**(9403): p. 157-163.
548. Conrad, N., et al., *Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK*. The Lancet, 2023. **401**(10391): p. 1878-1890.
549. Ngo, S.T., F.J. Steyn, and P.A. McCombe, *Gender differences in autoimmune disease*. Front Neuroendocrinol, 2014. **35**(3): p. 347-69.
550. Mallampalli, M.P., et al., *Role of environment and sex differences in the development of autoimmune diseases: a roundtable meeting report*. Journal of Women's health, 2013. **22**(7): p. 578-586.
551. Miquel, C.H., B. Faz-Lopez, and J.C. Guéry, *Influence of X chromosome in sex-biased autoimmune diseases*. J Autoimmun, 2023. **137**: p. 102992.
552. Souyris, M., et al., *Female predisposition to TLR7-driven autoimmunity: gene dosage and the escape from X chromosome inactivation*. Semin Immunopathol, 2019. **41**(2): p. 153-164.
553. Merrheim, J., et al., *Estrogen, estrogen-like molecules and autoimmune diseases*. Autoimmun Rev, 2020. **19**(3): p. 102468.
554. Nelson, J.L., et al., *Remission of rheumatoid arthritis during pregnancy and maternal-fetal class II alloantigen disparity*. Am J Reprod Immunol, 1992. **28**(3-4): p. 226-7.
555. ZAKARIJA, M. and J.M. MCKENZIE, *Pregnancy-Associated Changes in the Thyroid-Stimulating Antibody of Graves' Disease and the Relationship to Neonatal Hyperthyroidism**. The Journal of Clinical Endocrinology & Metabolism, 1983. **57**(5): p. 1036-1040.
556. BOYD, A.S., et al., *PSORIASIS AND PREGNANCY: HORMONE AND IMMUNE SYSTEM INTERACTION*. International Journal of Dermatology, 1996. **35**(3): p. 169-172.
557. Khamashta, M.A., G. Ruiz-Irastorza, and G.R. Hughes, *Systemic lupus erythematosus flares during pregnancy*. Rheumatic Disease Clinics of North America, 1997. **23**(1): p. 15-30.
558. Schubert, C., et al., *Postpartum relapse risk in multiple sclerosis: a systematic review and meta-analysis*. Journal of Neurology, Neurosurgery & Psychiatry, 2023. **94**(9): p. 718-725.
559. Castles, A., et al., *Effects of smoking during pregnancy: five meta-analyses*. American journal of preventive medicine, 1999. **16**(3): p. 208-215.

560. Cnattingius, S. and M. Lambe. *Trends in smoking and overweight during pregnancy: prevalence, risks of pregnancy complications, and adverse pregnancy outcomes*. in *Seminars in perinatology*. 2002. Elsevier.
561. DiFranza, J.R. and R.A. Lew, *Effect of maternal cigarette smoking on pregnancy complications and sudden infant death syndrome*. The European Journal of General Practice, 1995. **1**(3): p. 117-117.
562. Meltzer, H.M., et al., *Effect of dietary factors in pregnancy on risk of pregnancy complications: results from the Norwegian Mother and Child Cohort Study*. The American journal of clinical nutrition, 2011. **94**(suppl_6): p. 1970S-1974S.
563. Ovesen, P., S. Rasmussen, and U. Kesmodel, *Effect of prepregnancy maternal overweight and obesity on pregnancy outcome*. Obstetrics & Gynecology, 2011. **118**(2 Part 1): p. 305-312.
564. Ramachenderan, J., J. Bradford, and M. Mclean, *Maternal obesity and pregnancy complications: a review*. Australian and New Zealand Journal of Obstetrics and Gynaecology, 2008. **48**(3): p. 228-235.
565. Jaffar, F., K. Laycock, and M.S.B. Huda, *Type 1 Diabetes in Pregnancy: A Review of Complications and Management*. Curr Diabetes Rev, 2022. **18**(7): p. e051121197761.
566. Naik, V.D., et al., *Effects of nutrition and gestational alcohol consumption on fetal growth and development*. Nutr Rev, 2022. **80**(6): p. 1568-1579.
567. Upala, S., W.C. Yong, and A. Sanguankee, *Association between primary Sjögren's syndrome and pregnancy complications: a systematic review and meta-analysis*. Clin Rheumatol, 2016. **35**(8): p. 1949-1955.
568. Khizroeva, J., et al., *Infertility in women with systemic autoimmune diseases*. Best Pract Res Clin Endocrinol Metab, 2019. **33**(6): p. 101369.
569. Carp, H.J., C. Selmi, and Y. Shoenfeld, *The autoimmune bases of infertility and pregnancy loss*. J Autoimmun, 2012. **38**(2-3): p. J266-74.
570. Bobotsis, R., et al., *Psoriasis and adverse pregnancy outcomes: a systematic review of observational studies*. British Journal of Dermatology, 2016. **175**(3): p. 464-72.
571. Arvanitakis, K., et al., *Adverse pregnancy outcomes in women with celiac disease: a systematic review and meta-analysis*. Annals of Gastroenterology, 2023. **36**(1): p. 12-24.
572. Khashan, A.S., et al., *Pregnancy and the Risk of Autoimmune Disease*. PLOS ONE, 2011. **6**(5): p. e19658.
573. Sobanski, V., et al., *Special considerations in pregnant systemic sclerosis patients*. Expert Rev Clin Immunol, 2016. **12**(11): p. 1161-1173.
574. Auvinen, A.M., et al., *Type 1 and type 2 diabetes after gestational diabetes: a 23 year cohort study*. Diabetologia, 2020. **63**(10): p. 2123-2128.
575. Jorgensen, K.T., et al., *National cohort study of reproductive risk factors for rheumatoid arthritis in Denmark: a role for hyperemesis, gestational hypertension and pre-eclampsia?* Annals of the Rheumatic Diseases, 2010. **69**(2): p. 358-63.
576. Gleicher, N., *Reproductive failure prior to the onset of clinical autoimmune disease*. Rheumatology, 1999. **38**(6): p. 485-487.
577. Chakravarty, E., *Pre-disease pregnancy complications and systemic sclerosis: pathogenic or pre-clinical?* Arthritis Res Ther, 2012. **14**(1): p. 102.
578. Jorgensen, K.T., et al., *Increased risk of rheumatoid arthritis in women with pregnancy complications and poor self-rated health: a study within the Danish National Birth Cohort*. Rheumatology, 2014. **53**(8): p. 1513-9.
579. Ma, K.K., et al., *Adverse pregnancy outcomes and risk of subsequent rheumatoid arthritis*. Arthritis & Rheumatology, 2014. **66**(3): p. 508-12.
580. Page, M.J., et al., *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews*. Systematic Reviews, 2021. **10**(1): p. 89.
581. Team, T.E., *EndNote, Philadelphia, PA. Clarivate. EndNote 20. 64 bit*. 2013.
582. *Covidence Systematic Review Software*. Veritas Health Innovation, Melbourne Australia. www.covidence.org.
583. Aromataris E, Munn Z (Editors). *JB I Manual for Evidence Synthesis*. JBI, 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-01>.
584. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta*

Analysis. Available from: http://www.ohri.ca/programs/clinical_epidemiology/

oxford.asp.

585. RStudio Team (2019). *RStudio: Integrated Development*

for R. RStudio, Inc., Boston, MA URL

<http://www.rstudio.com/>.

586. R Core Team (2020). *R: A language and environment*

for statistical computing. R Foundation for

Statistical Computing, Vienna, Austria. URL

<https://www.R-project.org/>.

587. Bergink, V., et al., *Prevalence of autoimmune thyroid dysfunction in postpartum psychosis*. The British Journal of Psychiatry, 2011. **198**(4): p. 264-268.
588. Bergink, V., et al., *Comorbidity of autoimmune thyroid disorders and psychiatric disorders during the postpartum period: a Danish nationwide register-based cohort study*. Psychological Medicine, 2018. **48**(8): p. 1291-1298.
589. Hardy, C., et al., *Pregnancy outcome and family size in systemic lupus erythematosus: a case-control study*. Rheumatology (Oxford, England), 1999. **38**(6): p. 559-563.
590. Harpsoe, M.C., et al., *Risk of inflammatory bowel disease according to self-rated health, pregnancy course, and pregnancy complications: a study within the Danish National Birth Cohort*. PLoS ONE [Electronic Resource], 2013. **8**(3): p. e59698.
591. Jørgensen, K.T., et al., *Hyperemesis, gestational hypertensive disorders, pregnancy losses and risk of autoimmune diseases in a Danish population-based cohort*. Journal of Autoimmunity, 2012. **38**(2): p. J120-J128.
592. Julkunen, H., et al., *Fetal outcome in lupus pregnancy: a retrospective case-control study of 242 pregnancies in 112 patients*. Lupus, 1993. **2**(2): p. 125-131.
593. Kamper-Jorgensen, M., H.S. Gammill, and J.L. Nelson, *Preeclampsia and scleroderma: a prospective nationwide analysis*. Acta Obstetrica et Gynecologica Scandinavica, 2018. **97**(5): p. 587-590.
594. Kay, A. and F. Bach, *SUBFERTILITY BEFORE AND AFTER THE DEVELOPMENT OF RHEUMATOID ARTHRITIS IN WOMEN*. Ann Rheum Dis, 1965. **24**(2): p. 169-73.
595. Kither, H., et al., *Adverse pregnancy outcomes and subsequent development of connective tissue disease in the UK: an epidemiological study*. BJOG: An International Journal of Obstetrics & Gynaecology, 2020. **127**(8): p. 941-949.
596. Lin, C.Y., et al., *Postpartum Depression and Subsequent Autoimmune Diseases in Taiwan*. International Journal of Environmental Research & Public Health [Electronic Resource], 2018. **15**(8): p. 20.
597. Lin, L.T., et al., *Increased risk of systemic lupus erythematosus in pregnancy-induced hypertension: A nationwide population-based retrospective cohort study*. Medicine, 2016. **95**(30): p. e4407.
598. Nielsen, N.M., et al., *Reproductive history and risk of multiple sclerosis*. Epidemiology, 2011. **22**(4): p. 546-52.
599. Savitz, D.A., et al., *Pregnancy-induced hypertension and diabetes and the risk of cardiovascular disease, stroke, and diabetes hospitalization in the year following delivery*. American Journal of Epidemiology, 2014. **180**(1): p. 41-4.
600. Siamopoulou-Mavridou, A., et al., *Outcome of pregnancy in patients with autoimmune rheumatic disease before the disease onset*. Ann Rheum Dis, 1988. **47**(12): p. 982-7.
601. Spector, T.D. and A.J. Silman, *Is poor pregnancy outcome a risk factor in rheumatoid arthritis?* Annals of the Rheumatic Diseases, 1990. **49**(1): p. 12.
602. Stuart, A.E., I. Amer-Wahlin, and K.B.M. Kallen, *Neonatal delivery weight and risk of future maternal diabetes*. International Journal of Gynaecology & Obstetrics, 2018. **140**(1): p. 111-117.
603. Ulf-Møller, C.J., et al., *Reproductive factors and risk of systemic lupus erythematosus: nationwide cohort study in Denmark*. J Rheumatol, 2009. **36**(9): p. 1903-9.
604. van Wyk, L., et al., *Increased incidence of pregnancy complications in women who later develop scleroderma: a case control study*. Arthritis Research & Therapy, 2011. **13**(6): p. R183.
605. Wallenius, M., et al., *Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth*. Arthritis Rheum, 2011. **63**(6): p. 1534-42.

606. Wikstrom Shemer, E.A., et al., *Intrahepatic cholestasis of pregnancy and cancer, immune-mediated and cardiovascular diseases: A population-based cohort study*. Journal of Hepatology, 2015. **63**(2): p. 456-61.
607. Brann, E., et al., *Bidirectional association between autoimmune disease and perinatal depression: a nationwide study with sibling comparison*. Molecular Psychiatry, 2024. **09**: p. 09.
608. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023)*. Cochrane, 2023. Available from www.training.cochrane.org/handbook.
609. Tramèr, M.R., et al., *Impact of covert duplicate publication on meta-analysis: a case study*. Bmj, 1997. **315**(7109): p. 635-40.
610. von Elm, E., et al., *Different patterns of duplicate publication: an analysis of articles used in systematic reviews*. Jama, 2004. **291**(8): p. 974-80.
611. Bi, S., et al., *Long-term effects of preeclampsia on metabolic and biochemical outcomes in offspring: What can be expected from a meta-analysis?* Obesity Reviews, 2022. **23**(5): p. e13411.
612. Black, M., et al., *Planned Cesarean Delivery at Term and Adverse Outcomes in Childhood Health*. JAMA, 2015. **314**(21): p. 2271-9.
613. Bruce, A., M. Black, and S. Bhattacharya, *Mode of delivery and risk of inflammatory bowel disease in the offspring: systematic review and meta-analysis of observational studies*. Inflammatory Bowel Diseases, 2014. **20**(7): p. 1217-26.
614. Cardwell, C.R., et al., *Birthweight and the risk of childhood-onset type 1 diabetes: a meta-analysis of observational studies using individual patient data*. Diabetologia, 2010. **53**(4): p. 641-51.
615. Dalla Costa, G., et al., *Caesarean section and infant formula feeding are associated with an earlier age of onset of multiple sclerosis*. Multiple Sclerosis and Related Disorders, 2019. **33**: p. 75-77.
616. Nielsen, N.M., et al., *Maternal diabetes and risk of multiple sclerosis in the offspring: A Danish nationwide register-based cohort study*. Multiple Sclerosis, 2021. **27**(11): p. 1686-1694.
617. Nakamura, N., et al., *Mortality and neurological outcomes in extremely and very preterm infants born to mothers with hypertensive disorders of pregnancy*. Scientific reports, 2021. **11**(1): p. 1729.
618. Jones, W.R., *Autoimmune Disease and Pregnancy*. Australian and New Zealand Journal of Obstetrics and Gynaecology, 1994. **34**(3): p. 251-258.
619. Neiger, R., *Long-Term Effects of Pregnancy Complications on Maternal Health: A Review*. J Clin Med, 2017. **6**(8).
620. Panaitescu, A.M., et al., *Pregnancy Complications Can Foreshadow Future Disease-Long-Term Outcomes of a Complicated Pregnancy*. Medicina (Kaunas), 2021. **57**(12).
621. Okoth, K., et al., *Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review*. Bmj, 2020. **371**: p. m3502.
622. Cockrill, T., Del Junco, D. J., Arnett, F. C., Assassi, S., Tan, F. K., McNearney, T., ... Mayes, M. D. (2010). *Separate influences of birth order and gravidity/parity on the development of systemic sclerosis*. Arthritis Care and Research, 62(3), 418–424. <https://doi.org/10.1002/acr.20096>.
623. Pisa, F.E., et al., *Reproductive factors and the risk of scleroderma: an Italian case-control study*. Arthritis Rheum, 2002. **46**(2): p. 451-6.
624. Russo, P.A., S. Lester, and P.J. Roberts-Thomson, *Systemic sclerosis, birth order and parity*. Int J Rheum Dis, 2014. **17**(5): p. 557-61.
625. Lambe, M., et al., *Childbearing and the risk of scleroderma: a population-based study in Sweden*. Am J Epidemiol, 2004. **159**(2): p. 162-6.
626. Beneventi, F., et al., *Impact of pregnancy on progression of preclinical autoimmune disorders: a prospective cohort study*. Rheumatology, 2022. **62**(9): p. 2971-2978.
627. Antunes, M., et al., *Undifferentiated connective tissue disease: state of the art on clinical practice guidelines*. RMD Open, 2018. **4**(Suppl 1): p. e000786.
628. Spinillo, A., et al., *The effect of newly diagnosed undifferentiated connective tissue disease on pregnancy outcome*. Am J Obstet Gynecol, 2008. **199**(6): p. 632.e1-6.
629. Assad, S., et al. *Role of Sex Hormone Levels and Psychological Stress in the Pathogenesis of Autoimmune Diseases*. Cureus, 2017. **9**, e1315 DOI: 10.7759/cureus.1315.
630. Serena, C., et al., *Undifferentiated Connective Tissue Disease in Pregnancy: A Topic Yet to be Explored*. Front Pharmacol, 2022. **13**: p. 820760.
631. Robinson, D.P. and S.L. Klein, *Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis*. Horm Behav, 2012. **62**(3): p. 263-71.

632. Ding, J. and B.T. Zhu, *Unique effect of the pregnancy hormone estriol on antigen-induced production of specific antibodies in female BALB/c mice*. Steroids, 2008. **73**(3): p. 289-98.
633. Ubeda, F. and G. Wild, *Microchimerism as a source of information on future pregnancies*. Proceedings of the Royal Society of London - Series B: Biological Sciences, 2023. **290**(2005): p. 20231142.
634. Nelson, J.L., *The otherness of self: microchimerism in health and disease*. Trends Immunol, 2012. **33**(8): p. 421-7.
635. Bianchi, D.W., et al., *Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum*. Proc Natl Acad Sci U S A, 1996. **93**(2): p. 705-8.
636. Adams Waldorf, K.M. and J.L. Nelson, *Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy*. Immunological investigations, 2008. **37**(5-6): p. 631-644.
637. Al-Mufti, R., et al., *Fetal cells in maternal blood of pregnancies with severe fetal growth restriction*. Hum Reprod, 2000. **15**(1): p. 218-21.
638. Leung, T.N., et al., *Maternal plasma fetal DNA as a marker for preterm labour*. Lancet, 1998. **352**(9144): p. 1904-5.
639. Fugazzola, L., V. Cirello, and P. Beck-Peccoz, *Microchimerism and endocrine disorders*. J Clin Endocrinol Metab, 2012. **97**(5): p. 1452-61.
640. Luiro, K., et al., *Autoantibodies predict type 1 diabetes after gestational diabetes - a 23-year cohort study*. Frontiers in Endocrinology, 2023. **14**: p. 1286375.
641. British society of Immunology <https://www.immunology.org/sites/default/files/autoimmunity-briefing.pdf> assessed on October 2024.
642. Thomas, S.L., et al., *Burden of mortality associated with autoimmune diseases among females in the United Kingdom*. Am J Public Health, 2010. **100**(11): p. 2279-87.
643. Zhou, Q., et al., *China's community-based strategy of universal preconception care in rural areas at a population level using a novel risk classification system for stratifying couples' preconception health status*. BMC Health Services Research, 2016. **16**(1): p. 689.
644. Inversetti, A., et al., *Predictive biomarkers of pre-eclampsia and effectiveness of preventative interventions for the disease*. Expert opinion on biological therapy, 2014. **14**(8): p. 1161-1173.
645. Rolnik, D.L., *Prediction of preeclampsia and its prevention with aspirin*. 2018, Manchester Metropolitan University.
646. Jørgensen, K.T., et al., *Childbirths and risk of female predominant and other autoimmune diseases in a population-based Danish cohort*. Journal of Autoimmunity, 2012. **38**(2): p. J81-J87.
647. Reeves, P., et al., *Economic evaluations of public health implementation-interventions: a systematic review and guideline for practice*. Public Health, 2019. **169**: p. 101-113.
648. Denton, C.P., et al., *The 2024 British Society for Rheumatology guideline for management of systemic sclerosis*. Rheumatology, 2024.
649. Magee, L.A. and P. von Dadelszen, *Aspirin from early pregnancy to reduce preterm birth*. The Lancet Global Health, 2023. **11**(3): p. e314-e315.
650. Price, E., et al., *The management of Sjögren's syndrome: British Society for Rheumatology guideline scope*. Rheumatology, 2021. **60**(5): p. 2122-2127.
651. de Jong, P.G., et al., *Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia*. Cochrane Database Syst Rev, 2014. **2014**(7): p. Cd004734.
652. Kaandorp, S.P., et al., *Aspirin plus heparin or aspirin alone in women with recurrent miscarriage*. N Engl J Med, 2010. **362**(17): p. 1586-96.
653. Eleftheriadou, V., et al., *British Association of Dermatologists guidelines for the management of people with vitiligo 2021**. British Journal of Dermatology, 2022. **186**(1): p. 18-29.
654. Ezzedine, K., et al., *Pre-vs. post-pubertal onset of vitiligo: multivariate analysis indicates atopic diathesis association in pre-pubertal onset vitiligo*. British Journal of Dermatology, 2012. **167**(3): p. 490-495.
655. Harries, M.J., et al., *British Association of Dermatologists living guideline for managing people with alopecia areata 2024*. British Journal of Dermatology, 2024.
656. Smith, C.H., et al., *British Association of Dermatologists guidelines for biologic therapy for psoriasis 2023: a pragmatic update*. British Journal of Dermatology, 2023. **190**(2): p. 270-272.
657. Ferreira, C., et al., *Management of psoriasis in pregnancy - a review of the evidence to date*. Drugs Context, 2020. **9**.
658. NICE Guidelines:Adrenal insufficiency: identification and management <https://www.nice.org.uk/guidance/NG243> assessed in October, 2024.

659. *Intrapartum care for women with existing medical conditions or obstetric complications and their babies* <https://www.nice.org.uk/guidance/ng121/chapter/Recommendations#long-term-systemic-steroids:assessed> in October, 2023.
660. Alexander, E.K., et al., 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*®, 2017. **27**(3): p. 315-389.
661. *Diabetes in pregnancy: management from preconception to the postnatal period*:<https://www.nice.org.uk/guidance/ng3/chapter/Recommendations:assessed> in October 2024.
662. Ludvigsson, J.F., et al., *Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology*. *Gut*, 2014. **63**(8): p. 1210-1228.
663. Rubio-Tapia, A., et al., *ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease*. Official journal of the American College of Gastroenterology | ACG, 2013. **108**(5): p. 656-676.
664. Lamb CA, Kennedy NA, Raine T, et al *British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults* *Gut* 2019;68:s1-s106. assessed in October 2024.
665. Ward, M.M., et al., 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis & rheumatology*, 2019. **71**(10): p. 1599-1613.
666. Ward, M.M., et al., *American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis*. *Arthritis care & research*, 2016. **68**(2): p. 151-166.
667. Singh, J.A., et al., 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Journal of Psoriasis and Psoriatic arthritis*, 2019. **4**(1): p. 31-58.
668. Fraenkel, L., et al., 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis & Rheumatology*, 2021. **73**(7): p. 1108-1123.
669. Maddison, P., *Myasthenia gravis and pregnancy: pressing time for best practice guidelines*. *Journal of Neurology, Neurosurgery & Psychiatry*, 2014. **85**(5): p. 477-477.
670. Dobson, R., et al., *UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines*. *Practical Neurology*, 2019. **19**(2): p. 106-114.
671. Chen, C.C., C.H. Lin, and M.C. Lin, *Maternal autoimmune disease and risk of offspring autism spectrum disorder - a nationwide population-based cohort study*. *Front Psychiatry*, 2023. **14**: p. 1254453.
672. He, H., et al., *Association of Maternal Autoimmune Diseases With Risk of Mental Disorders in Offspring in Denmark*. *JAMA Network Open*, 2022. **5**(4): p. e227503-e227503.
673. Huang, H., et al., *Exposure to prescribed medication in early life and impacts on gut microbiota and disease development*. *EClinicalMedicine*, 2024. **68**: p. 102428.
674. Ying, X.-h., et al., *Maternal non-steroidal anti-inflammatory drug exposure during pregnancy and risk of miscarriage: a systematic review and meta-analysis*. *European Journal of Clinical Pharmacology*, 2022: p. 1-10.
675. O'Byrne, L.J., et al., *Fetal and maternal outcomes after maternal biologic use during conception and pregnancy: A systematic review and meta-analysis*. *BJOG: An International Journal of Obstetrics & Gynaecology*, 2022. **129**(8): p. 1236-1246.
676. Nielsen, O.H., et al., *Biologics for Inflammatory Bowel Disease and Their Safety in Pregnancy: A Systematic Review and Meta-analysis*. *Clin Gastroenterol Hepatol*, 2022. **20**(1): p. 74-87.e3.
677. Nielsen, O.H., et al., *Biologics for Inflammatory Bowel Disease and Their Safety in Pregnancy: A Systematic Review and Meta-analysis*. *Clinical Gastroenterology and Hepatology*, 2022. **20**(1): p. 74-87.e3.
678. Sánchez-García, V., et al., *Exposure to biologic therapy before and during pregnancy in patients with psoriasis: Systematic review and meta-analysis*. *J Eur Acad Dermatol Venereol*, 2023. **37**(10): p. 1971-1990.
679. Huang, W., et al., *Anti-tumor necrosis factor-α therapy may not be safe during pregnancy in women with inflammatory bowel disease: an updated meta-analysis and systematic review*. *BMC Pregnancy and Childbirth*, 2024. **24**(1): p. 251.
680. Barenbrug, L., et al., *Pregnancy and neonatal outcomes in women with immune mediated inflammatory diseases exposed to anti-tumor necrosis factor-α during pregnancy: A systemic review and meta-analysis*. *Journal of Autoimmunity*, 2021. **122**: p. 102676.

681. Xiao, W.-l., et al., *The relationship between maternal corticosteroid use and orofacial clefts-a meta-analysis*. Reproductive Toxicology, 2017. **69**: p. 99-105.
682. Bandoli, G., et al., *A Review of Systemic Corticosteroid Use in Pregnancy and the Risk of Select Pregnancy and Birth Outcomes*. Rheum Dis Clin North Am, 2017. **43**(3): p. 489-502.
683. Li, T., et al., *Glucocorticoids improve the pregnancy rate and outcome in women with unexplained positive autoantibodies: a systematic review and meta-analysis*. Frontiers in Medicine, 2022. **9**: p. 819406.
684. Witzel, S.J., *Lactation and the use of biologic immunosuppressive medications*. Breastfeed Med, 2014. **9**(10): p. 543-6.
685. Gisbert, J.P., *Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding*. Inflammatory Bowel Diseases, 2009. **16**(5): p. 881-895.
686. Fein, K.C., et al., *Placental drug transport and fetal exposure during pregnancy is determined by drug molecular size, chemistry, and conformation*. J Control Release, 2023. **361**: p. 29-39.
687. Jang, D.I., et al., *The Role of Tumor Necrosis Factor Alpha (TNF- α) in Autoimmune Disease and Current TNF- α Inhibitors in Therapeutics*. Int J Mol Sci, 2021. **22**(5).
688. Graham, J.J., M.S. Longhi, and M.A. Heneghan, *T helper cell immunity in pregnancy and influence on autoimmune disease progression*. J Autoimmun, 2021. **121**: p. 102651.
689. Giannella, L., et al., *Microbiome Changes in Pregnancy Disorders*. Antioxidants (Basel), 2023. **12**(2).
690. Shimizu, Y., et al., *Influence of Immune System Abnormalities Caused by Maternal Immune Activation in the Postnatal Period*. Cells, 2023. **12**(5).
691. Raine, C., K. Austin, and I. Giles, *Mechanisms determining the amelioration of rheumatoid arthritis in pregnancy: A systematic review*. Seminars in Arthritis and Rheumatism, 2020. **50**(6): p. 1357-1369.
692. Jethwa, H., et al., *Does Rheumatoid Arthritis Really Improve During Pregnancy? A Systematic Review and Metaanalysis*. J Rheumatol, 2019. **46**(3): p. 245-250.

Supplementary tables and figures Chapter 3

Table 3.1 List of codes

Disease	Read codes	SNOMEDCT Codes
1. Addison's disease	C154.00, C154011, C154100, C155.00, C154600, C154z00, C154z12, C154000, C154z11, PK13.00, A176.00, C153.00, C155z00, C154500, F395000, C155000.	5003009,186270000,363732003,386584007, 386584007,237744009,386584007, 34253008,93235007,237785004,237785004, 237785004,24867002,24867002,24867002, 24867002,24867002,65389002,83728000, 721290005,275437005,83728000,186270000, 34253008,36102002,24867002,36102002, 84027009,93235007,24867002,386584007, 721290005,386584007,34253008,24867002, 386584007,237692001,373662000,721290005, 24867002,84027009,55003009,93235007, 83728000,83728000,363732003,186270000, 186270000,237785004,766986002,16685009, 766986002.
2. Alopecia Areata	M240100, M240K00,	68225006,5860009,68225006,86166000, 68225006,68225006,311671002,19754005,

	M240B00, Myu6200.	68225006,68225006,19754005,86166000.
3. Ankylosing spondylitis and axial spondylarthr itis	N100.00, 2377, N100.11, N045000, 388p.00, 388p000, 38QL.00.	9631008,239805001,9631008,9631008, 162930007,441930001,9631008,9631008, 9631008,162930007,441680005,441562009, 441930001,239805001,441680005,713777005, 441562009,441562009,9631008,162930007, 441680005,441930001,9631008,9631008, 9631008.
4. Coeliac disease	J690.00, ZV7y700, 68W1.00, J690.14, J691.00, B562000, J690z00, ZC2C200, J690000, J690100, J690.11, 68W3.00, J695.00, J695.11, 68W4.00, 6648, 6648000, 8IAp.00, 9mB..00, 9mB1.00, 12E6.00, 13YB.00, 9mB2.00, SB22400.	197478000,197479008, 396331005, 396331005,442728009, ,473213008, 396331005,57662003,396331005 , 396331005,9250002,9250002,396331005, 45259000,47384003,396331005,94347008, 57850000,396331005,45259000,396331005, 45259000,440109001,396331005,396331005, 396331005,396331005,396331005,396331005, 396331005,396331005,45259000,442728009, 171397002, 47384003,430329007,396331005, 440109001,396331005,396331005,396331005, 443718009, 443718009,275404008,396331005,45259000, 396331005,45259000,9250002,45259000, 391475007,91867008,289134009,81704009, 181340007.391475007, 750891000000107, 1745881000006100, 752321000000102, 1747711000006100, 1745871000006100, 752301000000106, 1745861000006100, 750911000000105, 1747701000006100, 750871000000108, 1745841000006100, 752341000000109
5. Graves	C020.12, C020.11.	353295004,353295004,276177000,353295004, 237825005,276177000,353295004,276177000, 276177000,353295004,353295004,276177000, 237499004,
6. HASHIMOTO	C052.12, C052.11, C052.00, C121000, C05y.00, C05y400, C053.00, Cyu1400.	190454008,237538007,21983002,21983002, 21983002,45053005,45053005,84362007, 83728000,84362007,21983002,21983002, 21983002,21983002,21983002,21983002, 21983002,84362007,84362007,66944004, 237520009,237520009,27538003.
7. IBD	J40..11 J410100	24526004,34000006,64766004,160386006, 196578009,196976000,196987008,201728006,

J41..12	275129008,275549008,3815005,56287005,
J4...12	7620006,414153008,414156000,444548001,
14C4.11	34000006,34000006,56689002,34000006,418130002,
J410.00	418130002,64766004,34000006,34000006,
J411.00	64766004,196987008,34000006,50440006,
J412.00	50440006,196977009,700104004,295046003,
N045400	34000006,160386006,7620006,34000006,
J41..00	56689002,64766004,56287005,160386006,
J401z11	56689002,64766004,196977009,275129008,
J410300	52231000,52231000,7620006,3815005,
J400z00	3815005,38106008,414153008,56287005,
ZR3S.11	24526004,275549008,34000006,38106008,
J40..00	160386006,3815005, 201727001,
ZR3S.00	201805000,38106008,56689002,34000006,
N045300	196578009,56689002,414154002,700104004,
J41z.00	7620006,295046003,
J402.00	34000006,56287005,201728006,201805000,
N031000	3815005,38106008,64766004,196578009,
N031100	414154002,295046003,201807008,235714007,
J401z00	34000006,275129008,78324009,273364009,
J410400	128600008,14311001,608844008,235796008,
J41y.00	655231000033104, 1026501000006100,
J410200	906051000006102, 909671000000101,
J400200	906191000006109, 56689002, 50440006,
J08z900	8161000119106, 112561000119108
J436.00	
J410z00	
J436100	
J400500	
J401200	
J436000	
J400400	
J41yz00	
J401.00	
J410000	
J400.00	
J40..12	
J40z.00	
Jyu4100	
J40z.11	
J401000	
J400100	
J401100	
J400300	
Jyu4000	
J400000	
J413.00	

	8Cc5.00 8CA4W00 8Cc5.11	
8. MYASTHENIA Gravis	F380.00, F380z00, F381300, F381600, F381.00, F381500, F381100, F381400, F381z00, F380100, F381200.	91637004,193207007,193212008,193213003, 193214009,267604001,64766004,400140006, 193209005,91637004,83470009,193213003, 63491006,193209005,91637004,91637004, 193209005,91637004,91637004,398565003, 56989000,193209005,91637004,230686005, 230684008.
9. Multiple sclerosis	F20..00 F20..11 8Cc2.00 ZRVE.00 9mD1.00 F203.00 F20z.00 F202.00 F200.00 666B.00 666A.00 9kG..00 8CS1.00 F201.00 F207.00 F208.00 F204.00 F206.00 8Cc1.00 8Cc4.00 8Cc0.00 8IAb.00 9mD..00 9mD0.00 9mD2.00	983271000006105, 1747831000006100, 1747841000006100, 192929006, 983281000006108, 1747851000006100, 24700007 24700007, 983311000006105, 192927008 438511000 192926004, 1747861000006100, 439567002 192928003, 983261000006103, 367621000000103, 759131000000108, 759171000000105, 425500002 428700003, 426373005, 198491000000106, 192929006, 24700007, 905781000006102, 205631000000104, 811881000000109, 515931000000104, 24700007, 367561000000107, 192928003, 166411000000100, 758981000000100, 367591000000101, 367681000000102, 192926004 24700007, 908811000006108, 983291000006106, 1747821000006100, 425500002, 983301000006107, 759051000000102, 192926004, 759091000000105, 426373005
9. Psoriasis	M161000, M161B00, M161700, M161z00, M161600, 14F2.00, M16..00,M161D 00, M161A00,	37042000, 402311006, 238612002, 27520001, 866341000000101, 200969003, 402328009, 238602009, 200977004, 238600001, 10111000033105, 9014002, 238604005, 200966005, 200955003, 200965009, 25847004,, 9014002, 238600001, 200977004, 905681000006108, 200964008, 200972005, 200975007, 25847004,, 9014002, 37042000, 9014002, 866341000000101, 399937000,

	M16y000, M161H00 M161400 M161E00 M161100 M161500 M161.00 M161C00 M161F00 M161200 M16z.00 M16y.00 M161300 M161800 M161900 Myu3000 M161F11 M166.00 38Gg.00 M161J00	866341000000101, 238609000, 200977004, 9014002, 200975007, 27520001,200963002, 200967001, 81271001,161562002, 238600001, 402316001, 9014002, 161562002, 200971003, 1583831000006100, 866311000000102, 866311000000102, 25847004, 200969003, 200965009, 27520001
10.Psoriatic arthritis	M160.00, M160z00, M160200, M160000, N045200, M160100, Nyu1300, M160.11.	19514005,239803008,239812005,33339001, 33339001,33339001,200956002,200956002, 239812005,239803008,33339001.
11. Rheumatoid arthritis	N044.00, N043.00, N042200, H570.00, 66H..13, N040Q00, N040200, N041.00, N005.00, N043z00, N04..00, N040N00, N040S00, N04y000, N04y200, 2G27.00, N042z00, N040900	28880005,57160007,164456005,201764007, 201767000,201768005,201769002,201771002, 201779000,201780002,201781003,287006005, 33719002,398726004,398726004,69896004, 69896004,69896004,69896004,69896004, 69896004,69896004,69896004,69896004, 201796004, 201771002,201772009, 201777003,201779000, 1875611000006100, 1875581000006100, 1875571000006100, ,410795001,201770001,201785007, 201784006,201772009,398726004,69896004, 201783000,239920006,239920006,84801008, 84801008,410795001, 9631008,429192004,239793008,287006005,9631008,3 98640008, 201783000,164456005,201778008,201770001, 398640008,33719002,201796004,,201775006,6989600 4, 201766009,201775006,201777003,201774005,

	N040800, G5yA.00, N040100, N040000, N042100, N040700, N040B00, N042.00, G5y8.00, N043000, N040D00, N040K00, N040F00, N040R00, N04y011, N044.12, N040500, N040A00, N040600, N040H00, N040J00, N040G00, N040L00, N040C00, N040400, 66HB000, 9hR1.00, 9hR..00, 9hR0.00, N040M00, 9mM..00, 9mM0.00, 9mM1.00, 9mM3.00, 9mM2.00, N040E00, 9mM4.00, N040300.	201773004,201778008,33719002,275902004, 10713006,195136004,201776007, 239793008,398640008, 69896004,410793008,400054000,429192004, 84017003,33719002,57160007,398640008, 1048311000000100, 805941000000105, 805981000000102, 882321000000105, 1110961000000100, 909191000006103, 1048311000000100, 882481000000101, 1875591000006100, 1875601000006100, 847261000000104, 1932121000006100, 231041000000107, 239791005, 882401000000106, 882421000000102, 882441000000109, 1875561000006100, 805961000000106, 882461000000105, 1048311000000100
12. SJOGREN syndrome	N002.11, N002.00, F396700, H57y300.	193253000,302896008,302896008,193253000, 83901003,196137000,83901003,83901003, 83901003,83901003,193253000,83901003, 196137000,196137000, 193253000.
13. SLE	M154100, M154.00, M154z00, N000.00,	15084002,55464009,95644001,193178008, 193248005,200937007,200938002,200939005, 201436003, 1728151000006100, 7119001,55464009, 55464009,239887007,79291003,200936003, 167901007,165928001,239891002,68815009,

	N000400, N000000, M154700, N000300, H57y400, M154000, N000200, M154200, N000z00, F371000, M154500, ZRq9.00, M154400, K01x400, ZRq8.00, Nyu4300, M154600, M154300, F4D3300, Myu7800, ZRq8.11, F396100.	95644001,200938002,165928001,79291003, 165927006,200938002,37954002,37954002, 239891002,200940007,200941006,68815009, 55464009,79291003,309762007,200936003, 239891002,200936003,200942004,196138005, 55464009,165927006,238927000,238928005, 403486000,698694005,238652000.
14. Systemic sclerosis	N001.00, N001100, M210.00, M210400, N001.12, M210.11, N001000, F396600, N001.11, Nyu4500, M210z00, M210000, H572.00, K0H..00, K0J0.00, N001200.	22784002,31848007,444133002,193252005, 196133001,201048007,201443009,236502006, 201048007,89155008,206541009,298285004, 201048007,444133002,201048007,89155008, 31848007,201048007,443720007,31848007, 201048007,89155008,31848007,193252005, 298285004,196133001,201048007,89155008, 89155008,89155008,201048007,31848007, 31848007,31848007,298285004,236503001, 31848007,196133001,201048007,206541009.
15.T1DM	C100011, C10E.00, C108.00, C108700, C108800,C10ED 00, C10EM00, C10E.11,	190368000,190372001,190372001,290002008, 290002008,313435000,314771006,314893005, 314893005,46635009,401110002,703137001, 444073006,444073006, 71771000119100,46635009, 444073006,190372001,314893005,314771006, 421893009, 754101000000103,713705003,190368000, 314771006,422228004,421893009,190368000, 313435000,422228004,713705003,421893009, 421893009,420514000,420514000,401110002,

C108F11, C108.12, C108J12, C10E700, C108.11, C10EH00, C10E500, C108012, C10EP00, C108.13, C108B00, C108400, C10EL00, C10EK00, C108900, C10E800, C108711, C10EE00, C108J00, C10E900, C10EN00, C108712, C108C00, C108E11, C10E200, C10E400, C108F00, C108E00, C108500, C10E312, C108812, C10EC00, C108811, C10E000, C10E100, C10E300, C108211, C10EF00, C10E411, C10E.12, C108511, C108300, C10EJ00, C10E412, C10EQ00, C108D00,	420270002,421075007,420486006,237632004, 39710007,11530004, 31211000119101,39710007, 43959009,237632004, 230577008, 31211000119101, 49455004,4855003,201724008,421895002, 73211009,73211009,73211009, 385041000000108, 4855003,230577008, 49455004, 127013003, 421895002, 385041000000108, 201724008, 422183001, 420789003, 444073006, 420789003, 421365002,713702000, 713705003, 71771000119100, 739681000,314893005, 19429009,420825003, 31211000119101,420825003, 421365002,739681000,420486006,420514000, 290002008,713705003,190330002,314771006, 421468001,421075007,421893009,314771006, 421893009,444073006, 71771000119100 ,290002008,739681000,713702000, 421468001,420486006,421920002,422228004, 421893009,420789003,421920002,420918009, 421468001,422228004,420789003,420789003, 420486006,713702000,739681000,420825003, 420825003,421920002,739681000,420486006, 739681000,713702000,420918009,420918009, 421468001,420825003,421468001,421468001, 420789003,713702000,421893009, 314771006, 71771000119100,290002008,46635009, 190372001,7.18E+13,713705003,421075007, 73211009,11530004,422275004,127013003, 422275004,422228004,314771006,290002008, 420918009,314771006,420789003,703137001, 313435000,421468001,420918009,739681000, 421920002,420918009,739681000,420789003, 290002008,444073006,314893005,421893009, 420270002,199223000, 31211000119101,268519009, 268519009, 421468001,421920002, 420486006,190368000,46635009,313435000, 421893009,713705003,73211009,73211009, 43959009,422183001,420270002,420868002, 421920002,420825003,420918009,420918009

	C108411, C108J11, C108600, C108011, C108212, C10EM11, C108H11, C10EA11, C108911, C108G00, C108H00, C10EN11, C108D11, C10EB00, C108512, ZC2C900, C10EA00, C10E600, C108E12, C10E812, C10E311, C10EC11, C10EG00, C10E712, C10E511, C10E711, C108A11, C10E911, C108912, C108412, C10E912, C10EP11, C10E512, C108B11, C10E111, C10EE12, C10EF12, C10EC12, C10E611, C10ED12, C10EL11, C108112, 66At011, C10E811, C108311, C10P000,	

	C10EQ11, C10E612, C10P011, C10E011, C108F12, C108A12, C108D12, C10ED11, C108C11, C108612.	
16. VITILIGO	M295100, M295.00, M295z00, F4E5311, M295000.	87666009,201290009,23006000,23006000, 23006000,23006000,201290009,23006000, 23006000,56727007,23006000.

Table 3.2 Numbers of pregnancies and women in each database

	CPRD Gold	CPRD Aurum
Total pregnancies	1,456,992	3,708,968
AI	56,323 (3.87)	139,081 (3.75)
No AI	1,400,669 (96.13)	3,569,887 (96.25)
Total women	833, 394	1,998,078
AI	32,994 (3.96)	77,269 (3.87)
Non-AI	800,400 (96.04)	1,920,809 (96.13)

Table 3.3 Age standardised prevalence of autoimmune diseases 2000-2021

Year	All AI	AA	AD	AS	RA	Coded	UC	Crohn	IBD	MS	MG	Psoriasis	PsA	SS	SLE	SSc	GD	HD	T1DM	Vitiligo
2000	3.704	0.212	0.003	0.050	0.257	0.114	0.196	0.204	0.418	0.115	0.066	1.870	0.060	0.020	0.161	0.024	0.174	0.047	0.375	0.043
2001	3.625	0.211	0.003	0.069	0.268	0.130	0.228	0.228	0.477	0.152	0.065	1.831	0.054	0.009	0.106	0.007	0.175	0.033	0.495	0.044
2002	3.438	0.179	0.003	0.043	0.138	0.106	0.235	0.162	0.411	0.102	0.008	1.654	0.058	0.031	0.106	0.019	0.196	0.053	0.447	0.039
2003	3.420	0.214	0.004	0.046	0.224	0.155	0.185	0.157	0.363	0.140	0.013	1.776	0.049	0.008	0.103	0.015	0.188	0.087	0.482	0.042
2004	3.523	0.206	0.007	0.032	0.196	0.114	0.191	0.198	0.411	0.135	0.009	1.824	0.071	0.031	0.114	0.014	0.191	0.035	0.533	0.041
2005	3.421	0.180	0.006	0.058	0.173	0.144	0.222	0.168	0.415	0.132	0.011	1.683	0.070	0.010	0.070	0.028	0.200	0.053	0.436	0.039
2006	3.479	0.190	0.004	0.027	0.185	0.158	0.262	0.168	0.439	0.089	0.005	1.888	0.064	0.024	0.128	0.019	0.243	0.040	0.469	0.042
2007	3.488	0.224	0.002	0.031	0.163	0.128	0.229	0.225	0.463	0.091	0.014	1.770	0.042	0.012	0.059	0.009	0.255	0.069	0.431	0.041
2008	3.458	0.209	0.004	0.034	0.175	0.132	0.202	0.158	0.380	0.104	0.021	1.771	0.063	0.027	0.078	0.008	0.255	0.046	0.469	0.040
2009	3.553	0.212	0.005	0.035	0.160	0.121	0.261	0.206	0.475	0.094	0.009	1.796	0.045	0.020	0.094	0.015	0.249	0.048	0.495	0.041
2010	3.587	0.206	0.015	0.033	0.162	0.161	0.233	0.171	0.416	0.114	0.006	1.958	0.048	0.031	0.104	0.008	0.296	0.069	0.492	0.043
2011	3.725	0.232	0.010	0.039	0.150	0.154	0.203	0.219	0.434	0.124	0.013	1.958	0.065	0.018	0.100	0.013	0.262	0.054	0.428	0.043
2012	3.765	0.277	0.015	0.039	0.145	0.132	0.200	0.199	0.414	0.119	0.009	1.831	0.044	0.017	0.091	0.014	0.282	0.038	0.455	0.042
2013	3.830	0.291	0.004	0.026	0.129	0.147	0.199	0.179	0.385	0.125	0.019	1.950	0.043	0.030	0.091	0.018	0.321	0.049	0.419	0.042
2014	3.870	0.288	0.004	0.040	0.142	0.152	0.189	0.186	0.399	0.076	0.011	1.983	0.057	0.027	0.098	0.013	0.299	0.067	0.376	0.043
2015	3.922	0.306	0.006	0.041	0.150	0.182	0.215	0.202	0.424	0.084	0.019	1.981	0.060	0.037	0.091	0.011	0.346	0.072	0.421	0.044
2016	4.050	0.325	0.003	0.034	0.190	0.207	0.218	0.163	0.405	0.068	0.014	2.009	0.068	0.024	0.112	0.010	0.365	0.065	0.387	0.044
2017	4.121	0.324	0.006	0.029	0.186	0.219	0.231	0.217	0.448	0.076	0.016	1.889	0.068	0.034	0.098	0.014	0.349	0.074	0.386	0.044
2018	4.315	0.375	0.003	0.024	0.190	0.235	0.242	0.204	0.468	0.099	0.014	1.988	0.057	0.025	0.093	0.004	0.349	0.071	0.418	0.046
2019	4.259	0.357	0.004	0.028	0.151	0.242	0.223	0.183	0.404	0.083	0.015	1.993	0.091	0.015	0.086	0.022	0.352	0.093	0.421	0.045
2020	4.565	0.418	0.007	0.034	0.223	0.244	0.204	0.187	0.402	0.109	0.023	1.989	0.074	0.020	0.092	0.012	0.404	0.109	0.372	0.046
2021	4.705	0.416	0.005	0.038	0.221	0.269	0.207	0.210	0.416	0.129	0.006	2.036	0.069	0.036	0.068	0.015	0.352	0.118	0.428	0.048

Table 3.4 Crude prevalence of autoimmune diseases 2000-2021

Year	All AI	AA	AD	AS	CoED	Crohn	GD	HT	IBD	MS	MG	Psoriasis	PsA	RA	SS	SLE	SSc	T1DM	UC	Vitiligo
2000	3.512	0.190	0.002	0.044	0.090	0.198	0.177	0.039	0.398	0.103	0.010	1.859	0.048	0.125	0.008	0.081	0.010	0.297	0.187	0.153
2001	3.453	0.204	0.004	0.040	0.103	0.170	0.166	0.027	0.383	0.099	0.014	1.796	0.051	0.135	0.010	0.059	0.010	0.314	0.189	0.147
2002	3.262	0.186	0.004	0.035	0.102	0.167	0.158	0.037	0.359	0.074	0.011	1.712	0.051	0.107	0.015	0.065	0.010	0.303	0.176	0.141
2003	3.255	0.182	0.006	0.032	0.117	0.171	0.156	0.038	0.342	0.079	0.013	1.726	0.041	0.114	0.007	0.062	0.007	0.284	0.160	0.155
2004	3.376	0.184	0.006	0.034	0.101	0.182	0.178	0.030	0.357	0.088	0.009	1.786	0.050	0.113	0.010	0.065	0.005	0.346	0.164	0.145
2005	3.286	0.188	0.007	0.035	0.098	0.159	0.185	0.035	0.330	0.085	0.013	1.713	0.047	0.112	0.010	0.055	0.012	0.326	0.154	0.143
2006	3.343	0.179	0.006	0.018	0.105	0.168	0.205	0.038	0.339	0.068	0.008	1.748	0.045	0.099	0.012	0.073	0.009	0.341	0.160	0.165
2007	3.364	0.199	0.003	0.022	0.113	0.158	0.209	0.038	0.320	0.065	0.008	1.751	0.036	0.103	0.007	0.060	0.010	0.347	0.149	0.173
2008	3.355	0.203	0.006	0.026	0.112	0.154	0.210	0.042	0.305	0.068	0.010	1.750	0.040	0.100	0.011	0.060	0.007	0.351	0.135	0.159
2009	3.444	0.202	0.008	0.024	0.111	0.175	0.209	0.041	0.348	0.065	0.005	1.783	0.039	0.095	0.008	0.065	0.011	0.375	0.158	0.170
2010	3.494	0.198	0.005	0.028	0.113	0.162	0.235	0.051	0.330	0.057	0.005	1.848	0.032	0.092	0.009	0.061	0.009	0.348	0.154	0.177
2011	3.630	0.233	0.005	0.027	0.120	0.173	0.240	0.046	0.335	0.076	0.009	1.886	0.046	0.100	0.007	0.066	0.009	0.363	0.147	0.183
2012	3.649	0.251	0.008	0.026	0.120	0.182	0.241	0.044	0.345	0.070	0.009	1.889	0.039	0.092	0.010	0.066	0.008	0.367	0.149	0.191
2013	3.740	0.267	0.004	0.022	0.138	0.159	0.253	0.052	0.337	0.069	0.009	1.943	0.035	0.088	0.014	0.062	0.011	0.362	0.166	0.198
2014	3.787	0.274	0.005	0.027	0.161	0.168	0.250	0.054	0.347	0.070	0.011	1.957	0.044	0.098	0.010	0.063	0.008	0.328	0.165	0.217
2015	3.837	0.294	0.008	0.027	0.180	0.170	0.262	0.056	0.325	0.065	0.009	1.965	0.045	0.096	0.015	0.070	0.011	0.352	0.149	0.202
2016	3.989	0.315	0.006	0.027	0.194	0.173	0.293	0.059	0.364	0.065	0.013	1.984	0.047	0.121	0.013	0.071	0.009	0.358	0.178	0.210
2017	4.055	0.320	0.008	0.028	0.207	0.183	0.299	0.071	0.372	0.055	0.013	1.980	0.052	0.132	0.017	0.068	0.007	0.362	0.181	0.226
2018	4.260	0.371	0.006	0.027	0.227	0.184	0.324	0.070	0.385	0.072	0.008	2.051	0.049	0.136	0.021	0.072	0.005	0.389	0.189	0.229
2019	4.198	0.365	0.004	0.035	0.248	0.195	0.313	0.082	0.399	0.067	0.009	1.967	0.064	0.136	0.016	0.057	0.016	0.386	0.195	0.247
2020	4.518	0.398	0.008	0.038	0.281	0.198	0.339	0.091	0.422	0.078	0.009	2.109	0.060	0.156	0.014	0.062	0.013	0.389	0.207	0.269
2021	4.649	0.434	0.007	0.033	0.288	0.195	0.328	0.101	0.412	0.095	0.008	2.134	0.070	0.157	0.020	0.066	0.012	0.438	0.210	0.292

Table 3.5 Prevalence of autoimmune disease overall in women

year	numerator	percentage	Lower CI	Upper CI
Cohort2000	2799	3.14	3.03	3.26
Cohort2001	3109	3.16	3.06	3.28
Cohort2002	3209	3.03	2.93	3.13
Cohort2003	3609	3.09	2.99	3.19
Cohort2004	4176	3.31	3.21	3.41
Cohort2005	4273	3.23	3.13	3.32
Cohort2006	4389	3.26	3.17	3.36
Cohort2007	4618	3.35	3.26	3.45
Cohort2008	4675	3.36	3.26	3.45
Cohort2009	4923	3.49	3.39	3.59
Cohort2010	5089	3.64	3.54	3.74
Cohort2011	5149	3.70	3.60	3.80
Cohort2012	5074	3.76	3.66	3.86
Cohort2013	5134	3.90	3.80	4.01
Cohort2014	4992	3.99	3.88	4.10
Cohort2015	4996	4.12	4.01	4.23
Cohort2016	4859	4.25	4.13	4.36
Cohort2017	4981	4.46	4.34	4.59
Cohort2018	4969	4.52	4.39	4.64
Cohort2019	4829	4.46	4.34	4.58
Cohort2020	4714	4.84	4.71	4.98
Cohort2021	4339	5.08	4.93	5.22

Table 3.6 Average annual percent change

Autoimmune diseases	Prevalence % 2000	Prevalence % 2021	Annual average percent change* with 95% CI
Hashimoto thyroiditis	0.05	0.12	6.22 (5.44-7.00)
Coeliac disease	0.11	0.27	6.20 (5.21-7.2)
Alopecia areata	0.21	0.42	4.75 (4.05-5.46)
Grave's disease	0.17	0.35	4.40 (4.02-4.82)
Vitiligo	0.04	0.05	3.69 (3.30- 4.08)
Sjogren syndrome	0.02	0.04	3.48 (1.45-5.55)
Addison's disease	0.003	0.004	2.61 (0.25-5.03)
Rheumatoid arthritis	0.26	0.22	1.75 (0.47-3.00)
Systemic sclerosis	0.02	0.01	1.72 (-0.32-3.87)

Psoriatic arthritis	0.06	0.07	1.54 (0.26- 2.84)
T1DM	0.38	0.43	1.5 (1.04- 1.98)
Psoriasis	1.87	2.04	1.13 (0.95-1.31)
Ulcerative colitis	0.20	0.21	1.11 (0.34-1.89)
Crohn's disease	0.20	0.21	0.94 (0.49-1.40)
IBD	0.42	0.42	0.93 (0.36- 1.50)
SLE	0.16	0.07	0.19 (-0.37-0.76)
Myasthenia gravis	0.07	0.01	-0.52 (-2.46-1.45)
Ankyloising spondylitis	0.05	0.04	-0.74 (-0.24-0.92)
Multiple sclerosis	0.11	0.13	-0.77 (-1.85-0.31)

*AAPC=(Vt-Vt-1) ×100 where Vt is the value at year t and Vt-1 is the value at year t-1

Table 3.7 Characteristics systemic inflammatory disease

Characteristics	Sjögren's syndrome	SLE	Systemic sclerosis
Age categories			
15-20 yrs	Ref	Ref	Ref
21 - 30 yrs	1.56 (0.58-4.21)	2.95 (2.07-4.21)	1.07 (0.66-1.72)
31 - 40 yrs	6.00 (1.98-18.14)	5.60 (3.89-8.08)	2.06 (1.24-3.43)
40 - 49 yrs	15.51 (5.02-47.96)	9.57 (6.47-14.17)	3.58 (2.01-6.38)
BMI			
14-18.5	1.81 (0.69-2.03)	0.94 (0.71-1.24)	1.50 (0.85-2.65)
18.5-25	Ref	Ref	Ref
25-30	0.88 (0.66-1.17)	0.88 (0.77-1.00)	1.08 (0.77-1.52)
30-75	0.63 (0.45-0.88)	0.74 (0.61-0.90)	0.75 (0.46-1.20)
missing	0.66 (0.45-0.95)	0.99 (0.85-1.15)	0.89 (0.63-1.26)
IMD			
1.00	Ref	Ref	Ref
2.00	1.34 (0.85-2.09)	1.13 (0.92-1.39)	1.22 (0.72-2.08)
3.00	1.32 (0.87-2.00)	1.07 (0.89-1.29)	1.32 (0.81-2.15)
4.00	1.23 (0.82-1.84)	1.15 (0.95-1.39)	1.06 (0.64-1.76)
5.00	1.53 (1.02-2.30)	1.30 (1.07-1.58)	0.92 (0.55-1.54)
Missing	1.73 (1.11-2.69)	1.16 (0.92-1.46)	1.39 (0.81-2.37)
Ethnicity			
White	Ref	Ref	Ref
Mixed Race	0.54 (0.38-0.78)	0.94 (0.78-1.12)	1.09 (0.76-1.57)
Others	0.95 (0.34-2.64)	1.80 (1.15-2.83)	1.00
Black	1.00 (0.59-1.68)	2.62 (2.05-3.36)	0.55 (0.26-1.18)
South Asians	1.10 (0.72-1.68)	1.77 (1.46-2.16)	0.74 (0.26-1.18)
Missing	0.62 (0.42-0.91)	0.92 (0.78-1.08)	0.82(0.57-1.18)
Gravidity			
1	Ref	Ref	Ref
2.00	0.90 (0.74-1.09)	0.96 (0.88-1.05)	0.79 (0.63-0.99)
3.00	0.77 (0.59-0.99)	0.95 (0.86-1.06)	0.88 (0.66-1.18)
4.00	0.65 (0.49-0.86)	0.97 (0.85-1.10)	0.72 (0.50-1.02)
5+	0.45 (0.31-0.65)	1.00 (0.85-1.17)	0.61 (0.42-0.89)
Smoking status			
Nonsmokers	Ref	Ref	Ref
Ex-Smoker	0.73 (0.54-0.99)	1.04 (0.90-1.21)	0.87 (0.61-1.23)
Current Smokers	0.70 (0.51-0.98)	0.99 (0.86-1.13)	0.89 (0.63-1.24)
Missing data	0.75 (0.46-1.21)	1.01 (0.84-1.21)	1.07 (0.72-1.60)
Comorbidities			
Hypertension	1.28 (0.78-2.12)	3.51 (2.79-4.43)	2.53 (1.16-5.52)
T2DM	1.94 (0.79-1.48)	0.55 (0.34-0.89)	1.08 (0.30-3.90)
Depression	1.08 (0.79-1.48)	1.29(1.10-1.52)	1.03 (0.67-1.59)
Psychosis	1.17 (0.34-3.97)	0.85 (0.46-1.55)	0.99 (0.14-7.16)
Anxiety	1.36 (0.99-1.87)	1.15 (0.94-1.40)	0.94 (0.55-1.60)

