The impact of time, polycystic ovarian syndrome and pregnancy in Idiopathic Intracranial Hypertension

By

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A thesis submitted to the

University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

Institute of Metabolism and Systems Research

School of Medical and Dental Sciences

University of Birmingham

August 2023

Abstract

Background

Idiopathic intracranial hypertension (IIH) is characterised by elevated intracranial pressure (ICP) predominately affecting women of reproductive age with obesity. Its incidence is rising in line with obesity rates. There are unmet needs to evaluate the longitudinal visual and headache outcomes, identify prognostic factors, and assess the impact of comorbid conditions such as polycystic ovarian syndrome (PCOS) and the event of pregnancy. In addition, this work was undertaken during the coronavirus pandemic which significantly impacted hospital services and naturally forms the introductory chapter to this COVID-era thesis. This thesis was based on the prospective cohort study, IIH: Life, from Birmingham, and maternal health data from the UK Hospital Episodes Statistics dataset.

There was a clear need for a large prospective cohort study to evaluate visual and headache outcomes over time and help identify any prognostic markers. The benefit of this research was to improve the management of IIH patients by identifying the key modifiable risk factors that affect prognosis.

The commonest endocrinopathy in women of reproductive age is PCOS, which is known to affect pregnancy and fertility and prior literature indicates in more prevalent in women with IIH. Therefore, it is important to evaluate the comorbidity of PCOS and whether it impacts outcomes. Fertility and pregnancy may be impacted by shared mechanisms with PCOS including obesity, metabolic profiles and hyperandrogenism, or through alternative pathways. However, the impact of a diagnosis of IIH has not yet been established and warrants further research.

Pregnancy has the potential to impact IIH longitudinal outcomes due to the associated gestational weight gain, hormonal changes, and the limited treatment options. However, the outcomes have been under investigated with only two published studies, and therefore the guidance has often been to avoid pregnancy and avoid active labour. These themes form an important thread within this thesis.

This thesis aimed to assess the impact of time, PCOS, and pregnancy in IIH in order to improve the management of IIH in women of childbearing age.

Findings

Following the first COVID-19 lockdown, a significant impact on the incidence and management of IIH was observed. Amongst the patients seen in our emergency papilloedema clinic, approximately one-third presented with new onset IIH. Additionally, in individuals with previously diagnosed IIH, a majority (58%) experienced weight gain during the lockdown period, with an average increase of 6.2 kg (standard deviation (SD) 4.6). Importantly, this weight gain was found to be statistically associated with a significant worsening of papilloedema ($p=0.013$). Furthermore, the emergency CSF diversion surgery (shunting) rate rose 4.7-fold compared to the same period in 2019. Most worryingly, 13% of all IIH patients seen in those 2.5 months had surgical interventions with 21% of the new onset IIH group requiring surgery.

The longitudinal prospective cohort study, IIH: Life, included 490 patients with a confirmed IIH diagnosis. The cohort predominantly consisted of females (98%) with a mean body mass index (BMI) of 38 kg/m2. The study revealed that patients with the thickest ocular coherence tomography (OCT) retinal nerve fibre layer (≥400 µm) exhibited the worst visual outcomes. We noted a delayed decline in the visual field and OCT ganglion cell layer after 12 months. Within the medically managed cohort (n = 426), we found that disease duration and change in BMI had the greatest influence on visual outcomes. There was a substantial burden of headache observed, with a daily headache at presentation and a prior migraine history influencing the long-term headache prognosis.

Atypical presentations of IIH, characterized by asymptomatic or with a normal BMI at diagnosis, were uncommon (10%) and rare (3.7%) respectively. In the asymptomatic cohort most patients developed symptoms over the course of their follow up, and the trajectories were similar regardless of the initial presence or absence of symptoms. Although a normal BMI at the baseline visit was associated with worse visual field function, papilloedema measurements were analogous, and long-term outcomes did not significantly differ between the groups.

Comorbid PCOS in IIH was common (20%, 78/398) in our cohort based on the Rotterdam criteria. The presence of PCOS was associated with a 3.2-fold increased risk of self-reported fertility problems and 4.4-fold for requiring medical intervention for pregnancy. However, it was worth noting that comorbid PCOS did not adversely impact long-term vision or headache outcomes in people living with IIH.

Pregnancy in individuals with IIH presented unique challenges and considerations. An IIH diagnosis was associated with an increased risk of pre-eclampsia (5.3-fold) and gestational diabetes (2.7-fold) compared to the general population. Pre-eclampsia was also increased compared to a PCOS population (3-fold), but not gestational diabetes. Furthermore, reduced birth rates and increased caesarean section rates were also observed. In people with IIH who subsequently became pregnant, pregnancy did not adversely affect visual or headache outcomes and was akin to those with IIH that had never had a pregnancy. IIH diagnosed in pregnancy was rare (2%) but associated with greater papilloedema. However, visual field and acuity measurements were comparable to those with established IIH who became pregnant.

Conclusions

People with IIH were adversely affected by the first COVID-19 national lockdown. Overall IIH has been found to be negatively influenced by papilloedema severity, daily headache at presentation and a personal migraine history, but positively improved by weight loss. Whilst it was found there was a 20% comorbid PCOS prevalence and self-reported fertility problems in this IIH cohort; PCOS was not associated with longer-term adverse outcomes. IIH was also shown to impact fertility, preeclampsia risk, gestational diabetes risk and caesarean section rates. IIH outcomes were impacted when IIH was diagnosed in pregnancy but not in those with established IIH who had a subsequent pregnancy. This body of work has furthered the literature with these new findings of adverse maternal health associations, outlined the spectrum of IIH, and highlighted the neutral influence of pregnancy for the majority of women living with IIH.

Dedication

This thesis is for my wife Isla and my son Joseph.

It is for my parents Ok and Linda, my siblings Kristian and Maria, and my grandparents.

They have provided the inspiration and drive to learn, to observe, to grow and to love.

These qualities have helped me evolve as a father, a neurologist, and a researcher.

Acknowledgements

This PhD has been intellectually stimulating, challenging and an excellent introduction to academic research. I am truly indebted to my support synapse both on an academic and personal level. Thank you to everyone.

Firstly, I would like to extend my sincere gratitude to my supervisors, Professor Alexandra Sinclair and Professor Susan Mollan, whose exceptional expertise and visionary outlooks have shaped the trajectory of my PhD journey. Their mentorship has been transformative to my academic career from a dedicated neurology registrar to an accomplished academic clinical lecturer, especially amid the unprecedented challenges posed by a global pandemic. Their support has enabled me to hone my skills in literature reviews, project management, critical evaluation of data, statistical analysis, manuscript preparation and effective communication through both oral and poster presentations. In light of their remarkable expertise, invaluable advice, and generous investment of time, I am eternally grateful to Professor Sinclair and Professor Mollan.

I would also like to express my thanks to the exceptional ophthalmology and headache teams, both past and present, at the University of Birmingham and the Queen Elizabeth Hospital, Birmingham. Their invaluable contributions to this research, coupled with their unwavering support, have played an instrumental role in its success. Thank you for attentively listening to my suggestions and providing guidance when needed. I would like to extend my special thanks to Andreas Yiangou, James Mitchell, Benjamin Wakerley, Stephanie Gregg, Claire Fisher, Olivia Grech, Zerin Alimajstorovic, Yousef Hyder, Hannah Lyons, and Matilde Sassani for their support.

This research would not have been possible without the statistical expertise of Victoria Homer. She introduced and taught me the programming language of R and, with many hours of hard work, has enabled me to produce statistically sound results. I would also like to thank Jemma Mytton for her statistical assistance with some of the pregnancy research.

This research would not have been possible without the support of the patient charity IIHUK, and all the IIH patients who have contributed. IIHUK has supported the prospective database that a lot of this research is based upon, and they have enabled some of my research to be published open access, so it is accessible to patients, clinicians, and researchers.

To my cherished Isla, thank you for your patience, understanding and support. Your exceptional care and nurturing spirit especially towards Joseph has enriched both our lives. Joseph, I would like to thank you for your boundless energy, infectious giggles, and tender cuddles. They are a daily reminder of the world beyond work and the importance of research to improve the lives of others. To the rest of my family, a few lines cannot encapsulate the depths of appreciation I hold, as your support has encompassed the entirety of my existence thus far. Your support has enabled me to develop not just a researcher and a clinician, but also flourishing as a multifaceted individual. Thank you.

List of papers

The chapters within this thesis are from these publications:

1. Thaller M, Tsermoulas G, Sun R, Mollan SP, Sinclair AJ. Negative impact of COVID-19 lockdown on papilloedema and idiopathic intracranial hypertension. Journal of Neurology, Neurosurgery & Psychiatry. 2021;92:795-797.
2. Thaller M, Homer V, Hyder Y, Yiangou A, Liczkowski A, Fong AW, Virdee J, Piccus R, Roque M, Mollan SP, Sinclair AJ. The idiopathic intracranial hypertension prospective cohort study: evaluation of prognostic factors and outcomes. J Neurol. 2023 Feb;270(2):851-863. doi: 10.1007/s00415-022-11402-6.
3. Thaller M, Homer V, Mollan SP, Sinclair AJ. Asymptomatic idiopathic intracranial hypertension: Prevalence and prognosis. Clin Exp Ophthalmol. 2023 Aug;51(6):598-606. doi: 10.1111/ceo.14256.
4. Thaller M, Homer V, Abbott S, Hazlehurst J, Mollan SP, Sinclair AJ. Does a healthy weight body mass index at onset of Idiopathic Intracranial Hypertension change the outcomes? A United Kingdom prospective cohort study. Neuroophthalmology (under review). 2024.
5. Thaller M, Homer V, Sassani M, Mollan SP, Sinclair AJ. Longitudinal prospective cohort study evaluating prognosis in idiopathic intracranial hypertension patients with and without comorbid polycystic ovarian syndrome. Eye (Lond). 2023 Dec;37(17):3621-3628. doi: 10.1038/s41433-023-02569-x.
6. Thaller M, Mytton J, Wakerley BR, Mollan SP, Sinclair AJ. Idiopathic intracranial hypertension: Evaluation of births and fertility through the Hospital Episode Statistics dataset. BJOG. 2022 Nov;129(12):2019-2027. doi: 10.1111/1471-0528.17241.
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Additionally, I published these other first author publications:

- Thaller M, Adderley NJ, Subramanian A, Mollan SP, Sinclair AJ. Co-morbid Polycystic Ovarian Syndrome with Idiopathic Intracranial Hypertension. Neuroophthalmology. 2023 Jan 10;47(1):49-52. doi: 10.1080/01658107.2022.2162089.
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- Thaller M, Wakerley BR, Abbott S, et al. Managing idiopathic intracranial hypertension in pregnancy: practical advice. Pract Neurol. 2022 Aug;22(4):295-300. doi: 10.1136/practneurol-2021-003152.

I have contributed, with authorship, to this further relevant research during this PhD:

- Alimajstorovic Z, Mollan SP, Grech O, Mitchell JL, Yiangou A, Thaller M, Lyons H, Sassani M, Seneviratne S, Hancox T, Jankevics A, Najdekr L, Dunn W, Sinclair AJ. Dysregulation of Amino Acid, Lipid, and Acylpyruvate Metabolism in Idiopathic Intracranial Hypertension: A Non-targeted Case Control and Longitudinal Metabolomic Study. J Proteome Res. 2023 Apr;22(4):1127-1137. doi: 10.1021/acs.jproteome.2c00449.
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Abbreviations

A4	Androstenedione	**IRR**	Incidence rate ratio
BM	Basement membrane	**Lme4**	Linear mixed-effects model
BMI	Body mass index	**LMP**	Last menstrual period
CGRP	Calcitonin gene related peptide	**LOESS**	Locally weighted scatterplot smoothing
CS	Caesarean section	**LogMAR**	Logarithm of the minimum angle of resolution
CSF	Cerebrospinal fluid	**LP**	Lumbar puncture
CVST	Cerebral venous sinus thrombosis	**NHS**	National Health Service
DHEA	Dehydroepiandrosterone	**NIH**	National Institutes of Health
DVSS	Dural venous sinus stenting	**OCT**	Optical coherence tomography
GCL	Ganglion cell layer	**ONSF**	Optic nerve sheath fenestration
GDM	Gestational diabetes mellitus	**OP**	Opening pressure
GLP-1	Glucagon-like peptide-1	**OR**	Odds ratio
HAD A	Hospital Anxiety and Depression Scale – Anxiety	**PCOS**	Polycystic ovarian syndrome
HAD D	Hospital Anxiety and Depression Scale – Depression	**PMD**	Perimetric mean deviation
HADS	Hospital Anxiety and Depression Scale	**PPE**	Personal protective equipment
HES	Hospital episodes statistics	**PROMs**	Patient reported outcome measures
HIT-6	Headache Impact Test 6	**RNFL**	Retinal nerve fibre layer
HVF	Humphrey visual fields	**SARS-CoV-2**	Severe acute respiratory syndrome coronavirus 2
ICHD-3	International Classification of Headache Disorders 3rd edition	**SD**	Standard deviation
ICP	Intracranial pressure	**SITA**	Swedish Interactive Testing Algorithm
IIH	Idiopathic Intracranial Hypertension	**T**	Testosterone
IIHWOP	IIH without papilloedema	**TRT**	Total retinal thickness
ILM	Inner limiting membrane/layer	**UHB**	University Hospital Birmingham
IoM	Institute of Medicine	**UK**	United Kingdom

Chapter 1: General Introduction

1.1 Overview

Idiopathic intracranial hypertension (IIH) predominately affects women with obesity, and evidence suggests it is a neuro-metabolic disorder.[1-3] This condition is characterized by raised intracranial pressure (ICP), which typically manifests as papilloedema (the bilateral swelling of the optic nerve heads).

The revised diagnostic criteria stated papilloedema should be present, along with a lumbar puncture (LP) opening pressure (OP) of ≥25cm CSF, a normal neurological examination (except unilateral or bilateral 6th nerve palsy), no abnormality on neuroimaging, except those features related to raised ICP, and normal CSF constituents.[4] It is mandatory to exclude secondary causes, such as mass lesions, hydrocephalus, and cerebral venous sinus thrombosis (CVST). In clinical practice, it is accepted that a LP OP between 25 and 30 cmCSF may be normal for some people without papilloedema and the consensus is that the higher the OP the more likely the diagnosis of IIH when other features are met.[5] However, this is also dependent on the timing and positioning for the LP.[6]

The majority of people with IIH suffer from chronic headaches, which appears to be the predominant cause of reduced quality of life in this disease.[5, 7] While visual loss is a serious complication, it affects only a small portion of the people who require surgical intervention.[8] Other common symptoms reported include transient visual obscurations, pulsatile tinnitus, back pain, neck pain and dizziness.[9-11] Debilitating cognitive dysfunction and brain fog can significantly impact a patient's life but is reported to a lesser degree.[2, 5, 12]

Considering that the incidence of IIH has been documented to be rising with the global obesity pandemic,[13] there was an unmet need to evaluate the longitudinal outcomes, identify prognostic factors and assess for the impact of comorbid conditions, such as polycystic ovarian syndrome (PCOS), and pregnancy.

1.2 Epidemiology

IIH has always been considered a rare disorder, although its incidence has risen considerably in the last few decades. In an England wide hospital-based study the incidence of IIH was documented to increase from 2.26 to 4.69 per 100,000 of the population between 2002 and 2016, with the peak seen in females aged 25 years old (15.2 per 100,000).[13] A big data study using The Health Improvement Network (THIN) confirmed this between 2005 to 2017 where the incidence tripled from 2.5 to 9.3 per 100,000 person-years and prevalence increased from 26 to 79 per 100,000 women.[14] The escalating incidence significantly correlated with rising Body Mass Index (BMI),[13] markedly in the >30 kg/m^2 range,[14] and has been found in small data studies to be associated with recent weight gain.[15] A large meta-analysis determined world-wide, that the incidence of IIH correlated with country-specific obesity rates.[16, 17] In addition to the cost of the individual, both personal and financial of being diagnosed with a chronic disabling disease, there are significant healthcare costs. These costs are likely to be higher than predicted due to lack of medical understanding of the disease and the routes patients with IIH access care. In England, a health economic analysis projected health care costs alone to likely be £462.7 million by 2030.[13] As pathways for care may be changed with evidence from a recent randomised clinical trial, healthcare costs could peak, with high upfront costs for bariatric surgery, but in the longer term be lower than expected due to the sustained remission[18, 19] and reduction in the potential long-term morbidity and mortality associated with IIH.[19-21]

1.3 COVID-19

The COVID-19 pandemic started as I was planning my research areas and continued throughout my research time. The main challenges arose from recurrent lockdowns and the strain on healthcare resources. Within the National Health Service (NHS), there was deemed to be a need to prioritise emergency services and stop all non-essential clinical activities.

Regarding IIH care in Birmingham, the University Hospitals Birmingham (UHB) IIH service was closed, and the team redeployed to frontline services, including to the inpatient wards and the critical care unit. The continual use of personal protective equipment (PPE) was rolled out. National guidance was issued to avoid fundoscopy due to concerns about coronavirus transmission.[22, 23]

Beyond the healthcare setting, the media constantly reported on the horrendous death tolls and the strain on the NHS. This led to many reports of people with life-threatening diseases avoiding seeking medical help due to these pressures. Additionally, there were shortages in the shops, closure of leisure activities, a focus on working from home (bar key workers) and even guidance to limit outside activity time.

The true impact of the lockdown measures on healthcare only became apparent after the first wave of COVID-19 and the return of urgent non-emergency services, such as papilloedema clinics. Could the limits to accessing healthcare during the COVID-19 pandemic have affected people with IIH?

1.4 Longitudinal outcomes

The longer-term prognosis of IIH has only been studied in cohorts with a maximum sample size of 239 patients.[11, 24-26] Clinical trials and case-controlled cohort studies focused on specific subpopulations of IIH, such as new onset or chronic disease.[18, 27-29] Consequently, a need arose for a larger prospective cohort study of IIH across the spectrum of the disease.

1.4.1 Visual assessment

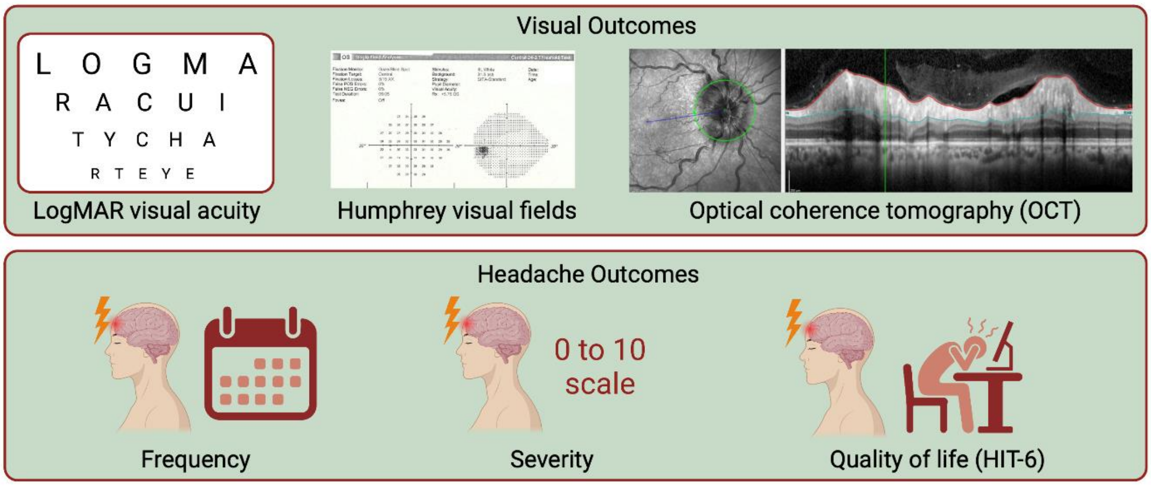
Assessment of IIH includes a detailed history, neurological examination, and appropriate imaging to rule out secondary causes. Neurological examination in IIH incorporates fundoscopy (a direct view of the retina and optic nerve head), visual acuity measurement, and cranial nerve examination. Further ophthalmological assessments include visual acuity measurements (LogMAR or Snellen are commonly used), visual field testing (most often Humphrey (automated static perimetry) or Goldmann (manual kinetic perimetry)), fundus photography and optical coherence tomography (OCT) imaging of the retina and optic nerve head.

LogMAR visual acuity is recommended over Snellen due to its increased reliability, with a standardised progression in size and the same number of letters per line.[30, 31] It is also important to correct for any refractive errors.[32] In the clinical data reported within this thesis, the LogMAR visual acuity was used.

The Humphrey visual field (HVF) perimetric mean deviation (PMD) has served as an endpoint for clinical trials, including in IIH.[27, 33] Visual fields have been used for decades to monitor ophthalmological diseases, and the IIH treatment trial demonstrated PMD improvement at 6 months in both eyes regardless of whether patients were treated with acetazolamide or placebo, although the benefit was greater in the medicated group.[27] PMD is used rather than the more specific pointwise analysis of the HVF as there was negligible improvement noted where the points were between 0dB and -10dB.[34] Therefore, PMD was recommended in medical treatment trials, as these IIH patients generally have the mildest affected baseline sensitivities.[34] Two longitudinal studies showed favourable outcomes in visual function in most IIH patients,[11, 24] however, significantly worse visual fields and visual acuity were observed in patients with severe papilloedema compared to those with mild swelling.[25, 35]

OCT imaging enables the non-invasive assessment of retinal and optic nerve head structure with the different retinal layers delineated.[36] This allows for more accurate differentiation between papilloedema and pseudopapilloedema than through direct fundus examination. Additionally, it enables objective quantification of the papilloedema, in particularly the peripapillary retinal nerve fibre layer thickness and total retinal thickness, facilitating monitoring over time.[36] Optic nerve head volume measurements on OCT have been shown to be positively correlated with ICP, where a reduction in the central thickness of 50µm correlated with an ICP reduction of 5 cmCSF.[37] Therefore, OCT could be used as an non-invasive marker of intracranial pressure, and integrated into clinical care. Measuring ICP is also possible through lumbar punctures or intracranial pressure monitors, however both are invasive therefore naturally associated with greater side effects.[38, 39] OCT does not replace the role of lumbar puncture in the diagnosis of IIH through the revised diagnostic criteria,[4] but could avoid the routine use of serial lumbar punctures and reserving it for those with deteriorating papilloedema at risk of visual loss.[5] Figure 1 illustrates the main outcomes assessed in IIH patients, with the OCT image illustrating papilloedema.

Figure 1 – Visual and headache outcomes in IIH.



1.4.2 Headache assessment

Headache is the commonest symptom and predominant disabler in IIH. It most commonly has a migraine-like phenotype and a positive relationship between ICP and headache has been demonstrated.[40] In clinical settings, headache is routinely assessed though deep headache phenotyping, which is based on the International Classification of Headache Disorders 3rd edition (ICHD-3).[41] It also involves identifying characteristics to enable monitoring of treatment response or need for escalation. Key characteristics include frequency (both any headache phenotype and migraine-like headache), severity (rated on a scale of 0-10, where 0 is no pain and 10 signifies the worst pain) and patient reported outcome measures (PROMs), such as the Headache Impact Test 6 (HIT-6) (Figure 1). The term “migraine-like headache” is used because although it meets ICHD-3 criteria for migraine, it is not a primary headache disorder due to its association with raised ICP. PROMs are important to assess, as IIH is associated with a decreased quality of life and significant disability.[7] The HIT-6 assesses pain, social functioning, role functioning, cognitive functioning, vitality and psychological distress.[42]

The ICHD-3 classifications most relevant to this research are:

- Migraine without aura (1.1). A recurrent headache disorder (at least 5 attacks) lasting 4-72 hours. Headache characteristics require two of the following four: unilateral location, pulsating quality, moderate or severe intensity, and aggravation by routine physical activity. Additionally during the headache at least one of: nausea/vomiting, or photophobia and phonophobia needs to be present.[41]

- Migraine with aura (1.2), which meets migraine criteria and those of aura. It requires recurrent attacks of unilateral fully reversible aura symptoms: visual, sensory, motor, speech, brainstem or retinal. They also need have at least three of these characteristics: spreading gradually over ≥5 minutes, two or more aura symptoms in succession, each aura symptom lasts 5-60 minutes, at least one is unilateral, at least one is positive (i.e. visual shimmering, lines, paraesthesia), or accompanied/followed by headache within 60 minutes.[41]
- Headache attributed to idiopathic intracranial hypertension (IIH) (7.1.1). Either a new headache or a significant worsening of a pre-existing headache, which is in temporal relationship to the IIH or accompanied by pulsatile tinnitus and/or papilloedema. It also requires a diagnosis of IIH and CSF pressure exceeding 25 cmCSF, or 28 cmCSF in obese children.[41]

Unfortunately, persistent post-IIH headache is common and persists after acutely raised ICP settles.[43] Underlying perturbed metabolic pathways may contribute to the headaches seen in IIH, including the production of acetate and its products, which is implicated in nociceptive signalling including through increased extracellular glutamate and modulation of AMP-activated protein kinase activity.[44] Compensatory CSF regulatory mechanisms inducing osmotic shifts may also induce headaches, for example the normalisation of CSF urea from low to normal concentrations once pressure normalises.[44] Furthermore, shared pathways previously identified in migraine could coexist in IIH, either due to the presence of comorbid migraine or common pathophysiology.

Additionally, there is a high use of opiates within the IIH population, demonstrating the significant headache burden associated with IIH and also putting patients at higher risk of medication overuse headache.[20, 43] Therefore, the long-term treatment of headache in IIH is of paramount importance, and standardised outcomes are needed for trials.[33] There is some positive real-world data for targeting the calcitonin gene related peptide (CGRP) receptor or ligand, in particularly through targeted monoclonal antibody therapy designed for migraines, as a treatment option for headache in IIH. [45, 46] Identifying IIH patients at increased risk of persistent post-IIH headache is also crucial, as they may benefit from a more rapid escalation in treatment.

1.4.3 Atypical presentations

Although IIH predominately affects people with obesity, it is not exclusively limited to this population.[13, 47] Other presentations are considered atypical and pose challenges for diagnosis and management, including patients with a healthy weight BMI and those who are asymptomatic at presentation.

Asymptomatic presentations refer to cases where papilloedema is incidentally discovered in the absence of headaches, tinnitus, transient visual obscurations or other visual symptoms.[48] The concern is that the recognition of IIH may be delayed in these cases, leading to worse outcomes. Additionally, the typical symptoms of an IIH relapse may be absent, further delaying sight saving surgical intervention in fulminant IIH with severe papilloedema. When the headache response to rising ICP was blunted by anti-CGRP monoclonal antibody therapy, a similar concern was raised, emphasizing the importance of weight monitoring and close ocular surveillance in physiologically or pharmacologically asymptomatic patients.[46]

A healthy weight or 'normal' BMI is classed by the World Health Organisation as 18.5-24.9kg/m^2.[49] While weight management has shown benefits in IIH, its effectiveness in patients without obesity remains uncertain and warrants further research.

To comprehensively understand the impact of these atypical IIH presentations on visual and headache outcomes, a large prospective study is needed. Such a study would provide valuable insights into the management and prognosis of these presentations.

1.4.4 Weight management

Obesity (BMI ≥30kg/m^2) is associated with IIH, and the adiposity is centripetal.[50, 51] Obesity is associated with numerous comorbidities including cardiovascular diseases.[52] Compared to age-, sex- and BMI-matched controls, IIH is associated with a 2-fold increase in cardiovascular disease risk.[14] Female IIH patients also face an increased risk of diabetes mellitus and arterial hypertension.[14, 53]

The connection between obesity and raised ICP, via an androgenic mechanism, has been demonstrated, with truncal fat mass correlating with lumbar puncture opening pressure.[50] Human studies have shown that weight gain both prior to diagnosis and post IIH diagnosis is associated with developing IIH or its recurrence.[54, 55] Additionally, in animal studies, a high fat diet, hydrocortisone exposure and adjuvant testosterone therapy have all been shown to increase CSF secretion.[56, 57] This provides insight into the relationship between weight gain and raised ICP in some patients, leading to IIH.

Weight loss, particularly reducing fat mass in the truncal region, is the only disease modifying therapy in IIH.[50, 58] Unfortunately, despite initial successful weight loss achieved through dietary and exercise changes, a proportion of this is regained over time, necessitating weight management services.[59] It is common to regain lost weight, leading to IIH relapses.[55] Bariatric surgery has been shown to significantly lower both weight and ICP at 12 and 24 months compared to community weight management.[18] Weight loss targets of 5-10% are often reported,[60] but in clinical practice, higher amounts are often required.[18, 61, 62] To normalise ICP, weight loss up to 24% total bodyweight may be required,[62] which can be almost impossible to achieve without surgical interventions.

1.4.5 Medications

Two medications are currently used in IIH: Acetazolamide and Topiramate.

Acetazolamide, a carbonic anhydrase inhibitor, is used off-label in IIH and can modestly improve visual function in IIH patients with mild visual loss[27] and improve quality of life.[63] In a study involving healthy rats, acetazolamide was shown to reduce intracranial pressure by 5%.[64] However, discontinuation is common, with 48% in a randomised controlled trial stopping within 12 months[65] although a subsequent trial reported 10% discontinuation at 6 months.[66] Side effects include diarrhoea, paraesthesia, fatigue and renal stones.[5] Side effects leading to cessation may limit its impact on longer term outcomes. Animal studies have shown teratogenicity,[67, 68] although a single retrospective series of 50 human pregnancies found no increase in adverse events,[69] which is why international opinion on its use varies and it is not recommended in pregnancy in the United Kingdom.[5, 70]

Topiramate is used off-label in IIH with in vivo and open-label study evidence of benefit.[64, 71] It also has a carbonic anhydrase effect, with a 22% improvement in ICP seen in healthy rats.[64] Topiramate is also effective for migraine prophylaxis[64, 72, 73] and may be useful in an IIH population with obesity, as can cause weight loss through appetite suppression.[5, 74, 75] Human pregnancy registry studies have highlighted its teratogenicity,[76] leading to its avoidance in women actively planning to conceive. At higher doses (>200 mg/day) the efficacy of the combined oral contraceptive pill can be reduced.[77, 78]

Therefore, using either Acetazolamide or Topiramate in women of reproductive age is potentially limited, especially when pregnancy is being planned. Globally, there is variability in the use of acetazolamide in pregnancy, although it is not recommended in recent guidelines.[5, 79]

There are other treatments undergoing clinical trials including the glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide.[29] This randomized, placebo-controlled, double-blind trial on 15 patients with IIH, demonstrated that exenatide significantly and meaningfully reduced ICP at 2.5 hours, 24 hours and 12 weeks.[29] This suggests that exenatide could be a beneficial future treatment option, both for ICP reduction and weight loss, as it is already licensed for the latter.

1.4.6 Surgical intervention

There are three main surgical options reserved for IIH with impending sight loss, fulminant IIH, and these are CSF diversion surgery (shunting), optic nerve sheath fenestration (ONSF) and dural venous sinus stenting (DVSS).[5] Additionally, any surgical option does not alter the metabolic phenotype and therefore this would still require the disease modifying therapy of weight loss. Local expertise and multidisciplinary team preferences typically dictate which procedure is performed. Furthermore, in the subset of patients who require surgical intervention in pregnancy, the options would the same as in patients who are not pregnant.[79]

Consensus guidelines have recommended ventriculoperitoneal shunting as the optimal surgical procedure for CSF diversion as it has the most evidence of efficacy in IIH.[5, 80] Complications of shunts include abdominal pain, infection, low pressure headaches, shunt obstruction, subdural haematoma and tonsillar herniation. It is important that they are performed by a skilled neurosurgeon with a specialist interest in CSF disorders, and with image guidance, adjustable valves, ICP monitoring device and laparoscopic insertion of the peritoneal end to lower the revision rates and enable future non-invasive pressure monitoring and adjustment.[8, 81, 82] In those with CSF shunts inserted prior to becoming pregnant can have a normal pregnancy and delivery.[79, 83, 84]

Optic nerve sheath fenestration (ONSF) is less commonly performed, in the UK[8] and in the USA[85] due to limited local surgical expertise, the complication rate, and little data on the longevity of the procedure.[80, 86] It should be considered when the local skills are available.

Dural venous sinus stenting (DVSS) is used globally however this is based on evidence only from case series and no randomised clinical trials.[86-89] There is debate in the literature as to whether the cerebral venous sinus stenosis is the cause or a consequence due to extrinsic compression of the raised ICP.[86, 88, 89] It may be of benefit in selected patients with IIH and an elevated pressure gradient and elevated ICP.[90] It is rarely performed in the UK[8] and complications include stent-adjacent stenosis, stent migration, thrombosis and rarely vessel perforation.

Further clinical trials are needed to directly compare outcomes for surgical interventions, and none are recommended for patients with IIH and headache alone.[5]

1.5 Polycystic ovarian syndrome (PCOS)

1.5.1 Androgens, IIH and PCOS

IIH and PCOS share the phenotypic characteristics of predominantly affecting reproductive aged females with obesity, as well as associated metabolic disease and hyperandrogenism. However, women with IIH exhibit a distinct pattern of androgen excess compared to those observed in PCOS and simple obesity, with lower serum dehydroepiandrosterone (DHEA), lower androstenedione (A4) and increased testosterone (T) in IIH in comparison to PCOS, with lower A4 and higher T compared to BMI matched controls.[91] In addition, the 11-oxygenated androgen pathway was not involved in IIH unlike in PCOS, thus indicating different androgen profiles.[91] Increased serum androgen levels have been associated with earlier IIH onset [92] and in female-to-male transgender patients after commencing testosterone therapy.[93]

CSF production and secretion occur at the choroid plexus though specialised epithelial cells which utilise the Na+/K+-ATPase ion pump to create an osmotic gradient.[94, 95] Acetazolamide, a carbonic anhydrase inhibitor, which is commonly used in IIH patients to lower intracranial pressure, has been shown to inhibit Na+/K+-ATPase.[96] The androgen-activating enzyme AKR1C3, responsible for activating androstenedione to testosterone, is expressed in the choroid plexus. After testosterone exposure, carbonic anhydrases II and III show increased expression, indicating that androgens can modulate CSF dynamics through the Na+/K+-ATPase.[91] IIH patient have been shown to have significantly higher CSF A4 and T than both lean and obese controls,[91] further supporting this mechanism as contributory to causing raised ICP, although the location of androgen activation remains unclear.

Hyperandrogenism is the potential driver of the metabolic syndrome seen in IIH. In PCOS, acute androgen exposure has been shown *in vivo* to suppress lipolysis and *in vitro* to increase *de novo* lipid synthesis.[97] IIH adipocytes appear transcriptionally and metabolically primed towards lipogenesis.[1] In IIH, there is also an insulin and leptin resistant phenotype and elevated systemic and adipose 11β-hydroxysteroid dehydrogenase activity, exceeding that driven by obesity.[1, 98] Bariatric surgery to induce weight loss has been associated with reduced intracranial pressure and 11β-hydroxysteroid dehydrogenase activity.[18, 98] Therefore, IIH with comorbid PCOS has the potential for a worse metabolic phenotype and, consequently, worse IIH outcomes due to being metabolically primed for weight gain.

1.5.2 Prevalence of PCOS

The prevalence of PCOS in the general population depends on the criteria used, such as the National Institutes of Health (NIH) or Rotterdam criteria. In the United Kingdom, the Rotterdam diagnostic criteria for PCOS are widely used, and require two of the three criteria: oligo-/anovulation, hyperandrogenism and polycystic ovaries.[99] It has also been suggested that there are four phenotypes with varying severity depending on the combination of the criteria.[100] The prevalence of PCOS in the general population has been estimated to be between 8% and 17.8%.[101-103] However, the study noted that many women (68-69%) in the community remained undiagnosed.[103] The NIH criteria do not require the presence of polycystic ovaries on ultrasound but rather both hyperandrogenism and menstrual irregularities, potentially leading to under-diagnosis when only one of these is present with polycystic ovaries, thus underestimating the prevalence of PCOS.

Given the concerns around rising IIH prevalence in females correlating with rising obesity rates,[13] there is a concern that comorbid PCOS could exacerbate this further. However, it only appears to minimally affect the PCOS prevalence.[104, 105]

The prevalence of comorbid PCOS in IIH patients has been reported to be between 15.5% and 57%.[106-108] However, these three previous studies have been underpowered, with the maximum sample size of any of the studies being 65 patients. A recent population-based study showed a 1.5-fold increase prevalence of diagnosed PCOS in participants with IIH compared to age- and BMI- matched controls, 7.4% and 4.9% respectively.[20, 109] However, prevalence in both groups is likely to be underestimated given the high reported rates of under-diagnosis, although the proportional increased prevalence is similar to a previous IIH and PCOS study (1.8-fold increase).[108]

The impact of comorbid PCOS on visual and headache outcomes in IIH has not been established and warrants evaluation. Recognition of comorbid PCOS enables its medical management, which may aid the weight loss required for IIH disease control. Metformin can aid weight loss in IIH with comorbid PCOS,[107] although this is not currently part of routine IIH clinical care.[5]

1.5.3 Infertility

PCOS has an ovarian source of hyperandrogenism, leading to the development of follicular arrest, polycystic ovaries, and anovulation, which impacts fertility and is the commonest cause of anovulatory infertility. A study of self-reported PCOS showed a 15-fold increase in infertility.[110] This has not been directly investigated in IIH; however, one study reported 12 out of 240 IIH patients having pregnancies in a 10-year period, accounting for 5% of the population.[111]

Weight loss prior to pharmacotherapy use for infertility has shown ovulatory benefits.[112, 113] The use of medications, such as clomiphene citrate, letrozole and metformin, are recommended for infertility management,[102] and could be beneficial in this illustrated combined cohort. Most first-line treatments have been shown improve clinical pregnancy, although a systematic review did not find beneficial effects in PCOS with obesity.[114] Exenatide use over a 12-week period was shown to improve pregnancy rates compared with metformin in a Chinese PCOS cohort with infertility and raised body mass index.[115] Therefore, identifying whether fertility is affected in IIH without PCOS, as well as recognising comorbid PCOS in IIH, potentially enables earlier recognition of fertility problems through awareness of a new at-risk group and more therapeutic options, which are already established in PCOS.

1.6 Pregnancy

One of the most common reasons why women of childbearing age experience body weight gain is pregnancy.[79] Consequently, there is a concern that pregnancy could induce a diagnosis of IIH, or exacerbate the disease in those already diagnosed with IIH. This could be due to either weight gain or hormonal fluctuations associated with pregnancy.

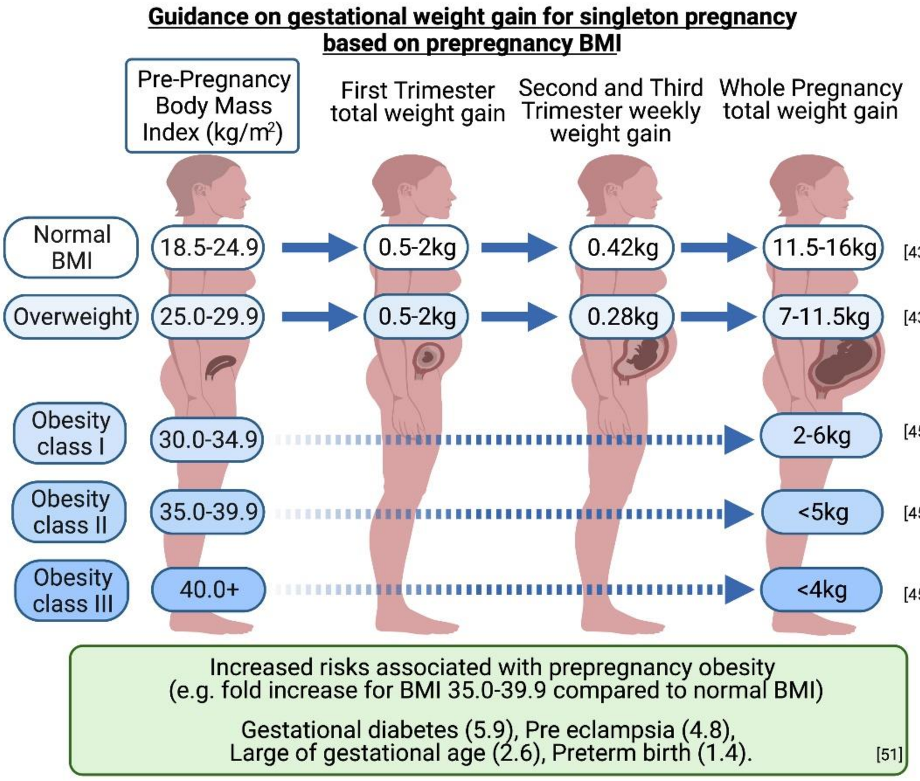
1.6.1 Pre-existing data in IIH

There is limited research on IIH during pregnancy, with guidance primarily based on retrospective case series with small sample sizes, leading to insufficient evaluation of longer-term outcomes. The largest previous study evaluated 109 IIH patients, of whom 24 had 36 pregnancies (although 3 patients had insufficient data) between 1939 and 1982.[116] The second study included 12 patients with 16 pregnancies out of 240 IIH patients between 1990 and 2000.[111] Both studies reported that if the IIH onset occurred during pregnancy, it was usually in the first half of the pregnancy.[111, 116] Additionally, 20% of patients with a pregnancy and IIH experienced a relapse of their IIH during pregnancy.[116] However, both studies reported good and similar visual outcomes compared to non-pregnant IIH.

1.6.2 Weight management in pregnancy

There was no evidence based guideline for gestational weight gain in IIH, until this publication.[79] Internationally, the US Institute of Medicine (IoM) guidelines (2009) provide guidance for weight gain in pregnancy for women with a BMI ≤30 kg/m^2.[117-119] However, they do not differentiate by individual obesity classes, which is crucial in women with IIH. For women with obesity, it is recommended to gain less weight during pregnancy than patients with lower BMIs.[79] Based on evidence subsequent to the 2009 guidelines, we created recommendations with declining weight gains as pre-pregnancy BMI increased (Figure 2).[79] An individualised approach is necessary with referral to weight management services where required. General management of gestational weight gain involves a combined approach of diet, physical activity, and behavioural change approaches,[120] as excessive gestational weight gain can significantly increase the long-term weight gain trajectory,[121] potentially increasing the risk of IIH deterioration or recurrence.

Figure 2 – Weight gain pregnancy guide from Thaller et al. Practical Neurology 2022.[77] References are associated with the publication and not this thesis.



1.6.3 Complications

Pre-eclampsia and gestational diabetes mellitus are two common complications in pregnancy that can have detrimental effects on both maternal and foetal health if not recognised and treated properly.

Pre-eclampsia affects 3-5% of pregnancies[122] and its prevalence has been noted to be increasing over time (6.7-fold increase between 1980 and 2003).[123] The exact causative mechanisms have not yet been fully established, but it is thought to be that abnormal placentation leads to placental ischaemia and subsequent systemic vascular dysfunction.[124] This vascular dysfunction causes the classical maternal features of hypertension, proteinuria due to renal involvement, and maternal organ dysfunction.[122] Early recognition is essential as uncontrolled pre-eclampsia can lead to potentially fatal complications, including eclampsia, organ failure, and stroke.

Gestational diabetes mellitus is the most common medical complication of pregnancy. The underlying metabolic abnormalities, including increased insulin resistance and beta-cell defects, are likely present before conception, and the additional stresses associated with pregnancy further increase the risk of developing diabetes.[125] Although various risk factors can predispose a person to developing it. Hyperglycaemia, high blood glucose, during pregnancy characterises the condition, which usually resolves after birth. However, women with a history of gestational diabetes mellitus are at increased risk of developing diabetes later in life.

Both pre-eclampsia and gestational diabetes share similar risk factors. Maternal obesity is a significant risk factor,[126-128] and metabolic syndrome has been shown to increase the risk of pre-eclampsia 1.6-fold and gestational diabetes by 3.7 times.[128] PCOS is known to be associated with an increased risk of both diseases, independent of obesity, although obesity remains a key contributory factor.[129] Therefore, given the elevated BMI observed in patients with IIH,[13] there is a need to evaluate the risk of these complications compared to a PCOS control group as well as to patients without either IIH or PCOS. It is currently unknown whether IIH is independently associated with these gestational complications, and earlier detection may be beneficial for both maternal and foetal health.

1.6.4 Delivery

Currently, there is no recommended method of delivery of babies from mothers with IIH.[5] It is noted that surgical delivery rates increase in cases of maternal obesity and excessive gestational weight gain.[130, 131] Additionally, there is a concern within the IIH population regarding a prolonged second stage of labour, although in reality the duration of contractions lead to relatively short Valsalva manoeuvres.[79] Therefore the decision to perform caesarean sections should be based solely on obstetric factors.[5, 83] Nevertheless, it is important to acknowledge that patient choice may have an influence on the surgical rates in reality.

1.7 Aims

One key aim was to establish the impact of the first COVID-19 lockdown on people with IIH. Given that IIH predominantly affects women of reproductive age with obesity, there was a hitherto unmet need to evaluate the longitudinal outcomes, identify prognostic factors, and assess the impact of comorbid conditions or events such as PCOS and pregnancy in people with IIH.

The Idiopathic Intracranial Hypertension Priority Setting Partnership set 10 key priorities for IIH research.[132] The four relevant ones for this thesis are: addressing the progression of IIH, predicting visual loss, monitoring visual function, and hormonal causes.

The aims of this thesis are to evaluate the:

- First COVID-19 lockdown's impact on people with papilloedema and IIH.
- Longitudinal visual and headache outcomes in IIH, and the impact of papilloedema severity.
- Impact of atypical presentations (asymptomatic and normal baseline BMI) on IIH outcomes.
- Prevalence and prognosis of comorbid PCOS in IIH.
- IIH diagnosis impacts on pregnancy – infertility, complications, and delivery.
- Timing of pregnancy and its impacts on IIH longitudinal outcomes.

To investigate these aims, the prospectively collected IIH Life cohort study's data would be used. This is collected at University Hospitals Birmingham, United Kingdom, led by Professors Sinclair and Mollan and accrued between 2012 and 2021 for this thesis. In addition, interrogation of the hospital episodes statistics (HES) data would enable addressing the aims focussing on infertility, pre-eclampsia, gestational diabetes, and methods of delivery/birth.

This uses data from all hospital admissions in England 2002-2019 as a much larger data set was required for these outcomes.

This IIH thesis will address the aims in 4 main chapters to highlight the impact of COVID-19, Time (Longitudinal outcomes), Ovarian pathology (PCOS) and Pregnancy in IIH.

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Chapter 2: Impact of the first COVID-19 lockdown on IIH (Thaller. JNNP. 2021)

Manuscript title:

Negative impact of COVID-19 lockdown on papilloedema and idiopathic intracranial hypertension.

Published as a letter:

Thaller M, Tsermoulas G, Sun R, Mollan SP, Sinclair AJ. Negative impact of COVID-19 lockdown on papilloedema and idiopathic intracranial hypertension. Journal of Neurology, Neurosurgery & Psychiatry. 2021;**92:**795-797. Doi: 10.1136/jnnp-2020-325519.

Involvement:

I was involved in data collection, data analysis, data interpretation, writing first manuscript and critical revision of the manuscript.

2.1 Abstract

Background: The neurological complications of SARS-CoV-2 infection were increasingly being recognised, as was the impact of enforced lockdown. The idiopathic intracranial hypertension (IIH) service was paused during the first UK national lockdown, despite papilloedema being a medical emergency. The aim of this study was to evaluate the impact on new onset papilloedema and existing IIH at a UK neuroscience centre.

Methods: A 10-week (15/05/2020 to 30/07/2020) prospective evaluation of emergency papilloedema and IIH assessments following the first lockdown. Visual, headache and psychological outcomes were assessed in patients enrolled to the IIH:Life database.

Results: One hundred and thirty patients were assessed and a diagnosis of IIH made in 123, of which 43 were new onset and 80 pre-existing IIH. Among the IIH cohort, 58% gained weight over lockdown (mean 6.2kg (SD 4.6)) and this was associated with a statistically significant increase in papilloedema (retinal nerve fibre layer thickness +15.5µm (57.3)). Emergency CSF diversion surgery was required in 13% (17/130) of patients, with 21% of new onset group requiring it, and there was a 367% increase compared to 2019 (same period).

Conclusions: The first lockdown negatively impacted IIH patients, with an increased rate of surgical interventions and with the majority gaining weight.

2.2 Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the COVID-19 global pandemic, which started in early 2020. During the first United Kingdom lockdown (26th March until 15th May 2020 when the initial NHS related easing of restrictions started), the focus of NHS care shifted to enable prioritisation of emergency and intensive care services. This resulted in staff redeployment and the cessation of non-emergency services, including the Idiopathic Intracranial Hypertension (IIH) service, and access to optometric and hospital services was limited to absolute emergencies. Idiopathic Intracranial Hypertension when presenting with sight threatening disease is an emergency, however, is reliant on the recognition of papilloedema, timely investigations, and a multi-disciplinary approach.[1]

Coronaviruses are spread by proximity to the upper respiratory tract and therefore the use of personal protective equipment (PPE) was made mandatory to reduce transmission rates. Concerns were raised about the risk of spread during fundoscopy given the close proximity to the patient required to perform it.[2, 3] Avoidance of direct fundoscopy potentially led to reduced recognition of papilloedema despite the availability of alternative more remote techniques, such as slit lamp fundoscopy and optical coherence tomography, to ophthalmologists and optometrists.

The neurological complications of SARS-CoV-2 infection were only starting to be recognised, based on case reports, following the first wave of the pandemic. Neurotropism of the coronavirus was reported4 and 4.9% of COVID-19 patients had neurological signs/symptoms warranting neuro imaging with 23% of these being abnormal.[5] The likely pathological drivers are prolonged hypoxaemia, coagulopathy, and endothelial disruption.[5]

2.2.1 Hypothesis

The first COVID-19 national lockdown had a detrimental impact on the detection of papilloedema and on the ongoing management of IIH.

2.2.2 Aims and Objectives

The aim of this study was to evaluate the impact of lockdown on those presenting with new onset papilloedema and on those with existing idiopathic intracranial hypertension (IIH) seen in the emergency papilloedema clinic at the University Hospitals Birmingham (a single neuroscience centre) in the UK. This would be done by assessing changes in weight, body mass index, visual function, headache frequency, shunt rates and quality of life measures.

2.3 Methods

2.3.1 Patient selection

A 10-week prospective evaluation (15/05/2020 to 30/07/2020), following the initial easing of restrictions within the NHS and the return of some redeployed staff, of emergency papilloedema and idiopathic intracranial hypertension (IIH) patients attending clinics at the Queen Elizabeth Hospital Birmingham.

The inclusion criteria were a diagnosis of IIH or secondary pseudotumor cerebri. For patients seen more than once in the study period, only their initial visit was included for analysis.

The reasons for clinic review were urgent referrals for new papilloedema, possible exacerbation of existing IIH or IIH follow up appointments previously cancelled due to the enforced national lockdown and deployment of staff to frontline services.

2.3.2 Measurements

Baseline data of age, sex, diagnosis including disease activity, weight, and body mass index were recorded. In those with an existing IIH diagnosis, additional data from their last review before lockdown was recorded.

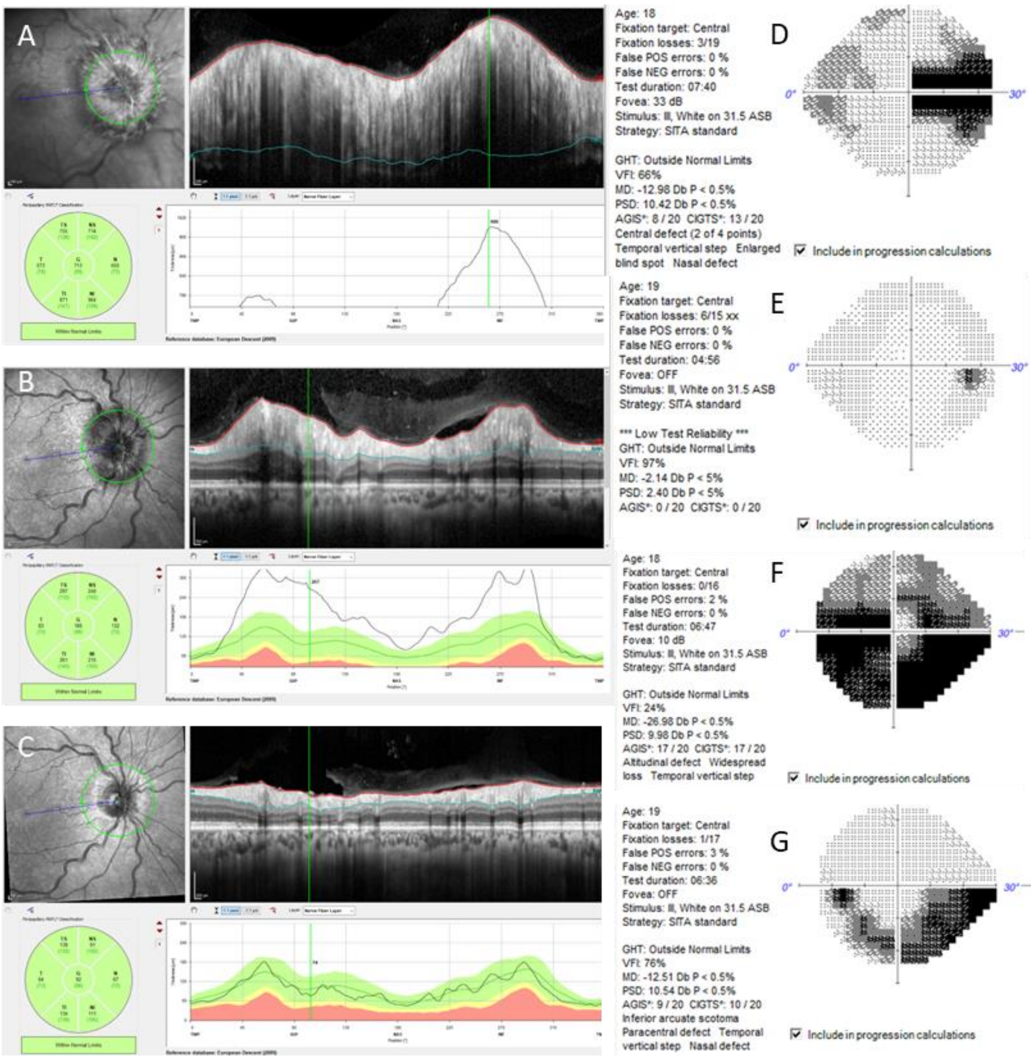
Visual function was measured by visual acuity (logarithm of the minimum angle of resolution (LogMAR)) and perimetric mean deviation (PMD) (Humphrey visual fields 24-2 (SITA) central threshold field). Papilloedema was measured by optical coherence tomography (OCT) average global peripapillary retinal nerve fibre layer thickness (RNFL).

Headache frequency (days per month) and the headache impact test-6 questionnaire (HIT-6) were noted. HIT-6 scores were graded as: 36-49 no (or little) impact, 50-55 some impact, 56-59 substantial, and 60-78 severe. [6] Depression and anxiety were evaluated by Hospital Anxiety and Depression Scale (HADS) scores: 0-7 normal, 8-10 mild, 11-14 moderate, 15-21 severe).[7] Cerebrospinal fluid (CSF) shunt data for IIH during the study period was compared to that from 2019, which was recorded retrospectively.

Figure 1 illustrates differing severities of papilloedema on OCT imaging, including automated segmentation inaccuracies in severe papilloedema,[8] and Humphrey visual field before (D and F) and after (E and G) CSF diversion surgery.

Figure 1 – Optical coherence tomography and Humphrey visual fields.

- *A. Optical coherence tomography (OCT) of the optic nerve head in patient with severe papilloedema, highlighting automated segmentation error for the retinal nerve fibre layer (RNFL).*
- *B. OCT RNFL showing papilloedema of a patient with active IIH.*
- *C. OCT RNFL of IIH in ocular remission (resolved papilloedema)*
- *D. Humphrey visual field (HVF) pre shunt for right eye showing enlarged blind spot (different patient from A-C).*
- *E. HVF resolution post shunt in right eye*
- *F. HVF pre shunt for left eye showing a significant upper and lower hemifield defect.*
- *G. HVF improvement post shunt in left eye but residual inferior arcuate defect.*



2.3.3 Statistical analysis

Statistical analysis and graph plotting were carried out on Microsoft Excel and GraphPad Prism v9.1, USA. Basic statistics used were means, standard deviations (SD) and chi-squared tests with the significance set at $p<0.05$. Worse eye data at post lockdown visit was reported. Missing data was excluded (constituting <16%). Values were considered statistically significant when P values were *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001.

Prospective data collection was approved by NHS National Research Ethics Committee (14/LO/1208), IIH: LIFE study.

2.4 Results

130 adult patients were assessed during the 10 weeks. 92% were female with mean age of 32.5 SD 9.3 years. 123 had IIH; of these 43 were new onset patients (new onset group) and 80 had a pre-existing diagnosis of IIH (follow-up group) (Figure 2). 7 had secondary causes of their raised intracranial pressure (Figure 2) (including 3 cerebral venous sinus thromboses with 2 secondary to COVID-19 and 1 other case also had COVID-19).

Figure 2 – CONSORT diagram.

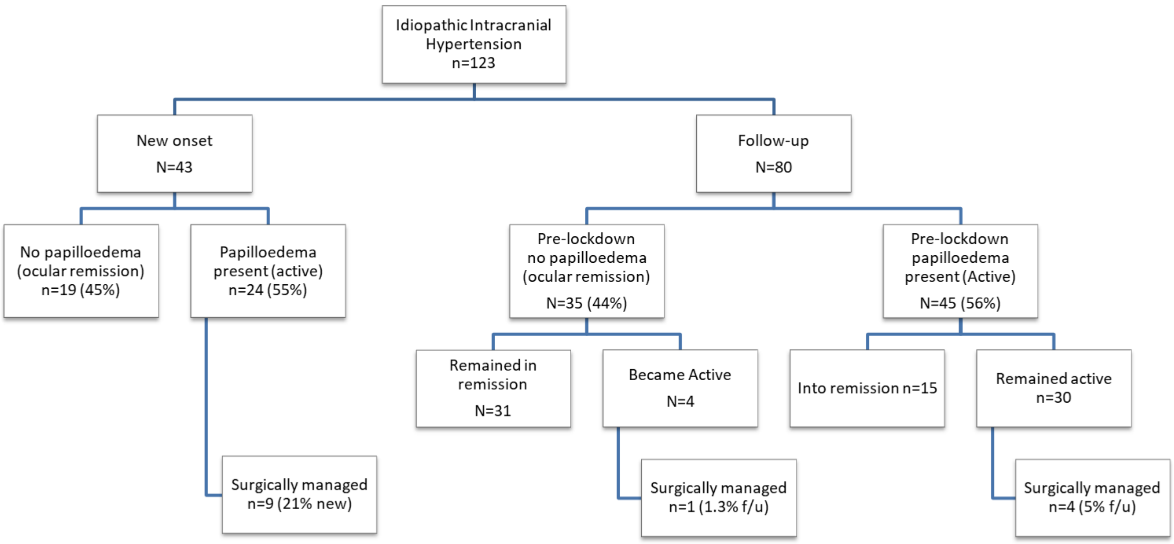


Table 1 demonstrates the baseline data for the first visit post lockdown in the whole study population, IIH cohort (new onset and follow-up groups) and those who required surgical intervention (CSF diversion surgery or ventriculoperitoneal shunts). Those with sight threatening IIH had the worst visual function. Within the IIH group there were 10 females who were pregnant, and their baseline data was similar to the main IIH cohort, however there was more papilloedema documented (RNFL 200.8µm (±134.50, n=9) and LogMAR visual acuity of 0.13 logunits (±0.13, n=7).

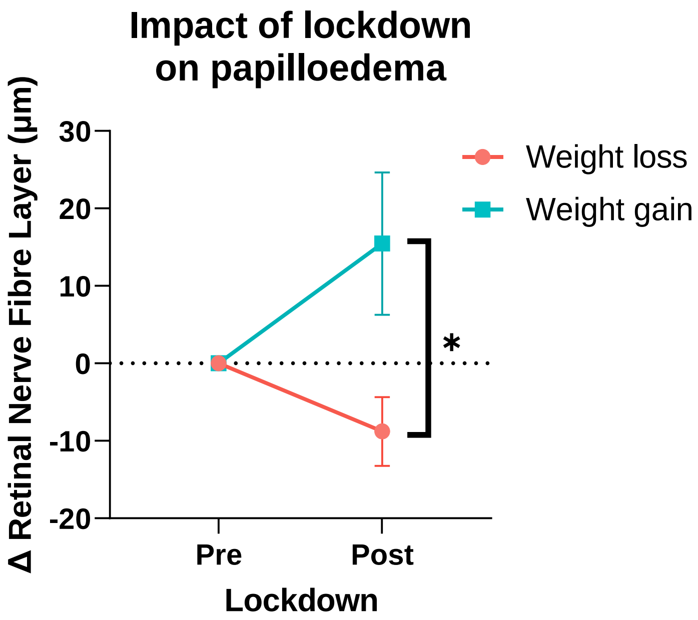
Table 1 – Baseline table for all, IIH diagnosed and CSF shunted patients.

	All patients	**IIH**	**Surgical intervention**
Cohort	130	123	17
Gender (F:M)	120:10	117:6	15:2
Age	32.5 (±9.3)	32.0 (±9.1)	28.5 (±9.4)
Weight (kg)	103.9 (±26.3) n=122	104.7 (±25.9) n=117	93.6 (±21.3) n=17
BMI (kg/m^2)	37.9 (±9.2) n=123	38.4 (±9.1) n=118	34.9 (±8.9) n=17
OCT RNFL worse eye (µm)	133.3 (±82.1) n=124	128.0 (±75.6) n=118	390.1 (±231.1) n=17
LogMAR acuity worse eye (logunits)	0.13 (±0.22) N=110	0.13 (±0.22) n=108	0.32 (±0.72) n=17
Humphrey visual field perimetric mean deviation worse eye (dB)	-5.67 (±8.7) n=56	-5.69 (±8.77) n=55	-11.47 (±11.0) n=10
Mean Headache days (/month)	17.2 (±12.9) n=105	17.1 (±12.9) n=100	
Mean migraine days (/month)	7.1 (±8.7) n=95	7.0 (±8.5) n=91	
HIT-6	59.1(±11.9) n=81	58.7 (±11.9) n=78	61 (±11.7) n=8
HAD A	9.8 (±5.0) n=81	9.8 (±5.0) n=78	9.5 (±5.4) n=8

HAD D	7.7 (±5.3) n=81	7.7 (±5.3) n=78	7.3 (±6.8) n=8

Amongst the IIH cohort, 58% gained weight over lockdown (increase of 6.2kg SD 4.6) and this was associated with a significant ($p=0.014$, $X^2=6.06$) increase in papilloedema (OCT RNFL increased by 15.5µm SD 57.3) compared to those who lost weight (Figure 3). In those IIH patients that lost weight (mean reduction of 6.0kg SD 5.6) there was an improvement in papilloedema (OCT RNFL improvement by 8.8µm SD 23.4).

*Figure 3 – Weight gain was associated with a statistically significant worsening of papilloedema with SEMs illustrated. *p=0.014*



In the IIH follow-up group 44% (35/80) were in remission (no papilloedema) at the last clinic visit prior to the lockdown. Of these 11% became active (recurrence of papilloedema with increased OCT RNFL), which was associated with a 4.3% increase in weight (mean +4.7kg SD 10) (Table 2). 67% of IIH patients with papilloedema prior to the pandemic had ongoing active papilloedema after the first lockdown. The mean weight (kg), BMI (kg/m^2) and papilloedema (retinal nerve fibre layer thickness (RNFL) (µm)) pre and post lockdown are shown in table 2. The individual change is not the pre lockdown mean subtracted from the post lockdown mean, but instead it is the mean of the individual changes seen in patients for whom both data points were recorded.

Table 2 – The impact of UK COVID-19 lockdown on IIH disease activity in those with known IIH pre lockdown

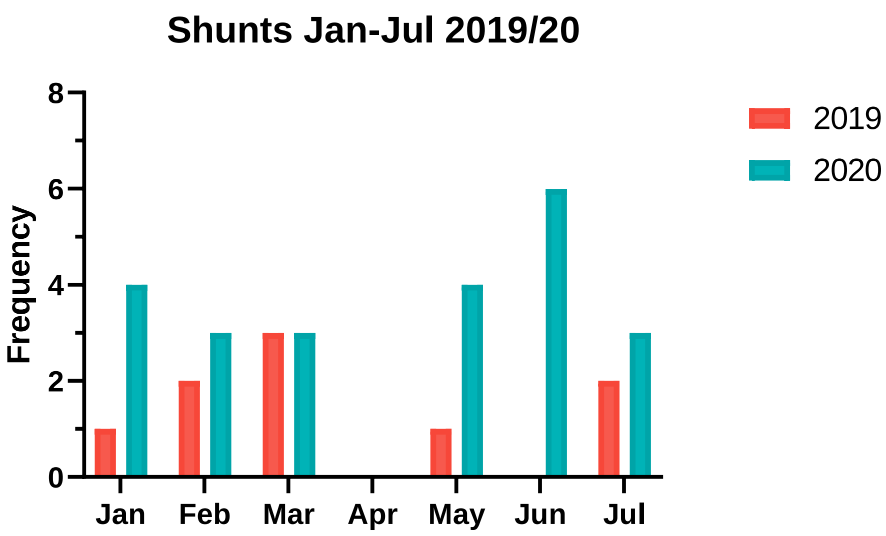
Change in IIH disease status (Pre-lockdown to post-lockdown)	**Assessment**	**Pre-Lockdown Mean (SD)**	**Post-Lockdown Mean (SD)**	**Individual Change Mean (SD)**
Remission to Active (n=4)	Weight	109.2 (12.0)	113.8 (15.2)	+4.7 (10.0)
	BMI	42.1 (8.0)	42.9 (10)	+0.8 (7.5)
	Papilloedema	102 (6)	128 (16)	+36 (22)
Active to Active (n=29)	Weight	99.6 (31.3)	103.5 (30.9)	+1.96 (6.3)
	BMI	37.1 (9.6)	38.0 (9.5)	+0.21 (3.4)
	Papilloedema	130 (39)	137 (70)	+5 (72)
Remission to Remission (n=30)	Weight	103.7 (21.1)	106.5 (21.3)	+4.2 (22.2)
	BMI	39.3 (8.6)	39.1 (8.3)	+0.9 (7.8)
	Papilloedema	89 (23)	88 (21)	-1 (12)
Active to Remission (N=15)	Weight	110.8 (24.9)	110.6 (26.3)	+0.7 (6.2)
	BMI	41.5 (10.4)	40.7 (9.8)	-0.3(2.6)
	Papilloedema	107 (44)	87 (18)	-15 (23)

Units: Weight kg, Body mass index (BMI) kg/m^2, Papilloedema – optical coherence tomography (OCT) retinal nerve fibre layer thickness (RNFL) µm. 2 patients not included due to data not available at initial time point.

Emergency CSF diversion surgery was required in 13% (17/130). All the surgery was for sight threatening disease (increasing severe papilloedema with declining visual fields that would result in permanent visual loss). 14/17 had IIH (weight gain consistently self-reported) and 3/17 had secondary pseudotumor cerebri. 21% of the new onset and 6.3% of the follow up groups underwent shunting. The CSF diversion rate May-July 2019 was 3 patients compared to 14 patients over a similar time period in 2020. This represented a 367% (or 4.7-fold) increase (Figure 4).

Acetazolamide was prescribed in 11.5% (15) and Topiramate in 12.3% (16) of IIH patients. These are both medical treatments for raised intracranial pressure.

Figure 4 - The number of shunts January to July in 2019 and 2020 for IIH at QEHB, with a marked 367% increase May-July 2020 compared to 2019.



Headache frequency and impact was very variable within the IIH population with mean headache days of 17 per month (Table 1), however a substantial proportion (17%) reported no headache. There was no significant change in headache frequency between last pre lockdown and first post lockdown visit. There was no significant change in HIT-6 scores following the first lockdown (Figure 5A). In this group 9.2% were on Erenumab (CGRP monoclonal antibody), which is a treatment for migraine.

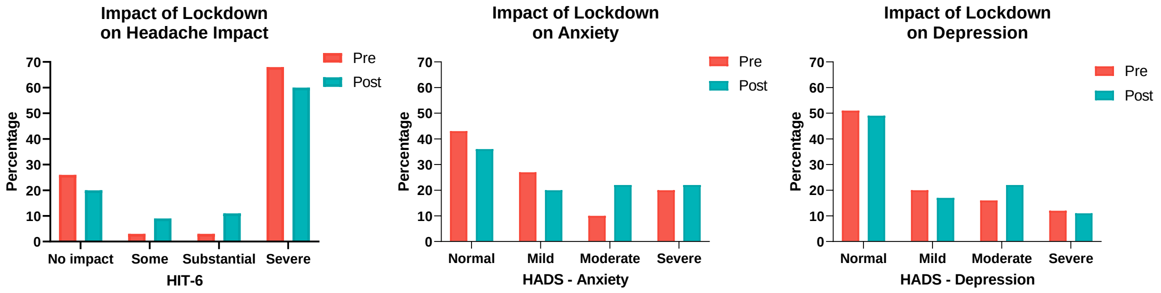
Anxiety and Depression scores post lockdown were raised (HADS>7) in 64% and 51% respectively. Whilst patients with pre-existing severe anxiety did not change following the Covid-19 lockdown, those with no or mild anxiety levels pre lockdown deteriorated (12% increased HADA score post lockdown) (Figure 5B, 5C).