Table 3.8 Characteristics dermatological autoimmune disease

Characteristics	Alopecia areata	Psoriasis	Vitiligo
Age categories			
15-20 yrs	Ref	Ref	Ref
21 - 30 yrs	1.22 (1.08-1.37)	1.04(1.01-1.08)	0.95 (0.85-1.06)
31 - 40 yrs	1.08 (1.01-1.15)	1.14 (1.10-1.19)	0.98 (0.87-1.10)
40 - 49 yrs	1.11 (1.03-1.20)	1.12 (1.07-1.19)	1.01 (0.86-1.18)
BMI			
14-18.5	0.89 (0.77-1.04)	0.90 (0.85-0.95)	0.99 (0.85-1.16)
18.5-25	Ref	Ref	Ref
25-30	1.01 (0.95-1.07)	1.06 (1.04-1.09)	0.89 (0.82-0.96)
30-75	0.98 (0.89-1.07)	1.18 (1.14-1.21)	0.74 (0.67-0.81)
missing	0.79 (0.72-0.86)	0.96 (0.93-0.99)	0.80 (0.73-0.87)
IMD			
1	Ref	Ref	Ref
2	1.02 (0.95-1.09)	0.96 (0.92-1.01)	1.09 (0.97-1.22)
3.00	1.03 (0.93-1.14)	0.97 (0.93-1.01)	1.24 (1.11-1.39)
4.00	0.98 (0.93-1.05)	1.02 (0.97-1.06)	1.34 (1.19-1.52)
5.00	0.98 (0.87-1.10)	0.98 (0.94-1.03)	1.43 (1.27-1.61)
Missing	0.85 (0.72-1.01)	1.20 (1.14-1.27)	0.91 (0.78-1.05)
Ethnicity			
White	Ref	Ref	Ref
Mixed Race	1.05 (0.93-1.19)	0.87 (0.84-1.01)	1.19 (1.06-1.33)
Others	1.26 (0.93-1.72)	0.61 (0.47-0.78)	1.40 (1.00-1.96)
Black	1.00 (0.90-1.12)	0.19 (0.17-0.21)	1.82 (1.56-2.13)
South Asians	1.75 (1.50-2.03)	0.48 (0.45-0.51)	2.86 (2.55-2.31)
Missing	0.80 (0.72-0.88)	0.78 (0.75-0.81)	0.96 (0.87-1.06)
Gravidity			
2.00	1.06 (1.00-1.11)	1.09 (1.07-1.11)	0.97 (0.92-1.02)
3.00	1.13 (1.08-1.18)	1.14 (1.11-1.16)	0.99 (0.93-1.06)
4.00	1.21 (1.13-1.29)	1.20 (1.17-1.23)	1.00 (0.93-1.08)
5+	1.21 (0.14-1.28)	1.29 (1.25-1.33)	1.03 (0.94-1.13)
Smoking status			
Nonsmokers	Ref	Ref	Ref
Ex-Smoker	1.28 (1.20-1.36)	1.32 (1.28-1.35)	1.06 (0.97-1.16)
Current Smoker	1.42(1.33-1.51)	1.41 (1.38-1.45)	0.91(0.84-0.98)
Missing data	0.94 (0.80-1.09)	0.95 (0.91-0.99)	0.76 (0.68-0.85)
Comorbidities			
Hypertension	0.91 (0.74-1.12)	1.00 (0.92-1.08)	0.97 (0.77-1.24)
T2DM	0.96 (0.77-1.21)	1.24 (1.10-1.39)	1.05 (0.74-1.49)
Depression	1.26 (1.17-1.34)	1.17 (1.13-1.21)	1.14 (1.02-1.26)
Psychosis	1.09 (0.89-1.35)	0.99 (0.85-1.14)	1.41 (0.95-2.08)
Anxiety	1.34 (1.26-1.42)	1.14 (1.10-1.18)	1.28 (1.14-1.44)

Table 3.9 Characteristics endocrine autoimmune disease

Characteristics	Addison disease	Graves diseases	Hashimoto thyroiditis	T1DM
Age categories				
15-20 yrs	Ref	Ref	Ref	Ref

21 - 30 yrs	7.96 (1.84-34.39)	3.23 (2.63-3.96)	1.56 (1.19-2.04)	0.84 (0.73-0.96)
31 - 40 yrs	11.26 (2.56-49.60)	6.51 (5.26-8.05)	2.90 (2.17-3.87)	0.66 (0.57-0.77)
40 - 49 yrs	11.88 (2.46-57.31)	8.74 (6.97-10.95)	4.27 (3.10-5.87)	0.71 (0.58-0.87)
BMI				
14-18.5	2.48 (1.25-4.92)	1.07 (0.93-1.22)	1.01 (0.73-1.39)	0.40 (0.30-0.55)
18.5-25	Ref	Ref	Ref	Ref
25-30	0.95 (0.62-1.45)	0.99 (0.93-1.06)	1.04 (0.91-1.19)	1.62 (1.48-1.77)
30-75	0.97 (0.58-1.63)	0.98 (0.91-1.06)	1.29 (1.10-1.51)	1.04 (0.92-1.18)
missing	1.10 (0.70-1.75)	0.73 (0.67-0.79)	0.87 (0.73-1.03)	0.27 (0.23-0.32)
IMD				
1.00	Ref	Ref	Ref	Ref
2.00	1.40 (0.75-2.60)	1.01 (0.82-1.25)	1.01 (0.82-1.25)	1.04 (0.83-1.30)
3.00	1.18 (0.61-2.29)	1.30 (1.07-1.57)	1.30 (1.07-1.57)	1.06 (0.84-1.35)
4.00	0.70 (0.34-1.46)	1.24 (1.01-1.53)	1.24 (1.01-1.53)	1.12 (0.90-1.40)
5.00	1.79 (0.94-3.42)	1.17 (0.94-1.45)	1.17 (0.94-1.45)	1.07 (0.86-1.33)
Missing	1.63 (0.73-3.65)	1.21 (0.95-1.53)	1.21 (0.95-1.53)	1.29 (1.07-1.56)
Ethnicity				
White	Ref	Ref	Ref	Ref
Mixed Race	0.60 (0.32-1.14)	0.92 (0.83-1.01)	0.74 (0.61-0.90)	0.92 (0.82-1.03)
Others	1.00	1.44 (1.12-1.86)	1.99 (1.33-2.97)	1.09 (0.58-2.04)
Black	0.13 (0.03-0.55)	1.30 (1.16-1.47)	0.42 (0.29-0.62)	0.59 (0.36-0.97)
South Asians	0.25 (0.10-0.53)	1.58 (1.42-1.75)	0.88 (0.69-1.11)	0.72 (0.48-1.09)
Missing	0.80 (0.51-1.28)	0.72 (0.66-0.79)	0.70 (0.58-0.84)	1.03 (0.78-1.37)
Gravidity				
1	Ref	Ref	Ref	Ref
2.00	0.87 (0.66-1.16)	1.13 (1.07-1.19)	1.03 (0.93-1.14)	0.91 (0.83-1.00)
3.00	1.90 (0.63-1.29)	1.25 (1.18-1.32)	0.88 (0.78-1.00)	0.82 (0.73-0.92)
4.00	0.57 (0.35-0.93)	1.25 (1.17-1.34)	0.89 (0.77-1.02)	0.77 (0.67-0.89)
5+	0.62 (0.35-1.09)	1.23 (1.14-1.32)	0.79 (0.67-0.94)	0.70 (0.61-0.80)
Smoking status				
Nonsmokers	Ref	Ref	Ref	Ref
Ex-Smoker	0.92 (0.58-1.45)	1.16 (1.08-1.24)	0.88 (0.75-1.02)	0.98 (0.87-1.10)
Current Smoker	0.59 (0.38-0.91)	0.96 (0.90-1.03)	0.71 (0.61-0.83)	0.82 (0.74-0.91)
Missing data	0.74 (0.43-1.28)	0.95 (0.85-1.06)	0.78 (0.61-0.99)	0.82 (0.66-1.03)
Comorbidities				
Hypertension	1.00	1.14 (0.96-1.35)	0.94 (0.59-1.49)	2.76 (2.59-2.94)
T2DM	2.56 (0.78-8.38)	1.16 (0.88-1.52)	1.15 (0.62-2.15)	
Depression	1.12 (0.72-1.74)	1.13 (1.03-1.23)	0.89 (0.73-1.09)	1.47 (1.41-1.53)
Psychosis	3.29 (0.90-12.11)	1.33 (0.96-1.85)	1.19 (0.59-2.38)	0.70 (0.57-0.86)
Anxiety	1.22 (0.77-1.94)	1.20 (1.08-1.32)	1.24 (1.01-1.53)	0.85 (0.80-0.89)

Table 3.10 Characteristics gastrointestinal autoimmune disease

Characteristics	Coeliac disease	Crohn's disease	Ulcerative colitis	IBD
Age categories				
15-20 yrs	Ref	Ref	Ref	Ref
21 - 30 yrs	1.06 (0.93-1.20)	3.19 (2.62-3.89)	3.47 (2.76-4.37)	3.14 (2.70-3.65)
31 - 40 yrs	1.36 (1.18-1.56)	5.53 (4.51-6.78)	7.44 (5.89-9.40)	5.82 (4.96-6.83)
40 - 49 yrs	1.67 (1.39-2.01)	6.79 (5.51-8.52)	10.98 (8.53-14.13)	7.86 (6.62-9.33)
BMI				
14-18.5	1.29 (1.11-1.51)	1.48 (1.28-1.71)	1.20 (1.03-1.40)	1.27 (1.14-1.42)
18.5-25	Ref	Ref	Ref	Ref
25-30	0.78 (0.72-0.85)	0.83 (0.77-0.90)	0.86 (0.79-0.93)	0.85 (0.80-0.90)
30-75	0.62 (0.56-0.70)	0.76 (0.69-0.84)	0.64 (0.57-0.71)	0.71 (0.66-0.76)
missing	0.78 (0.68-0.89)	0.77 (0.71-0.85)	0.82 (0.75-0.90)	0.80 (0.75-0.85)
IMD				
1.00	Ref	Ref	Ref	Ref
2.00	1.13 (0.96-1.20)	1.18 (1.04-1.33)	1.36 (1.18-1.57)	1.23 (1.13-1.35)
3.00	1.22 (1.07-1.38)	1.07 (0.58-1.97)	1.38 (1.21-1.57)	1.35 (1.23-1.48)
4.00	1.36 (1.19-1.54)	0.29 (0.23-0.38)	1.64 (1.44-1.87)	1.54 (1.41-1.68)
5.00	1.35 (1.18-1.53)	0.45 (0.37-0.54)	1.81 (1.59-2.06)	1.70 (1.56-1.85)
Missing	1.46 (1.27-1.68)	0.95 (0.86-1.04)	1.40 (1.21-1.62)	1.47 (1.33-1.64)
Ethnicity				
White	Ref	Ref	Ref	Ref

Mixed Race	0.68 (0.61-0.76)	0.81 (0.72-0.90)	0.80 (0.72-0.89)	0.82 (0.76-0.89)
Others	0.62 (0.40-0.95)	1.07 (0.58-1.97)	0.90 (0.63-1.26)	1.01 (0.71-1.45)
Black	0.21 (0.15-0.30)	0.29 (0.23-0.38)	0.41 (0.32-0.53)	0.35 (0.30-0.43)
South Asians	0.74 (0.63-0.87)	0.45 (0.37-0.54)	0.66 (0.56-0.78)	0.57 (0.50-0.64)
Missing	0.75 (0.67-0.84)	0.95 (0.86-1.04)	0.93 (0.84-1.03)	0.94 (0.88-1.01)
Gravidity				
1	Ref	Ref	Ref	Ref
2.00	0.94 (0.88-0.99)	0.97 (0.92-1.02)	0.93 (0.88-0.98)	0.96 (0.93-1.00)
3.00	0.88 (0.82-0.95)	0.94 (0.88-1.00)	0.91 (0.85-0.97)	0.93 (0.88-0.97)
4.00	0.81 (0.74-0.89)	0.92 (0.85-1.01)	0.93 (0.85-1.01)	0.92 (0.87-0.98)
5+	0.84 (0.74-0.95)	0.81 (0.73-0.89)	0.87 (0.79-0.96)	0.84 (0.79-0.90)
Smoking status				
Nonsmokers	Ref	Ref	Ref	Ref
Ex-Smoker	0.83 (0.76-0.91)	1.37 (1.27-1.49)	0.95 (0.90-1.09)	1.19 (1.12-1.26)
Current Smoker	0.69 (0.63-0.75)	1.11 (1.03-1.21)	0.55 (0.52-0.59)	0.82 (0.77-0.87)
Missing data	0.60 (0.52-0.68)	0.90 (0.79-1.02)	0.86 (0.81-0.91)	0.88 (0.81-0.96)
Comorbidities				
Hypertension	0.76 (0.57-1.02)	1.23 (0.96-1.58)	0.80 (0.68-0.95)	1.05 (0.88-1.24)
T2DM	1.20 (0.76-1.88)	0.77 (0.49-1.20)	1.57 (1.25-1.97)	1.32 (0.99-1.76)
Depression	1.18 (1.06-1.33)	1.24 (1.12-1.37)	1.00 (0.94-1.07)	1.15 (1.07-1.24)
Psychosis	1.48 (1.02-2.16)	0.90 (0.95-1.19)	0.72 (0.50-1.05)	0.79 (0.55-1.15)
Anxiety	1.45 (1.30-1.63)	1.06 (0.95-1.19)	1.15 (1.07-1.24)	1.08 (0.99-1.18)

Table 3.11 Characteristics musculoskeletal autoimmune disease

Characteristics	Ankylosing spondylitis	Psoriatic arthritis	Rheumatoid arthritis
Age categories			
15-20 yrs	Ref	Ref	Ref
21 - 30 yrs	8.22 (3.11-21.73)	2.62 (1.81-3.78)	2.63 (2.04-3.39)
31 - 40 yrs	23.43 (8.75-62.75)	5.556 (3.81-811)	6.28 (4.85-8.14)
40 - 49 yrs	33.53 (12.35-91.06)	7.73 (5.16-11.58)	11.47 (8.76-15.01)
BMI			
14-18.5	0.88 (0.57-1.36)	0.86 (0.59-1.26)	1.18 (0.96-1.45)
18.5-25	Ref	Ref	Ref
25-30	0.96 (0.76-1.17)	1.22 (1.05-1.41)	1.07 (0.97-1.18)
30-75	0.87 (0.68-1.09)	1.78 (1.50-2.10)	1.09 (0.97-1.23)
missing	0.99 (0.79-1.23)	1.10 (0.91-1.33)	1.00 (0.90-1.11)
IMD			
1.00	Ref	Ref	Ref
2.00	1.55 (1.14-2.11)	1.06 (0.83-1.35)	0.98 (0.85-1.13)
3.00	1.88 (1.39-2.54)	1.25(1.00-1.57)	1.04 (0.90-1.21)
4.00	2.10 (1.54-2.86)	1.38 (1.10-1.73)	1.05 (0.91-1.22)
5.00	1.61 (1.19-2.18)	1.23 (0.96-1.58)	0.98 (0.86-1.13)
Missing	1.61 (1.15-2.26)	1.60 (1.25-2.05)	1.04 (0.89-1.22)
Ethnicity			
White	Ref	Ref	Ref
Mixed Race	0.75 (0.58-0.97)	0.77 (0.64-0.93)	0.94 (0.83-1.06)
Others	0.74 (0.33-1.69)	1.73 (0.86-3.47)	0.87 (0.57-1.32)
Black	0.25 (0.09-0.69)	0.12 (0.06-0.27)	0.86 (0.69-1.07)
South Asians	0.56 (0.36-0.86)	0.63 (0.46-0.85)	1.34 (1.15-1.57)
Missing	1.02 (0.82-1.27)	0.85 (0.71-1.02)	0.86 (0.76-0.97)
Gravidity			
1	Ref	Ref	Ref
2.00	0.98 (0.86-1.12)	0.93 (0.84-1.03)	0.95 (0.89-1.02)
3.00	0.93 (0.80-1.09)	0.90 (0.79-1.02)	0.88 (0.81-0.95)
4.00	0.91 (0.74-1.11)	0.84 (0.72-0.99)	0.81 (0.73-0.90)
5+	0.77 (0.61-0.97)	0.89 (0.75-1.05)	0.74 (0.66-0.82)
Smoking status			
Nonsmokers	Ref	Ref	Ref
Ex-Smoker	1.11 (0.91-1.34)	1.23 (1.05-1.44)	0.92 (0.82-1.03)
Current Smoker	0.94 (0.78-1.13)	1.11 (0.96-1.29)	0.91 (0.83-1.01)
Missing data	1.05 (0.78-1.41)	1.01 (0.80-1.26)	0.94 (0.82-1.09)
Comorbidities			

Hypertension	1.31 (0.80-2.13)	1.25 (0.80-1.96)	1.74 (1.42-2.13)
T2DM	0.59 (0.20-1.73)	1.73 (1.12-2.68)	1.02 (0.75-1.38)
Depression	1.49 (1.18-1.90)	1.34 (1.10-1.63)	1.32 (1.17-1.48)
Psychosis	0.26 (0.07-1.06)	0.79 (0.82-1.26)	1.10 (0.69-1.75)
Anxiety	0.86 (0.66-1.12)	1.02 (0.82-1.26)	1.01 (0.88-1.16)

Table 3.12 Characteristics neurological autoimmune disease

Characteristics	Multiple sclerosis	Myasthenia gravis
Age categories		
15-20 yrs	Ref	Ref
21 - 30 yrs	8.56 (4.63-15.81)	2.94 (1.39-6.23)
31 - 40 yrs	26.23 (14.07-48.90)	5.40 (2.56-11.37)
40 - 49 yrs	47.58 (25.52-88.70)	10.91 (4.62-25.81)
BMI		
14-18.5	1.18 (0.91-1.53)	1.09 (0.49-2.46)
18.5-25	Ref	Ref
25-30	0.94 (0.84-1.06)	1.14 (0.84-1.55)
30-75	0.84 (0.72-0.97)	1.27 (0.88-1.85)
missing	0.93 (0.81-1.07)	1.17 (0.77-1.78)
IMD		
1.00	Ref	Ref
2.00	1.22 (1.01-1.48)	1.01 (0.65-1.57)
3.00	1.18 (0.97-1.44)	0.72 (0.45-1.17)
4.00	1.38 (1.13-1.68)	01.06 (0.65-1.70)
5.00	1.28 (1.05-1.55)	0.88 (0.51-1.50)
Missing	1.40 (1.13-1.74)	0.73 (0.38-1.38)
Ethnicity		
White	Ref	Ref
Mixed Race	0.99 (0.85-1.17)	0.82 (0.50-1.32)
Others	1.21(0.78-1.87)	0.17 (0.02-1.24)
Black	0.59 (0.43-0.82)	1.32 (0.77-2.25)
South Asians	0.52 (0.38-0.70)	0.70 (0.43-1.16)
Missing	0.86 (0.75-0.98)	1.13 (0.74-1.71)
Gravidity		
1	Ref	Ref
2.00	0.95 (0.87-1.03)	0.76 (0.62-0.92)
3.00	0.85 (0.77-0.95)	0.97 (0.74-1.26)
4.00	0.83 (0.73-0.94)	0.74 (0.53-1.03)
5+	0.63 (0.54-0.72)	0.71 (0.48-1.04)
Smoking status		
Nonsmokers	Ref	Ref
Ex-Smoker	1.31 (1.16-1.48)	0.61 (0.39-0.95)
Current Smoker	1.07 (0.95-1.21)	0.85 (0.61-1.18)
Missing data	1.19 (1.00-1.41)	0.74 (0.44-1.25)
Comorbidities		
Hypertension	1.13 (0.81-1.56)	1.10 (0.50-2.40)
T2DM	1.15 (0.67-1.96)	0.64 (0.14-2.89)
Depression	1.55 (1.34-1.79)	0.90 (0.55-1.47)
Psychosis	1.52 (0.88-2.65)	1.28 (0.29-5.77)
Anxiety	1.07 (0.90-1.26)	0.94 (0.58-1.52)

Table 3.13 Characteristics by grouping of organ system of autoimmune disease

Characteristics	Systemic inflammatory ds	Dermatological disorders	Endocrine disorders	Gastrointestinal disorders	Musculoskeletal disorders	Neurological disorders
Age categories						
15-20 yrs	Ref	Ref	Ref	Ref	Ref	Ref
21 - 30 yrs	2.46 (1.86-3.26)	1.01 (0.97-1.04)	1.66 (1.49-1.85)	1.92 (1.74-2.10)	2.92 (2.37-3.58)	6.49 (4.04-10.42)
31 - 40 yrs	5.01 (3.75-6.70)	1.09 (1.06-1.13)	2.58 (2.30-2.90)	3.19 (2.88-3.52)	6.91 (5.61-8.51)	18.59 (11.52-30.02)

40 - 49 yrs	9.20 (6.73-12.58)	1.08 (1.03-1.14)	3.33 (2.93-3.79)	4.19 (3.74-4.71)	11.52 (9.26-14.34)	34.19 (21.05-55.53)
BMI						
14-18.5	1.04 (0.83-1.31)	0.90 (0.86-0.95)	0.90 (0.80-1.01)	1.28 (1.17-1.40)	1.05 (0.88-1.26)	1.17 (0.92-1.49)
18.5-25	Ref	Ref	Ref	Ref	Ref	Ref
25-30	0.89 (0.79-1.00)	1.04 (1.02-1.06)	1.14 (1.09-1.20)	0.83 (0.79-0.87)	1.08 (1.00-1.17)	0.96 (0.86-1.07)
30-75	0.73 (0.62-0.87)	1.12 (1.09-1.15)	1.03 (0.97-1.10)	0.68 (0.64-0.73)	1.21 (1.10-1.32)	0.88 (0.76-1.01)
missing	0.94 (0.82-1.07)	0.93 (0.90-0.95)	0.63 (0.58-0.67)	0.79 (0.74-0.84)	1.03 (0.94-1.12)	0.96 (0.84-1.09)
IMD						
1.00	Ref	Ref	Ref	Ref	Ref	Ref
2.00	1.12 (0.94-1.35)	0.98 (0.94-1.02)	1.01 (0.93-1.09)	1.19 (1.10-1.29)	1.06 (0.94-1.19)	1.18 (0.99-1.41)
3.00	1.11 (0.94-1.30)	1.00 (0.96-1.04)	1.07 (0.98-1.16)	1.31 (1.21-1.41)	1.18 (1.06-1.33)	1.10 (0.92-1.32)
4.00	1.13 (0.95-1.33)	1.04 (1.00-1.08)	1.05 (0.97-1.15)	1.47 (1.37-1.58)	1.25 (1.11-1.40)	1.32 (1.10-1.58)
5.00	1.27 (1.07-1.50)	1.02 (0.97-1.06)	1.10 (1.01-1.20)	1.58 (1.47-1.70)	1.11 (0.99-1.25)	1.21 (1.01-1.45)
Missing	1.22 (1.01-1.48)	1.15 (1.09-1.20)	1.43 (1.30-1.57)	1.46 (1.34-1.59)	1.23 (1.09-1.40)	1.29 (1.06-1.58)
Ethnicity						
White	Ref	Ref	Ref	Ref	Ref	Ref
Mixed Race	0.91 (0.78-1.06)	0.91 (0.88-0.94)	1.38 (1.28-1.49)	0.78 (0.73-0.83)	0.86 (0.78-0.95)	0.97 (0.84-1.13)
Others	1.50 (0.99-2.28)	0.72 (0.60-0.85)	1.39 (1.10-1.74)	0.89 (0.65-1.23)	1.04 (0.71-1.53)	1.07 (0.70-1.65)
Black	2.15 (1.73-2.67)	0.37 (0.34-0.40)	1.00 (0.90-1.12)	0.31 (0.26-0.36)	0.60 (0.49-0.73)	0.70 (0.53-0.92)
South Asians	1.57 (1.32-1.87)	0.76 (0.72-0.81)	1.22 (1.11-1.34)	0.62 (0.56-0.68)	1.03 (0.90-1.17)	0.54 (0.42-0.71)
Missing	0.88 (0.76-1.02)	0.79 (0.77-0.82)	0.68 (0.63-0.74)	0.89 (0.83-0.94)	0.88 (0.80-0.96)	0.88 (0.78-1.00)
Gravidity						
1	Ref	Ref	Ref	Ref	Ref	Ref
2.00	0.93 (0.86-1.00)	1.07 (1.06-1.09)	1.11 (1.07-1.16)	0.95 (0.92-0.98)	0.95 (0.90-1.00)	0.93 (0.86-1.00)
3.00	0.91 (0.82-1.00)	1.12 (1.10-1.15)	1.15 (1.09-1.21)	0.91 (0.88-0.95)	0.89 (0.84-0.95)	0.86 (0.79-0.95)
4.00	0.88 (0.78-0.99)	1.18 (1.15-1.21)	1.15 (1.09-1.22)	0.89 (0.85-0.93)	0.84 (0.78-0.91)	0.82 (0.73-0.92)
5+	0.87 (0.76-1.00)	1.26 (1.22-1.29)	1.11 (1.04-1.18)	0.84 (0.79-0.89)	0.78 (0.71-0.85)	0.64 (0.56-0.73)
Smoking status						
Nonsmokers	Ref	Ref	Ref	Ref	Ref	Ref
Ex-Smoker	0.98 (0.87-1.11)	1.29 (1.26-1.32)	1.07 (1.01-1.13)	1.08 (1.03-1.13)	1.03 (0.94-1.12)	1.22 (1.09-1.38)
Current Smoker	0.92 (0.82-1.04)	1.37 (1.34-1.40)	0.89 (0.84-0.94)	0.78 (0.74-0.82)	0.97 (0.90-1.05)	1.04 (0.93-1.17)
Missing data	0.98 (0.84-1.15)	0.93 (0.89-0.96)	0.85 (0.77-0.93)	0.79 (0.74-0.85)	0.97 (0.87-1.09)	1.12 (0.96-1.32)
Comorbidities						
Hypertension	3.11 (2.50-3.86)	0.99 (0.92-1.06)	0.89 (0.76-1.05)	0.97 (0.83-1.13)	1.59 (1.33-1.91)	1.12 (0.83-1.52)
T2DM	0.73 (0.48-1.10)	1.17 (1.06-1.30)	3.34 (2.78-4.03)	1.29 (1.01-1.65)	1.10 (0.87-1.41)	1.08 (0.65-1.79)
Anxiety	1.15 (0.97-1.37)	1.17 (1.13-1.21)	1.10 (1.01-1.20)	1.19 (1.12-1.27)	0.98 (0.88-1.09)	1.05 (0.90-1.24)
Depression	1.23 (1.07-1.42)	1.18 (1.15-1.22)	0.96 (0.89-1.04)	1.16 (1.09-1.23)	1.35 (1.23-1.49)	1.46 (1.27-1.68)
Psychosis	0.94 (0.55-1.58)	1.03 (0.90-1.17)	1.25 (0.93-1.68)	0.97 (0.74-1.26)	0.90 (0.61-1.35)	1.50 (0.89-2.53)

Text 3.1 Summary of characteristics by grouping of organ system of autoimmune disease

When autoimmune disorders categorised according to the systems, all the system has higher odds in women with increasing age.

When compared with women of BMI 18.5 to <25 kg/m² there was an increased odds of systemic, gastrointestinal, and neurological disorders gastrointestinal disorders in women with a lower BMI (<18.5 kg/m²). Whereas the odds of endocrine and dermatological disorders increased with a higher BMI (≥25 kg/m²).

For most autoimmune diseases groups, women living in the least deprived areas had a higher odds of having the autoimmune disease; however, Endocrine disorders were more prevalent in women living in the most deprived areas.

Compared to women from the white ethnic group, all the other ethnicities had a lower odds of having most of the autoimmune diseases. However, there was a higher odds of having sytemic disorders in women from the black and Asian ethnic group and endocrine disorders in all non white ethnic group.

When compared to non smokers, the odds of having most of the autoimmune diseases were higher in women who were smokers. However, the odds of systemic disorders, were lower in smokers overall and lower odds of endocrine and gastrointestinal disorders in current smoker when compares with non smokers.

Women with more than two or three pregnancies were at higher odds of having dermatological and endocrine disorders when compared with women with one pregnancy.

However, the the odds of systemic or musculoskeletal disorders were higher in women with hypertension and odds of all other organ system groups are higher in women with T2DM except for systemic disorders. The odds of most of the autoimmune diseases were higher among women with mental health disorders.

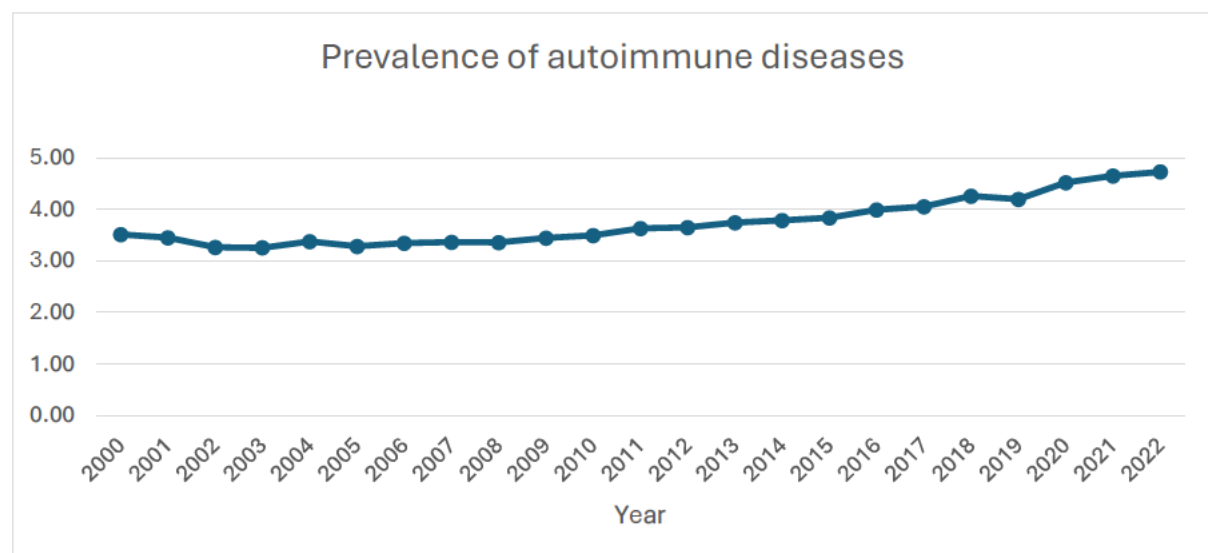


Figure 3.1 Crude prevalence of autoimmune diseases 2000-2021

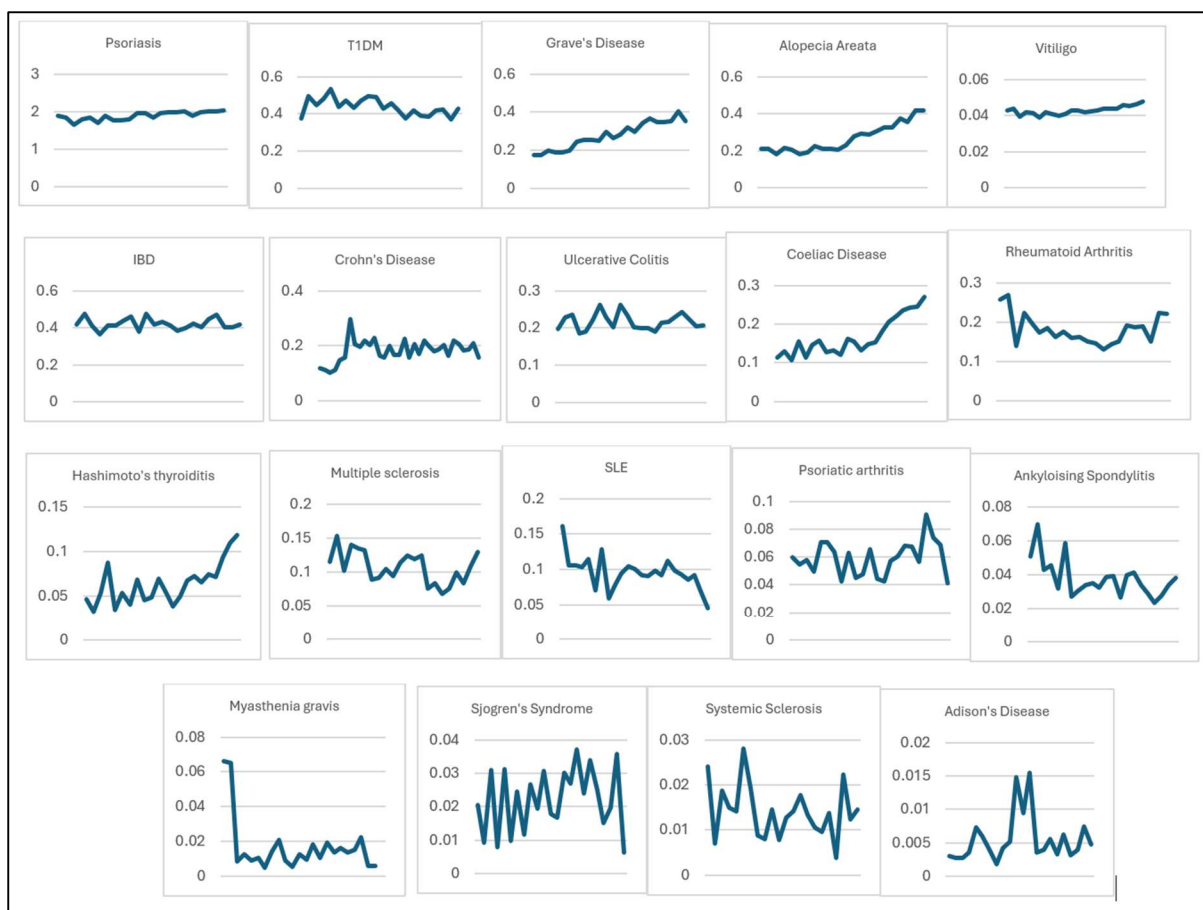


Figure 3.2 Age standardised prevalence trends for specific autoimmune diseases

Table 3.14 Search term for autoimmune diseases

exp Autoimmune Diseases/
(auto?immune adj2 (disease* or condition*)).mp.
exp Psoriasis/
psoria\$.mp.
exp Vitiligo/
vitiligo.mp.
(leucoderma or leukoderma).mp.
exp Alopecia Areata/
alopecia areata.mp.
((alopecia adj totalis) or (alopecia adj universalis)).mp.
exp Lupus Erythematosus, Systemic/
(systemic lupus or sle).mp.
arthritis psoriatic.mp. or exp Arthritis, Psoriatic/
Ankylosing spondylitis.mp. or exp Spondylitis, Ankylosing/
Spondylarthritis/
(axial adj2 spondylarthritis).tw.

(axial adj2 spa).tw.
(ankylos\$ or spondyl\$).tw.
(bekhterev\$ or bechterew\$).tw.
(Marie adj struempell\$).tw.
(AS or axSPA).tw.
Sacroiliitis/
((axial or spin\$ or peripheral or vertebral or enthesitis) adj3 (joint\$ or spondyloarthritis or arthritis or ankylosing)).tw.
exp Arthritis, Rheumatoid/
((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat\$ or reumat\$ or revmarthrit\$) adj3 (arthrit\$ or artrit\$ or diseas\$ or condition\$ or nodule\$)).mp.
sjogren syndrome.mp. or exp Sjögren's Syndrome/
exp Celiac Disease/
(c?eliac adj disease*).mp.
inflammatory bowel disease.mp. or exp Inflammatory Bowel Diseases/
ulcerative colitis.mp. or exp Colitis, Ulcerative/
Crohn's disease.mp. or exp Crohn Disease/
multiple sclerosis.mp. or exp Multiple Sclerosis/
Systemic Sclerosis.mp.
exp Scleroderma, Systemic/
((systemic adj scler?) or sclero?).mp.
crest syndrome.mp. or exp CREST Syndrome/
graves disease.mp. or exp Graves Disease/
(grave? adj3 (diseas? or thyrotoxicos? or hyperthyr?)).mp.
exp Thyroiditis, Autoimmune/
autoimmune thyroid.mp.
Hashimoto Disease.mp.
exp Hashimoto Disease/
myasthenia gravis.mp. or exp Myasthenia Gravis/
addison disease.mp. or exp Addison Disease/
type 1 diabetes.mp. or exp Diabetes Mellitus, Type 1/ or ("typ? 1 diabet*" or "typ? I diabet*" or "typ?1 diabet*" or "typ?I diabet*").mp. or (("insulin* depend*" or "insulin?depend*") not ("non-insulin* depend*" or "non insulindepend*")).mp. or (IDDM or T1DM or T1D).mp. or autoimmune diabetes.mp.

Table 3.15 Fertility rates of women with any autoimmune disease and without in CPRD Gold and Aurum (2000-2021)

	CPRD Gold N=4,153,082		CPRD Aurum N=10,394,392	
	Non-AI	AI	Non-AI	AI
Overall matched	48.54 (48.33 - 48.75)	52.34 (51.91 - 52.78)	57.07 (56.91 - 57.23)	65.75 (65.40 - 66.10)
Overall (15-50 yrs)	57.45		65.88	

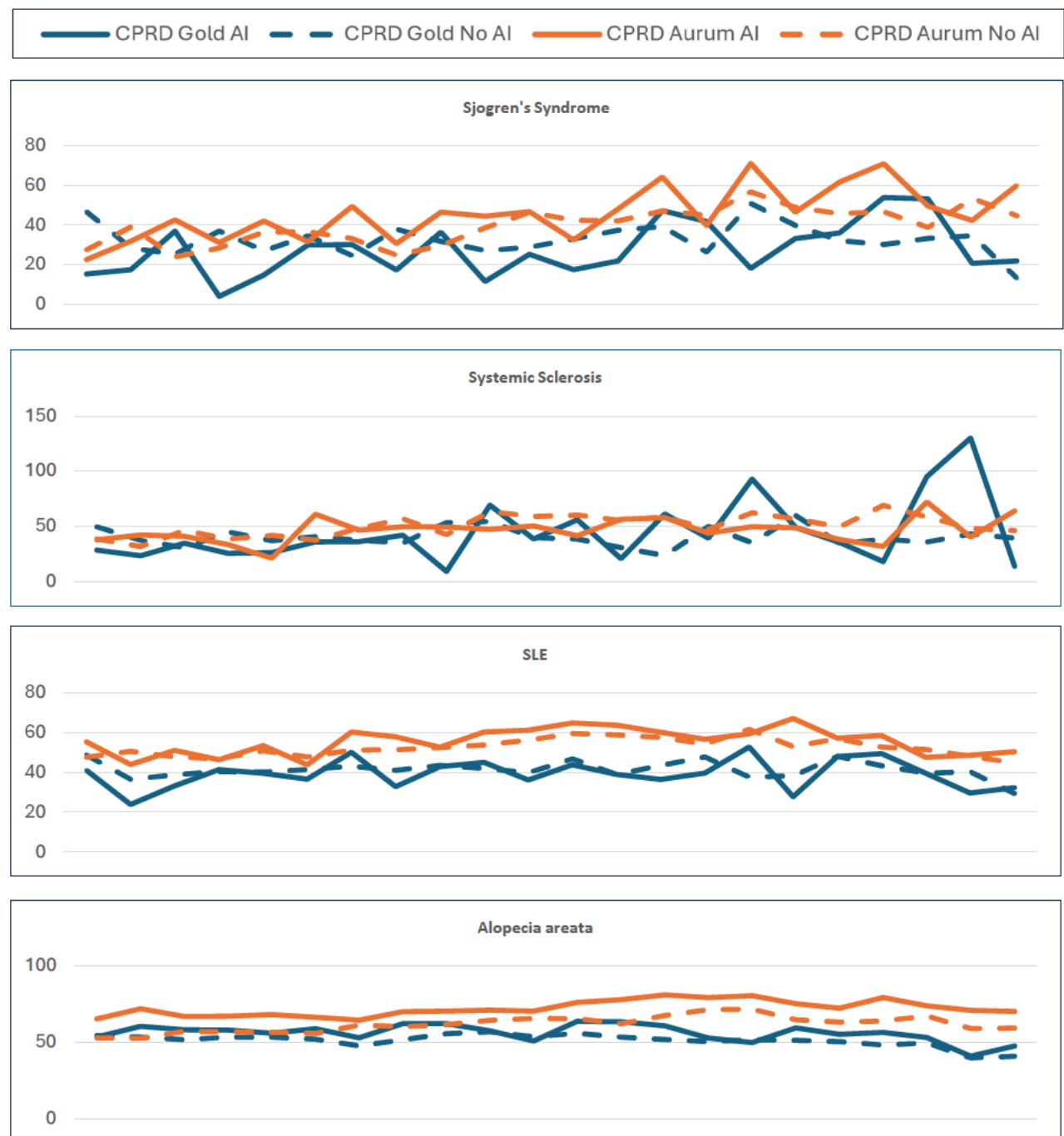
Overall matched 15 - 19 yrs	64.01 (63.41 - 64.61)	68.83 (67.57-70.10)	72.86 (72.37 - 73.35)	82.42 (81.36 - 83.49)
Overall matched 20 - 24 yrs	93.14 (92.25 - 94.03)	100.54 (98.65 - 102.45)	96.78 (96.19 - 97.37)	100.39 (99.13 - 101.66)
Overall matched 25 - 29 yrs	85.41 (84.69 - 86.13)	89.43 (87.95 - 90.94)	89.33 (88.86 - 89.80)	100.73 (99.71 - 101.77)
Overall matched 30 - 34 yrs	53.32 (52.82 - 53.82)	59.25 (58.21 - 60.30)	60.31 (59.96 - 60.67)	74.56 (73.76 - 75.36)
Overall matched 35 - 39 yrs	22.74 (22.42 - 23.07)	25.42 (24.74 - 26.11)	27.78 (27.52 - 28.04)	37.82 (37.21 - 38.44)
Overall matched 40 - 44 yrs	6.10 (5.90 - 6.30)	7.36 (6.93 - 7.81)	9.94 (9.75 - 10.13)	13.28 (12.83 - 13.74)
Overall matched 45 - 50 yrs	1.49 (1.33 - 1.66)	1.74 (1.41 - 2.12)	3.27 (3.09 - 3.45)	4.43 (4.02 - 4.87)
Year 2000	49.73 (48.51 - 50.97)	49.66 (47.25 - 52.17)	51.57 (50.76 - 52.40)	59.21 (57.49 - 60.97)
Year 2001	47.91 (46.78 - 49.06)	50.25 (48.00 - 52.57)	49.87 (49.04 - 50.70)	59.54 (57.81 - 61.30)
Year 2002	46.78 (45.70 - 47.89)	50.16 (48.03 - 52.36)	49.88 (49.04 - 50.73)	57.54 (55.85 - 59.27)
Year 2003	47.01 (45.98 - 48.06)	50.66 (48.66 - 52.73)	50.37 (49.51 - 51.23)	59.97 (58.26 - 61.72)
Year 2004	46.43 (45.45 - 47.42)	52.13 (50.22 - 54.09)	48.97 (48.12 - 49.83)	62.38 (60.65 - 64.14)
Year 2005	47.48 (46.53 - 48.43)	51.68 (49.88 - 53.53)	48.79 (47.94 - 49.66)	59.09 (57.42 - 60.79)
Year 2006	46.31 (45.38 - 47.25)	51.54 (49.76 - 53.37)	50.47 (49.60 - 51.35)	63.05 (61.34 - 64.79)
Year 2007	46.78 (45.83 - 47.75)	53.45 (51.64 - 55.32)	51.89 (51.01 - 52.77)	64.91 (63.20 - 66.66)
Year 2008	46.86 (45.90 - 47.85)	52.32 (50.53 - 54.15)	52.59 (51.71 - 53.48)	65.58 (63.88 - 67.31)
Year 2009	49.50 (48.49 - 50.52)	55.53 (53.68 - 57.43)	54.90 (54.00 - 55.80)	67.33 (65.62 - 69.06)
Year 2010	49.36 (48.32 - 50.40)	55.18 (53.32 - 57.09)	56.12 (55.22 - 57.04)	69.72 (68.00 - 71.46)
Year 2011	50.35 (49.28 - 51.45)	57.48 (55.56 - 59.45)	57.71 (56.79 - 58.63)	72.27 (70.54 - 74.03)
Year 2012	48.95 (47.87 - 50.05)	56.00 (54.08 - 57.97)	59.67 (58.75 - 60.60)	71.11 (69.42 - 72.84)
Year 2013	48.37 (47.25 - 49.51)	55.91 (53.94 - 57.92)	61.69 (60.75 - 62.64)	72.60 (70.90 - 74.33)
Year 2014	48.43 (47.23 - 49.65)	52.59 (50.61 - 54.64)	62.49 (61.54 - 63.46)	71.47 (69.79 - 73.17)
Year 2015	47.69 (46.41 - 49.01)	53.88 (51.76 - 56.06)	62.85 (61.91 - 63.80)	69.37 (67.75 - 71.03)
Year 2016	48.64 (47.17 - 50.15)	53.22 (50.96 - 55.55)	60.61 (59.71 - 61.53)	68.66 (67.07 - 70.27)
Year 2017	47.92 (46.34 - 49.54)	53.26 (50.88 - 55.73)	59.88 (59.00 - 60.77)	67.06 (65.52 - 68.62)
Year 2018	47.45 (45.82 - 49.12)	52.09 (49.66 - 54.61)	59.25 (58.40 - 60.12)	68.55 (67.02 - 70.10)
Year 2019	46.18 (44.54 - 47.86)	49.63 (47.20 - 52.16)	60.09 (59.23 - 60.95)	66.56 (65.06 - 68.08)
Year 2020	42.85 (41.21 - 44.53)	45.23 (42.81 - 47.74)	54.18 (53.37 - 55.00)	64.43 (62.97 - 65.91)
Year 2021	38.83 (37.17 - 40.55)	41.60 (39.16 - 44.15)	53.58 (52.76 - 54.40)	63.66 (62.21 - 65.13)

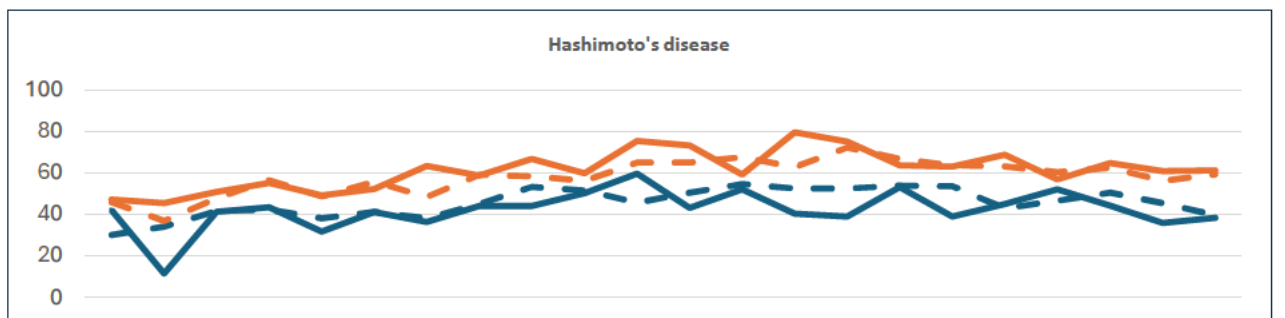
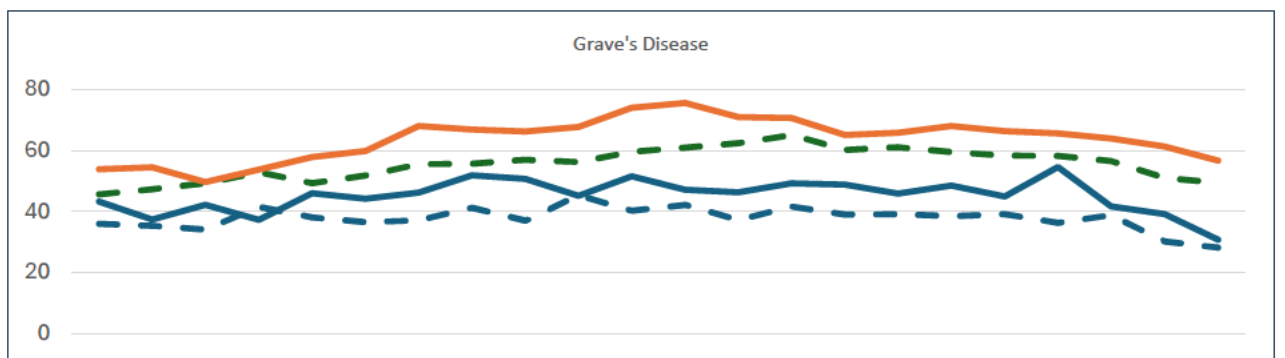
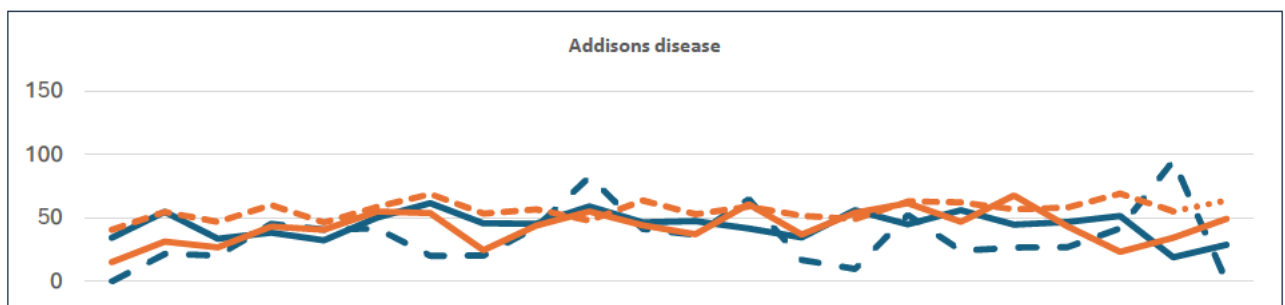
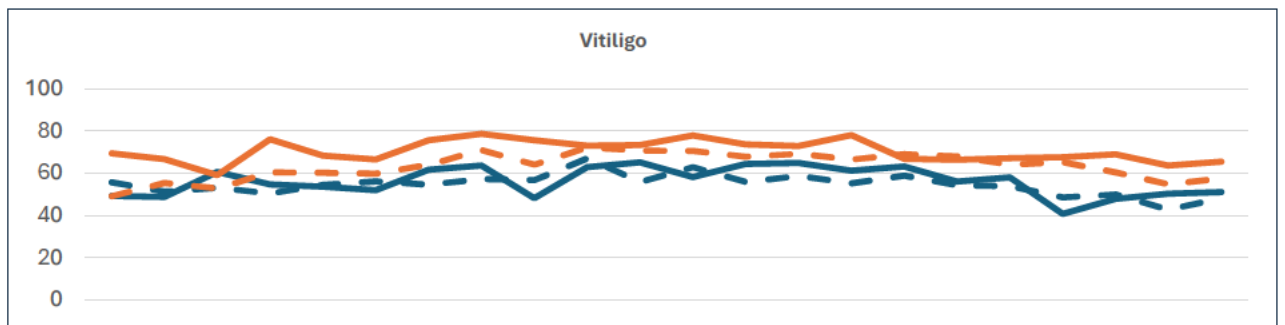
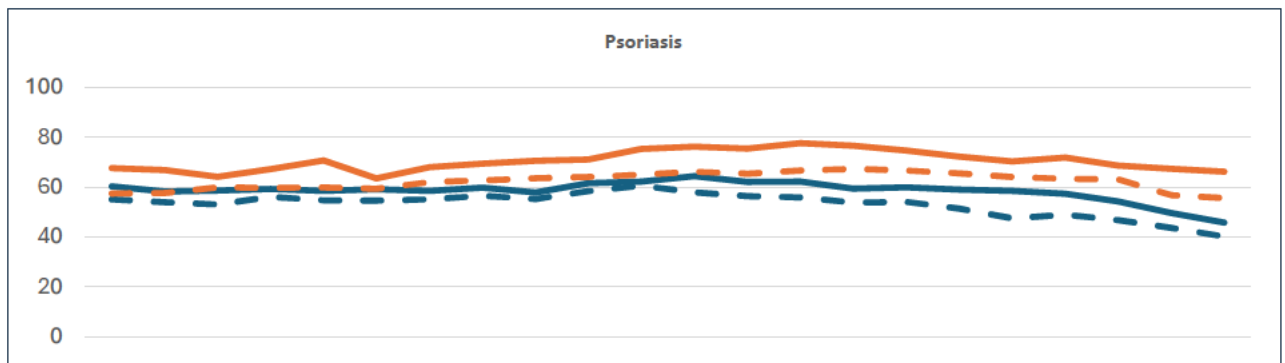
Supplementary text 3.2

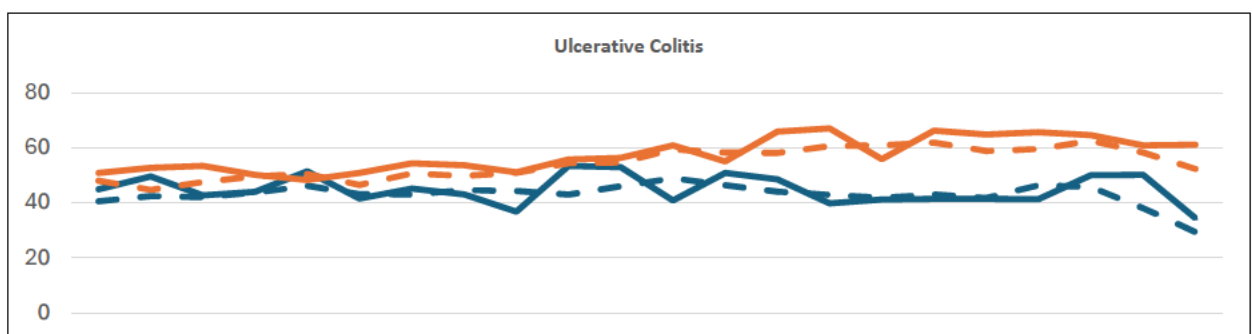
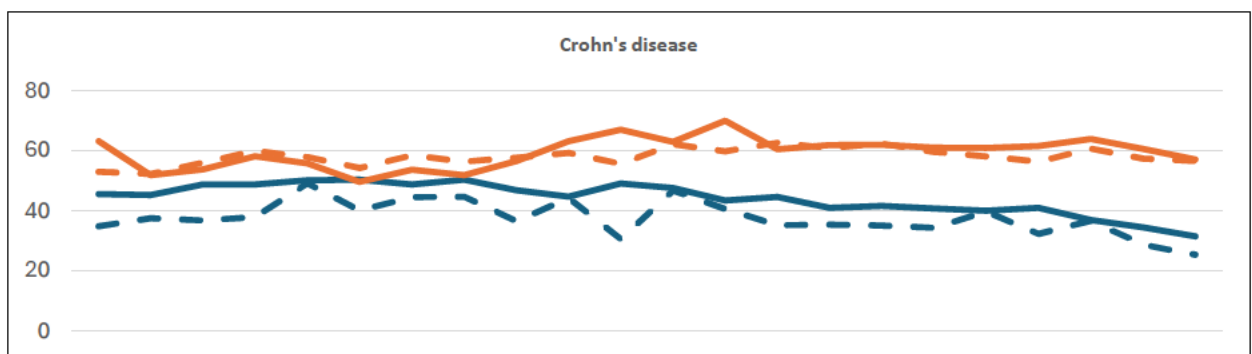
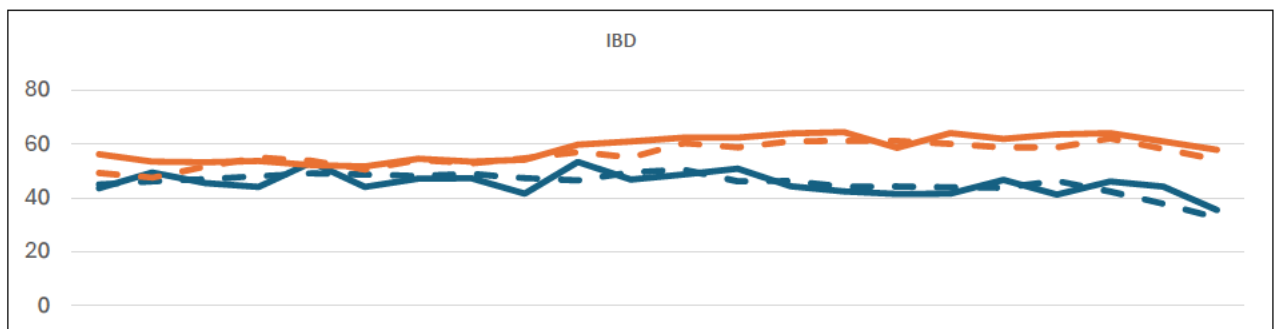
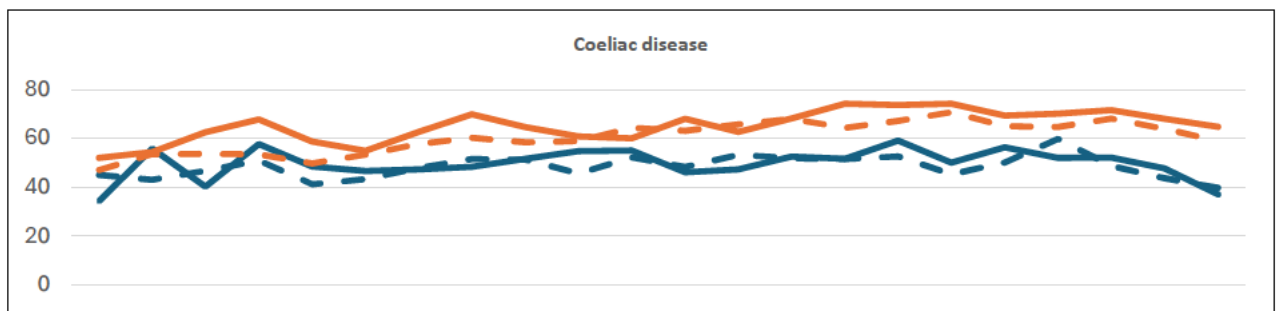
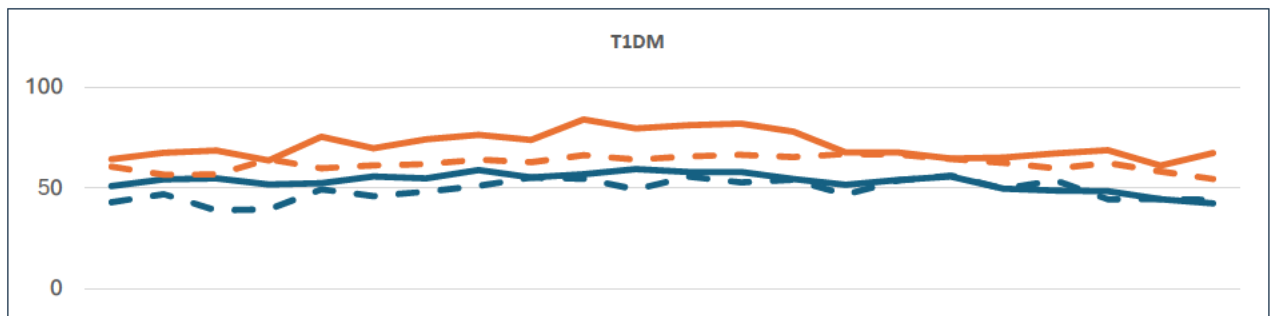
Higher fertility rates are observed in women with autoimmune conditions compared to those without such conditions, as reported in both databases across the time period 2000-2021. These conditions are all dermatological disorders (alopecia areata, vitiligo, psoriasis) and gastrointestinal disorders (coeliac disease, IBD including Crohn's disease or ulcerative colitis), SLE, Sjogren's syndrome and T1DM. However, few of the conditions report lower fertility rates in women with the condition than without, like Addison's disease, ankylosing spondylitis.

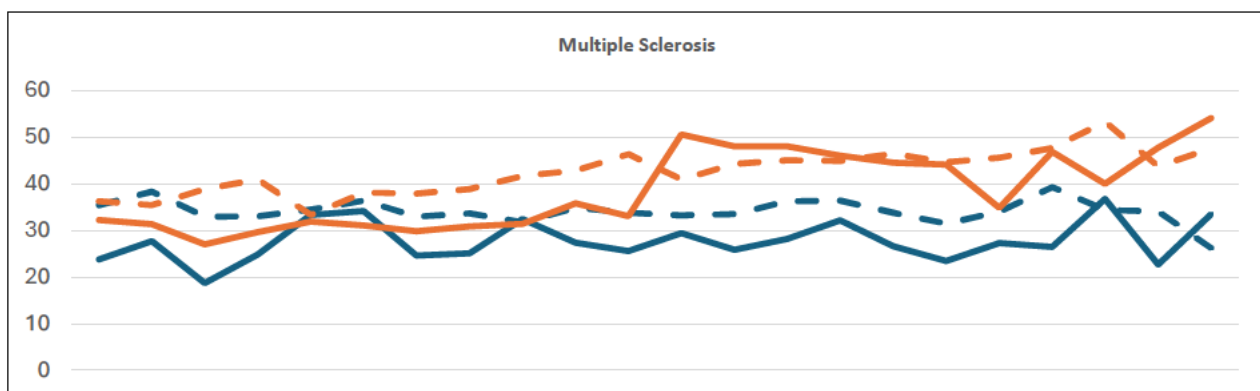
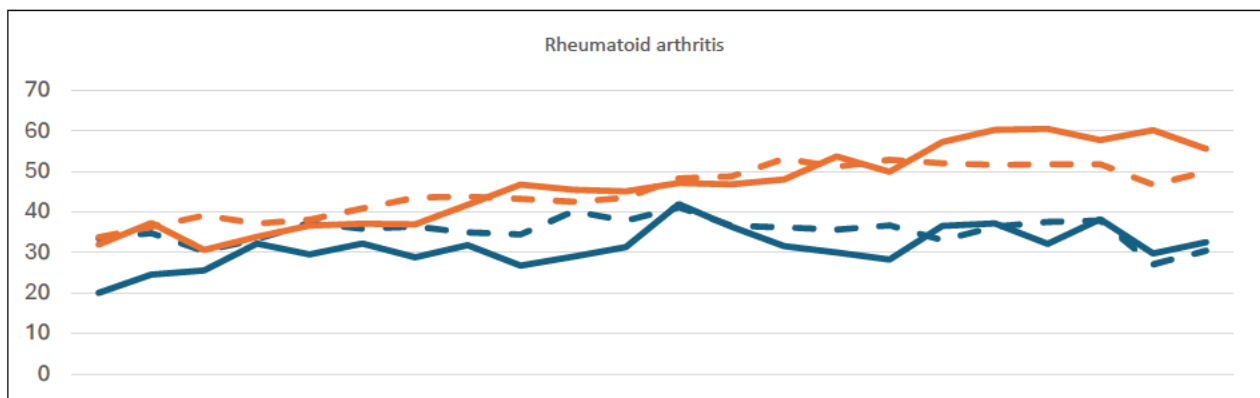
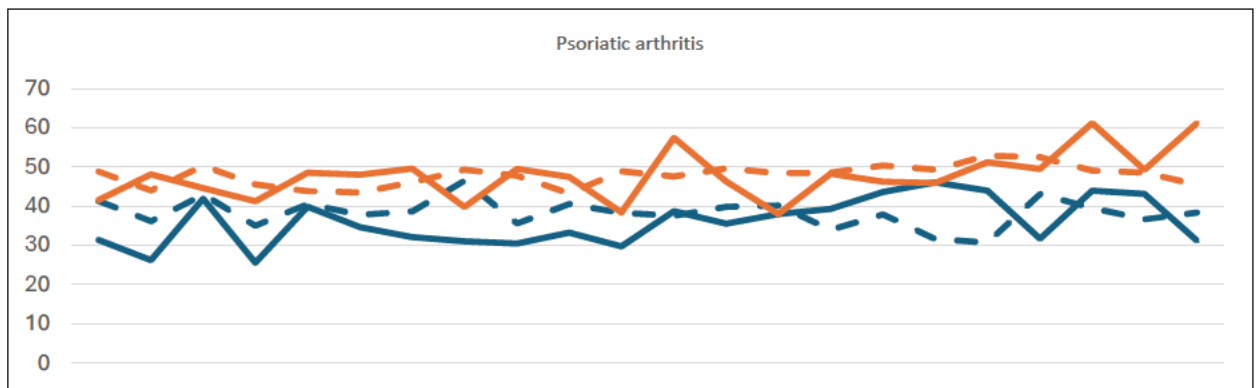
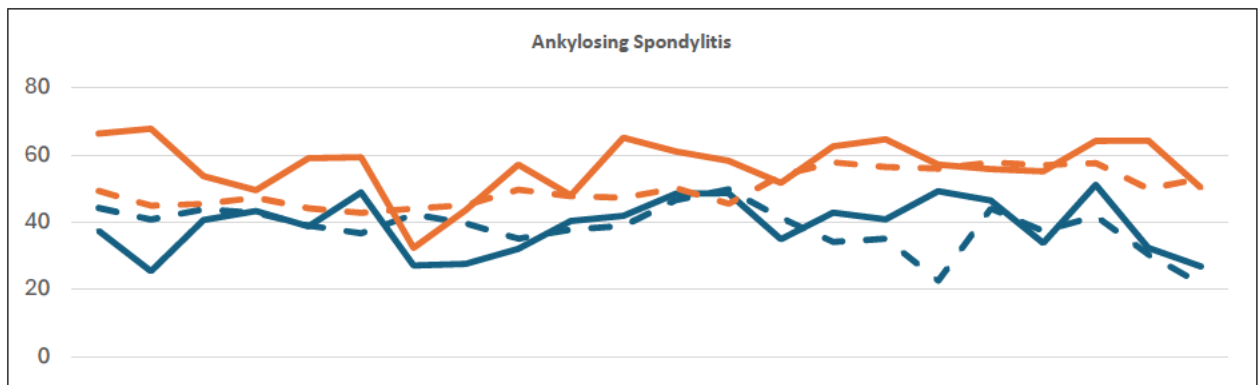
Psoriatic arthritis and rheumatoid arthritis showed variable fertility trends over time. In the first decade (appx 2000-2010), women with these conditions had lower fertility rates compared to those without, but this trend reversed in the later decade (2011-2021). There was also variation between datasets: the Aurum dataset showed an increase in fertility rates for women with psoriatic arthritis, while the Gold dataset indicated a decrease over time. In contrast, rheumatoid arthritis showed an increase in fertility trends in the later decade in Gold dataset while decrease in Aurum dataset.

Women with systemic sclerosis reported to have lower fertility rates than without the condition, however the trend is reversed after 2018. Fertility rates in women with multiple sclerosis or myasthenia gravis been lower than those in women without the condition. However, following 2020, fertility rates among women with MS have shown an improvement, with that are now equal to or even higher than those observed in women without these conditions. Over time, fertility trends show an increase in women with most of the autoimmune diseases. However, women with alopecia areata, psoriasis, Grave's disease, Hashimoto thyroiditis or ankylosing spondylitis show decrease in the fertility trends.









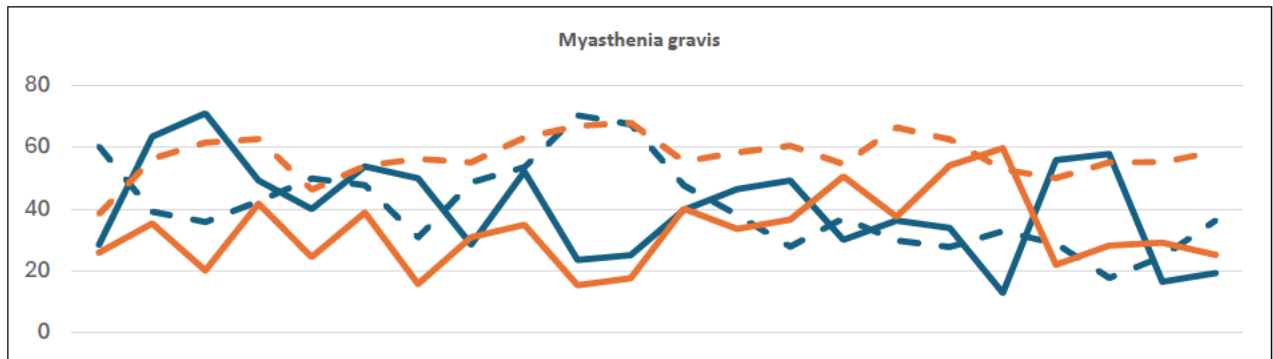


Figure 3.3 Fertility rates of women with individual autoimmune diseases and without in CPRD Gold and Aurum (2000-2021)

Table 3.16 Fertility rates of women with individual autoimmune diseases and without in CPRD Gold and Aurum (2000-2021)

	CPRD Gold		CPRD Aurum	
	No Sjogren syndrome	Sjogren syndrome	No Sjogren syndrome	Sjogren syndrome
Year 2000	46.69 (33.04 - 64.08)	15.07 (3.11 - 44.04)	27.41 (20.47 - 35.94)	22.50 (11.23 - 40.27)
Year 2001	28.39 (18.37 - 41.90)	17.31 (4.72 - 44.33)	38.97 (30.55 - 49.00)	31.73 (17.76 - 52.34)
Year 2002	25.24 (16.17 - 37.56)	36.80 (16.83 - 69.85)	23.84 (17.39 - 31.90)	42.50 (25.96 - 65.63)
Year 2003	36.91 (26.25 - 50.46)	3.88 (0.10 - 21.60)	28.28 (21.12 - 37.09)	31.04 (16.97 - 52.08)
Year 2004	26.84 (18.11 - 38.32)	14.65 (3.99 - 37.50)	36.40 (27.97 - 46.57)	41.90 (24.83 - 66.23)
Year 2005	34.54 (24.90 - 46.69)	29.78 (13.62 - 56.52)	36.60 (28.13 - 46.83)	31.42 (16.73 - 53.73)
Year 2006	24.45 (16.49 - 34.90)	29.94 (13.69 - 56.84)	33.06 (25.04 - 42.83)	49.39 (30.17 - 76.28)
Year 2007	37.94 (27.68 - 50.77)	17.12 (5.56 - 39.96)	24.76 (17.99 - 33.24)	30.45 (16.21 - 52.07)
Year 2008	31.71 (22.21 - 43.90)	36.29 (17.40 - 66.74)	29.56 (22.14 - 38.66)	46.43 (28.36 - 71.71)
Year 2009	26.93 (18.03 - 38.67)	11.37 (2.35 - 33.24)	38.57 (30.07 - 48.74)	44.36 (26.71 - 69.27)
Year 2010	28.77 (19.27 - 41.32)	25.04 (9.19 - 54.51)	46.43 (37.09 - 57.41)	46.68 (28.51 - 72.09)
Year 2011	32.88 (22.49 - 46.42)	17.27 (4.70 - 44.21)	42.29 (33.43 - 52.78)	32.44 (17.73 - 54.42)
Year 2012	37.31 (26.13 - 51.65)	21.71 (7.05 - 50.65)	42.07 (33.20 - 52.58)	48.03 (29.73 - 73.42)
Year 2013	39.11 (27.24 - 54.40)	47.22 (22.64 - 86.84)	47.03 (37.62 - 58.09)	64.15 (42.62 - 92.71)
Year 2014	26.28 (16.27 - 40.18)	41.68 (18.00 - 82.13)	44.94 (36.04 - 55.36)	39.70 (23.53 - 62.74)
Year 2015	50.83 (35.97 - 69.77)	17.91 (3.69 - 52.34)	56.67 (46.79 - 68.02)	71.13 (49.26 - 99.39)
Year 2016	39.75 (25.73 - 58.68)	33.09 (10.74 - 77.22)	48.90 (40.15 - 58.99)	46.35 (29.70 - 68.96)
Year 2017	32.17 (19.37 - 50.24)	35.84 (11.64 - 83.65)	45.71 (37.42 - 55.28)	61.61 (42.66 - 86.09)
Year 2018	30.10 (17.54 - 48.20)	53.85 (21.65 - 110.96)	46.69 (38.41 - 56.23)	70.99 (50.72 - 96.67)
Year 2019	33.16 (19.32 - 53.10)	53.19 (19.52 - 115.78)	38.70 (31.31 - 47.30)	49.46 (32.86 - 71.48)
Year 2020	34.52 (18.87 - 57.91)	20.57 (2.49 - 74.31)	53.56 (44.82 - 63.52)	42.21 (27.31 - 62.31)
Year 2021	13.13 (4.26 - 30.65)	21.75 (2.63 - 78.57)	44.58 (36.61 - 53.78)	59.86 (41.69 - 83.25)
	No SLE	SLE	No SLE	SLE
Year 2000	48.54 (40.62 - 57.57)	40.91 (27.18 - 59.12)	47.58 (42.91 - 52.61)	55.17 (45.38 - 66.44)
Year 2001	36.50 (30.13 - 43.81)	23.82 (14.34 - 37.20)	50.48 (45.66 - 55.67)	43.83 (35.16 - 54.00)
Year 2002	38.75 (32.58 - 45.76)	33.14 (22.20 - 47.60)	47.69 (43.02 - 52.73)	50.93 (41.53 - 61.83)
Year 2003	40.40 (34.44 - 47.10)	41.26 (29.61 - 55.98)	46.81 (42.20 - 51.79)	46.19 (37.24 - 56.65)
Year 2004	40.11 (34.49 - 46.38)	39.35 (28.59 - 52.83)	50.78 (46.00 - 55.92)	53.26 (43.60 - 64.41)
Year 2005	41.38 (35.92 - 47.44)	36.47 (26.60 - 48.79)	47.64 (43.00 - 52.63)	43.75 (35.04 - 53.97)
Year 2006	43.04 (37.46 - 49.21)	49.96 (38.21 - 64.17)	51.11 (46.34 - 56.24)	60.17 (49.93 - 71.89)
Year 2007	40.96 (35.46 - 47.06)	32.74 (23.28 - 44.76)	51.36 (46.61 - 56.46)	57.72 (47.74 - 69.18)
Year 2008	43.39 (37.73 - 49.66)	42.76 (31.84 - 56.23)	52.35 (47.58 - 57.48)	52.52 (43.08 - 63.41)
Year 2009	41.90 (36.28 - 48.14)	44.95 (33.67 - 58.80)	53.74 (48.93 - 58.89)	60.12 (50.01 - 71.69)
Year 2010	39.86 (34.31 - 46.05)	36.10 (25.90 - 48.97)	56.17 (51.26 - 61.42)	61.11 (50.91 - 72.76)
Year 2011	46.70 (40.64 - 53.41)	43.65 (32.18 - 57.87)	59.52 (54.47 - 64.90)	64.69 (54.24 - 76.57)
Year 2012	38.86 (33.28 - 45.10)	38.91 (28.04 - 52.60)	58.80 (53.86 - 64.08)	63.67 (53.46 - 75.27)
Year 2013	43.46 (37.39 - 50.23)	36.29 (25.55 - 50.02)	57.44 (52.54 - 62.67)	59.97 (50.11 - 71.21)
Year 2014	47.75 (40.97 - 55.32)	39.55 (27.70 - 54.76)	54.30 (49.57 - 59.36)	56.58 (47.02 - 67.51)

Year 2015	37.51 (31.12 - 44.82)	52.77 (37.70 - 71.85)	61.52 (56.50 - 66.86)	59.23 (49.49 - 70.33)
Year 2016	38.16 (30.98 - 46.50)	27.66 (16.11 - 44.28)	52.93 (48.30 - 57.88)	67.03 (56.67 - 78.74)
Year 2017	47.92 (39.39 - 57.76)	47.81 (31.23 - 70.05)	56.79 (52.00 - 61.89)	57.06 (47.57 - 67.90)
Year 2018	43.29 (34.77 - 53.28)	49.35 (31.94 - 72.86)	52.64 (48.09 - 57.51)	58.33 (48.77 - 69.21)
Year 2019	39.58 (31.13 - 49.61)	39.40 (23.35 - 62.27)	51.46 (46.94 - 56.29)	47.45 (38.85 - 57.39)
Year 2020	40.19 (31.27 - 50.86)	29.56 (15.28 - 51.64)	48.08 (43.71 - 52.77)	48.46 (39.75 - 58.51)
Year 2021	29.41 (21.37 - 39.48)	32.24 (16.66 - 56.31)	44.70 (40.41 - 49.32)	50.24 (41.21 - 60.66)
	No Systemic sclerosis	Systemic sclerosis	No Systemic sclerosis	Systemic sclerosis
Year 2000	49.68 (30.75 - 75.94)	28.51 (5.88 - 83.32)	38.46 (29.05 - 49.94)	37.74 (20.63 - 63.32)
Year 2001	37.25 (22.43 - 58.17)	23.32 (4.81 - 68.15)	31.82 (23.12 - 42.72)	42.18 (23.61 - 69.58)
Year 2002	30.92 (18.01 - 49.51)	34.68 (11.26 - 80.93)	46.21 (35.43 - 59.24)	40.97 (22.40 - 68.73)
Year 2003	45.10 (30.65 - 64.02)	25.58 (6.97 - 65.49)	38.53 (28.69 - 50.65)	33.36 (16.66 - 59.70)
Year 2004	37.05 (25.00 - 52.89)	26.28 (8.53 - 61.33)	41.85 (31.62 - 54.35)	21.28 (8.55 - 43.84)
Year 2005	40.74 (28.53 - 56.40)	35.97 (15.53 - 70.87)	37.46 (27.80 - 49.39)	60.90 (37.20 - 94.05)
Year 2006	37.29 (25.67 - 52.37)	36.12 (15.59 - 71.17)	48.52 (37.45 - 61.85)	46.38 (25.96 - 76.50)
Year 2007	35.10 (23.85 - 49.82)	41.91 (19.16 - 79.55)	56.75 (44.71 - 71.03)	49.63 (28.37 - 80.60)
Year 2008	53.43 (39.26 - 71.04)	9.34 (1.13 - 33.72)	42.55 (32.15 - 55.26)	49.42 (28.25 - 80.25)
Year 2009	54.51 (40.05 - 72.49)	69.16 (38.71 - 114.06)	63.31 (50.43 - 78.49)	47.20 (26.42 - 77.86)
Year 2010	39.62 (27.27 - 55.64)	38.63 (16.68 - 76.11)	58.97 (46.46 - 73.81)	50.37 (28.79 - 81.79)
Year 2011	38.50 (25.98 - 54.97)	55.83 (27.87 - 99.89)	60.26 (47.55 - 75.31)	41.49 (22.09 - 70.94)
Year 2012	30.75 (19.70 - 45.75)	20.78 (5.66 - 53.20)	55.30 (43.27 - 69.65)	56.26 (33.34 - 88.92)
Year 2013	23.56 (13.72 - 37.72)	61.21 (30.56 - 109.53)	58.64 (46.05 - 73.62)	57.76 (34.23 - 91.29)
Year 2014	50.05 (34.46 - 70.29)	39.17 (14.37 - 85.26)	47.36 (35.96 - 61.23)	43.72 (23.28 - 74.76)
Year 2015	35.21 (21.51 - 54.38)	92.64 (49.33 - 158.42)	62.33 (49.19 - 77.90)	49.58 (27.75 - 81.78)
Year 2016	59.65 (39.95 - 85.67)	48.88 (17.94 - 106.39)	56.55 (44.48 - 70.88)	48.69 (27.25 - 80.31)
Year 2017	34.67 (19.82 - 56.31)	35.35 (9.63 - 90.50)	49.57 (38.09 - 63.43)	38.02 (19.65 - 66.42)
Year 2018	38.17 (22.24 - 61.11)	18.13 (2.20 - 65.49)	69.05 (55.52 - 84.87)	31.77 (15.24 - 58.43)
Year 2019	35.81 (20.04 - 59.06)	95.01 (45.56 - 174.72)	58.50 (46.24 - 73.01)	72.26 (45.81 - 108.43)
Year 2020	43.21 (24.70 - 70.16)	130.10 (67.22 - 227.25)	48.13 (36.98 - 61.58)	40.31 (21.46 - 68.93)
Year 2021	39.40 (19.67 - 70.50)	13.96 (0.35 - 77.79)	46.27 (35.47 - 59.31)	63.74 (39.46 - 97.44)
	No Alopecia	Alopecia	No Alopecia	Alopecia
Year 2000	54.49 (49.08 - 60.34)	53.50 (43.33 - 65.33)	52.87 (49.09 - 56.88)	65.33 (57.16 - 74.34)
Year 2001	53.52 (48.45 - 58.97)	60.41 (50.16 - 72.13)	52.67 (48.92 - 56.64)	71.93 (63.38 - 81.30)
Year 2002	51.67 (46.98 - 56.70)	58.24 (48.59 - 69.25)	57.33 (53.45 - 61.43)	66.92 (58.74 - 75.92)
Year 2003	53.46 (48.95 - 58.27)	57.97 (48.89 - 68.25)	56.95 (53.16 - 60.95)	67.12 (59.06 - 75.98)
Year 2004	53.45 (49.21 - 57.97)	55.91 (47.45 - 65.44)	56.64 (52.93 - 60.53)	68.11 (60.15 - 76.85)
Year 2005	52.02 (48.07 - 56.20)	58.84 (50.60 - 68.04)	55.90 (52.34 - 59.64)	66.31 (58.62 - 74.73)
Year 2006	47.74 (44.01 - 51.71)	52.85 (45.18 - 61.45)	61.21 (57.56 - 65.03)	64.42 (57.06 - 72.47)
Year 2007	51.64 (47.78 - 55.72)	62.11 (53.80 - 71.34)	60.26 (56.76 - 63.93)	70.03 (62.52 - 78.19)
Year 2008	55.80 (51.82 - 60.00)	62.16 (53.90 - 71.32)	61.67 (58.22 - 65.28)	70.42 (63.09 - 78.36)
Year 2009	56.87 (52.89 - 61.08)	57.38 (49.51 - 66.15)	64.45 (61.02 - 68.02)	71.05 (63.88 - 78.81)
Year 2010	53.78 (49.91 - 57.87)	50.79 (43.40 - 59.08)	65.72 (62.36 - 69.22)	70.30 (63.36 - 77.79)
Year 2011	55.86 (51.91 - 60.03)	63.82 (55.49 - 73.03)	65.50 (62.25 - 68.87)	76.10 (69.10 - 83.62)
Year 2012	53.51 (49.64 - 57.60)	63.38 (55.06 - 72.61)	62.21 (59.15 - 65.40)	77.85 (70.99 - 85.19)
Year 2013	51.82 (47.96 - 55.91)	60.74 (52.47 - 69.94)	67.59 (64.46 - 70.84)	81.02 (74.23 - 88.26)
Year 2014	50.54 (46.62 - 54.71)	52.74 (44.79 - 61.69)	71.36 (68.23 - 74.60)	79.17 (72.63 - 86.15)
Year 2015	51.65 (47.51 - 56.05)	49.80 (41.78 - 58.90)	71.72 (68.68 - 74.85)	80.50 (74.09 - 87.33)
Year 2016	51.40 (46.99 - 56.12)	59.35 (50.02 - 69.92)	64.69 (61.91 - 67.56)	75.26 (69.29 - 81.62)
Year 2017	50.57 (45.97 - 55.50)	55.19 (45.72 - 66.04)	63.20 (60.54 - 65.95)	72.22 (66.55 - 78.26)
Year 2018	48.32 (43.65 - 53.34)	56.38 (46.51 - 67.73)	64.09 (61.50 - 66.75)	79.26 (73.51 - 85.35)
Year 2019	49.60 (44.76 - 54.83)	53.06 (43.27 - 64.42)	67.13 (64.54 - 69.79)	73.82 (68.40 - 79.54)
Year 2020	39.91 (35.40 - 44.83)	41.09 (32.21 - 51.66)	59.00 (56.63 - 61.44)	70.95 (65.78 - 76.41)
Year 2021	40.94 (36.09 - 46.26)	47.61 (37.38 - 59.77)	59.43 (57.08 - 61.84)	70.15 (65.08 - 75.50)
	No Psoriasis	Psoriasis	No Psoriasis	Psoriasis
Year 2000	55.13 (53.29 - 57.02)	60.29 (56.54 - 64.23)	57.55 (56.25 - 58.88)	67.61 (64.84 - 70.47)
Year 2001	53.98 (52.30 - 55.71)	58.23 (54.82 - 61.81)	57.79 (56.50 - 59.11)	66.89 (64.15 - 69.72)
Year 2002	53.05 (51.48 - 54.67)	58.70 (55.44 - 62.11)	59.90 (58.59 - 61.23)	64.24 (61.58 - 66.99)
Year 2003	56.15 (54.63 - 57.71)	59.31 (56.23 - 62.52)	59.87 (58.58 - 61.18)	67.29 (64.60 - 70.07)
Year 2004	54.79 (53.37 - 56.23)	58.55 (55.68 - 61.54)	59.96 (58.69 - 61.25)	70.70 (67.98 - 73.51)
Year 2005	54.64 (53.31 - 56.00)	59.17 (56.43 - 62.01)	59.40 (58.15 - 60.66)	63.54 (60.99 - 66.17)
Year 2006	55.22 (53.90 - 56.56)	58.56 (55.87 - 61.34)	62.16 (60.91 - 63.43)	68.02 (65.42 - 70.69)
Year 2007	56.60 (55.27 - 57.95)	59.80 (57.09 - 62.61)	62.76 (61.52 - 64.02)	69.53 (66.94 - 72.20)
Year 2008	55.31 (54.00 - 56.64)	57.86 (55.20 - 60.60)	63.72 (62.49 - 64.96)	70.60 (68.03 - 73.24)
Year 2009	58.53 (57.18 - 59.90)	61.66 (58.92 - 64.50)	64.17 (62.95 - 65.40)	71.15 (68.59 - 73.77)
Year 2010	60.59 (59.21 - 61.99)	62.26 (59.49 - 65.13)	65.07 (63.86 - 66.30)	75.46 (72.86 - 78.12)
Year 2011	57.99 (56.62 - 59.38)	64.53 (61.67 - 67.49)	66.19 (64.98 - 67.41)	76.25 (73.67 - 78.90)
Year 2012	56.43 (55.07 - 57.82)	62.10 (59.27 - 65.04)	65.47 (64.28 - 66.67)	75.47 (72.93 - 78.08)

Year 2013	55.96 (54.57 - 57.38)	62.31 (59.39 - 65.33)	66.79 (65.59 - 68.01)	77.84 (75.28 - 80.47)
Year 2014	53.89 (52.47 - 55.34)	59.41 (56.44 - 62.50)	67.42 (66.22 - 68.63)	76.64 (74.10 - 79.25)
Year 2015	54.18 (52.68 - 55.72)	59.90 (56.76 - 63.18)	66.79 (65.61 - 67.98)	74.77 (72.30 - 77.32)
Year 2016	51.42 (49.85 - 53.03)	59.01 (55.66 - 62.51)	65.57 (64.43 - 66.73)	72.31 (69.91 - 74.78)
Year 2017	47.61 (46.01 - 49.25)	58.56 (55.03 - 62.25)	64.13 (63.01 - 65.27)	70.35 (68.01 - 72.76)
Year 2018	48.97 (47.29 - 50.70)	57.35 (53.73 - 61.15)	63.43 (62.33 - 64.54)	71.96 (69.61 - 74.36)
Year 2019	46.76 (45.07 - 48.50)	54.30 (50.68 - 58.11)	63.11 (62.02 - 64.22)	68.67 (66.39 - 71.01)
Year 2020	43.74 (42.04 - 45.50)	49.63 (46.03 - 53.43)	56.84 (55.80 - 57.89)	67.38 (65.12 - 69.69)
Year 2021	40.21 (38.49 - 42.00)	45.81 (42.18 - 49.68)	55.67 (54.64 - 56.72)	66.28 (64.03 - 68.59)
	No Vitiligo	Vitiligo	No Vitiligo	Vitiligo
Year 2000	55.64 (49.41 - 62.44)	49.20 (38.13 - 62.49)	49.15 (45.10 - 53.47)	69.36 (60.01 - 79.75)
Year 2001	51.28 (45.69 - 57.36)	48.76 (38.41 - 61.03)	55.35 (51.10 - 59.86)	66.55 (57.49 - 76.63)
Year 2002	53.16 (47.75 - 59.01)	60.62 (49.53 - 73.46)	52.85 (48.74 - 57.20)	59.08 (50.67 - 68.48)
Year 2003	50.44 (45.46 - 55.83)	54.66 (44.66 - 66.23)	60.46 (56.17 - 65.00)	76.00 (66.57 - 86.39)
Year 2004	54.49 (49.50 - 59.85)	53.58 (44.08 - 64.52)	60.25 (56.07 - 64.66)	68.29 (59.57 - 77.94)
Year 2005	56.10 (51.29 - 61.23)	51.87 (42.90 - 62.16)	59.79 (55.73 - 64.06)	66.40 (58.01 - 75.67)
Year 2006	54.66 (50.02 - 59.62)	61.58 (51.90 - 72.54)	64.04 (59.96 - 68.32)	75.49 (66.77 - 85.04)
Year 2007	57.25 (52.58 - 62.22)	63.59 (53.91 - 74.50)	71.04 (66.86 - 75.42)	78.70 (70.02 - 88.16)
Year 2008	56.79 (52.20 - 61.67)	48.21 (39.97 - 57.65)	64.05 (60.18 - 68.11)	66.55 (67.29 - 84.63)
Year 2009	67.02 (62.07 - 72.26)	62.89 (53.49 - 73.46)	72.23 (68.21 - 76.42)	72.95 (64.98 - 81.63)
Year 2010	55.86 (51.37 - 60.63)	65.14 (55.60 - 75.83)	70.66 (66.79 - 74.71)	73.20 (65.42 - 81.65)
Year 2011	62.81 (58.05 - 67.86)	58.11 (49.10 - 68.30)	70.59 (66.80 - 74.54)	77.82 (69.96 - 86.33)
Year 2012	55.88 (51.45 - 60.59)	64.38 (54.96 - 74.95)	67.88 (64.24 - 71.67)	73.57 (66.10 - 81.66)
Year 2013	58.79 (54.14 - 63.74)	64.84 (55.21 - 75.66)	69.11 (65.50 - 72.88)	72.88 (65.61 - 80.73)
Year 2014	55.22 (50.52 - 60.24)	61.19 (51.41 - 72.29)	66.52 (63.06 - 70.11)	78.03 (70.66 - 85.96)
Year 2015	58.85 (53.63 - 64.45)	63.19 (52.52 - 75.40)	69.04 (65.63 - 72.59)	66.82 (60.20 - 73.98)
Year 2016	54.39 (48.90 - 60.31)	56.07 (45.15 - 68.84)	67.97 (64.69 - 71.37)	66.26 (59.87 - 73.14)
Year 2017	53.88 (48.11 - 60.15)	57.94 (46.15 - 71.82)	64.11 (61.02 - 67.30)	67.07 (60.82 - 73.78)
Year 2018	48.60 (42.91 - 54.83)	40.81 (30.66 - 53.25)	65.20 (62.18 - 68.32)	67.54 (61.44 - 74.08)
Year 2019	49.95 (44.01 - 56.48)	47.85 (36.51 - 61.59)	60.34 (57.48 - 63.30)	68.83 (62.78 - 75.30)
Year 2020	42.77 (37.02 - 49.16)	50.22 (37.93 - 65.21)	54.79 (52.12 - 57.56)	63.55 (57.88 - 69.63)
Year 2021	48.15 (41.53 - 55.53)	51.08 (37.79 - 67.52)	57.46 (54.74 - 60.27)	65.33 (59.61 - 71.45)
	No Addison's disease	Addison's disease	No Addison's disease	Addison's disease
Year 2000	34.36 (17.15 - 61.49)	0.00 (0.00 - 48.10)	40.70 (27.84 - 57.45)	15.34 (3.16 - 44.82)
Year 2001	54.90 (33.53 - 84.79)	21.57 (2.61 - 77.93)	54.75 (39.29 - 74.28)	31.26 (11.47 - 68.05)
Year 2002	33.63 (17.91 - 57.51)	20.54 (2.49 - 74.20)	46.88 (32.46 - 65.51)	26.78 (8.70 - 62.49)
Year 2003	38.25 (22.28 - 61.24)	45.35 (14.73 - 105.84)	60.41 (44.22 - 80.57)	43.13 (18.62 - 84.99)
Year 2004	32.35 (18.84 - 51.79)	40.88 (13.27 - 95.41)	46.36 (32.47 - 64.18)	40.63 (17.54 - 80.07)
Year 2005	50.22 (33.63 - 72.12)	41.59 (15.26 - 90.53)	58.82 (43.22 - 78.22)	55.14 (27.53 - 98.66)
Year 2006	61.71 (43.22 - 85.43)	20.10 (4.15 - 58.74)	68.99 (52.52 - 88.99)	53.76 (26.84 - 96.20)
Year 2007	45.73 (30.14 - 66.54)	20.55 (4.24 - 60.06)	53.42 (38.96 - 71.48)	24.40 (7.92 - 56.95)
Year 2008	45.41 (29.67 - 66.54)	43.03 (15.79 - 93.65)	56.89 (41.95 - 75.43)	43.96 (20.10 - 83.44)
Year 2009	59.01 (41.11 - 82.07)	82.63 (42.70 - 144.34)	48.08 (34.19 - 65.73)	54.98 (27.45 - 98.38)
Year 2010	46.33 (30.79 - 66.97)	41.47 (15.22 - 90.26)	63.91 (48.28 - 82.99)	44.17 (20.20 - 83.84)
Year 2011	47.36 (30.94 - 69.40)	36.69 (11.91 - 85.62)	53.11 (39.16 - 70.42)	37.04 (15.99 - 72.99)
Year 2012	41.65 (25.78 - 63.67)	64.95 (28.04 - 127.98)	59.14 (44.03 - 77.76)	60.97 (32.47 - 104.27)
Year 2013	34.70 (20.22 - 55.56)	16.95 (2.05 - 61.23)	51.86 (37.97 - 69.17)	36.88 (15.92 - 72.67)
Year 2014	56.15 (35.97 - 83.54)	9.76 (0.25 - 54.40)	49.34 (35.99 - 66.02)	54.07 (27.94 - 94.44)
Year 2015	44.92 (26.62 - 71.00)	52.54 (17.06 - 122.62)	63.14 (47.94 - 81.62)	61.64 (33.70 - 103.43)
Year 2016	56.13 (33.79 - 87.65)	24.28 (2.94 - 87.71)	62.27 (47.75 - 79.83)	46.98 (23.45 - 84.07)
Year 2017	44.57 (23.73 - 76.21)	26.81 (3.25 - 96.86)	56.89 (43.20 - 73.54)	67.67 (39.42 - 108.35)
Year 2018	46.74 (26.16 - 77.09)	27.11 (3.28 - 97.94)	58.33 (45.02 - 74.35)	43.37 (21.65 - 77.61)
Year 2019	51.57 (28.86 - 85.06)	41.83 (8.63 - 122.25)	69.21 (54.53 - 86.62)	23.19 (8.51 - 50.48)
Year 2020	19.09 (6.20 - 44.55)	95.46 (35.03 - 207.78)	55.20 (42.02 - 71.21)	34.41 (15.74 - 65.33)
Year 2021	28.68 (10.52 - 62.42)	0.00 (0.00 - 73.59)	63.85 (49.78 - 80.67)	49.31 (26.25 - 84.32)
	No Grave	Grave	No Grave	Grave
Year 2000	40.40 (35.97 - 45.22)	43.21 (34.31 - 53.71)	45.68 (42.47 - 49.08)	53.90 (47.06 - 61.46)
Year 2001	39.36 (35.33 - 43.73)	37.38 (29.73 - 46.39)	47.37 (44.12 - 50.80)	54.49 (47.61 - 62.07)
Year 2002	37.78 (34.05 - 41.81)	42.22 (34.53 - 51.11)	49.39 (46.10 - 52.85)	49.67 (43.17 - 56.88)
Year 2003	45.37 (41.58 - 49.42)	37.26 (30.53 - 45.02)	52.88 (49.53 - 56.40)	53.80 (47.10 - 61.19)
Year 2004	41.46 (38.06 - 45.08)	45.93 (38.85 - 53.93)	49.40 (46.23 - 52.72)	57.90 (51.07 - 65.38)
Year 2005	39.63 (36.50 - 42.97)	44.14 (37.58 - 51.50)	51.92 (48.75 - 55.23)	59.86 (53.05 - 67.29)
Year 2006	40.25 (37.11 - 43.58)	46.24 (39.60 - 53.66)	55.54 (52.38 - 58.84)	68.06 (61.00 - 75.72)
Year 2007	44.51 (41.23 - 48.00)	51.91 (44.86 - 59.75)	55.76 (52.67 - 58.99)	66.95 (60.11 - 74.35)
Year 2008	40.09 (37.00 - 43.37)	50.76 (43.83 - 58.47)	57.08 (54.04 - 60.25)	66.26 (59.65 - 73.41)
Year 2009	48.78 (45.38 - 52.37)	45.16 (38.66 - 52.44)	56.28 (53.34 - 59.34)	67.80 (61.28 - 74.82)
Year 2010	43.49 (40.28 - 46.89)	51.61 (44.60 - 59.40)	59.68 (56.72 - 62.75)	74.15 (67.48 - 81.30)

Year 2011	45.45 (42.14 - 48.94)	47.10 (40.38 - 54.62)	61.01 (58.11 - 64.02)	75.70 (69.13 - 82.71)
Year 2012	40.30 (37.19 - 43.60)	46.34 (39.67 - 53.81)	62.56 (59.69 - 65.53)	71.01 (64.82 - 77.63)
Year 2013	44.97 (41.62 - 48.53)	49.26 (42.25 - 57.10)	65.15 (62.24 - 68.16)	70.77 (64.70 - 77.26)
Year 2014	42.36 (38.99 - 45.94)	48.83 (41.60 - 56.96)	60.26 (57.52 - 63.09)	65.12 (59.37 - 71.28)
Year 2015	42.67 (39.15 - 46.43)	45.89 (38.56 - 54.22)	61.17 (58.48 - 63.96)	65.88 (60.23 - 71.91)
Year 2016	42.36 (38.55 - 46.44)	48.46 (40.34 - 57.74)	59.57 (57.00 - 62.23)	68.08 (62.52 - 74.01)
Year 2017	43.08 (39.09 - 47.37)	44.96 (36.77 - 54.42)	58.41 (55.93 - 60.97)	66.37 (61.01 - 72.08)
Year 2018	40.29 (36.33 - 44.57)	54.64 (45.41 - 65.19)	58.35 (55.93 - 60.85)	65.68 (60.47 - 71.21)
Year 2019	42.94 (38.78 - 47.42)	41.70 (33.49 - 51.31)	56.66 (54.30 - 59.10)	64.04 (58.97 - 69.43)
Year 2020	33.97 (30.13 - 38.16)	39.15 (30.94 - 48.86)	51.01 (48.79 - 53.30)	61.35 (56.44 - 66.57)
Year 2021	32.11 (28.16 - 36.46)	30.74 (23.16 - 40.01)	49.60 (47.41 - 51.86)	56.74 (52.04 - 61.75)
	No Hashimoto	Hashimoto	No Hashimoto	Hashimoto
Year 2000	30.10 (22.54 - 39.37)	41.96 (25.26 - 65.52)	45.82 (39.37 - 53.02)	47.08 (34.59 - 62.61)
Year 2001	34.07 (26.51 - 43.11)	11.59 (4.25 - 25.23)	36.85 (31.07 - 43.38)	45.50 (33.19 - 60.88)
Year 2002	41.62 (33.59 - 50.99)	41.27 (26.16 - 61.93)	47.83 (41.22 - 55.20)	50.80 (37.70 - 66.97)
Year 2003	42.31 (34.64 - 51.18)	43.37 (28.58 - 63.09)	56.49 (49.29 - 64.45)	55.00 (41.32 - 71.76)
Year 2004	38.07 (31.23 - 45.97)	31.61 (19.81 - 47.86)	48.53 (41.97 - 55.82)	49.05 (36.16 - 65.03)
Year 2005	41.18 (34.46 - 48.84)	41.06 (28.08 - 57.96)	55.63 (48.67 - 63.30)	52.13 (39.05 - 68.18)
Year 2006	38.19 (31.69 - 45.63)	36.26 (24.09 - 52.40)	48.49 (42.15 - 55.51)	63.18 (48.86 - 80.38)
Year 2007	45.00 (37.95 - 52.98)	43.95 (30.44 - 61.42)	59.01 (52.16 - 66.51)	58.62 (45.15 - 74.86)
Year 2008	53.29 (45.56 - 61.96)	44.00 (30.47 - 61.48)	58.24 (51.66 - 65.42)	66.65 (52.60 - 83.30)
Year 2009	51.56 (43.99 - 60.05)	50.06 (35.60 - 68.44)	56.11 (49.74 - 63.07)	59.75 (46.75 - 75.24)
Year 2010	45.73 (38.66 - 53.72)	59.57 (43.61 - 79.45)	64.87 (58.10 - 72.22)	75.31 (60.86 - 92.16)
Year 2011	50.44 (42.88 - 58.94)	43.05 (29.63 - 60.45)	64.93 (58.29 - 72.12)	73.04 (59.02 - 89.38)
Year 2012	54.58 (46.75 - 63.35)	51.95 (37.11 - 70.74)	67.58 (60.95 - 74.72)	59.06 (46.76 - 73.61)
Year 2013	52.47 (44.79 - 61.09)	40.24 (27.15 - 57.45)	62.72 (56.41 - 69.53)	79.46 (65.30 - 95.77)
Year 2014	52.42 (44.54 - 61.29)	38.91 (25.85 - 56.23)	72.14 (65.57 - 79.19)	74.96 (61.49 - 90.50)
Year 2015	53.86 (45.64 - 63.14)	53.12 (37.20 - 73.53)	66.80 (60.79 - 73.25)	63.60 (51.80 - 77.28)
Year 2016	53.50 (44.92 - 63.25)	38.95 (24.95 - 57.95)	63.61 (58.06 - 69.54)	62.96 (51.79 - 75.82)
Year 2017	42.97 (35.11 - 52.07)	44.91 (29.34 - 65.81)	63.07 (57.82 - 68.67)	68.57 (57.45 - 81.21)
Year 2018	46.56 (38.26 - 56.11)	51.92 (34.77 - 74.57)	60.30 (55.46 - 65.44)	56.77 (47.25 - 67.64)
Year 2019	50.41 (41.73 - 60.37)	44.09 (28.25 - 65.60)	62.41 (57.67 - 67.45)	64.69 (54.88 - 75.75)
Year 2020	45.42 (37.19 - 54.93)	35.77 (21.54 - 55.86)	56.10 (51.76 - 60.70)	60.77 (51.64 - 71.06)
Year 2021	39.70 (31.57 - 49.27)	38.32 (23.07 - 59.85)	59.22 (54.82 - 63.87)	61.02 (52.04 - 71.11)
	No T1DM	T1DM	No T1DM	T1DM
Year 2000	50.90 (46.40 - 55.72)	42.95 (34.98 - 52.19)	60.71 (57.68 - 63.84)	64.44 (58.36 - 70.98)
Year 2001	54.25 (50.07 - 58.69)	46.99 (39.43 - 55.59)	56.77 (53.91 - 59.74)	67.56 (61.42 - 74.13)
Year 2002	54.77 (50.89 - 58.88)	38.93 (32.55 - 46.19)	56.85 (54.05 - 59.77)	68.68 (62.62 - 75.18)
Year 2003	51.75 (48.30 - 55.38)	39.45 (33.56 - 46.08)	64.45 (61.54 - 67.47)	63.81 (58.08 - 69.95)
Year 2004	52.42 (49.21 - 55.77)	49.45 (43.32 - 56.21)	59.89 (57.12 - 62.75)	75.64 (69.50 - 82.18)
Year 2005	55.80 (52.72 - 59.01)	46.01 (40.51 - 52.06)	61.31 (58.56 - 64.16)	69.77 (63.95 - 75.98)
Year 2006	54.83 (51.83 - 57.95)	48.26 (42.73 - 54.30)	61.94 (59.20 - 64.77)	74.23 (68.30 - 80.54)
Year 2007	59.02 (55.93 - 62.23)	51.17 (45.51 - 57.34)	64.20 (61.44 - 67.05)	76.47 (70.50 - 82.82)
Year 2008	55.35 (52.39 - 58.43)	55.26 (49.42 - 61.61)	62.96 (60.27 - 65.74)	73.94 (68.16 - 80.09)
Year 2009	56.83 (53.83 - 59.96)	54.57 (48.76 - 60.89)	66.39 (63.65 - 69.23)	84.27 (78.13 - 90.76)
Year 2010	59.47 (56.39 - 62.68)	49.34 (43.78 - 55.40)	64.26 (61.58 - 67.02)	79.68 (73.75 - 85.95)
Year 2011	58.02 (54.92 - 61.25)	55.71 (49.74 - 62.20)	65.80 (63.10 - 68.58)	81.29 (75.31 - 87.61)
Year 2012	57.95 (54.85 - 61.18)	52.82 (46.98 - 59.20)	66.66 (63.96 - 69.44)	82.09 (76.13 - 88.39)
Year 2013	54.45 (51.38 - 57.66)	54.09 (48.03 - 60.69)	65.55 (62.87 - 68.31)	78.14 (72.36 - 84.25)
Year 2014	51.55 (48.45 - 54.80)	46.83 (41.02 - 53.23)	67.03 (64.35 - 69.80)	67.81 (62.47 - 73.49)
Year 2015	53.98 (50.66 - 57.47)	53.81 (47.28 - 60.99)	66.71 (64.09 - 69.42)	67.80 (62.54 - 73.39)
Year 2016	55.82 (52.23 - 59.58)	56.23 (49.12 - 64.08)	64.63 (62.08 - 67.26)	64.71 (59.65 - 70.09)
Year 2017	49.71 (46.19 - 53.43)	49.91 (42.98 - 57.65)	62.63 (60.15 - 65.18)	65.25 (60.22 - 70.58)
Year 2018	48.70 (45.16 - 52.46)	53.83 (46.50 - 61.98)	59.94 (57.55 - 62.40)	67.32 (62.28 - 72.65)
Year 2019	48.48 (44.88 - 52.30)	44.38 (37.62 - 51.99)	62.52 (60.09 - 65.03)	68.90 (63.83 - 74.26)
Year 2020	44.39 (40.82 - 48.19)	44.63 (37.62 - 52.58)	58.26 (55.91 - 60.68)	61.35 (56.57 - 66.43)
Year 2021	42.47 (38.80 - 46.39)	44.12 (36.81 - 52.46)	54.56 (52.27 - 56.91)	67.48 (62.44 - 72.82)
	No Ankylosing spondylitis	Ankylosing spondylitis	No Ankylosing spondylitis	Ankylosing spondylitis
Year 2000	44.25 (33.69 - 57.08)	37.40 (19.32 - 65.32)	49.24 (42.47 - 56.78)	66.41 (51.14 - 84.80)
Year 2001	40.80 (31.36 - 52.21)	25.41 (12.19 - 46.74)	44.89 (38.40 - 52.17)	67.84 (52.24 - 86.62)
Year 2002	43.82 (34.58 - 54.77)	40.62 (24.07 - 64.19)	45.51 (39.07 - 52.71)	53.70 (40.11 - 70.43)
Year 2003	42.81 (34.29 - 52.81)	43.32 (27.15 - 65.58)	47.24 (40.65 - 54.61)	49.45 (36.46 - 65.56)
Year 2004	39.01 (31.37 - 47.95)	38.70 (24.26 - 58.60)	44.12 (37.67 - 51.37)	59.00 (44.57 - 76.62)
Year 2005	36.65 (29.54 - 44.94)	48.84 (33.18 - 69.32)	42.77 (36.36 - 49.98)	59.29 (44.54 - 77.36)
Year 2006	42.33 (34.72 - 51.10)	27.03 (15.75 - 43.28)	44.00 (37.46 - 51.34)	32.35 (21.66 - 46.46)
Year 2007	39.68 (32.21 - 48.36)	27.53 (16.04 - 44.08)	45.05 (38.40 - 52.52)	43.54 (30.96 - 59.52)

Year 2008	35.07 (27.97 - 43.42)	32.03 (19 29 - 50.03)	49.64 (42.54 - 57.59)	57.14 (42.41 - 75.33)
Year 2009	37.84 (30.35 - 46.62)	40.34 (25.57 - 60.53)	47.79 (40.84 - 55.59)	47.95 (34.41 - 65.05)
Year 2010	38.86 (31.04 - 48.06)	41.85 (26.53 - 62.80)	47.31 (40.28 - 55.21)	65.17 (49.10 - 84.83)
Year 2011	46.64 (37.69 - 57.07)	48.44 (31.04 - 72.07)	50.17 (42.98 - 58.23)	61.06 (45.46 - 80.28)
Year 2012	49.75 (40.39 - 60.63)	48.64 (30 83 - 72.99)	45.44 (38.63 - 53.10)	58.25 (43.09 - 77.01)
Year 2013	41.31 (32.54 - 51.70)	34.93 (19 96 - 56.72)	53.93 (46.39 - 62.33)	51.67 (37.39 - 69.60)
Year 2014	34.13 (25.78 - 44.33)	42.82 (24 95 - 68.56)	57.82 (50.08 - 66.41)	62.57 (46.59 - 82.27)
Year 2015	35.12 (26.06 - 46.30)	40.84 (22 33 - 68.53)	56.42 (48.74 - 64.97)	64.63 (48.41 - 84.54)
Year 2016	22.61 (14.77 - 33.13)	49.23 (26 92 - 82.60)	56.00 (48.58 - 64.23)	57.13 (42.27 - 75.53)
Year 2017	44.02 (32.46 - 58.37)	46.46 (24.01 - 81.16)	57.73 (50.36 - 65.89)	55.77 (41.52 - 73.32)
Year 2018	37.32 (26.41 - 51.22)	33.74 (14.57 - 66.48)	57.00 (49.77 - 65.00)	55.13 (41.17 - 72.30)
Year 2019	41.80 (29.86 - 56.92)	51.18 (26.45 - 89.40)	57.60 (50.54 - 65.37)	64.19 (49.22 - 82.29)
Year 2020	30.38 (20.19 - 43.90)	32.35 (13.00 - 66.64)	49.93 (43.49 - 57.05)	64.26 (49.70 - 81.75)
Year 2021	21.64 (12.60 - 34.64)	26.76 (8.69 - 62.45)	53.03 (46.48 - 60.24)	50.25 (37.64 - 65.73)
	No PSA	PSA	No PSA	PSA
Year 2000	41.27 (33.39 - 50.45)	31.31 (18.56 - 49.49)	48.83 (43.43 - 54.71)	41.59 (32.09 - 53.00)
Year 2001	36.15 (29.38 - 44.02)	26.15 (15.50 - 41.33)	43.97 (38.86 - 49.58)	48.11 (37.85 - 60.31)
Year 2002	42.93 (35.95 - 50.88)	41.89 (28 65 - 59.13)	50.32 (44.84 - 56.29)	44.56 (34.67 - 56.39)
Year 2003	35.01 (29.07 - 41.80)	25.58 (16.03 - 38.73)	45.55 (40.37 - 51.21)	41.19 (31.72 - 52.60)
Year 2004	40.54 (34.52 - 47.31)	39.86 (28 35 - 54.49)	43.83 (38.76 - 49.38)	48.51 (38.16 - 60.81)
Year 2005	37.78 (32.28 - 43.94)	34.61 (24.49 - 47.51)	43.51 (38.45 - 49.04)	47.98 (37.68 - 60.24)
Year 2006	38.68 (33.12 - 44.91)	32.11 (22.49 - 44.45)	46.11 (40.92 - 51.77)	49.53 (39.02 - 61.99)
Year 2007	46.51 (40.39 - 53.29)	31.00 (21.47 - 43.31)	49.32 (43.91 - 55.22)	39.77 (30.35 - 51.19)
Year 2008	35.58 (30.20 - 41.65)	30.43 (20 95 - 42.73)	47.80 (42.45 - 53.64)	49.44 (38.82 - 62.07)
Year 2009	40.56 (34.78 - 47.04)	33.22 (23.14 - 46.20)	43.25 (38.16 - 48.82)	47.46 (37.06 - 59.86)
Year 2010	38.30 (32.55 - 44.78)	29.66 (20.01 - 42.35)	48.94 (43.57 - 54.79)	38.40 (29.16 - 49.64)
Year 2011	37.54 (31.75 - 44.07)	38.73 (27.41 - 53.16)	47.59 (42.40 - 53.24)	57.40 (46.09 - 70.63)
Year 2012	39.82 (33.84 - 46.56)	35.48 (24.57 - 49.58)	49.67 (44.38 - 55.42)	46.31 (36.30 - 58.22)
Year 2013	40.15 (34.00 - 47.09)	37.96 (26.44 - 52.79)	48.40 (43.17 - 54.09)	38.00 (29.00 - 48.91)
Year 2014	33.92 (28.12 - 40.55)	39.27 (27.03 - 55.15)	48.56 (43.39 - 54.17)	48.27 (38.10 - 60.33)
Year 2015	37.90 (31.45 - 45.29)	43.59 (30.00 - 61.21)	50.40 (45.23 - 56.00)	46.21 (36.47 - 57.75)
Year 2016	31.60 (25.24 - 39.07)	46.05 (31.07 - 65.74)	49.34 (44.35 - 54.75)	45.90 (36.39 - 57.12)
Year 2017	30.75 (24.06 - 38.72)	43.91 (28.41 - 64.82)	52.92 (47.80 - 58.43)	51.22 (41.24 - 62.88)
Year 2018	43.12 (34.88 - 52.71)	31.66 (18.44 - 50.68)	52.46 (47.46 - 57.85)	49.50 (39.85 - 60.77)
Year 2019	39.49 (31.54 - 48.83)	43.93 (27 85 - 65.92)	49.09 (44.30 - 54.25)	61.15 (50.49 - 73.41)
Year 2020	36.63 (28.86 - 45.84)	43.08 (27.00 - 65.22)	48.54 (43.77 - 53.69)	49.21 (39.67 - 60.35)
Year 2021	38.40 (30.15 - 48.21)	31.19 (17.45 - 51.43)	45.47 (40.78 - 50.54)	61.17 (50.37 - 73.60)
	No RA	RA	No RA	RA
Year 2000	33.46 (29.52 - 37.77)	20.10 (14 36 - 27.37)	33.82 (31.42 - 36.36)	31.92 (27.36 - 37.01)
Year 2001	34.83 (31.07 - 38.92)	24.53 (18.48 - 31.93)	36.40 (33.85 - 39.09)	37.23 (32.18 - 42.86)
Year 2002	30.37 (27.00 - 34.05)	25.59 (19.58 - 32.88)	39.13 (36.42 - 41.99)	30.64 (25.97 - 35.92)
Year 2003	33.41 (30.02 - 37.07)	32.20 (25.72 - 39.81)	37.18 (34.50 - 40.01)	33.82 (28.81 - 39.44)
Year 2004	37.21 (33.83 - 40.84)	29.48 (23.58 - 36.41)	38.14 (35.40 - 41.05)	36.62 (31.32 - 42.56)
Year 2005	35.88 (32.67 - 39.31)	32.18 (26 24 - 39.06)	40.88 (37.99 - 43.94)	37.06 (31.61 - 43.19)
Year 2006	36.35 (33.08 - 39.85)	28.82 (23.14 - 35.47)	43.60 (40.57 - 46.80)	36.92 (31.39 - 43.14)
Year 2007	34.95 (31.68 - 38.47)	31.79 (25 69 - 38.91)	43.77 (40.68 - 47.03)	41.71 (35.72 - 48.41)
Year 2008	34.48 (31.19 - 38.02)	26.78 (21.10 - 33.52)	43.21 (40.12 - 46.48)	46.69 (40.29 - 53.82)
Year 2009	40.18 (36.53 - 44.10)	28.98 (22 91 - 36.16)	42.50 (39.40 - 45.78)	45.46 (39.08 - 52.58)
Year 2010	37.88 (34.24 - 41.81)	31.33 (24 81 - 39.05)	43.47 (40.31 - 46.81)	45.10 (38.66 - 52.29)
Year 2011	41.19 (37.24 - 45.45)	41.97 (34.08 - 51.15)	48.29 (44.91 - 51.86)	47.12 (40.43 - 54.59)
Year 2012	36.64 (32.83 - 40.77)	36.38 (28 85 - 45.28)	48.81 (45.36 - 52.45)	46.78 (40.03 - 54.34)
Year 2013	36.24 (32.27 - 40.57)	31.54 (24 24 - 40.36)	53.15 (49.52 - 56.98)	47.96 (41.08 - 55.66)
Year 2014	35.63 (31.50 - 40.15)	30.02 (22.55 - 39.17)	51.14 (47.61 - 54.86)	53.67 (46.40 - 61.75)
Year 2015	36.67 (32.28 - 41.49)	28.23 (20 67 - 37.66)	52.89 (49.40 - 56.57)	49.90 (43.04 - 57.54)
Year 2016	33.08 (28.56 - 38.12)	36.57 (27 23 - 48.08)	52.04 (48.67 - 55.60)	57.19 (50.02 - 65.10)
Year 2017	36.39 (31.32 - 42.05)	37.14 (27.09 - 49.69)	51.65 (48.35 - 55.13)	60.22 (53.00 - 68.15)
Year 2018	37.53 (32.19 - 43.50)	32.08 (22.47 - 44.41)	51.79 (48.53 - 55.21)	60.48 (53.37 - 68.29)
Year 2019	37.90 (32.39 - 44.09)	38.18 (27 27 - 51.99)	51.76 (48.53 - 55.16)	57.70 (50.81 - 65.27)
Year 2020	27.11 (22.30 - 32.65)	29.73 (19 91 - 42.69)	46.74 (43.72 - 49.92)	60.18 (53.25 - 67.76)
Year 2021	30.45 (25.00 - 36.73)	32.55 (21 63 - 47.05)	49.92 (46.79 - 53.21)	55.55 (48.91 - 62.85)
	No Coeliac	Coeliac	No Coeliac	Coeliac
Year 2000	45.08 (38.09 - 52.98)	34.30 (22.79 - 49.57)	47.13 (42.92 - 51.63)	52.01 (43.36 - 61.88)
Year 2001	43.09 (37.00 - 49.91)	55.83 (42.17 - 72.50)	53.52 (49.06 - 58.27)	54.33 (45.55 - 64.31)
Year 2002	46.73 (40.79 - 53.30)	40.14 (29.49 - 53.38)	53.67 (49.24 - 58.39)	62.43 (53.04 - 72.99)
Year 2003	51.01 (45.30 - 57.24)	57.62 (45 69 - 71.71)	53.38 (49.00 - 58.05)	67.67 (57.96 - 78.53)
Year 2004	41.31 (36.52 - 46.56)	48.48 (38 32 - 60.50)	49.83 (45.66 - 54.28)	58.67 (49.77 - 68.70)
Year 2005	43.40 (38.78 - 48.42)	46.68 (37 34 - 57.65)	53.41 (49.16 - 57.93)	54.93 (46.43 - 64.52)