Figure 5 – Comparison between the visit pre first lockdown (last visit before 23rd March 2020) and post lockdown (15th May to 30th July 2020) in known IIH patients.

A. *Headache Impact Test (HIT-6) scores. No (or little) impact 36-49, some impact 50-55, substantial 56-69 and severe 60-78.*[6]

B. *Hospital Anxiety and Depression Scale (HADS) – Anxiety scores. Normal ≤7, mild 8-10, moderate 11-14 and severe 15-21.*[7]

C. *Hospital Anxiety and Depression Scale (HADS) – Depression scores. Normal ≤7, mild 8-10, moderate 11-14 and severe 15-21.*



2.5 Discussion

The unprecedented strategies instigated globally to deal with the COVID-19 pandemic resulted in much of the world's population being subjected to lockdowns of variable durations. This study demonstrated the negative impact this required quarantine had for UK patients who presented with new onset papilloedema and those with pre-existing papilloedema due to IIH.

CSF diversion surgery is typically performed in 7.6% of those with IIH.[9] Here, 11.4% required emergency surgery to save vision. The 367% increase in surgical intervention in our centre, following lockdown, was a major concern. Potential reasons underlying this include impaired access to emergency care given main areas were COVID-19 dedicated, longer routine waiting times given the closure of the IIH service, reservations about seeking help due to the continuous media coverage about the COVID-19 burden on the NHS, and lifestyle changes imposed by quarantine, leading to weight gain. Recognition of papilloedema would have been expected to have been reduced due to the potential risk of COVID-19 transmission and national guidance.[2, 3] COVID-19 drove transition to telemedicine, further impairing access to fundoscopy.

Weight gain is a risk factor for the development and the recurrence of IIH.[10] The UK COVID Symptom Study of 1.6 million people reported an average weight gain since March 2020 of 0.78kg,[11] double that which was documented over the Christmas period. In comparison, the average weight gain in our cohort, within which is a wide spectrum of IIH disease states, was 1.13kg. Those patients whose IIH became active gained the most weight followed by those whose disease remained active (Table 2). This study showed that weight gain was associated with significant worsening of papilloedema compared to weight loss (Figure 2), which highlighted the importance of weight management in IIH even in a pandemic situation. The reduction in physical activity, caused by the COVID-19 lockdown, could have contributed to the documented weight gain as could dietary change with lifestyle changes.

There were increased numbers of patients who reported anxiety and depression in this cohort. There is an increased risk of depression (adjusted hazard ratio 1.38) and anxiety (adjusted hazard ratio 1.40) in women with IIH compared to age and BMI control population but similar to migraine controls.[12] A progressive detrimental psychological impact of lockdown has been documented, particularly affecting those between 18-30 years,[13] and treating comorbid mental health is important.

There are limitations inherent in this study's design. The inferences of our findings might be limited by the single-centre design and by the redistribution of emergency services in the region, potentially leading to reporting bias; however, this is the largest IIH service in the UK. The retrospective 2019 shunt data also has potential for reporting bias. We purposefully altered our clinical protocol to reduce patient contact to minimise COVID-19 transmission risk; hence visual field examination was omitted in patients with improving papilloedema based on OCT imaging. Documentation of weight change post-lockdown was limited to those with both pre and post lockdown measurements, although subjective descriptions of weight gain were described by the majority.

2.6 Conclusions

This study demonstrated that the national lockdown, caused by the COVID-19 pandemic, increased the risk of disease deterioration and CSF shunting both in those with existing and with new IIH. To help mitigate the risk of underdiagnosis, fundoscopy with appropriate personal protective equipment, should still be performed. Patients should be encouraged to seek medical or ophthalmological review when they have worsening symptoms such as rapid visual impairment regardless of whether there are pandemic restrictions. Prioritisation of patients who have gained weight may identify those with increasing papilloedema. In the future, provision should be made to support patients with IIH, papilloedema or potential symptoms of raised intracranial pressure, by limiting disruption to neurological and ophthalmological services that investigate and manage papilloedema.

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Chapter 3: Impact of time on IIH

Chapter 3.1 IIH prospective cohort study (Thaller. J Neurol. 2023)

Manuscript title:

The idiopathic intracranial hypertension prospective cohort study: evaluation of prognostic factors and outcomes

Published:

Thaller M, Homer V, Hyder Y, Yiangou A, Liczkowski A, Fong AW, Virdee J, Piccus R, Roque M, Mollan SP, Sinclair AJ. The idiopathic intracranial hypertension prospective cohort study: evaluation of prognostic factors and outcomes. J Neurol. 2023 Feb;270(2):851-863. doi: 10.1007/s00415-022-11402-6.

Involvement:

I was involved in data collection, data analysis, data interpretation, writing first manuscript and critical revision of the manuscript.

3.1.1 Abstract

Background: There is limited longitudinal data evaluating outcomes in Idiopathic intracranial hypertension (IIH). We aimed to evaluate the long-term outcomes in a real-world cohort of patients with IIH and sought to establish the prognostic factors.

Methods: A longitudinal prospective cohort study was conducted over nine years (2012-2021). Data included demographics and disease status. All consenting patients with IIH were recruited. Visual outcomes included visual acuity, Humphrey visual field and optical coherence tomography (OCT) imaging measurements. Headache frequency, severity, and impact were noted. We analysed the key variables impacting visual and headache outcomes.

Results: The cohort contained 490 patients with a confirmed IIH diagnosis. 98% were female with a mean body mass index (BMI) of 38 kg/m^2. Those with the highest OCT retinal nerve fibre layer had the worst visual outcomes. We noted a delayed decline, in the visual field and OCT ganglion cell layer after 12 months. In the medically managed cohort (n=426), we found that disease duration and change in BMI had the greatest influence on visual outcomes. There was high burden of headache, with daily headache at presentation and prior migraine history influencing long term headache prognosis.

Conclusions: There is a delayed decline in visual outcomes in those with most severe papilloedema. Disease duration and change in BMI were the key visual prognostic factors, therefore those with more acute disease may require closer monitoring. Improving prognosis in IIH should focus on the potentially modifiable factor of weight management.

3.1.2 Introduction

Idiopathic intracranial hypertension (IIH) predominately affects women with obesity and emerging evidence suggests it is a neuro-metabolic disorder.[1-3] It is a condition of raised intracranial pressure (ICP) which can lead to chronic headaches, visual loss and cognitive dysfunction.[2, 4, 5] It has a number of comorbid conditions such as obstructive sleep apnoea, infertility, increased pregnancy complications, and long-term risk of adverse cardiovascular outcomes.[6-8] For the majority of patients the visual prognosis is good. However, poor visual prognostic factors that have previously been demonstrated include male sex, ethnicity, high grade papilloedema, >30 transient visual obscurations per month and decreased visual acuity at baseline.[9-11] Headaches associated with IIH are problematic, debilitating, and persistent.[12-14] Weight loss is currently the only known disease modifier in IIH [15] and the recent IIH Weight Trial showed that bariatric surgery was superior over community weight management in lowering the intracranial pressure [16] with it also being cost-effective.[17] Maintenance of weight loss especially by dietary means can be difficult.[3] Reports state that IIH relapse is common, occurring between 9-28% in IIH patients.[13, 18, 19] Pharmacological interventions currently consist of off label use of acetazolamide, topiramate and other diuretics.[5, 20] When papilloedema is sight threatening, surgical intervention is often required.[5, 21, 22]

Within the literature there are few large cohorts describing the longitudinal course of IIH.[13, 23-25] Most were performed retrospectively or focus on particular interventions[26, 27] or investigate specific risks such as sex or ethnicity.[11, 28] There is a need for large prospective cohort studies evaluating the real world clinical course of IIH. Whilst there has been a number of randomised controlled trials and small case-controlled cohort studies, these define specific populations for their inclusion criteria such as new onset disease (as in the IIH Treatment Trial) [20, 29, 30] or chronic disease (as in the IIH Weight Trial) [16] and therefore do not focus on the whole disease spectrum. We aimed to evaluate the long-term outcomes in a prospectively collected real-world cohort of patients with IIH irrespective of disease timing. We hypothesised that those with the greatest papilloedema would have worse visual outcomes, and those with the greatest burden of headache at the start of the disease may have more headaches throughout the disease course. We evaluated all patients but also aimed to determine the key prognostic indicators in those managed exclusively medically (no IIH surgical interventions).

3.1.3 Methods

3.1.3.1 Study population

The IIH:Life study is an ongoing prospective observational cohort study of patients with IIH attending a specialist clinic at a single tertiary neuroscience centre in the United Kingdom (University Hospitals Birmingham NHS Foundation Trust (UHB)). Data presented in this manuscript was prospectively collected at the time of their routine clinical visits over a nine-year period (between April 23rd 2012 and Sep 8th 2021). All sequential consenting patients were included, and written informed consent obtained from all the patients.

3.1.3.2 Diagnosis of IIH

Patients eligible for inclusion were those with a confirmed diagnosis of IIH as per the modified Dandy criteria: this includes papilloedema, neuroimaging excluding a venous sinus thrombosis or structural lesion, lumbar puncture opening pressure >25 cmCSF in a properly performed procedure.[31] Patients were enrolled at their first visit to the neuro-ophthalmology outpatient clinic. They were either initially diagnosed at UHB or at another referring hospitals within the United Kingdom. Those who were referred with a potential diagnosis of IIH but in whom the diagnosis was not confirmed, those with a secondary cause of intracranial hypertension, and those with IIH without papilledema (IIHWOP) were excluded from the study. The medically treated cohort were evaluated as were those managed without surgical intervention (defined as a cerebrospinal fluid (CSF) diversion, optic nerve sheath fenestration (ONSF) or venous sinus stenting intervention for IIH conducted at any time).

3.1.3.3 Data Collection

The following data was collected: age, sex, dates of clinical visits, date of first diagnostic lumbar puncture (used to as a surrogate marker of disease duration, defined as time from the first diagnostic lumbar puncture to baseline clinical visit at the IIH clinic), Body mass index (BMI), diagnostic lumbar puncture opening pressure, ICP medication prescription (acetazolamide, topiramate, other diuretics (furosemide and amiloride)), acute and preventative treatments, details regarding any surgeries for IIH and International Classification of Headache Disorders 3rd edition (ICHD-3) diagnoses. Visual outcomes included visual acuity (measured using Logarithm of the Minimum Angle of Resolution (LogMAR)) and perimetric mean deviation (PMD; Humphrey 24–2 (Swedish Interactive Testing Algorithm (SITA) central threshold)). Papilloedema measures included Frisén grading (0-5 where 0 equates to no papilledema and 5 where all vessels are at least partially obscured by oedema)[32, 33] as established by a suitably trained neuro-ophthalmology specialist following dilated slit lamp examination; and optical coherence tomography (OCT) imaging (Heidelberg Spectralis™) parameters of average global peripapillary retinal nerve fibre layer (RNFL); a manually measured total retinal thickness (TRT); and macular ganglion cell layer (GCL) volume (1, 2.22, 3.45mm volume scan), by macular volume and/or posterior pole methods. Automated segmentation of retinal layers by OCT software may have inaccuracies in moderate to severe papilloedema.[34] To ensure accuracy, manual segmentation of RNFL and TRT was performed in peripapillary scans, in addition to manual segmentation of the basement membrane (BM) and inner limiting membrane (ILM) for cross-sectional slices of optic disc scans where appropriate.

Headache outcomes were evaluated by assessing headache frequency (monthly headache days), migraine-like headache frequency (monthly migraine-like headache days)[35], headache severity (0-10 numerical rating scale, where 0 is no pain and 10 equates to the most severe pain), and headache disability using the Headache Impact Test-6 (HIT-6) test.[36] A month is defined as the previous 28 days (4 weeks). Details of presence of daily headache at baseline in the last month,[35] prior history of migraine, familial history of migraine, and analgesic use were also collected as these were felt to be factors that could potentially influence headache prognosis.

3.1.3.4 Disease status definition

At the baseline clinical visit, following confirmation of a diagnosis of IIH, disease status was determined. Active IIH was defined as those with active papilloedema Frisén grade $\geq$ 1 in at least one eye and IIH in ocular remission was defined as those with no evidence of papilloedema.

IIH relapse was defined as a change from Frisen 0 to 1 based on RNFL measures from ≤100µm to ≥109µm in the same eye.[33]

3.1.3.5 Statistical Analysis

Continuous and categorical variables were reported as mean (standard deviation (SD)) and number (percentage), respectively. Statistical analyses were performed using R (v4.1.0). [37]

To assess longitudinal visual outcomes, adjustments were made for the effects of disease status at time of entry to the IIH Life study (either active IIH or IIH ocular remission); effect of time from the first lumbar puncture to enrolment (as the proxy for disease duration); lumbar puncture opening pressure at registration (both continuously and categorised <25, 25-29.9,30-39.9, or >40 cmCSF); BMI at first visit; BMI at each visit; and age at first visit. Models were developed independently for each visual outcome using forward stepwise regression, with our null models adjusting for disease status and ICP medication, as our *a priori* hypothesis was that such factors were likely to have the greatest effect on visual outcomes.

Regression models were fitted using lme4.[38] We assumed continuous form of our dependent variables for all outcomes. Population-level terms were used to estimate the average response value, an adjustment for time from study registration to outcome measure, and an interaction between variables of interest and time. Patient-level intercepts were included to address serial correlation in responses, and the nesting of measurements from eyes within patient (as modelling included data from both eyes, where available). Where covariates were added to models, they were transformed or centred around the median value as appropriate. Models were developed independently for each visual outcome.

For headache outcomes, in those with active IIH initially, the effect of any surgical intervention was explored. Further analyses then explored the effects of medication overuse, previous personal migraine history, familial history of migraine, presence of daily headache at registration, disease duration, and BMI. Analogous processes and models to those employed for visual outcomes were used for headache outcomes, with independent models developed for each headache outcome.

LOESS (locally weighted scatterplot smoothing) graphs were constructed prior to regression analysis in order to ascertain the relationship between variables and any emergent trends.

3.1.3.6 Patient and public involvement

IIHUK, a national patient charity that supports carers and patients with IIH (Registered Charity in England and Wales no 1143522 & Scotland SCO43294), endorsed and helped develop the IIH Life database concept and questionnaires included. The James Lind Alliance Priority Setting Partnership was commissioned by IIHUK to establish the top 10 research priorities in IIH,[39] and this research is based on addressing some of these priorities.

IIHUK contributed to funding the project. The Medical Research Council (MRC) MR/KO15184/1, National Institute of Health Research (NIHR) Healthcare Quality Improvement Partnership (HQIP) grant NIHR-CS-011-028 and the Sir Jules Thorne Award for biomedical science have helped fund this project.

3.1.4 Results

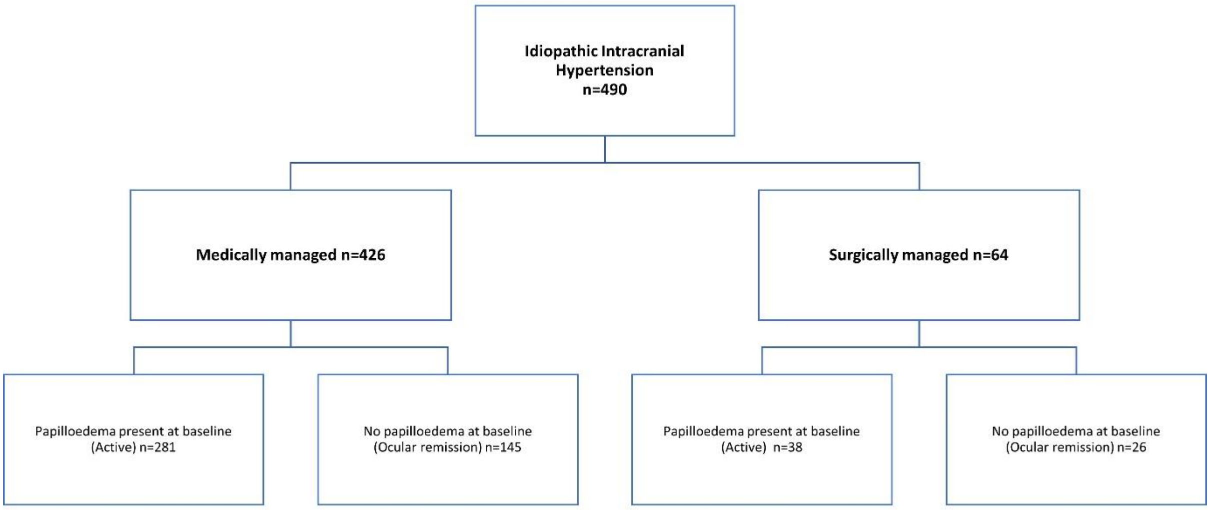
This analysis includes 490 patients with a confirmed diagnosis of IIH, with a mean disease duration of 17 (range 0-312) months. 161 patients had a single visit, with 329 having multiple visits (mean 4 visits; range 2-17 encounters). Those who attended more than once had a median duration of follow up of 17 (range 0-87) months. Baseline characteristics noted that there were very few men within this cohort (n=9), with the ratio of women: men being 53:1 (Table 1). In the medically managed cohort (n=426), at their first visit 281 had active IIH and 145 were noted to have IIH in ocular remission (Figure 1). In the surgery cohort, 38 at the first visit all had active IIH and 26 were in ocular remission (but either had surgery prior to enrolment or subsequently due to relapse) (Figure 1).

Table 1 – Baseline demographics table

	All IIH	**Medically managed**	**Surgically managed**
Total number (n)	490	426	64
Sex			
Female (n)	481	420	61
Male (n)	9	6	3
Status			

Active (n (%))	319 (65%)	281 (66%)	38
Ocular remission (n (%))	171 (35%)	145 (34%)	26
Age, years (mean (SD))	31.5 (9.4)	31.6 (9.5)	30.6 (9.0)
BMI, kg/m^2 (mean (SD))	38.1 (9.3)	37.8 (9.5)	40.2 (7.9)
Weight, kg (mean (SD))	103.0 (26.7)	101.9 (26.9)	110.2 (24.5)
CSF opening pressure, cmCSF (mean (SD))	36.5 (6.0)	34.7 (4.5)	35.3 (7.1)
Disease duration, months (mean (SD))	17.2 (36.8)	16.0 (32.0)	26.5 (62.0)

Figure 1 - CONSORT diagram.



Prescriptions of ICP-lowering medications at first visit included acetazolamide (n=131, 27%; mean dose 1032mg/day, range 250mg to 4g daily), topiramate (n=44, 9%; mean dose 135mg/day, range 25mg to 400mg daily), and other diuretics (n=21, 4%). Prescriptions of ICP-lowering medications during follow-up were noted of acetazolamide (n=115, 23%), topiramate (n=51, 10%), and other diuretics (furosemide n=1, 0.2%). Analgesic use was common at first visit (n=224, 46%) with some patients using more than one class. Prescriptions of the following analgesic medications were noted at baseline visit:

paracetamol (n=129, 24%), ibuprofen (n=64, 13%), triptan (n=57, 11%), co-codamol (n=48, 9%), naproxen (n=31, 6%) and tramadol (22, 4%). In the sub-group of patients that reported headache on more than 15 days of the month (n=111, 23%), the analgesic use was higher: paracetamol (n=40, 36%), triptan (n=35, 32%), ibuprofen (n=19, 17%), co-codamol (n=20, 15%) and naproxen (n=11, 10%). Medication overuse was recorded in 18% of patients at baseline (n=87), with commonest culprit medications being paracetamol (n=49, 56%), opiates (n=36, 41%) and ibuprofen (n=22, 25%). Migraine prophylaxis at baseline was recorded with topiramate (n=73, 14%), amitriptyline (n=59, 11%) and propranolol (n=28, 5%) having been prescribed.

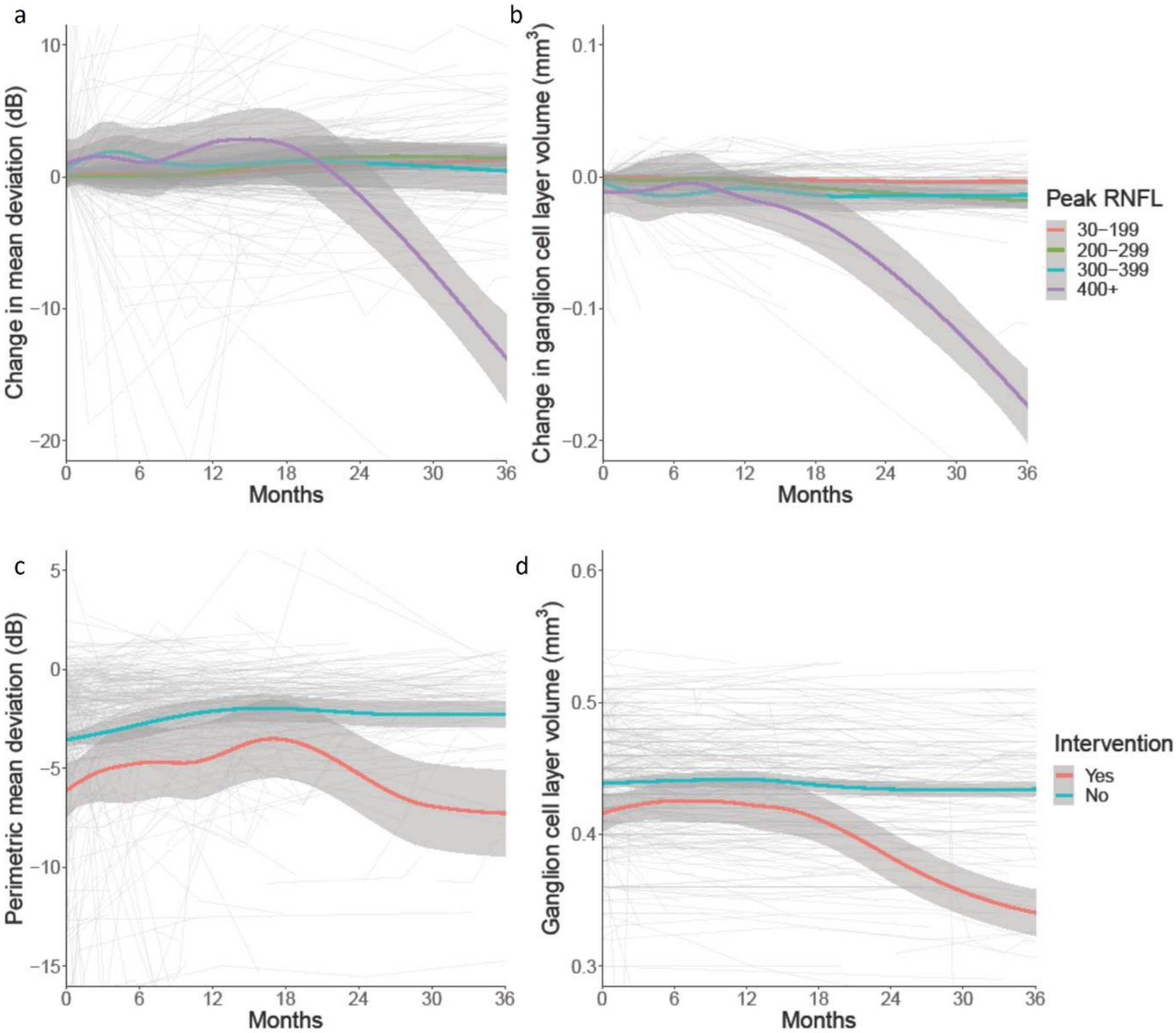
IIH relapse was only noted in 18 (3.7%) patients whilst under follow up and only 2 of these had previously been in ocular remission at baseline visit.

3.1.4.1 Factors affecting long term visual outcomes in IIH

The most prominent factor influencing long-term visual function (as measured by PMD) was the extent of papilloedema measured by the highest global RNFL on OCT for individual patients during the course of follow-up. Of note the decline in PMD mirrored the reduction in the macular GCL volume (Figure 2), in particular for those with RNFL ≥400µm or TRT ≥800µm. However, the GCL and PMD decline was delayed and was not observed until greater than 12 months following the first encounter.

Figure 2 - Longitudinal visual data categorised by peak global retinal nerve fibre layer thickness or surgical intervention.

a. *Longitudinal data of Humphrey visual field perimetric mean deviation (PMD) in IIH categorised by peak global retinal nerve fibre layer thickness, and LOESS smoothers added to show trends across the categories.*
b. *Longitudinal data of macular ganglion cell layer (GCL) volume in IIH categorised by peak global retinal nerve fibre layer thickness, and LOESS smoothers added to show trends across the categories.*
c. *Longitudinal data of Humphrey visual field perimetric mean deviation (PMD) in IIH categorised by surgical intervention or not, and LOESS smoothers added to show trends across the categories.*
d. *Longitudinal data of macular ganglion cell layer (GCL) volume in IIH categorised by surgical intervention or not, and LOESS smoothers added to show trends across the categories.*



The cohort was then dichotomised into those medically or surgically managed. Amongst those who were medically managed the GCL volume remained stable over time. Whilst in those who underwent a surgical intervention there was a worse prognosis where both the PMD and macular GCL volume significantly declined after 12 months (Table 2; Figure 2).

Table 2 – Impact of surgical intervention over time (months) on perimetric mean deviation (PMD) and macular ganglion cell layer volume (GCL)

		0	6	12	24	36
Humphrey visual field perimetric mean	**Intervention**	-6.20 (4.59), 45	-4.45 (4.24), 19	-4.51 (3.65), 16	-4.89 (3.24), 10	-9.70 (4.18), 8
	No Intervention	-3.55 (3.41), 351	-2.77 (4.40), 168	-2.02 (3.95), 134	-2.19 (3.05), 90	-2.18 (3.18), 49

deviation, dB (mean (SD), n)						
Macular ganglion cell layer volume, mm³ (mean (SD), n)	**Intervention**	0.414 (0.035), 24	0.429 (0.031), 11	0.421 (0.027), 9	0.384 (0.022), 6	0.321 (0.028), 6
	No Intervention	0.439 (0.026), 224	0.441 (0.031), 116	0.443 (0.027), 92	0.434 (0.022), 64	0.436 (0.023), 42

3.1.4.2 Factors affecting long term visual outcomes in medically managed IIH

Favourable visual outcomes were noted in the sub-group of IIH patients that were medically managed (n=426; Table 3). Visual acuity was minimally affected in this large sub-group and remained similar over time (Table 3). The presence or absence of papilloedema (for those with active IIH and IIH in ocular remission respectively) at the first encounter had no apparent influence on long term visual acuity (Table 4; Figure 3). PMD for the medically managed cohort was initially observed to improve over the first 12 months following enrolment with subsequent stabilisation (Figure 3B).

Table 3 - Visual and headache outcomes for medically managed IIH patients

	Months				
	0	6	12	24	36
LogMAR visual acuity, logunits (mean (SD), n)	0.04 (0.16), 337	0.02 (0.21), 175	0.00 (0.16), 147	-0.03 (0.13), 96	-0.04 (0.14), 59
Humphrey visual field perimetric mean deviation, dB (mean (SD), n)	-3.38 (3.44), 351	-2.72 (4.50), 168	-2.03 (4.01), 134	-2.19 (3.08), 90	-2.18 (3.22), 49
Global peripapillary	127.3 (39.0), 277	118.6 (45.8), 136	120.8 (40.0), 110	106.4 (31.3), 74	103.4 (33.1), 48

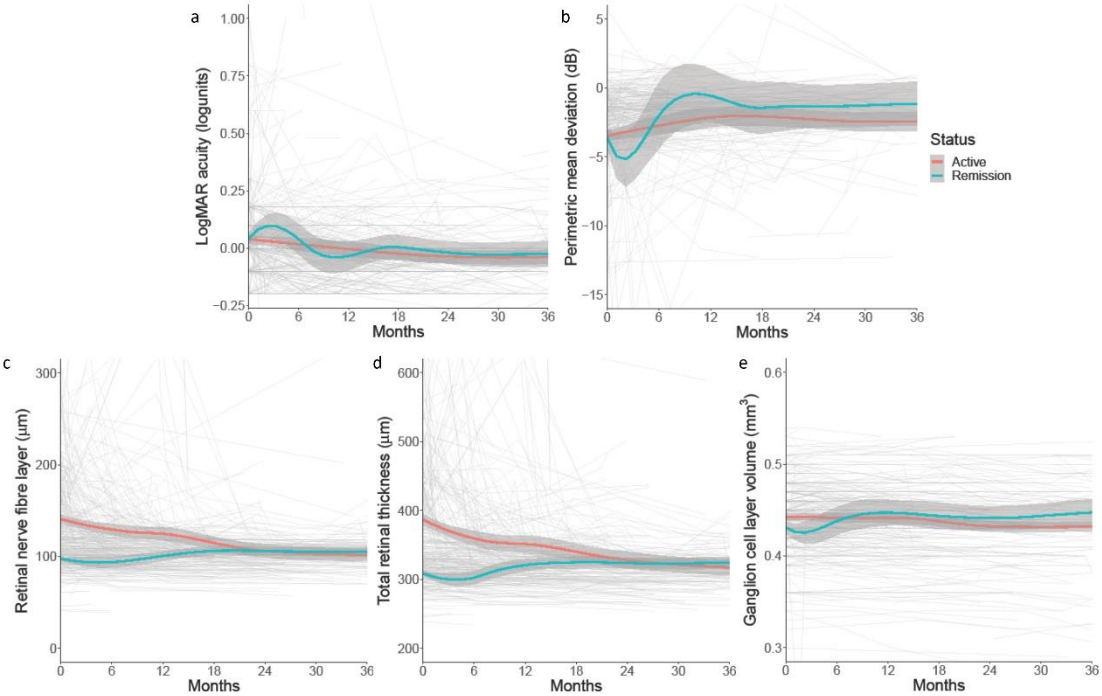
retinal nerve fibre layer, µm (mean (SD), n)					
Global peripapillary total retinal thickness, µm (mean (SD), n)	360.5 (56.2), 277	342.5 (64.8), 136	343.1 (57.4), 110	327.2 (44.6), 74	318.1 (48.9), 48
Macular ganglion cell layer volume, mm^3 (mean (SD), n)	0.439 (0.031), 327	0.441 (0.035), 151	0.443 (0.030), 118	0.434 (0.024), 81	0.436 (0.026), 51
Headache frequency, days/month (mean (SD), n)	21.0 (12.2), 304	19.2 (14.0), 146	19.1 (12.4), 127	16.6 (10.2), 85	16.1 (11.4), 53
Migraine-like frequency, days/month (mean (SD), n)	10.0 (8.6), 224	8.8 (9.5), 104	7.9 (9.1), 94	8.4 (7.3), 67	8.0 (8.2), 45
Headache severity, visual analogue scale 0-10 (mean (SD), n)	6.3 (2.9), 304	5.7 (3.6), 154	5.8 (3.0), 130	5.9 (2.6), 89	5.5 (2.9), 58
Headache Impact Test 6, score 36-78 (mean (SD), n)	55.7 (15.7), 197	57.6 (17.6), 107	55.7 (17.5), 107	58.6 (14.6), 76	59.5 (15.7), 44

Table 4 - Baseline and trajectory comparison for visual outcomes in active and ocular remission IIH calculated through regression modelling.

	Baseline		**Trajectory**	
	Active	Ocular remission	Active (units/month)	Ocular remission (units/month)
LogMAR visual acuity, logunits	0.025 (95% CI: 0.003, 0.047)	0.044 (95% CI: 0.013, 0.075)	-0.0007 (95% CI: -0.0014, -0.0001)	-0.0012 (95% CI: -0.0029, 0.0004)
Humphrey visual field perimetric mean deviation, dB	-3.37 (95% CI: -3.96, -2.78)	-3.39 (95% CI: -4.27, -2.51)	+0.027 (95% CI: 0.004, 0.050)	+0.071 (95% CI: 0.021, 0.120)
Global peripapillary retinal nerve fibre layer, µm	137.42 (95% CI: 132.31, 142.54)	97.45 (95% CI: 89.87, 105.02)	-1.27 (95% CI: -1.54, -1.00)	+0.037 (95% CI: -0.54, 0.61)
Global peripapillary total retinal thickness, µm	384.86 (95% CI: 376.17, 393.54)	308.27 (95% CI: 295.85, 320.7)	-2.63 (95% CI: -3.09, -2.17)	+0.246 (95% CI: -0.68, 1.17)
Macular ganglion cell layer volume, mm^3	0.440 (95% CI: 0.434, 0.446)	0.427 (95% CI: 0.419, 0.436)	-0.0005 (95% CI: -0.0006, -0.0003)	-0.0002 (95% CI: -0.0004, 0.0001)

Figure 3 - Longitudinal visual data from medically managed IIH patients categorised by disease status – active disease (papilloedema present at enrolment) versus ocular remission (no papilloedema at enrolment), and LOESS smoothers added to show trends across the categories.

a. *LogMAR visual acuity (log units)*
b. *Perimetric mean deviation measured by Humphrey visual field 24-2 testing (dB)*
c. *Retinal nerve fibre layer thickness measured on Optical Coherence Tomography (µm)*
d. *Total retinal thickness of optic nerve head measured on Optical Coherence Tomography (µm)*
e. *Macular ganglion cell layer volume measured on Optical Coherence Tomography (mm^3)*



There was little difference in the trajectory of PMD over time between those initially seen with active IIH versus IIH in ocular remission (Table 4). Patients with active IIH at first visit had a higher mean RNFL compared to those in remission (active IIH 137.42µm (95% Confidence Interval (CI): 132.31, 142.54); IIH in ocular remission 97.45µm (95% CI: 89.87, 105.02)) (Table 4; Figure 3C). The trajectory in the active IIH group reduced by -1.27 µm/month (95% CI: -1.54, -1.00) as compared to minimal change in the IIH ocular remission group 0.037 µm/month (95% CI: -0.54, 0.61) (Table 4). At 40 months post-enrolment, RNFL thickness was comparable between these groups. As expected, the TRT showed a similar trend to the RNFL (Table 4; Figure 3D) with the trajectory in the active IIH group reducing by -2.63 µm/month (95% CI: -3.09, -2.17), as compared to minimal change in the IIH ocular remission group of 0.25 µm/month (95% CI: -0.68, 1.17).

Considering excellent correlation between the macular volume and posterior pole measures of macular GCL(mm^3) within our cohort (Pearson correlation 0.98 (95% CI: 0.97, 0.98), we combined these analogous measures. At a patients' first visit GCL volume was significantly reduced for those in ocular remission (0.43 mm^3 (95% CI: 0.42, 0.44)) compared to those with active IIH (0.44 mm^3 (95% CI: 0.43, 0.45), Table 4). We also noted that duration of disease was longer in those in ocular remission (mean 32 (Standard Deviation (SD) 58)) months compared to those who were active (mean 13 months (SD 29)). Long term analysis revealed GCL volume stability over time with no significant difference between the active and ocular remission at enrolment groups (Figure 3E).