Year 2006	47.92 (43.17 - 53.05)	47.22 (37.97 - 58.04)	57.80 (53.45 - 62.41)	62.64 (53.63 - 72.73)
Year 2007	51.62 (46.73 - 56.88)	48.28 (38.97 - 59.14)	60.25 (55.87 - 64.89)	69.83 (60.44 - 80.26)
Year 2008	51.31 (46.49 - 56.49)	51.62 (42.09 - 62.67)	58.43 (54.23 - 62.87)	64.60 (55.79 - 74.41)
Year 2009	45.76 (41.26 - 50.62)	54.69 (44.95 - 65.91)	58.90 (54.79 - 63.22)	60.80 (52.46 - 70.09)
Year 2010	52.32 (47.51 - 57.49)	55.01 (45.25 - 66.24)	64.37 (60.19 - 68.76)	59.93 (51.89 - 68.86)
Year 2011	48.30 (43.68 - 53.28)	46.05 (37.17 - 56.41)	63.16 (59.13 - 67.40)	67.94 (59.55 - 77.18)
Year 2012	53.30 (48.50 - 58.44)	47.28 (38.30 - 57.74)	65.78 (61.78 - 69.96)	62.61 (54.78 - 71.25)
Year 2013	51.90 (47.16 - 56.98)	52.48 (43.01 - 63.41)	68.03 (64.04 - 72.20)	68.06 (60.09 - 76.81)
Year 2014	51.63 (46.83 - 56.78)	51.55 (41.99 - 62.64)	64.31 (60.56 - 68.24)	74.25 (66.15 - 83.07)
Year 2015	52.69 (47.69 - 58.07)	59.11 (48.63 - 71.19)	67.16 (63.50 - 70.97)	73.65 (65.91 - 82.06)
Year 2016	45.26 (40.37 - 50.57)	49.97 (39.80 - 61.95)	70.73 (67.15 - 74.46)	74.12 (66.69 - 82.16)
Year 2017	50.18 (44.91 - 55.89)	56.27 (45.19 - 69.24)	64.98 (61.69 - 68.41)	69.32 (62.48 - 76.70)
Year 2018	59.81 (54.09 - 65.98)	51.99 (41.47 - 64.36)	64.65 (61.51 - 67.91)	70.07 (63.48 - 77.17)
Year 2019	48.72 (43.65 - 54.21)	52.10 (41.67 - 64.34)	68.10 (64.99 - 71.33)	71.47 (65.02 - 78.39)
Year 2020	43.68 (38.84 - 48.95)	47.72 (37.72 - 59.55)	63.96 (61.06 - 66.98)	67.97 (61.94 - 74.42)
Year 2021	39.78 (35.03 - 44.98)	37.03 (28.12 - 47.86)	58.88 (56.15 - 61.70)	64.72 (58.97 - 70.89)
	No IBD	IBD	No IBD	IBD
Year 2000	44.99 (41.45 - 48.75)	43.61 (36.82 - 51.28)	49.33 (47.11 - 51.63)	56.23 (51.59 - 61.18)
Year 2001	46.21 (42.92 - 49.68)	49.41 (42.75 - 56.82)	47.57 (45.40 - 49.82)	53.47 (48.94 - 58.31)
Year 2002	47.07 (43.95 - 50.35)	45.47 (39.43 - 52.17)	51.63 (49.38 - 53.97)	53.20 (48.68 - 58.03)
Year 2003	48.15 (45.21 - 51.24)	44.08 (38.54 - 50.18)	54.98 (52.65 - 57.38)	53.69 (49.16 - 58.54)
Year 2004	49.11 (46.34 - 52.01)	53.24 (47.51 - 59.46)	53.83 (51.54 - 56.20)	52.10 (47.65 - 56.86)
Year 2005	48.64 (46.01 - 51.38)	44.03 (39.09 - 49.42)	50.65 (48.44 - 52.93)	51.76 (47.33 - 56.49)
Year 2006	48.21 (45.60 - 50.93)	47.19 (42.09 - 52.73)	54.13 (51.86 - 56.47)	54.48 (49.96 - 59.29)
Year 2007	48.91 (46.27 - 51.67)	47.23 (42.07 - 52.84)	52.90 (50.66 - 55.21)	53.40 (48.93 - 58.17)
Year 2008	47.43 (44.83 - 50.14)	41.53 (36.71 - 46.80)	54.81 (52.54 - 57.14)	54.14 (49.66 - 58.92)
Year 2009	46.52 (43.94 - 49.22)	53.34 (47.85 - 59.29)	57.02 (54.72 - 59.39)	59.74 (55.05 - 64.72)
Year 2010	49.58 (46.87 - 52.40)	46.75 (41.56 - 52.41)	55.06 (52.81 - 57.38)	60.95 (56.22 - 65.98)
Year 2011	50.49 (47.71 - 53.39)	48.74 (43.34 - 54.63)	60.31 (57.96 - 62.73)	62.38 (57.60 - 67.45)
Year 2012	46.15 (43.47 - 48.95)	50.88 (45.28 - 56.99)	58.74 (56.43 - 61.11)	62.34 (57.60 - 67.38)
Year 2013	46.27 (43.51 - 49.17)	44.33 (38.96 - 50.23)	61.05 (58.68 - 63.48)	63.96 (59.15 - 69.06)
Year 2014	44.16 (41.34 - 47.13)	42.35 (36.88 - 48.41)	61.14 (58.78 - 63.57)	64.42 (59.58 - 69.54)
Year 2015	44.28 (41.29 - 47.42)	41.48 (35.76 - 47.85)	61.21 (58.88 - 63.61)	58.54 (53.98 - 63.39)
Year 2016	43.99 (40.78 - 47.38)	41.56 (35.41 - 48.48)	60.13 (57.84 - 62.48)	64.09 (59.36 - 69.09)
Year 2017	43.78 (40.40 - 47.37)	46.62 (39.71 - 54.37)	58.82 (56.58 - 61.11)	61.95 (57.35 - 66.82)
Year 2018	46.37 (42.78 - 50.17)	41.26 (34.60 - 48.84)	58.75 (56.55 - 61.01)	63.58 (58.98 - 68.43)
Year 2019	42.35 (38.83 - 46.11)	46.04 (38.76 - 54.30)	62.08 (59.84 - 64.39)	63.99 (59.41 - 68.84)
Year 2020	37.88 (34.42 - 41.60)	44.22 (36.78 - 52.72)	58.16 (55.99 - 60.39)	60.97 (56.52 - 65.68)
Year 2021	32.70 (29.30 - 36.39)	35.54 (28.54 - 43.73)	54.32 (52.22 - 56.48)	57.85 (53.51 - 62.45)
	No Crohn	Crohn	No Crohn	Crohn
Year 2000	51.16 (45.63 - 57.17)	44.92 (34.95 - 56.84)	53.10 (49.68 - 56.69)	63.21 (55.92 - 71.19)
Year 2001	50.27 (45.29 - 55.64)	46.97 (37.62 - 57.94)	52.35 (48.99 - 55.89)	51.88 (45.34 - 59.10)
Year 2002	53.58 (48.76 - 58.76)	45.53 (36.83 - 55.65)	56.14 (52.69 - 59.77)	53.86 (47.22 - 61.17)
Year 2003	53.23 (48.75 - 58.00)	46.16 (38.04 - 55.50)	60.04 (56.47 - 63.77)	58.21 (51.34 - 65.75)
Year 2004	54.39 (50.19 - 58.84)	57.74 (49.22 - 67.32)	57.92 (54.46 - 61.55)	55.81 (49.13 - 63.14)
Year 2005	54.45 (50.49 - 58.64)	47.45 (40.21 - 55.62)	54.37 (51.05 - 57.85)	49.74 (43.49 - 56.63)
Year 2006	52.68 (48.80 - 56.80)	52.19 (44.62 - 60.68)	58.47 (55.05 - 62.05)	53.71 (47.25 - 60.82)
Year 2007	54.33 (50.37 - 58.51)	52.41 (44.74 - 61.02)	56.46 (53.13 - 59.96)	51.91 (45.59 - 58.86)
Year 2008	50.70 (46.89 - 54.75)	43.60 (36.65 - 51.48)	57.73 (54.39 - 61.22)	56.61 (50.07 - 63.77)
Year 2009	48.50 (44.76 - 52.47)	51.96 (44.36 - 60.49)	59.32 (55.97 - 62.81)	63.22 (56.37 - 70.68)
Year 2010	53.05 (49.09 - 57.26)	37.15 (30.70 - 44.56)	55.76 (52.54 - 59.13)	66.99 (59.95 - 74.62)
Year 2011	51.56 (47.60 - 55.76)	54.84 (46.79 - 63.88)	62.23 (58.83 - 65.78)	63.03 (56.23 - 70.42)
Year 2012	47.27 (43.43 - 51.35)	48.32 (40.70 - 56.95)	59.90 (56.60 - 63.35)	70.07 (62.94 - 77.79)
Year 2013	48.65 (44.69 - 52.87)	42.57 (35.27 - 50.94)	62.76 (59.35 - 66.31)	60.52 (53.91 - 67.72)
Year 2014	44.95 (40.98 - 49.21)	43.09 (35.48 - 51.85)	60.98 (57.62 - 64.49)	61.87 (55.17 - 69.15)
Year 2015	45.84 (41.61 - 50.38)	43.18 (35.17 - 52.47)	62.50 (59.13 - 66.01)	62.03 (55.36 - 69.28)
Year 2016	45.33 (40.81 - 50.20)	42.98 (34.38 - 53.09)	59.63 (56.37 - 63.03)	61.12 (54.56 - 68.26)
Year 2017	44.75 (40.00 - 49.92)	49.61 (39.79 - 61.13)	58.17 (54.99 - 61.49)	60.98 (54.49 - 68.03)
Year 2018	46.03 (41.03 - 51.47)	41.61 (32.38 - 52.67)	56.52 (53.44 - 59.74)	61.59 (55.16 - 68.57)
Year 2019	41.82 (36.94 - 47.17)	46.83 (36.71 - 58.88)	60.78 (57.58 - 64.10)	64.00 (57.46 - 71.10)
Year 2020	39.41 (34.47 - 44.86)	38.19 (28.69 - 49.83)	57.47 (54.36 - 60.72)	60.68 (54.32 - 67.58)
Year 2021	36.63 (31.59 - 42.24)	35.03 (25.45 - 47.02)	56.69 (53.59 - 59.93)	57.09 (50.90 - 63.84)
	No UC	UC	No UC	UC
Year 2000	40.57 (35.75 - 45.85)	44.79 (34.98 - 56.49)	48.03 (44.99 - 51.22)	50.75 (44.67 - 57.43)
Year 2001	42.42 (37.86 - 47.39)	49.44 (39.90 - 60.57)	44.68 (41.75 - 47.75)	52.66 (46.42 - 59.51)
Year 2002	42.10 (37.83 - 46.72)	42.65 (34.25 - 52.49)	47.53 (44.51 - 50.71)	53.33 (47.02 - 60.25)
Year 2003	43.70 (39.64 - 48.06)	43.85 (35.90 - 53.04)	49.58 (46.49 - 52.82)	50.04 (43.93 - 56.75)

Year 2004	46.08 (42.16 - 50.26)	51.39 (43.29 - 60.57)	50.39 (47.27 - 53.65)	48.28 (42.29 - 54.88)
Year 2005	43.06 (39.44 - 46.93)	41.43 (34.46 - 49.40)	46.44 (43.45 - 49.58)	50.73 (44.57 - 57.52)
Year 2006	42.99 (39.38 - 46.85)	45.12 (37.86 - 53.38)	50.62 (47.52 - 53.86)	54.26 (47.91 - 61.21)
Year 2007	44.63 (40.93 - 48.58)	42.99 (35.84 - 51.15)	49.68 (46.61 - 52.91)	53.59 (47.26 - 60.53)
Year 2008	44.27 (40.59 - 48.20)	36.64 (30.06 - 44.24)	50.93 (47.82 - 54.18)	50.98 (44.82 - 57.75)
Year 2009	43.02 (39.37 - 46.92)	53.40 (45.35 - 62.47)	54.34 (51.14 - 57.69)	55.66 (49.22 - 62.71)
Year 2010	46.04 (42.20 - 50.13)	52.84 (44.72 - 62.01)	54.64 (51.43 - 58.00)	56.22 (49.75 - 63.30)
Year 2011	48.88 (44.84 - 53.18)	40.77 (33.54 - 49.09)	59.41 (56.06 - 62.90)	60.74 (54.01 - 68.08)
Year 2012	46.30 (42.34 - 50.52)	50.72 (42.50 - 60.07)	58.20 (54.92 - 61.64)	54.93 (48.57 - 61.91)
Year 2013	44.05 (40.06 - 48.34)	48.43 (40.16 - 57.91)	58.15 (54.85 - 61.60)	65.80 (58.83 - 73.37)
Year 2014	42.91 (38.78 - 47.36)	39.70 (31.88 - 48.86)	60.59 (57.24 - 64.09)	67.01 (59.96 - 74.66)
Year 2015	41.83 (37.54 - 46.47)	41.12 (32.71 - 51.04)	60.85 (57.54 - 64.31)	55.79 (49.45 - 62.70)
Year 2016	43.00 (38.26 - 48.16)	41.36 (32.30 - 52.17)	61.88 (58.58 - 65.32)	66.17 (59.35 - 73.57)
Year 2017	41.66 (36.75 - 47.03)	41.34 (31.76 - 52.89)	58.79 (55.62 - 62.09)	64.76 (58.08 - 72.00)
Year 2018	46.40 (41.06 - 52.24)	41.22 (31.38 - 53.18)	59.46 (56.32 - 62.74)	65.56 (58.92 - 72.73)
Year 2019	45.69 (40.22 - 51.71)	49.91 (38.60 - 63.50)	62.53 (59.33 - 65.86)	64.49 (57.97 - 71.53)
Year 2020	37.98 (32.82 - 43.72)	50.07 (38.30 - 64.32)	58.22 (55.15 - 61.41)	60.80 (54.52 - 67.61)
Year 2021	29.35 (24.58 - 34.79)	34.44 (24.37 - 47.27)	52.29 (49.38 - 55.32)	61.06 (54.76 - 67.88)
	No MS	MS	No MS	MS
Year 2000	44.99 (41.45 - 48.75)	23.80 (16.76 - 32.81)	36.32 (33.54 - 39.27)	32.27 (27.16 - 38.05)
Year 2001	35.51 (31.00 - 40.49)	27.76 (20.67 - 36.49)	35.50 (32.72 - 38.46)	31.36 (26.26 - 37.17)
Year 2002	38.37 (34.00 - 43.15)	18.73 (13.19 - 25.82)	38.96 (35.99 - 42.10)	27.06 (22.26 - 32.59)
Year 2003	33.04 (29.17 - 37.29)	24.84 (18.66 - 32.41)	41.01 (37.91 - 44.29)	29.63 (24.50 - 35.51)
Year 2004	33.07 (29.37 - 37.10)	33.34 (26.44 - 41.49)	33.40 (30.57 - 36.42)	31.96 (26.54 - 38.17)
Year 2005	34.57 (30.97 - 38.46)	34.19 (27.49 - 42.02)	38.20 (35.12 - 41.47)	31.07 (25.63 - 37.33)
Year 2006	36.48 (32.95 - 40.28)	24.65 (18.94 - 31.54)	38.01 (34.89 - 41.33)	29.85 (24.44 - 36.10)
Year 2007	33.06 (29.65 - 36.75)	25.11 (19.21 - 32.26)	38.96 (35.77 - 42.35)	30.91 (25.34 - 37.36)
Year 2008	33.71 (30.18 - 37.54)	32.49 (25.59 - 40.66)	41.76 (38.42 - 45.32)	31.47 (25.77 - 38.07)
Year 2009	31.81 (28.32 - 35.62)	27.37 (20.88 - 35.23)	42.96 (39.52 - 46.62)	35.83 (29.63 - 42.94)
Year 2010	34.96 (31.20 - 39.05)	25.59 (19.17 - 33.48)	46.42 (42.77 - 50.30)	33.12 (27.06 - 40.13)
Year 2011	33.86 (30.05 - 38.01)	29.47 (22.32 - 38.18)	41.03 (37.56 - 44.73)	50.65 (42.96 - 59.31)
Year 2012	33.32 (29.43 - 37.58)	25.84 (18.98 - 34.36)	44.40 (40.73 - 48.30)	48.12 (40.53 - 56.72)
Year 2013	33.56 (29.51 - 38.01)	28.22 (20.66 - 37.64)	45.16 (41.39 - 49.18)	48.11 (40.44 - 56.80)
Year 2014	36.33 (31.92 - 41.19)	32.22 (23.67 - 42.85)	45.03 (41.24 - 49.07)	46.13 (38.54 - 54.78)
Year 2015	36.47 (31.80 - 41.64)	26.64 (18.45 - 37.23)	46.54 (42.69 - 50.65)	44.62 (37.11 - 53.20)
Year 2016	33.84 (29.04 - 39.21)	23.46 (15.33 - 34.38)	44.73 (40.97 - 48.74)	44.16 (36.73 - 52.65)
Year 2017	31.49 (26.56 - 37.08)	27.33 (18.01 - 39.76)	45.69 (41.89 - 49.75)	34.91 (28.31 - 42.59)
Year 2018	34.15 (28.71 - 40.32)	26.50 (16.98 - 39.44)	47.72 (43.86 - 51.82)	46.96 (39.29 - 55.69)
Year 2019	39.38 (33.27 - 46.28)	36.84 (25.03 - 52.29)	53.42 (49.33 - 57.76)	40.03 (32.99 - 48.13)
Year 2020	34.46 (28.67 - 41.09)	22.73 (13.47 - 35.92)	43.78 (40.05 - 47.77)	47.85 (40.09 - 56.67)
Year 2021	34.10 (28.13 - 40.97)	33.53 (21.48 - 49.89)	47.74 (43.80 - 51.94)	54.20 (45.82 - 63.67)
	No Myasthenia	Myasthenia	No Myasthenia	Myasthenia
Year 2000	60.35 (39.77 - 87.80)	28.44 (5.87 - 83.13)	38.37 (28.09 - 51.17)	47.14 (25.77 - 79.10)
Year 2001	39.12 (23.55 - 61.08)	63.51 (27.42 - 125.14)	56.37 (43.69 - 71.59)	59.45 (35.23 - 93.96)
Year 2002	35.77 (21.85 - 55.25)	71.11 (34.10 - 130.77)	61.61 (48.29 - 77.47)	38.62 (19.95 - 67.46)
Year 2003	42.59 (28.30 - 61.55)	49.17 (21.23 - 96.89)	62.74 (49.59 - 78.30)	67.44 (41.75 - 103.09)
Year 2004	49.90 (34.95 - 69.09)	39.98 (16.07 - 82.37)	46.32 (35.17 - 59.88)	44.57 (24.37 - 74.78)
Year 2005	47.71 (33.42 - 66.06)	53.78 (25.79 - 98.91)	54.07 (42.15 - 68.32)	63.61 (38.86 - 98.24)
Year 2006	30.79 (19.30 - 46.61)	49.90 (22.82 - 94.73)	56.33 (43.83 - 71.29)	32.58 (15.62 - 59.91)
Year 2007	48.71 (33.93 - 67.75)	28.36 (9.21 - 66.18)	55.12 (42.88 - 69.75)	53.84 (30.78 - 87.44)
Year 2008	53.62 (37.94 - 73.59)	52.15 (23.84 - 98.99)	63.25 (50.00 - 78.94)	58.79 (34.84 - 92.92)
Year 2009	70.45 (51.94 - 93.40)	23.43 (6.38 - 59.98)	67.04 (53.77 - 82.59)	31.76 (15.23 - 58.40)
Year 2010	67.50 (49.04 - 90.61)	24.93 (6.79 - 63.82)	67.98 (54.52 - 83.76)	34.93 (17.44 - 62.50)
Year 2011	47.68 (32.17 - 68.06)	39.67 (14.56 - 86.35)	55.43 (43.13 - 70.15)	65.53 (40.03 - 101.21)
Year 2012	38.11 (24.16 - 57.19)	46.36 (18.64 - 95.51)	58.34 (45.48 - 73.71)	57.46 (33.47 - 91.99)
Year 2013	27.79 (15.88 - 45.13)	49.23 (19.79 - 101.43)	60.54 (47.28 - 76.36)	61.60 (36.51 - 97.36)
Year 2014	37.00 (22.60 - 57.15)	29.93 (8.15 - 76.62)	54.58 (41.94 - 69.83)	79.75 (50.55 - 119.66)
Year 2015	29.79 (16.67 - 49.13)	36.20 (9.86 - 92.70)	66.51 (52.74 - 82.78)	63.13 (37.41 - 99.77)
Year 2016	27.68 (13.28 - 50.91)	33.86 (6.98 - 98.95)	62.62 (49.66 - 77.94)	82.79 (54.08 - 121.31)
Year 2017	32.74 (16.35 - 58.59)	12.72 (0.32 - 70.87)	52.83 (41.10 - 66.85)	89.24 (59.77 - 128.17)
Year 2018	28.75 (13.14 - 54.57)	55.88 (15.23 - 143.08)	50.09 (38.82 - 63.62)	41.02 (21.84 - 70.15)
Year 2019	17.62 (5.72 - 41.11)	57.85 (15.76 - 148.12)	55.10 (43.27 - 69.17)	49.23 (28.14 - 79.95)
Year 2020	24.53 (9.00 - 53.40)	16.33 (0.41 - 90.99)	55.28 (43.26 - 69.62)	50.84 (29.06 - 82.56)
Year 2021	36.30 (15.67 - 71.53)	19.12 (0.48 - 106.50)	58.63 (45.96 - 73.72)	45.80 (25.04 - 76.84)

Supplementary tables and figures Chapter 4

Supplementary text 4.1

Quality assessment

Of the 46 initially included reviews, four reviews were subsequently excluded due to being critically low in quality. They were quality assessed using the AMSTAR2 tool. The critical domains which are important for a review to be high quality review are Protocol registered before commencement of the review (item 2), Adequacy of the literature search (item 4), Justification for excluding individual studies (item 7), Risk of bias from individual studies being included in the review (item 9), Appropriateness of meta-analytical methods (item 11), Consideration of risk of bias when interpreting the results of the review (item 13). Assessment of presence and likely impact of publication bias (item 15). The four reviews which were excluded did not qualify on more than 3 items of the critical domain listed.

Out of the remaining 42 reviews, 20 were rated as of moderate quality and remaining were low in quality. None of the reviews were rated high quality. The critical domains that were not met in the reviews were, firstly almost 23% of these reviews did not take in account risk of bias while interpreting the results, while almost 26% of the studies did not report the disclosure of the funding or conflict of interest. Further almost 15 % of the studies did not register protocol before commencing the review or reported the justification of the studies which were excluded. Also 5-6% of the studies did not include risk of bias assessment of the included studies. In most of the included systematic reviews, the quality of the primary studies was assessed through Newcastle-Ottawa scale. And most of the reviews study quality varied moderate to high quality of studies.

Reviews with overlapping primary studies and update of reviews

The overlapping association was noted with most autoimmune conditions reporting various pregnancy outcomes except for autoimmune conditions, myasthenia gravis, multiple sclerosis, and systemic sclerosis, as only one review for each of these conditions was identified. CCA less than 5% indicates low overlap and CCA 10 or above indicates moderate/high overlap. Where reviews had a high overlap (CCA $\geq 10\%$), Cochrane review was selected over a non-Cochrane review. If there were no Cochrane reviews, then a review was selected if: it had higher AMSTAR quality rating, reported more adverse pregnancy outcomes, was conducted recently, included a meta-analysis, or had a larger sample size. In cases where the reviews had non-overlapping association (CCA $< 10\%$), the reviews were retained and the data from primary studies of the reviews were extracted and without double counting of the primary studies a meta-analysis was conducted to generate pooled effect sizes. Overlapping association between many reviews. The degree of overlap (CCA) ranged from 0% to 66%. Where the overlap was high with CCA $\geq 10\%$ one review was retained and the others were excluded based on the criteria for exclusion or inclusion as reported earlier. Nine reviews were excluded owing to high overlap

Highly overlapping reviews (CCA > 10%) High overlap was noted with two reviews reporting association of axial spondyloarthritis and small for gestational age (n=6), preterm birth

(n=13), pre-eclampsia (n=7) and caesarean section (n=11) (n=number of primary studies included). Both were reviews from same year and moderate quality, hence review with larger sample size was selected. Reviews reporting association of coeliac disease and preterm birth (n=7), Intra uterine growth retardation (n=11), stillbirth (n=5), low birth weight (n=6) had high overlap. High overlap was also noted in the reviews reporting Inflammatory bowel disease and stillbirth (n=11), preterm birth (n=31), small for gestational (n=18). Reviews reporting psoriasis and miscarriage (n=8), caesarean section (n=11) were also overlapping with high CCA. Since one of the reviews presented the result in narrative analysis the review with meta-analysis was preferred to report the results. Reviews reporting psoriatic arthritis and pre-eclampsia (n=10), caesarean section (n=10), preterm birth (n=10), small for gestational age (n=8). Reviews reporting gestational diabetes in women with systemic lupus erythematosus (n=6) also reported high overlap. The newer review though included less number of studies (n=13,883) but large sample size was selected to report the results. Thyroid autoimmunity (all) and preterm birth (n=23), recurrent miscarriage (n=19) or miscarriage (n=27), gestational diabetes (n=30) and postpartum depression (n=19) in presence of thyroid autoimmunity had high overlap. Thyroid autoimmunity (TPO) and preterm birth (n=29) was reported by many reviews and high overlap was seen. Furthermore, while evaluating the association of Crohn's disease and ulcerative colitis with preterm birth high overlap was observed.

Moderate to low overlapping reviews (CCA<10%)-Two reviews reporting association of coeliac disease and small for gestational age and pre-eclampsia had low CCA suggesting nonoverlapping association with CCA 0% because of the difference in inclusion criteria one of the reviews included cohort studies and other included case control studies. Two reviews reporting IBD and caesarean section had low CCA with one overlapping study. as one review was from 2007 and included older studies and another new review did not take in account the older studies. There was overlap of few studies which were counted once when meta-analysing the primary studies. Two reviews reporting IBD and caesarean section had low CCA with one overlapping study. as one review was from 2007 and included older studies and another new review did not take in account the older studies. There was overlap of few studies which were counted once when meta-analysing the primary studies. Two reviews reporting psoriasis and preterm birth and low birth weight reported weak overlap and hence results from both are presented, one of the reviews reports summary estimates and another narrative analysis.

CCA of less than 10% was observed in reviews estimating the association of small for gestational age and AxSpa or SLE, and preterm birth and SLE or rheumatoid arthritis, Caesarean section and IBD.

Three reviews reporting preterm birth in women with SLE had nonoverlapping associations. The nonoverlap was because the reviews searched strategy was restricted to certain year and they used different databases to run the searches Due to missing data the odds ratios from the primary studies were used to meta-analyse and not the primary data. 2 primary

studies (Bernardo 2014 and Yuen) were overlapping they were counted once, and all primary studies were meta-analysed to present the summary effect size appendix fig 13. Similarly, two reviews reporting low birth weight, caesarean section and small for gestational age with SLE as exposure were non-overlapping. The primary studies from these reviews were also meta-analysed to get a summary effect appendix. The non-overlapping association was also noted in reviews reporting thyroid autoimmunity (TgAb) and preterm birth and gestational diabetes. In case of all the non-overlapping reviews the data from primary studies were extracted and meta-analysed without double counting and summary estimates were presented.

Data synthesis- Various pregnancy complications have been reported for each autoimmune condition and after carefully examining the overlap only the nonoverlapping results have been presented. After quantification of overlap between the review in form of CCA

1. CCA $\geq 10\%$ =Two reviews with high overlap (CCA $> 10\%$). One review was selected to present the results based on the criteria mentioned earlier.
2. CCA $<10\%$ =Few overlapping primary studies between the reviews. Data from the primary studies of the overlapping reviews was extracted and a meta-analysis (random effect) was performed without double counting the overlapping primary studies included in the reviews.
3. CCA=0%=No overlapping primary studies between the reviews. Data from the primary studies of these reviews was extracted and a meta-analysis (random effect) was performed to get the summary estimate.
4. The details of the overlapping association are presented in Table 7, 8 and 9. Leung et al present their results separately for cohort studies and registries for a few of the outcomes (low birth weight, preterm birth and small for gestational age), which were combined to present a summary estimate.
5. A further two reviews (Leung et al and Cornish et al) had non-overlapping associations reporting inflammatory bowel disease and low birth weight. As there was some missing data (no information of number of participants in the exposed population group or the control group in the manuscript or supplementary material) odds ratio from the studies were combined.

The results were presented in the form of odds ratios in the forest plots. In the reviews where summary estimates were reported as either a risk ratio or hazards ratio, we used an appropriate method of conversion to calculate the odds ratio.

When presenting association of thyroid autoimmunity, thyroid autoimmunity(all) refers to presence of both thyroglobulin antibodies(TgAb) and thyroid peroxidase antibodies(TPO), whereas thyroid autoimmunity(TPO) suggests only presence of thyroid autoantibodies has been studies.

When presenting the association of thyroid autoimmunity, 'thyroid autoimmunity (all)' refers to the presence of both thyroglobulin antibodies (TgAb) and thyroid peroxidase antibodies (TPO). Whereas 'thyroid autoimmunity (TPO)' indicates only the presence of thyroid

peroxidase autoantibodies has been studied. The details of the overlapping association are presented in Table 7, 8 and 9. Leung et al present their results separately for cohort studies and registries for few outcomes (low birth weight, preterm birth and small for gestational age) which were combined to present a summary estimate. Further two reviews (leung et al and Cornish et al) had non-overlapping association reporting low birth weight in Inflammatory bowel disease, due to missing data odds ratio from the studies are combined.

Update of reviews

The reviews were carefully examined following guidelines from Garner et al to identify whether the reviews needed to be updated (9). A systematic review with meta-analysis was considered out of date if a newly published study led to a change of the result by at least 50%. To evaluate the need to update the reviews, the RAND and OTTAWA methods were used. Details of the methods are presented in Table 10. Most of the reviews included were published in the last 10 years (2014-2021). To identify the need and possibility of updating the older included reviews, a scoping search was conducted to identify new primary studies for the given exposures and outcome. A few new studies were identified for some exposures such as IBD or coeliac disease. However, none of the study results were contradictory to findings of existing included reviews or would change the conclusion by 50% or more if included in the umbrella review. After consultation with experts, it was concluded that the reviews at this stage are not required to be updated.

Heterogeneity

All the included meta-analysis reported statistical heterogeneity between the included studies. Most calculated the heterogeneity among the studies using I^2 and values ranged from 0-98%. Most of the reviews have taken into account the level of heterogeneity while reporting the results. Three meta-analysis reported Q test with P values ranging from 0.0001-0.03. The meta-analysis performed in this umbrella review to combine the non-overlapping reviews reported I^2 statistics ranging from 0-98%. Details in table 6.

Publication bias

Most of the included meta-analyses included funnel plots, Egger's linear regression, and Begg's rank correlation test to evaluate potential publication bias qualitatively or quantitatively. The studies reported variable publication bias, but seven meta-analysis did not report publication bias. There were 13 meta-analyses conducted in this review, out of which 6 meta-analysis included less than 10 studies and so publication bias could not be assessed. For the remaining 6 meta-analysis the potential publication bias was assessed using Egger's test via funnel plot asymmetry and has a low risk of publication bias (table 9 along with the forest plots).

Table 4.1 Deviations from the protocol

<u>1</u>	AxSpA and thyroid autoimmunity were added to the list of included exposure conditions. Thyroid autoimmunity additionally included the presence of thyroglobulin antibodies (TgAb) or thyroid peroxidase antibodies (TPOab)
<u>2</u>	Instead of the preferred reporting items for systematic review and meta-analysis (PRISMA) checklist, the PRIOR checklist was used as it is specific for the reporting of umbrella reviews.

Table 4.2 Search Strategy OVID MEDLINE

Ovid MEDLINE(R) ALL	
1	exp Autoimmune Diseases/
2	(auto?immune adj2 (disease* or condition*)).mp.
3	exp Psoriasis/
4	psoria\$.mp.
5	exp Vitiligo/
6	vitiligo.mp.
7	(leucoderma or leukoderma).mp.
8	exp Alopecia Areata/
9	alopecia areata.mp.
10	((alopecia adj totalis) or (alopecia adj universalis)).mp.
11	exp Lupus Erythematosus, Systemic/
12	(systemic lupus or sle).mp.
13	arthritis psoriatic.mp. or exp Arthritis, Psoriatic/
14	Ankylosing spondylitis.mp. or exp Spondylitis, Ankylosing/
15	Spondylarthritis/
16	(axial adj2 spondylarthritis).tw.
17	(axial adj2 spa).tw.
18	(ankylos\$ or spondyl\$).tw.
19	(bekhterev\$ or bechterew\$).tw.
20	(Marie adj struempell\$).tw.
21	(AS or axSPA).tw.
22	Sacroiliitis/
23	((axial or spin\$ or peripheral or vertebral or enthesitis) adj3 (joint\$ or spondyloarthritis or arthritis or ankylosing)).tw.
24	exp Arthritis, Rheumatoid/
25	((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat\$ or reumat\$ or revmarthrit\$) adj3 (arthritis or artrit\$ or diseas\$ or condition\$ or nodule\$)).mp.
26	sjogren syndrome.mp. or exp Sjögren's Syndrome/

27	exp Celiac Disease/
28	(c?eliac adj disease*).mp.
29	inflammatory bowel disease.mp. or exp Inflammatory Bowel Diseases/
30	ulcerative colitis.mp. or exp Colitis, Ulcerative/
31	Crohn's disease.mp. or exp Crohn Disease/
32	multiple sclerosis.mp. or exp Multiple Sclerosis/
33	Systemic Sclerosis.mp.
34	exp Scleroderma, Systemic/
35	((systemic adj scler?) or sclero?).mp.
36	crest syndrome.mp. or exp CREST Syndrome/
37	graves disease.mp. or exp Graves Disease/
38	(grave? adj3 (diseas? or thyrotoxicos? or hyperthyr?)).mp.
39	exp Thyroiditis, Autoimmune/
40	autoimmune thyroid.mp.
41	Hashimoto Disease.mp.
42	exp Hashimoto Disease/
43	(thyroid adj autoantibodies).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
44	thyroid.mp. and exp autoantibodies/
45	myasthenia gravis.mp. or exp Myasthenia Gravis/
46	addison disease.mp. or exp Addison Disease/
47	type 1 diabetes.mp. or exp Diabetes Mellitus, Type 1/ or ("typ? 1 diabet*" or "typ? I diabet*" or "typ?1 diabet*" or "typ?I diabet*").mp. or (("insulin* depend*" or "insulin?depend*") not ("non-insulin* depend*" or "non insulindepend*")).mp. or (IDDM or T1DM or T1D).mp. or autoimmune diabetes.mp.
48	exp Pregnancy Complications/
49	(pregnancy adj complication?).mp.
50	exp Abortion, Spontaneous/
51	((recurrent adj2 miscarr?) or miscarr?).mp.
52	(early adj3 pregnancy loss?).mp.
53	miscarriage.mp.
54	exp Stillbirth/
55	(stillbirth or (still adj birth)).mp.
56	exp Fetal Death/
57	((f?etal adj death\$) or (f?etal adj demise\$)).mp.
58	exp Hypertension, Pregnancy-Induced/
59	(gestational hypertension or (pregnancy adj3 hypertensi\$)).mp.
60	(preeclampsia or pre-eclampsia).mp.
61	exp Pre-Eclampsia/
62	(eclampsia or tox?emia).mp.

63	exp Eclampsia/
64	hclp.mp. or exp HELLP Syndrome/
65	exp Placenta Accreta/
66	(placenta adj accreta).mp.
67	placenta percreta.mp.
68	placenta increta.mp.
69	(morbidly adj3 adherent placenta).mp.
70	abnormally invasive placenta.mp.
71	exp Abruptio Placentae/
72	Placenta? abruption.mp.
73	exp Placenta Previa/
74	Placenta pr?evia.mp.
75	low lying placenta.mp.
76	exp Hyperemesis Gravidarum/
77	Hyperemesis Gravidarum.mp.
78	exp Morning Sickness/
79	morning sickness.mp.
80	exp Diabetes, Gestational/
81	GDM.mp.
82	((pregnan\$ or gestation\$ or prenatal\$ or antenatal\$ or pre-natal\$ or ante-natal\$ or maternal\$) adj2 diabet\$) or gestational diabetes).mp.
83	((tub\$\$ adj3 pregnanc\$) or (cornual adj3 pregnanc\$) or (heterotopic adj3 pregnanc\$) or (abdomin\$ adj3 pregnanc\$) or (extrauterine adj3 pregnanc\$) or (interstitial adj3 pregnanc\$) or (cervi\$ adj3 pregnanc\$) or (ovar\$ adj3 pregnanc\$) or (cesarean scar adj3 pregnanc\$)).mp.
84	exp Pregnancy, Ectopic/
85	ectopic pregnancy.mp.
86	exp Gestational Trophoblastic Disease/
87	gestational trophoblastic.mp.
88	exp Hydatidiform Mole/
89	((hydatid? adj2 mole?) or (molar adj2 pregnanc?)).mp.
90	exp Choriocarcinoma/
91	choriocarcinoma.mp.
92	exp Pregnancy, Multiple/
93	((pregnanc* or gestation*) adj (twin* or triplet* or quadruplet* or quintuplet* or multiple or multi?f?et*)).mp.
94	(Monochorionic or dichorionic).mp.
95	exp Postpartum Hemorrhage/
96	(postpartum hemorrhage or post partum hemorrhage or postpartum haemorrhage or post partum haemorrhage).mp.
97	obstetric haemorrhage.mp.
98	obstetric labor, premature.mp.
99	exp Obstetric Labor, Premature/

100	(premature labor or premature labour or preterm labor or preterm labour or preterm birth).mp.
101	exp Cesarean Section/
102	exp Cesarean Section, Repeat/
103	(caesarean or cesarean or caesarian or cesarian or cesarien or caesarien or c-section or c section).mp.
104	cesarean.mp.
105	exp Extraction, Obstetrical/
106	exp Obstetrical Forceps/
107	((operative or instrumental or assisted or forcep* or ventouse* or vacuum*) adj1 (deliver* or birth*)).mp.
108	exp Infant, Low Birth Weight/
109	low birth weight.mp.
110	(low birth weight* adj4 very low birth weight*).mp.
111	exp Infant, Small for Gestational Age/
112	(small adj3 gestational age).mp.
113	(intra?uterine growth adj2 (restriction* or retardation)).mp.
114	iugr.ti,ab.
115	exp Fetal Growth Retardation/
116	(fetal growth adj2 (restriction? or retardation)).mp.
117	exp Depression, Postpartum/
118	postpartum depression.mp.
119	((postpartum* or post partum* or post-partum* or postnatal* or post natal* or post-natal* or perinatal* or peri natal* or peri-natal* or puerp*) and (depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder*)).mp.
120	((postpartum* or post partum* or post-partum* or postnatal* or post natal* or post-natal or perinatal* or peri natal* or peri-natal* or puerp*) and (psychos#s or psychotic)).mp.
121	(psychosis adj3 after childbirth).mp.
122	((third or fourth or 3rd or 4th) adj degree) and tear*).mp.
123	((anal near adj2 sphincter) or (rectal adj mucosa) or rectum or (anal adj epithelium) or anus or (recto?vaginal adj2 fistulae) or (anorectal adj mucosa) or (anal adj skin)) and (tear* or injur* or damage* or lacerat* or rupture* or trauma)).mp.
124	((obstetric* and anal and sphincter and injur*) or (anal and sphincter and injur*)).mp.
125	(exp Pregnancy/ or exp Obstetrics/ or (pregnan* or obstetric*).mp.) and (exp Cholestasis/ or exp Cholestasis, Intrahepatic/)
126	pelvic girdle pain.mp. or exp Pelvic Girdle Pain/
127	(symphysis pubis adj3 (pain\$ or dysfunction\$)).mp.
128	Pubic Symphysis Diastasis.mp. or exp Pubic Symphysis Diastasis/
129	Sacroiliac joint dysfunction.mp.
130	PGP.mp.
131	pregnancy outcome.mp. or exp Pregnancy Outcome/

132	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
133	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130
134	132 and 133
135	(systematic\$ adj2 (review\$ or overview)).ti,ab.
136	(systematic\$ adj5 review\$).tw,sh.
137	meta-analysis.mp. or exp meta-analysis/
138	135 or 136 or 137
139	134 and 138

Table 4.3 List of excluded studies

No	Year and Author	Year	Title	Reason for exclusion
1.	Anderson	2023	Andersen ML, Jølving LR, Stenager E, Knudsen T, Nørgård BM. Maternal Multiple Sclerosis and Health Outcomes Among the Children: A Systematic Review. Clin Epidemiol. 2023;15:375-89.	Low quality
2.	Balsells	2009	Balsells M, Garcia-Patterson A, Gich I, Corcoy R. Maternal and fetal outcome in women with type 2 versus type 1 diabetes mellitus: a systematic review and metaanalysis. Journal of Clinical Endocrinology & Metabolism. 2009;94(11):4284-91.	Comparator group different
3.	Bansal	2020	Pregnancy and lupus nephritis in developing countries: A systematic review	No comparator group

4.	Bobotis	2016	Bobotsis R, Gulliver W, Monaghan K, Lynde C, Fleming P. Psoriasis and adverse pregnancy outcomes: a systematic review of observational studies. British Journal of Dermatology. 2016;175(3):464-72.	High overlap
5.	Bundhun	2018	Bundhun PK, Soogund MZS, Huang F. Arterial/venous thrombosis, fetal loss and stillbirth in pregnant women with systemic lupus erythematosus versus primary and secondary antiphospholipid syndrome: a systematic review and meta-analysis. BMC Pregnancy & Childbirth. 2018;18(1):212.	Comparator group different
6.	Cellini	2020	Recurrent Pregnancy Loss in Women with Hashimoto's Thyroiditis with Concurrent Non-Endocrine Autoimmune Disorders	Not a systematic review
7.	Chaudhary	2019	Pregnancy outcomes in a long-term follow-up cohort of pediatric onset systemic lupus erythematosus (PSLE) at a tertiary care center in North-West India	Study design
8.	Crawford	2016	Thyroid Autoimmunity and Reproductive Function	Not a systematic review
9.	Dama	2016	Dama M, Steiner M, Lieshout RV. Thyroid peroxidase autoantibodies and perinatal depression risk: A systematic review. Journal of Affective Disorders. 2016;198:108-21.	High overlap
10	Derakhshan	2020	Association of maternal thyroid function with birthweight: a systematic review and individual-participant data meta-analysis	Not required exposure
11	Dong	2019	Dong Y, Dai Z, Wang Z, Wang H, Yuan F, Zhu Y, et al. Risk of	High overlap

			gestational diabetes mellitus in systemic lupus erythematosus pregnancy: a systematic review and meta-analysis. BMC Pregnancy & Childbirth. 2019;19(1):179.	
12	Essouma	2020	Outcomes of systemic lupus erythematosus pregnancies and associated factors in sub-Saharan Africa: A systematic scoping review	Not a systematic review
13	Finkelsztejn	2011	Finkelsztejn A, Brooks JB, Paschoal FM, Jr., Fragoso YD. What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature. BJOG: An International Journal of Obstetrics & Gynaecology. 2011;118(7):790-7.	Critically low study quality
14	Foulon		Defining the Most Appropriate Delivery Mode in Women with Inflammatory Bowel Disease: A Systematic Review	Outcome not of interest
15	Gizzo, S.	2013	An update on diabetic women obstetrical outcomes linked to preconception and pregnancy glycemic profile: a systematic literature review	Outcome not of interest
16	Gonzalez-Blanco,	2010	Glycaemic control and pregin women with type 1 diabetes: A systematic review and meta-analysis comparison between lispro and regular insulin	Outcome not of interest
17	Grygiel-Gorniak	2011	Rheumatic Diseases in Reproductive Age-the Possibilities and the Risks	Not a systematic review
18	Hage, M. P.	2010	The link between thyroid function and depression	Population not pregnant women
19	Hamroun	2020	Hamroun S, Hamroun A, Bigna JJ, Allado E, Forger F, Molto A. Fertility and pregnancy outcomes	High overlap

			in women with spondyloarthritis: A systematic review and meta-analysis. <i>Annals of the Rheumatic Diseases</i> . 2020;79(SUPPL 1):742-3.	
20	Hashash	2015	Pregnancy and inflammatory bowel disease	Not a systematic review
21	Hayslett	1992	The effect of systemic lupus erythematosus on pregnancy and pregnancy outcome	Not a systematic review
22	He	2015	Effect of thyroid autoantibodies per se on pregnancy outcomes in euthyroid women undergoing IVF/ICSI	Population not pregnant women
23	He, H.	2016	Effect of thyroid autoimmunity per se on assisted reproduction treatment outcomes: A meta-analysis	Population not pregnant women
24	Houtchens	2016	A review of observational studies of women with MS and pregnancy	Not a systematic review
25	Huang	2022	Huang W, Wu T, Jin T, Zhang Y, Wang J, Qi J, et al. Maternal and fetal outcomes in pregnant women with rheumatoid arthritis: a systematic review and meta-analysis. <i>Clinical Rheumatology</i> . 2022:1-16.	High overlap
26	Ideguchi	2013	Pregnancy outcomes in Japanese patients with SLE: retrospective review of 55 pregnancies at a university hospital	Study design
27	Jaffar	2021	Type 1 Diabetes in Pregnancy: A Review of Complications and Management	Not a systematic review
28	Jia, M	2019	Meta-analysis of the association between maternal subclinical hypothyroidism and gestational diabetes mellitus	Exposure not of interest
29	Kane.S	2003	Inflammatory bowel disease in pregnancy	Not a systematic review

30	Kent	2021	Is the link between elevated TSH and gestational diabetes mellitus dependant on diagnostic criteria and thyroid antibody status: a systematic review and meta-analysis	Exposure not of interest
31	Kim	2021	Kim MA, Kim YH, Chun J, Lee HS, Park SJ, Cheon JH, et al. The Influence of Disease Activity on Pregnancy Outcomes in Women With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. <i>Journal of Crohn's & colitis</i> . 2021;15(5):719-32.	Exposure not of interest
32	Lamah	2002	Inflammatory bowel disease and pregnancy	Not a systematic review
33	Laube	2021	Assisted Reproductive Technology in Crohn's Disease and Ulcerative Colitis: A Systematic Review and Meta-Analysis	Population not pregnant women
34	Levia	2017	Leiva P, Schwarze JE, Vasquez P, Ortega C, Villa S, Crosby J, et al. There is no association between the presence of anti-thyroid antibodies and increased reproductive loss in pregnant women after ART: a systematic review and meta-analysis. <i>JBRA Assisted Reproduction</i> . 2017;21(4):361-5.	Population group not appropriate
35	Li M Wang	2016	Li M, Wang SW, Huang S, Mao Y. Relationship between the thyroid autoimmunity and the risk of preterm birth in pregnant women: a meta-analysis. [Chinese]. <i>Zhonghua fu chan ke za zhi</i> . 2016;51(5):339-44.	High overlap
36	Lopezeon	2020	A systematic review and meta-analyses of pregnancy and fetal outcomes in women with multiple sclerosis. <i>IMI2 conception</i>	Exposure not of interest

37	McDonald	2018	Monitoring of Systemic Lupus Erythematosus Pregnancies: A Systematic Literature Review	Not a systematic review
38	Meissner	2021	Meissner Y, Rudi T, Fischer-Betz R, Strangfeld A. Pregnancy in women with psoriatic arthritis: A systematic literature review of disease activity and adverse pregnancy outcomes. <i>Seminars in Arthritis & Rheumatism</i> . 2021;51(3):530-8.	Comparator group different
39	Mintziori	2012	Thyroid diseases and female reproduction	Not a systematic review
40	Mintziori	2016	The impact of thyroid autoimmunity on IVF/ICSI outcome: Re-evaluation of the findings	Not a systematic review
41	Mokbel	2021	Pregnancy outcomes in women with ankylosing spondylitis: a scoping literature and methodological review	Not a systematic review
42	Moroni	2022	The impact of preeclampsia in lupus nephritis	Not a systematic review
43	Munoz Munoz	2022	Comparing pregnancy outcomes in patients with criteria and non-criteria autoimmune disease: A systematic review	Exposure not of interest
44	Nazarpur	2016	Nazarpour S, Ramezani Tehrani F, Simbar M, Azizi F. Thyroid autoantibodies and the effect on pregnancy outcomes. <i>Journal of Obstetrics & Gynaecology</i> . 2016;36(1):3-9.	Critically low quality-
45	Negro	2011	Negro R. Thyroid autoimmunity and pre-term delivery: Brief review and meta-analysis. <i>Journal of Endocrinological Investigation</i> . 2011;34(2):155-8.	High overlap
46	Ogallar	2018	Myasthenia gravis and pregnancy. [Spanish]	Not a systematic review

47	Pacu	2013	Thyroid antibodies and risk of Preterm delivery: A meta-analysis of prospective cohort studies	Full text not found
48	Park	2016	The influence of disease activity on birth outcomes in patients with inflammatory bowel disease: Meta-analysis	Duplicate of included study
49	Petri	1998	Pregnancy in SLE	Not a systematic review
50	Piccoli	2013	Type 1 diabetes, diabetic nephropathy, and pregnancy: a systematic review and meta-study	Not a systematic review
51	Picconi	2020	Piccioni MG, Tabacco S, Giannini A, Deroma M, Logoteta A, Monti M. Myasthenia gravis in pregnancy, delivery and newborn. Minerva Ginecologica. 2020;72(1):30-5.	Critically low study quality
52	Prummel	2004	Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. European Journal of Endocrinology. 2004;150(6):751-5.	Critically low quality-
53	Schmidt	2022	Schmidt PMS, Longoni A, Pinheiro RT, Assis AM. Postpartum depression in maternal thyroidal changes. Thyroid Research. 2022;15(1) (no pagination).	High overlap
54	Sim [316]	2023	Sim BL, Daniel RS, Hong SS, Matar RH, Ganiel I, Nakanishi H, et al. Pregnancy Outcomes in Women With Rheumatoid Arthritis: A Systematic Review and Meta-analysis. JCR: Journal of Clinical Rheumatology. 2023;29(1):36-42.	High overlap
55	Smyth	2010	Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus	Comparator group different

			nephritis. Clinical Journal of The American Society of Nephrology: CJASN. 2010;5(11):2060-8.	
56	Tian	2023	Tian L, Zhang Z, Mao Y, Zong M. Association between pregnant women with rheumatoid arthritis and preeclampsia: A systematic review and meta-analysis. Medicine (Baltimore). 2023;102(26):e34131.	High overlap
57	Toulis	2010	Toulis KA, Goulis DG, Venetis CA, Kolibianakis EM, Negro R, Tarlatzis BC, et al. Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: a meta-analysis. European Journal of Endocrinology. 2010;162(4):643-52.	Population group different
58	Wang	2012	Wang P, Wang Z, He X, Xu D, Wang B. Thyroid antibodies and risk of preterm delivery: A meta-analysis of prospective cohort studies. European Journal of Endocrinology. 2012;167(4):455-64.	High overlap
59	Wu	2015	Wu H, Hong T, Gao H, Wang H. [Effects of thyroid autoimmunity on pregnancy outcomes in euthyroid women receiving in vitro fertilization: a meta-analysis]. Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal]. 2015;95(46):3770-4.	Population group different
60	Yang	2015	Yang Y, Li Q, Wang Q, Ma X. Thyroid antibodies and gestational diabetes mellitus: a meta-analysis. Fertility & Sterility. 2015;104(3):665-71.e3.	High overlap

Table 4.4 Data extraction form

Study ID
PDF available
Authors
Year
Geographical area
Review aims and objectives
Databases searched
Additional information source (e.g grey literature)
Search period
Population
Health care setting
Exposure
Comparator
Covariates
Definition of exposure
Definition of outcomes
Data synthesis methods
Quality assessment tool
Publication year range for included studies
Countries included
Study design
Number of studies included in qualitative analysis (narrative synthesis where meta-analysis was not done / possible by the review authors)
Number of meta-analysis
Outcomes
Summar estimates
Number of studies included in each meta-analysis
Number exposed
Events exposed
Number unexposed
Events unexposed
Number of participants (if reported)
Author's conclusion

Table 4.5 Quality Assessment of included studies using AMSTAR 2 Tool

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
1. Arafa 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate

2.	Arvanitakis 2023	Yes	Yes	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate	
3.	Banner 2022	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No MA	No MA	No	Yes	No MA	Low	
4.	Blagojevic 2020	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	No	Yes	Low	
5.	Bundhun 2017	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Low	
6.	Chen 2011	Yes	No	Yes	Partial Yes	No	Yes	No	Partial Yes	No	No	Yes	Yes	Yes	No	Yes	Low	
7.	Cornish,2007	Yes	Partial Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	
8.	Dong 2020	Yes	Partial Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate	
9.	Dong,2020	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Low	
10.	Geng 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	
11.	Hew 2020	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Low	
12.	He X 2012	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Moderate	
13.	Korevar 2020	Yes	Yes	Yes	Yes	No	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	
14.	Leung 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	
15.	Li M 2016	Yes	Yes	Yes	Partial Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate	
16.	Lou J 2021	Yes	Yes	No	Partial Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Low	
17.	Maguire 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	
18.	Milandi 2020	Yes	Yes	Yes	Yes	Yes	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	
19.	Modrego 2021	Yes	Yes	Yes	Yes	Yes	Yes	No	Partial Yes	Yes	Yes	No MA	c	Yes	Yes	No MA	Low	
20.	O Toole 2015	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate	
21.	Saccone 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Low	
22.	Talvera 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Moderate	
23.	Tandon 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Moderate	
24.	Tersingini 2014	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes	Low	
25.	Thangaratnam	Yes	Partial Yes	Yes	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Moderate	
26.	Tong 2016	Yes	Yes	Yes	Partial Yes	No	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	
27.	Upala 2015	Yes	Yes	Yes	Partial Yes	No	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	
28.	Wei 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	
29.	Xie 2021	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	
30.	Yu 2016	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Low	
31.	Zhang 2017	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Low	
32.	Jiamin 2023	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	
Overlapping Excluded Reviews																		
1.	Bobotis,2016										No							
		Yes	Yes	Yes	Yes	Yes	No	No	Partial Yes	Partial Yes	Yes	MA	No MA	No	No	No MA	Yes	Low
2.	Dama, 2016	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No MA	No MA	No	Yes	No	No	Low
3.	Dong, 2019	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
4.	Hamroun, 2020	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
5.	Li M,2016	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Low
6.	Negro, 2011	Yes	Partial Yes	No	Partial Yes	No	No	No	Partial Yes	Partial Yes	No	Yes	No	No	No	No	No	Low
7.	Schmidt, 2022	Yes	Yes	Yes	Yes	Yes	No	No	Partial Yes	Partial Yes	Yes	No MA	No MA	No	No	No MA	Yes	Low
8.	Wang, 2012	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No MA	No MA	No	Yes	No MA	No	Low
9.	Yang 2015	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
10.	Huang 2022	Yes	Yes	Yes	Partial Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
11.	Sim 2023	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Low
12.	Tian 2023	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Low
Excluded systematic reviews																		
1.	Finkelsztejn,2011	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	V.Low
2.	Nazarpour,2016	Yes	No	No	No	Yes	Yes	No	No	No	No	No MA	No MA	No	No	No MA	No	V.Low
3.	Piccioni,2020	Yes	No	No	No	Yes	Yes	No	No	No	No	No MA	No MA	No	No	No MA	No	V.Low
4.	Prummel 2004	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	V.Low
5.	Anderson 2023	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	V.Low

No MA= No meta-analysis. Item 1: inclusion of PICO elements? Item 2: review methods established before conduct of review? Item 3: explanation for selection of study designs to be included in review? Item 4: use of a comprehensive search strategy? Item 5: selection of studies in duplicate? Item 6: data extraction in duplicate? Item 7: provision of list of excluded studies with justification for exclusion? Item 8: description of included studies in adequate detail? Item 9: satisfactory technique for risk of bias? Item 10: sources of funding for included studies reported? Item 11: proper methods for metaanalysis? Item 12: potential risk of bias in included studies discussed? Item 13: risk of bias accounted for in interpreting results? Item 14: heterogeneity discussed? Item 15: if meta-analysis conducted was publication bias discussed? Item 16: disclosure of funding or conflict of interest?

Table 4.6 Overall study citation matrix showing the areas of overlap between autoimmune conditions and pregnancy outcomes.

	AxSpA	Coeliac disease	IBD	Psoriasis	Psoriatic arthritis	SLE	Rheumatoid arthritis	sjögren's syndrome	Thyroid autoimmunity (all)	Thyroid autoimmunity (TPO)
Meta- age		Arvanitakis 2022		Bobotis 2016 Xie 2021			Sim 2023 Jiamin 2023		Chen 2011 Vanden 2011	

		Tersingini 2014 22%		37.5%			37.5%		25.9%	
Recurrence rate									Dong 2020 Vanden 2011 21%	
Pre-eclampsia	Maguire2020 Hamroun2020 57%	Sacoone 2016 Tersingini 2014 Arvanitakis 2022 28.5%			Xie 2021 Hamroun 2020 20%		Huang 2022 Sim 2023 Jiamin 2023 Tian 2023 31%			
Gestational diabetes mellitus						Hew 2020 Dong 2019 33%	Huang 2022 Sim 2023 Jiamin 2023 Tian 2023 20%		Yang 2015 Lou 2021 20%	
Caesarean section	Maguire2020 Hamroun2020 54%		Cornish 2007 Tandon 2020 7%	Bobotis 2016 Xie 2021 36.3%	Xie 2021 Hamroun 2020 30%	He W2020 Bundhun 2017 0%	Huang 2022 Sim 2023 Jiamin 2023 Tian 2023 37%			
Pain at birth	Maguire2020 Hamroun2020 30.7%	Sacoone 2014 Tersingini 2016 Arvanitakis 2022 25%	Cornish 2007 Leung 2021 O'Toole 2015 20.9%	Bobotis 2016 Xie 2021 15%	Xie 2021 Hamroun 2020 20%	He W2020 Wei 2017 Bundhun 2017 3.1%	Huang 2022 Sim 2023 Jiamin 2023 Tian 2023 23.2%	Upala 2016 Geng 2022 16%	Hex 2012 LiM 2014 Wang 2016 41%	Hex 2012 Zhang 2017 Korevar 2020 Thang.2011 Negro 2011 LiM 2014 13%
Intake of magnesium etc.		Sacoone 2014 Tersingini 2016 Arvanitakis 2022 29%								
Small for gestational age	Maguire2020 Hamroun2020 30%	Sacoone 2014 Tersingini 2016 0%	Cornish 2007 Leung 2021 O'Toole 2015 22%		Xie 2021 Hamroun 2020 14.2%	He W2020 Bundhun 2017 0%	Huang 2022 Sim 2023 Jiamin 2023 Tian 2023 32.3%			
Stillbirth		Sacoone 2014 Tersingini 2016 Arvanitakis 2022 42.8%	Cornish 2007 Tandon 2020 18%				Sim 2023 Jiamin 2023 20%			
Low birth weight		Sacoone 2014 Tersingini 2016 20%	Cornish 2007 Leung 2021 7%	Bobotis 2016 Xie 2021 14.2%		He W2020 Bundhun 2017 0%	Sim 2023 Jiamin 2023 30.7%			
High CCA and high overlap (CCA >10%) one of the reviews chosen based on the criteria										
Low CCA(CCA<10%), non-overlapping association										
No overlapping reviews										

CCA = Corrected covered area. Calculation = $CCA (\%) = N - r / rc - r$: Where N = number of included publications (sum of checked boxes), r = number of rows (primary studies), c = number of columns (number of systematic review)

Overlapping association between studies looking at association of axial spondyloarthropathy and pre-eclampsia, Caesarean section, small for gestational age and preterm birth

Axial spondyloarthropathy		
Axial spondyloarthropathy and pre-eclampsia	Maguire 2020	Hamroun2020
Outcome	Pre-eclampsia	Pre-eclampsia
1. Jakobsson GL, 2016	X	X
2. Mork S, Voss A 2019	X	
3. Park EH 2019		X
4. Park 2019	X	X
5. Zbinden A 2018	X	X
6. Smith CJF 2020	X	X
7. Ostensen M 1983		X
	5	6

CCA-57%		
Axial spondyloarthritis and Caesarean section		
	Caesarean section	Caesarean section
1. Jakobsson GL 2016	X	X
2. Kristjansdottir SR 2019	X	
3. Mork S, Voss A 2019	X	
4. Ostensen 1998	X	
5. Ostensen 2004	X	
6. Ostensen M 1983	X	X
7. Park EH 2019	X	X
8. Smith CJF 2020	X	X
9. Timur H 2016	X	X
10. Zbinden A 2018	X	X
11. Zhou 2012	X	
	11	6
CCA-54.5%		
Outcome	Small for gestational age	Small for gestational age
1. Jakobsson GL, 2016	X	X
2. Mork S, Voss A 2019	X	
3. Park 2019	X	X
4. Strouse 2019	X	
5. Timur H 2016		X
6. Zbinden A 2018	X	X
	5	4
CCA-66.6%		
Axial spondyloarthritis and Preterm birth		
	Preterm birth	Preterm birth
1. Conor 1980	X	
2. Jakobsson GL 2016	X	X
3. Kristjansdottir SR 2019	X	
4. Mork S Voss A 2019	X	
5. Ostensen 1998	X	
6. Ostensen M 1983	X	X
7. Park EH 2019	X	X
8. Smith CJF 2020	X	X
9. Strouse J 2019	X	
10. Timur 2016		
11. Timur H 2016	X	X
12. Zbinden A 2018	X	X
13. Zhou 2012	X	
	11	6
CCA-30.7%		

Overlapping association between studies looking at association of Coeliac disease and Pre-eclampsia, Miscarriage, intra-uterine growth restriction, stillbirth, small for gestational age and preterm birth and low birth weight

Coeliac disease and miscarriage		
Primary studies	Tersingini 2014	Arvanitakis 2022
1. Greco 2004	X	X
2. Grode 2018		X
3. Kotze 2020		X
4. Martinelli 2000	X	X
5. Moleski 2015		X
6. Molteni 1990		X
7. Moleski 2019		X
8. Sher 1996	X	
9. Tata 2005	X	
CCA=22%	4	7

Coeliac disease and Pre-eclampsia			
Primary studies	Sacoone 2016	Tersingini 2014	Arvanitakis 2022
Outcome	Pre-eclampsia	Pre-eclampsia	Pre-eclampsia
1. Abdul sultan 2014	X		
2. Greco 2004	X		X
3. Martinelli 2000	X		
4. Sheiner 2006	X	X	
5. Tata 2005	X	X	X
6. Celdir 2021			X
7. Elliott 2019			X
	5	2	4
CCA-28.5%			
Coeliac disease and intra-uterine growth retardation(IUGR)			
Outcome	Intrauterine growth restriction	Intrauterine growth restriction	Intrauterine growth restriction
1. Abdul Sultan A,2014	X		
2. Gasbarrini 2000		X	
3. Greco L 2004	X	X	X
4. Kumar 2011		X	X
5. Ludvigsson JF 2005		X	
6. Martinelli P 2000	X	X	
7. Martinelli 2010	X		
8. Norgard B 1999		X	X

9. Sharma 2007		X	
10. Sheiner E 2006	X	X	X
11. Tata LJ 2005	X		
12. Elliott 2019			X
	6	8	5
CCA-29%			
Coeliac disease and Stillbirth			
Outcome	Stillbirth	Stillbirth	Stillbirth
1. Abdul Sultan A 2014	X		X
2. Greco L 2004	X		
3. Martinelli P 2000	X	X	X
4. Sher KS 1994	X		X
5. Tata LJ 2005	X	X	X
6. Grode 2018			X
7. Pogacar 2019			X
N	5	2	6
CCA-42.8%			
Coeliac disease and Small for gestational age (SGA)			
Primary studies			
Outcome	Small for gestational age	Small for gestational age	
1. Greco 2004	X		
2. Khashan 2010	X		
3. Marterrili 2000	X		
4. McCarty 2009	X		
5. Salvatore 2007		X	
6. Wolf 2008		X	
	4	2	
CCA 0%			

Coeliac disease and Preterm birth			
Outcome	Preterm birth	Preterm birth	Preterm birth
1. Abdul Sultan A 2014	X		X
2. Greco L, 2004	X		
3. Khashan AS, 2010	X	X	X
4. Ludvigsson JF 2005	X		X
5. Ludvigsson JF 2001		X	
6. Martinelli P 2000	X	X	X
7. Salvatore 2007		X	
8. Elliott 2019			X
9. Celdir 2021			X
10. Moleski 2015			X

11. Nargard 1999			X
12. Abecassis 2019			X
	5	4	9
CCA-25%			
Coeliac disease and Low birth weight			
Primary studies			
Outcome	Low birth weight	Low birth weight	
1. Addul sultan 2014	X		
2. Ciacci 1996		X	
3. Ludvigsson 2005	X	X	
4. Martinelli 2012	X		
5. Ozgor 2000		X	
CCA-20%	3	3	

Overlapping association between studies looking at association of inflammatory bowel disease and, Caesarean section, small for gestational age, still birth, low birth weight, preterm birth

Primary studies	Cornish 2007	Tandon 2020
Outcome	Caesarean section	Caesarean section
1. Bortoli A 2007		X
2. Bortoli A 2011		X
3. Bush MC 2004	X	
4. Dominitz JA 2002	X	
5. Duricova 2019		X
6. Elbaz G, 2005	X	X
7. Fedorkow DM 1989	X	
8. Kornfeld D 1997	X	
9. Leung YP 2015		X
10. Moser MA 2000		X
11. Oron G 2012		X
12. Porter RJ 1986	X	
13. Yokoyama 2017		X
	6	8
CCA-7.6%		
Inflammatory bowel disease and Stillbirth		
Primary studies	Cornish 2007	O toole 2015
Outcome	Stillbirth	Stillbirth
1. Dominitz JA 2002	X	
2. Elbaz G 2005	X	
3. Fedorkow DM 1989	X	X

4. Fonager K 1998			X
5. Kornfeld D 1997	X		X
6. Mahadevan U 2017			X
7. Nguyen GC 2009			X
8. Norgard B 2000			X
9. Porter 2008			X
10. Stephansson O 2010			X
11. Stephansson O 2011			X
	4		9
CCA-18%			
Inflammatory bowel disease and small for gestational age			
IBD and SGA	Cornish 2007	Leung 2021	O toole 2015
1. Cleary 2011			X
2. Dominitz JA 2002	X	X	X
3. Elbaz G 2005	X	X	X
4. Fedorkov 1989			X
5. Freud 2016		X	
6. Kornfeld D 1997	X		X
7. Leung YP 2015		X	
8. Lin 2010		X	X
9. Ludvigsson JF 2002	X		
10. Mahadevan U 2017			X
11. Moser MA 2000	X	X	
12. Nguyen GC 2009			X
13. Oron G 2010		X	
14. Oron G 2012			X
15. Raatikainen 2011		X	X
16. Shand 2016		X	
17. Stephansson O 2010			X
18. Stephansson O 2011			X
N	5	9	12
CCA 22.2%			
c			
Inflammatory bowel disease and preterm birth			
Primary studies	Cornish 2007	Leung 2021	O toole 2015
	Preterm birth	Preterm birth	Preterm birth
1. Kornfeld D 1997	X		X
2. Fonager K 1998			X
3. Norgard B 2000	X		X
4. Larzilliere 1998	X		
5. Baird DD 1990			X
6. Bush MC 2004		X	X
7. Dominitz JA 2002	X	X	X
8. Elbaz G 2005	X	X	X
9. Ludvigsson JF 2002	X		X
10. Moser MA 2000		X	

11. Porter RJ 1986	X		X
12. Bortlik M 2013		X	
13. Bortoli A 2011		X	X
14. Bortoli A 2007		X	
15. Freud 2016		X	
16. Lin 2010		X	
17. Leung YP 2015		X	
18. Raatikainan 2011		X	X
19. Oron G 2012		X	X
20. Langaagerd 2007			X
21. Schnitizer 2011		X	
22. Duricova D 2019		X	
23. Shand 2016		X	
24. Sultan 2016		X	
25. Mahadevan U 2017			X
26. Fedorkov 1989			X
27. Cleary 2011			X
28. Mayberry JF 1986			X
29. Nguyen GC, 2009			X
30. Norgard B 2003			X
31. Stephansson O 2010			X
N	7	16	21
CAA- 20.9%			
Primary studies	Cornish 2007		Leung 2021
outcome	low birth weight		low birth weight
1. Baird DD 1990	X		
2. Dominitz JA 2002			X
3. Duricova D 2019			X
4. Elbaz G 2005	X		X
5. Emerson 2013			X
6. Freud 2016			X
7. Kornfeld D 1997	X		
8. Larzilliere I 1998	X		
9. Leung YP 2015			X
10. Lin 2010			X
11. Raatikainan 2011			X
12. Schnitizer 2011			X
13. Sultan 2016			X
14. Yokoyama			X
	4		11
CCA-7.1%			

Overlapping association between studies looking at association of Psoriasis and miscarriage, caesarean section, preterm birth, low birth weight

Psoriasis and miscarriage		
Primary studies	Bobotsis 2016	Xei 2021
Outcome	Miscarriage	Miscarriage
1. Ben-David G 2008.	X	
2. Cohen-Barak E 2011	X	X
3. Kimball AB 2014	X	
4. Lima XT 2013	X	X
5. Polachek A 2017		X
6. Schaufelberg BW 2014	X	
7. Seeger JD 2007.	X	X
8. Yurkon K 2014	X	
	7	4
CCA-37.5%		
Psoriasis and Caesarean section		
Outcome	Caesarean section	Caesarean section
1. Amiri 2016		X
2. Bandoli G 2020		X
3. Ben-David G 2008	X	X
4. Broms G 2018		X
5. Chiou 2017		X
6. Cohen-Barak E 2011	X	X
7. Lima XT 2013	X	X
8. Polachek A 2017		X
9. Remaeus K 2019		X
10. Smith CJF 2019		X
11. Yang YW, 2010	X	X
	4	11
CCA-36.3%		
Psoriasis and Preterm birth		
	Preterm birth	Preterm birth
1. Amiri 2016		X
2. Bandoli G 2020		X
3. Bandoll and chambers 2017		X
4. Ben-David G 2008	X	
5. Broms G 2018		X
6. Cohen-Barak E 2011	X	
7. Kimball AB 2014	X	
8. Lambe M 2020		X
9. Lima XT 2013	X	X
10. Remaeus 2019		X
11. Smith CJF 2019		X

12. Strouse J 2019		X
13. Yang YW 2010	X	X
N	5	10
CCA-15.3%		
Psoriasis low birth weight	Low birth weight	Low birth weight
1. Ben 2006		X
2. Broms 2018		X
3. Chiou 2017		X
4. Cohen,2017	X	
5. Lima 2011		X
6. Smith 2019		X
7. Yang 2011	X	X
CCA 14.2%	6	2

Overlapping association between studies looking at association of psoriatic arthritis with pre-eclampsia and preterm birth, Caesarean section, small for gestational age

Psoriatic arthritis and Pre-eclampsia		
Primary studies	Xei 2021	Hamroun 2020
Outcome	Pre-eclampsia	Pre-eclampsia
1. Amiri 2016	X	
2. Bandoli 2017	X	
3. Bandoli 2020	X	
4. Bro 2018	X	
5. Chiou 2017	X	
6. Lambe 2020	X	
7. Polacheck 2019		X
8. Remaeus 2019	X	X
9. Smith 2019	X	X
10. Zbinden 2018		X
	8	4
CCA=20%		
	Caesarean section	Caesarean section
1. Amiri 2016	X	
2. Bandoli 2020		X
3. Ben David 2008	X	
4. Broms 2018	X	
5. Chiou 2017	X	
6. Cohen Barak 2010	X	
7. Lima 2011	X	
8. Polachek 2019	X	X
9. Remaeus 2019	X	X
10. Smith 2019	X	X

	10	3
CCA 30%		
	Preterm birth	Preterm birth
1. Amiri 2016	X	
2. Bandoli and Chambers 2017	X	
3. Bandoli 2020	X	
4. Bro 2018	X	
5. Lambe 2020	X	
6. Lima 2011	X	
7. Remaeus 2019	X	X
8. Smith 2019	X	X
9. Strouse 2019	X	
10. Yang 2011	X	
CCA 20%	10	2
	Small for gestational age	Small for gestational age
1. Amiri 2016	X	
2. Bandoli 2020	X	
3. Broms 2017	X	
4. Chiou 2017	X	
5. Lambe 2020	X	
6. Ramaeus 2019	X	X
7. Strouse 2019	X	
	7	1
CCA=14.2%		

Overlapping association between studies looking at association of Rheumatoid arthritis and pre-eclampsia, gestational diabetes, Caesarean section, small for gestational age and preterm birth

Primary studies	Huang 2022	Sim 2023	Tian 2023	Jiamin 2023
Outcome	Pre-eclampsia	Pre-eclampsia		
1. Smith 2020	X			x
2. Williams 2019	X			
3. Aljiary 2018	X	X	X	X
4. Wallenius2014	X	X	X	
5. Norgard 2010	X	X		X
6. Lin 2010	X	X		X
7. Reed 2006	X	X	X	X

8. Abdulrahman		X		X
9. Al Rayes		X		X
10. Bandoli and Chambers 2017		X	X	X
11. Heng-Ching 2009			X	
12. Jørgensen 2009			X	
13. Nørgaard 2010			X	X
14. Barnabe 2011			X	X
15. Eudy 2018				X
16. Yang 2021				x
17. Zbinden 2018				X
18. Park 2022				X
19. Singh 2023				
CCA=31%	7	8	8	14
	Gestational diabetes	Gestational diabetes		Gestational diabetes
1. Keeling 2020	X			X
2. Smith 2020	X			X
3. Aljary 2018	X	X		X
4. Nørgaard 2010	X			
5. Abdulrahman 2020		x		X
6. Bandoli and Chambers		x		X
7. Psofai 2015				X
8. Eudy 2018				X
9. Galappatthy 2017				X
10. Nørgaard 2010				X
11. Singh 2023				X
CCA=20%	4	3		10
	Caesarean section	Caesarean section		
1. Hellgren 2021	X			
2. Keeling 2020	X			X
3. Smith 2020	X			X
4. Williams 2019	X			
5. Kishore 2019	X			
6. Zbinden 2018	X			X
7. Wallenius 2014	X	X		
8. Barnabe 2010	X			X
9. Nørgaard 2010	X	X		X
10. Lin 2010	X	X		X
11. Reed 2006	X	X		X
12. Eudy 2005		X		X

13. Aljary 2006		X		X
14. Al Rayes 2008		X		X
15. Abdulrahman 2007		X		X
16. Jolving 2018				X
17. Park 2022				X
18. Tarplin 2022				X
19. Singh 2013				X
20. Bobrica 2023				X
CCA=37.5%	11	8		16
	Small for gestational age	Small for gestational age		
1. Hellgren 2021	X			
2. Keeling 2020	X			X
3. Williams 2019	X			
4. Strouse 2019	X			X
5. Aljary 2018	X			X
6. Zbinden 2018	X			X
7. Wallenius 2014	X			
8. Ma 2014	X			X
9. Barnabe 2011	X			X
10. Norgard 2010	X	X		X
11. Lin 2010	X	X		X
12. Reed 2006	X	X		X
13. Jacobsen 2003	X			
14. Jolving 2018				X
15. Tsai 2022				X
16. Singh 2022				X
17. Bobrica 2023				X
CCA=32.3%	13	3		13
	Preterm birth	Preterm birth		Preterm birth
1. Hellgren 2021	X			
2. Keeling 2020	X			X
3. Smith 2020	X			X
4. Williams 2019	X			
5. Strouse 2019	X			
6. Kishore 2019	X			
7. Zbinden 2018	X			X
8. Wallenius 2014	X	X		
9. Rom 2014	X			
10. Ma 2014	X			X
11. Barnabe 2011	X			X
12. Lin 2010	X			X
13. Reed 2006	X			X
14. AL Rayes 2005		X		X

15. Aljary 2004		X		X
16. Bandoli and Chambers 2017		X		X
17. Eudy 2005		X		X
18. Norgard 2009		X		X
19. Strouse 2019				X
20. Posfai 2015				X
21. Jolving 2018				X
22. Knudsen 2020				X
23. Knudsen 2021				X
24. Park 2022				X
25. Tarplin 2022				X
26. Tsai 2022				X
27. Singh 2022				X
28. Bobrica 2023				x
CCA=23.2%	13	6		22
	Stillbirth	Stillbirth		Stillbirth
1. Al Rayes 2021		X		X
2. Eudy		X		
3. Norgard 2010	X	X		X
4. Galappatthy 2017				X
5. Rom 2016				X
6. Wallenius 2015	X			X
7. Tarplin 2022				x
8. Keeling 2020	X			
9. Strouse 2019	X			
10. Ajiary 2018	X			
CCA 20%	5	3		6
	Miscarriage			Miscarriage
1. Wallenius 2015	X			X
2. Nathan 1984	X			X
3. AL Rayes 2021				x
4. Eudy 2018				X
5. Galappatthy 2017				X
6. Park 2022				X
7. Tarplin 2022				
CCA= 14%	2			6

	Gestational HT			Gestational HT
1. Keeling 2020	X			X
2. Smith 2019	X			x
3. Kishore 2019	X			
4. Barnabe 2010	X			
5. Posfai 2015				x
6. Galappatthy 2017				X
7. Rom 2018				X
8. Aijary 2018				x
CCA=25%	4			6
	LBW			
1. Strouse 2019	X			X
2. Wallenius 2014	X			
3. Ma 2014	X			X
4. Lin 2010	X			X
5. Reed 2006	X			X
6. Posfai 2015				X
7. Abdulrahman 2020				X
8. Galappatthy 2017				X
9. Knudsen 2021				X
10. Park 2022				x
11. Tsai 2022				X
12. Singh 2023				X
13. Bobrica 2023				X
CCA 30.7%	5			12

Overlapping association between studies looking at association of Sjögren's syndrome and preterm birth

Primary studies	Upala 2016	Geng 2022
1. Carolis 2014	X	X
2. Takaya 2011	X	
3. Siamopoulou Mavridou 2010	X	
4. Skopouli 2008	X	
5. Hussein et al 2011	X	X
6. C Ballester 2016		X
7. L Li 2019		X
8. R Priori 2013		X
9. B Elliott 2019		X

10. JJ Yang 2021		X
11. HJ Haga 2005		X
12. JF Xu 2019		X
CCA=16.6%	5	9

Overlapping association between studies looking at association of systemic lupus erythematosus (SLE) and gestational diabetes mellitus (GDM), Preterm birth, Low birth weight, Caesarean section, small for gestational age

SLE and Gestational diabetes mellitus(GDM)			
	He W 2020	Dong 2019	
	Gestational diabetes mellitus	Gestational diabetes mellitus	
1. Abdwani 2018	X	X	
2. Bandoli G 2019	X		
3. Gallappathy 2017		X	
4. Phansenee S 2018	X	X	
5. Wu J 2018		X	
6. Yuen 2008		X	
	3	5	
CCA 33%			
SLE and Preterm birth (PTB)			
	He W 2020	Wei 2017	Bundhun 2017
Outcome	Preterm birth	Preterm birth	Preterm birth
1. Abdwani 2018	X		
2. Arkema 2016			X
3. Bandoli G 2019	X		
4. Bernardo 2014		X	X
5. Georgiio 2000		X	
6. Gnacio 2018	X		
7. Hamed 2013		X	
8. Julkunen 1993		X	
9. Ling 2018	X		
10. Molokhia 2007		X	
11. Phansenee S 2018	X		
12. Wu J 2018	X		
13. Yan Yuen 2008		X	X
14. Barnabe 2011			
15. Jackobsen 2015			X
16. Wallenius 2014			X
	6	6	5
CCA-3.1%			

SLE and Low birth weight (LBW)			
	Bundhun 2017	He W 2020	
	Low birth weight	Low birth weight	
1. Arkema 2016	X		
2. Walleinus 2014	X		
3. Abdwani 2017		X	
4. Gnacio 2018		X	
5. Phasene 2017		X	
CCA -0%	2	3	
SLE and Caesarean section			
	Bundhun 2017	He W 2020	
1. Aekema 2016	X		
2. Bamabe 2011	X		
3. Nili 2013	X		
4. Walleinus 2014	X		
5. Bandoli 2019		X	
6. Gnacio 2018		X	
7. Phansene 2017		X	
8. Wu 2017		X	
	4	4	
CCA 0%			
SLE and small for gestational age SGA	Bundhun 2017	HeW 2020	
1. Bandoli 2019		X	
2. Barnabe 2011	X		
3. Chen 2010	X		
4. Gnacio 2018		X	
5. Nili 2013	X		
6. Phansene 2017		X	
7. Wallenius 2014	X		
8. Wu 2017		X	
	4	4	
CCA 0%			

Overlapping association between studies looking at association of thyroid autoantibodies(all) and recurrent pregnancy loss, miscarriage, gestational diabetes melitus, postpartum depression, preterm birth

Thyroid Autoimmunity and recurrent pregnancy loss		
Primary studies	Dong 2020	Vanden 2011

1. Ashrafi 2007	X	
2. Bagis 2001	X	
3. Bellver 2008		X
4. Bussen 1997	X	X
5. Dendrinios 2000	X	X
6. Esplin 1998	X	
7. Iravani 2008	X	X
8. Kutteh 1999	X	X
9. Laba 2013	X	
10. Lakshmi 2016	X	
11. Mecacci 2000	X	X
12. Motak 2013	X	
13. Motak Pochrzest 2013	X	
14. Pratt 1993	X	
15. Raye Green 2011	X	
16. Roberts 1966	X	X
17. Shoenfield 2008		X
18. Ticconi 2011	X	
19. Tulppala 1993	X	
	15	8
CCA-21%		
Thyroid autoimmunity (all) and miscarriage		
	Chen 2011	Vanden 2011
1. Bagis 2007	X	
2. Benhadi 2009		X
3. Bussen 1997	X	
4. Dendrinios 2000	X	
5. Esplin 1998	X	
6. Glinioer 1991	X	
7. Glinioer 1994	X	
8. Iijama 1997	X	X
9. Iravani 2008	X	
10. Kilic 2008	X	
11. Kutteh 1999	X	
12. Lejeune 1993	X	X
13. Marai 2004	X	
14. Muller 1999	X	
15. Negro 2005	X	X
16. Negro 2006	X	X
17. Poppe 2004		X
18. Poppe 2003	X	
19. Pratt 1993	X	
20. Pratt 1993	X	
21. Roberts 1998		X
22. Rushworth 2000		X

23. Sezer 2009	X	X
24. Sieiro 2004	X	X
25. Singh 1995		X
26. Stagnaro-Green 1990	X	X
27. Todorova 2008	X	
CCA-25.9%	22	12
Thyroid autoimmunity(all) and gestational diabetes mellitus(GDM)		
	Yang 2015	Lou 2021
	GDM	GDM
1. Agarwal 2006	X	
2. Bhat 2018		X
3. Chen 2014	X	X
4. Corrales 2014	X	X
5. Haddow 2016		X
6. Huang 2019		X
7. Kang 2014	X	
8. Karakosta 2012	X	X
9. Kumru 2015		X
10. Li 2013	X	
11. Li 2020		X
12. Lin 2014	X	
13. Mannisto 2010	X	X
14. Mannisto 2011	X	
15. Montaner 2008	X	X
16. Negro 2011	X	X
17. Nokavo 2010	X	
18. Oleveri 2000	X	
19. Oliveri 1997	X	
20. Ortega-Gonzales 2000	X	
21. Pradhan 2013		X
22. Sert 2020		X
23. Tang 2013	X	
24. Wang 2014	X	
25. Wang H2011	X	
26. Wang XM 2011	X	
27. Ying 2016		X
28. Yuan 2020		X
29. Zhang 2013	X	
30. Zhao 2013	X	
CCA 20%	21	15

Thyroid autoimmunity and postpartum depression			
	Dama 2016	Schmidt 2018	Milandi 2020

1. Albacar 2010	X	X	X
2. Bergink 2011		X	
3. Bunevicius 2009	X		
4. Groer and Vaughan 2013	X	X	
5. Harris 1993	X	X	X
6. Kent 1999		X	
7. Kon 1999	X		
8. Kuijpers 2001	X	X	X
9. Lambrinoudaki 2010		X	
10. Lazarus 1996	X	X	
11. Le Donne 2012	X	X	
12. Oretti 1997	X		
13. Pedersen 2016		X	
14. POP 1993	X	X	
15. Pop 2006	X		X
16. Ruschi 2008		X	
17. Sylven 2013		X	
18. Wesseloo 2018		X	X
19. Zhang 2019		X	
	11	15	5
CCA-31.5%			
Thyroid autoimmunity (all) and preterm birth			
Primary studies	He X 2012	Li M 2016	Li M Wang 2014
Outcome	preterm birth	preterm birth	preterm birth
1. Ashoor G 2011	X	X	
2. Ashoor G 2011-TPOAb	X		
3. Bhattacharya 2016	X		
4. Chen X 2015	X	X	
5. Ghafoor F 2006	X	X	X
6. Glinoeer D 1994	X	X	X
7. Haddow JE 2010	X	X	X
8. Iijima T 1997 TGAAb	X	X	
9. Iijima T 1997 TPOAb	X		
10. Jiang YY 2011	X		

11. Karakosta 2012			X
12. Korevar2013		X	X
13. Lan Y 2013		X	X
14. Liu X 2012		X	X
15. Mannisto T 2009-TGAb	X	X	
16. Mannisto T 2009-TPOAb	X		
17. Nambiar V 2011	X	X	X
18. Negro R 2006	X		X
19. Negro R 2011	X		X
20. Stagnaro- Green A 1990	X	X	
21. Bhattacharya 2016		X	
22. Saki 2014		X	
23. Cleary 2008		X	
CCA 41%	16	16	10

Overlapping association between studies looking at association of thyroid peroxidase antibodies (TPO) and preterm birth

Thyroid autoimmunity (Thyroid peroxidase antibody) and preterm birth						
Primary studies TPO and Preterm birth	HeX 2012	Korevaar 2020	Negro 2011	Li M 2014	Thangaratinam 2011	Zhang 2017
1. ABCD		X				
2. ALSPAC		X				
3. Ashnoor G 2011	X					X
4. Blddal		X				
5. Chen		X				
6. Chinese name				X		
7. Chinese names				X		
8. EFSOCH		X				

9. Generation R		X				
10. Ghafoor	X	X	X	X	X	
11. Girona		X				
12. Glinoeer 1994	X		X	X	X	
13. Haddow			X	X	X	
14. HAppy		X				
15. Jiang 2011	X					
16. Karakosta				X		
17. Korevar				X		
18. Lijima 1997	X		X		X	
19. Mannisto 2009	X		X			
20. Mosso		X				
21. Nambiar 2011	X			X		
22. Negro 2006	X		X	X	X	
23. Negro R 2011	X		X	X		
24. NFBC		X				
25. POPOVA		X				X
26. Rhea		X				
27. Viva		X				
28. Western Australia		X				
29. Xu 2012						X
CCA=13.7%	9	15	7	10	5	3

Overlapping association between studies looking at association of preterm birth and ulcerative colitis and Crohn's disease

Preterm birth in ulcerative colitis	Cornish 2007	Otoole 2015
1. Baird 1990	X	X
2. Bush 2004	X	X
3. Dominitz 2002	X	X
4. Elbaz 2005	X	X
5. Larzille 2002	X	
6. Ludvigson 2002	X	X
7. Norgard 2000	X	X
8. Porter 1986	X	X
9. Norgard 2003		X
10. Langagergarrrd 2007		X
11. Nguyen 2009		X
12. Stephansson 2010		X

13. Raatikainen 2011		X
14. Bartolli 2011		X
15. Stephannson 2011		X
CCA 53%	8	15

Preterm birth in Crohn's disease	Cornish	Otoole
1. Baird 1990	X	X
2. Bush 2004	X	X
3. Dominitz 2002	X	X
4. Elbaz 2005	X	X
5. Larzille	X	
6. Ludvigson 2002	X	X
7. Moser 2001	X	
8. Fonager 1988	X	X
9. Porter 1986	X	X
10. Mayberry 1986		X
11. Norgard 2003		X
12. Langagergarrrd 2007		X
13. Nguyen 2009		X
14. Stephansson 2010		X
15. Raatikainen 2011		X
16. Bartolli 2011		X
CCA=50%	9	15

Table 4.7-Overlapping and non-overlapping associations by corrected covered area (CCA) calculations

Index	Author, Year	Quality	AI condition	Outcome	Data analysis	CCA	Decision
1	Maguire 2020	Moderate	Axial spondyloarthropathy	Pre-eclampsia	MA (5)	57%	Yes
	Hamroun 2020	Low			MA (6)		No
2	Maguire 2020	Moderate	Axial spondyloarthropathy	Caesarean section	MA (11)	54%	Yes
	Hamroun 2020	Low			MA (6)		No

3	Maguire 2020	Moderate	Axial spondyloarthropathy	Small for gestational age	MA (5)	66%	Yes
	Hamroun 2020	Low			MA (4)		No
4	Maguire 2020	Moderate	Axial spondyloarthropathy	Preterm birth	MA (11)	30.7 %	Yes
	Hamroun 2020	Low			MA (6)		No
5	Tersingini 2014	Low	Coeliac disease	Miscarriage	MA (4)	22%	No
	Arvanitakis s 2022	Moderate			MA (7)		Yes
6	Saccoone 2016	Low	Coeliac disease	Pre-eclampsia	MA (5)	28.5 %	No
	Tersingini 2014	Low			MA (2)		No
	Arvanitakis s 2022	Moderate			MA (4)		Yes
7	Saccoone 2016	Low	Coeliac disease	Intrauterine growth restriction	MA (6)	29%	No
	Tersingini 2014	Low			MA (8)		No
	Arvanitakis s 2022	Moderate			MA (5)		Yes
8	Saccoone 2016	Low	Coeliac disease	Small for gestational age	MA (4)	0%	Yes
	Tersingini 2014	Low			MA (2)		Yes
9	Saccoone 2016	Low	Coeliac disease	Stillbirth	MA (5)	42.8 %	No
	Tersingini 2014	Low			MA (2)		No
	Arvanitakis s 2022	Moderate			MA (6)		Yes
10	Saccoone 2016	Low	Coeliac disease	Preterm birth	MA (5)	25%	No
	Tersingini 2014	Low			MA (4)		No
	Arvanitakis 2022	Moderate			MA (9)		Yes
11	Saccoone 2016	Low	Coeliac disease	Low birth weight	MA (3)	12%	Yes
	Tersingini 2014	Low			MA (3)		No

12	Cornish 2007	Moderate	Inflammatory bowel disease	Caesarean section	MA (6)	7.1%	Yes
	Tandon 2020	Moderate			MA (8)		Yes
13	Cornish 2007	Moderate	Inflammatory bowel disease	Stillbirth	MA (4)	18%	No
	O toole 2015	Moderate			MA (9)		Yes
14	Cornish 2007	Moderate	Inflammatory bowel disease	Small for gestational age	MA (5)	22%	No
	Leung 2021	Moderate			MA (9)		Yes
	O toole 2015	Moderate			MA (12)		No
15	Cornish 2007	Moderate	Inflammatory bowel disease	Preterm birth	MA (7)	20.9 %	No
	Leung 2021	Moderate			MA (16)		Yes
	O toole 2015	Moderate			MA (21)		No
16	Cornish 2007	Moderate	Inflammatory bowel disease	Low birth weight	MA(4)	14.3 %	Yes
	Leung 2021	Moderate			MA (11)		Yes
17	Bobotis 2016	Low	Psoriasis	Miscarriage	NA (7)	37.5 %	No
	Xei 2021	Moderate			MA (4)		Yes
18	Bobotis 2016	Low	Psoriasis	Caesarean section	NA (5)	36.3 %	No
	Xei 2021	Moderate			MA (10)		Yes
19	Bobotis 2016	Low	Psoriasis	Preterm birth	NA (5)	15%	No
	Xei 2021	Moderate			MA (10)		Yes
20	Bobotis 2016	Low	Psoriasis	Low birth weight	NA (2)	14.2 %	No
	Xei 2021	Moderate			MA (6)		Yes
21	Xei 2021	Moderate	Psoriasis Arthritis	Pre - eclampsia	MA (8)	20%	Yes

	Hamroun 2020	Low			MA (4)		No
22	Xei 2021	Moderate	Psoriasis Arthritis	Caesarean section	MA (10)	30%	Yes
	Hamroun 2020	Low			MA (4)		No
23	Xei 2021	Moderate	Psoriasis A	Preterm birth	MA (10)	20%	Yes
	Hamroun 2020	Low			MA (2)		No
24	Xei 2021	Moderate	Psoriasis A	Small for gestational age	MA (7)	14.2 %	Yes
	Hamroun 2020	Low			MA (1)		No
25	Huang 2022	Moderate	Rheumatoid arthritis	Pre-eclampsia	MA (7)	37.5 %	Yes
	Sim 2023	Low			MA (8)		No
	Tian 2023	Moderate			MA(8)		No
	Jiamin 2023	Moderate			MA(14)		Yes
26	Huang 2022	Moderate	Rheumatoid arthritis	Gestational diabetes mellitus	MA (4)	20%	No
	Sim 2023	Low			MA (3)		No
	Jiamin 2023	Moderate			MA(10)		Yes
27	Huang 2022	Moderate	Rheumatoid arthritis	Caesarean section	MA (11)	37.5 %	No
	Sim 2023	Low			MA(8)		No
	Jiamin 2023	Moderate			MA(16)		Yes
28	Huang 2022	Moderate	Rheumatoid arthritis	Small for gestational age	MA (13)	23.3 %	No
	Sim 2023	Low			MA (3)		No

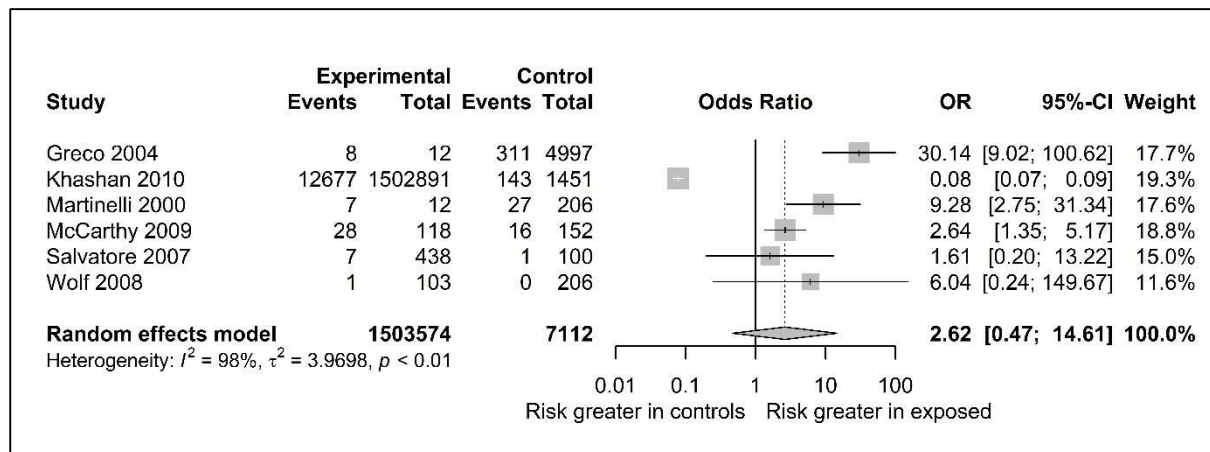
	Jiamin 2023	Moderate			MA(13)		Yes
29	Huang 2022	Moderate	Rheumatoid arthritis	Preterm birth	MA(13)	23.2 %	No
	Sim 2023	Low			MA(6)		No
	Jiamin 2023	Moderate			MA(22)		Yes
30	Huang 2022	Moderate	Rheumatoid arthritis	Gestational hypertension	MA(4)	25%	No
	Jiamin 2023	Moderate			MA()		Yes
31	Jiamin 2023	Moderate		Miscarriage	MA(2)	14%	Yes
	Huang 2022	Moderate	Rheumatoid arthritis		MA(6)		No
32	Jiamin 2023	Moderate		Low birth weight	MA(12)	14%	Yes
	Sim 2023	Low			MA(5)		No
	Huang 2022	Moderate	Rheumatoid arthritis		MA(5)		No
33	Jiamin 2023	Moderate		Stillbirth	MA(5)	14%	Yes
	Sim 2023	Low			MA(3)		No
	Huang 2022	Moderate	Rheumatoid arthritis		MA(6)		No
34	Upala 2016	Moderate	Sjögren's syndrome	Preterm birth	MA (5)	16.6 %	No
	Geng 2022	Moderate			MA (9)		Yes
35	HeW 2020	Low	SLE	Gestational diabetes mellitus	MA(3) 13,883	33%	Yes
	Dong 2019	Low			MA (5) 3432		No
36	Hew 2020	Low	SLE	Preterm birth	MA(6)	3.1%	Yes
	Wei 2017	Low			MA (6)		Yes
	Bundhun 2017	Low			MA (5)		Yes

37	Bundhun 2017	Low	SLE	Caesarean section	MA (4)	0%	Yes
	HeW 2020	Low			MA (4)		Yes
38	Bundhun 2017	Low	SLE	Small for gestational age	MA (4)	0%	Yes
	HeW 2020	Low			MA (4)		Yes
39	Bundhun 2017	Low	SLE	Low birth weight	MA (2)	0%	Yes
	HeW 2020	Low	SLE		MA (3)		Yes
40	Dong	Low	TAA(all)	Miscarriage	MA (15)	25.9 %	Yes
	Vanden 2011	low			MA (8)		No
41	Chen 2011	Moderate	TAA(all)	Recurrent miscarriage	MA (22)	21%	Yes
	Van den 2011	Low			MA (12)		No
42	Yang 2015	Low	TAA(all)	Gestational diabetes mellitus	MA (21)	20%	No
	Lou 2021	Low			MA (15)		Yes
43	Dama 2016	Low	TAA(all)	Postpartum depression	Na (11)	31%	No
	Schmidt 2018	Low			NA (15)		No
	Minaldi 2020	Low			MA (5)		Yes
44	Li M 2016	Low	TAA(all)	Preterm birth	MA (16)	41%	Yes
	LiM W 2012	Low			MA (10)		No
	Hex 2012	Moderate			MA (16)		No
45	Negro 2011	Low	TPO	Preterm birth	NA (7)	13%	No
	Korevar 2020	Moderate			MA (15)		Yes
	Thangaratinam 2011	Moderate			MA (5)		No
	Zhang 2017	Low			MA (3)		No
	Li M 2014	Low			MA (10)		No

Table 4.8 Forest plots of the meta-analysis performed in the study

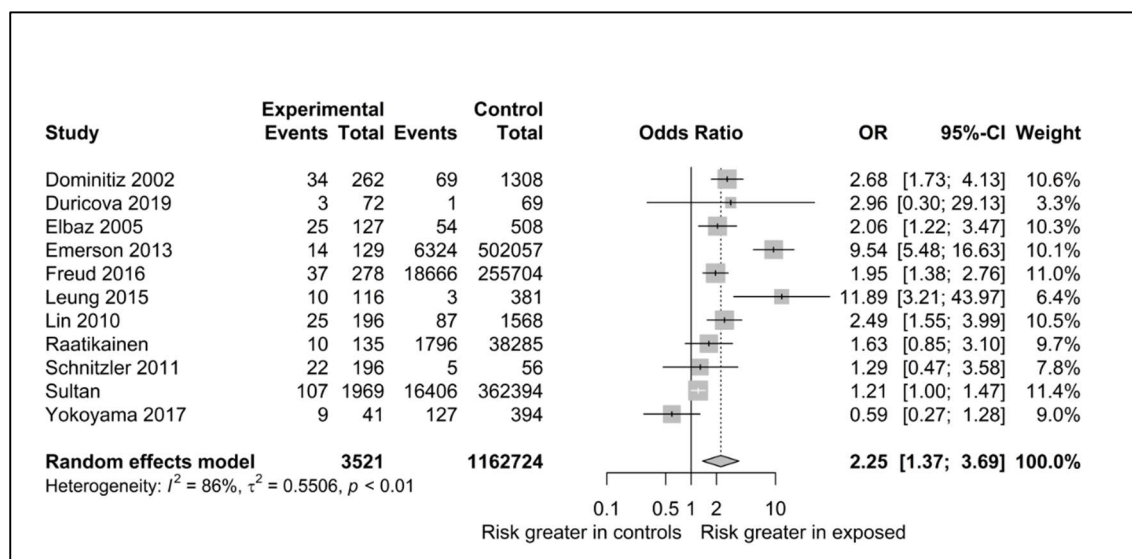
Coeliac disease

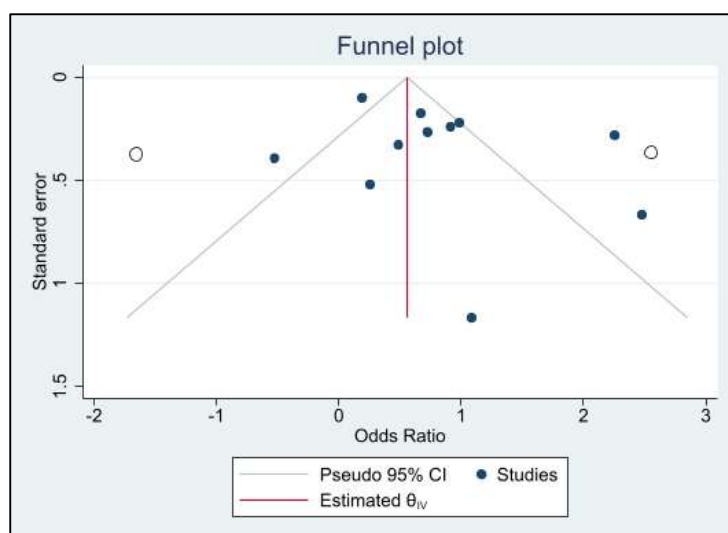
Meta-analysis of Sacoone and Tersingini -Looking at association of SGA and Coeliac disease
No overlap as Sacoone 2016 included cohort studies and Tersingini 2014 included case control studies.



IBD

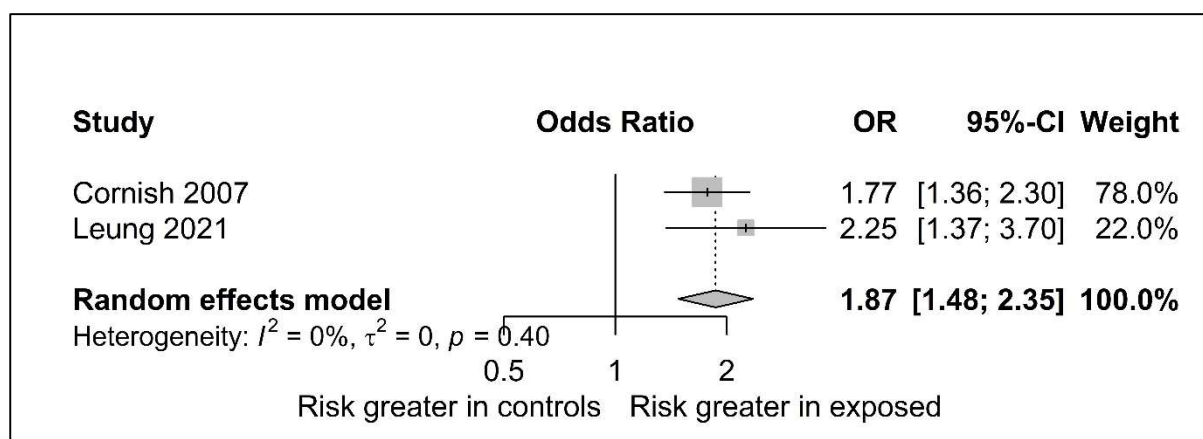
Meta-analysis of Leung et al -cohort studies and registries -Looking at association of low birth weight and IBD



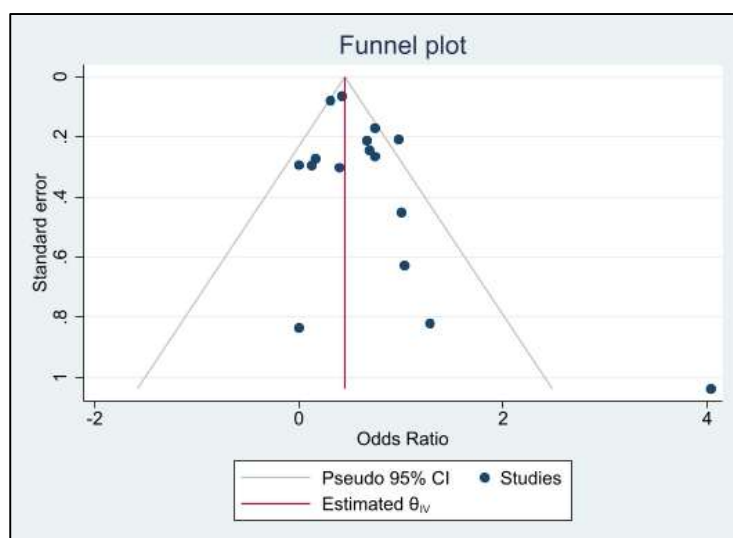
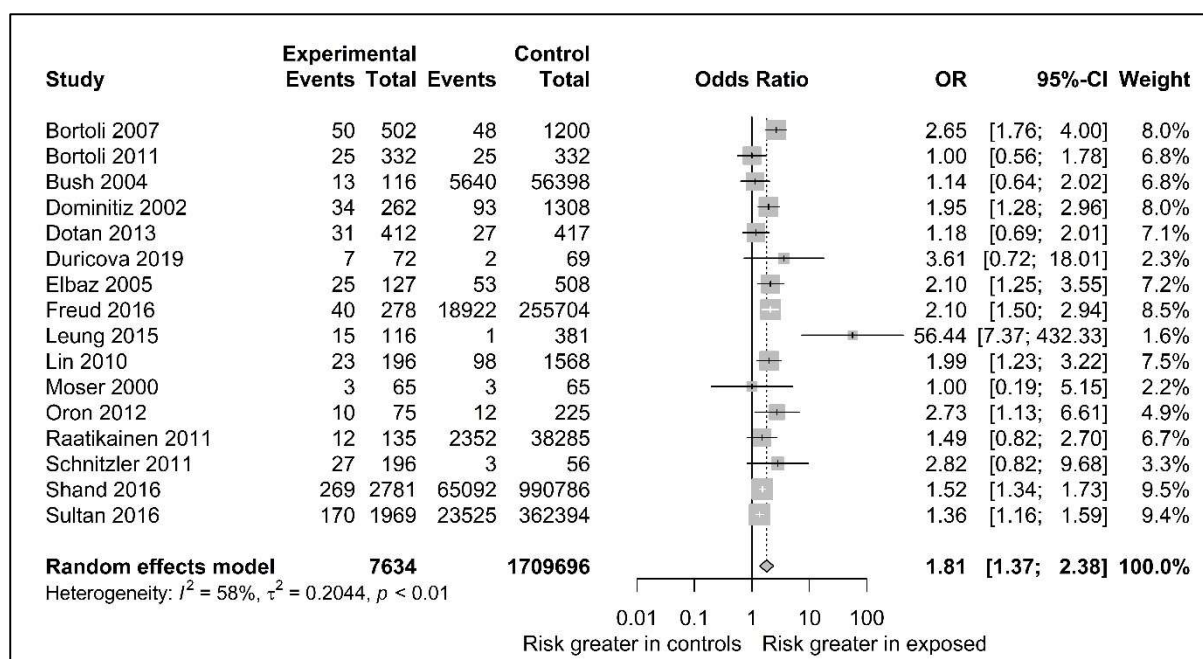


Funnel plot to assess the publication bias

Meta-analysis of Leung et al and Cornish further combined-Looking at association of low birth weight and IBD

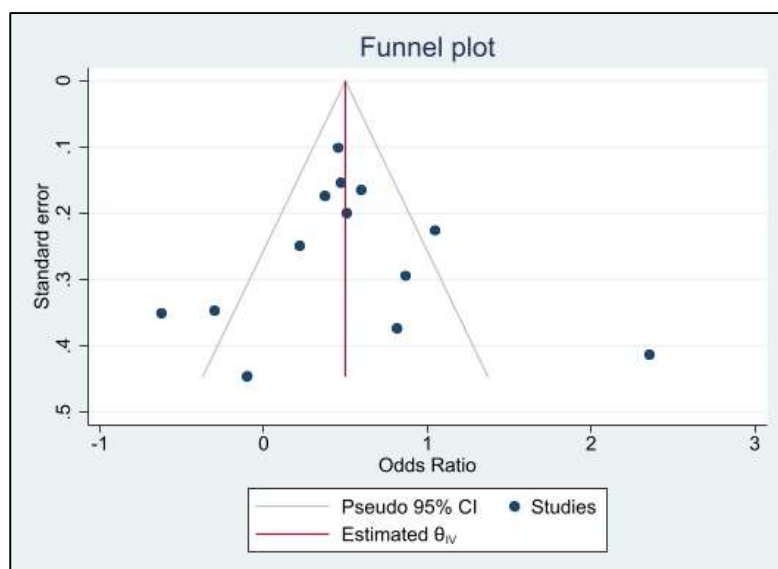
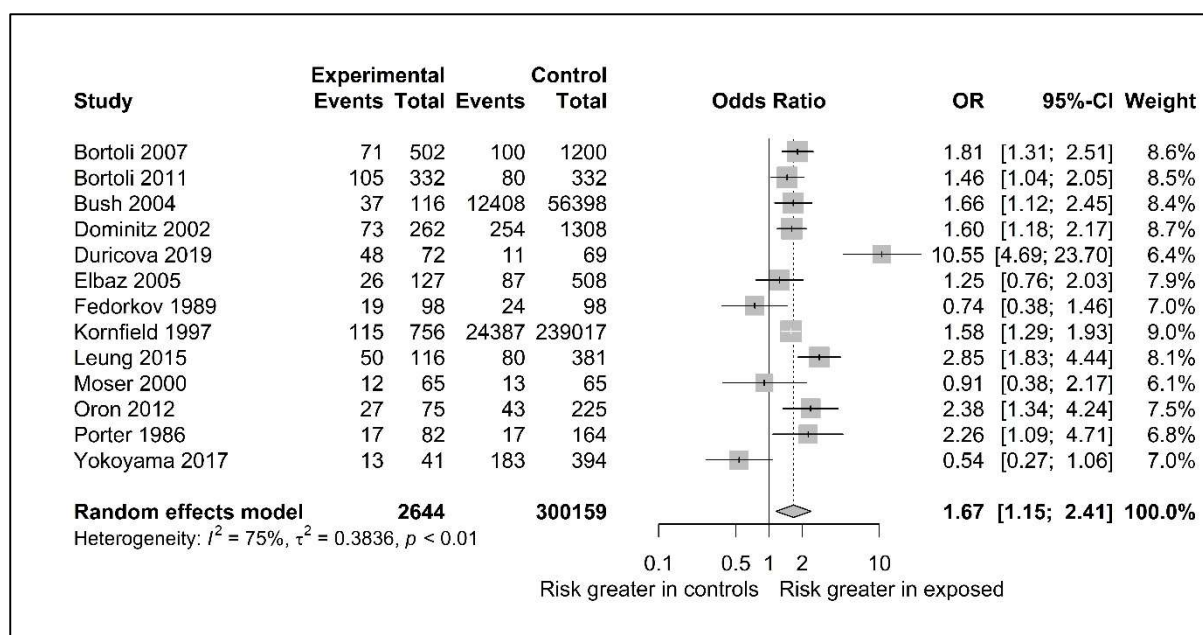


Meta-analysis of Leung et al -cohort studies and registries -Looking at association of Preterm Birth and IBD

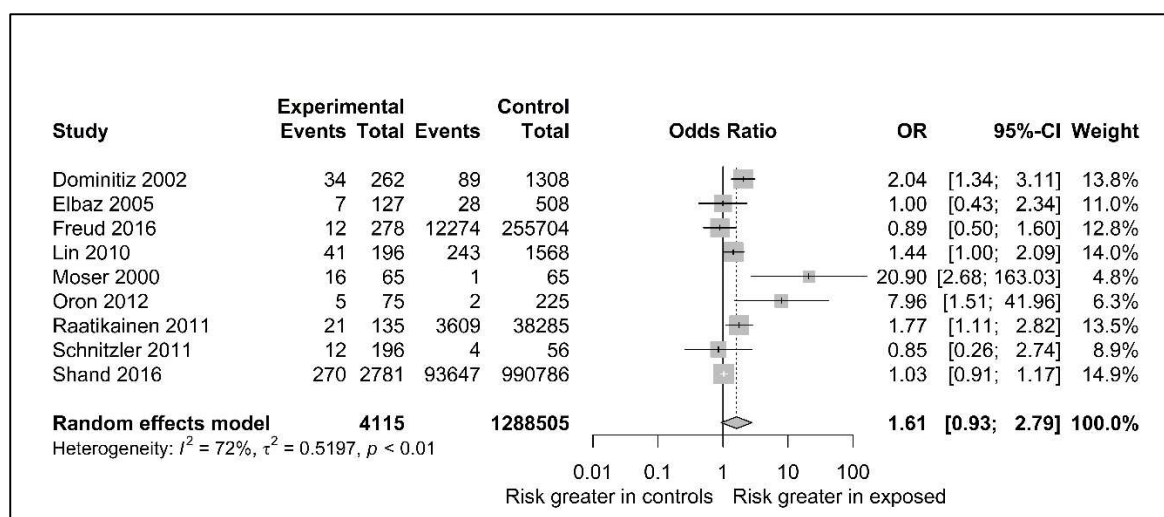


Funnel plot to access the publication bias

Meta-analysis of Cornish and Tandon Looking at the association of Caesarean section and IBD Slight overlap as Cornish 2007 and Tandon 2020 ,Elbaz 2005 only overlapping study