A stepwise regression evaluated which additional factors affected visual (visual acuity, PMD, RNFL, TRT and GCL volume) prognosis. The change in BMI was the most influential factor affecting PMD, RNFL and macular GCL volume outcomes (Table 5). Whilst diagnostic lumbar puncture opening pressure, disease duration, baseline BMI were less influential (Table 5).

Table 5 - Factors affecting visual prognosis in medically managed IIH cohort.

(- p>0.08, +/- p=0.05-0.08, + p≤0.05, ++ p≤0.01, +++ p≤0.001, ++++ p≤0.0001)

	LogMAR visual acuity, logunits	Humphrey visual field perimetric mean deviation, dB	Global peripapillary retinal nerve fibre layer, µm	Global peripapillary total retinal thickness, µm	Macular ganglion cell layer volume, mm^3
Disease duration	-	+/-	+	++	-
Diagnostic LP opening pressure	-	-	-	++	-
Baseline BMI	-	-	-	-	+
Change in BMI	-	+	+++	+/-	++++
ICP medication During v never	-	-	-	-	-

3.1.4.3 Factors affecting long term headache outcomes

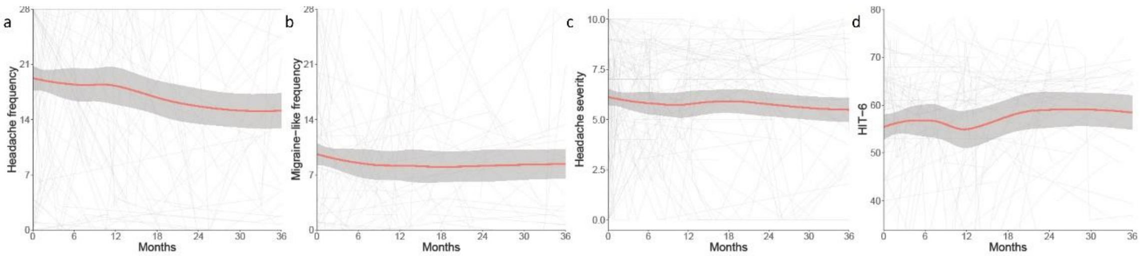
In the medically managed patients (n=281) there was a high burden of headache (Table 3). The mean headache frequency at baseline was 21 days/month (SD 12.2), which improved over time, with stable migraine-like headache frequency, headache severity and headache disability (Table 3). As a result of sparse headache data in the ocular remission cohort, we focussed our inferences on the medically managed cohort with papilloedema (active disease) at the first encounter (Figure 4).

Figure 4 - Longitudinal headache data from medically managed IIH patients with active disease (papilloedema present at enrolment), and LOESS smoothers added to show trends across the categories.

a. *Headache frequency (days per month)*
b. *Migraine-like headache frequency (days per month)*

c. Headache mean severity of predominant headache (0-10 numerical rating scale)

d. Headache Impact Test 6 (HIT6) (quality of life measure score 36-78)



Headache frequency showed a more rapid rate of improvement in this active group as compared to the whole cohort (-0.46 days per month/month (95% CI: -0.67, -0.25), versus -0.20 days per month/month (95% CI: -0.28, -0.12)). Stepwise regression analysis showed that the only factors affecting long term headache frequency were the occurrence of daily headache at diagnosis and a personal migraine history. Disease duration, change in BMI and family history of migraine were not significantly influential (Table 6).

Table 6 - Factors affecting headache prognosis in medically managed active IIH cohort.

(- p>0.08, +/- p=0.05-0.08, + p≤0.05, ++ p≤0.01, +++ p≤0.001, ++++ p≤0.0001)

	Headache frequency	**Migraine-like headache frequency**	**Headache severity**	**Headache Impact Test 6**
Disease duration	-	-	++	-
Change in BMI	+/-	-	-	-
Daily headache at baseline	++++	++++	++++	-
Migraine Personal history	++++	++++	++++	-
Migraine Family history	-	-	+	-
Analgesic overuse	-	-	-	-
ICP medication During v never	-	-	-	-

Monthly migraine-like headache days occurred with a frequency of 8.14 days/month (95% CI: 7.09, 9.18) at baseline. There was a relatively little improvement over time (-0.06 days per month/month (95% CI: -0.12, -0.01)) (Figure 4). The only factors affecting migraine-like headache frequency outcomes were personal migraine history (higher baseline frequency by 4.7 days/month (95% CI: 2.38, 6.98) and trajectory -0.1 days per month/month (95% CI: -0.28, 0.02)) and daily headache at diagnosis (higher baseline frequency by 4.2 days/month (95% CI: 2.32, 6.13)). There was no significant effect of disease duration, BMI, familial history of migraine or medication overuse (Table 6).

Headache severity was reported as moderate at the first visit (6.1 out of 10 (95% CI: 5.74, 6.40)) and remained stable (Figure 4). A personal migraine history was a poor prognostic indicator as it increased headache severity (increase of 1.6 units (95% CI: 0.76, 2.35)). To a lesser extent disease duration affected the prognosis by increasing headache severity by 0.03 per year of disease duration (95% CI: 0.008, 0.043) (Table 6).

Overall headache disability, as measured by the HIT-6, was high at first visit with a mean score 56.47 (95% CI: 54.58, 58.37) and showed no significant improvement over time (0.08 units per month (95% CI: -0.04, 0.21), Figure 4). None of the factors explored affected longitudinal HIT-6 scores (Table 6).

3.1.5 Discussion

In this study those with the greatest papilloedema, RNFL >400µm or TRT ≥800µm, had greatest loss of macular GCL volume. Importantly there was a delay of over 12 months from baseline visit before the visual field and OCT measurements revealed this decline. Increases in BMI and disease duration had the most influence on visual prognosis. This potentially suggests that preventing high grades of papilloedema and modifying BMI early may be beneficial for long-term visual outcomes. Headache outcomes showed marked heterogeneity in this cohort, with regression modelling showing a personal migraine history and daily headache at diagnosis were the principal factors influencing worst headache prognosis. For those that presented in ocular remission, the disease course was favourable with only 2 cases having relapse, both of which were associated with weight gain.

In those with active papilloedema at enrolment, OCT RNFL improved over time (Figure 3 and Table 4) and the literature would support these findings.[10] Automated RNFL thickness measures may be compromised in moderate to severe papilloedema and accurate segmentation is essential. We recognise that this can be time consuming in busy clinical practice when the automated segmentation fails.[34, 40-43] As part of this study we chose to manually segment all the individual OCTs to denote RNFL and we elected to manually produce a TRT measurement derived from the RNFL scan, where required. Our results for TRT are similar to those for RNFL, which is important evidence for the integration of TRT in preference to RNFL into clinical practice, due to greater accuracy in moderate to severe papilloedema. OCT may be a more sensitive marker for disease status than measures of visual function, such as PMD, and is a more objective measure than Frisén grading.[32, 33] A positive association between intracranial pressure and OCT central thickness and RNFL has been previously demonstrated, highlighting the use of OCT as surrogate marker for intracranial pressure measurements.[33] In those patients who presented in ocular remission and demonstrated substantially thinner RNFL at follow up, it is likely that their intracranial pressure had settled, as compared to those who presented with active disease.[13]

Macular GCL thickness is a measure of neuronal axonal loss[44] and is positively correlated with visual field loss at 12 months[33] and following papilloedema resolution.[45] Progressive decline over 12 months in both RNFL and GCL has previously been shown in acute optic neuritis [46] highlighting that OCT measures change over a longer time frame, reflecting the long-term term fall out of optic neuropathy. Our findings here in IIH, showed a decline in GCL volume in those with severe papilloedema (as defined by a RNFL ≥400µm or TRT ≥800µm, Figure 2) with a corollary decline in PMD also noted. This decline in parameters was noted after 12 months, thus indicating the need for long term follow up and monitoring of patients who previously had severe papilloedema. This difference may be because severe IIH has exerted a greater intracranial pressure on the optic nerve, leading to ischaemia, causing a worse optic neuropathy and subsequent atrophy;[47] often by the time surgical intervention occurs the damage may be evidently irreversible. Future work needs to define what clinical biomarkers could be used to ensure timely intervention and reduction of this long-term damage.[39]

For the majority, visual field PMD showed mild improvement, interestingly there was little difference in trajectory between the active and remission groups (those with and without papilloedema at enrolment). Our cohort’s improvement is more modest than previous presented longitudinal data but has the advantage of being in a prospective and much larger cohort.[10] Our PMD plateau was very similar to that seen in the IIH Treatment Trial, at approximately -2dB.[20] Beyond 18 months the mean PMD was stable in the majority of our cohort, which is reassuring for patients, but also indicates that if there is a clinically relevant deterioration during follow-up it may be important to screen for relapse or investigate for another non-related pathology.

IIH is well known to be associated with obesity.[3] Obesity is likely to be one manifestation of the underlying metabolic disease with adipocytes being transcriptionally and metabolically primed towards lipogenesis and adipose accumulation.[1] Weight reduction is challenging but appears to be the only treatment so far found to modify disease course in IIH.[15, 16] Here we found change in BMI was the most important factor to influence visual outcomes. Increasing BMI during follow up was shown to be associated with worsening of OCT RNFL and PMD, highlighting the importance of weight management in IIH patients and is an ongoing area of research.[3] Our relapse rate was 3.7% in the whole cohort and 1.4% in those in ocular remission at enrolment, which is lower than previously reported in the literature, and this may reflect the increasing evidence and awareness of the importance of weight management in this disease.[3, 15, 16] Additional factors may include early discussion in a sensitive fashion around weight management as a disease modifying therapy and early referral to community dieticians and Tier 3 weight management services. The low relapse rate may also be due to monitoring papilloedema through OCT imaging therefore detecting deteriorations earlier.

Headache is a common symptom in the IIH population, which was also reflected in this cohort, with a high baseline HIT-6 score.[12, 14] The trajectory for headache frequency showed a slow improvement over time, likely reflecting identification, and treatment. In this analysis the two main factors influencing high headache frequency and worse prognosis were a personal migraine history and daily headache at baseline. This has previously not been demonstrated. Therefore, it may be important to adjust for migraine history and daily headache in future IIH headache trials as they may influence clinical trial outcomes.[48] Interestingly regression analysis did not show that medication overuse alone influenced headache frequency in IIH, although this may be due to inadequate powering for this outcome and in the real world there are multiple interconnected factors that can contribute to headache, one of which may be medication overuse and we only assessed medication overuse in a rare secondary headache disorder. There are however disputes as to whether medication overuse is a cause or consequence of the chronification of headaches.[49] The advent of CGRP therapy may impact headache outcomes in IIH in the future.[50-52]

This was a prospectively collected study of real-world clinical practice and has some inherent limitations. As it is within a tertiary referral centre, a number of patients from the cohort would have been seen initially at other hospitals. The results may not be generalisable to other settings in particularly where access to neuro-ophthalmology and headache expertise is more limited, however demonstrates prognostic factors of a rare disease in a large population. Whilst neuroimaging is requested for review, the clinical details are not routinely requested, other than what is stated in the referral letter. Therefore, baseline data for each participant could have been at a different point in their actual disease course. To reduce this bias, we defined disease duration from the LP to the first encounter in our clinic. We also recognise that patients report symptoms of IIH in a variable time frame before an actual diagnosis. Although the study aimed to capture all outcomes, some were missing due to patient preference. Also, as per clinical practice some individuals who presented in ocular remission were discharged, some were lost to follow up, and hence these groups had no further clinic appointments or data collected. This resulted in the reduction of the number of patients over the course of the study. We therefore advise caution in over interpreting the long-term outcomes as seen in the LOESS smoothers curve due to the reducing sample size over the course of the study. To reduce the bias of missing data, we elected to only analyse headache outcomes in those with active papilloedema, rather than those who presented in remission, as this latter group were more likely to be discharged and had less follow up data. Likewise due to the challenges of data collection for intracranial pressure lowering medications, such as confirming dose, duration, and inability to ensure compliance, we only reported baseline data and did not further analyse their effects on outcomes here. This was also the case for analgesic frequency. In the future our IIH Life study may collect more detailed descriptions of medications and other factors. Also, future analysis could be compared to a control group which may allow for more insights into the long-term outcomes of IIH to be discovered.

3.1.6 Conclusions

In this prospective real world longitudinal cohort of individuals with IIH presenting to a tertiary referral centre, the outcomes were generally good. However, decline in PMD and macular GCL volume is delayed and seen during follow up beyond 12 months. A minority of patients required sight saving surgery, and generally had worse long-term outcomes for their visual parameters. The headache burden was high in this cohort and prognosis was impacted by previous migraine diagnosis and occurrence of daily headaches at first visit. Targeted headache treatment remains an unmet clinical need. Body weight modification and disease duration appear to have the main influence for visual outcomes, and hence why we would recommend active early weight management for patients with IIH with a raised BMI.

3.1.7 References

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Chapter 3.2 Asymptomatic IIH (Thaller. Clin Exp Ophthalmol. 2023)

Manuscript title:

Asymptomatic idiopathic intracranial hypertension: Prevalence and prognosis.

Published:

Thaller M, Homer V, Mollan SP, Sinclair AJ. Asymptomatic idiopathic intracranial hypertension: Prevalence and prognosis. Clin Exp Ophthalmol. 2023 Aug;51(6):598-606. doi: 10.1111/ceo.14256.

Involvement:

I was involved in data collection, data analysis, data interpretation, writing first manuscript and critical revision of the manuscript.

3.2.1 Abstract

Background: Little is known about the presentation and prognosis of asymptomatic idiopathic intracranial hypertension (IIH). Papilloedema can be found incidentally on routine fundus examination, with many of these patients actually having symptoms on direct questioning. The aim was to evaluate visual and headache outcomes in people with IIH who present with or without symptoms.

Methods: Prospective observational cohort study, between 2012 and 2021, 343 people with confirmed IIH diagnosis were enrolled in the IIH:Life database. Outcomes such as vision (LogMAR); Humphrey visual field perimetric mean deviation (PMD) and optical coherence tomography (OCT)) and headache were evaluated using LOESS (locally weighted scatterplot smoothing) graphs and regression analysis.

Results: One hundred and twenty-one people had incidentally found papilloedema, with 36 people with completely asymptomatic presentations. Those with asymptomatic IIH at diagnosis had similar visual prognosis compared to those with symptomatic disease. Sixty-six percent of the asymptomatic cohort became symptomatic during follow-up, and of these the predominant symptoms was headache (96%). Headache frequency during follow-up was lower in the asymptomatic cohort.

Conclusions: The prognosis of those with IIH who present with or without symptoms is similar.

3.2.2 Introduction

Papilloedema, swelling of both optic discs caused by raised intracranial pressure (ICP), is required for the definite diagnosis of Idiopathic Intracranial Hypertension (IIH).[1, 2] Typically these patients present with headaches and visual disturbances,[3-6] however increasingly people are referred to ophthalmology and IIH clinics with incidental papilloedema following routine optician reviews or neurological examination,[7] with many of these actually having symptoms on direct questioning.[8]

The precise prevalence of asymptomatic IIH is unclear from the literature. Children appear to have fewer symptoms than adults[9] [10] but the previous literature has been based on small case series or case reports. Additionally asymptomatic patients at baseline may not remain asymptomatic.[8]

Incidental finding of papilloedema on routine examination is more prevalent in UK compared to US populations (48% v 30%; $p<0.001$),[7] however this may indicate different access to ophthalmological assessments rather than a true variation, and in this study they were unable to assess whether the patients were asymptomatic. As IIH predominantly affects reproductive aged women with obesity,[1, 4, 11, 12] [13] screening for papilloedema in people with obesity has been suggested however this would not meet the criteria for an acceptable screening program with one large bariatric surgery study finding that incidental papilloedema was rare (4/606, 0.66%).[14]

Theoretically those with no symptoms may have a delay in their diagnosis, or silent relapses and therefore may have the potential for adverse longer-term visual outcomes, as compared to those with symptoms. Alternatively, those who are asymptomatic at presentation could indicate that the disease itself may begin well before people have symptoms. There is an absence of longitudinal outcome data in the asymptomatic subset of IIH and evaluation of their outcomes may guide management decisions. This study therefore aimed to evaluate the visual and headache outcomes for people diagnosed with asymptomatic IIH at presentation, and follow them up to determine their disease course, and compare them to those with symptoms at presentation of IIH.

3.2.3 Methods

3.2.3.1 Ethics statement

This study conformed to the tenets of the Declaration of Helsinki. The study was ethically approved by National Health Service National Research Ethics Committee (14/LO/1208), IIH:LIFE study. Written informed consent was obtained from all participants.

3.2.3.2 Patients

Eligible patients were those who met the revised diagnostic criteria for IIH[2] and had data recorded for IIH symptomatology at diagnosis (including "incidental papilloedema"). Patients with secondary causes of raised ICP and IIH without papilloedema were excluded.

3.2.3.3 Symptom status

Incidental papilloedema was defined as papilloedema which was found following routine examination most likely in the setting of routine optician or optometry tests. Some of these patients on direct questioning in the hospital setting were not necessarily asymptomatic. Asymptomatic status was defined as there being a total absence of headache, transient visual obscurations (TVOs), pulsatile tinnitus and other visual symptoms when papilloedema was detected. This was based on direct questioning of symptoms at their first clinical visit.

3.2.3.4 Outcomes

Visual outcomes were the logarithm of the minimum angle of resolution (LogMAR) visual acuity, Humphrey visual field perimetric mean deviation (PMD) and optical coherence tomography (OCT) imaging measures (average global peripapillary retinal nerve fibre layer (RNFL), a manually measured peripapillary total retinal thickness (TRT), and macular ganglion cell layer (GCL) volume). Headache outcomes were assessed by headache frequency (monthly headache days), migraine-like headache frequency (monthly migraine-like headache days), headache severity (0-10 numerical rating scale), and headache disability using the Headache Impact Test-6 (HIT-6).

3.2.3.5 Statistical analysis

The methods for data collection and statistical analysis have previously been reported.[4] Statistical analysis was performed using R v4.1.0. Mean and standard deviations for continuous variables, and percentages for binary or categorical variables were used for summary statistics. Regression modelling used lme4[15] with the creation of LOESS (locally weighted scatterplot smoothing) graphs prior to regression analysis to ascertain the relationship between variables and any emergent trends.

3.2.4 Results

A total of 343 patients were included, and their baseline characteristics are at Table 1. The prevalence of incidental papilloedema in this cohort was 35% (121/343). Asymptomatic IIH at time of papilloedema recognition was found to be uncommon (10%, 36/343) (Table 1) and only 3.5% (12/343) remained asymptomatic during the follow-up period.

Table 1 – Baseline table by whether asymptomatic at diagnosis

	All	Asymptomatic	Symptomatic
IIH patients (n)	343	36	307
Surgical intervention (n)	37	1	36
Females (n)	336	33	303
Age (SD) (years)	30.9 (9.0)	30.1 (9.8)	30.9 (8.9)
BMI (SD) (kg/m^2)	38.4 (8.5)	35.8 (5.8)	38.7 (8.8)
Weight (SD) (kg)	101.2 (24.7)	99.1 (20.0)	101.4 (25.2)
Diagnostic lumbar puncture opening pressure (SD) (cmCSF)	34.8 (10.5)	36.3 (7.5)	34.6 (10.7)

Headaches were the most common symptom (90%, 307/343) in the cohort either at diagnosis or whilst being followed up. The other symptoms in descending frequency were tinnitus (40%, 137/343), visual disturbances (36%, 125/343) and transient visual obscurations (TVOs) (30%, 102/343). Only a third of those who were asymptomatic at baseline remained so during follow-up (12/36, 33%). In those who progressed from asymptomatic to symptomatic the most frequent symptom was headache (23/24, 96%), with other symptoms being less common (tinnitus (9/24, 38%), visual disturbances (2/24, 8%) and transient visual obscurations (1/24, 4%)).

Asymptomatic IIH patients had similar age, lower body mass index (BMI) and higher diagnostic lumbar puncture opening pressure (LP OP) than those with symptoms (Table 1), although the differences were not significant. The surgical intervention rate was lower in those with an asymptomatic presentation (asymptomatic 1/36, 2.8% compared to 36/307, 11.7% for symptomatic). The sole asymptomatic patient who underwent surgical management and became symptomatic 3 months after initial review, with CSF diversion surgery 6 months after initial presentation.

A personal migraine history was present in 42% (15/36) of the asymptomatic group and 47% (145/307) of the symptomatic cohort. A family history of migraine was present in 28% (10/36) of the asymptomatic group and 22% (68/307) of the symptomatic group. In those patients who subsequently became symptomatic 46% (11/24) had a previous history and 33% (8/24) family history of migraines, which in contrast to those remaining asymptomatic of 33% (4/12) and 17% (2/12) respectively, although the differences were not statistically significant.

Where patients had at least 1 follow-up visit (n=234), the median follow-up (range) was 19.5 (1-87) months, and this was longer for the asymptomatic subset (25 (1-72) months, n=27) than symptomatic (19 (1-87) months).

3.2.4.1 Visual function outcomes

Incidental papilloedema at diagnosis did not influence visual acuity or visual fields at baseline and over time their trajectories were similar with a slow improvement noted (Table 2, Figure 1A, 1B). OCT imaging measures of RNFL and TRT were slightly worse on average in the incidental cohort at baseline although this was not statistically significantly (Table 2, Figure 2A, 2B). Both groups improved over time (Table 2). Macular ganglion cell layer volumes were comparable between the groups with a very slow deterioration in both groups over time (Table 2, Figure 2C).

Table 2 - Baseline and trajectory for visual and headache outcomes according to incidental papilloedema at diagnosis calculated by regression modelling.

	Baseline estimate (units)	**Change per month (units/month)**
LogMAR visual acuity, logunits		
Incidental	-0.0049 (95% CI: -0.0594, 0.0495	-0.0005 (95% CI: -0.0023, 0.0014)
Not Incidental	0.0449 (95% CI: 0.0077, 0.0821)	-0.002 (95% CI: -0.0034, -0.0005)
Humphrey visual field perimetric mean deviation, dB		
Incidental	-2.5491 (95% CI: -3.8485, -1.2496)	0.0544 (95% CI: -0.0328, 0.1416)
Not Incidental	-3.6149 (95% CI: -4.4927, -2.737)	0.1254 (95% CI: 0.0599, 0.1909)
Global peripapillary retinal nerve fibre layer, µm		
Incidental	142.77 (95% CI: 125.55, 159.99)	-1.78 (95% CI: -2.76, -0.81)
Not Incidental	133.4 (95% CI: 122.05, 144.75)	-1.45 (95% CI: -2.17, -0.72)
Global peripapillary total retinal thickness, µm		
Incidental	372.58 (95% CI: 348.79, 396.36)	-2.52 (95% CI: -3.65, -1.4)
Not Incidental	360.2 (95% CI: 344.47, 375.93)	-2.33 (95% CI: -3.17, -1.49)
Macular ganglion cell layer volume, mm^3		
Incidental	0.4412 (95% CI: 0.426, 0.4564)	-0.0006 (95% CI: -0.001, -0.0003)
Not Incidental	0.4439 (95% CI: 0.4339, 0.4539)	-0.0003 (95% CI: -0.0005, 0)
Headache frequency (days/month)		
Incidental	17.93 (95% CI: 14.9, 20.96)	0.01 (95% CI: -0.24, 0.26)

Not Incidental	20.2 (95% CI: 17.87, 22.53)	-0.18 (95% CI: -0.4, 0.04)
Migraine-like headache frequency (days/month)		
Incidental	5.43 (95% CI: 2.58, 8.29)	0.21 (95% CI: -0.03, 0.44)
Not Incidental	10.06 (95% CI: 7.99, 12.12)	-0.15 (95% CI: -0.35, 0.05)
Headache severity (0-10 scale)		
Incidental	6.0852 (95% CI: 5.2133, 6.957)	0.0333 (95% CI: -0.0346, 0.1011)
Not Incidental	6.7345 (95% CI: 6.1173, 7.3516)	-0.0372 (95% CI: -0.0945, 0.0202)
HIT-6 (score 36-78)		
Incidental	61.67 (95% CI: 58.09, 65.25)	0.15 (95% CI: -0.06, 0.37)
Not Incidental	60.86 (95% CI: 58.23, 63.48)	-0.05 (95% CI: -0.22, 0.11)

Figure 1 - Longitudinal visual function data categorised by symptoms at diagnosis, with Incidental papilloedema illustrated. LOESS smoothers added to show trends across the categories.

a. LogMAR visual acuity (log units)

b. Perimetric mean deviation measured by Humphrey visual field 24-2 testing (dB)

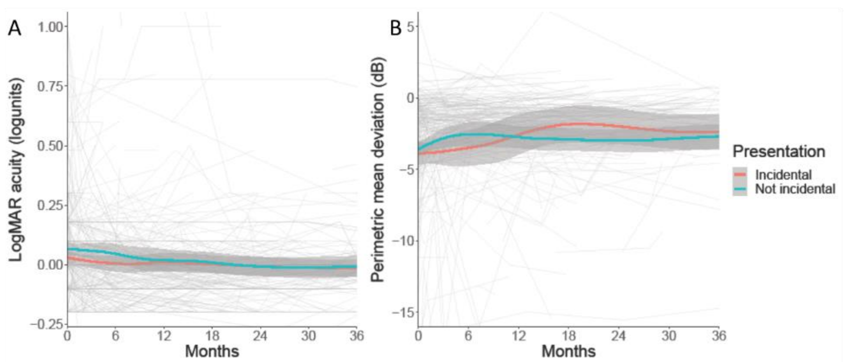
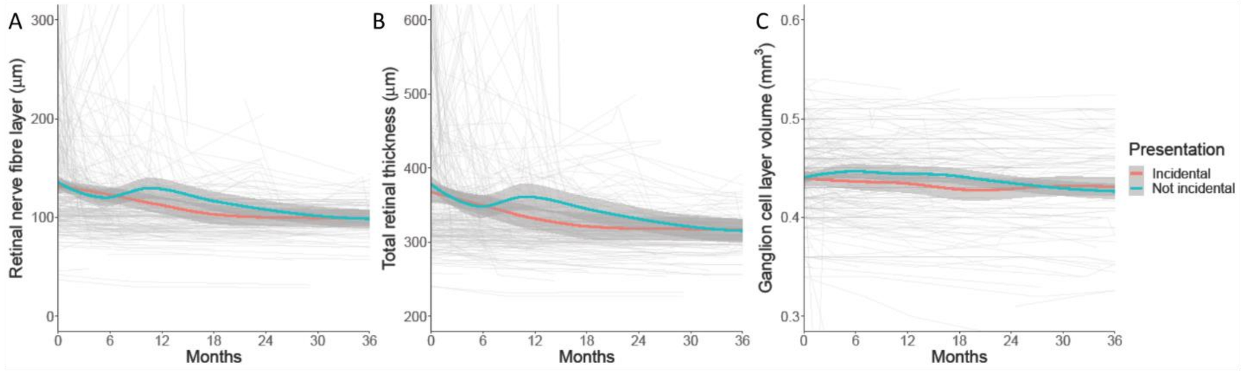


Figure 2 - Longitudinal visual OCT data categorised by symptoms at diagnosis, with Incidental papilloedema illustrated. LOESS smoothers added to show trends across the categories.

a. Retinal nerve fibre layer thickness measured on Optical Coherence Tomography (µm)

b. Total retinal thickness of optic nerve head measured on Optical Coherence Tomography (µm)

c. Macular ganglion cell layer volume measured on Optical Coherence Tomography (mm^3)



Evaluating those who were asymptomatic or symptomatic at presentation visual acuity (LogMAR) (Figure 3A), HVF mean deviation (Figure 3B) and OCT imaging measures (Figures 4A-C) did not significantly differ (Table 3). Their progression over time was comparable between the groups (Table 3, Figures 3A, 3D, 4A-C). The visual outcomes were good for both groups.

Table 3 – Baseline and trajectory for visual and headache outcomes according to symptom status at diagnosis calculated by regression modelling.

	Baseline estimate (units)	**Change per month (units/month)**
LogMAR visual acuity, logunits		
Asymptomatic	-0.0275 (95% CI: -0.1201, 0.0652)	-0.0008 (95% CI: -0.003, 0.0015)
Symptomatic	0.0365 (95% CI: 0.0037, 0.0692)	-0.0016 (95% CI: -0.0029, -0.0003)
Humphrey visual field perimetric mean deviation, dB		
Asymptomatic	-2.1358 (95% CI: -4.5059, 0.2343)	0.0553 (95% CI: -0.0719, 0.1826)
Symptomatic	-3.4023 (95% CI: -4.1677, -2.6368)	0.1065 (95% CI: 0.0481, 0.165)
Global peripapillary retinal nerve fibre layer, µm		
Asymptomatic	140.52 (95% CI: 110.82, 170.21)	-1.81 (95% CI: -3.06, -0.56)
Symptomatic	135.68 (95% CI: 125.65, 145.72)	-1.49 (95% CI: -2.15, -0.82)

Global peripapillary total retinal thickness, µm		
Asymptomatic	373.69 (95% CI: 332.64, 414.73)	- 2.98 (95% CI: -4.45, -1.52)
Symptomatic	362.81 (95% CI: 348.92, 376.71)	-2.23 (95% CI: -2.99, -1.48)
Macular ganglion cell layer volume, mm^3		
Asymptomatic	0.4514 (95% CI: 0.4251, 0.4778)	-0.0006 (95% CI: -0.001, -0.0002)
Symptomatic	0.442 (95% CI: 0.4331, 0.4508)	-0.0003 (95% CI: -0.0005, -0.0001)
Headache frequency (days/month)		
Asymptomatic	13.6 (95% CI: 8.06, 19.14)	0.06 (95% CI: -0.36, 0.47)
Symptomatic	20.07 (95% CI: 18.13, 22.01)	-0.12 (95% CI: -0.3, 0.06)
Migraine-like headache frequency (days/month)		
Asymptomatic	3.6 (95% CI: -1.4, 8.59)	0.18 (95% CI: -0.21, 0.58)
Symptomatic	9.11 (95% CI: 7.29, 10.92)	-0.03 (95% CI: -0.2, 0.13)
Headache severity (0-10 scale)		
Asymptomatic	6.2393 (95% CI: 4.4749, 8.0037)	0.0178 (95% CI: -0.0973, 0.133)
Symptomatic	6.5451 (95% CI: 6.0147, 7.0755)	-0.0131 (95% CI: -0.0606, 0.0345)
HIT-6 (score 36-78)		
Asymptomatic	59.77 (95% CI: 52.83, 66.7)	0.28 (95% CI: -0.06, 0.63)
Symptomatic	61.33 (95% CI: 59.1, 63.55)	-0.04 (95% CI: -0.18, 0.11)

Figure 3 - Longitudinal visual function data categorised by symptoms at diagnosis, with Asymptomatic presentations illustrated. LOESS smoothers added to show trends across the categories.

a. LogMAR visual acuity (log units)

b. Perimetric mean deviation measured by Humphrey visual field 24-2 testing (dB)

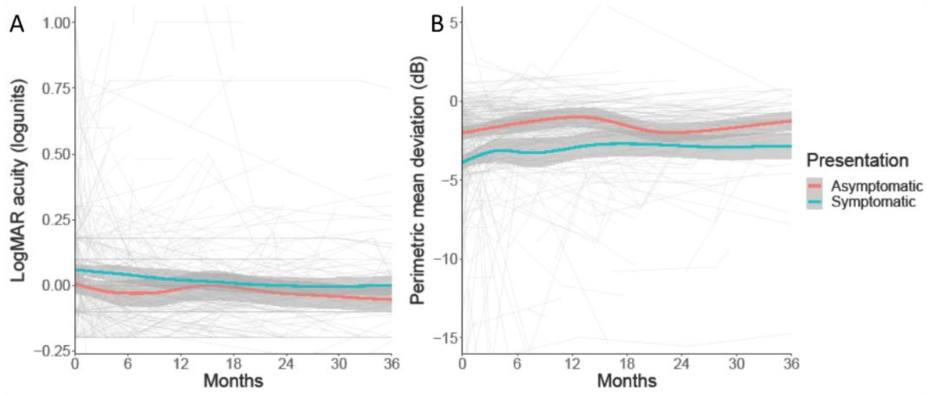
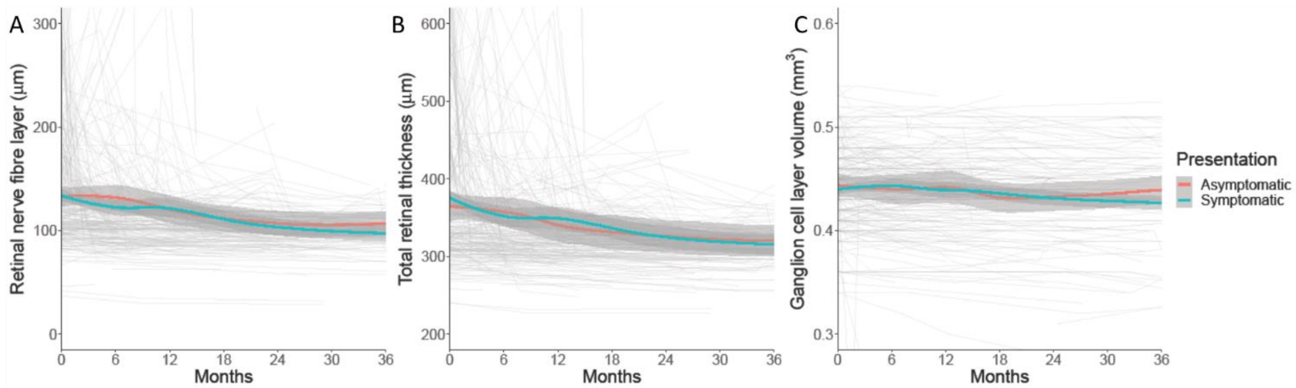


Figure 4 - Longitudinal visual OCT data categorised by symptoms at diagnosis, with Asymptomatic presentations illustrated. LOESS smoothers added to show trends across the categories.

a. Retinal nerve fibre layer thickness measured on Optical Coherence Tomography (µm)

b. Total retinal thickness of optic nerve head measured on Optical Coherence Tomography (µm)

c. Macular ganglion cell layer volume measured on Optical Coherence Tomography (mm³)



Disease duration was the main influencing factor in determining baseline visual function in the asymptomatic group. Duration of disease influenced the baseline (time of database entry) estimates of VA, RNFL, and TRT (VA: increase of 0.00095 LogMAR/months (95% CI:

0.000171-0.001729); RNFL: decrease of 0.37 μm/month (95% CI: -0.61, -0.13); TRT decrease of 0.3307μm/month (95% CI: -0.5717, -0.0897)), reflecting a slightly worse visual acuity and reduced OCT parameters the longer the disease duration. However, the trajectory following initial visit was not significantly influenced by disease duration, as only VA showed a small worsening of 0.00005 LogMAR/month (95% CI: 0.000003, 0.000096). Age had a small impact on macular GCL with thinner baseline GCL of 0.0011 mm^3/year (95% CI: -0.0021, -0.0001). A personal or family history of migraine did not impact visual outcomes.

3.2.4.2 Headache outcomes

Incidental presentations had a higher baseline headache and migraine-like headache frequency (Figures 5A, 5B) than those with asymptomatic presentations (Figures 6A, 6B), although both were lower than the symptomatic group (Tables 2 and 3, Figures 6A, 6B). The headache severity and HIT-6 quality-of-life measure were comparable between the groups (Tables 2 and 3, Figures 5C, 5D, 6C, 6D).

Figure 5 - Longitudinal headache data categorised by symptoms at diagnosis, with Incidental papilloedema illustrated. LOESS smoothers added to show trends across the categories.

a. Headache frequency (days per month)
b. Migraine-like headache frequency (days per month)
c. Headache mean severity of predominant headache (0-10 numerical rating scale)
d. Headache Impact Test 6 (HIT6) (quality of life measure score 36-78)

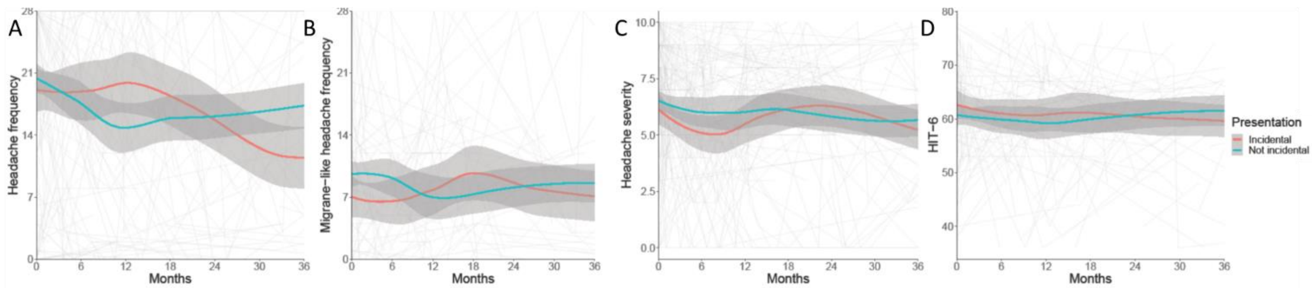
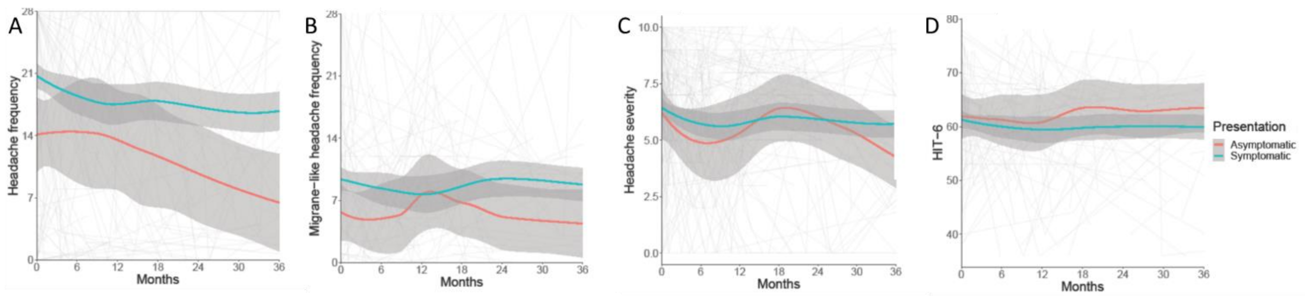


Figure 6 - Longitudinal headache data categorised by symptoms at diagnosis, with Asymptomatic presentations illustrated. LOESS smoothers added to show trends across the categories.

- *a. Headache frequency (days per month)*
- *b. Migraine-like headache frequency (days per month)*
- *c. Headache mean severity of predominant headache (0-10 numerical rating scale)*
- *d. Headache Impact Test 6 (HIT6) (quality of life measure score 36-78)*



The asymptomatic patients had lower headache and migraine-like frequency at baseline visit compared to the symptomatic cohort (Table 3, Figure 6A, 6B), as would be expected. Of note, headache, and migraine-like frequency at baseline (time of enrolment to database) were not zero due to some patients developing headaches after papilloedema detection and IIH diagnosis but prior to review, with the headaches over time reflecting that of the 24 patients who became symptomatic during follow-up 23 reported headaches. Headache outcomes did not change over time.

Daily headache at baseline visit was the main influential marker for worse outcomes (with a baseline headache frequency 17.31 days/month higher (95% CI: 15.11, 19.51) but better reduction over time by 0.86 days/month (95% CI: -1.17, -0.56) and headache severity (baseline 3.02 points higher (95% CI: 2.15, 3.89) but trajectory better by 0.13 points/month (95% CI: -0.21, -0.04))). A personal migraine history in this cohort was associated with a worse baseline headache disability (HIT-6 score) by 3.13 points (95% CI: 0.09, 6.16)) but for other measures only in univariate analysis, not when combined with daily headache at baseline.

3.2.5 Discussion

This is the first prospective study to assess the long-term outcomes of people with IIH who were asymptomatic at diagnosis with a comparison to those who were symptomatic. The comparable outcomes between these groups highlight that presenting without symptoms is not associated with either favourable or detrimental visual outcomes. Interestingly two thirds of these asymptomatic patients became symptomatic over the course of follow-up, with almost all subsequently reporting headaches.

Incidental papilloedema was a common presentation with over one third of IIH patients presenting to this neuro-ophthalmology service, however on directing questioning many had symptoms. This study's incidental papilloedema prevalence data is comparable to a study in North America (30.0%) but lower than previous reported in the United Kingdom (48.1%) of the rate of incidental finding of papilloedema on routine examination in consecutive cohorts presenting for evaluation of IIH in two tertiary centres.[7] 10% of people were completely asymptomatic at their first visit and this is higher than another retrospective study in adults, which showed 3.6% (5/139) patients were asymptomatic.[16] However their portion of asymptomatic presentations of IIH was similar to our proportion who remained asymptomatic through follow-up (3.5%, 12/343). This highlights that most will develop symptoms through the course of their follow-up and although managing asymptomatic IIH can be a concern for clinicians, it is actually a rare occurrence.

There were similar proportions of personal and family history of migraine in the asymptomatic and symptomatic groups which could indicate that the potential predisposition to headache may be similar. There was a higher prevalence of a prior migraine history in those cases who transitioned from no symptoms to suffering symptoms which could reflect the cyclical nature of migraine headaches.

The similar outcomes demonstrated in the incidental papilloedema group, and the asymptomatic group could indicate that those asymptomatic people are at the milder end of the IIH clinical spectrum. This is further supported by the lower surgical intervention rates in the asymptomatic cohort (Table 1). The higher diagnostic lumbar puncture opening pressure in asymptomatic cohort highlights that the presence of symptoms may not be due to the absolute level of ICP. There may be many factors that determine whether an individual is experiencing symptoms.

Studying conditions of asymptomatic papilloedema is helpful as there remains many answered questions as to the development of papilloedema and the duration and severity required for permanent visual loss. This study of asymptomatic IIH may be interesting to clinicians, as one could consider those that who are asymptomatic may present late which could confer worse outcomes but reassuringly here are similar to symptomatic IIH. On the other hand, those who are asymptomatic could be in a pre-symptomatic phase with evidenced similar outcomes. Parallels from this series could be drawn to Astronauts undergoing long duration spaceflights that are relatively asymptomatic and through routine screening are found to meet the criteria to be diagnosed with spaceflight associated neuro-ocular syndrome (SANS).[17, 18] Therefore continued follow-up of those with an asymptomatic presentation of papilloedema is warranted rather than reassurance and should be managed as symptomatic people.

The limitations of this study include the underestimation of asymptomatic prevalence due only patients with a clear absence of all symptoms being included, and some symptoms may have been due to other conditions beyond IIH and therefore could have still been asymptomatic from their IIH. For example, a person with a prior history of migraine, may have had recurrence of migraine during follow-up that was unrelated to their IIH diagnosis. This data is routinely collected clinical data and therefore standardised follow-up intervals in the cohort were not possible and as follow-up was dependent on disease status and papilloedema severity. As per clinical practice, some individuals were discharged either completely or back to more local services, as well as some being lost to follow up, which meant there was a reduction in the number of patients under longer term follow up, therefore this data should be interpreted in that context. Additionally, although the study aimed to capture all outcomes, patient preference meant some were missing and this was more marked for patient reported outcomes such as questionnaires, although this was minimised where possible in clinic by recommending full completion. All patients had their data evaluated and where possible missing data completed from alternative sources, i.e. clinical noting. In future, comparison between asymptomatic IIH and a non-IIH control group may be beneficial to enable better insights into the outcomes illustrated here, and whether early pathophysiological mechanisms are different.

3.2.6 Conclusions

Incidentally discovered papilloedema is a common occurrence, however on direct questioning truly asymptomatic IIH has been found to be uncommon and becomes rare on follow-up as many begin to experience symptoms. Asymptomatic disease does not have either a beneficial or detrimental effect on visual outcomes as compared to symptomatic disease. This subpopulation of people with IIH may need routine eye examinations throughout the course of their lives to detect asymptomatic deterioration in papilloedema.

3.2.7 References

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Chapter 3.3 Normal BMI in IIH (Thaller. Neuroophthalmology. 2024)

Manuscript title:

Does a healthy weight body mass index at onset of Idiopathic Intracranial Hypertension change the outcomes? A United Kingdom prospective cohort study.

Published:

Thaller M, Homer V, Abbott S, Hazlehurst J, Mollan SP, Sinclair AJ. Does a healthy weight body mass index at onset of Idiopathic Intracranial Hypertension change the outcomes? A United Kingdom prospective cohort study. Neuroophthalmology (under review). 2023.

Involvement:

I was involved in data collection, data analysis, data interpretation, writing first manuscript and critical revision of the manuscript.

3.3.1 Abstract

Background: Idiopathic Intracranial Hypertension predominantly affects reproductive aged females with obesity. However, the prevalence and impact of a healthy weight body mass index (BMI) at disease presentation is not known. This study aimed to evaluate the visual and headache outcomes stratified by the presenting BMI.

Methods: This was a longitudinal prospective cohort study (IIH Life) based in a tertiary neuro-ophthalmology IIH service, University Hospitals Birmingham NHS Trust, United Kingdom recruiting consecutive patients living with IIH between 2012 and 2021. Those with a presenting BMI were included. Outcome measures included visual outcomes of LogMAR visual acuity, Humphrey visual field perimetric mean deviation, optical coherence tomography (OCT) measurements and headache outcomes of frequency, severity, and Headache Impact Test-6 score.

Results: 375 people with IIH and a documented baseline BMI. 3.7% of the entire cohort had a healthy weight BMI at IIH presentation, and 15.5% BMI <30kg/m^2. Baseline PMD was worse in patients without obesity, however OCT papilloedema measures were similar. The presence of obesity was associated with a small but significant greater worsening in visual acuity but slower macular ganglion cell layer loss. There was no impact on PMD or papilloedema prognosis related to baseline obesity. Headache outcomes showed heterogeneity, with worse baseline headache frequency in patients with obesity. No BMI group was associated with worse headache outcomes.

Conclusions: Patients with a healthy weight BMI, or those without obesity, at baseline make up a small proportion of IIH patients. BMI at presentation does not appear to influence long-term visual or headache outcomes.

3.3.2 Introduction

Idiopathic Intracranial Hypertension (IIH) predominantly affects women of reproductive years living with obesity.[1-4] IIH is caused by raised intracranial pressure, which can lead onto visual loss, chronic headaches and cognitive dysfunction.[5-7] Atypical IIH is a term given to people who meet the diagnostic criteria for IIH but do not fit the typical phenotype, including males or females living without obesity.[5] Obesity is defined by the World Health Organisation as a body mass index (BMI) ≥30kg/m^2,[8] which is reduced to 27.5 kg/m^2 in some ethnic groups due to increased cardiometabolic risk at a lower BMI.[9, 10]

The adiposity associated with IIH is centripetal,[11, 12] and is correlated with lumbar puncture opening pressure.[11] A two-fold increase in cardiovascular disease risk has been found in people living with IIH, in comparison to age-, sex- and BMI- matched controls.[13] Other metabolic complications are associated with IIH, such as diabetes mellitus, gestational diabetes, pre-eclampsia and arterial hypertension.[13-15] In animal studies both high fat diet and IIH-associated inflammatory factor exposed female rats showed increased CSF secretion.[16] The adipocytes in IIH appear to be metabolically primed for lipogenesis[17] with an additional insulin and leptin resistant phenotype in excess of that driven by obesity alone.[17, 18] IIH is also associated with hypertestosteronism in females, independent of obesity, and testosterone increases CSF secretion through the Na+/K+-ATPase pump in the choroid plexus.[19] There is also debate in the literature about whether IIH is caused by problems with CSF secretion or drainage (including cerebral venous stenosis), or a combination of both, and multiple factors are likely to influence both these mechanisms.[20, 21] Currently the only disease modifying therapy for IIH is weight loss,[5, 22] with weight loss shown to be associated with improvement in papilloedema.[23, 24] Although this was not shown to benefit IIH symptoms of headache, pulsatile tinnitus or visual problems.[24] For those with a BMI ≥35kg/m^2 disease remission, defined as normalisation of intracranial pressure (ICP), may require up to 24% weight loss.[3]

The presence of a healthy weight BMI on IIH and associated pathophysiology has not been studied. This may be because a healthy weight BMI at IIH diagnosis is uncommon.[4, 25-27] In other conditions, such as space flight associated neuro-ocular syndrome (SANS) where there is swelling of the optic nerve head, it is unknown whether body weight influences the clinical outcomes. The long-term outcomes for those with a healthy weight BMI have previously been reported in a single retrospective study, which found better visual outcomes in those with a healthy weight BMI as compared to those with an increased BMI.[4] It is unclear whether this may be due to fewer metabolic drivers for CSF secretion or reabsorption, potentially hyperandrogenism without insulin resistance, leptin resistance or adipocyte priming. Metabolic alterations related to obesity have been thought to be the main pathological drivers of IIH given improvement associated with weight loss, although in the subset of IIH with a healthy weight BMI there may be a different underlying pathogenesis.

This study is the first to prospectively assess the prognosis in IIH in a cohort of people with a healthy weight BMI. The hypothesis is that IIH patients without obesity would have different visual and headache outcomes compared to typically obese IIH counterparts.

3.3.3 Methods

The methodology[7] for this prospective observational cohort study has been published, and ethically approved by NHS National Research Ethics Committee (14/LO/1208), IIH:LIFE study. Eligible patients were those who met the revised diagnostic criteria for Idiopathic Intracranial Hypertension in adults[28] and had a baseline BMI recorded. The revised diagnostic criteria require the presence of papilloedema, a normal neurological examination (except sixth nerve palsy), normal brain parenchyma (no hydrocephalus, mass, structural lesion or meningeal enhancement) on neuroimaging, exclusion of venous sinus thrombosis, normal CSF constituents and an elevated lumbar puncture opening pressure ≥25 cmCSF.[28] Patients with secondary causes for raised intracranial pressure or IIH without papilloedema were excluded. Therefore, all patients diagnosed with IIH had papilloedema, rather than diagnosed purely on neuroradiological or venographic features. All patients gave written informed consent to participate in this study. Data was collected between April 2012 and September 2021.

This study separated patients according to their BMI status. Patients were initially categorised as having (≥30 kg/m^2) or not having obesity (<30 kg/m^2) at baseline visit. Then subsequently by World Health Organisation (WHO) BMI categories[8]: healthy weight body mass index (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obesity class 1 (30.0-34.9 kg/m^2) and obesity class 2 and above (≥35.0 kg/m^2). Although IIH is not currently recognised as an obesity related disease in the UK, with regards to NHS funding for bariatric surgery, this may change in future and therefore obesity class 2 and above was used as the highest grouping.[10] BMI groups were not adjusted by ethnicity.

Visual outcomes were: LogMAR visual acuity (measured using Logarithm of the Minimum Angle of Resolution), Humphrey visual field perimetric mean deviation (PMD) (24-2 SITA standard) and optical coherence tomography (OCT, Heidelberg Spectralis™) measures of average global peripapillary Retinal Nerve Fibre Layer Thickness (RNFL), automatically measured Total Retinal Thickness (TRT) (by the software on the RNFL circle and extracted as TRT) and macular ganglion cell layer (GCL) volume (1, 2.22, 3.45mm ETDRS plot with the volume measurement as given by the software which would include all 9 sectors, by the pre-set macular volume and/or posterior pole methods). To ensure accuracy of segmentation of the retinal layers in moderate to severe papilloedema, manual segmentation of RNFL and TRT was performed in peripapillary scans and in cross-sectional slices of optic disc scans for the basement membrane (BM) and inner limiting layer (ILM), where appropriate. During the course of the study, the scanning protocol for GCL changed, however excellent correlation has been shown between the macular volume and posterior pole measures (Pearson correlation 0.98).[7]

Headache outcomes were assessed by monthly headache days (days/month), monthly migraine-like headache days (days/month), headache severity (0-10 numerical rating scale, where 0 is no pain and 10 equates to the most severe), and headache disability using the Headache Impact Test-6 (HIT-6) score (score is between 36 and 78).

The methods for data collection and statistical analysis have previously been reported.[7] Statistical analysis was performed using R v4.1.0 and lme4[29] used for regression modelling. Statistical significance is indicated by 95% confidence intervals and is met when the intervals do not cross zero. LOESS (locally weighted scatterplot smoothing) graphs were created prior to regression analysis to ascertain the variables' relationships and any trends.

Patient and public involvement

IIHUK, a national patient charity (Registered Charity in England and Wales no 1143522 & Scotland SCO43294) that supports carers and patients living with IIH endorsed and helped develop the IIH Life concept and questionnaire.

3.3.4 Results

In this nine-year longitudinal cohort study, 375 people with IIH and a documented baseline BMI were prospectively recruited. A healthy weight BMI was uncommon at presentation (3.7%, 14/375). Patients with higher BMI categories were more common with 11.7% (44/375) classed as overweight, 20% (75/375) obesity class 1 and 64.5% (242/375) obesity class 2 and above (Table 1).

Table 1 - Baseline table by baseline BMI

	All	**Baseline BMI (kg/m²)**			
		18.5-24.9	25-29.9	30-34.9	35+
N	375	14	44	75	242
Surgical	53	1	2	14	36
Females	370	13	43	75	239
Age (mean (SD), N), years	31.7 (9.8), 375	26.5 (6.6), 14	33.5 (13.5), 44	31.0 (9.5), 75	31.9 (9.2), 242
Body mass index (mean (SD), N), kg/m²	38.8 (9.1), 375	22.7 (1.4), 14	27.1 (1.6), 44	32.0 (1.5), 75	43.9 (6.8), 242
Diagnostic CSF opening pressure (mean (SD), N), cmCSF	35.6 (8.9), 323	34.8 (6.5), 14	36.5 (9.0), 40	36.5 (11.0), 64	35.1 (8.3), 205

Patients with a healthy weight BMI had the lowest diagnostic CSF opening pressure (Table 1). Cerebrospinal fluid diversion surgery rates (during follow-up for this study) were lower for those with a healthy weight BMI at presentation (7%) compared to patients with IIH and higher BMIs, with 3.5% of overweight, 19% of obesity class 1, and 15% of obesity class 2+ (Table 1). Similar proportions of patients were treated with ICP lowering medications in all groups: 57% of healthy weight BMI, 61% of overweight, 63% obesity class 1 and 54% obesity class 2+.

Median (range) follow up in this cohort was 17 months (1-86) for those with at least one follow up visit. This was analogous to the BMI groups: healthy weight BMI (21 (3-33) months), overweight (14 (1-86) months), obesity class 1 (19 (1-70) months) and obesity class 2 and above (17 (1-80) months).

3.3.4.1 Presence of obesity

A BMI <30 kg/m^2 (normal or overweight BMI) at baseline visit was associated with worse baseline Humphrey visual field perimetric mean deviation (PMD) than patients with obesity (-5.65 dB (95% CI: -7.51, -3.80) versus -3.20 dB (-3.98, -2.41)) (Table 2).

Table 2- Baseline estimates and trajectory from regression modelling for obesity BMI cut-off (30kg/m^2)

	Baseline estimate (units)	**Change per month (units/month)**
LogMAR visual acuity, logunits		
BMI < 30	0.0146 (95% CI: -0.0498, 0.079)	0.0033 (95% CI: 0.0014, 0.0052)
BMI $\geq$ 30	0.0201 (95% CI: -0.0076, 0.0478)	-0.0007 (95% CI: -0.0015, 0.0002)
Humphrey visual field perimetric mean deviation, dB		
BMI < 30	-5.65 (95% CI: -7.51, -3.8)	0.06 (95% CI: 0, 0.13)
BMI $\geq$ 30	-3.2 (95% CI: -3.98, -2.41)	0.05 (95% CI: 0.02, 0.07)
Global peripapillary retinal nerve fibre layer, µm		
BMI < 30	139.84 (95% CI: 119.64, 160.03)	-1.98 (95% CI: -3.18, -0.77)
BMI $\geq$ 30	135.98 (95% CI: 128.09, 143.88)	-1.27 (95% CI: -1.7, -0.84)
Global peripapillary total retinal thickness, µm		
BMI < 30	383.16 (95% CI: 354.09, 412.24)	-2.98 (95% CI: -4.49, -1.48)
BMI $\geq$ 30	361.83 (95% CI: 350.78, 372.88)	-1.96 (95% CI: -2.44, -1.47)
Macular ganglion cell layer volume, mm^3		

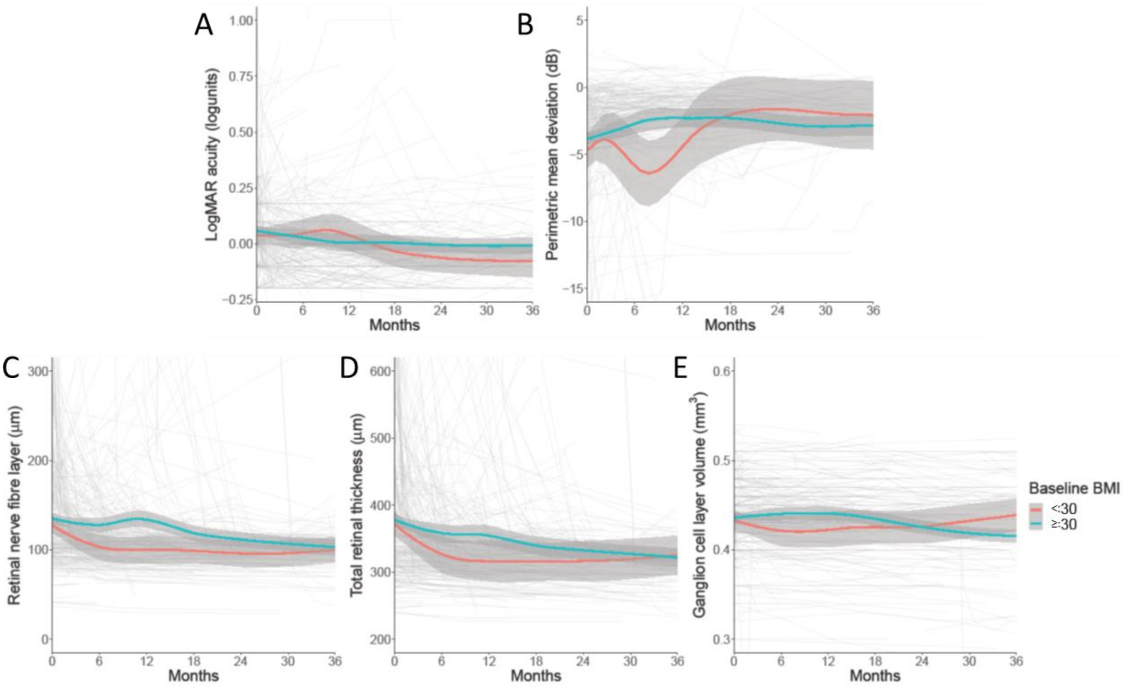
BMI < 30	0.440533 (95% CI: 0.420416, 0.46065)	-0.000921 (95% CI: -0.001407, -0.000436)
BMI ≥ 30	0.442757 (95% CI: 0.434659, 0.450856)	-0.000363 (95% CI: -0.000516, -0.000209)
Headache frequency (days/month)		
BMI < 30	15.95 (95% CI: 12.02, 19.87)	-0.12 (95% CI: -0.32, 0.08)
BMI ≥ 30	20.32 (95% CI: 18.63, 22)	-0.17 (95% CI: -0.26, -0.07)
Migraine-like headache frequency (days/month)		
BMI < 30	8.41 (95% CI: 5.06, 11.77)	- 0.02 (95% CI: -0.22, 0.18)
BMI ≥ 30	9.16 (95% CI: 7.69, 10.63)	-0.1 (95% CI: -0.19, -0.01)
Headache severity (VAS 0-10)		
BMI < 30	5.34 (95% CI: 4.32, 6.35)	0.01 (95% CI: -0.06, 0.07)
BMI ≥ 30	6.19 (95% CI: 5.75, 6.63)	-0.02 (95% CI: -0.05, 0.01)
Headache Impact Test (HIT-6) (score 36-78)		
BMI < 30	61.57 (95% CI: 58.04, 65.09)	-0.1 (95% CI: -0.32, 0.13)
BMI ≥ 30	61.27 (95% CI: 59.74, 62.8)	-0.01 (95% CI: -0.11, 0.09)

The presence of obesity did not however influence baseline visual acuity, papilloedema measured by OCT (RNFL and TRT) or macular ganglion cell layer volume (Table 2).

Visual outcomes over time however were affected differently (Figure 1). Visual acuity had a worse trajectory in those with a BMI <30 kg/m^2 compared to patients with obesity at baseline (Table 2, Figure 1). There was a small additional statistically significant worsening (increase) in acuity of 0.004 logunits/month (95% CI: 0.002, 0.0061) in the former group compared to the latter, although this would likely remain clinically imperceptible. The PMD trajectory, it did not differ between the groups with similar long-term outcomes (Figure 1). The macular ganglion cell layer, which is structurally important for central and more focussed vision, volume declined slightly quicker in patients without obesity (Table 2) with a statistically significant greater decline of 0.000559 mm^3/month (95% CI: -0.001068, -0.00005). This may not be of clinical significance given the small level of decline.

Figure 1 – Longitudinal visual data from baseline visit for IIH patients categorised by whether BMI <30 or ≥30 kg/m2, and LOESS smoothers added to show trends across the categories.

- *a. LogMAR visual acuity (logunits)*
- *b. Perimetric mean deviation measured by Humphrey visual field 24-2 testing (dB)*
- *c. Retinal nerve fibre layer thickness measured on Optical Coherence Tomography (µm)*
- *d. Total retinal thickness of optic nerve head measured on Optical Coherence Tomography (µm)*
- *e. Macular ganglion cell layer volume measured on Optical Coherence Tomography (mm^3)*

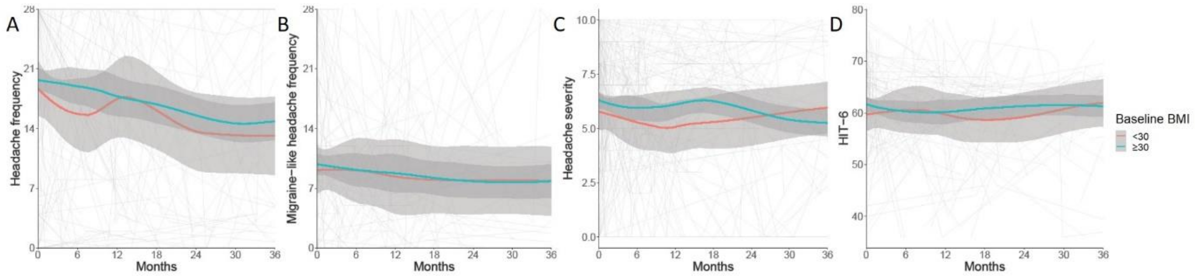


Papilloedema OCT trajectories were similar between the groups (Table 2) however in the initial six months following the baseline visit, patients with a BMI <30 kg/m^2 had a more rapid additional reduction in RNFL of 10.79µm/month (95% CI: -26.51, +4.92) and TRT of 5.90µm/month (95% CI: -36.29, +24.48) (Figure 1). This was not statistically significant.

The headache and migraine-like headache frequencies were high in the IIH cohort at baseline (Table 2, Figure 2). The mean baseline frequency was lower in patients with BMI <30 kg/m^2 (15.95 days/month (12.02, 19.87) versus 20.32 (18.63, 22.00) with obesity) (Table 2) and this was significantly lower in the non-obesity group by -4.37 days/month (95%CI: -8.64, -0.11)). Migraine-like headache frequency did not significantly differ between patients with or without obesity (9.16 (7.69, 10.63) and 8.41 (5.06, 11.77) respectively) (Table 2, Figure 2). Headache severity was moderate in both groups, 5-6 out of 10 (Table 2), and did not significantly differ at baseline or in trajectory (Figure 2). Headaches had a substantial impact on quality of life as measured by the HIT-6 (mean scores 61-62 /78) (Table 2), with very similar scores and confidence intervals (on average 61 out of 78) (Figure 2). The trajectories were not significantly different between <30 kg/m^2 and ≥30 kg/m^2 groups for any of the headache outcomes.

Figure 2 – Longitudinal headache data from baseline visit for IIH patients categorised by whether BMI <30 or ≥30 kg/m2, and LOESS smoothers added to show trends across the categories.

a. Headache frequency (days per month)
b. Migraine-like headache frequency (days per month)
c. Headache mean severity of predominant headache (0-10 numerical rating scale)
d. Headache Impact Test 6 (HIT6) (quality of life measure score 36-78)



3.3.4.2 BMI groups

PMD was significantly worse (more negative) at baseline in those patients with a healthy weight BMI (-9.0 (-12.8, -5.2)) compared to those with obesity class 1 or class 2+ (-2.8 (-4.4, -1.2) and -3.3 (-4.2, -2.4) respectively) (Table 3). It was also worse, but not significantly so, compared to the overweight group (-4.5 (-6.6, -2.4)) (Table 3, Figure 3). OCT TRT papilloedema measurement was significantly worse for overweight patients compared to those with healthy weight BMI, 80.54µm (95% CI: 12.22, 148.86) higher, but not for either of the obesity groups (Figure 3). Macular GCL at baseline in the healthy weight BMI group was 0.3998mm^3 (0.3556, 0.4441) (Table 3) and was significantly higher for both overweight and obesity class 2+ categories compared to healthy weight BMI, 0.0508 (95% CI: 0.0012, 0.1004) and 0.0451 (95% CI: 0, 0.0903) respectively, but not obesity class 1 (Figure 3). When compared to a healthy weight BMI, no other group significantly differed at baseline for visual acuity or OCT RNFL outcomes (Figure 3).