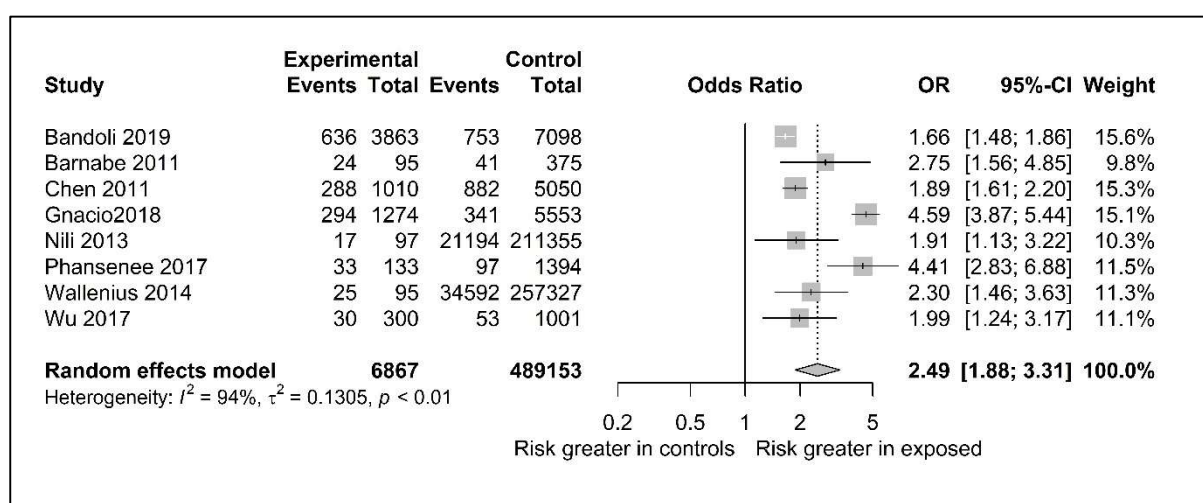


Meta-analysis of cohort and case control studies Leung looking at association of SGA and IBD

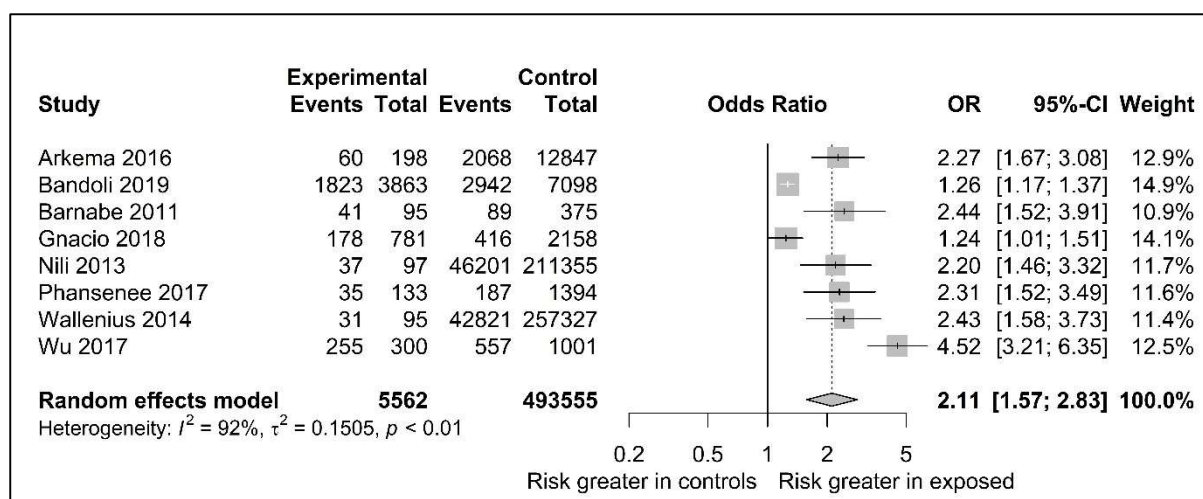


Forest plot SLE

Meta-analysis of Bundhun and HeW Looking at the association of SGA and SLE. No overlap as Bundhun included studies only 2001-2016 and Hew included newer studies

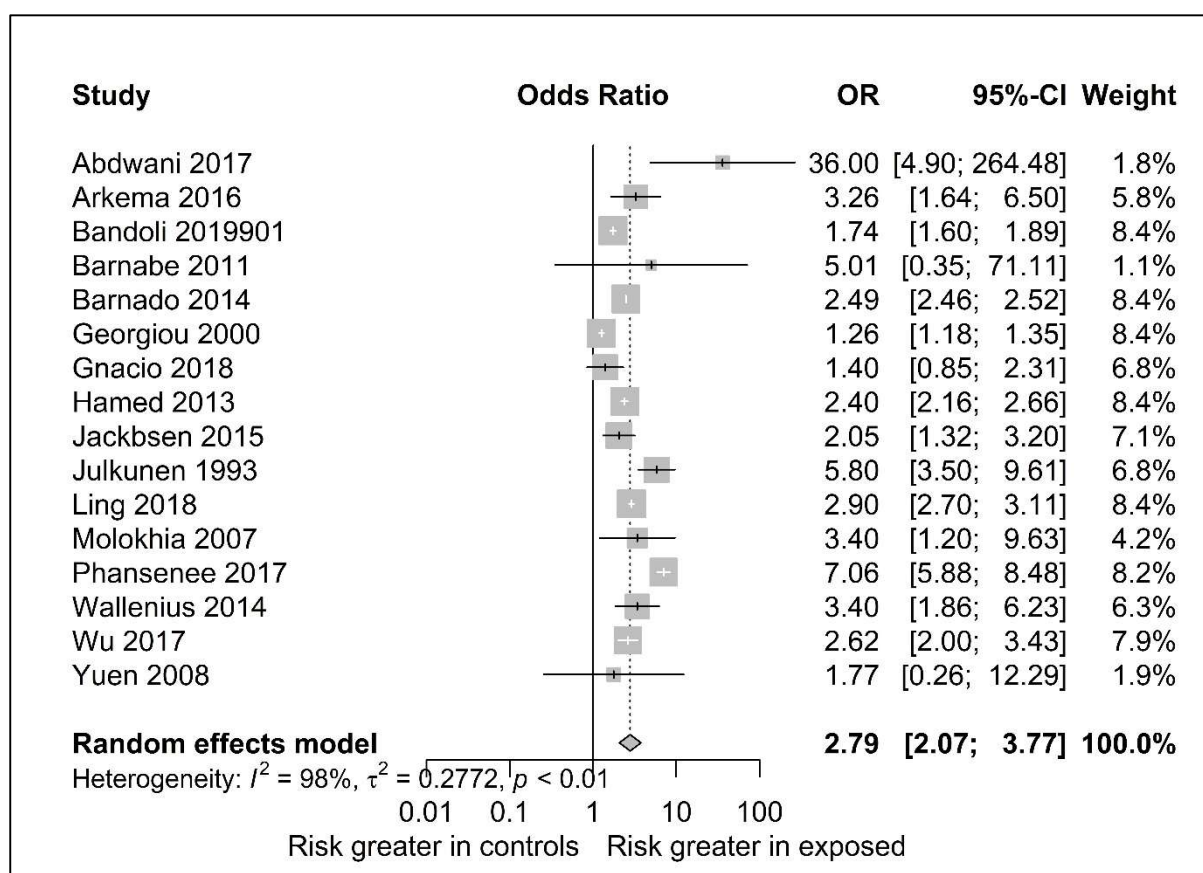


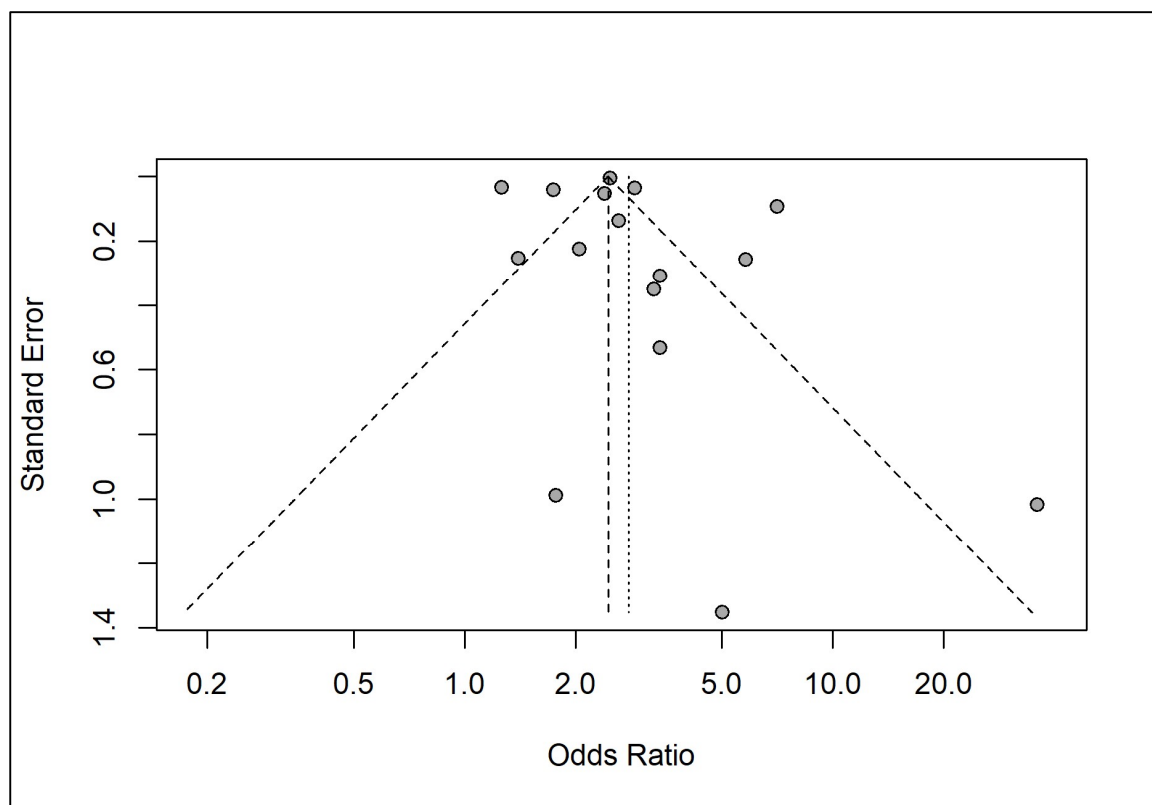
Meta-analysis of Bundhun and HeW Looking at the association of Caesarean section and SLE No overlap as Bundhun included studies only 2001-2016 and Hew included newer studies



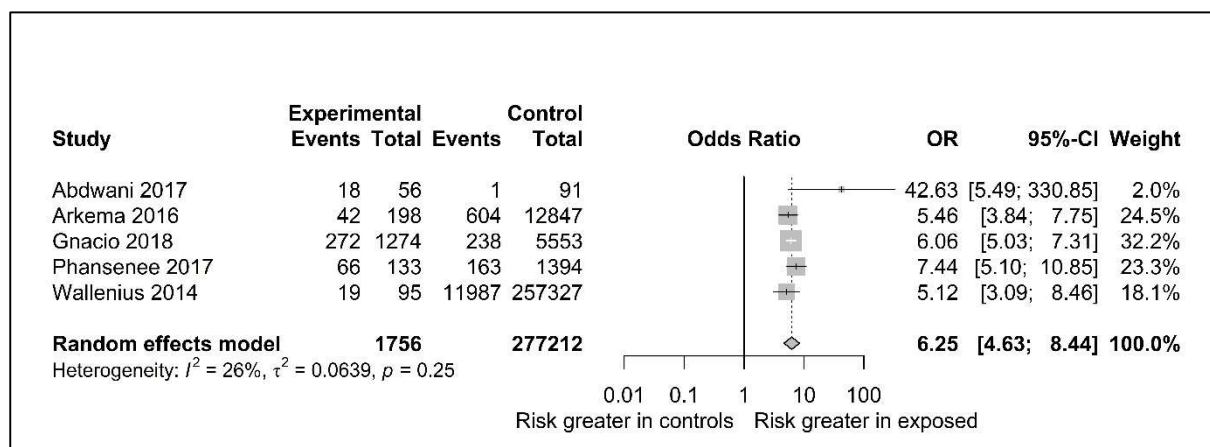
Meta-analysis of Hew ,Bundhun, Wei association pf PTB and SLE-less overlap as He w searched for studies after 2016,whereas Bundhun 2001-2016 and Wei before 2016 and searched different databases, Wei also was looking at other outcomes

Bernardo 2014 and Yuen overlap studies



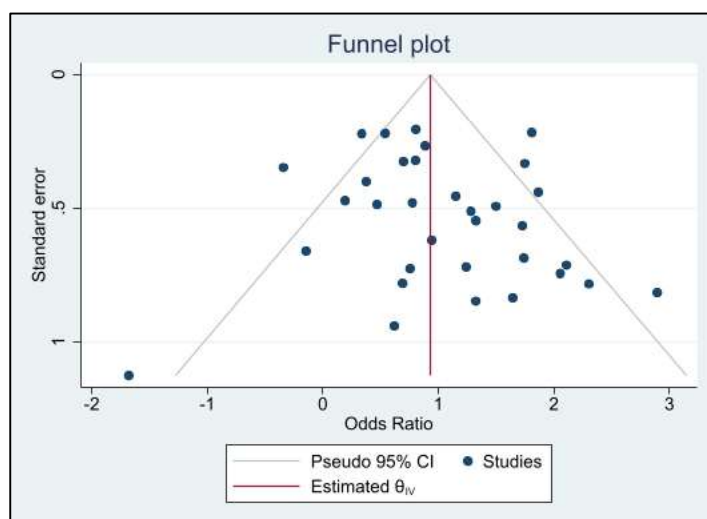
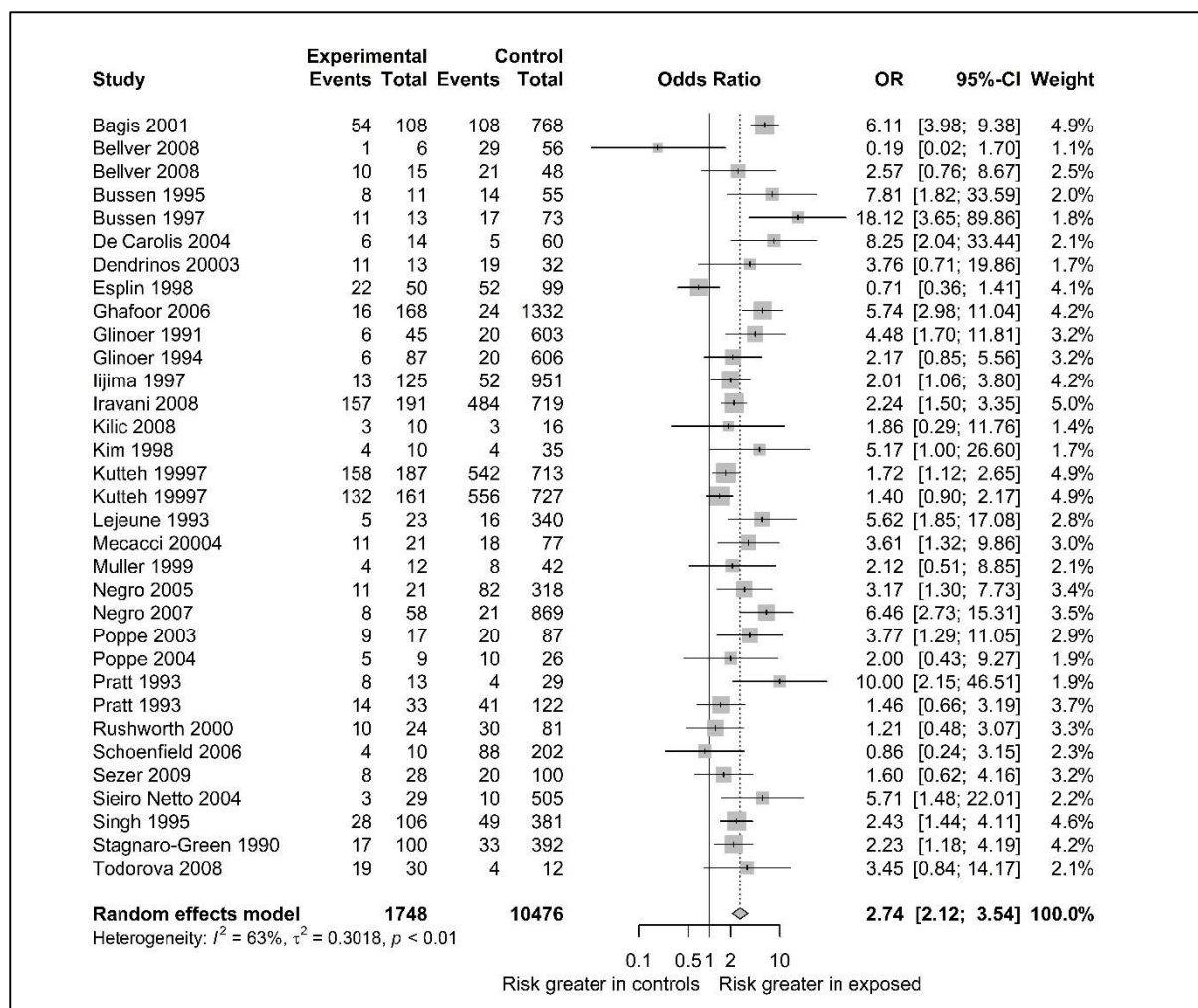


SLE LBW HEW AND BUNDHUN less overlap as He w searched for studies after 2016,whereas Bundhun 2001-2016



Forest plot Thyroid autoimmunity

Meta-analysis of cohort and case control studies looking at association of miscarriage and thyroid autoimmunity Thangiratham



Meta-analysis of cohort and case control studies Chen 2011 looking at association TAA and Miscarriage

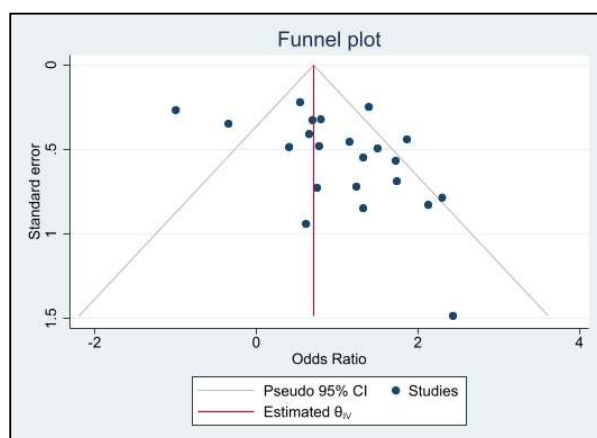
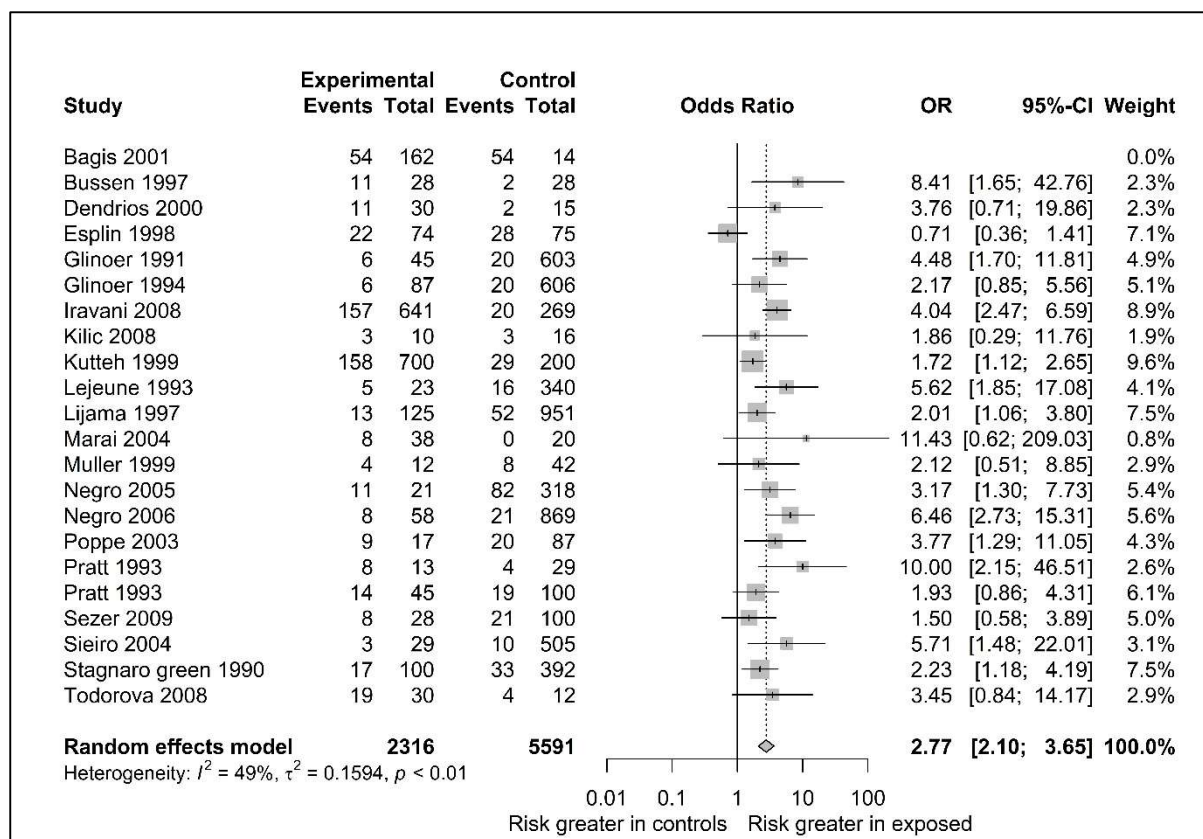
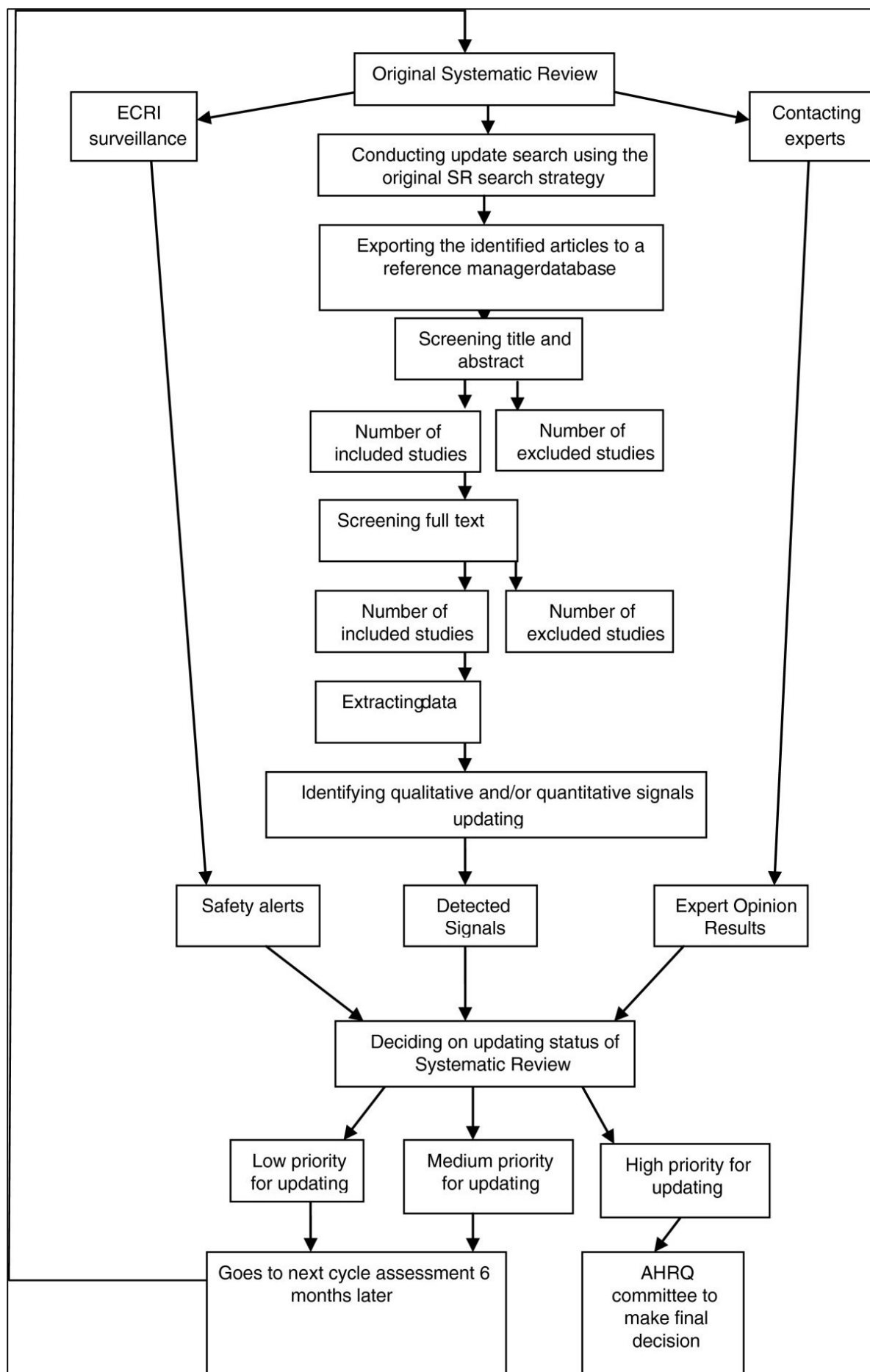


Table 4.9 Evaluation for need to update



Ottawa's label	Ottawa method
	Qualitative criteria for potentially invalidating signals
A1	Opposing findings: a pivotal* trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier
A2	Substantial harm: a pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision-making
A3	A superior new treatment: a pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm
	Qualitative criteria for signals of major changes
A4	Important changes in effectiveness short of 'opposing findings'
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or non-pivotal trial
	Quantitative criteria signals of changes in evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
RAND's label	RAND method indications for the need for an update
1	Original conclusion is still valid, and this portion of the original report does not need updating. This conclusion was reached if we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid
2	Original conclusion is possibly out-of-date, and this portion of the original report may need updating. This conclusion was reached if we found some new evidence that might change the CER conclusion, and/or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out-of-date
3	Original conclusion is probably out-of-date, and this portion of the original report may need updating. This conclusion was reached if we found substantial new evidence that might change the CER conclusion, and/or a majority of

Ottawa's label	Ottawa method
	responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out-of-date
4	Original conclusion is out-of-date. This conclusion was reached if we found new evidence that rendered the CER conclusion out-of-date or no longer applicable; we classified the CER conclusion as out-of-date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce <i>prima facie</i> evidence that a conclusion was out-of-date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, and so on

Abbreviation: CER comparative effectiveness review, FDA Food and Drug Administration.

*a pivotal trial is defined as trial that is published in one of the top five general medical journals or a trial whose sample size is at least triple that of the largest trial in the original systematic review.

Legend: Table 1 presents the criteria used to determine if a conclusion is out of date within an SR (here CER). Criteria A1 to B2 come from the Ottawa method and criteria 1 to 4 are based on the RAND method

Source (flow diagram and tables): Ahmadzai N, Newberry SJ, Maglione MA, Tsertsvadze A, Ansari MT, Hempel S, et al. A surveillance system to assess the need for updating systematic reviews. Syst Rev. 2013;2:104

Table 4.10. General characteristics of systematic reviews included in the umbrella review

Author Year	Geographical area	Countries included	Database searched	search period	Studies included year range	Number of studies included	Study design	Exposure	Outcome	Data synthesis method	Quality assessment tool	Quality of the primary studies	Funding
Arafa 2021.	Egypt	US, Finland Turkey, England	MEDLINE (PubMed) Cochrane Library, and Google Scholar	inception -Oct.- 2020	2002 - 2019	8	Retrospective and prospective cohort studies	Multiple sclerosis	PE,	meta-analysis	NOS	All studies were reported as moderate to high quality	Not reported
Arvanitakis 2022	Greece	Slovenia, USA, Italy, Israel, Denmark, Sweden, Brazil	Medline, Cochrane Library and Scopus	inception till 12th April 2022,	1990 - 2021	18	Cohort and case control studies	Coeliac disease	Miscarriage, IUGR, PE, stillbirths,, PPH	meta-analysis	NOS	Two studies rated as high quality, six studies as moderate, one study as poor quality.	Not reported
Banner 2021	Canada	Norway, Portugal, Brazil, Taiwan, Mexico,	Ovid MEDLINE, (2) Ovid EMBASE, (3) Ovid	inception -July 2020	1968 - 2020	32	randomized controlled trials, prospective	Myasthenia gravis	CS,P TB	Descriptive	Quality Assessment Tool for Case Series	All studies were reported either moderate or low in quality.	The authors received

		Turkey, Tunisia, China, France, China, Switzerland, US, Yugoslavia, Poland, Canada, Spain, Croatia, Canada	EBM Reviews – Cochrane Central Register of Controlled Trials, (4) PubMed (Non-Medline records), (5) Web of Science and (6) LILACS (Latin American & Caribbean Health Science Literature).				ve or retrospective cohort studies and case series o						no financial support for the research, authorship and/or publication of this article
Blagojevic 2020	USA	Italy, Egypt, USA	PubMed, Cochrane, EMBASE, and Web of Science.	1950 and February 1, 2018,	1989 - 2017	16	randomized clinical trials, retrospective or observational studies, registries, case series with and without controls, and case reports with ≥ 10 pregnancies.	Systemic sclerosis	PE, LBW, PTB, IUGR, Miscarriage	Meta-analysis	NOS	One study reported to be of high quality, four were of medium quality, and three were of low quality	Not reported
Bundhun 2017.	China	Sweden, Canada, USA, Taiwan, Denmark, USA, Trinidad, Iran, Norway, Canada, Quebec	Cochrane Database of Randomized Controlled Trials, EMBASE (www.sciencedirect.com) database, and Medline database:	2001-2016	2001 - 2016	11	Case control, Cohort studies	SLE	PE, EP, CS, miscarriage, SGA, LBW, PTB	Meta-analysis	Not reported	No information	This research was supported by National Natural Science Foundation of China (No. 81560046), Scientific

													Project of Guangxi Higher Education (No. KY2015ZD028) and the Youth Science Foundation of Guangxi Medical University (No. GXMUYSF201308)
Chen 2011.	China	Brazil, Belgium, USA, Japan, Netherlands, Italy, Bulgaria, Turkey	Medline, PubMed, EMBASE and the Cochrane library	inception -2010	2005 - 2010	22	Case control studies and cohort studies	TAA(a	Miscarriage	Meta-analysis	Not reported	No information	Not reported
Cornish 2007	UK	NA	Medline	1980 and 2006	1986 - 2005	13	case-control studies and cohort studies	IBD	PTB, SGA, SB, CS,	MA	Quality of Reporting of Meta-analyses (QUORUM) guidelines.	Out of 12 studies six were reported to be high quality	Not reported
Dong 2020	USA	NA	The PubMed, EMBASE, Web of Science, and CENTRAL databases	inception -2018	1996 - 2008	17	case control and cohort study, observational, case series	TAA(all)	Recurrent miscarriage	MA	NOS	No information	Not reported
Dong 2020	China	America, China, Oman, Thailand, Sweden, Egypt, Danish, Norway, Canada	Web of Science, Cochrane Library, and PubMed	inception to June 30, 2018	2011 - 2018	10	Cohort and case control	SLE	PE	MA	NOS	All studies were reported high in quality	Not reported
Geng 2022	China	NA	CNKI, Wanfang Database, Cqvip	Inception - March, 2022	2005 to March	9	Cohort studies	Sjogren's syndrome	Miscarriage	MA	NOS	Out of nine studies four reported to be high quality	No funding was

			Database , PubMed, Web of Science, Embase and Cochrane Library		h 2022				PTB, LBW				recei ved.
He W 2020	China	NA	MEDLINE (PubMed , Cochrane Central, Web of Science, EMBASE, and Google Scholar	2017- 2019	2017 - 2019	6		SLE	PE, SB, Fetal loss, Misc arria ge, ,CS ,IUG R, GDM ,PTB, SGA, LBW	MA	Grade	All studies reported to be moderate quality	Non e
HeX 2012	China	USA, Japan, Belgium, Finland, China, Europe, India	PubMed, Embase, and Wangfan g	inception -2012	2000 - 2012	1 1	prospecti ve cohort studies	TAA(all)	Prete rm birth	MA	NOS	All studies reported to be high quality	Non e
Huang 2022	China	sedan,De nmark,Can ada,USA ,switzerla nd	Medline (PubMed , EMBASE, and Web of Science	Inception -2021	2003 - 2021	1 8	observati onal studies including cohort, case- control, and cross- sectional studies	Rheumat oid arthritis	PE, GHT ,GD M, ,PTB LBW, SGA, stillbi rth/ neon ata/ perin atal deat h, misc arria ge	MA	NOS	Four studies were of moderate quality, and the rest were of high quality.	This stud y was fund ed by the Medi cal Healt h Scien ce and Tech nolo gy Proje ct of Zheji ang Provi ncial Healt h Com missi on (202 OKY4 29)
Koreva ar 2020	Netherl ands	Netherla nd, Chile, Australia	Ovid MEDLINE , EMBASE, Web of Science, Cochrane Central Register	inception 2018	1990 - 2018	1 9	Cohort studies	TPO	PTB	Meta- analysis	NA	All studies reported to be high quality	This work was supp orte d by repli catio n

			of Controlle d Trials, and Google Scholar database s										studi es grant 401. 16.0 20 from the Neth erlan ds Orga nizati on for Scien tific Rese arch.
Leung 2021	Canada	UK, Spain, Europe, Netherla nds, Norway, Korea, Italy France, Israel, India, Finland, Portugal, Australia , Canada	g Medline, Embase, and the Cochrane Central Register of Controlle d Trials	inception -2019	1990 - 2018	7 2	Cohort and case control	IBD	PTB, LBW, SGA	Meta- analysis	NOS	Out of 62 studies, 36 studies reported to be moderate quality, and 23 studies were high quality studies.	Not repo rted
Li, M 2016	China	Asia, Europe	MEDLINE , Excerpta Medica, Wan Fang, China Biological Medicine disc, and China National Knowled ge Infrastruc ture	inception -2016	1997 - 2016	1 8	retrospec tive and prospecti ve cohort studies	TAA (all)	PTB	MA	NOS	All studies were rated high quality studies	Nati onal Natu ral Scien ce Foun datio n of Chin a
Lou 2020	China	Chile China, Kuwait, Turkey, Finland, USA, Japan, India, Pakistan, Ireland, Greece	PubMed, Embase, MEDLINE , and Cochrane	inception -2020	2008 - 2020	4 4	Cohort and case control studies	TAA (all)	GDM	MA	Revman	No information	Natu ral Scien ce Foun datio n of Chin a
Maguir e 2020	Ireland	Hungary, Norway Croatia, Brazil, Canada, China, Sweden, Turkey, Iceland, Korea,	EMBASE, Medline (OVID), CINAHL, Cochrane library (central), Web of Science, and	inception -2019	1980 - 2019	1 8	Case- control trials, observati onal studies, cross sectional studies and case	AxSPa	CS , PE, PTB, GDM IUGR ,SB, LBW, SGA	MA	NOS	Ten studies reported to be high quality, Four moderate quality and four poor qualities.	e Irish Socie ty of Rheu mato logy on beha lf of

		USA, Denmark, Switzerland	Maternity and Infant Care (MID IRS online)				series (with n >5) were considered for inclusion						UCB as part of the Rheumatology Patient Improvement Fund for Ireland
Milandi 2020	Netherlands	Spain, UK, Netherlands	MEDLINE, EMBASE, Web of Science, Cochrane Library, and CINAHL	March to October 2018	1993 - 2019	5	cohort studies	TPO	PPD	MA	NOS	All the included studies were considered as high quality.	This work was supported by Ministero dell'Università e della Ricerca Scientifica, Italy.
Modrego 2021	Spain	NA	PubMed, Cochrane Library and EMBASE	1967 to October 2019	1981 - 2019	17	cohort studies	Multiple sclerosis	PTB, LBW	MA	Not mentioned but quality of primary studies was analysed.	No information	None
O'Toole 2015	USA	NA	PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov	1980 and 2014	1986 - 2014	23	case control and cohort studies	IBD	PTB, SGA, SB, CS	MA	NOS	All studies reported to be moderate to low study quality	Not reported
Saccone 2016	Italy	Italy, UK, Sweden, Israel, Ireland, Northern Europe.	Medline, PROSPERO, Scopus, ClinicalTrials.gov, EMBASE, Science direct, the Cochrane Library) were searched	inception -2015	2000 - 2014	10	cohort studies	Coeliac disease	PTB, IUGR, SB, LBW, SGA, PE	MA	ROB assessment tool	All studies were reported to be high quality studies	Not reported

Sim 2023	UK	NA	MEDLINE , EMBASE, Cochrane , and Scopus.	Inception - May 2022	2009 - 2020	13	Cohort and case control studies	Rheumatoid arthritis	Stillbirth, PTB	MA	NA	Six studies were reported to be high quality and three were moderate quality	Not reported
Talavera 2021	USA	UK, Denmark, USA	MEDLINE , Web of Science, and CINAHL databases	inception -2020	2012 - 2019	5	cohort, case-control, and cross-sectional studies	IBD	EP	MA	GRADE (Grading of Recommendations, Assessment Development and Evaluations)	All studies are categorized as moderate or low	None
Tandon 2020	Canada	NA	Medline, Embase and Cochrane Central Register of Controlled Trials	inception -2015	2007 - 2017	53	Case control, case series, cohort studies	IBD	CS, GDM , PE, miscarriage, termination of pregnancy	MA	NOS	12 studies moderate quality and 34 studies were high quality	None
Tersigni 2014	Italy	NA	Medline and Embase Current Contents databases	inception -2012	1996 - 2013	24	Case control, case series, cohort studies	Coeliac disease	miscarriage, recurrent miscarriage, stillbirth, IUGR , LBW, SGA)	MA	NOS	No information	None
Thangaratnam 2011	UK	NA	s Medline, Embase, Cochrane Library, and SCISEARCH	inception -2011	1991 - 2011	36	Case control, case series, cohort studies	TPO	Miscarriage, PTB	MA	NOS	Nine studies reported high quality and ten reported moderate quality	None
Tong 2016	China	NA	g PubMed, Embase, and Cochrane database	inception -2015	2009 - 2015	7	Case control, case series, cohort studies	TPO	IUGR , LBW, miscarriage	MA	NOS	All 13 studies had high quality	Not reported
Upala 2015	USA	NA	MEDLINE and EMBASE	inception -2016	2000 - 2015	7	Case control, case series, cohort studies	Sjögren's syndrome	PTB, SB, Miscarriage , LBW, SGA, IUGR ,	MA	NOS	One high quality study, 3 low quality studies and rest were evaluated as moderate quality	None

Wei 2017	China	Saudi Arabia, USA, China, Spain, China, Greece, Egypt, Korea, Turkey, UK, Japan, Mexico	PubMed, Embase, Medline and Cochrane Library	inception -2016	1990 - 2016	24	Case control, case series, cohort studies	SLE	PTB	MA	Science Citation Index	All high-quality studies	This work was supported by the National Natural Science Foundation of China (Grant Number 81301371), the Guangdong Natural Science Foundation
Xie 2021	China	USA, Israel, China, Denmark, Sweden, Canada	PubMed, EMBASE and the Cochrane Library)	inception -2020	2007 - 2020	16	Case control or cohort	Psoriasis and psoriatic arthritis	Psoriasis-CS, PTB, PE or PE, GDM GTN, Miscarriage, APH/PPH, SGA, LBW, Neonatal mortality SB	MA	NOS	No information	National Natural Science Foundation of China
Yu 2017	China	NA	PubMed, ISI Web of Science, Cochrane Library, Embase and SCOPUS	1990-2017	1990 - 2017	100	Case control or cohort	databases and 2 from reference lists.	PTB, LBW, SGA, SB, GHT, PE, CS	type 1 DM		No information	Not reported
Zhang 2016	China	Belgium, Brunei, Spain, Italy, UK, China, India,	PubMed, Cochrane Library, Science Direct, Embase,	inception -2015	2003 - 2015	7	Case control or cohort	TPO	adverse obstetric outcome	MA	NOS	No information	Not reported

			Chinese Biomedicine and Wanfang data						s: miscarriage, PTB, GHT, placental abruption, IUGR				

GHT-gestational hypertension, PE-pre-eclampsia, GDM gestational diabetes mellitus, CS-Caesarean section, IUGR-intrauterine growth restriction, SGA-small for gestational age, PTB-preterm birth, LBW-low birth weight, AxSpa-axial spondyloarthritis, IBD-inflammatory bowel disease, SLE-systemic lupus erythematosus, T1DM-type 1 diabetes mellitus, NOS-Newcastle Ottawa scale for quality assessment, TPO thyroid peroxidase antibodies, TAA- thyroid antibodies all,

Table 4.11 Tabular presentation of findings: Meta-analysis

Autoimmune condition	Author Year	Outcome	No of studies	No. of participants	Summary estimates	I ²
Multiple sclerosis	Arafa 2021	Pre-eclampsia	8	10012075	OR 0.99 (0.89-1.09)	I ² =0%
Coeliac disease	Arvanitakis 2022	Caesarean section	9	17961825	RR 1.10 (1.03-1.16)	I ² =0%
		Miscarriage	7	86219	RR 1.35 (1.10-1.65)	I ² =62%
		Postpartum haemorrhage	4	15030472	RR 1.11 (0.96-1.27)	I ² =0%
		Intrauterine Growth restriction	5	17472005	RR 1.68(1.34-2.10)	I ² =39%
		Pre-eclampsia	4	14887501	RR 1.04(0.88-1.23)	I ² =0%
		Stillbirth	6	453365	RR 1.57 (1.17-2.10)	I ² =51%
		Preterm birth	9	19445871	RR 1.29 (1.12-1.49)	I ² =58%
Systemic sclerosis	Blagojevic 2020	Miscarriage	6	5623	OR 1.6 (1.29-2.22)	P=0.006
		Intrauterine growth restriction	3	11203959	OR 3.2 (2.21-4.53)	P=0.48
		Preterm birth	7	12195889	OR 2.4 (1.14-4.86)	P=0
		Pre-eclampsia	2	3959	OR 2.2 (2.21-4.53)	P=0.10

		Low birth weight	4	4577	OR 3.8 (2.16-6.56)	P=0.80
		Gestational hypertension			OR 2.80 (2.28-3.39)	P=0.70
		Caesarean section			OR 2.30 (1.37-3.80)	
SLE	Bundhun 2017	Caesarean section	4	482389	RR 1.85 (1.63-2.10)	I ² =0%
		Pre-eclampsia	4	288306	RR 1.91 (1.44-2.53)	I ² =44%
		Gestational hypertension	4	498259	RR 1.99 (1.54-2.56)	I ² =38%
		Miscarriage	4	2974	RR 1.51 (1.26-1.82)	I ² =38%
		Ectopic pregnancy	2	1461	RR 1.79 (0.57-5.59)	I ² =0%
Thyroid autoimmunity (all)	Chen 2011	Miscarriage	14	5469	OR 2.77 (2.10-3.65)	I ² =49%
Inflammatory bowel disease	Cornish 2007	Stillbirth	4	242174	OR 1.48 (0.89 - 2.47)	I ² =11.3%
		Caesarean section	6	298934	OR 1.50 (1.26 -1.79)	I ² =6.9%
		Preterm birth	8	299821	OR 1.87 (1.52 -2.31)	I ² =9.4%
Thyroid autoimmunity (all)	Dong 2020	Recurrent pregnancy loss-	17	3600	OR 1.94 (1.43-2.84)	I ² =51%
SLE	Dong 2020	Pre-eclampsia	10	9456789	RR 2.99 (2.31-3.88)	I ² =76%
Sjogren's syndrome	Geng 2022	Miscarriage	5	-	RR 8.85 (3.10-25.26)	I ² =53%
		Preterm birth	9	-	RR 2.27 (1.46-3.52)	I ² =63%
		Low birth weight	5	-	RR 1.99 (1.34-2.97)	I ² =42%
Systemic Lupus erythematosus	He W 2020	Preterm birth	6	8797314	RR (2.33 (1.78-3.05)	I ² =94%
		Caesarean section	4	11651	RR 1.38	I ² =95%

					(1.11-1.70)	
		Gestational diabetes mellitus	4	9603	RR 0.97 (0.57-1.60)	I ² =80%
		Pre-eclampsia	4	8789888	RR 3.38 (3.15-3.62)	I ² =0%
		LBW	3	8501	RR 4.78 (3.65-6.26)	I ² =59%
		Stillbirth	2	1499	RR 16.49 (2.95-92.13)	I ² =0%
		IUGR	2	1448	RR 6.98 (0.33-147.02)	I ² =79%
		Miscarriage	3	8792890	RR 4.70 (3.02-7.29)	I ² =66%
Thyroid autoimmunity (all)	He X 2012	Preterm birth	14	Both 40609	RR 1.41 (1.08-1.84)	I ² =75%
			9	Tgab 19191	RR 0.88 (0.60-1.29)	I ² =71%
			3	TPOab 11108	RR 1.69 (1.9-2.41)	I ² =0%
Rheumatoid arthritis	Huang 2022	Caesarean section	11	NA	OR 1.39 (1.24-1.55)	I ² =85%
		Pre-eclampsia	7	NA	OR 1.48 (1.19-1.83)	I ² =81%
		Gestational hypertension	4	NA	OR 1.34 (1.07-1.68)	I ² =53%
		Gestational diabetes mellitus	4	NA	OR 1.40 (0.94-2.09)	I ² =82%
		Miscarriage	2	NA	OR 1.16 (1.04-1.29)	I ² =68%
		Small for gestational age	13	NA	OR 1.49 (1.22-1.82)	I ² =87%
		Low birth weight	5	NA	OR 1.45 (1.30-1.63)	I ² =0%
		Preterm birth	13	NA	OR 1.58 (1.44-1.74)	I ² =63%
		Stillbirth/neonatal/perinatal death	4	NA	OR 1.38 (1.09-1.74)	I ² =0%
	Jiamin	Stillbirth	3	872048	OR	I ² =0%

Rheumatoid arthritis	2023				1.99 (1.12-3.54)	
		Preterm birth	6	9919225	OR 1.83 (1.55-2.17)	I ² =67%
Thyroid autoimmunity (TPO)	Korevar 2020	Preterm birth	14	42608	OR, 1.33 (1.15-1.56)	I ² =0%
Inflammatory Bowel disease	Leung 2021	Preterm birth observational	9	5150	OR 2.13 (1.35-3.36)	I ² =66%
		Preterm birth registries	7	1706443	OR 1.57 (1.37-1.79)	I ² =34%
		Small for gestational age observational	4	854	OR 2.77 (0.70-10.96)	I ² =76%
		Small for gestational age registries	6	1287651	OR 1.36 (0.99-1.86)	I ² =74%
		Low birth weight observational	5	1014	OR 2.78 (1.16-6.66)	I ² =60%
		Low birth weight-registries	6	1161316	OR 2.45 (1.43-4.21)	I ² =91%
Thyroid autoimmunity (TPO)	Li M 2016	Preterm birth	19	42733	OR 1.88 (1.32-2.67)	I ² =83%
Thyroid autoimmunity (all)	Lou J 2021	Gestational diabetes mellitus TPO	13	31842	OR 1.65 (1.13-2.40)	I ² =74%
		Gestational diabetes mellitus TgAb	3	7284	OR 1.88 (1.13-3.12)	I ² =0%
		Gestational diabetes mellitus both	2	4445	OR 0.69 (0.44-1.07)	I ² =0%
		Gestational diabetes mellitus All combined	18	43571	OR 1.49 (1.07-2.07)	I ² =75%
Axial spondyloarthritis	Maguire, 2020	Caesarean section	12	121396272	OR 1.85 (1.462-3.0)	I ² =72%
		Preterm birth	11	1215684	OR 0.84 (0.39-1.81)	I ² =93%
		Pre-eclampsia	7	1210607	OR 1.74 (0.85-3.54)	I ² =81%
		Gestational diabetes Mellitus	3	895	OR 0.88 (0.24-3.21)	I ² =45%

		Intra-uterine growth retardation	2	148	OR 1.05 (0.24-4.49)	I ² =0%
		Low birth weight	8	15842	OR 1.47 (0.98-2.21)	I ² =34%
		Stillbirth	5	2795	OR 0.70 (0.26-1.85)	I ² =0%
		Small for gestational age	5	1207386	OR 1.66 (0.93-2.25)	I ² =72%
		Miscarriage	1	56	OR 0.75 (0.03-19.77)	I ² =0%
Thyroid autoimmunity (TPO)	Milandi 2020	Postpartum depression	5	2483	RR 1.49 (1.1-2.00)	I ² =47%
IBD	O toole 2015	Stillbirth	10	2964983	OR 1.57 (1.03-2.38)	I ² =30
		Preterm birth	33	4638932	OR 1.85 (1.67-2.05)	I ² =31%
		Small for gestational age	13	4132914	OR 1.36 (1.16-1.60)	I ² =56%
Coeliac disease	Saccone 2016	Preterm birth-unadjusted	5	4686461	OR 1.40 (1.18-1.66)	I ² =43%
		Preterm birth-adjusted	5	-	OR 1.35 (1.09-1.66)	I ² =0%
		Intra-uterine growth retardation	6	2903065	OR 2.48 (1.32-4.67)	I ² =77%
		Small for gestational age	4	6906	OR 4.52 (1.02-20.08)	I ² =95%
		Low birth weight	3	3177908	OR 1.63 (1.06-2.51)	I ² =75%
		Stillbirth	5	376032	OR 4.84 (1.08-21.75)	I ² =90%
		Pre-eclampsia	5	519627	OR 2.45 (0.90-6.70)	I ² =88%
Coeliac disease or Inflammatory bowel disease (IBD)	Talvera 2021	Ectopic pregnancy-IBD	2	9276714	OR 1.26(1.11-1.44)	I ² =19%
		Ectopic pregnancy Coeliac disease	2	70898	OR 1.21 (0.85-1.71)	I ² =48%

		Ectopic pregnancy ulcerative colitis	2	9276714	OR 1.03 (0.87-1.23)	I ² =0%
		Ectopic pregnancy Crohn's disease	2	9276714	OR 1.51 (1.21-1.88)	I ² =52%
Inflammatory bowel disease (IBD)	Tandon 2020	Caesarean section	7	3174	OR 1.79 (1.16- 2.77)	I ² =83%
		Pre-eclampsia	2	800	OR 4.65 (0.76-28.35)	I ² =0%
		Miscarriage	3	1700	OR 1.63 (0.49-5.43)	I ² =90%
		Gestational diabetes mellitus	3	927	OR 2.96 (1.47-5.98)	I ² =0%
Coeliac disease	Tersigni 2014	Intra-uterine growth retardation	3	400	OR 8.73 (3.23-23.58)	I ² =0%
		Small for gestational age	2	841	OR 2.36 (0.40-14.13)	I ² =0%
		Recurrent miscarriage	6	1164	OR 5.82 (2.30-14.74)	I ² =0%
		Adverse pregnancy outcomes	15	8983	OR 4.97 (2.88-8.57)	I ² =0%
Thyroid autoimmunity (all)	Thangaratina m,2011	Preterm birth	5	12566	OR 2.07 (1.17-3.68)	I ² =78%
		Miscarriage-case control studies	10	3604	OR 1.80 (1.25- 2.60)	I ² =56%
		Miscarriage-cohort studies	19	8522	OR 3.90 (2.48 .12)	I ² =81%
Thyroid autoimmunity (TPO)	Tong 2016	Intra-uterine growth restriction	7	15269	OR 1.57 (0.77-3.18)	I ² =82%
Sjogren syndrome	Upala 2015	Stillbirth	3	NA	OR 1.05 (0.37–2.97)	I ² =0%
		Preterm birth	5	NA	OR 2.10 (0.59– 7.46)	I ² =59 %
		Fetal loss	4	NA	OR 1.77 (1.28–2.46)	I ² =0%
Systemic lupus erythematosu s	Wei 2017	Preterm birth	6	NA	RR 2.05 (1.27-3.32)	I ² =66.5%
Psoriasis	Xei 2021	Caesarean section	5	NA	OR 1.26	I ² =92%

					(1.05-1.51)	
		Preterm birth	6	NA	OR 1.22 (1.04-1.42)	I ² =83.1%
		Miscarriage	2	NA	OR 1.10 (1.01-1.20)	I ² =0%
		Small for gestational age	4	NA	OR 1.01 (0.92-1.11)	I ² =49%
		Stillbirth	3	NA	OR 1.17 (0.84-1.63)	I ² =67%
		Low birth weight	4	NA	OR 1.14 (0.87-1.49)	I ² =81%
		Gestational hypertension	3	NA	OR 1.29 (1.15-1.45)	I ² =32%
		Pre-eclampsia	5	NA	OR 1.25 (1.09-1.42)	I ² =66%
		Gestational diabetes mellitus	3	NA	OR 1.19 (1.09-1.30)	I ² =0%
Type 1 diabetes mellitus	Yu 2017					
		Preterm birth	15	NA	OR 4.36 (3.72-5.12)	NA
		Small for gestational age 10 th percentile	7	NA	OR 0.68 (0.56-0.83)	NA
		Stillbirth	12	NA	OR 3.97 (3.44-4.58)	NA
		Gestational hypertension	7	NA	OR 2.68 (1.85-3.89)	NA
		Pre-eclampsia	10	NA	OR 4.19 (3.08-5.71)	NA
		Caesarean section	17	NA	OR 3.97 (3.31-4.77)	NA
Thyroid autoimmunity (TPO)	Zhang 2016	Miscarriage	9	13301	OR 2.02 (1.13-3.62)	I ² =65%
		Gestational hypertension	8	20599	OR 1.29 (1.00-1.45)	I ² =0%
		Small for gestational age	3	9161	OR 1.61 (0.211.12)	I ² =89%
		placental abruption in pregnancy	3	13394	OR 0.42 (0.12-1.43)	I ² =0%

		Preterm birth	9	20573	OR 1.39 (1.11-1.76)	I ² =0%
Psoriatic arthritis	Xei 2021	Caesarean section	4	NA	OR 1.45 (1.27-1.66)	I ² =0%
		Preterm birth	4	NA	OR 1.48 (1.24-1.78)	I ² =0%
		Miscarriage	1	NA	OR 1.35 (0.79-2.32)	I ² =0%
		Small for gestational age	3	NA	OR 0.99 (0.72-1.36)	I ² =8%
		Stillbirth	3	NA	OR 1.06 (0.46-2.46)	I ² =0%
		Low birth weight	2	NA	OR 1.15 (0.84-1.58)	I ² =0%
		Gestational hypertension	2	NA	OR 1.49 (1.09-2.06)	I ² =0%
		Pre-eclampsia	3	NA	OR 1.45 (1.13-1.85)	I ² =0%
		Gestational diabetes mellitus	5	NA	OR 1.26 (0.90-1.77)	I ² =0%

OR=odds ratio, RR=Risk ratio

Table 4.12 Tabular presentation of findings: Narrative syntheses

Autoimmune condition	Author year	Outcome	No. of Studies included	Sample size	Narrative summary	Authors conclusion	Quality of the review (AMSTAR 2 rating)
Myasthenia gravis	Banner 2022	Caesarean section	31	824	The overall rate of caesarean delivery done for MG was 25/824 (3.0%), with an additional 249/824 (30.2%) women having a caesarean delivery for an	Women with MG are at increased risk of requiring assisted vaginal delivery or caesarean delivery compared to	Low

					obstetric indication	the general population	
		Preterm birth, less than 34 weeks	19		PTB less than 34- and 37-weeks' gestation occurred in 14/327 (4.3%) and 69/579 (11.9%) pregnancies, respectively.	14/327 (4.3%) and 69/579 (11.9%) pregnancies, respectively	
		Preterm birth, less than 37 weeks	25				
		Small for gestational age	12	250	gestational age, 55/ 390 (14.1%) neonates were smaller than the 10th percentile.		
Multiple sclerosis	Modrego 2021	Preterm birth Or Low birthweight	17	NA	Seventeen studies focused specifically on the effects of MS on pregnancy with peripartum outcomes; 14 were retrospective and three were prospective	In 12 of them, there were no significant differences in preterm deliveries, in two retrospective cohorts, there was an increased number of infections and preterm deliveries an increased number of preterm deliveries and low birth weight, low birth weight.	Low