Table 3 - Baseline and trajectory for visual and headache outcomes by baseline BMI

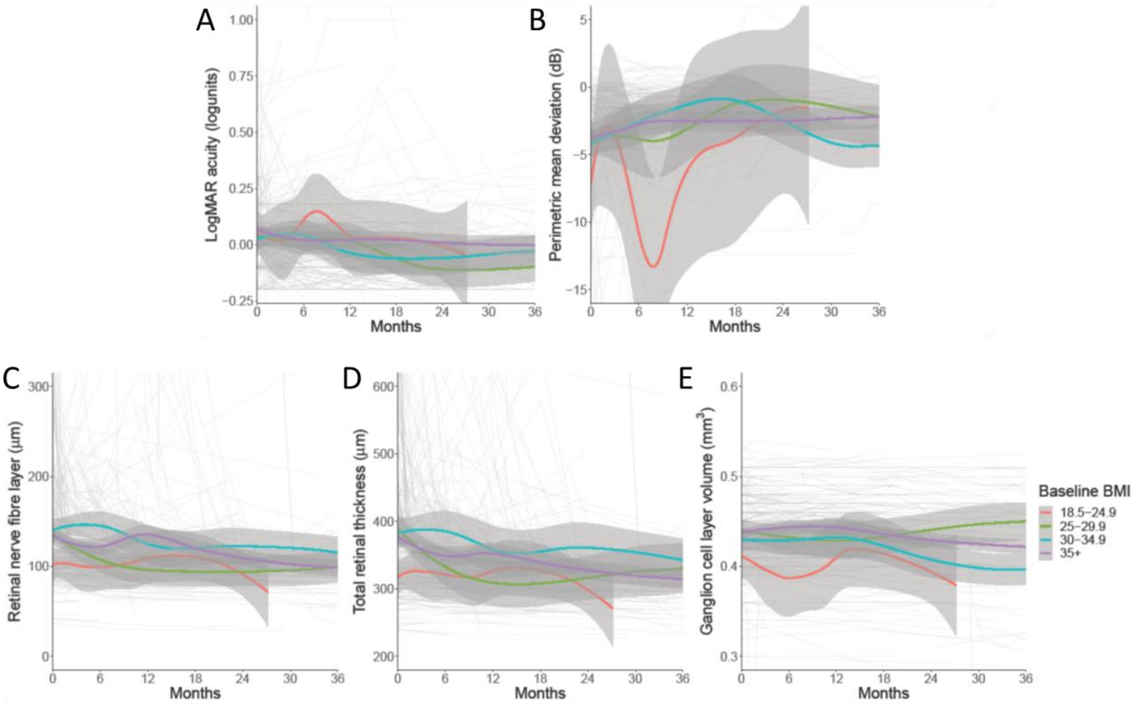
	Baseline estimate (units)	Change per month (units/month)
LogMAR visual acuity, logunits		
Healthy weight BMI (18.5-24.9 kg/m^2)	0.0612 (95% CI: -0.0709, 0.1932)	0.0021 (95% CI: -0.002, 0.0062)
Overweight (25.0-29.9 kg/m^2)	0.0007 (95% CI: -0.0731, 0.0746)	0.0036 (95% CI: 0.0015, 0.0058)
Obesity, class 1 (30.0-34.9 kg/m^2)	-0.0165 (95% CI: -0.0748, 0.0417)	0.0001 (95% CI: -0.0017, 0.0019)
Obesity, class 2 (35.0+ kg/m^2)	0.031 (95% CI: -0.0006, 0.0625)	-0.0009 (95% CI: -0.0019, 0)
Humphrey visual field perimetric mean deviation, dB		
Healthy weight BMI (18.5-24.9 kg/m^2)	-8.9967 (95% CI: -12.7581, -5.2354)	0.0326 (95% CI: -0.1299, 0.1951)
Overweight (25.0-29.9 kg/m^2)	-4.5161 (95% CI: -6.6363, -2.3958)	0.0685 (95% CI: -0.0009, 0.138)
Obesity, class 1 (30.0-34.9 kg/m^2)	-2.8149 (95% CI: -4.4375, -1.1923)	0.0253 (95% CI: -0.0243, 0.0749)
Obesity, class 2 (35.0+ kg/m^2)	-3.321 (95% CI: -4.2083, -2.4336)	0.0564 (95% CI: 0.0243, 0.0885)
Global peripapillary retinal nerve fibre layer, µm		
Healthy weight BMI (18.5-24.9 kg/m^2)	109.36 (95% CI: 65.85, 152.86)	-1.29 (95% CI: -3.77, 1.18)
Overweight (25.0-29.9 kg/m^2)	148.22 (95% CI: 125.37, 171.07)	-2.19 (95% CI: -3.56, -0.81)
Obesity, class 1 (30.0-34.9 kg/m^2)	126.43 (95% CI: 109.82, 143.04)	-1.66 (95% CI: -2.56, -0.77)
Obesity, class 2 (35.0+ kg/m^2)	138.54 (95% CI: 129.55, 147.53)	-1.16 (95% CI: -1.65, -0.68)
Global peripapillary total retinal thickness, µm		
Healthy weight BMI (18.5-24.9 kg/m^2)	321.39 (95% CI: 261.78, 381.01)	-2.28 (95% CI: -4.99, 0.43)
Overweight (25.0-29.9 kg/m^2)	401.94 (95% CI: 368.56, 435.31)	-3.37 (95% CI: -5.17, -1.56)
Obesity, class 1 (30.0-34.9 kg/m^2)	352.69 (95% CI: 329.5, 375.89)	-2.87 (95% CI: -3.85, -1.88)
Obesity, class 2 (35.0+ kg/m^2)	363.9 (95% CI: 351.38, 376.42)	-1.68 (95% CI: -2.23, -1.13)
Macular ganglion cell layer volume, mm^3		

Healthy weight BMI (18.5-24.9 kg/m^2)	0.3998 (95% CI: 0.3556, 0.4441)	-0.001 (95% CI: -0.0018, -0.0002)
Overweight (25.0-29.9 kg/m^2)	0.4506 (95% CI: 0.4282, 0.4731)	-0.0009 (95% CI: -0.0015, -0.0003)
Obesity, class 1 (30.0-34.9 kg/m^2)	0.4352 (95% CI: 0.4183, 0.4521)	-0.0003 (95% CI: -0.0007, 0)
Obesity, class 2 (35.0+ kg/m^2)	0.445 (95% CI: 0.4358, 0.4541)	-0.0004 (95% CI: -0.0005, -0.0002)
Headache frequency (days/month)		
Healthy weight BMI (18.5-24.9 kg/m^2)	13.5 (95% CI: 4.72, 22.28)	-0.15 (95% CI: -0.59, 0.28)
Overweight (25.0-29.9 kg/m^2)	16.6 (95% CI: 12.28, 20.91)	-0.1 (95% CI: -0.34, 0.14)
Obesity, class 1 (30.0-34.9 kg/m^2)	19.44 (95% CI: 16.34, 22.54)	-0.09 (95% CI: -0.27, 0.08)
Obesity, class 2 (35.0+ kg/m^2)	20.74 (95% CI: 18.76, 22.72)	-0.2 (95% CI: -0.32, -0.08)
Migraine-like headache frequency (days/month)		
Healthy weight BMI (18.5-24.9 kg/m^2)	4.34 (95% CI: -2.32, 10.99)	0.16 (95% CI: -0.2, 0.53)
Overweight (25.0-29.9 kg/m^2)	9.79 (95% CI: 5.97, 13.61)	-0.09 (95% CI: -0.33, 0.15)
Obesity, class 1 (30.0-34.9 kg/m^2)	6.52 (95% CI: 3.96, 9.07)	0.0 (95% CI: -0.16, 0.15)
Obesity, class 2 (35.0+ kg/m^2)	10.46 (95% CI: 8.68, 12.23)	-0.15 (95% CI: -0.26, -0.05)
Headache severity (VAS 0-10)		
Healthy weight BMI (18.5-24.9 kg/m^2)	5.73 (95% CI: 3.54, 7.93)	-0.09 (95% CI: -0.2, 0.02)
Overweight (25.0-29.9 kg/m^2)	5.14 (95% CI: 3.99, 6.28)	0.06 (95% CI: -0.02, 0.14)
Obesity, class 1 (30.0-34.9 kg/m^2)	6.55 (95% CI: 5.67, 7.43)	-0.04 (95% CI: -0.1, 0.01)
Obesity, class 2 (35.0+ kg/m^2)	6.06 (95% CI: 5.55, 6.57)	-0.01 (95% CI: -0.04, 0.02)
Headache Impact Test (HIT-6) (score 36-78)		
Healthy weight BMI (18.5-24.9 kg/m^2)	61.67 (95% CI: 54.4, 68.95)	-0.27 (95% CI: -0.67, 0.13)
Overweight (25.0-29.9 kg/m^2)	61.33 (95% CI: 57.28, 65.37)	0.0 (95% CI: -0.27, 0.28)
Obesity, class 1 (30.0-34.9 kg/m^2)	61.18 (95% CI: 58.19, 64.17)	-0.07 (95% CI: -0.27, 0.14)

Obesity, class 2 (35.0+ kg/m^2)	61.29 (95% CI: 59.51, 63.08)	0.01 (95% CI: -0.1, 0.13)

Figure 3 – Longitudinal visual data from baseline visit for IIH patients categorised baseline body mass index group, and LOESS smoothers added to show trends across the categories.

- *a. LogMAR visual acuity (logunits)*
- *b. Perimetric mean deviation measured by Humphrey visual field 24-2 testing (dB)*
- *c. Retinal nerve fibre layer thickness measured on Optical Coherence Tomography (µm)*
- *d. Total retinal thickness of optic nerve head measured on Optical Coherence Tomography (µm)*
- *e. Macular ganglion cell layer volume measured on Optical Coherence Tomography (mm^3)*

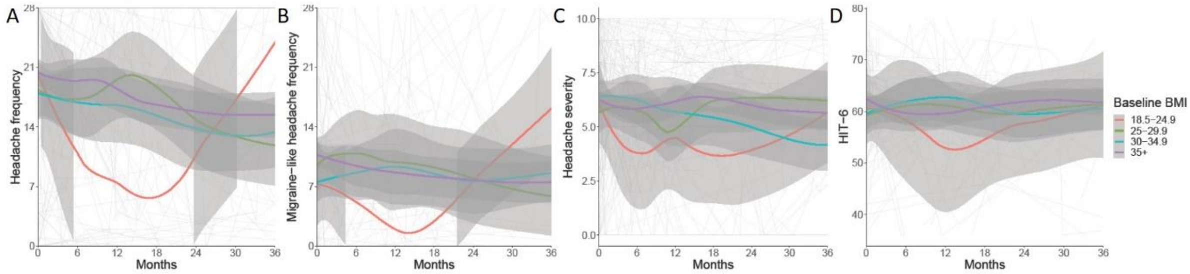


Trajectories for all visual outcomes did not differ compared to healthy weight BMI at baseline group (Table 3, Figure 3).

Higher headache frequency was reported on average in those with higher baseline BMIs (Table 3, Figure 4). There was no group significantly different from healthy weight BMI at baseline (Figure 4) due to wide confidence intervals. Similarly, migraine-like headache frequency, headache severity and HIT6 did not differ by BMI group at baseline (Figures 4B, 4C, 4D).

Figure 4 – Longitudinal headache data from baseline visit for IIH patients categorised by baseline body mass index group, and LOESS smoothers added to show trends across the categories.

a. *Headache frequency (days per month)*
b. *Migraine-like headache frequency (days per month)*
c. *Headache mean severity of predominant headache (0-10 numerical rating scale)*
d. *Headache Impact Test 6 (HIT6) (quality of life measure score 36-78)*



Trajectories for headache outcomes were similar for all outcomes (Table 3, Figure 4) apart from headache severity in the overweight group which had a worse trajectory by 0.15 units/month (95% CI: 0.02, 0.29) compared to healthy weight BMI patients.

3.3.5 Discussion

In this prospective longitudinal cohort of people living with IIH a healthy weight BMI at presentation is uncommon (3.7%). Headache frequency was higher in IIH patients with obesity as compared to those without. Over time the headache outcomes were similar between BMI classes and those with/without obesity. Both IIH without obesity and in those with a healthy weight BMI were associated with worse visual fields at baseline and similar papilloedema measures. Initial papilloedema was observed to improve quicker in patients without obesity, while both groups had similar longer-term outcomes.

The prevalence of a healthy weight BMI in this study is very similar to a previous large study of IIH.[4] Those with a healthy weight BMI, including those without obesity, had worse visual field function at baseline, despite similar OCT papilloedema measures. This could potentially reflect a delay in diagnosis due to a lower suspicion of IIH in a person with a healthy weight BMI. OCT imaging measures have been shown to be a more acute marker of disease activity[7] as well as a better correlation to intracranial pressure than clinical symptoms.[30, 31] Thus the comparable OCT measures, with worse PMD, may indicate a delayed presentation of the disease.[7] A statistical difference was seen in the visual acuity and macular ganglion cell layer volume trajectories between those with obesity and those without (Table 2). However, the clinical significance is uncertain due to the small magnitude of this variation which is likely not be perceivable by the patient or of clinical significance. The potential is that over a longer period the rate of decline that occurs with age may be enhanced by the decline caused by IIH. The trajectories of the headache outcomes were not significantly different between <30 kg/m^2 and ≥30 kg/m^2. This is consistent in that baseline BMI potentially has a greater influence on visual outcomes than headache outcomes which may be influenced additionally by more significant factors as previous demonstrated in the literature.[7]

Although IIH predominantly affects reproductive aged women with obesity,[1, 5, 7, 32] there are atypical presentations.[4, 33] Defining patients by whether obesity was present at baseline visit is a clinically useful, although this involves an arbitrary cut off at 30 kg/m^2, due to the increased metabolic risks associated with obesity. It is important for clinicians to note that baseline BMI did not impact the trajectory of visual or headache outcomes. While for some this could be reassuring; it is important to actively manage those who do not have obesity. However, the only disease modifying therapy in IIH so far is weight loss,[2, 3, 5, 7, 22] and its role in patients with a normal baseline BMI is not understood. A larger, more recent IIH study showed that change in BMI was a prognostic marker for visual outcomes,[7] and it can be more difficult in other scenarios including pregnancy.[15, 34]

Although the outcomes based on BMI are similar for people living with IIH, it should not be concluded that the underlying pathogenesis is the same. The pathogenesis has not been investigated and needs further research. IIH has been shown to be associated with hypertestosteronism independent of obesity[19] with metabolic priming towards lipogenesis.[17, 18] In people with obesity, significant weight loss of 24% body weight is often required for disease remission.[3, 24, 35] Potential pathogenesis in lean IIH could be inferred from the phenotypically similar condition of polycystic ovarian syndrome (PCOS), although may be found to be different in future research. In PCOS, one study reported 42% of the patients had a healthy weight BMI (classed as BMI 18.5-23 kg/m^2) with a significantly lower prevalence in lean PCOS of deranged lipid profiles, impaired glucose tolerance test and insulin resistance.[36] Treatment for insulin resistance with metformin has been shown to lessen hyperandrogenism in PCOS[37] and has also been shown to potentially be of benefit in

IIH.[38] Although we did not use metformin in our IIH clinical practice, therefore would have only had it prescribed for other indications and we did not record its use. Therefore in IIH without obesity or with a normal baseline BMI, there may still be a role for dietary modifications and pharmacotherapy to avoid future weight gain as this has been shown to potentially be of benefit in lean PCOS, without weight loss.[39] In addition, where there is a history of weight gain prior to IIH diagnosis, recommendations would be for weight loss regardless of BMI as long as the prior weight was not detrimental to their health.[5] There is a need for further IIH research into the metabolic profile of IIH without obesity, as there could be at similar metabolic complication risks despite lower body weight, and this could warrant an alternative management approach.

IIH with a healthy weight BMI, or without obesity, may more closely reflect spaceflight associated neuro-ocular syndrome (SANS) given the healthy weight BMIs seen in astronauts. SANS occurs during long duration spaceflight and risks include hyperopic refractive error shifts, acute visual loss, and cognitive changes. OCT changes have been noted in SANS with some similarities to IIH, and an increase in total retinal thickness of 20µm is used as the earliest indication of optic disc oedema.[40, 41] Therefore by studying the impact of a healthy weight BMI in IIH, there could be translational benefit for future space travel.

The major limitation in that this study was the relatively small sample size for healthy weight BMI patients, although this reflects similar sizes in other IIH populations where proportion was 4%[4] therefore reflective of the rarity of atypical IIH in an already rare condition. Baseline BMI was used to categorise patients; however, lead-time bias may have been induced with some initial visits being elsewhere prior to tertiary neuro-ophthalmology referral. To minimise this, we created a surrogate marker of disease duration was created as the time from the diagnostic lumbar puncture to the first encounter at baseline visit, adjusted for it in the multivariate regression modelling. Additionally, we were unable to ascertain symptom onset within our cohort accurately as this may predate diagnosis by an uncertain and variable duration. Visual function assessments are challenging for patients to perform with both intra-visit and inter-visit factors known to influence reliability. A more extensive list of limitations has previously been published for this cohort.[7]

This study continues a discussion on the extent to which obesity impacts the outcomes of headache and vision in people with IIH. The metabolic risks of the condition are being discovered and imply more risk to long-term morbidity and mortality. For example, the cardiovascular risks are two-fold greater in people with IIH compared to BMI-matched controls. The impact of IIH with or without obesity on metabolic outcome is yet to be established. This is especially important because extensive weight loss is known to result in IIH remission.[3] However, in this subset of IIH the underlying pathological mechanisms may be different requiring alternative treatment approaches. It would be of interest to perform a dedicated study of venography to understand the prevalence of venous sinus stenosis and its association with obesity, hyperandrogenism, metabolic disease and IIH.[20, 42]

3.3.6 Conclusions

People with a normal body mass index make up a minority of IIH patients. They appear to have similar visual and headache outcomes to people living with IIH and obesity. At the baseline visit, people without obesity had worse visual field function but similar papilloedema measures, compared to people living with obesity, however their long-term outcomes were similar. The metabolic phenotype is yet to be discovered in patients without obesity and it may be people of a healthy weight BMI are more susceptible to sequelae of IIH at lower body weights. Further research will require much larger sample sizes to investigate this subgroup of IIH.

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Chapter 4: Comorbid PCOS in IIH (Thaller. Eye. 2023)

Manuscript title:

Longitudinal prospective cohort study evaluating prognosis in Idiopathic Intracranial Hypertension patients with and without comorbid polycystic ovarian syndrome

Published:

Thaller M, Homer V, Sassani M, Mollan SP, Sinclair AJ. Longitudinal prospective cohort study evaluating prognosis in idiopathic intracranial hypertension patients with and without comorbid polycystic ovarian syndrome. Eye (Lond). 2023 Dec;37(17):3621-3628. doi: 10.1038/s41433-023-02569-x.

Involvement:

I was involved in data collection, data analysis, data interpretation, writing first manuscript and critical revision of the manuscript.

4.1 Abstract

Introduction: Idiopathic intracranial hypertension (IIH) and polycystic ovary syndrome (PCOS) are hyperandrogenic metabolic disorders that affect women of reproductive age living with obesity. The previously reported prevalence of comorbid PCOS in IIH patients is highly variable and the longitudinal impact on visual and headache outcomes are unknown.

Methods: In this prospective longitudinal cohort study patients were identified from the IIH: Life database over a nine-year period (2012-2021). Data collected included demographics and PCOS questionnaire data. Key visual and detailed headache outcomes were recorded. We analysed the key variables for influential outcomes of vision and headache. Logistical regression methods were used to model long term visual and headache outcomes.

Results: 398 women with IIH and documented PCOS questionnaires were followed up for a median of 10 months (range 0-87). Prevalence of PCOS in IIH was 20% (78/398) diagnosed by the Rotterdam criteria. Patients with IIH and comorbid PCOS reported higher self-reported fertility problems (3.2-fold increased risk) and increased need for medical help in becoming pregnant (4.4-fold increased risk). Comorbid PCOS in IIH patients does not adversely impact long-term vision or headache outcomes. The headache burden was high in both cohorts studied.

Conclusions: The study demonstrated that comorbid PCOS in IIH is common (20%). Diagnosing comorbid PCOS is important as it can impact on fertility and is known to have long-term adverse cardiovascular risks. Our data suggests that a diagnosis of PCOS in those with IIH does not significantly exacerbate long term vision or headache prognosis.

4.2 Introduction

Idiopathic Intracranial Hypertension (IIH) is a disease of raised intracranial pressure (ICP) diagnosed by the modified Dandy criteria which typically affects women of reproductive age with obesity.[1-3] The condition causes papilloedema, with a consequent risk of visual loss and chronic disabling headaches.[2, 4]

Polycystic ovarian syndrome (PCOS) occurs in women living with obesity of childbearing age which is of a similar phenotype to that observed in IIH. Prevalence of comorbid PCOS in people with IIH is raised according to the literature with 15% of the population affected according to NIH criteria and 1.5-fold increased prevalence of comorbid PCOS in IIH patients over age and BMI matched controls.[5-7] PCOS can be diagnosed by the Rotterdam criteria.[8] The Rotterdam criteria requires at least 2 of the 3 features of menstrual irregularities (oligo-/ anovulation), hyperandrogenism (manifested as hirsutism, acne and alopecia, or biochemical signs), and multiple ovarian cysts (≥12 follicles in each ovary measuring 2-9mm in diameter, ± ovarian volume >10ml), with the exclusion of other causes.[8] The NIH criteria require both menstrual irregularities and hyperandrogenism features to be present but polycystic ovaries are not required.[9]

There are several major metabolic features that are common to IIH and PCOS. They are both hyperandrogenic disorders, although characterised by distinct hormonal signatures: androstenedione is predominantly elevated in PCOS, whereas testosterone in IIH.[10] Truncal adiposity and insulin resistance are features of both diseases which also share alterations in adipose tissue functions driving lipogenesis in excess to that attributable to obesity alone.[11-14] In addition, both conditions are associated with an increased risk of cardiovascular disease,[15, 16] cognitive impairment,[17-19] and obstructive sleep apnoea.[20, 21]

PCOS has an established relationship to adverse reproductive health[22-24] and recently this has been reported in IIH where reduced fertility was noted as well as increased risk of pre-eclampsia and gestational diabetes.[25]

Thus, despite IIH and PCOS being distinct clinical entities with differential profiles of androgenic steroid dysregulation, they share numerous similar disease manifestations.[10] They have also been observed to coexist, although the exact prevalence of comorbid PCOS in

IIH has not clearly been established, as published results are highly variable, ranging from 15% to 57% of IIH patients having concomitant PCOS.[7, 26, 27]

We hypothesised that in patients with coexisting IIH and PCOS, the metabolic phenotype could be exacerbated, leading to increased morbidity. Amongst patients with IIH, we aimed to evaluate the impact of comorbid PCOS on fertility, as well as the visual and headache prognosis over time.

4.3 Methods

4.3.1 Study type

A prospective longitudinal observational cohort study was conducted, nested within the IIH: Life study. Data was prospectively collected from consecutive IIH patients attending a specialist IIH clinic at the University Hospitals Birmingham (UHB) NHS Foundation Trust between 2012 and 2021. Data from every sequential visit was recorded and informed consent obtained. The study was ethically approved by NHS National Research Ethics Committee (14/LO/1208), IIH: Life study.

4.3.2 Eligibility

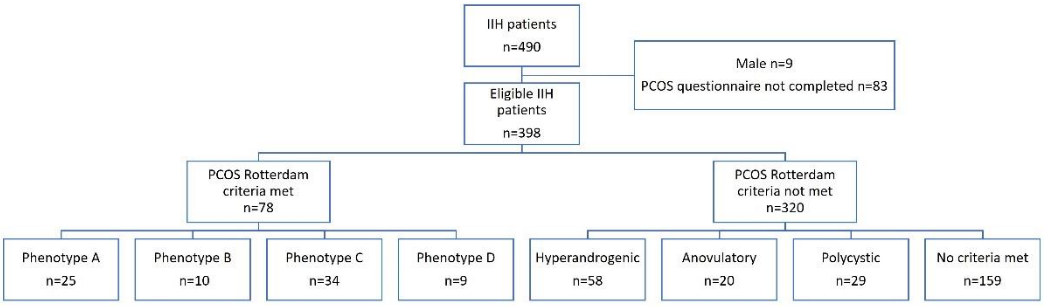
Patients eligible for inclusion were those with a confirmed diagnosis of IIH as per the modified Dandy criteria.[28] In addition only those consenting to complete the self-reported PCOS questionnaire were eligible (Appendix 1). Those referred with a potential diagnosis of IIH but in whom the diagnosis was not confirmed, those diagnosed with a secondary cause of intracranial hypertension, men, and patients with IIH without papilloedema were excluded.

4.3.3 Diagnosis of PCOS

PCOS diagnosis was established using the Rotterdam criteria [8] thus capturing those with existing confirmed PCOS and those unaware of the diagnosis. The Rotterdam criteria for diagnosis of PCOS require two of the three following criteria after exclusion of other aetiologies: oligo/anovulation, biochemical or clinical signs of hyperandrogenism, and polycystic ovaries (i.e. ≥12 follicles 2-9mm diameter) in each ovary and/or ovarian volume

>10ml).[8] Those meeting Rotterdam criteria, were further subdivided into four PCOS phenotypes: A) All three criteria met; B) with hyperandrogenism and oligo/anovulation; C) with hyperandrogenism and polycystic ovaries; D) with oligo/anovulation and polycystic ovaries (Figure 1).[24] A diagnosis of PCOS by the Rotterdam criteria was used throughout the analyses to define the PCOS cohort. In addition, we reported descriptive statistics utilising the NIH criteria for PCOS (which comprise a combination of phenotypes A and B).[9] These are, which was the original diagnostic criteria and are now superseded, but are included in this study to allow comparison with data from historical studies.

Figure 1 - CONSORT diagram



	Phenotype A	**Phenotype B**	**Phenotype C**	**Phenotype D**	**Hyperandro-genism**	**Oligo/ Anovulation**	**Polycystic**	**No criteria met**
Hyperandrogenism	+	+	+	-	+	-	-	-
Oligo/anovulation	+	+	-	+	-	+	-	-
Polycystic ovaries	+	-	+	+	-	-	+	-

4.3.4 Data collection

Patients were enrolled at their first visit to the neuro-ophthalmology clinic. We collected information on patient demographics and the following: body mass index (BMI), body weight, diagnostic lumbar puncture opening pressure, time from diagnostic lumbar puncture to baseline visit (as a surrogate for disease duration), and whether any surgical intervention for IIH was performed. A PCOS questionnaire was completed (Appendix 1) as was a maternal health questionnaire (Appendix 2).

Visual outcomes were assessed by visual acuity (VA) through the logarithm of the minimum angle of resolution (LogMAR), visual field by perimetric mean deviation (PMD, using a Humphrey visual field 24-2 SITA standard) and optical coherence tomography (OCT) imaging

(Heidelberg Spectralis™) measurements including global peripapillary retinal nerve fibre layer thickness (RNFL), total retinal thickness (TRT) and macular ganglion cell layer volume (1, 2.22, 3.45mm volume scan, by either/both of macular volume and posterior pole methods). TRT was calculated peripapillary cross-sectional imaging using manual segmentation to the basement membrane. This has been reported to be a potentially more accurate measure as automated segmentation in moderate to severe papilloedema using the proprietary software can be inaccurate.[29]

Headache outcomes were assessed by headache frequency (number of days per month), migraine-like headache days (number of days per month), headache severity (0-10 numerical rating pain scale, where 0 is no pain to 10 the most severe), and headache disability using the headache impact test-6 (HIT-6) test.[30] We also collected information on medication overuse, previous migraine history, familial history of migraine, and presence of daily headache (defined as headache days of $\geq$28 days/month) at patient's first visit to the specialist clinic.[31]

4.3.5 Statistical Analysis

Analysis was performed using R (v4.1.0) (https://www.R-project.org/). Summary statistics are presented as mean and standard deviation (SD) for continuous variables, and numbers and percentages for binary or categorical variables.

For visual outcomes (VA, PMD, RNFL, TRT and GCL), the effects of having a PCOS diagnosis versus not were analysed. Data for both eyes were used. Further analyses then investigated important prognostic factors for each outcome, these included the effect of disease duration, the diagnostic lumbar puncture opening pressure (both continuously and categorised <25, 25-29.9,30-39.9, or ≥ 40 cmH_2O), BMI at first visit, BMI at each visit, total bodyweight at first visit, total bodyweight at each visit, and baseline RNFL (for non-RNFL outcomes). Models were developed independently for each of the visual outcomes using forward stepwise regression, with our null models adjusting for PCOS as our *a priori* hypothesis was that this factor was likely to have the greatest effect on outcomes.

For headache outcomes (headache frequency, migraine frequency, headache severity, and HIT-6), the effect of PCOS diagnosis was explored. Further analyses then explored important factors for each outcome exploring the effect of the same covariates as listed under visual outcomes in addition to personal migraine history and daily headache at registration (defined as headache days >28 days/month). Models were developed independently for each headache outcome. Comparable processes and models to those employed for visual outcomes were used for headache outcomes, with independent models developed for each headache outcome.

Locally weighted scatterplot smoothing (LOESS) graphs were created prior to regression analysis to ascertain any nascent trends and the association between variables. Regression models were fitted using lme4,[32] with an assuming that dependent variables were continuous. Average response values, an adjustment for time from registration to IIH: LIFE, and an interaction between variables of interest and time-point were estimated using population-level terms. As serial correlation in responses and the nesting of measurements from both eyes occurred, we included patient-level intercepts to address this. There were no diagnostic problems in model fitting. Covariates were transformed or centred around the median value as appropriate when added to models. Independent models were developed for each outcome. There was no imputation for missing data.

4.3.6 Patient and public involvement

All patients consented for anonymised use of their clinical data, as well as the additional questionnaire data, to be collected and analysed through the IIH: Life database. IIHUK, a national patient charity (Registered Charity in England and Wales no 1143522 & Scotland SCO43294) that supports carers and patients with IIH, endorsed and helped develop the IIH Life concept and questionnaires.

4.4 Results

490 patients with a confirmed diagnosis of IIH were recruited. Of these 9 were male and 83 did not elect to complete the PCOS questionnaire and were therefore excluded. A confirmed diagnosis of PCOS was made in 78/398 (20%) according to the Rotterdam criteria, whereas 35/398 (9%) met the NIH Criteria (Table 1). Isolated symptomatic hyperandrogenism occurred in 58/398 (15%), oligo/anovulation in 20/398 (5%) and polycystic ovaries in 29/398

(7%) patients (Figure 1). For the remainder of the analysis, whenever a diagnosis of PCOS is stated, this is by Rotterdam criteria.

Table 1 - Baseline table by PCOS diagnosis

	All	PCOS Rotterdam Yes	PCOS Rotterdam No	PCOS NIH Yes	PCOS NIH No
IIH patients (n)	398	78	320	35	363
Surgical intervention (n)	63	20	43	11	52
Age (Mean (SD)) (years)	31.1 (8.5)	30.5 (7.8)	31.2 (8.7)	30.7 (9.4)	31.1 (8.4)
Body mass index (Mean (SD)) (kg/m^2)	38.9 (8.9)	39.9 (9.5)	38.6 (8.8)	40.8 (9.9)	38.7 (8.8)
Diagnostic lumbar puncture opening pressure (Mean (SD)) (cmCSF)	35.3 (8.2)	35.3 (7.0)	35.3 (8.4)	36.7 (6.9)	35.1 (8.3)

Questionnaire data had missing data fields in 115 patients, however, 9 still met 2 of 3 diagnostic criteria (hyperandrogenism and polycystic ovaries). The most common missing data point being menstrual irregularity (n=102), polycystic ovaries (n=15) and hyperandrogenism (n=13).

BMI at the baseline visit was not significantly higher in the IIH patients with comorbid PCOS compared to those with IIH alone (39.9 (SD 9.5) and 38.6 (SD 8.8), p=0.25) (Table 1). Analogously, there were no significant differences in diagnostic lumbar puncture opening pressures readings between the cohorts (35.3 (SD 7.0) and 35.3 (SD 8.4) respectively, p>0.99) (Table 1).

4.4.1 Maternal health questionnaire

Data from the maternal health questionnaire, demonstrated that IIH patients with comorbid PCOS were more likely, than IIH patients without PCOS, to report difficulties conceiving (35/71 (49%) versus 43/279 (15%), respectively, p<0.0001). IIH patients with comorbid PCOS were also more likely than IIH patients without PCOS to requiring medical assistance to conceive (14/70 (20%) versus 13/288 (5%), respectively, p<0.001). Amongst the IIH patents with PCOS, there was a 3.2-fold increased risk for self-reported fertility issues and 4.4-fold increase of requiring medical assistance to conceive compared to those with IIH alone.

4.4.2 Vision measures

At baseline IIH patients with and without PCOS had similar visual acuity (LogMAR), visual fields (PMD), OCT measures of papilloedema (RNFL and TRT) and ganglion cell layer volume (Table 2).

Table 2 - Baseline and trajectory (change per month) for visual and headache outcomes by PCOS diagnosis through regression modelling

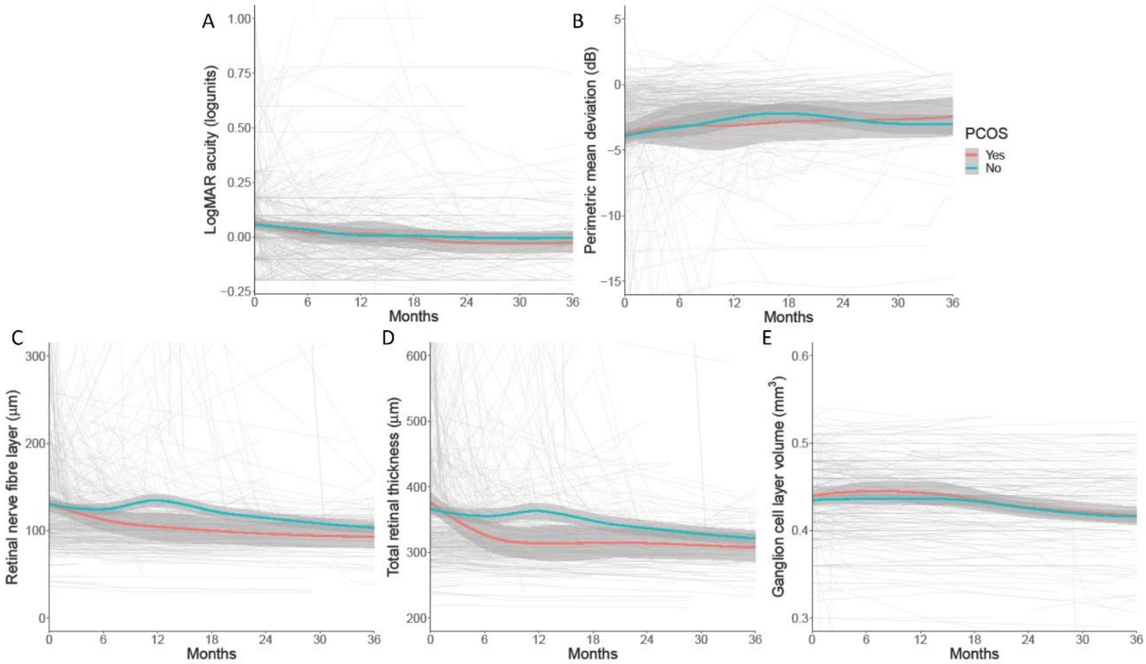
	Baseline estimate (units)	**Change per month. (units/month)**
LogMAR visual acuity, logunits		
PCOS	0.0704 (95% CI: 0.0027, 0.138)	-0.0019 (95% CI: -0.0043, 0.0005)
No PCOS	0.0109 (95% CI: -0.0197, 0.0415)	-0.0012 (95% CI: -0.0025, 0.0001)
Humphrey visual field perimetric mean deviation, dB		
PCOS	-2.88 (95% CI: -4.8, -0.96)	0.06 (95% CI: -0.05, 0.17)
No PCOS	-3.47 (95% CI: -4.29, -2.65)	0.06 (95% CI: 0.02, 0.1)
Global peripapillary retinal nerve fibre layer, µm		
PCOS	141.77 (95% CI: 120.36, 163.18)	-1.44 (95% CI: -2.67, -0.2)
No PCOS	137.76 (95% CI: 128.19, 147.33)	-1.34 (95% CI: -1.99, -0.69)
Global peripapillary total retinal thickness, µm		
PCOS	372.33 (95% CI: 342.33, 402.34)	-2.53 (95% CI: -3.95, -1.12)
No PCOS	366.15 (95% CI: 352.74, 379.56)	-2.22 (95% CI: -2.99, -1.46)
Macular ganglion cell layer volume, mm^3		
PCOS	0.446 (95% CI: 0.4252, 0.4668)	-0.0006 (95% CI: -0.0009, -0.0002)
No PCOS	0.438 (95% CI: 0.429, 0.447)	-0.0004 (95% CI: -0.0006, -0.0002)
Headache frequency, days/month		
PCOS	21.04 (95% CI: 16.68, 25.4)	-0.28 (95% CI: -0.5, -0.06)
No PCOS	18.45 (95% CI: 16.17, 20.74)	-0.11 (95% CI: -0.25, 0.03)

Migraine-like headache frequency, days/month		
PCOS	10.22 (95% CI: 6.51, 13.93)	-0.12 (95% CI: -0.29, 0.05)
No PCOS	8.81 (95% CI: 6.78, 10.84)	-0.09 (95% CI: -0.21, 0.03)
Headache severity, VAS 0-10		
PCOS	6.6 (95% CI: 5.52, 7.69)	-0.0077 (95% CI: -0.0511, 0.0357)
No PCOS	6.43 (95% CI: 5.82, 7.03)	-0.0039 (95% CI: -0.0722, 0.0643)
HIT-6, score 36-78		
PCOS	59.3 (95% CI: 55.6, 63.01)	0.07 (95% CI: -0.19, 0.33)
No PCOS	61.22 (95% CI: 58.69, 63.75)	0.01 (95% CI: -0.17, 0.18)

The visual outcomes for the IIH cohort with or without comorbid PCOS were then evaluated (Table 2, Figure 2). Visual acuity outcomes were similar between groups and demonstrated no significant changes over time (Figure 2A). PMD was similar between the groups showing a gradual improvement following diagnosis and plateauing after approximately 18 months (figure 2B).

Figure 2 - Longitudinal visual data from IIH patients categorised by PCOS diagnosis by Rotterdam criteria, and LOESS smoothers added to show trends across the categories.

- *a. LogMAR visual acuity (logunits)*
- *b. Perimetric mean deviation measured by Humphrey visual field 24-2 testing (dB)*
- *c. Retinal nerve fibre layer thickness measured on Optical Coherence Tomography (μm)*
- *d. Total retinal thickness of optic nerve head measured on Optical Coherence Tomography (μm)*
- *e. Macular ganglion cell layer volume measured on Optical Coherence Tomography (mm^3)*



Papilloedema measured by OCT analysis of the RNFL and TRT improved more rapidly in those with PCOS (RNFL, -0.134 µm/month (95% CI: -1.524, 1.255) and TRT, -0.315 µm/month (95% CI: 1.916, 1.286)) although this was not statistically significant (Figure 2C). In the first 12 months from baseline visit, those patients with comorbid PCOS showed a 20% improvement in TRT (-87.96µm (SD 99.23)) compared to those without PCOS +1.25% (+4.57µm (SD 42.85)), but the difference was not statistically significant (Figure 2D). Overall, the longer-term papilloedema outcomes were not significantly different in the IIH compared to the IIH with PCOS cohort. Macular ganglion cell layer volume did not differ between groups either at baseline or over longitudinal follow up. (Figure 2E).

4.4.3 Factors affecting visual prognosis

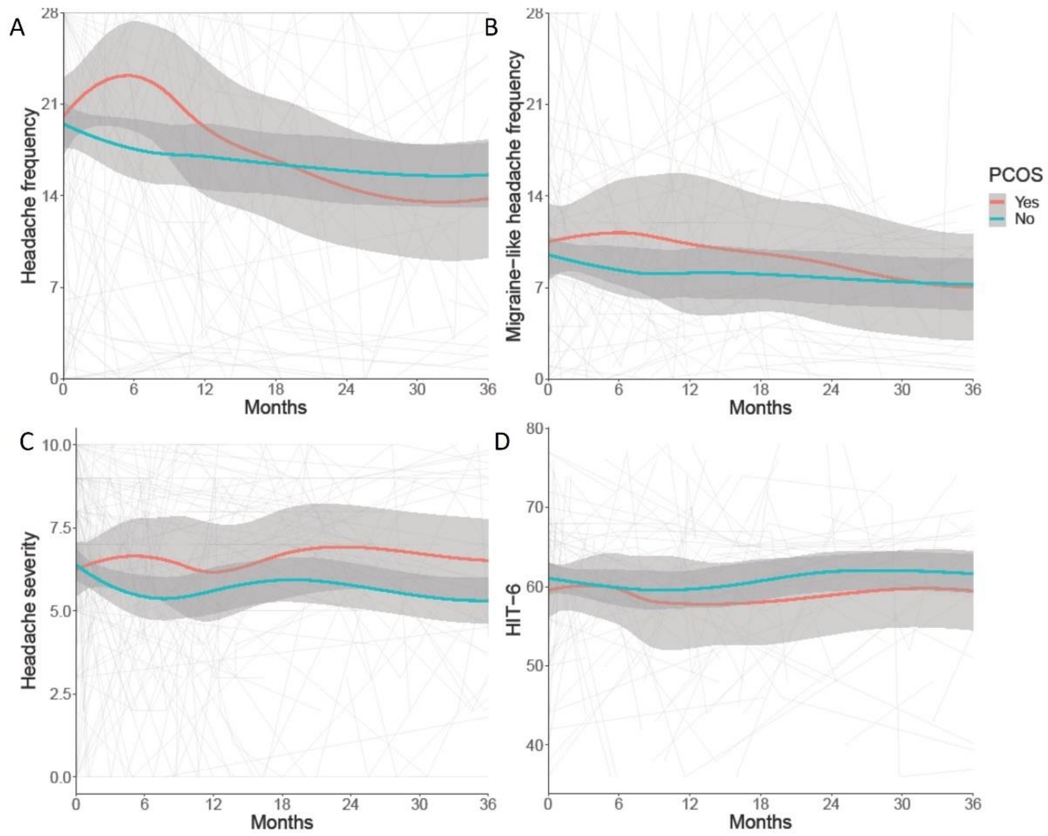
The factors affecting long term visual prognosis in IIH alone and IIH with comorbid PCOS were then evaluated. Papilloedema was significantly influenced by the duration of disease prior to the baseline visit (RNFL -0.34µm/month (95%CI: -0.559, -0.118) and TRT - 0.55µm/month (95%CI: -0.86, -0.25) whilst lumbar puncture opening pressure, BMI and total bodyweight did not. Of these factors only the duration of disease influenced the long term LogMAR acuity (0.0008 log units (95%CI: 0.0001, 0.0015). None of these factors impacted the long-term prognosis for visual field PMD although disease duration and first BMI trended towards a significant relationship. Likewise for macular ganglion cell layer volume there was a trend toward significance for total bodyweight.

4.4.4 Headache measures

At baseline both the IIH and the IIH with comorbid PCOS cohorts demonstrated high headache morbidity (headache frequency, migraine-like headache frequency, headache severity and quality of life (HIT-6)) (Table 2, Figure 3A, B, C and D).

Figure 3 - Longitudinal headache data from IIH patients categorised by PCOS diagnosis by Rotterdam criteria, and LOESS smoothers added to show trends across the categories.

a. *Headache frequency (days per month)*
b. *Migraine-like headache frequency (days per month)*
c. *Headache mean severity of predominant headache (0-10 numerical rating scale)*
d. *Headache Impact Test 6 (HIT6) (quality of life measure score 36-78)*



Headache outcomes (headache frequency, migraine-like headache frequency, headache severity and HIT-6 score) show marked variability and no statistically significant difference between cohorts at baseline or over the period of longitudinal follow up (Table 2, Figure 3).

Interestingly, headache frequency was observed to improve more rapidly in the PCOS cohort, after an initial peak at 6 months (Figure 3A). In the IIH cohort with comorbid PCOS, the headache frequency improved by 14% (-2.82 days/month (SD 18.16)) at 12 months and 54% (-10.87 days/month (SD 16.82)) at 24 months. This is in contrast to the IIH cohort without PCOS where headache frequency improved by 4% (-0.65 days/month (SD 9.17)) at 12 months and 24% (-4.28 days/month (SD 9.78)) at 24 months.

4.4.5 Factors affecting headache outcomes

The factors influencing long term headache prognosis were then evaluated. The only factor influencing long term headache prognosis in both the IIH and IIH with PCOS cohorts was the occurrence of daily headache at baseline. Personal migraine history, family history of migraine, disease duration, lumbar puncture, BMI, and total bodyweight did not significantly impact headache prognosis in either cohort.

4.5 Discussion

Whilst the comorbid occurrence of PCOS in IIH patients is well known, the clinical impact of a PCOS diagnosis in those with IIH has not yet been evaluated. This is the first prospective longitudinal study of IIH patients with PCOS compared to those with IIH alone. The study provides two key messages. Patients with IIH and PCOS report higher infertility. Comorbid PCOS in IIH patients does not adversely impact long term vision or headache prognosis.

IIH has been shown to be associated with decreased fertility [25] and infertility has been established in PCOS (although prevalence is highly variable, as it is in the general population).[23, 33-35] This study adds to the literature by illustrating that dual pathology (IIH and PCOS) may be associated with increased fertility difficulties. The causes are likely multifactorial, but it is plausible that hyperandrogenism, insulin resistance and obesity, factors common to both PCOS and IIH may be important contributors.[25] Our results have implications for clinical practice as they suggest that in those with IIH should have PCOS identified as they may benefit from gynaecological or endocrinological specialist management. Discussing fertility with patients may also include that pregnancy does not adversely impact visual outcomes in IIH in those with well controlled IIH at the time of conception (particularly in those who have resolved papilloedema).[36]

The OCT imaging measures of papilloedema demonstrated gradual recovery over time in IIH.[37] In this study a comorbid diagnosis of PCOS did not significantly affect visual outcomes in IIH patients. Obesity is common in both IIH and PCOS. In this study, those with IIH and PCOS had similar baseline BMI to those with IIH alone suggesting that PCOS does not exacerbate the obesity phenotype in IIH. Weight loss is the only current disease modifying therapy for IIH,[37-39] and has been shown to reduce papilloedema and ICP.[40-42] Weight loss is also beneficial in PCOS, improving reproductive, metabolic and psychological features.[24, 33, 43] There is evidence that the addition of metformin in IIH patients with PCOS could enhance weight loss,[44] so could be considered. It is not known if patients with PCOS and IIH experience more difficulty achieving and maintaining weight loss. Specialist support to assist weight loss is advised in IIH irrespective of a diagnosis of PCOS.[39]

Headache morbidity in the study was high and predominantly migraine-like in character, as previously described.[4, 45-48] Headaches are a dominant driver of reduced quality of life in IIH and appear to be more refractory to preventive treatment than migraine headaches.[49] Additionally, medication overuse headache is common in IIH with high use of opiates.[6] Obesity and metabolic syndrome exacerbate migraine headaches and hence we hypothesised that co-existing PCOS in IIH patients could exacerbate headache morbidity as a result of compounding the adverse metabolic phenotype. Additionally, increased headache due to migraine has been noted in patients with PCOS.[50, 51] However, we did not find that PCOS was associated with a worse headache prognosis in IIH patients. The headache morbidity was high in the entire IIH cohort, both with and without PCOS. Headache showed little improvement over time and large variability within the IIH population studied. Ongoing severe headaches in IIH are well established and can continue even after papilloedema and ICP resolve as persistent post-IIH headaches.[4] In these case CGRP monoclonal antibody therapies have shown promise for managing headaches in IIH.[47, 48]

This study has also highlighted that a diagnosis of PCOS in IIH patients is common, occurring in 20% using Rotterdam criteria (9% by NIH criteria). This is in keeping with the literature which reported 15% by NIH criteria.[7] It is possible that previous studies reporting up to 57% of comorbid POCS and IIH were an overestimate.[26, 27] Regardless of the discrepancies in published results, the prevalence rate of PCOS in IIH remains higher than that observed in the general population (8-13%).[7, 33, 52] A recent large population study showed a 1.5-fold increased prevalence of comorbid PCOS in IIH patients over age and BMI matched controls.[5, 6]

As with any study there are limitations. This prospectively collected real-world cohort study was based in a tertiary referral centre and therefore a number of patients were initially assessed at other referring hospitals. However, in all cases the diagnosis was confirmed at the tertiary referral centre. This contributed to baseline visits occurring after different lengths of disease duration (documented as time from diagnostic lumbar puncture to initial visit in the tertiary referral centre). Time to diagnosis was however, adjusted for in the regression modelling. Although the study aimed to capture all outcomes for consecutive cases, patient preference meant some data were inevitably missing. As per clinical practice, some patients were lost to follow-up and others discharged (for example due to disease remission or referral to alternative hospitals). We cannot exclude the possibility that the results were influenced by those lost to follow-up, nonetheless, this is a limitation inherent to longitudinal studies of this kind. There was also missing questionnaire data, hence, it cannot be excluded that a few PCOS cases might have not been captured. The use of the PCOS questionnaire was an efficient means to identify as many undiagnosed PCOS cases as possible in this IIH cohort, which is important as PCOS remains undiagnosed in the majority of cases (approximately 69% according to published literature).[34] Patients did not routinely undergo ovarian ultrasound as this is invasive and instead were reliant on patient reporting however where clinically and symptomatically indicated this would have been done either in the community or through endocrinology. The missing data associated with menstrual irregularity may reflect a reluctance to provide personal information seemingly unrelated to IIH headaches and vision, and this should be addressed in future studies. Pragmatically we have used OCT imaging outcome measures that are available through proprietary software.

We did not make account of anatomical differences (such as myopia and hypermetropia) that may alter optic nerve head and retinal measurements due to the size of this cohort. In future studies accounting for these changes and indeed the presence of peripapillary hyperreflective ovoid mass structures would be important as they could influence the relationship with other outcomes. Potential other work that is important would be to consider employing analogous analyses to assess whether concomitant PCOS and IIH have adverse impacts on cardiovascular morbidity, cognitive function, and weight loss methods.

4.6 Conclusion

The study demonstrated that comorbid PCOS in IIH is common (20%) and is associated with higher infertility. Our data suggests that a diagnosis of PCOS in those with IIH does not exacerbate long term vision or headache prognosis. It remains unknown if PCOS in IIH impacts long term risk of cardiometabolic complications and weight management.

4.7 Supplementary information

4.7.1 Polycystic ovarian syndrome questionnaire

Idiopathic intracranial hypertension can be associated with other hormonal conditions. By answering the questions below, it can help guide us as to whether this might be the case. Your medical team may discuss this further with you.

Menstrual Cycle

Do you have regular periods? Yes □ No□ N/A on contraception □

If No, do you get less than 9 periods in a year? Yes □ No□

Body Hair

Do you have excess body hair? Yes □ No□

Polycystic ovaries

Have you been found to have Polycystic ovaries? Yes □ No□

Have you been diagnosed with Polycystic ovary syndrome? Yes □ No□ Unsure □

If you have any questions having filled out the above questionnaire, please ask your medical team.

4.7.2 Maternal health questionnaire

Pregnancy and Fertility

Number of previous pregnancies

Number of previous miscarries

Have you postponed plans to get pregnant due to IIH? Yes □ No□

Have you had difficulties getting pregnant? Yes □ No□

Have you ever required to medical help to get pregnant? Yes □ No□

Has IIH influenced your decision to breastfeed? Yes □ No□

Has your choice of contraception been affected by IIH? Yes □ No□

If yes, has contraception stopped? Yes □ No□

Has contraception altered? Yes □ No□

Has pregnancy resulted from inadequate contraception due to changes made by your IIH?
Yes □ No□

4.7.3 Supplementary table - Visual outcomes according to the presence of PCOS by Rotterdam criteria from LOESS smoothers

		Months			
		0	12	24	36
LogMAR visual acuity, logunits (mean (SD), n)	PCOS	0.060 (0.124), 64	-0.008 (0.129), 24	-0.025 (0.109), 21	-0.028 (0.124), 16
	No PCOS	0.055 (0.192), 334	0.010 (0.186), 140	-0.003 (0.149), 86	-0.008 (0.169), 57
Humphrey visual field perimetric mean deviation, dB (mean (SD), n)	PCOS	-3.73 (3.52), 67	-3.04 (3.76), 24	-2.68 (3.24), 19	-3.05 (4.12), 12
	No PCOS	-3.92 (3.80), 327	-2.49 (4.13), 129	-2.57 (3.25), 82	-3.43 (3.39), 47
Global peripapillary retinal nerve fibre layer, µm (mean (SD), n)	PCOS	131.67 (39.72), 66	105.87 (41.18), 26	96.65 (34.34), 21	94.18 (36.92), 14
	No PCOS	130.85 (43.19), 312	130.63 (42.15), 129	113.68 (31.96), 77	104.07 (33.21), 48
Global peripapillary total retinal thickness, µm (mean (SD), n)	PCOS	377.73 (66.79), 66	317.14 (72.80), 27	314.55 (57.93), 22	308.56 (62.07), 14
	No PCOS	366.93 (73.56), 310	358.61 (71.51), 129	336.03 (55.05), 81	320.18 (57.01), 49
Macular ganglion cell layer volume, mm^3 (mean (SD), n)	PCOS	0.440 (0.030), 65	0.444 (0.031), 25	0.428 (0.026), 21	0.415 (0.028), 13
	No PCOS	0.435 (0.038), 303	0.437 (0.037), 120	0.424 (0.028), 75	0.413 (0.030), 48

4.7.4 Supplementary table - Visual and headache outcomes by NIH criteria

	Baseline estimate (units)	**Change per month (units/month)**
LogMAR visual acuity, logunits		
Confirmed PCOS by NIH criteria	0.0429 (95% CI: -0.0475, 0.1334)	-0.0022 (95% CI: -0.0048, 0.0005)
No PCOS by NIH criteria	0.0184 (95% CI: -0.0111, 0.048)	-0.0011 (95% CI: -0.0024, 0.0001)
Humphrey visual field perimetric mean deviation, dB		
Confirmed PCOS by NIH criteria	-3.66 (95% CI: -6.27, -1.04)	0.06 (95% CI: 0.02, 0.1)
No PCOS by NIH criteria	-3.35 (95% CI: -4.14, -2.57)	0.07 (95% CI: -0.06, 0.2)
Global peripapillary retinal nerve fibre layer, µm		
Confirmed PCOS by NIH criteria	145.28 (95% CI: 116.49, 174.07)	-1.26 (95% CI: -2.62, 0.1)
No PCOS by NIH criteria	137.76 (95% CI: 128.57, 146.95)	-1.4 (95% CI: -2.04, -0.76)
Global peripapillary total retinal thickness, µm		
Confirmed PCOS by NIH criteria	374.76 (95% CI: 334.18, 415.33)	-2.06 (95% CI: -3.64, -0.49)
No PCOS by NIH criteria	366.49 (95% CI: 353.63, 379.36)	-2.36 (95% CI: -3.1, -1.61)
Macular ganglion cell layer volume, mm^3		
Confirmed PCOS by NIH criteria	0.448 (95% CI: 0.4203, 0.4757)	-0.0005 (95% CI: -0.0009, -0.0002)
No PCOS by NIH criteria	0.4384 (95% CI: 0.4297, 0.4471)	-0.0004 (95% CI: -0.0006, -0.0002)
Headache frequency, days/month		
Confirmed PCOS by NIH criteria	19.36 (95% CI: 13.62, 25.1)	-0.21 (95% CI: -0.46, 0.04)
No PCOS by NIH criteria	18.96 (95% CI: 16.79, 21.14)	-0.14 (95% CI: -0.27, 0)
Migraine-like headache frequency, days/month		
Confirmed PCOS by NIH criteria	7.79 (95% CI: 2.95, 12.63)	-0.05 (95% CI: -0.24, 0.15)
No PCOS by NIH criteria	9.35 (95% CI: 7.43, 11.27)	-0.11 (95% CI: -0.22, 0.01)

Headache severity, VAS 0-10		
Confirmed PCOS by NIH criteria	6.98 (95% CI: 5.45, 8.51)	-0.0171 (95% CI: -0.0974, 0.0633)
No PCOS by NIH criteria	6.4 (95% CI: 5.83, 6.96)	-0.005 (95% CI: -0.0463, 0.0364)
HIT-6, score 36-78		
Confirmed PCOS by NIH criteria	57.95 (95% CI: 52.79, 63.12)	0.15 (95% CI: -0.14, 0.43)
No PCOS by NIH criteria	61.19 (95% CI: 58.9, 63.48)	-0.01 (95% CI: -0.18, 0.16)

4.8 References

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Chapter 5: Impact of pregnancy in IIH

Chapter 5.1: Impact of IIH on pregnancy (Thaller. BJOG. 2022)

Manuscript title:

Idiopathic intracranial hypertension: evaluation of births and fertility through the hospital episode statistic dataset.

Published:

Thaller M, Mytton J, Wakerley BR, Mollan SP, Sinclair AJ. Idiopathic intracranial hypertension: Evaluation of births and fertility through the Hospital Episode Statistics dataset. BJOG. 2022 Nov;129(12):2019-2027. doi: 10.1111/1471-0528.17241.

Involvement:

I was involved in data acquisition, data analysis, data interpretation, writing first manuscript and critical revision of the manuscript.

5.1.1 Abstract

Objective: Idiopathic intracranial hypertension (IIH) predominantly affects women of reproductive age with obesity and women have a distinct profile of hyperandrogenism and insulin resistance. Polycystic ovary syndrome (PCOS) has an established adverse fertility phenotype that typically affects obese women. As IIH may impact reproductive health, we sought to evaluate fertility, gestational complications, and pregnancy outcome in IIH.

Design: Prospective cohort study from English Hospital Episode Statistic dataset

Setting: English hospitals, United Kingdom

Population: Women aged 18-45 years seen in English hospitals between 1st April 2002 and 31st March 2019. Patients were required to have an IIH diagnosis and were compared to those with PCOS and general population female controls.

Main outcome measures: Pregnancies resulting in live births, complications of gestational diabetes and pre-eclampsia, and method of delivery.

Results: Data was collected from 17587 IIH, 199633 PCOS, and 10947012 general population women. The live birth rate, adjusted for age, was significantly lower amongst women with IIH (54.1%) compared to PCOS (67.9%), $p<0.0001$ and general population (57.7%), $p<0.0001$. Pre-eclampsia and gestational diabetes risks were higher following a diagnosis of IIH (5.3-fold and 2.7-fold respectively, $p<0.0001$) compared to the general population controls. Following a diagnosis of IIH, elective caesarean section rates were more than twice that of general population (OR 2.4) and prior to a diagnosis of IIH (OR 2.2).

Conclusions: This data indicates there are lower age-adjusted total pregnancy rates, increased risk of pre-eclampsia and gestational diabetes and a doubling of elective caesarean section rates in those with a diagnosis of IIH.

5.1.2 Introduction

Idiopathic intracranial hypertension (IIH) is a disorder of raised intracranial pressure typically manifesting in reproductive aged women with obesity. The incidence in women has increased by over 350% in the last decade to 9.3 per 100,000.[1-4] Typical manifestations of the disease are debilitating headaches and visual loss,[5, 6] with many having cognitive dysfunction[7] and obstructive sleep apnoea.[8] More recently, evidence is pointing towards a condition of metabolic dysregulation.[9] IIH patients have preferentially distributed truncal adiposity[10] as well as increased risk of cardiovascular disease[3] and insulin resistance in excess to that driven by obesity.[11] IIH adipocyte function demonstrates a distinct transcriptional profile with adipocytes programmed for lipogenesis and weight gain.[11]

IIH patients have a unique hormone signature characterised by androgen excess with increased serum testosterone, and increased CSF testosterone and androstenedione, which has been found to be distinct to that observed in polycystic ovarian syndrome (PCOS) and simple obesity.[12] IIH is phenotypically similar to PCOS, with both conditions typically occurring in women of reproductive age with obesity. A community based PCOS study found a self-reported association of a 15-fold increase in infertility.[13] The impact of IIH on reproductive health is not known and is an area declared as a high priority by patients.[14] We hypothesised that fertility may be reduced in IIH, there may be an increase in the metabolic complications of gestational diabetes and pre-eclampsia, and that there may be an increased surgical delivery rate. The aims of this study were to evaluate the impact of a diagnosis of IIH on women's fertility rates, pregnancy complications (gestational diabetes mellitus and pre-eclampsia) and method of delivery using the English National Health Service (NHS) Hospital Episode Statistics (HES) dataset.

5.1.3 Methods

5.1.3.1 Study design

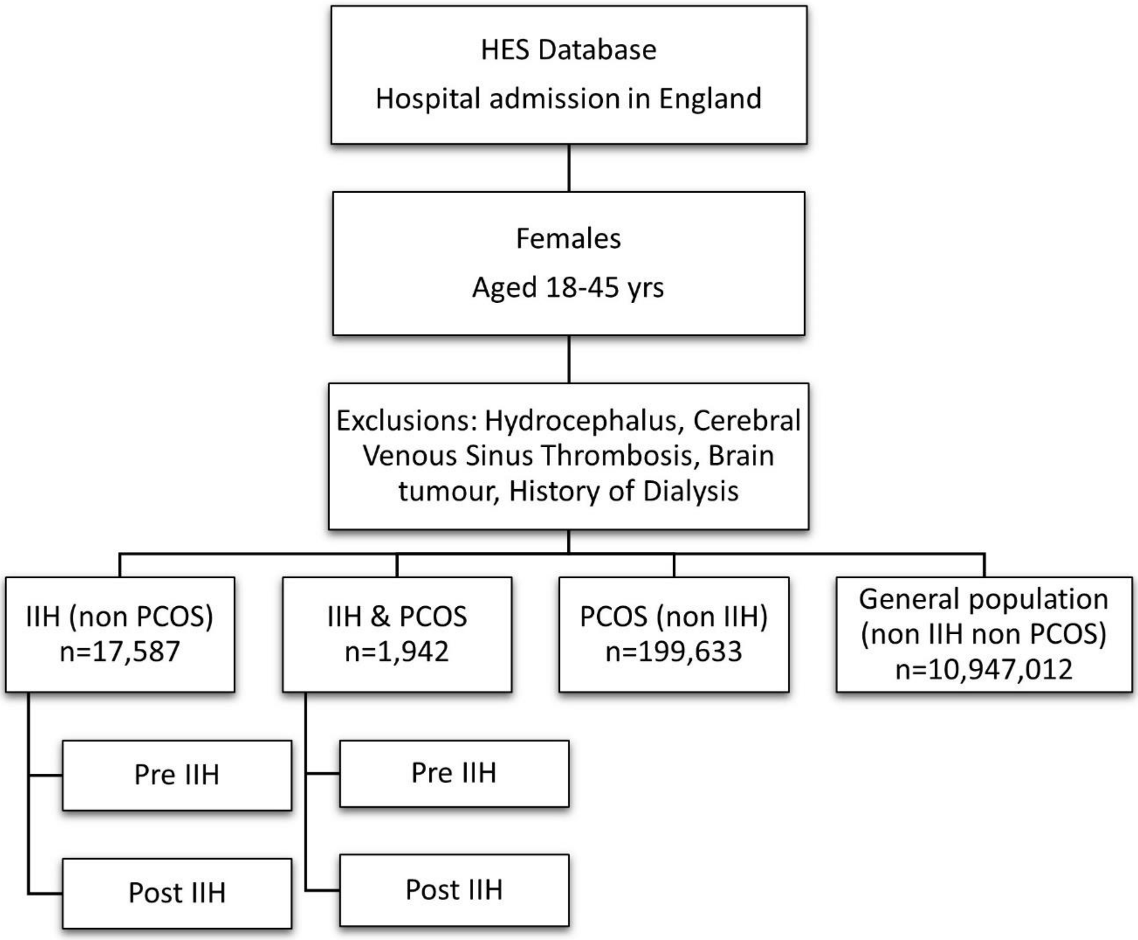
Data were obtained from the English National Health Service (NHS) Hospital Episode Statistics (HES) dataset, a registered administrative dataset. All women, aged between 18 and 45 years, admitted to all hospitals (both private and public) in England between 1st April 2002 and 31st March 2019 were selected. Clinical episodes are defined as admissions to ambulatory care (i.e. for lumbar punctures), emergency room visits and inpatient care. Each clinical episode taking place in National Health Service (NHS) hospitals or NHS commissioned activity in the independent sector was recorded. Each record was anonymised and comprised specific demographic details of the admitted patient including, age group, gender, ethnicity, and geographical information such as the location of treatment and domicile. Coding was either ICD-10 (International Classification of Diseases, tenth revision)[15] or OPCS-4 (Office of Population, Censuses and Surveys Classification of Interventions and Procedures, 4th revision) codes.[16] Body Mass Index (BMI) is not recorded within HES data.

University Hospitals Birmingham NHS Foundation Trust possesses a Data Re-Use Agreement for the interrogation of the HES. The research involved non-identifiable information, previously collected during patient care and available for public use. Where there are less than 5 people in any category the results were not made available to ensure anonymisation is upheld. University Hospitals Birmingham National Health Service Foundation Trust approved this study (Registered Code, Clinical Audit Registration and Management System: CARMS-17157).

A diagnosis of IIH in the United Kingdom is made by the hospital specialist. Typically, they should follow the consensus guidelines for this diagnosis which include the presence of papilloedema; normal neurologic examination except for cranial nerve abnormalities; normal neuroimaging (except for the accepted signs of raised intracranial pressure) including venography; a raised lumbar puncture opening pressure (≥25 cm cerebrospinal fluid (CSF) in adults); and with normal CSF constituents.[6] This diagnosis would be coded by the administrative staff and transmitted to the HES data set on a yearly basis. While the inclusion criteria for diagnosis details to 31st March 2019, pregnancy outcome data was extracted up to 31st March 2020, so that all participants had at least one year follow up.

Three further groups were extracted for comparison purposes with the same age range and time frame; women diagnosed with PCOS and no IIH (PCOS), women with both IIH and PCOS diagnoses (IIH & PCOS), and women admitted for any other reason without IIH and without PCOS (general population) (Figure 1). Exclusion criteria were applied to help refine the data and ensure against miscoding of secondary causes of raised intracranial pressure such as brain tumours, hydrocephalus, and cerebral venous sinus thrombosis. Due to the very high number of admitted patient care episodes and comorbidities we excluded those with a history of dialysis. These were likely to represent a secondary cause of raised intracranial pressure and the high admission rates would have potentially biased the results. Those who resided outside of England or whose residence was unknown were also excluded as accurate longitudinal patient tracking was not always possible. Date of diagnosis for IIH (first coded) was used to enable comparison of data before (pre-IIH) and after IIH diagnosis (post-IIH). Patients were not directly involved in this study.

Figure 1 - CONSORT diagram for patient groups included in this study.



5.1.3.2 Data collection

All coded pregnancies, births, and losses (miscarriages and stillbirths) were collected. Supplementary Table 1 states the ICD-10 or OPCS-4 codes included and excluded from this study. The data was analysed by age at pregnancy and number of pregnancies/births/losses per female. Fertility was evaluated using a surrogate measure of the number of women without any pregnancies during this study period as well as the total fertility rate, which is age adjusted and based on the age specific fertility rate.

Gestational complications of gestational diabetes (GDM) and pre-eclampsia were compared, with gestational hypertension without proteinuria (ICD10 O13) alone excluded from the latter. Delivery method (normal live delivery, assisted live delivery, emergency, or elective caesarean section (CS)) and number of births were also retrieved. The data was divided by the occurrences pre or post IIH diagnosis for both the IIH and IIH & PCOS groups. The codes used for inclusion, exclusion and outcomes are stated in Supplementary Table 1.

5.1.3.3 Statistical analysis

The data were initially explored through descriptive analysis of variables using *t* tests for quantitative variables and McNemar's *binomial* tests for categorical variables to compare different groups. Poisson regression analysis was used to model the total number of pregnancies per patient with adjustments for age at first pregnancy and timing of IIH diagnosis in relation to their first pregnancy. Patients were included in this analysis if they had at least one pregnancy. Odds ratios were calculated using Woolf logit method[17] through logistic regression to enable comparison in complication and method of delivery outcomes between the IIH, PCOS and general population groups.

All statistical analyses were conducted using GraphPad Prism™ (version 9.1.0, USA) with level of statistical significance set a $p<0.5$.

5.1.4 Results

5.1.4.1 Demographics

Pregnancy data was analysed for 17587 patients diagnosed with IIH, 199633 with PCOS, 1942 IIH&PCOS, and 10947012 in the general population. In the general population, the incidence of IIH was 3.1, PCOS was 44.8, and IIH with comorbid PCOS was 0.36 per 100000 women (2018-2019). Mean age at pregnancy was similar post IIH diagnosis, PCOS and general populations (Table 1).

Table 1 - Demographics, pregnancy complications and assisted delivery method. The complication and assisted delivery percentages are of those who had at least one pregnancy.

		IIH		PCOS	IIH & PCOS		General population
		Pre IIH	Post IIH		Pre IIH	Post IIH	
Demographics	Females 18 - 45 years, number	17587		199633	1942		10947012
	Pregnancies, number	12419	7261	277067	1262	918	11848846
	Pregnancy losses, number (%)	1017 (8.2%)	548 (7.5%)	35177 (12.7%)	160 (12.7%)	98 (10.7%)	962828 (8.1%)
	Females with zero pregnancies, number (%)	10607 (60.3%)	12774 (72.6%)	59860 (30.0%)	1221 (62.9%)	1319 (67.9%)	4464198 (40.8%)
	Age at pregnancy, mean (SD)	25.0 (5.1)	28.6 (5.0)	29.0 (5.5)	24.7 (4.8)	29.4 (4.9)	29.6 (5.8)

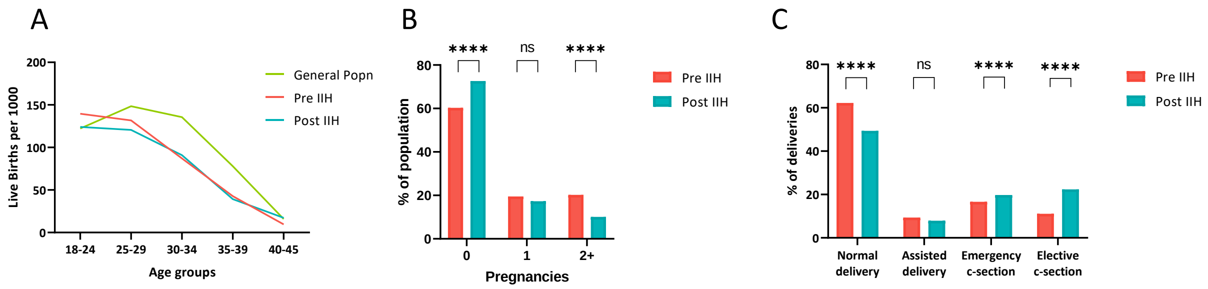
Complications	Gestational diabetes, number (%)	310 (4.4%)	591 (12.3%)	16444 (11.8%)	59 (8.2%)	128 (20.6%)	322596 (5.0%)
	Pre-eclampsia, number (%)	290 (4.2%)	570 (11.8%)	6055 (4.3%)	41 (5.7%)	59 (9.5%)	161546 (2.5%)
Assisted Delivery	Assisted vaginal delivery, number (%)	1067 (9.4%)	528 (7.9%)	29405 (12.2%)	122 (10.2%)	57 (6.9%)	1302447 (12.0%)
	Elective c-section, number (%)	1266 (11.1%)	1500 (22.3%)	30275 (12.5%)	125 (11.3%)	224 (27.3%)	1171464 (10.8%)
	Emergency c-section, number (%)	1900 (16.7%)	1325 (19.7%)	44231 (18.3%)	199 (18.1%)	199 (24.2%)	1615195 (14.8%)

5.1.4.2 Fertility and pregnancy

During the study, 19680 pregnancies were reported in women who were diagnosed with IIH. This compared with 277067 in PCOS, 2180 in IIH+PCOS, and 11848846 in the general population. Pregnancy losses (miscarriage or stillbirth) were reported in 1565 IIH, 35177 PCOS, 258 IIH+PCOS, and 962828 in the general population.

In the childbearing ages between 25 and 39 years, the age-specific fertility rate (Figure 2A) was lower in IIH, regardless of whether pre or post IIH diagnosis, compared to the general population. After adjusting for age at first pregnancy confounder, through Poisson regression modelling, the IIH pregnancy rate was lower in IIH than general population (incidence rate ratio (IRR) 0.53 (0.52-0.54, p <0.001)), reflecting that this is not an age effect. The predicted total number of pregnancies in IIH was 0.95 (0.94-0.96) in contrast to 1.80 (1.80-1.80) for the general population.

Figure 2 – A: Age specific fertility rate in IIH (pre and post diagnosis) and general population in 2015. B: Impact on pregnancy numbers following an IIH diagnosis. C: Impact on delivery method following an IIH diagnosis. **** = McNemar p<0.0001, ns = non-significant.