Supplementary tables and figures chapter 5

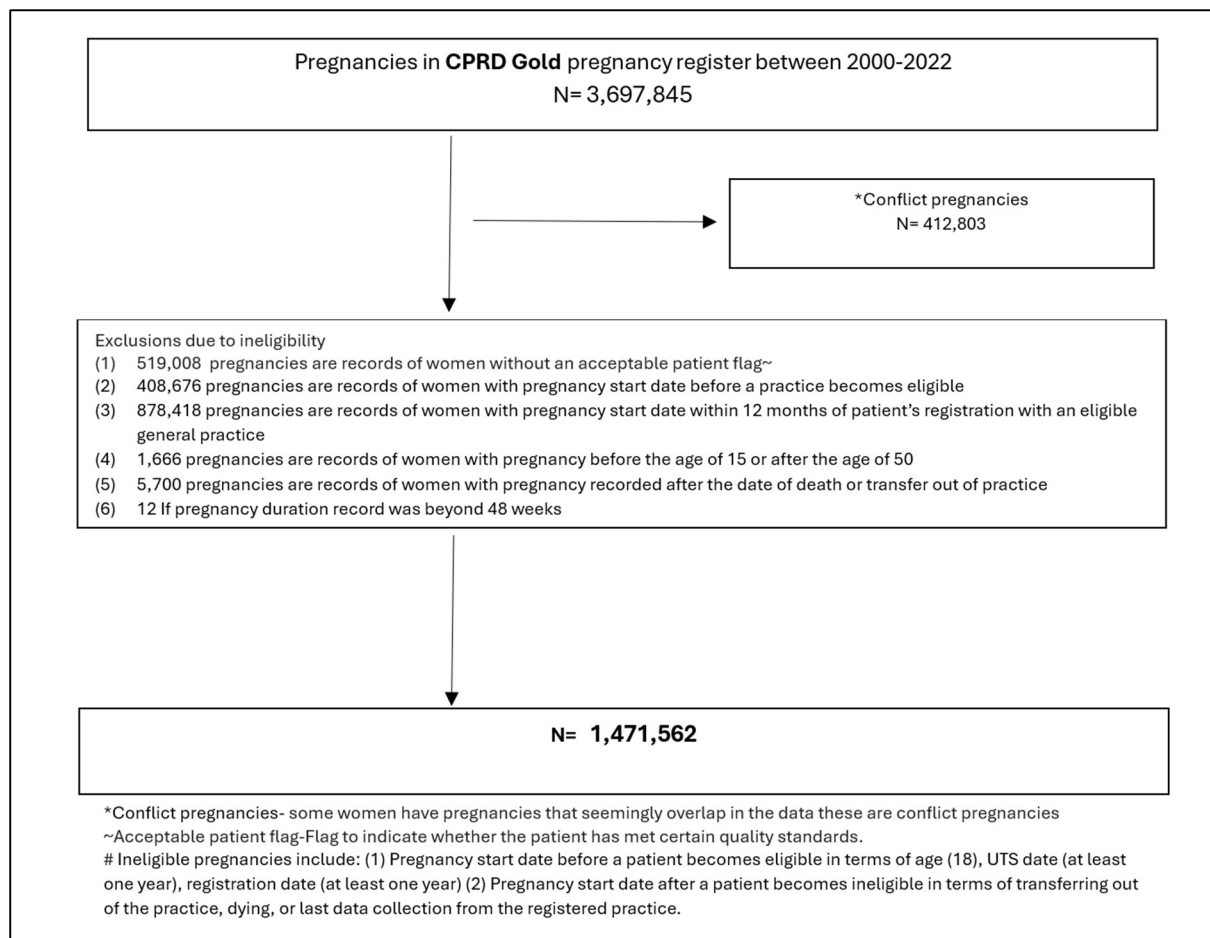


Figure 5.1 Flowchart of the study selection for CPRD Gold pregnancy cohort

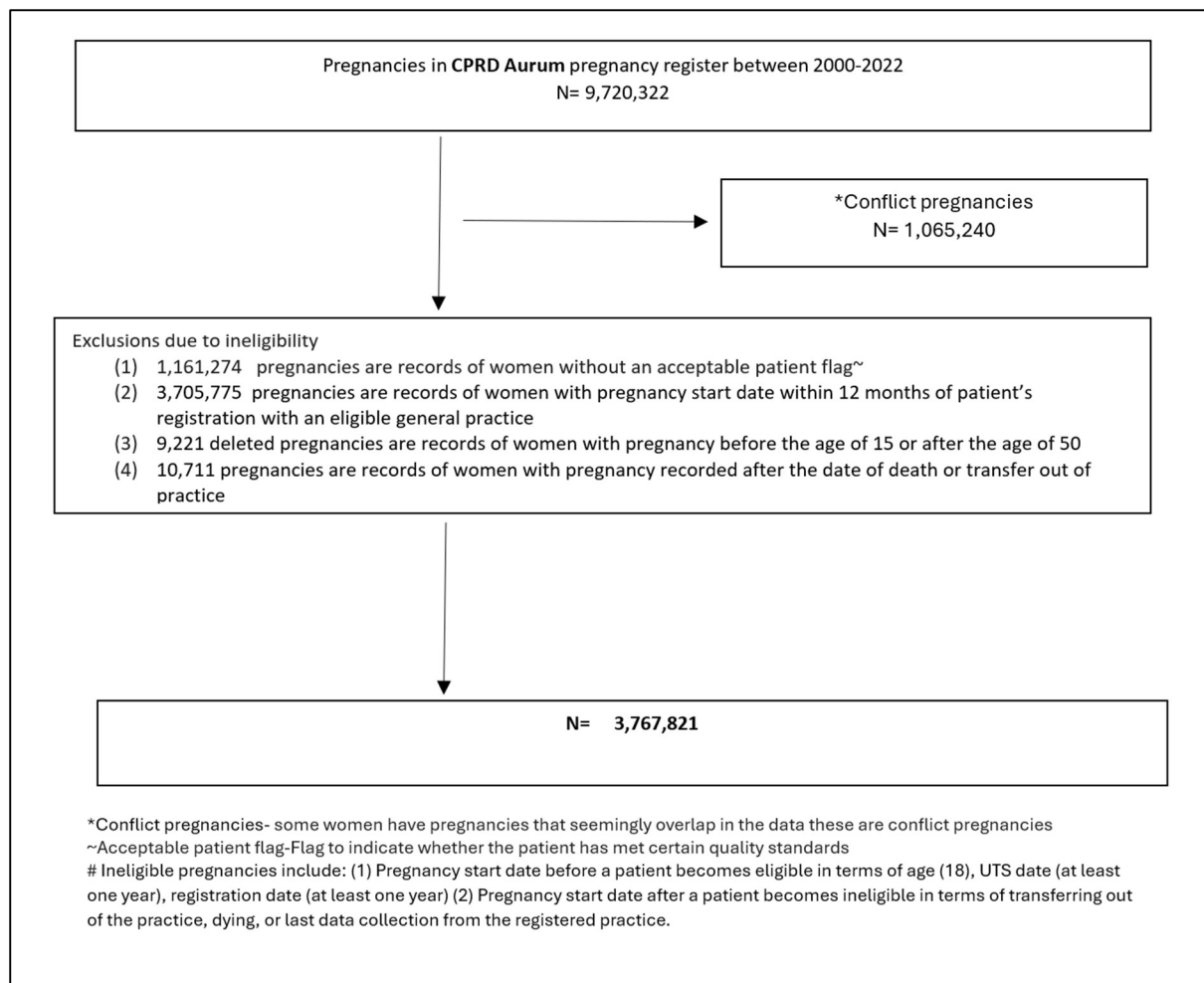


Figure 5.2 Flowchart of the study selection for CPRD Aurum pregnancy cohort

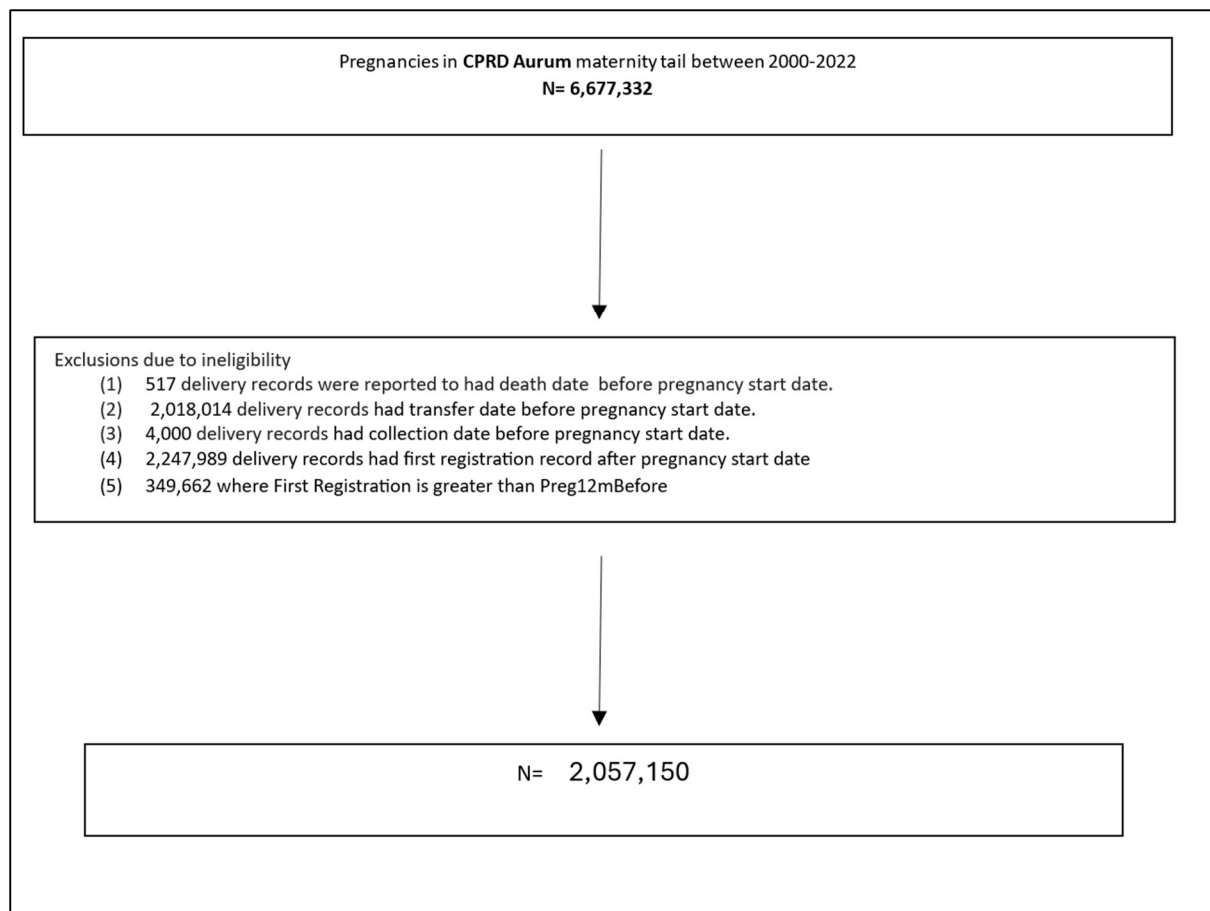


Figure 5.3 Flowchart of the study selection for CPRD Aurum maternity tail

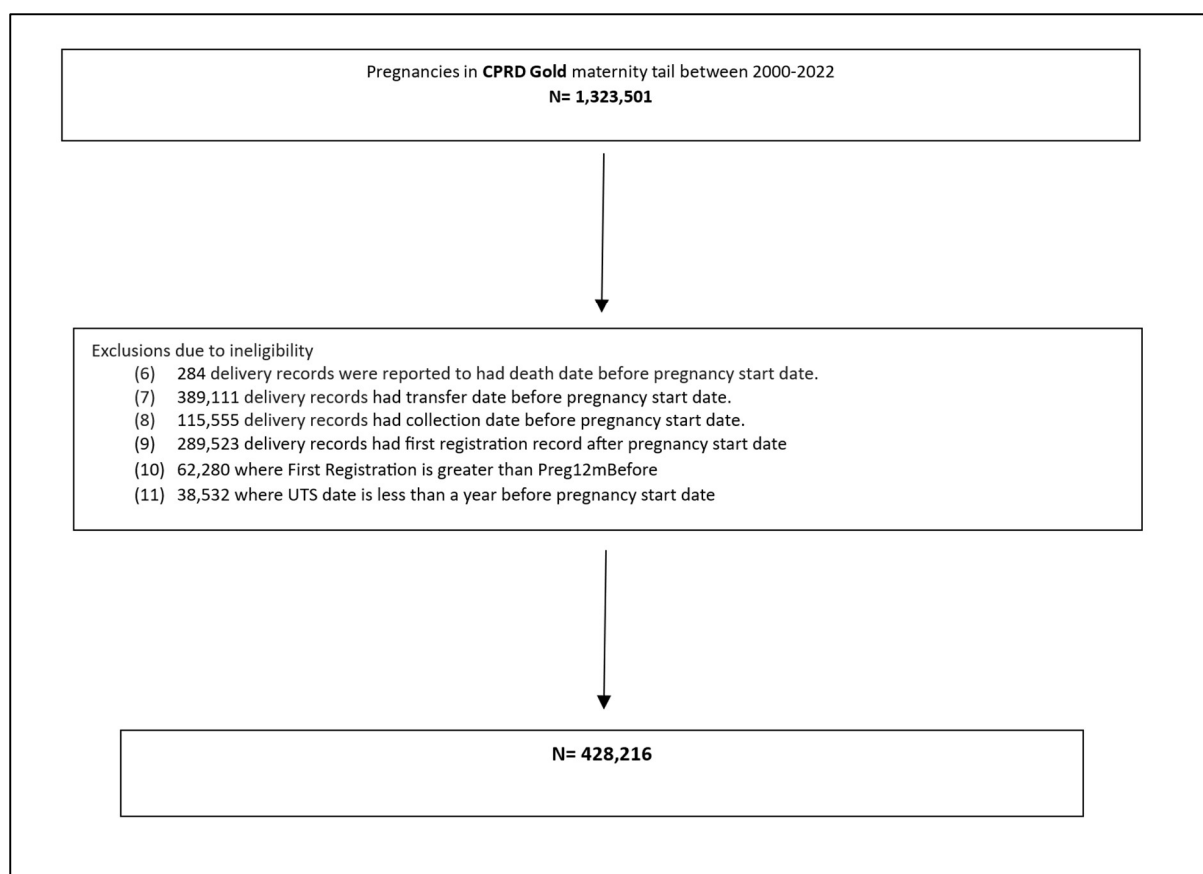


Figure 5.4 Flowchart of the study selection for CPRD GOLD maternity tail

Table 5.1 Definition of Hyperemesis gravidarum

Time frame	Base cohort
Pregnancy start date- 42 weeks	Primary care Primary Care-Read codes/SNOMED CT codes
Pregnancy start date- 42 weeks	Secondary care=ICD codes

Table 5.2 Definition of Ectopic pregnancy

Time Frame	Base cohort
Pregnancy start date-30 weeks	Primary care Read codes/SNOMED CT codes
Pregnancy start date-30 weeks	Secondary care-ICD 10 codes
No timeline	Pregnancy register Flag==7

Table 5.3 Definition of Miscarriage

Time frame	Base cohort
Pregnancy start date-24 weeks +6 weeks	Primary care-Read codes/SNMOMED CT code
Pregnancy start date-24 weeks +6 weeks	Secondary care=ICD codes
No timeline	Pregnancy register Flag==4

Table5. 1Definition of Gestational hypertension

Exclude	Before Pregnancy start date+20*7 Read codes/SNOMED CT codes	Hypertension diagnosis in primary and secondary care Drug codes (Thiazides, calcium channel blockers, Ace inhibitors, ARB's, Aliskiren alpha blocker)
Base cohort CPRD Gold N=1,455,922 CPRD Aurum N= 3,684,536		
Include	Pregnancy start date+20 weeks up to Pregnancy end date +6weeks	Diagnostic codes for hypertension, gestational hypertension, pre-eclampsia or eclampsia Additionally, drugs codes for (amlodipine, doxazosin, labetalol, methyldopa, nifedipine)
Include	Pregnancy start date+20 weeks up to Pregnancy end date +6weeks	Secondary care=ICD codes Gestational hypertension, pre-eclampsia, eclampsia

Table 5.2 Definition of Pre-eclampsia/Eclampsia

Exclude	Before Pregnancy start date+20*7 Read codes/SNOMED CT codes	Hypertension diagnosis in primary and secondary care Drug codes (Thiazides, calcium channel blockers, Ace inhibitors, ARB's, Aliskiren alpha blocker)
Base cohort CPRD Gold N=1,455,922 CPRD Aurum N= 3,684,536		

Include	Pregnancy start date+20 weeks up to Pregnancy end date +6weeks	Diagnostic codes for pre-eclampsia or eclampsia Additionally, drugs codes for (amlodipine, doxazosin, labetalol, methyldopa, nifedipine)
Include	Pregnancy start date+20 weeks up to Pregnancy end date +6weeks	Secondary care=ICD codes pre-eclampsia, eclampsia

Table 5.3 Definition of Gestational diabetes

Exclude	Before Pregnancy start date+20*7 Read codes/SNOMED CT codes	T1DM&T2DM diagnosis in primary and secondary care Drug codes (Acarbose, Meglitinides, Insulin, GLP-1, DPP4inhibitors)
Base cohort CPRD Gold N=1,455,922 CPRD Aurum N= 3,684,536		
Include	Pregnancy start date+20 weeks up to Pregnancy end date +6weeks	Diagnostic codes for gestational diabetes Additionally, drugs codes for insulin, metformin
Include	Pregnancy start date+20 weeks up to Pregnancy end date +6weeks	Secondary care=ICD codes Gestational diabetes

Table5. 5.4Definition of antenatal anxiety

Exclude	Before Pregnancy start date Read codes/SNOMED CT codes	Anxiety diagnosis in primary and secondary care Drug codes (Anxiolytic, propranolol, IAPT codes)
Base cohort CPRD Gold N= 1,303,681 CPRD Aurum N= 3,275,122		
Include	Pregnancy start date up to Pregnancy end date +6weeks	Diagnostic codes for anxiety Additionally, drugs codes for anxiolytics
Include	Pregnancy start date up to Pregnancy end date +6weeks	Secondary care=ICD codes anxiety

Table 5.5 Definition of antenatal depression

Exclude	Before Pregnancy start date Read codes/SNOMED CT codes	Depression diagnosis in primary and secondary care Drug codes (propranolol, SSRI, TCA depressants, MAOI, other antidepressants, IAPT codes)
Base cohort CPRD Gold N= 1,267,141 CPRD Aurum N= 3,074,060		
Include	Pregnancy start date up to Pregnancy end date +6weeks	Diagnostic codes for depression Additionally, drugs codes for (propranolol, SSRI, TCA depressants, MAOI, other antidepressants, IAPT codes)
Include	Pregnancy start date up to Pregnancy end date +6weeks	Secondary care=ICD codes depression

Table 5.9 Definition of postnatal anxiety

Exclude	Before Pregnancy end date Read codes/SNOMED CT codes	Anxiety diagnosis in primary and secondary care Drug codes (Anxiolytic, propranolol, IAPT codes)
Base cohort CPRD Gold N= 1,298,290 CPRD Aurum N= 3,259,742		
Include	Pregnancy end date + 1year	Diagnostic codes for anxiety Additionally, drugs codes for anxiolytics
Include	Pregnancy end date + 1year	Secondary care=ICD codes anxiety

Table 5.10 Definition of postnatal depression

Exclude	Before Pregnancy end date Read codes/SNOMED CT codes	Depression diagnosis in primary and secondary care Drug codes (propranolol, SSRI, TCA depressants, MAOI, other antidepressants, IAPT codes)
Base cohort CPRD Gold N= 1,259,932 CPRD Aurum N= 3,059,618		
Include	Pregnancy end date + 1year	Diagnostic codes for depression

		Additionally, drugs codes for (propranolol, SSRI, TCA depressants, MAOI, other antidepressants, IAPT codes)
Include	Pregnancy end date + 1year	Secondary care=ICD codes depression

Table 5.11 Definition of Preterm birth

Time frame	Base cohort
Delivery cohort	Gestational age
HES linked	Secondary care=ICD codes

Table 5.62 Definition of Small for gestational age

Time frame	Base cohort
Delivery cohort	Birthweight below the 10th percentile for gestational age and sex, based on international standards. Birthweight, gestational age, and sex were entered into INTERGROWTH-21st project software to calculate weight-for-gestational-age centiles.

Table 5.73 Definition of Caesarean section

Time frame	Base cohort
Delivery cohort	Calculated from Delivery method variable in maternity tail and OPCS coded in HES linked data

Table 5.84 Definition of Stillbirth

Time frame	Base cohort
Delivery cohort	Stillbirth was defined using the birth status variable from the maternity tail

Table 5.15 Clinical codes for the outcomes

	CPRD Gold	CPRD Aurum	ICD 10
Miscarriage	L04..11	198650006	O02.0
	L02..00	13384007	O02.1
	L040111	43306002	O03
	L045x00	307746006	O03.0

L042x00	307749004	O03.1
L043y00	59363009	O03.2
L040100	286996009	O03.3
L040w00	10697004	O03.4
L041x00	2781009	O03.5
L043x00	198656000	O03.6
L043x11	13384007	O03.7
L042000	307752007	O03.8
L040400	184339009	O03.9
L040x00	43306002	
L045100	34614007	
L043z11	34614007	
L042100	161752007	
L045211	184339009	
L045111	2781009	
L045x11	16607004	
L043y11	2781009	
L044111	307746006	
L043100	59363009	
L041200	16863000	
L044000	16863000	
L044200	198647008	
L10zz11	198657009	
L04..00	198645000	
7E08800	16607004	
L010.00	307735008	
L044.00	2781009	
L041.00	307746006	
L042.00	59363009	
L043.00	16607004	
1542	184339009	
L043.11	413338003	
L045.11	10697004	
L02..11	58990004	
1542400	16863000	
L044.11	16607004	
L04z.00	161747002	
L041z00	17369002	
1542200	44979007	
L042z00	156073000	
L041z11	307737000	
L045.00	62688006	
L045z00	156073000	
L011.00	450810001	
L040011	198646004	
L041100	17369002	
L040.00	198661003	

	1542500	16607004	
	1542300	156072005	
	L010.11	307737000	
	L040900	156072005	
	1542Z00	307733001	
	L041y00	198645000	
	L044z00	307737000	
	L044z11	18489003	
	L045z11	198644001	
	1542700	198645000	
	L042y00	156072005	
	L040z00	198656000	
	L041w00	17369002	
	L045y11	59363009	
	1542100	161748007	
	L045y00	198645000	
	1542600	7000009	
	9535	198660002	
	L041000	198656000	
	L043z00	199088001	
	L044y00	161744009	
	L040y00	35999006	
	L040000	307737000	
	L044x00	59363009	
	L044y11	307738005	
	L042w00	35999006	
	L044x11	307733001	
	L02..12	156072005	
	L040500	275421004	
	L045000	198655001	
	L044100	8.65741E+14	
	L041500	73790007	
		307749004	
		307752007	
		198648003	
		48485000	
		609442008	
		67465009	
		156072005	
		176833006	
		307748007	
		161744009	
		35999006	
		161752007	
		307733001	
		307735008	
		307733001	

		307748007	
		737318003	
		198649006	
		156073000	
		59363009	
		34614007	
		156073000	
		161749004	
		307734007	
		307735008	
		59363009	
		161751000	
		59363009	
		161749004	
		156072005	
		275425008	
		161751000	
		9.06451E+14	
		156072005	
		307748007	
		17369002	
		198645000	
		198644001	
		34614007	
		161744009	
		199087006	
		198659007	
		198663000	
		156073000	
		307733001	
		59363009	
		16607004	
		176833006	
		307752007	
		17369002	
		307737000	
		30806007	
		307750004	
		198645000	
		17369002	
		161745005	
		59363009	
		59363009	
		161750004	
		156073000	
		307737000	
		17369002	

		156072005 307735008 737943000 307734007 237036002 17369002 17369002 161748007 16863000 184339009 307738005 275425008 307748007 176833006 67465009 275421004 609525000 307752007 156072005 307733001 307750004 161747002 85116003 161750004 59363009	
Hyperemesis Gravidarum	L13..11 L131000 L131200 L13..12 L130.00 L130000 L130z00 L130200 L131.00 L131z00 L130100 L131100	19569008 14094001 199028004 14094001 199025001 14094001 199025001 19569008 199023008 19569008 129598007 199022003 199027009 199025001 19569008 19569008 199025001 14094001	O21.0 O21.1
Ectopic pregnancy	L03..00 1544 584E.00 L03y200	81130000 276881003 31601007 79586000	O00 O00.0 O00.1 O00.2

	L511.00	69532007	O00.8. O36.7
	L03y000	176928008	O83.3, O00.9
	L032.00	198624007	
	L03y300	198617006	
	L03y500	82661006	
	7E19000	198617006	
	L031200	440537001	
	7E13300	609525000	
	L031.00	370382007	
	7E13100	79586000	
	7E19011	34801009	
	L03y100	34801009	
	L03z.00	387617009	
	7E19012	35656003	
	L031000	237253003	
	L031z00	176928008	
	Lyu0000	31601007	
	L030.00	63596003	
	L03y.00	79586000	
	L031100	161763005	
	L03yz00	176929000	
	L030000	17433009	
		79290002	
		387616000	
		34801009	
		79586000	
		9899009	
		198620003	
		237253003	
		237254009	
		161763005	
		87605005	
		176929000	
		198626009	
		34801009	
		387615001	
		198620003	
		34801009	
		31601007	
		271415006	
		34801009	
		173300003,	
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		906511000006107,	
		609525000	
		31601007	

Gestational hypertension	L123200 L123.00 L123500 L123z00 L123600 L123100 L123000 L123400 L123300	198966006 48194001 237279007 237279007 237279007 237279007 198965005 198967002 307632004 48194001, 695711000000100, 40521000119100, 198968007 48194001, 695711000000100, 237279007 48194001	O13
Pre-eclampsia/Eclampsia	L124.12 L126300 L125.00 15A4.00 L12B.00 L124300 L126000 L125400 Q000.11, L124600, L124.00 L126.00 15A3.00 L124.11 L126100 L124500 L129.00, L12A.00, L126500 L125000 L125z00 L125100 L127100 L127.00 L126600 L127000 L124400 L124100 L127300 L124000 L124z00 L125200	1861661000006100, 398254007 161806007, 105651000119100, 237283007, 398254007, 41114007 46764007 41114007, 95605009, 237283007 46764007 15938005 46764007 237283007 15938005 15394000 95605009, 398254007, 648001000000103, 15938005 161807003 398254007 398254007 41114007 198992004 15394000 15938005 41114007 41114007	O11 O14.0 O14.1 O14.2, O14.9, O15.0 O15.1 O15.2, O15.9, O14 O15

	L124200	198992004	
	L126z00	398254007	
	L125300	237283007	
	L126200	46764007	
	L126400	41114007	
	L127200, Lyu1.00,	46764007	
	L127z00	198983002	
	L127400	198997005	
	15AB.00	198991006	
		398254007,	
		398254007,	
		648001000000103,	
		398254007	
		41114007	
		237281009	
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		15938005	
		198984008	
		198985009	
		95605009	
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		198974007	
		15394000,	
		95605009,	
		198999008	
		198974007	
		398254007	
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		46764007	
		268794002	
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		199003007	
		41114007	
		398254007	

		398254007 95605009 198992004 198993009 398254007 46764007	
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Anxiety	E200.00 E200300 E200100 Eu41012	228560001 386810004 313087008 54587008	F06.4 F40 F40.0 F40.1

Eu41200	313087008	F40.2
Z522400	191723004,	F40.8, F40.9,
Eu41111	1818111000006100,	F41
E202B00	313087008	F41.0
E202800	162723006,	F41.1
E200400	853241000006103,	F41.2
E202000	17496003	F41.3
E202C00	191733007	F41.8, F41.9,
Eu40000	17496003	F60.6
E202100	48694002	F93.0
E200z00	231501003	F93.1
E200500	38617005	F93.2
E200200	64165008	
Eu41.00	191722009	
E292000	386810004	
E200000	313087008	
Eu40z11	21897009,	
Eu41211	1861181000006100,	
Z4L1.00	54307006	
Eu41000	371631005	
Eu60600	231504006	
8G94.00	48694002	
Eu40.00	192108001,	
Eu40200	1037451000000100,	
E202.12	386810004	
Eu41100	47372000	
Eu40213	21897009,	
Eu40100	972931000006101,	
Eu40300	191709001	
Eu40214	386810004	
E202200	25501002	
2258	231504006	
Eu40012	54587008	
Eu34114	11806006,	
Eu40011	191725006,	
Eu51511	197480006	
Eu93000	54587008	
Eu40212,	192108001	
E202300,	21897009	
Eu40011	47372000,	
Eu51511	851141000006108,	
Eu93000	18193002	
Eu40212,	191722009	
E202500,	231528008	
Eu41y00	17496003	
Eu93100	54587008	
Eu41z11	58963008	

	Z481.00 Z4I7211 Eu40y00 E202600 Eu41y11 8HHp.00 E202700 Eu93200 E2D0.00, E202400 Eu40z00, E2D0z00 Eu41300 Eu41113 Eu93y12 Eu45215 Eu40211 1B13.12 8IH5300	25501002, 933461000000100, 191723004, 563201000000101, 197480006 198288003 191722009 198288003 386808001 231504006 386810004 371631005 11806006, 199101000000102, 54307006, 191724005, 197480006 231504006 56576003 13438001 70691001 198288003 21897009 371631005 231504006 198288003 19887002 247854002 34563004 61569007 231504006 192611004 419145002, 1037471000000100, 79015004 191708009, 197480006, 162723006 197480006 386810004 54307006, 909691000006109, 710060004, 191726007, 192611004 197480006 21897009	

		70691001 371631005 207363009 228560001, 386810004, 563201000000101, 70691001 48694002, 851351000006108, 54587008 54587008 13438001 25501002	
Depression	E2B..00 Eu32z11 E200300 E204.00 E204.11 E2B1.00 Eu41200, Eu25111, 9kQ..00 E112.14 E135.00 E290.00 E11..12 62T1.00, Eu32z00, E2B0.00 Eu32z12 Eu33.00 Eu32.00 Eu53012 E112.11 Eu32z14 E113700 E112.12 Eu32y00 E113.11 E112.13 E112z00 Eu32.13 Eu34113 Eu41211 Eu34100 E130.00 Eu34111	1771531000006100, 1972451000006100, 1972541000006100, 1972541000006100, 1972911000006100, 1973381000006100, 1975211000006100, 1975261000006100, 1975321000006100, 1976921000006100, 310495003 395072006 191613003 82218004 401174001 15639000, 1086471000000100, 15639000, 609311000000100, 84760002, 430421000000104, 310497006, 784051000000106, 397701000000102, 191495003, 251000119105, 1975231000006100, 15639000, 36923009, 395072006, 79298009, 465441000000108, 231500002	F20.4, F25.1, F32 F32.0 F32.1 F32.2 F32.3 F32.8, F32.9, F33, F33.0 F33.1 F33.2 F33.3, F33.8, F33.9, F34.1 F41.2 F92.0

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	Eu33.12	231542000,	
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		28475009 192046006, 87512008, 191604000 191455000 40568001, 1823881000006100, 231500002, 1976411000006100, 1976211000006100, 923921000000104, 413973005 310495003 300706003 415044007 78667006 58703003, 36923009, 191676002, 251000119105, 191604000, 939961000006100, 268621008, 717261000000109, 397701000000102, 191613003 192079006 191659001, 1086471000000100, 191495003 310497006, 1972311000006100, 1972131000006100	
Preterm Birth	Calculate from the gestational age variable in the maternity tail Gestational age<37weeks	O60 O60.1 O60.2 O60.3 P07.2 P07.3 P59.0 P61.2	
Caesarean section	Calculated from Delivery method variable in maternity tail and OPCS coded in HES linked data ICD10 Codes	OPCS Codes R17 R17.1 R17.2	

	O82	R17.8
	O82.0	R17.9
	O82.1	R18
	O82.2	R18.1
	O82.8	R18.2
	O82.9	R18.8
		R18.9
		R19
		R19.1
		R19.8
		R19.9
		R20
		R20.1
		R20.2
		R20.8
		R20.9
		R21
		R21.1
		R21.2
		R21.3
		R21.4
		R21.5
		R21.8
		R21.9
		R22
		R22.1
		R22.2
		R22.3
		R22.8
		R22.9
		R23
		R23.1
		R23.2
		R23.8
		R23.9
		R24
		R24.9
		R25
		R25.1
		R25.2
		R25.8
		R25.9
		R27

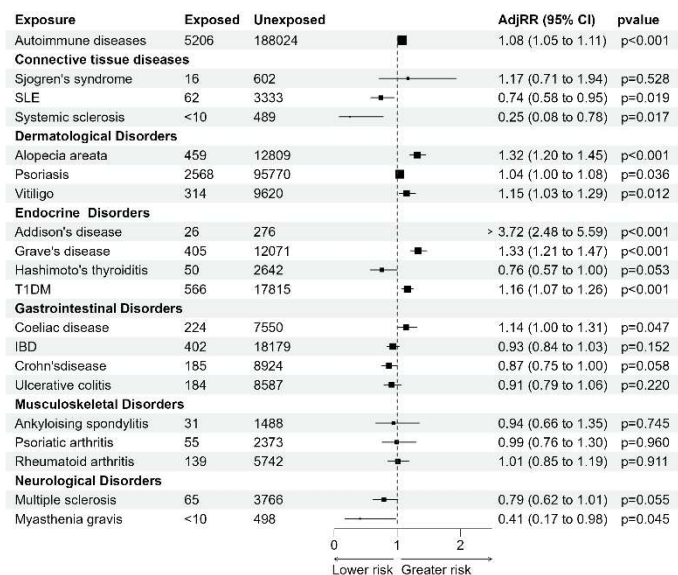


Figure 5.5 Forest plot describing association of autoimmune diseases in women and Hyperemesis gravidarum

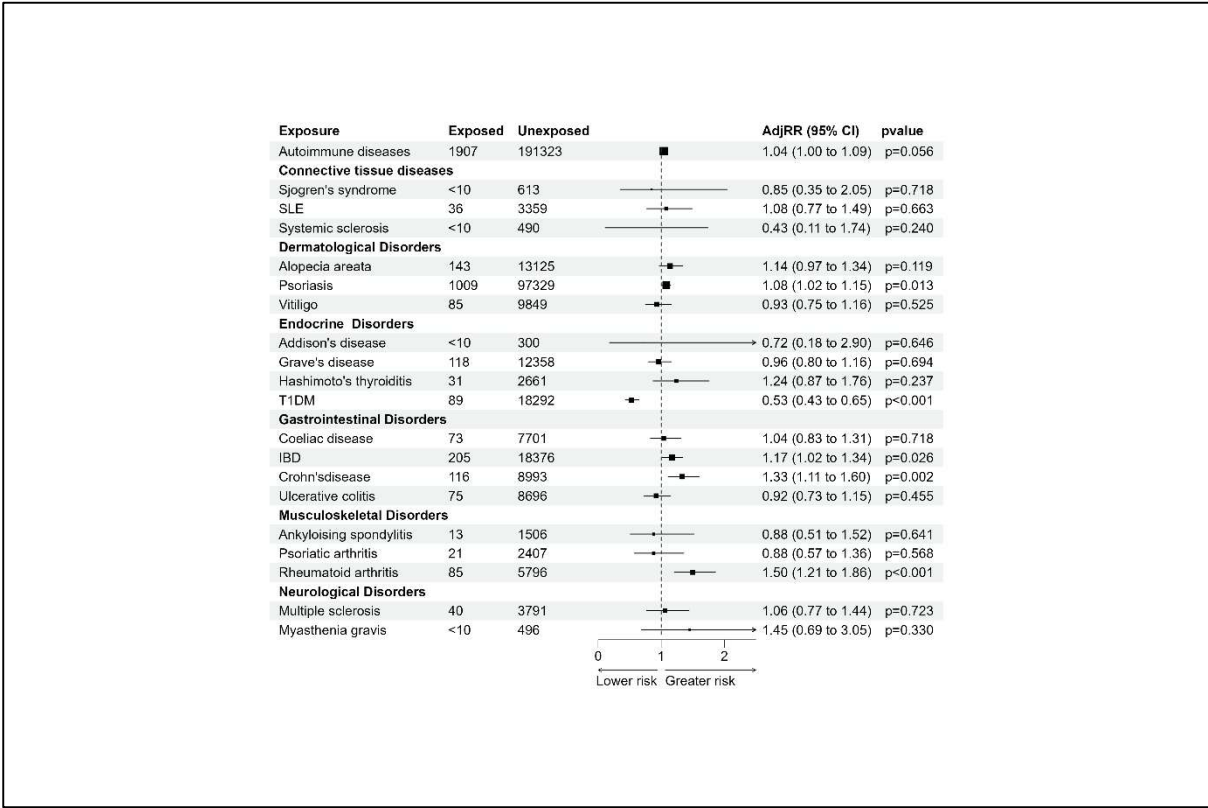


Figure 5.6 Forest plot describing association of autoimmune diseases in women and Ectopic pregnancy

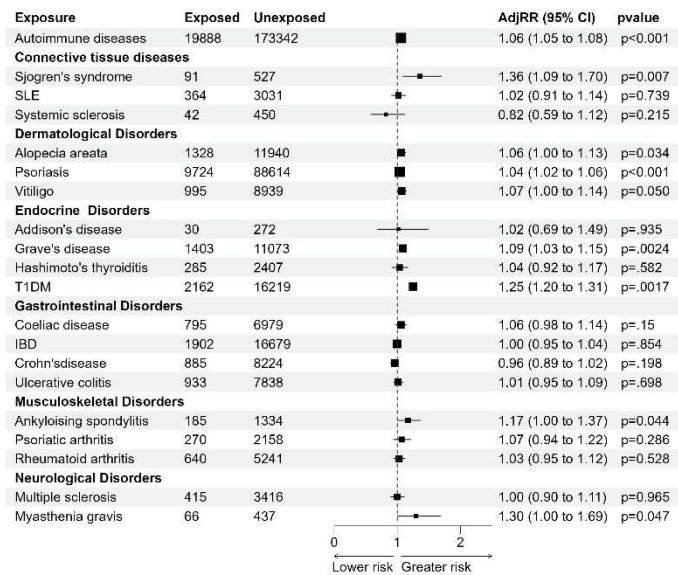


Figure 5.7 Forest plot describing association of autoimmune diseases in women and Miscarriage

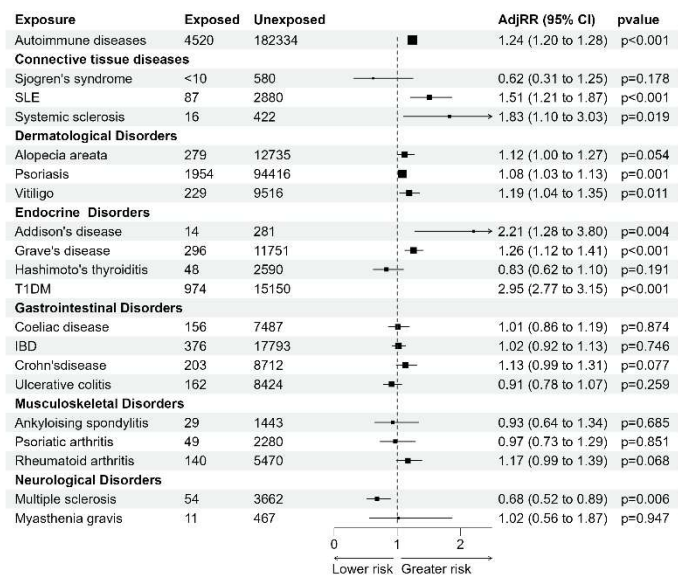


Figure 5.8 Forest plot describing association of autoimmune diseases in women and Gestational hypertension

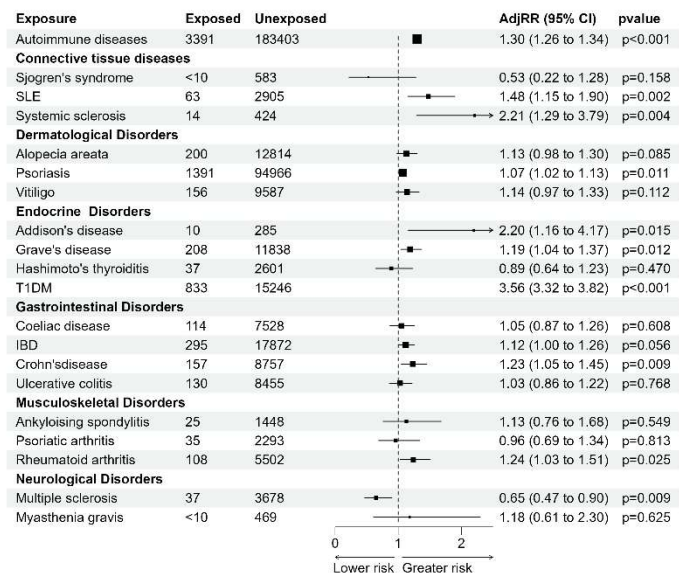


Figure 5.9 Forest plot describing association of autoimmune diseases in women and Pre-eclampsia

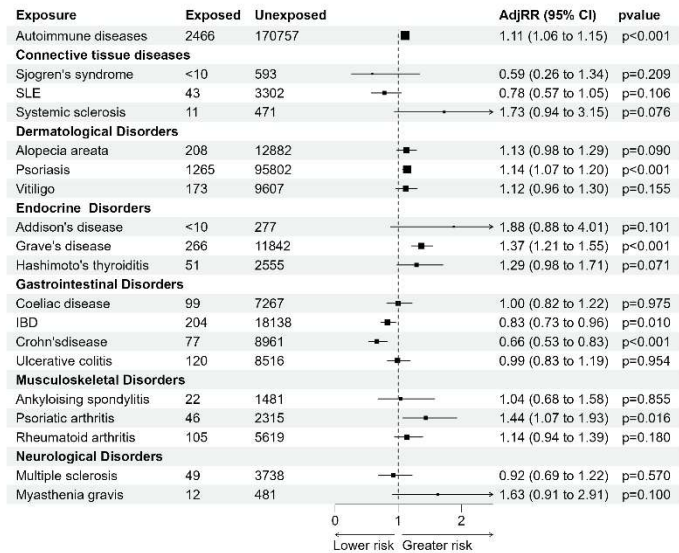


Figure 5.10 Forest plot describing association of autoimmune diseases in women and Gestational diabetes mellitus

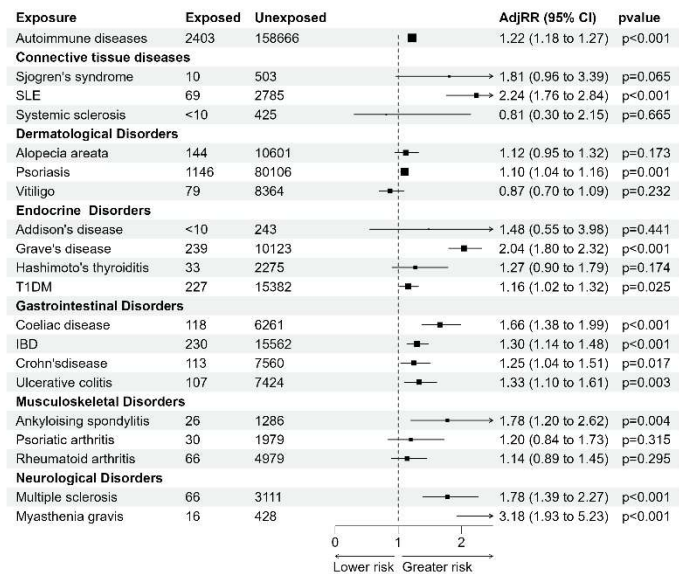


Figure 5.11 Forest plot describing association of autoimmune diseases in women and Antenatal anxiety

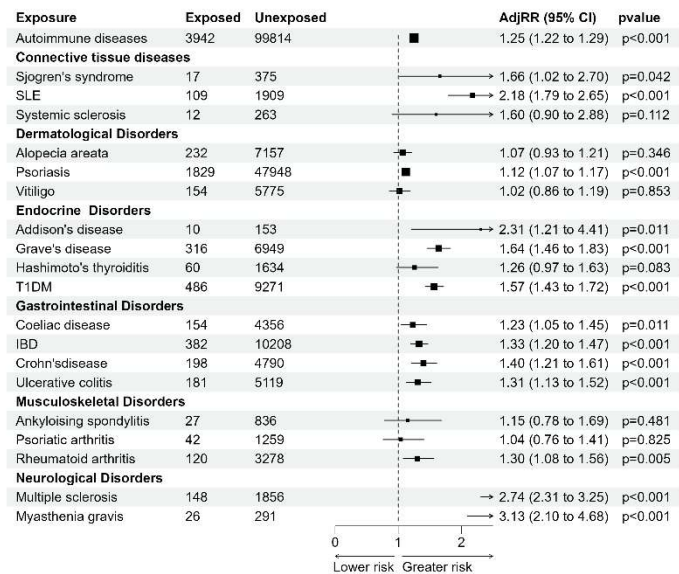


Figure 5.12 Forest plot describing association of autoimmune diseases in women and Antenatal depression

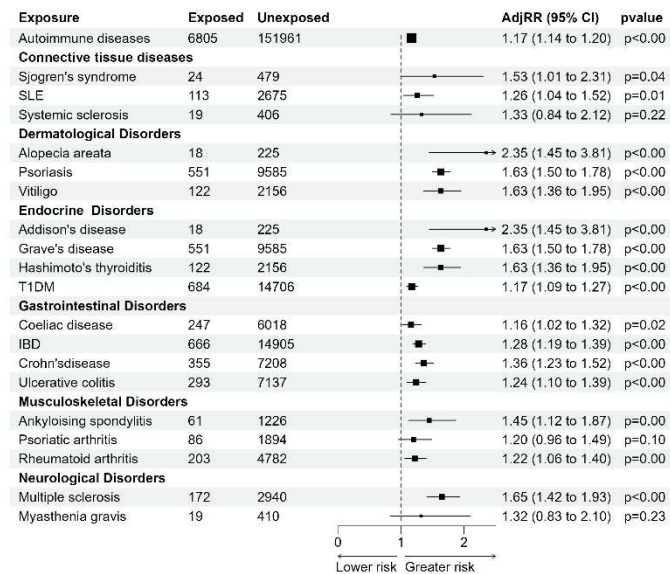


Figure 5.13 Forest plot describing association of autoimmune diseases in women and postnatal anxiety

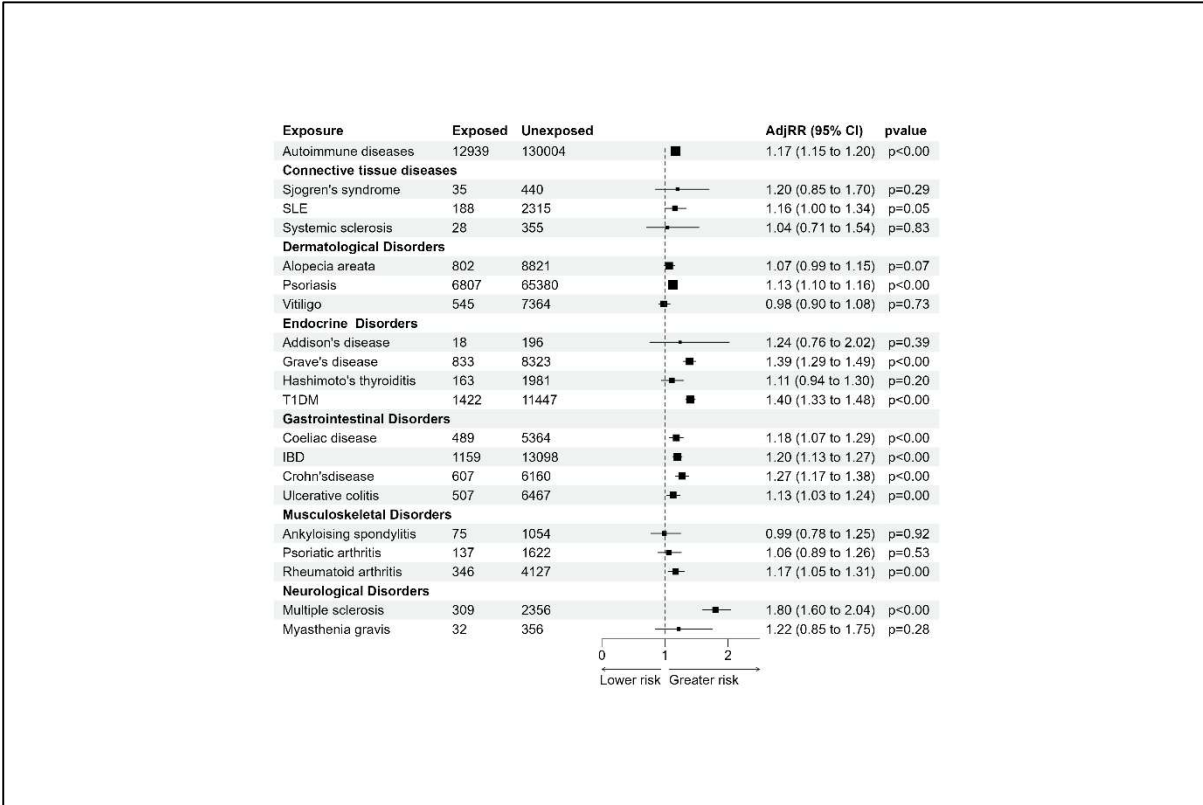


Figure 5.14 Forest plot describing association of autoimmune diseases in women and postnatal depression

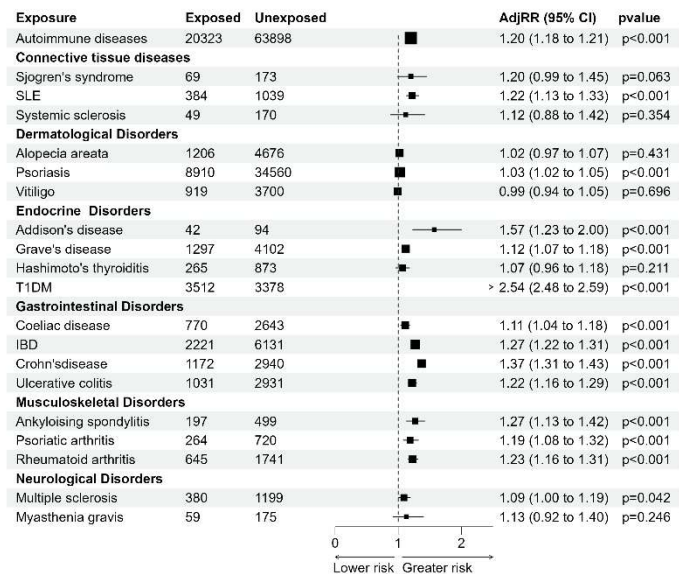


Figure 5.15 Forest plot describing association of autoimmune diseases in women and Caesarean section

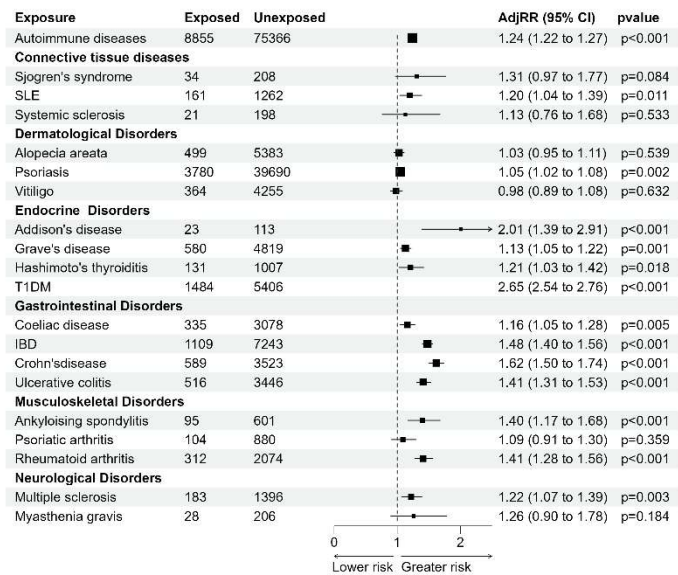


Figure 5.16 Forest plot describing association of autoimmune diseases in women and Elective Caesarean section

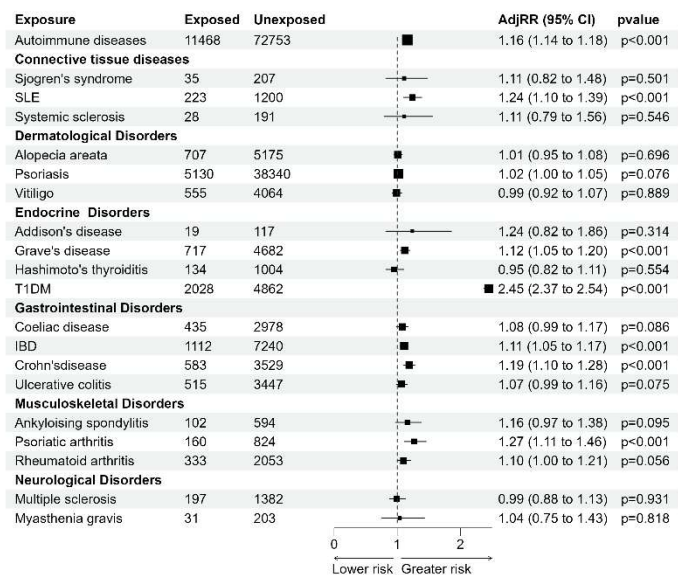


Figure 5.17 Forest plot describing association of autoimmune diseases in women and Emergency Caesarean section

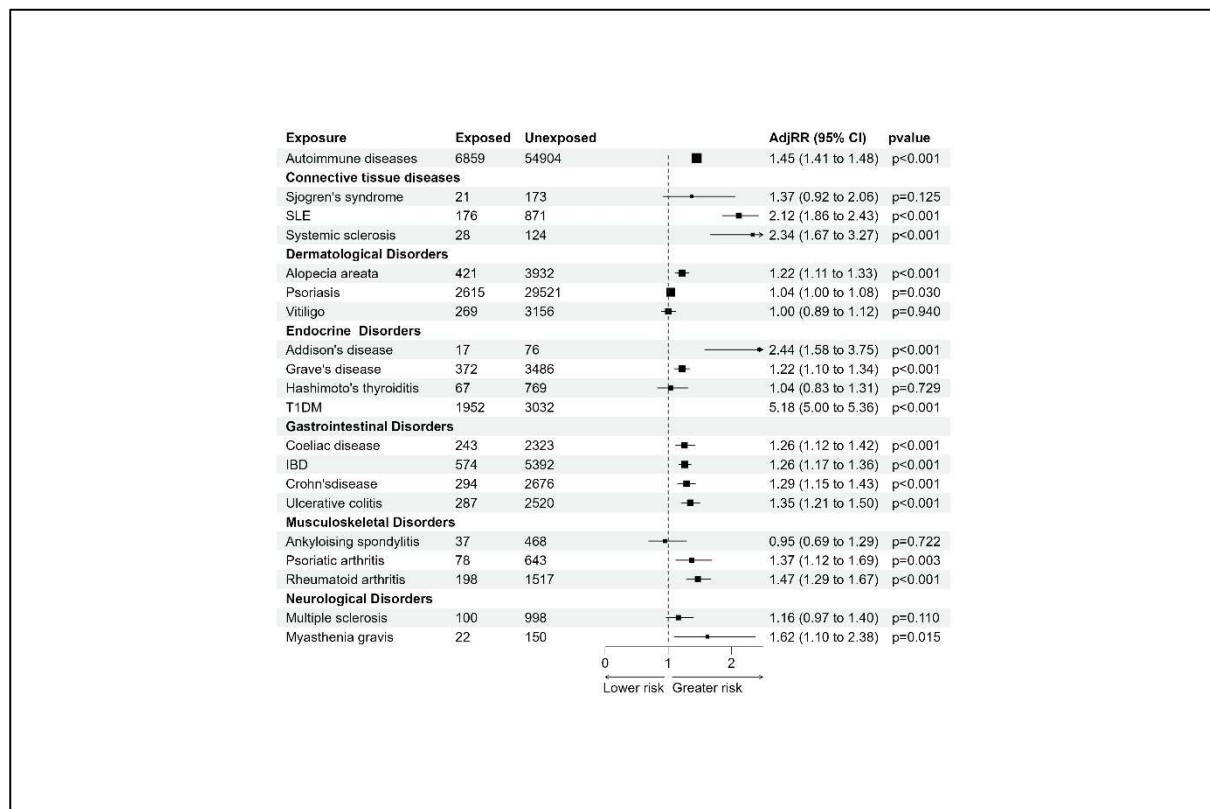


Figure 5.18 Forest plot describing association of autoimmune diseases in women and Preterm birth

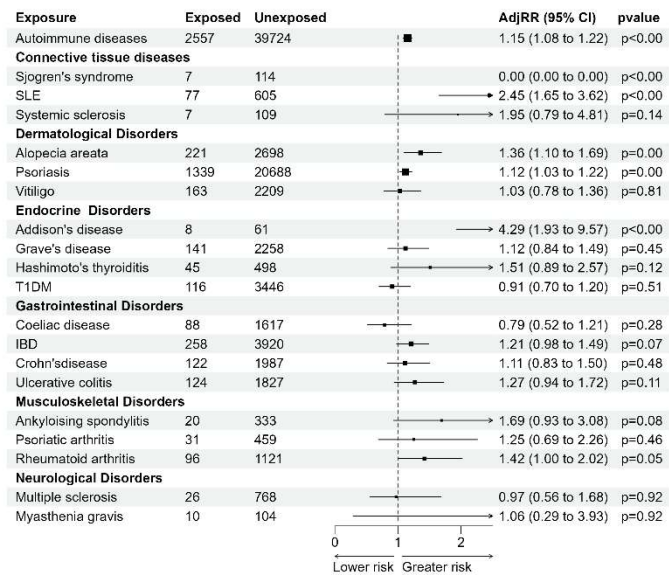


Figure 5.19 Forest plot describing association of autoimmune diseases in women and Small for gestational age

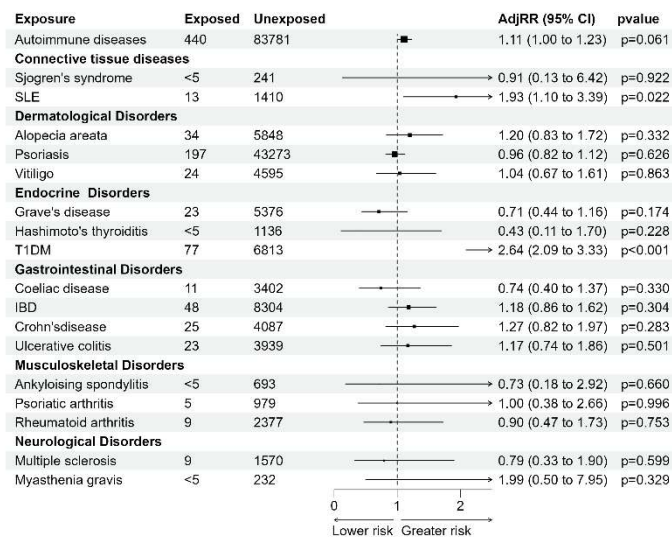


Figure 5.20 Forest plot describing association of autoimmune diseases in women and Stillbirth

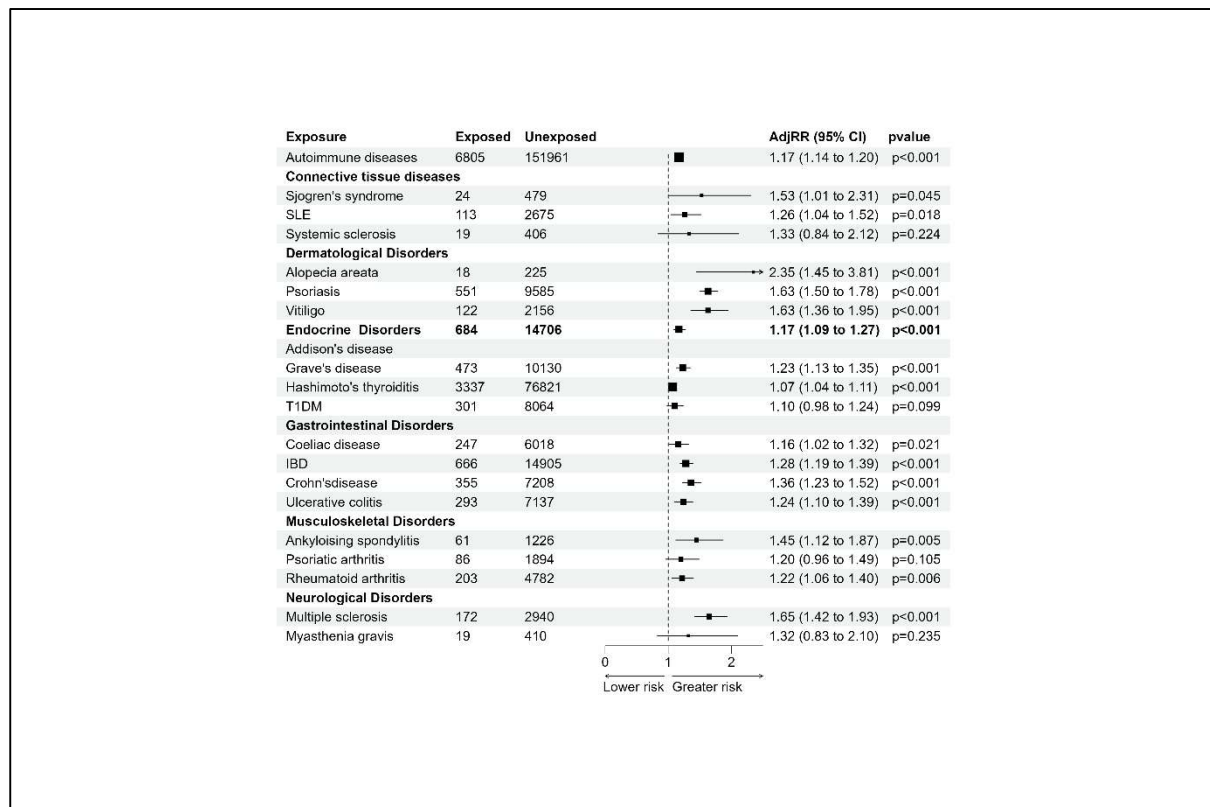


Figure 5.21 Forest plot describing association of autoimmune diseases in women and Perinatal anxiety

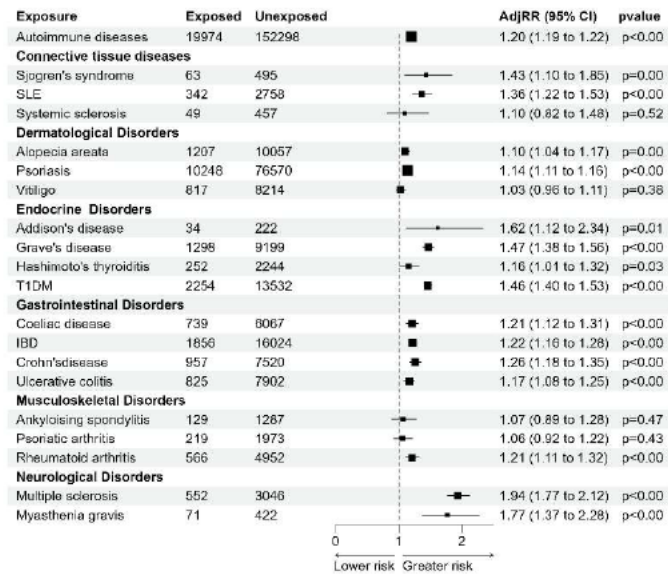


Figure 5.22 Forest plot describing association of autoimmune diseases in women and Perinatal depression

Table 5.17 Heat Map-diseases and adverse pregnancy outcomes

	Hypertension Gravidarum	Ectopic pregnancy	Miscarriage	Gestational hypertension	Pre-eclampsia / Eclampsia	GDM	PTB	SGA	CS	Stillbirth	Anxiety	Depression
Any AID												
Sjögren's S												
SLE												
Systemic S												
Alopecia A												
Psoriasis												
Vitiligo												
Addison Ds												
Graves' Ds												
Hashimoto D												
T1DM												
Celiac Ds												
IBD												
Crohn Ds												
Ulcerative C												
Ankylosing S												
Psoriatic A												

Rheumatoid												
Multiple S												
Myasthenia												
	Inverse association with HR less than 1 and confidence interval not crossing null											
	No association HR less than 1 and confidence interval crossing null											
	Association suggestive of adverse effect but no significant association as confidence interval crossing null											
	Clear association with HR greater than 1 and confidence interval not crossing null											
	Significant association with HR above 2 and confidence intervals on the right side											

Supplementary tables and figures chapter 6

Table 6.9 Search Strategy MEDLINE

1	exp Autoimmune Diseases/
2	(auto?immune adj2 (disease* or condition*)).mp.
3	exp Psoriasis/
4	psoria\$.mp.
5	exp Vitiligo/
6	vitiligo.mp.
7	(leucoderma or leukoderma).mp.
8	exp Alopecia Areata/
9	alopecia areata.mp.
10	((alopecia adj2 totalis) or (alopecia adj2 universalis)).mp.
11	exp Lupus Erythematosus, Systemic/
12	(systemic lupus or sle).mp.
13	arthritis psoriatic.mp. or exp Arthritis, Psoriatic/
14	Ankylosing spondylitis.mp. or exp Spondylitis, Ankylosing/
15	Spondylarthritis/
16	(axial adj2 spondylarthritis).tw.
17	(axial adj2 spa).tw.
18	(ankylos\$ or spondyl\$).tw.
19	(bekhterev\$ or bechterew\$).tw.
20	(Marie adj2 struempell\$).tw.
21	(AS or axSPA).tw.
22	Sacroiliitis/
23	((axial or spin\$ or peripheral or vertebral or enthesitis) adj3 (joint\$ or spondyloarthritis or arthritis or ankylosing)).tw.
24	exp Arthritis, Rheumatoid/
25	((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat\$ or reumat\$ or revmarthrit\$) adj3 (arthrit\$ or artrit\$ or diseas\$ or condition\$ or nodule\$)).mp.
26	sjogren syndrome.mp. or exp Sjögren's Syndrome/
27	exp Celiac Disease/
28	(c?eliac adj2 disease*).mp.
29	inflammatory bowel disease.mp. or exp Inflammatory Bowel Diseases/
30	ulcerative colitis.mp. or exp Colitis, Ulcerative/

31	Crohn's disease.mp. or exp Crohn Disease/
32	multiple sclerosis.mp. or exp Multiple Sclerosis/
33	Systemic Sclerosis.mp.
34	exp Scleroderma, Systemic/
35	((systemic adj scler?) or sclero?).mp.
36	crest syndrome.mp. or exp CREST Syndrome/
37	graves disease.mp. or exp Graves Disease/
38	(grave? adj3 (diseas? or thyrotoxicos? or hyperthyr?)).mp.
39	exp Thyroiditis, Autoimmune/
40	autoimmune thyroid.mp.
41	Hashimoto Disease.mp.
42	exp Hashimoto Disease/
43	(thyroid adj autoantibodies).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
44	thyroid.mp. and exp autoantibodies/
45	myasthenia gravis.mp. or exp Myasthenia Gravis/
46	addison disease.mp. or exp Addison Disease/
47	type 1 diabetes.mp. or exp Diabetes Mellitus, Type 1/ or ("typ? 1 diabet*" or "typ? I diabet*" or "typ?1 diabet*" or "typ?I diabet*").mp. or (("insulin* depend*" or "insulin?depend*") not ("non-insulin* depend*" or "non insulindepend*")).mp. or (IDDM or T1DM or T1D).mp. or autoimmune diabetes.mp.
48	exp Pregnancy Complications/
49	(pregnancy adj complication?).mp.
50	exp Abortion, Spontaneous/
51	((recurrent adj2 miscarr?) or miscarr?).mp.
52	(early adj3 pregnancy loss?).mp.
53	miscarriage.mp.
54	exp Stillbirth/
55	(stillbirth or (still adj birth)).mp.
56	exp Fetal Death/
57	((f?etal adj death\$) or (f?etal adj demise\$)).mp.
58	exp Hypertension, Pregnancy-Induced/
59	(gestational hypertension or (pregnancy adj3 hypertensi\$)).mp.
60	(preeclampsia or pre-eclampsia).mp.
61	exp Pre-Eclampsia/
62	(eclampsia or tox?emia).mp.
63	exp Eclampsia/
64	hellp.mp. or exp HELLP Syndrome/
65	exp Placenta Accreta/
66	(placenta adj accreta).mp.
67	placenta percreta.mp.
68	placenta increta.mp.
69	(morbidly adj3 adherent placenta).mp.
70	abnormally invasive placenta.mp.

71	exp Abruptio Placentae/
72	Placenta? abruption.mp.
73	exp Placenta Previa/
74	Placenta pr?evia.mp.
75	low lying placenta.mp.
76	exp Hyperemesis Gravidarum/
77	Hyperemesis Gravidarum.mp.
78	exp Morning Sickness/
79	morning sickness.mp.
80	exp Diabetes, Gestational/
81	GDM.mp.
82	((pregnan\$ or gestation\$ or prenatal\$ or antenatal\$ or pre-natal\$ or ante-natal\$ or maternal\$) adj2 diabet\$) or gestational diabetes).mp.
83	((tub\$\$ adj3 pregnanc\$) or (cornual adj3 pregnanc\$) or (heterotopic adj3 pregnanc\$) or (abdomin\$ adj3 pregnanc\$) or (extrauterine adj3 pregnanc\$) or (interstitial adj3 pregnanc\$) or (cervi\$ adj3 pregnanc\$) or (ovar\$ adj3 pregnanc\$) or (cesarean scar adj3 pregnanc\$)).mp.
84	exp Pregnancy, Ectopic/
85	ectopic pregnancy.mp.
86	exp Gestational Trophoblastic Disease/
87	gestational trophoblastic.mp.
88	exp Hydatidiform Mole/
89	((hydatid? adj2 mole?) or (molar adj2 pregnanc?)).mp.
90	exp Choriocarcinoma/
91	choriocarcinoma.mp.
92	exp Pregnancy, Multiple/
93	((pregnanc* or gestation*) adj (twin* or triplet* or quadruplet* or quintuplet* or multiple or multi?f?et*)).mp.
94	(Monochorionic or dichorionic).mp.
95	exp Postpartum Hemorrhage/
96	(postpartum hemorrhage or post-partum hemorrhage or postpartum haemorrhage or post-partum haemorrhage).mp.
97	obstetric haemorrhage.mp.
98	obstetric labor, premature.mp.
99	exp Obstetric Labor, Premature/
100	(premature labor or premature labour or preterm labor or preterm labour or preterm birth).mp.
101	exp Cesarean Section/
102	exp Cesarean Section, Repeat/
103	(caesarean or cesarean or caesarian or cesarian or cesarien or caesarien or c-section or c section).mp.
104	cesarean.mp.
105	exp Extraction, Obstetrical/
106	exp Obstetrical Forceps/
107	((operative or instrumental or assisted or forcep* or ventouse* or vacuum*) adj1 (deliver* or birth*)).mp.

108	exp Infant, Low Birth Weight/
109	low birth weight.mp.
110	(low birth weight* adj4 very low birth weight*).mp.
111	exp Infant, Small for Gestational Age/
112	(small adj3 gestational age).mp.
113	(intra?uterine growth adj2 (restriction* or retardation)).mp.
114	iugr.ti,ab.
115	exp Fetal Growth Retardation/
116	(fetal growth adj2 (restriction? or retardation)).mp.
117	exp Depression, Postpartum/
118	postpartum depression.mp.
119	((postpartum* or post partum* or post-partum* or postnatal* or post natal* or post-natal* or perinatal* or peri natal* or peri-natal* or puerp*) and (depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder*)).mp.
120	((postpartum* or post partum* or post-partum* or postnatal* or post natal* or post-natal* or perinatal* or peri natal* or peri-natal* or puerp*) and (psychos#s or psychotic)).mp.
121	(psychosis adj3 after childbirth).mp.
122	((third or fourth or 3rd or 4th) adj degree) and tear*).mp.
123	((anal near adj2 sphincter) or (rectal adj mucosa) or rectum or (anal adj epithelium) or anus or (recto?vaginal adj2 fistulae) or (anorectal adj mucosa) or (anal adj skin)) and (tear* or injur* or damage* or lacerat* or rupture* or trauma)).mp.
124	((obstetric* and anal and sphincter and injur*) or (anal and sphincter and injur*)).mp.
125	(exp Pregnancy/ or exp Obstetrics/ or (pregnan* or obstetric*).mp.) and (exp Cholestasis/ or exp Cholestasis, Intrahepatic/)
126	pelvic girdle pain.mp. or exp Pelvic Girdle Pain/
127	(symphysis pubis adj3 (pain\$ or dysfunction\$)).mp.
128	Pubic Symphysis Diastasis.mp. or exp Pubic Symphysis Diastasis/
129	Sacroiliac joint dysfunction.mp.
130	PGP.mp.
131	pregnancy outcome.mp. or exp Pregnancy Outcome/

Table 6.10 The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1 and 2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract page 1 and 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Background page 2, 3 paragraph 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Background

			page2.3 Paragraph 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods, Page 3,4 paragraph 1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Inclusion and exclusion criteria Page 4,5 paragraph 2,3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3-4 paragraph 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3,4 paragraph 1& Appendix Table 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 3,4 Methods, paragraph 2,3,4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3,4,11,12 Methods, paragraph 2,3,4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 3,4,12 Methods, paragraph 2,3,4 Table 1-2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3 Methods, paragraph 2,3,4 Figure
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5-8,22-30 Figure 1 Appendix table 4.1,4.2,4.3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 3,4 Data analysis
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 3,4 Data analysis
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3,4 Methods, paragraph 2,3,4 Table 3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 3,4 Figure 1 Appendix table 4.1,4.2,4.3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 3,4,5 Data analysis
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 4 Data analysis

Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 4 Methods, paragraph 2,3,4 Figure 2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 4,5 Figure 1 Appendix table 4.1,4.2,4.3
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5-9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix table 3
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 1 and Table 4.1,4.2,4.3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results page 5- 9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results page 5- 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results page 5- 9 Figure 1-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Discussion Paragraph 2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion Page 10-12
	23b	Discuss any limitations of the evidence included in the review.	Discussion Page 10-12
	23c	Discuss any limitations of the review processes used.	Discussion Page 10-12
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion Page 10-12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods Page3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 12
Competing interests	26	Declare any competing interests of review authors.	Page 12
Availability of data, code and other	27	Report which of the following are publicly available and where they can be found template data collection forms; data extracted from included studies; data used for all analyses;	Page 12

materials		analytic code; any other materials used in the review.	

Table 6.3 List of excluded studies

Author/year		Reason for exclusion
1.	Akiyama C, Shirai T, Sato H, Fujii H, Ishii T, Harigae H. Association of various myositis-specific autoantibodies with dermatomyositis and polymyositis triggered by pregnancy. <i>Rheumatology International</i> . 2022;42(7):1271-80.	Outcome
2.	Akkaya C, Kocagoz SZ, Turan OF, Taskapilioglu O, Kirli S. Onset of multiple sclerosis following post-partum depressive and manic episodes. <i>Psychiatry and Clinical Neurosciences</i> . 2007;61(6):698-9.	Study design Letter to editor
3.	Alijotas-Reig J, Esteve-Valverde E. Pregnancy and autoimmune diseases. <i>Medicina Clinica</i> . 2017;148(4):161-3.	Study design
4.	Auger N, Quach C, Healy-Profitos J, Dinh T, Chasse M. Early predictors of Guillain-Barre syndrome in the life course of women. <i>International Journal of Epidemiology</i> . 2018;47(1):280-8.	Outcome
5.	Badihian N, Riahi R, Goli P, Badihian S, Poursafa P, Kelishadi R. Prenatal and perinatal factors associated with developing multiple sclerosis later in life: A systematic review and meta-analysis. <i>Autoimmunity Reviews</i> . 2021;20(6):102823.	Population
6.	Barrett PM, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Stillbirth is associated with increased risk of long-term maternal renal disease: a nationwide cohort study. <i>American Journal of Obstetrics & Gynecology</i> . 2020;223(3):427.e1-.e14.	Outcome
7.	Boldingh MI, Maniaol AH, Brunborg C, Weedon-Fekjaer H, Verschuuren JJ, Tallaksen CM. Increased risk for clinical onset of myasthenia gravis during the postpartum period. <i>Neurology</i> . 2016;87(20):2139-45.	Exposure
8.	Brown HK, Barrett K, Scime NV. Perinatal mental illness and maternal autoimmune disease: A review	Study design

	of current evidence and avenues for future research. <i>Frontiers in Neuroendocrinology</i> . 2022;65:100975.	
9.	Dhillon-Smith RK, Tobias A, Smith PP, Middleton LJ, Sunner KK, Baker K, et al. The Prevalence of Thyroid Dysfunction and Autoimmunity in Women with History of Miscarriage or Subfertility. <i>Journal of Clinical Endocrinology & Metabolism</i> . 2020;105(8):01.	Outcome
10.	Dissanayake TD, Maksymowych WP, Keeling SO. Peripartum issues in the inflammatory arthritis patient: A survey of the RAPPORT registry. <i>Scientific Reports</i> . 2020;10(1):3733.	Comparator group not as per inclusion criteria
11.	Driul L, Bertozzi S, Londero AP, Fruscalzo A, Rusalen A, Marchesoni D, et al. Risk factors for chronic pelvic pain in a cohort of primipara and secondipara at one year after delivery: association of chronic pelvic pain with autoimmune pathologies. <i>Minerva Ginecologica</i> . 2011;63(2):181-7.	Outcome
12.	Efe C, Purnak T, Ozaslan E. Autoimmune hepatitis in the postpartum period. <i>Clinics & Research in Hepatology & Gastroenterology</i> . 2012;36(4):391-3.	Study design
13.	Erlinger S. Intrahepatic cholestasis of pregnancy: A risk factor for cancer, autoimmune and cardiovascular diseases? <i>Clinics & Research in Hepatology & Gastroenterology</i> . 2016;40(2):139-40.	Study design
14.	Gibbins KJ, Tebo AE, Nielsen SK, Branch DW. Antiphospholipid antibodies in women with severe preeclampsia and placental insufficiency: a case-control study. <i>Lupus</i> . 2018;27(12):1903-10.	Outcome
15.	Gleicher N. Postpartum depression, an autoimmune disease? <i>Autoimmunity Reviews</i> . 2007;6(8):572-6.	Outcome
16.	Gokce A, Benlioglu C, Baydemir K, Kalafat E, Atabekoglu C. Cesarean delivery: A predisposing factor for autoimmune thyroid disease in iodine replete women? <i>European Journal of Obstetrics, Gynecology, & Reproductive Biology</i> . 2018;224:131-2.	Study design
17.	Gouveri E, Tews D. A case of type 1 diabetes mellitus after gestational diabetes. <i>Hippokratia</i> . 2021;25(2):95.	Study design

18.	Honig A, Engel JB, Segerer SE, Kranke P, Hausler S, Wurfel W. Pregnancy-triggered antiphospholipid syndrome in a patient with multiple late miscarriages. <i>Human Reproduction</i> . 2010;25(11):2753-4.	Outcome
19.	Inceni M, Baroni MG, Cossu E. Testing for type 1 diabetes autoantibodies in gestational diabetes mellitus (GDM): is it clinically useful? <i>BMC Endocrine Disorders</i> . 2019;19(1):44.	Study design
20.	Jorgensen KT, Pedersen BV, Nielsen NM, Jacobsen S, Frisch M. Childbirths and risk of female predominant and other autoimmune diseases in a population-based Danish cohort. <i>Journal of Autoimmunity</i> . 2012;38(2-3):J81-7.	Exposure
21.	Kalra B, Kalra S, Chhabra B. Posthumous Caesarean section in women with type 1 diabetes mellitus: two cases at one hospital in Northern India. <i>Diabetologia</i> . 2010;53(11):2452-3.	Study design
22.	Kirty K, Sarda Y, Jacob A, Venugopala D. Wernicke's encephalopathy post hyperemesis gravidarum misdiagnosed as Guillain-Barre syndrome: lessons for the frontline. <i>BMJ Case Reports</i> . 2021;14(3):16.	Study design
23.	Kiss E, Kiss CG, Poor G. [Systemic autoimmune disorders and pregnancy]. <i>Orvosi Hetilap</i> . 2011;152(43):1715-23.	Outcome
24.	Kitzmiller JL, Ferrara A, Peng T, Cissell MA, Kim C. Preexisting Diabetes and Pregnancy. <i>National Institute of Diabetes and Digestive and Kidney Diseases</i> . 2018;5:08.	Outcome
25.	Kopp TI, Pinborg A, Glazer CH, Magyari M. Women with female infertility seeking medically assisted reproduction are not at increased risk of developing multiple sclerosis. <i>Human Reproduction</i> . 2022;37(6):1324-33.	Population
26.	Koslowsky B, Grisaru-Granovsky S, Livovsky DM, Milgrom Y, Goldin E, Bar-Gil Shitrit A. Pregnancy-Onset Inflammatory Bowel Disease: A Subtle Diagnosis. <i>Inflammatory Bowel Diseases</i> . 2018;24(8):1826-32.	Population
27.	Kotsev S. Ogilvie's syndrome following cesarean delivery: The Dubai's case. <i>Saudi Journal of Anaesthesia</i> . 2011;5(3):335-8.	Study design and Outcome

28.	Koubi M, Rossi P, Arcani R, Gomes De Pihno Q, Chau C, Blanc J, et al. Relevance of systematic anti-nuclear antibodies testing after obstetrical complications. <i>Journal of Reproductive Immunology</i> . 2021;148:103437.	Outcome
29.	Lewandowski K, Hincz P, Grzesiak M, Cajdler-Luba A, Salata I, Wilczynski J, et al. new onset Addison's disease presenting as prolonged hyperemesis in early pregnancy. <i>Ginekologia Polska</i> . 2010;81(7):537-40.	Study design
30.	Li X, Zhang W, Lin J, Liu H, Yang Z, Teng Y, et al. Risk factors for adverse maternal and perinatal outcomes in women with preeclampsia: analysis of 1396 cases. <i>Journal of Clinical Hypertension</i> . 2018;20(6):1049-57.	outcome
31.	Liu B, Song L, Li H, Zheng X, Yuan J, Liang Y, et al. History of spontaneous miscarriage and the risk of diabetes mellitus among middle-aged and older Chinese women. <i>Acta Diabetologica</i> . 2018;55(6):579-84.	Outcome-add to discussion
32.	McDonald SD, Han Z, Walsh MW, Gerstein HC, Devereaux PJ. Kidney disease after preeclampsia: a systematic review and meta-analysis. <i>American Journal of Kidney Diseases</i> . 2010;55(6):1026-39.	Outcome
33.	McHugh NJ, Reilly PA, McHUGH LA. Pregnancy outcome and autoantibodies in connective tissue disease. <i>The Journal of rheumatology</i> . 1989;16(1):42-6.	Comparator
34.	Mittal A, Dexter S, Marcus S, Tremble J. First presentation of Addison's disease in the 2nd trimester of pregnancy. <i>Journal of Obstetrics & Gynaecology</i> . 2011;31(4):342.	Study design
35.	Moberg JY, Laursen B, Thygesen LC, Magyari M. Reproductive history of the Danish multiple sclerosis population: A register-based study. <i>Multiple Sclerosis</i> . 2020;26(8):902-11.	Outcome
36.	Munoz CM, Goulden B, Ahmed K, Alijotas-Reig J, Giles I. Risk of adverse pregnancy outcomes prior to the	Study design

	onset of an autoimmune rheumatic disease: a systematic review. <i>Rheumatology</i> . 2022;05:05.	
37.	Negishi M, Shimomura K, Proks P, Nakahara R, Murakami M, Shimomura Y, et al. Development of postpartum Graves' disease and type 1 diabetes after delivery in a patient with gestational diabetes. <i>Journal of Diabetes Investigation</i> . 2011;2(4):328-30.	Study design
38.	Nguyen AL, Vodehnalova K, Kalincik T, Signori A, Havrdova EK, Lechner-Scott J, et al. Association of Pregnancy With the Onset of Clinically Isolated Syndrome. <i>JAMA Neurology</i> . 2020;77(12):1496-503.	Population
39.	Nicolini G, Degli Esposti D, Ianniello E, Moroni L, Bacchelli S, Cicero AFG, et al. Long-term consequences of previous preeclampsia and complicated pregnancy: analysis of echocardiographic aspects. <i>Journal of Cardiovascular Medicine</i> . 2021;22(12):939-45.	outcome
40.	O'Donoghue K. Pregnancy and the risk of autoimmune disease: An exploration. <i>Chimerism</i> . 2011;2(3):84-5.	Outcome
41.	Okoth K, Subramanian A, Chandan JS, Adderley NJ, Thomas GN, Nirantharakumar K, et al. Long term miscarriage-related hypertension and diabetes mellitus. Evidence from a United Kingdom population-based cohort study. <i>PLoS ONE [Electronic Resource]</i> . 2022;17(1):e0261769.	Outcome
42.	Ostensen M, Villiger PM, Forger F. Interaction of pregnancy and autoimmune rheumatic disease. <i>Autoimmunity Reviews</i> . 2012;11(6-7):A437-46.	Outcome
43.	Perricone C, de Carolis C, Perricone R. Pregnancy and autoimmunity: a common problem. <i>Best Practice & Research in Clinical Rheumatology</i> . 2012;26(1):47-60.	Study design
44.	Peschken CA, Robinson DB, Hitchon CA, Smolik I, Hart D, Bernstein CN, et al. Pregnancy and the risk of rheumatoid arthritis in a highly predisposed North American Native population. <i>Journal of Rheumatology</i> . 2012;39(12):2253-60.	Population
45.	Petri M, Allbritton J. Fetal outcome of lupus pregnancy: a retrospective case-control study of the Hopkins Lupus Cohort. <i>Obstetrical & gynecological survey</i> . 1993;48(11):717-8.	Case series

46.	Rajewski M, Skrzypczak J. [Frequency of antiphospholipid antibodies and antiphospholipid syndrome in women with recurrent miscarriages]. <i>Ginekologia Polska</i> . 2011;82(1):32-8.	Outcome
47.	Silman AJ, Roman E, Beral V, Brown A. Adverse reproductive outcomes in women who subsequently develop rheumatoid arthritis. <i>Ann Rheum Dis</i> . 1988;47(12):979-81.	Comparator
48.	Tabacco S, Ludovisi M, D'Alfonso A, Palermo P, Roncone R, T DEV, et al. Perinatal mental illness and autoimmune diseases: a qualitative systematic review. <i>Minerva Obstetrics and Gynecology</i> . 2022;02:02.	Study design
49.	Ting Tai Y, Mohd Noor N. A rare case of a mother with gestational diabetes complicated with fulminant type 1 diabetes mellitus post-delivery. <i>Journal of the Royal College of Physicians of Edinburgh</i> . 2022;52(2):120-3.	Study design
50.	Tufano A, Coppola A, Maruotti GM, Martinelli P, Cerbone AM, Di Minno G. HELLP syndrome and its relation with the antiphospholipid syndrome. <i>Blood Transfusion</i> . 2014;12(1):114-8.	Outcome
51.	Unnikrishnan R, Shanthi Rani CS, Anjana RM, Uthra SC, Vidya J, Sankari GU, et al. Postpartum development of type 1 diabetes in Asian Indian women with gestational diabetes. <i>Indian Journal of Endocrinology and Metabolism</i> . 2016;20(5):702-6.	Study design
52.	van den Boogaard E, Cohn DM, Korevaar JC, Dawood F, Vissenberg R, Middeldorp S, et al. Number and sequence of preceding miscarriages and maternal age for the prediction of antiphospholipid syndrome in women with recurrent miscarriage. <i>Fertility & Sterility</i> . 2013;99(1):188-92.	Outcome
53.	Wucher H, Lepercq J, Timsit J. Onset of autoimmune type 1 diabetes during pregnancy: Prevalence and outcomes. <i>Best Practice & Research Clinical Endocrinology & Metabolism</i> . 2010;24(4):617-24.	Study design
54.	You Q, Jiang Q, Shani I, Lou Y, Huang S, Wang S, et al. Miscarriage, stillbirth and the risk of diabetes in women: A systematic review and meta-analysis.	Outcome

	Diabetes Research and Clinical Practice. 2023;195:110224.	
55.	Zhang L, Ding D, Yu L, Qi H, Han C, Jiang J, et al. Primary biliary cirrhosis associated with myasthenia gravis after postpartum: a case report. Journal of Medical Case Reports [Electronic Resource]. 2021;15(1):498.	Study design

Table 6.4 Quality assessment of the Cohort studies using NOS (Newcastle Ottawa scale)

Author Year	Representative ness of the cohort	Selecti on of the non- expose d cohort	Ascertainm ent of Exposure	Demonstrat ion that outcome of interest was not present at start of stud	Comparabi lity of cohorts based on the design or analysis	Assessm ent of AI	Was follo w-up long enou gh	Adequa cy of follow up	Over all Score	Sampl e size
Auvine n 2020	Low	High	Low	Unclear	Low	High	Low	Low	Fair	782
Bergink 2011	Low	Low	Low	Low	Unclear	Low	Low	High	Good	148
Bergink 2018	Low	Low	Low	Low	Unclear	Low	Low	High	Fair	31277 9
Brann 2023	Low	Low	Low	Low	Unclear	Low	Low	High	Fair	530,39 7
Harpso e 2013	Low	Low	Low	Low	Low	Low	Low	Low	Good	55699
Jorgens en KT 2014 Increas ed	Low	Unclea r	Low	Low	Low	Low	Low	Low	Good	97077
Jørgens en KT 2012 hyper	Low	Low	Low	Unclear	Low	Low	Low	Low	Good	15645 67
Jørgens en KT 2010 nationa l	Unclear	Low	Low	Low	Low	Low	Low	Unclear	Fair	21400 56
Kamper 2018	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Good	15377 47
Khasha n 2011	Low	Low	Low	Low	Unclear	Low	Low	Low	Good	10356 39
Lee 2022	Low	Low	Low	Low	High	Low	Low	Unclear	Fair	22609 52

Lin 2016	Low	Low	Low	Low	Low	Low	Low	Unclear	Good	58421
Lin 2018	Low	Low	Low	Low	High	Low	Low	Low	Fair	145455
Mao 2022	Low	Low	Low	Unclear	Low	Low	Low	Low	Good	11997
Mikkelsen 2022	Low	Low	Low	Unclear	Low	Low	Low	Low	Good	1513544
Nielsen 2011	Low	Low	Low	Low	Unclear	Low	Low	Low	Good	2140000
Savitz 2014	Unclear	Low	Low	Low	Low	Low	Low	High	Fair	978545
Stuart 2018	Low	Low	Low	Low	Low	Low	Low	Unclear	Good	1873440
Ulf-Møller 2009	Low	Low	Low	Low	Unclear	Low	Low	Low	Good	2140000
Wikström 2015	Low	Low	Low	Low	Unclear	Low	Low	Low	Good	125281

Table 6.5 Quality assessment of the case control studies using NOS (Newcastle Ottawa scale)

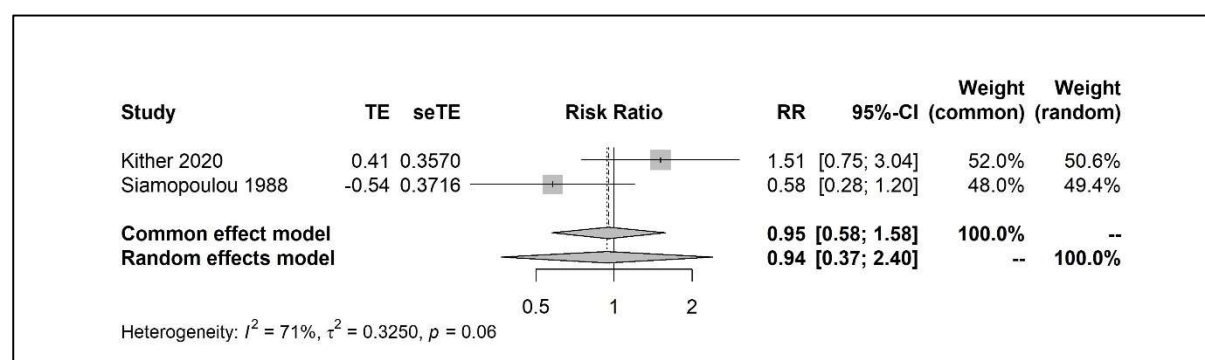
Authors	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Overall score	Sample size
Hardy 1999	Low	Low	Low	Unclear	Low	Low	Low	High	Fair	414
Julkunen 1993	Low	high	Low	Unclear	Low	Low	Low	High	Fair	898
Kay 1965	Low	Unclear	Low	Low	Low	Low	Low	low	Good	418
Kither 2020	Low	Low	Low	Low	Low	Low	Low	Unclear	Good	117446
Ma 2014	Low	Unclear	Unclear	Low	Low	Low	Low	Unclear	Good	1102
Siamopolou 1988	Low	Low	Unclear	Low	Low	Low	Low	Unclear	Good	419
Spector 1990	Low	Low	Low	Low	Low	Unclear	Low	Low	Good	657
Van Wyk 2011	Low	Low	Unclear	Low	Low	Low	Low	Low	Good	206
Wallenius 2011	Low	Low	Low	Low	Low	Low	Low	Unclear	Good	2200000

Table 6.6 Quality assessment of the cross-sectional studies using NOS (Newcastle Ottawa scale)

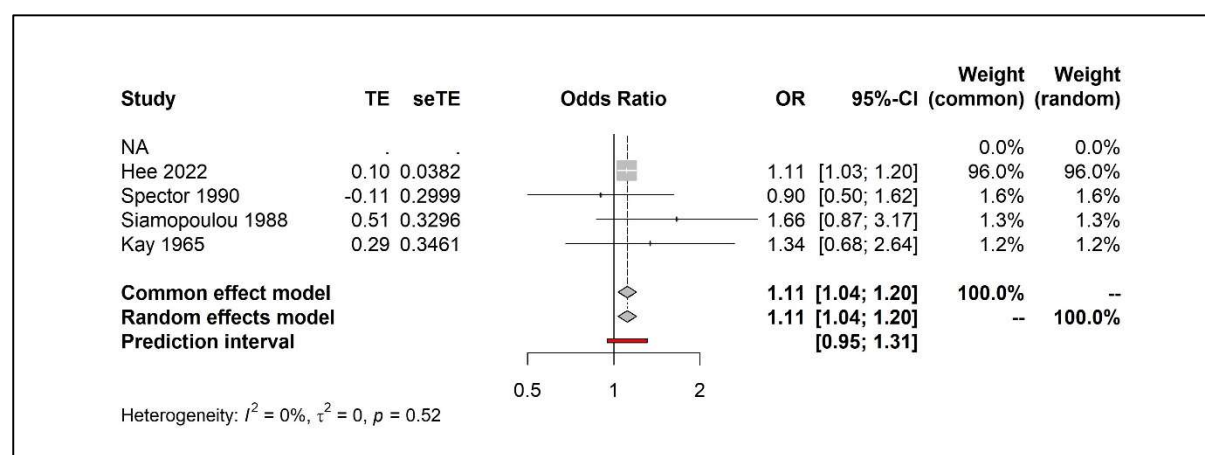
Authors/year	Representativeness of the sample	Sample size	Non respondents	Ascertainment of the exposure (risk factor)	Comparability of subjects in different outcome groups on the basis of design or analysis. Confounding factors controlled	Assessment of outcome:	Statistical test:	Overall	Weight
Hee 2022	Low	Low	<u>Unclear</u>	Low	Low	Low	Low	Good	299629

Figure 6.7 Meta-analysis performed in this review

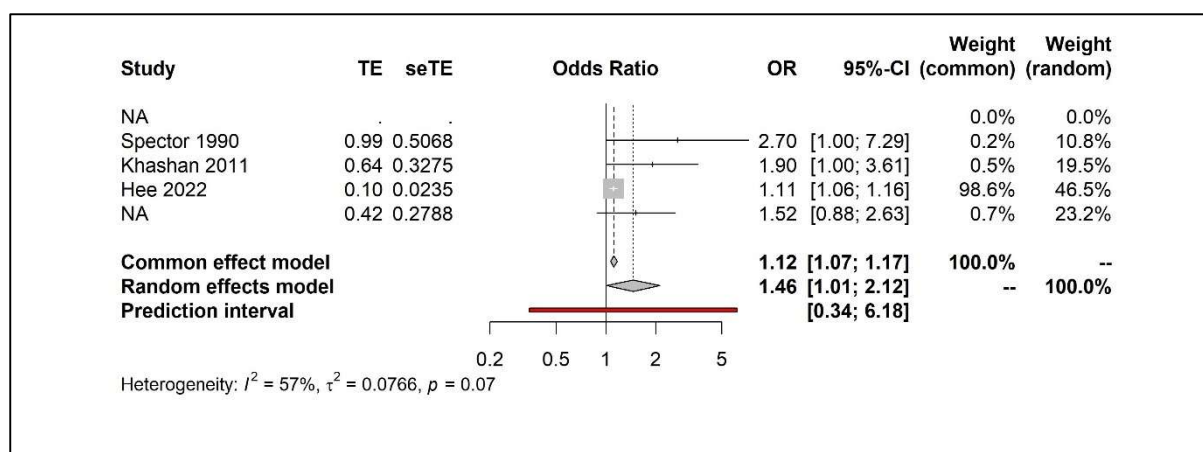
Meta-analysis of two studies reporting association of miscarriage and future development of SLE



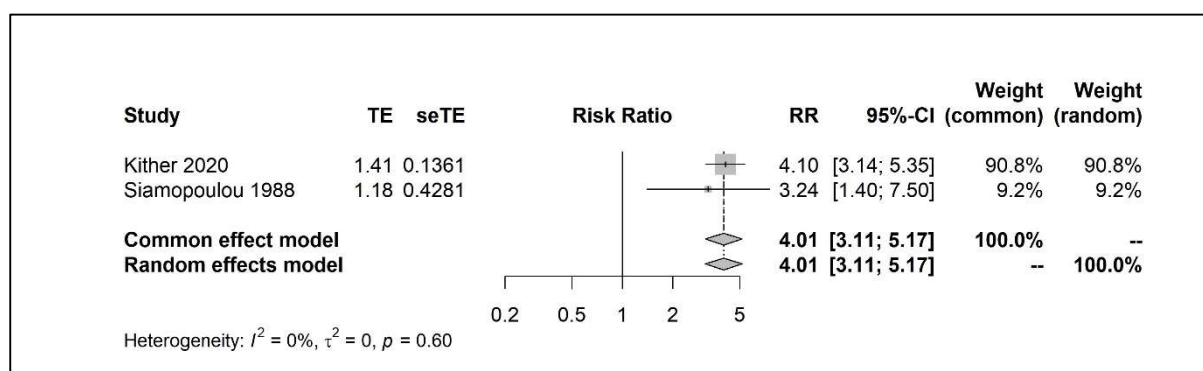
Meta-analysis of two studies reporting association of miscarriage and future development of rheumatoid arthritis (odds ratios)



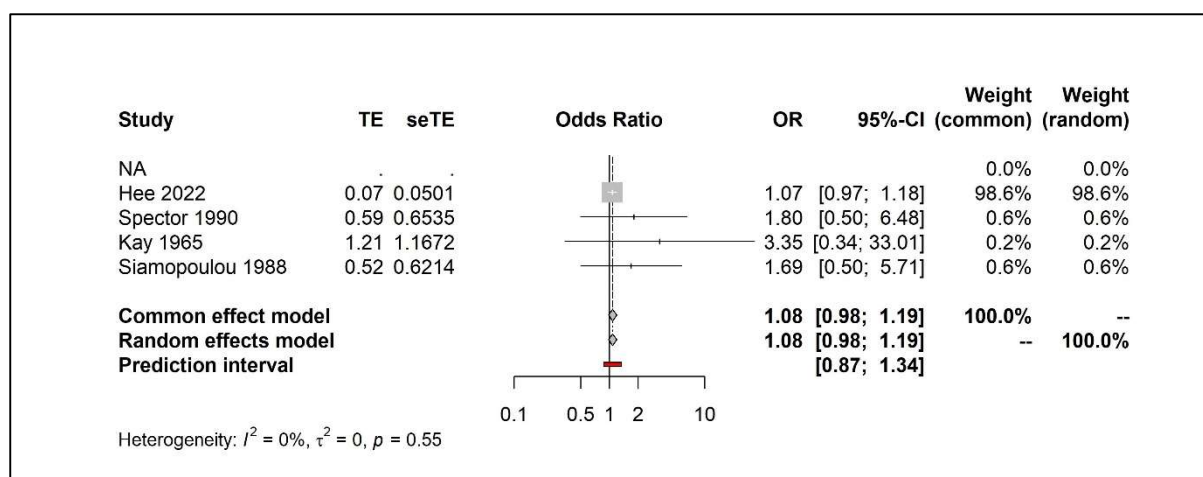
Meta-analysis of two studies reporting association of induced abortion and future development of rheumatoid arthritis



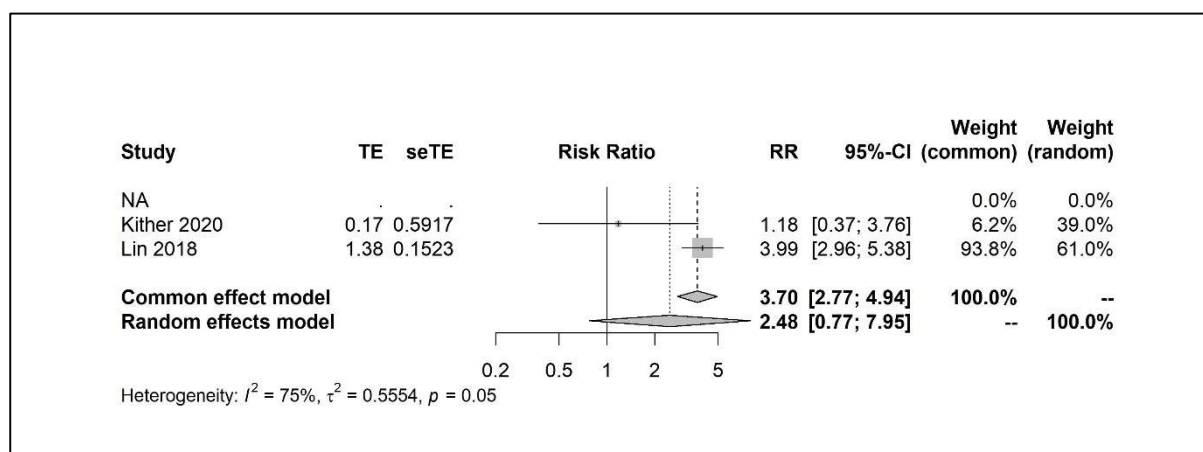
Meta-analysis of two studies reporting association of stillbirth and future development of SLE (risk ratio)



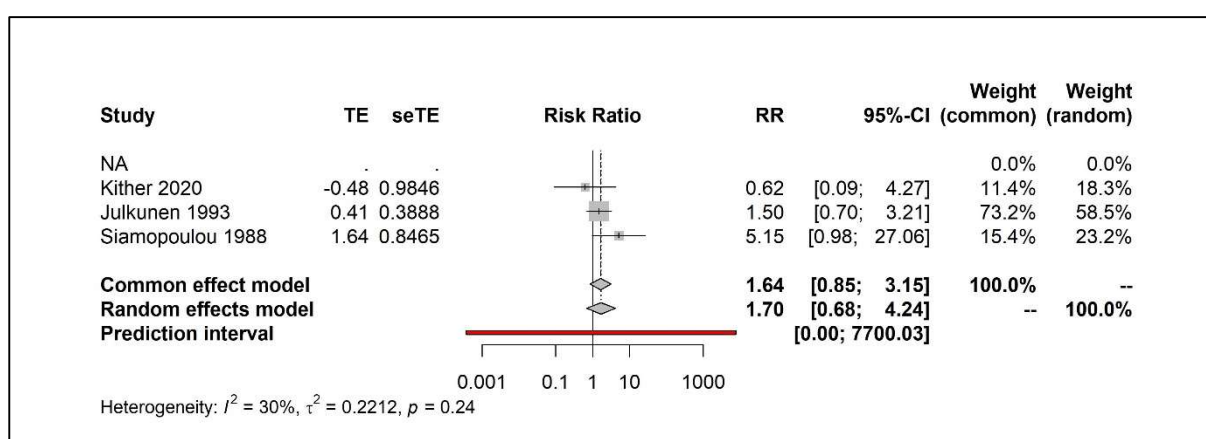
Meta-analysis of two studies reporting association of stillbirth and future development of rheumatoid arthritis



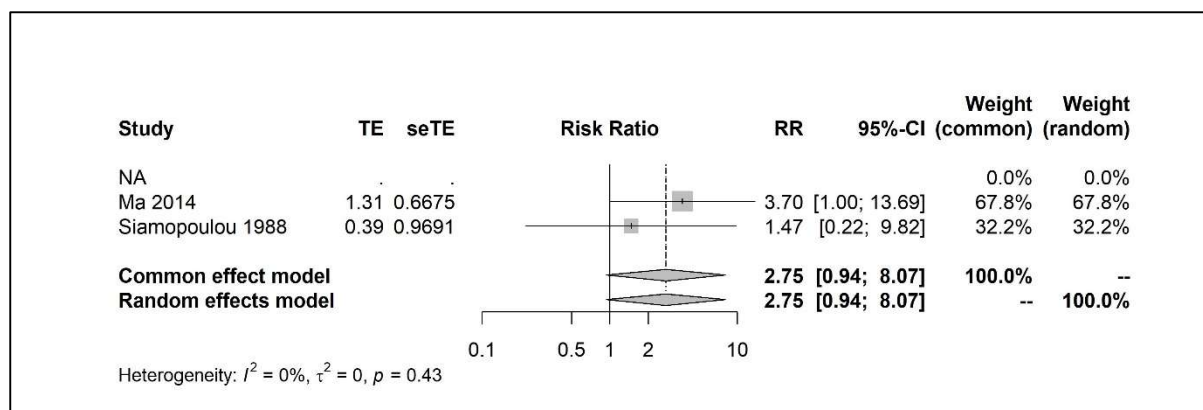
Meta-analysis of two studies reporting association of gestational hypertension or pre-eclampsia and future development of SLE



Meta-analysis of two studies reporting association of preterm birth and future development of SLE



Meta-analysis of two studies reporting association of preterm birth and future development of rheumatoid arthritis



Meta-analysis of two studies reporting association of gestational diabetes and future development of T1DM

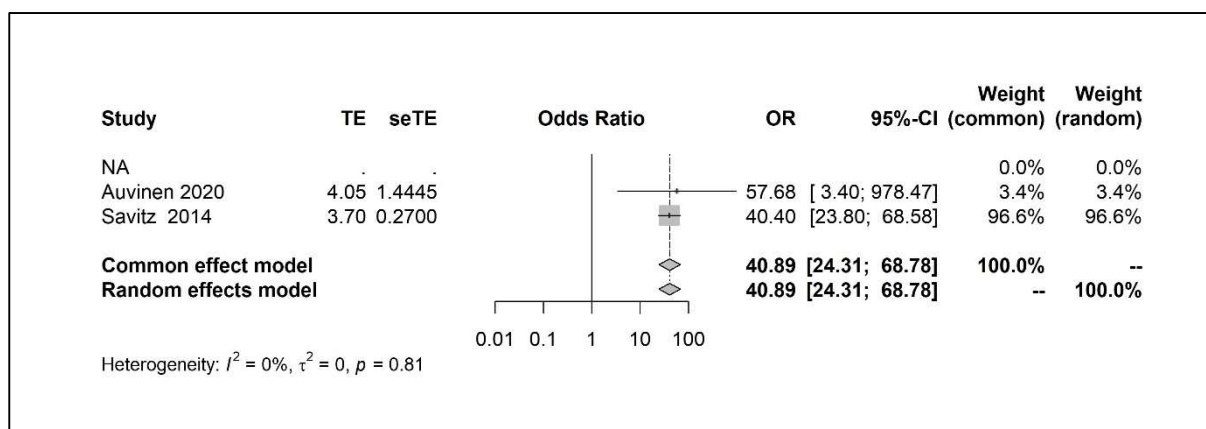
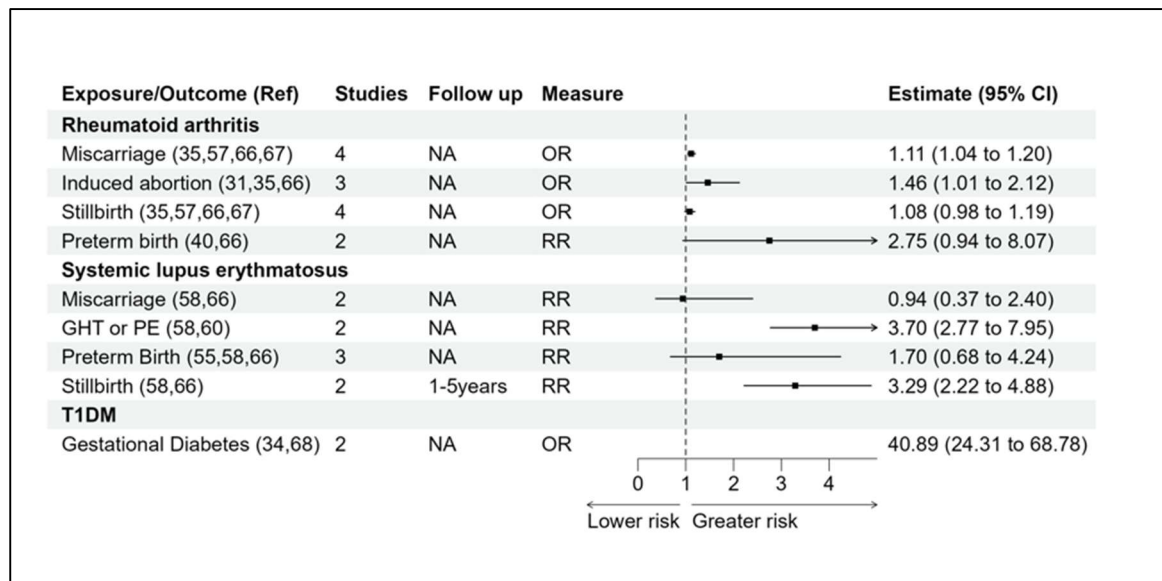
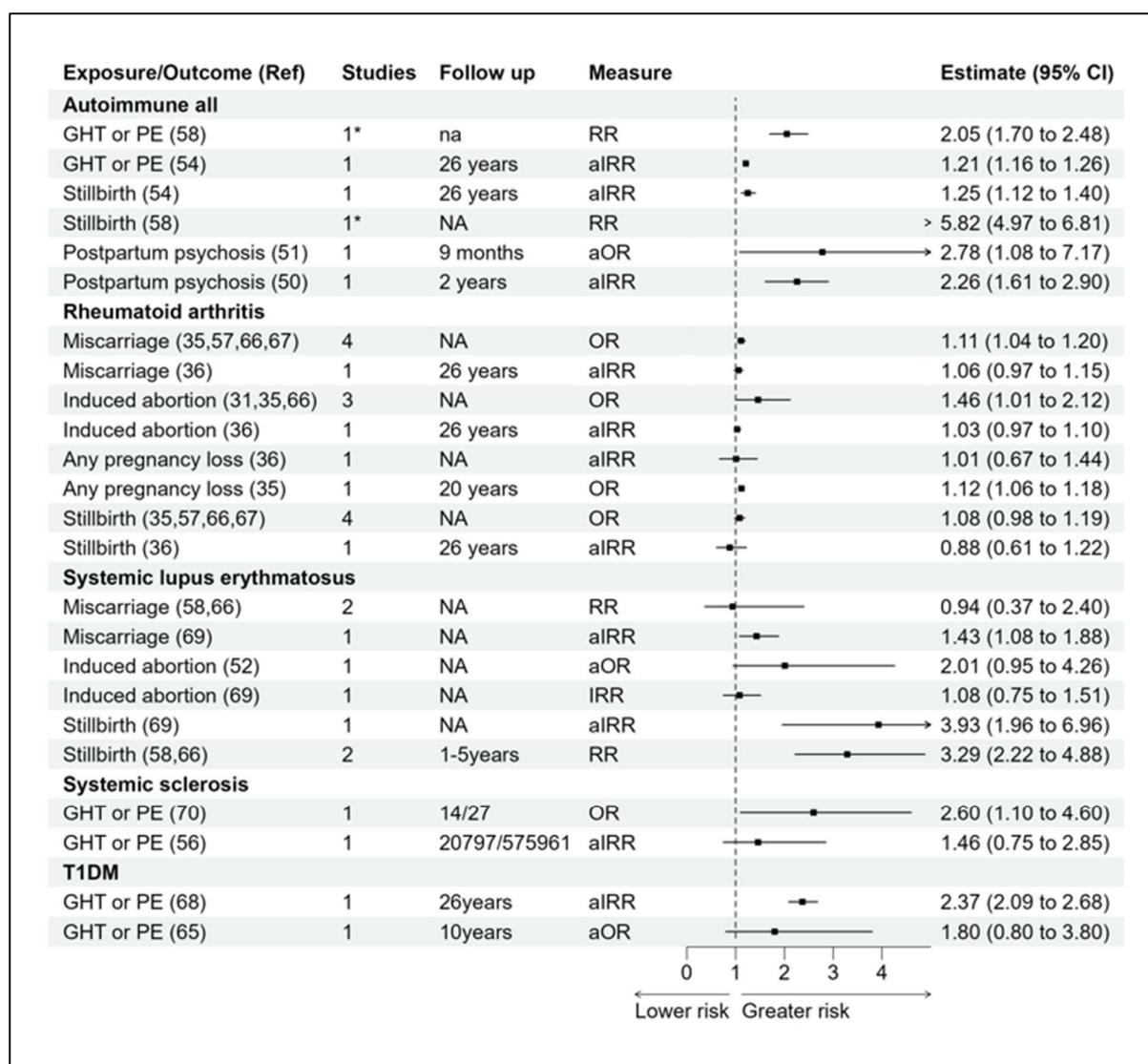


Figure 6.8 The new findings from this review



GHT or PE=Gestational hypertension or pre-eclampsia, , HR=hazard ratio, RR=risk ratio, IRR=incidence rate ratio, OR=odds ratio, NA=not available, '*'=Case control study

Figure 6.9 The mixed findings of this review



GHT or PE=Gestational hypertension or pre-eclampsia, , HR=hazard ratio, RR=risk ratio, IRR=incidence rate ratio, OR=odds ratio, NA=not available, '*'=Case control study

Table 6.10 Cohort studies with same or overlapping cohorts

Study	Cohort (all cohort studies)	Exposure	Outcome
1. Ulff-Møller,2009	1935-1989 The cohort consisted of 4.4 million women and men born between 1935 and 1989.	Abortion (spontaneous, missed, induced), ectopic pregnancy, molar pregnancy	Systemic lupus erthematosus

2. Jorgensen, 2010 Extended report	1935-1989 women and men born in 1935–89. This cohort was linked to national health registries	Abortion (spontaneous, missed, induced), ectopic pregnancies, hydatidiform moles, hyperemesis gravidarum, gestational hypertension, and pre-eclampsia	Rheumatoid arthritis
3. Neilson 2011	1935-1989 all Danish women and men (4.4 million) born between 1935 and 1989 and alive in 1968 or later	Miscarriage, stillbirth ectopic pregnancy, hyperemesis gravidarum, gestational hypertension, pre- eclampsia)	Multiple sclerosis
4. Khashan, 2011	1962-1992 all women born in Denmark between January 1, 1962 and December 31, 1992.	Induced abortion, Caesarean section	All autoimmune diseases, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease
5. Jorgensen, 2012	1955-1993 Danish women born between 1955 and 1993	Abortion (spontaneous, missed, induced), ectopic pregnancies Stillbirth Hyperemesis gravidarum, gestational hypertension, preeclampsia,	Various autoimmune diseases
6. Harpose 2013	Pregnancies 1996-2002 completing 86,054 full-term pregnancies (.37 weeks of gestation).	Gestational hypertension, pre- eclampsia, hyperemesis gravidarum	Inflammatory bowel disease
7. Jorgensen, 2014	Pregnancies 1996-2002	Gestational hypertension,	Rheumatoid arthritis

		pre-eclampsia, hyperemesis gravidarum	
8. Kamper 2018	Women born 1978-2010	Pre-eclampsia	Systemic sclerosis
9. Mikkelsen,2022	1957-1977 All women born between 1957– 1997 and living in Denmark between 1977– 2017	Miscarriage	Myasthenia gravis

Table 6.11 Data Extraction form

Author/Year
Geographical area
Population
Database/health care setting
Exposure
Comparator
Outcomes
Definition of exposure and ascertainment methods
Definition of outcome and ascertainment methods
Study design
Age mean control
Age mean case
Data analysis method
Population case
Comparator case
Population control
Comparator control
Total number
Summary estimate
i ²
Follow up period
Author's conclusion
Strengths and limitations of the study
Funding