Following IIH diagnosis, the number of pregnancies decreased by 41.5% from 12419 to 7261 (Table 1). Following diagnosis of IIH in patients with comorbid PCOS pregnancies decreased by 27.2% from 1262 to 918. Following a diagnosis of IIH women were less likely to have a further pregnancy compared to prior to an IIH diagnosis (IRR 0.83 (0.80-0.86, <0.001)). The number of women with ≥2 pregnancies post IIH diagnosis were lower (1775, 10.1%) than prior to a IIH diagnosis (3553, 20.2%) (Figure 2B) despite a similar mean age pre and post IIH diagnosis (Table 1). Infertility, inferred by the absence of pregnancies, occurred in 60.3% of women pre-IIH diagnosis and increased to 72.6% (p<0.0001) post-IIH diagnosis (Figure 2B) (Table 1), in comparison to 40.8% of the general population.

5.1.4.3 Timing of IIH diagnosis and pregnancy

We explored the timing of IIH diagnosis and pregnancy. Where there was a pre-IIH diagnosis pregnancy, the last pregnancy occurred more than three years before in 62.5%. Where IIH was diagnosed during pregnancy, this was predominantly in the second and third trimester (1035 (5.9%) of IIH patients overall) with a reduced diagnostic proportion (219 (1.2%)) during the immediate 6 months post-partum.

5.1.4.4 Complications

Gestational diabetes was higher in IIH (12.3%) and PCOS (11.8%) compared to the general population (5.0%) (Table 1). In those prior to a diagnosis of IIH, gestational diabetes was lower (4.4%). The risk of developing gestational diabetes was higher following an IIH diagnosis (OR 3.01 (2.61-3.48), p<0.0001) and when compared to the general population (OR 2.67 (2.45-2.91), p<0.0001) (Figure 3), but no different to patients with PCOS (p=0.2751).

Figure 3 - Odds Ratio (OR), 95% confidence interval (CI), p-values (p) post IIH diagnosis compared to A: General population, B: PCOS and C: Pre-IIH.

A

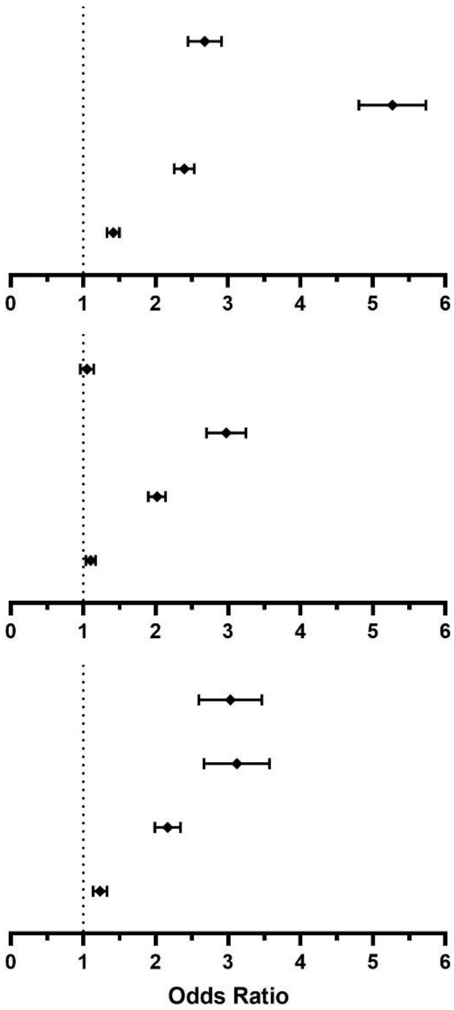
	OR	95% CI	P
Gestational Diabetes	2.67	2.45 - 2.91	<0.0001
Pre eclampsia	5.26	4.82 - 5.74	<0.0001
Elective C-section	2.39	2.26 - 2.54	<0.0001
Emergency C-section	1.42	1.33 - 1.50	<0.0001

B

	OR	95% CI	P
Gestational Diabetes	1.05	0.96 - 1.15	0.275
Pre eclampsia	2.97	2.71 - 3.25	<0.0001
Elective C-section	2.02	1.90 - 2.14	<0.0001
Emergency C-section	1.10	1.04 - 1.17	0.002

C

	OR	95% CI	P
Gestational Diabetes	3.01	2.61 - 3.48	<0.0001
Pre eclampsia	3.10	2.68 - 3.59	<0.0001
Elective C-section	2.16	1.99 - 2.35	<0.0001
Emergency C-section	1.23	1.14 - 1.33	<0.0001



Pre-eclampsia was higher in IIH (11.8%), compared to general population (2.5%), PCOS (4.3%) and in those prior to a diagnosis of IIH (4.2%). The probability of developing pre-eclampsia in IIH was higher than the general population (OR 5.26 (4.82-5.74), p<0.0001), PCOS (OR 2.97 (2.71-3.25), p<0.0001) and compared to those prior to a diagnosis of IIH (OR 3.10 (2.68-3.59), p<0.0001) (Figure 3).

5.1.4.5 Delivery method

Rates of assisted vaginal delivery, elective and emergency caesarean section were evaluated (figure 2C). We found that occurrence of elective caesarean section doubled following IIH diagnosis (11.1% to 22.3%) (Figure 2C) with the probability being statistically significantly higher (OR 2.16, 95% CI: 1.99-2.35, p<0.0001). Additionally, the probability of elective caesarean section was statistically significantly higher compared to the general population (OR 2.39, 95% CI: 2.26-2.54, p<0.0001) and PCOS groups (OR 2.01, 95% CI: 1.90-2.14, p<0.0001) (Figure 3). The highest probability of elective caesarean section was amongst those with both IIH and PCOS (OR 3.12, 2.67-3.64, p<0.0001). Emergency caesarean section was also consistently higher in patients with IIH (Figure 3).

5.1.5 Discussion

5.1.5.1 Main findings

This large observational study found that patients with IIH had statistically significantly fewer pregnancies, more pregnancy related complications (gestational diabetes and pre-eclampsia) and were more likely to have caesarean sections. Although fertility normally reduces with increased age, this study indicates that age specific fertility rates at the vast majority of time points were lower in IIH both pre- and post-diagnosis compared to the general population.

5.1.5.2 Interpretation

This is the first study to report that people with IIH may have reduced fertility. The cause of this reduction is likely to be multifactorial. Obesity is known to affect fertility.[10, 18, 19] It increases the risk of menstrual irregularities typically as a result of anovulation.[19] This is through decreased luteinizing hormone pulse amplitude [20], which can lead to abnormal oocyte recruitment and quality.[21] Circulating adipokines secreted by adipose tissue, i.e. leptin and TNF-α, have been shown to vary over the menstrual cycle[22-24] and influence multiple levels of the hypothalamic-pituitary-gonadal axis[18-20] and therefore prolonged hyperleptinaemic states may impact fertility.[24] Hyperleptinaemia in excess to that driven by obesity has been shown in IIH[11] and therefore may influence fertility in IIH. These findings are unlikely to be driven by obesity alone as we have compared them to a hospital based PCOS population that also is typically associated with obesity.

Metabolic syndrome is associated with older age at pregnancy and infertility, independent of obesity.[25] IIH is a condition characterised by metabolic dysfunction with truncal adiposity as well as insulin resistance and double the risk of cardiovascular disease in excess to that driven by obesity.[3, 11]

The hyperandrogenism in IIH [12] may also contribute to reproductive dysfunction as it is hypothesised to in PCOS.[13, 26] In PCOS reproductive function improves with dedicated treatment and further investigation for people with IIH may be benefical.[27, 28] Treating metabolic perturbations with Glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to improve menstrual regularity and increase fertility rates in women with PCOS and obesity.[29] GLP-1 receptor agonists are emerging as a potential treatment option for IIH with pre-clinical data demonstrating their ability to reduce ICP and clinical efficacy data emerging.[30, 31]

A change in behaviour in people with a new diagnosis of IIH may contribute to the observed reduction in overall pregnancies and multiple parity. Behaviour change may be impacted by health professional interactions and advice. There could be concerns that pregnancy could drive weight gain, a known risk factor for exacerbation of IIH.[32, 33] Targeting disease remission prior to conception is recommended and hence people with IIH may wish to delay their pregnancy until this has been achieved.[33] Indeed, medicines used to lower intracranial pressure have potential teratogenic risks (acetazolamide or topiramate) which may alter family planning decisions following a diagnosis.[6, 33]

We observed higher pregnancy related complications in patients with IIH. This in part may be explained by pre-pregnancy obesity and excessive weight gain in early pregnancy, which are known to increase the risk of gestational diabetes and preeclampsia.[34] The increase in gestational diabetes and pre-eclampsia in IIH is likely to be driven by metabolic dysregulation although the precise mechanism is yet to be established. Metabolic syndrome is an established risk factor for gestational diabetes and pre-eclampsia.[35] When compared to PCOS, the gestational diabetic risk were not statistically significantly different and this likely reflects similar metabolic profiles, including a hyperandrogenic component, independent of obesity.[36] Pre-eclampsia in IIH however warrants further investigation to establish the pathophysiological process, as this risk appears to be greater in people with IIH as compared to those with PCOS. The increased risk of complications in IIH are of clinical significance as they highlight the need for increased surveillance during pregnancy.[6] Pregnancy losses in IIH were comparable to the general population, unlike in PCOS where it is elevated (Table 1) and this reflects previous PCOS literature with a reported OR of 1.71 (1.19-2.45).[36] This should be reassuring to IIH patients that there is no increased risk.

Maternal obesity is known to increase operative delivery rates[37] and excessive gestational weight gain increases the caesarean probability by 30%.[38] Elective and emergency caesarean sections were statistically significantly more likely to occur in IIH as suggested by previous literature.[2] The doubling of the elective rates is of clinical significance as these are not due to perinatal complications but rather a planned decision prior to labour. It remains unclear whether patient and doctor concerns about normal vaginal delivery in IIH play an important role. However, raised BMI, as a cause for this increased caesarean section rate is unlikely to be the dominant driver given higher rates than the phenotypically similar PCOS (Figure 3B). The literature reports that caesarean section rates are noted to be higher in PCOS compared to obesity matched cohorts studies (OR 1.55, 1.13-2.10)[36] and PCOS with gestational diabetes (OR 1.72, 1.26-2.37).[36, 39-41] This highlights factors beyond maternal obesity are likely to contribute to operative delivery rates in these hyperandrogenic disorders. The second stage of labour only transiently elevates intracranial pressure and is unlikely to impact on optic nerve function, except in the rare case of a pregnant person with fulminant IIH, therefore this is little evidence to recommend an elective caesarean section, purely based on a IIH diagnosis alone.[6, 33, 42]

5.1.5.3 Strengths and limitations

Idiopathic intracranial hypertension is a rare disease but of increasing incidence and the HES data source enables large sample analysis on a national basis, which enables the recognition of trends potentially not identifiable from a single hospital data source. The 11 million female general population controls enable interpretation against an unaffected cohort, with the additional PCOS cohort facilitating comparisons to a population predisposed to obesity with known fertility and gestational problems. We adjusted for age as this is a known confounder for fertility and gestational complications.

There are limitations to HES data as it is reliant on clinical record keeping and coding.[43] It may be sensitive to inconsistencies[44, 45] but method of delivery has been reported to be coded consistently.[46] Deliveries and births are linked through HES and 98% remain linked[44] with missing data reducing over time. Previous historical data for delivery method stated 15% missing data[45], however in a separate study the missing delivery method was only 0.8%.[46] We cannot ensure that every person fulfilled the diagnostic criteria for IIH, however the diagnosis is made in a hospital setting. IIH HES data[1, 2] has comparable rates of incidence and prevalence to the primary care data from evaluation of The Health Improvement Network (THIN) database.[3]

When interrogating HES data, it is important to be cognisant that for some diseases there may be inherent bias due to a lack of clear clinical criteria that is used by clinicians for a particular diagnosis (for example, the difference between primary pre-eclampsia and superimposed pre-eclampsia). The HES dataset is hospital based, therefore community diagnoses that don't result in hospital review or management would be underestimated, as in PCOS. This may account for the differences seen in PCOS fertility here (table 1) as compared to the literature self-reported PCOS rates of infertility.[13] This would also be the case for early miscarriages that may not need hospital or day case admissions. In addition, there may be unseen coding bias for example an emergency and semi-elective c-section delivery does not have an international definition and has the potential to be prone to variability in coding between hospitals.

Numerical data, i.e., BMI values, are not part of this data source and so BMI could not directly be adjusted for, however comparison was made to a PCOS population who share an obesity phenotype with IIH, therefore controlling in part for an obesity effect. Similarly, those patients who do not attend hospital would not be accounted for. Infertility defined by the age specific fertility rate is not perfect because it does not account for an individual's relationship status or choice not to have children. Sensitive data, such as Reproductive Medicine codes for In Vitro Fertilization, are not recorded within HES so we are unable to establish the role of fertility treatments played in the fertility rates shown. Ectopic pregnancies were not specifically analysed in this study.

Analysing large data sets can be prone to type 1 statistical error, however here we have provided descriptive outcomes rather than analysing efficacy data. The clinical context of the interpretation of the results remains important. HES offers the opportunity to find signals in rare diseases such as IIH that require further research in prospective studies to validate the findings.

5.1.6 Conclusions

Women with IIH had lower age-adjusted total pregnancy rates than those with PCOS and the general population. Pregnancy complication risks, including pre-eclampsia and gestational diabetes, were much higher in IIH. Following a diagnosis of IIH elective caesarean section rates were more than doubled. A number of factors may contribute to these findings including patient choice and systemic metabolic dysfunction. Specialist input to support reproductive health in IIH may improve outcomes.

5.1.7 Supplementary information

5.1.7.1 Table 1: Pregnancy in IIH Coding

IIH diagnosis

- ICD10 G932

Exclusions

- Hydrocephalus (ICD10 G91)
- Cerebral Venous Sinus Thrombosis (ICD10 G08)
- Brain Tumour (ICD10 C70, C71)
- History of Dialysis (OPCS X401, X402, X403, X406) (ICD10 Z992, Z49)

PCOS diagnosis

- ICD10 E282

Pregnancy coding

- Normal Spontaneous Delivery (ICD10 O80 or OPCS R249)
- Instrumental Delivery (ICD10 O81 or OPCS R21, R22)
- Elective C Section (ICD10 O820 or OPCS R17)
- Emergency C Section (ICD10 O821 or OPCS R18)
- Multiple Deliveries (ICD10 O84)
- Outcome of Delivery (ICD10 Z37)
- Maternal Care for Intrauterine Death (ICD10 O364)
- Missed Abortion (ICD10 O021)
- Spontaneous Abortion (ICD10 O03)

Gestational diabetes

- ICD10 O244
- ICD10 O249

Pre-eclampsia

- ICD10 O13 (gestational hypertension without proteinuria)
    - Excluded from pre-eclampsia analysis
- ICD10 O140
- ICD10 O141
- ICD10 O149

5.1.8 References

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5.2 Impact of pregnancy on IIH (Thaller. Neurology. 2023)

Manuscript title:

Disease course and long-term outcomes in pregnant women with idiopathic intracranial hypertension: The IIH prospective maternal health study

Published:

Thaller M, Homer V, Mollan SP, Sinclair AJ. Disease Course and Long-term Outcomes in Pregnant Women with Idiopathic Intracranial Hypertension: The IIH Prospective Maternal Health Study. Neurology. 2023 Apr 11;100(15):e1598-e1610. doi: 10.1212/WNL.0000000000206854.

Involvement:

I was involved in data collection, data analysis, data interpretation, writing first manuscript and critical revision of the manuscript.

5.2.1 Abstract

Background: Idiopathic intracranial hypertension (IIH) most typically occurs in women of childbearing age with increased weight as a key risk factor for development or exacerbation of the disease. Pregnancy is common in this group of patients. The longer-term impact of pregnancy on IIH has not been established and was the aim of this study.

Methods: A prospective cohort study (IIH Life) recruited consecutive patients with IIH between 2012-2021 and evaluated outcomes including: vision (LogMAR visual acuity; Humphrey visual field perimetric mean deviation (PMD); optical coherence tomography (OCT) imaging) and headache. Four cohorts were evaluated: those with IIH diagnosed for the first time whilst pregnant; those with established IIH who became pregnant; those with a pregnancy prior to their diagnosis of IIH; and those with IIH who never became pregnant.

Results: 377 people with IIH agreed to participate in the IIH Life maternal health study. Mean follow up was 17.5 months (standard deviation (SD) 20.5). IIH diagnosed in pregnancy was rare. Patients diagnosed with IIH whilst pregnant had greater papilloedema (mean OCT total retinal thickness +11.59 µm/month (95% CI: 1.25, 21.93)), although they had comparable visual field and acuity measures compared to those with established IIH who became pregnant during their disease course (-1.2 µm/month (95% CI: -2.6, 0.21)). In those with established IIH, pregnancy did not adversely affect visual or headache outcomes over time and the trajectory was akin to those with IIH that never had a pregnancy. Headache outcomes showed variability reflecting the IIH cohort as a whole.

Discussion: A diagnosis of IIH whilst pregnant was rare but associated with more severe papilloedema. Long term visual outcomes in IIH were analogous irrespective of the timing of the pregnancy. This data is reassuring however close vigilance of IIH clinical features during pregnancy is recommended.

5.2.2 Introduction

Idiopathic intracranial hypertension (IIH) is a disease characterised by elevated intracranial pressure (ICP) associated with increased total body weight.[1] IIH incidence is rising commensurate with global obesity rates in women[2, 3] and occurs most typically in women of child bearing age with increased bodyweight.[4, 5] Weight gain can exacerbate disease[6-8] and weight loss has been shown to induce remission.[9-11] One of the most common reasons why a woman of childbearing age gains body weight is pregnancy.[12] There is consequently a concern that pregnancy could induce a diagnosis of IIH, or those with an existing diagnosis of IIH could undergo an exacerbation of their disease secondary to becoming pregnant.

Approximately 38% of normal pregnancy weight gain is due to the baby, amniotic fluid and placenta.[13] In healthy pregnant women the location of the weight gain is predominantly distributed in the hips, back and thighs,[13] whereas in those with IIH the adipose distribution has been shown to be in the truncal region.[14] In women with obesity, there is a lower fat mass gain during pregnancy than in other body mass index (BMI) groups,[15] with a negative correlation between fat mass gain and BMI.[15, 16] The avoidance of excessive gestational weight gain is important due to the risk of IIH exacerbation, higher postpartum fat mass retention, and both maternal and foetal complications.[12, 15, 17]

The aetiology of IIH is not fully understood but evidence is emerging to suggest that IIH is not exclusively a disease of the neuro-ophthalmic axis but a systemic metabolic disease.[18-24] IIH is noted in association with truncal obesity, increased risk of type 2 diabetes mellitus, greater insulin resistance and doubled the risk of cardiovascular disease compared to age, gender and BMI matched individuals.[14, 19, 25-27] Additionally adipose tissue in IIH is metabolically distinct being transcriptionally primed for increased calorie intake with a unique depot-specific lipogenic profile.[19] IIH patients also demonstrate altered hormonal metabolism with a unique phenotype of serum and cerebrospinal fluid (CSF), androgen excess and dysregulated glucocorticoid metabolism.[24] The features of systemic metabolic dysregulation in IIH are likely relevant to the reduced fertility rates and an increased risk of gestational complications including pre-eclampsia and gestational diabetes mellitus.[28]

There are very few studies of IIH in pregnancy, with only two retrospective studies. Digre et al in 1984 evaluated 24 IIH patients with 36 pregnancies, and Huna-Baron and Kupersmith in 2002 assessed 12 IIH patients with 16 pregnancies.[29, 30] Consequently there is limited data on which to guide treatment in this area, especially in women who are pregnant at the time of IIH diagnosis. Concern remains that IIH patients could experience disease exacerbation in pregnancy due to weight gain and hormonal fluctuation. Indeed, historically IIH patients were often counselled not to become pregnant. The long-term impact of pregnancy on the disease course of IIH also lacks evidence. This study aimed to find if IIH patients diagnosed during pregnancy had a more severe disease course and adverse longer-term outcomes. Additionally, the aim was to determine if people with an existing diagnosis of IIH, who subsequently become pregnant, had worse long-term outcomes compared to those who never became pregnant.

5.2.3 Methods

5.2.3.1 Study Design

A prospective observational cohort study (IIH: Life) was conducted to evaluate outcomes in women with IIH over time. The patients attended a tertiary referral neuro-ophthalmology clinic at a single neuroscience centre in Birmingham, United Kingdom (University Hospitals Birmingham (UHB) NHS Foundation Trust). Data was prospectively collected over a nine-year period, between 23rd April 2012 and 8th September 2021, at the time of their routine clinical visits. All sequential patients were included with written informed consent. Recruits included people who were either initially diagnosed at UHB or at other referring hospitals within the United Kingdom and subsequently transferred to UHB. The follow up visits occurred according to clinical practice, and data from each clinic attendance was recorded.

5.2.3.2 Study population

All participants had a confirmed diagnosis of IIH using the modified Dandy criteria.[31] The criteria required the presence of papilloedema, normal neuroimaging (except for signs of raised intracranial pressure), lumbar puncture opening pressure >25 cmH_2O in a properly performed procedure, and all secondary causes of raised intracranial pressure are excluded.

All those included gave written informed consent to take part and completed the IIH Life maternal health study questionnaire. Those who were referred with a potential diagnosis of IIH, but in whom the diagnosis was not confirmed, those with a secondary cause of intracranial hypertension, and those with IIH without papilloedema (IIHWOP) were excluded from the study. In addition, male patients were excluded.

5.2.3.3 Data collection

The following data was collected: clinical history, BMI, weight, date of visits, diagnostic lumbar puncture date for disease duration (surrogate measure defined as time from the first diagnostic lumbar puncture to baseline visit), diagnostic lumbar puncture opening pressure, ICP medication prescription (acetazolamide, topiramate, other diuretics (frusemide and amiloride)) and details of IIH related surgery. The self-reported maternal health questionnaire data (see Appendix 1) and the routinely collected clinical visit data determined whether patients were pregnant at the initial IIH diagnosis or had been prior to their diagnosis or became pregnant during follow-up. Within the maternal health questionnaire patients are asked how many pregnancies and miscarriages they have had.

Visual outcomes were assessed by LogMAR (Logarithm of the minimum angle of resolution) visual acuity, Humphrey visual field perimetric mean deviation (PMD) (24-2 Swedish Interactive Testing Algorithm (SITA) central threshold) and Optical Coherence Tomography (OCT) measures (using Heidelberg Spectralis™) of global peripapillary Retinal Nerve Fibre Layer Thickness (RNFL), global peripapillary Total Retinal Thickness (TRT), and macular ganglion cell layer (GCL) volume (1, 2.22, 3.45mm volume scan). Frisén papilloedema grading (0-5 where 0 equates to no papilloedema)[32, 33] was established by a suitably trained neuro-ophthalmology specialist following a dilated slit lamp examination.

Headache outcomes were assessed by headache frequency (monthly headache days), migraine-like headache frequency (monthly migraine-like days), headache severity (0-10 numerical rating scale, where 0 is no pain and 10 is the most severe pain), and headache disability using the Headache Impact Test-6 (HIT-6) test.[34]

5.2.3.4 Statistical Analysis

Continuous and categorical variables were reported as mean (standard deviation (SD)) and number (percentage), respectively. Statistical analysis was performed using R (v4.1.0).[35] Missing data due to patient choice or lost to follow up were excluded.

Four groups of patients were defined according to timing of pregnancy in relation to IIH diagnosis or disease course. These were: 1) IIH diagnosed in pregnancy, 2) those with established IIH who became pregnant, 3) pregnancy exclusively occurring prior to IIH diagnosis and 4) IIH patients who were never pregnant. The effect of these timings was compared for visual and headache outcomes. The disease course was compared between the four groups.

Further analyses explored disease factors that were hypothesised to impact long term outcomes, including the effect disease duration, diagnostic lumbar puncture opening pressure (both continuously and categorised <25, 25-29.9,30-39.9, or 40+ cmH_20), BMI at first visit, BMI at each visit, body weight at first visit, body weight at each visit, change in gestational weight (for groups 1 and 2), any surgical intervention and age at first visit. Models were developed independently for each visual outcome using forward stepwise regression, with null models adjusting for pregnancy timing.

Linear mixed-effects model (lme4) fitting was used for regression models.[36] A continuous form of our dependent variables was assumed for all outcomes. The average response value, an adjustment for time from registration to outcome measure, was estimated using population-level terms and an interaction between variables of interest and time-point. Patient-level intercepts addressed serial correlation in responses, and the nesting of measurements from eyes within patient (as modelling included data from both eyes, where available). Where covariates were added to models, they were transformed or centred around the mean value as appropriate. Each visual outcome had independent modelling.

For headache outcomes initially the effect of pregnancy timing was explored. Further analyses explored the effect of previous personal migraine history, family history of migraine, BMI, and daily headache at registration. Models were developed independently for each headache outcome.

5.2.3.5 Standard Protocol Approvals, Registrations, and Patient Consents

The study was ethically approved by the National Health Service National Research Ethics Committee (14/LO/1208). Written informed consent was obtained from all participants in the study.

5.2.3.6 Patient and public involvement

IIHUK, a national patient charity (Registered Charity in England and Wales no 1143522 & Scotland SCO43294) that supports carers and people with IIH endorsed and helped developed the IIH Life concept and questionnaire. IIHUK contributed to funding the project. The Medical Research Council (MRC), National Institute of Health Research (NIHR) Healthcare Quality Improvement Partnership (HQIP) grant and the Sir Jules Thorne Award for biomedical science contributed to this longitudinal project.

5.2.3.7 Data Availability

The corresponding author takes full responsibility for the data, the analyses and interpretation, and the conduct of the research. They have full access to all the data; and has the right to publish any and all data separate and apart from any sponsor. Proposals for data access should be made to the corresponding author. Reasonable scientifically sound proposals, from appropriately qualified research groups, will provide data beginning 12 months and ending 3 years after publication of this article to researchers whose proposed use of the data is approved by the corresponding author. Requesters will need to sign a data access agreement, which will cover the terms and conditions of the release of data and will include publication requirements, authorship, acknowledgements, and obligations for the responsible use of data.

5.2.4 Results

The analysis included 377 women who had a confirmed diagnosis of IIH and had completed the maternal health questionnaire. As categorised, four groups consisted of: group 1 in whom IIH was diagnosed in pregnancy (2%, 6/377 patients); group 2 were participants with established IIH who became pregnant during their disease course (12%, 46/377 patients);

group 3 were individuals that only had pregnancies prior to their diagnosis of IIH (48%, 181/377 patients); and group 4 were IIH patients who were never pregnant either prior to their disease or during the course of this study (38%, 144/377 patients) (Table 1).

Table 1 – Baseline table by timing of pregnancy in relation to IIH disease course

	All	**IIH diagnosed in pregnancy**	**Established IIH who become pregnant**	**Pregnancy exclusively occurring prior to IIH diagnosis**	**IIH patients who were never pregnant**
N	377	6	46	181	144
Surgically managed (n, (%))	58 (15%)	0 (0%)	8 (17%)	30 (17%)	20 (14%)
Age, years (mean (SD))	31.1 (8.4)	26.5 (4.8)	27.6 (4.8)	34.4 (8.3)	28.5 (8.0)
BMI, kg/m^2 (mean (SD))	39.0 (8.9)	38.3 (7.6)	37.9 (8.5)	39.2 (8.7)	39.0 (9.4)
Weight, kg (mean (SD))	104.3 (25.8)	106.2 (18.8)	101.1 (22.9)	105.0 (24.7)	104.0 (28.1)
Diagnostic lumbar puncture opening pressure, cmCSF (mean (SD))	35.2 (8.0)	22.0 (n/a)	35.9 (9.9)	33.6 (7.5)	36.9 (7.4)

Miscarriage data was also sought and found rare with one patient in group 2 reported one miscarriage during the IIH disease course, with a subsequent successful pregnancy during which data was recorded.

Amongst the entire cohort, 15% (58) of patients required surgical intervention for the management of sight threatening papilloedema during their disease course but none whilst pregnant. None of the IIH diagnosed in pregnancy group (group 1) required surgical intervention for sight threatening papilloedema. The proportion of patients undergoing surgical intervention for sight threatening papilloedema at any point was comparable between the three remaining groups (those with a pregnancy during the IIH disease course (8,17%), pregnancy prior to IIH diagnosis but not during IIH disease course (30, 17%) and those with IIH but never pregnant (20, 14%)).

Baseline characteristics for the four groups did differ (Table 1), however, baseline BMI was similar between the groups. No patients were treated with acetazolamide, topiramate or diuretics during pregnancy, with three cases stopping when pregnancy was confirmed. Time from diagnostic LP to conception, an estimate of disease duration before pregnancy, was 26.6 (19.3) months for those pregnant during their IIH disease course. Mean follow up was 17.5 (SD 20.5) months for all patients, although this was 25.2 (SD 20.3) months if excluded those with a single visit.

5.2.4.1 Self-reported maternal health questionnaire

The questionnaire revealed that 16% (61/370) postponed pregnancy plans due to having a diagnosis of IIH, 22% (78/350) reported difficulties getting pregnant, 31% (113/360) reported that IIH had affected their choice of contraception and 7% (22/329) stated that a pregnancy resulted from inadequate contraception due to a change made due to having IIH.

5.2.4.2 Visual prognosis in those who became pregnant during the IIH disease course.

In group 2 (established IIH who became pregnant) the visual outcomes were comparable to those in group 4 (IIH who never had a pregnancy) (Figure 1, Table 2).

Figure 1 - Longitudinal visual data from baseline visit for IIH patients categorised by timing of pregnancy in relation to IIH diagnosis/disease, and LOESS smoothers added to show trends across the categories.

- *a. Perimetric mean deviation measured by Humphrey visual field 24-2 testing (dB)*
- *b. Retinal nerve fibre layer thickness measured on Optical Coherence Tomography (µm)*
- *c. Total retinal thickness of optic nerve head measured on Optical Coherence Tomography (µm)*
- *d. Macular ganglion cell layer volume measured on Optical Coherence Tomography (mm³)*

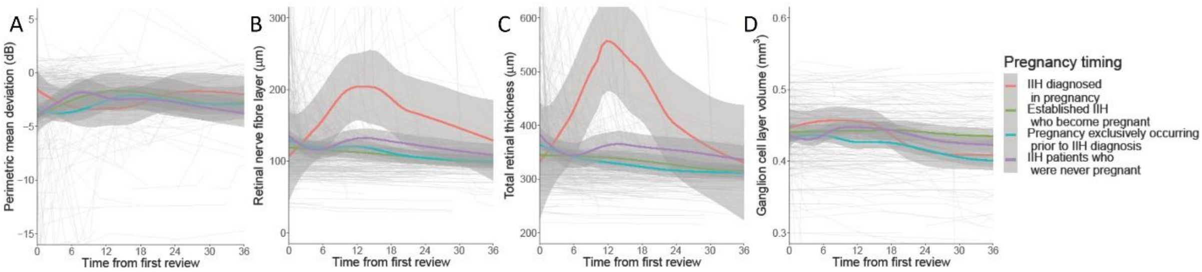


Table 2 - Baseline and trajectory (change per month) for visual and headache outcomes by timing of pregnancy by regression modelling

		Baseline estimate (units)	Change per month (units/month)
LogMAR visual acuity, logunits			
Group 1	IIH diagnosed in pregnancy	-0.1001 (95% CI: -0.4031, 0.2029)	-0.0046 (95% CI: -0.0208, 0.0115)
Group 2	Established IIH who become pregnant	-0.0607 (95% CI: -0.1296, 0.0083)	0.0016 (95% CI: -0.0003, 0.0035)
Group 3	Pregnancy exclusively occurring prior to IIH diagnosis	0.0255 (95% CI: -0.0108, 0.0618)	-0.0004 (95% CI: -0.002, 0.0012)
Group 4	IIH patients who were never pregnant	0.0111 (95% CI: -0.0269, 0.0491)	-0.0017 (95% CI: -0.0033, -0.0001)
Humphrey visual field perimetric mean deviation, dB			
Group 1	IIH diagnosed in pregnancy	1.17 (95% CI: -8.01, 10.36)	-0.3769 (95% CI: -0.8513, 0.0975)
Group 2	Established IIH who become pregnant	-4.27 (95% CI: -6.30, -2.24)	0.0406 (95% CI: -0.0202, 0.1015)
Group 3	Pregnancy exclusively occurring prior to IIH diagnosis	-3.44 (95% CI: -4.55, -2.34)	0.0561 (95% CI: 0.003, 0.1092)
Group 4	IIH patients who were never pregnant	-3.25 (95% CI: -4.39, -2.12)	0.0573 (95% CI: 0.009, 0.1056)
Global peripapillary retinal nerve fibre layer, µm			
Group 1	IIH diagnosed in pregnancy	123.28 (95% CI: 15.27, 231.30)	6.6 (95% CI: -3.09, 16.29)
Group 2	Established IIH who become pregnant	121.38 (95% CI: 93.94, 148.81)	-0.69 (95% CI: -1.87, 0.48)
Group 3	Pregnancy exclusively occurring prior to IIH diagnosis	133.93 (95% CI: 121.62, 146.24)	-1.23 (95% CI: -2.01, -0.46)
Group 4	IIH patients who were never pregnant	144.53 (95% CI: 131.98, 157.07)	-1.99 (95% CI: -2.81, -1.18)
Global peripapillary total retinal thickness, µm			

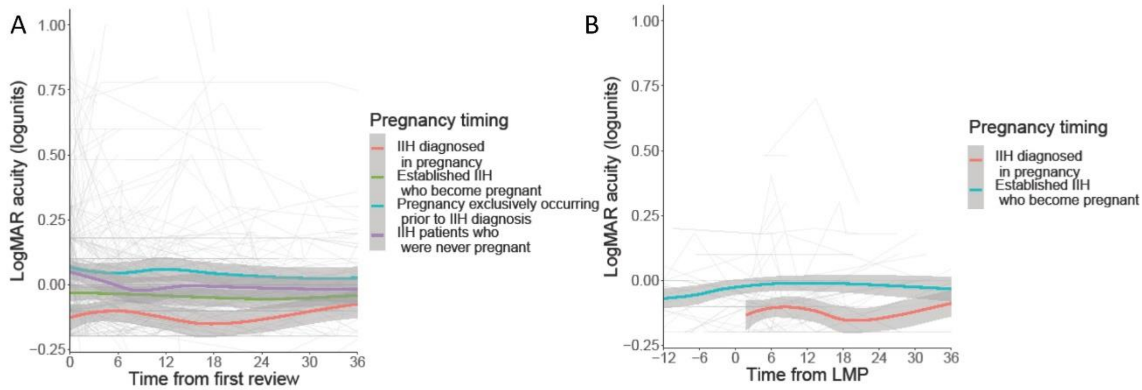
Group 1	IIH diagnosed in pregnancy	369.66 (95% CI: 233.34, 505.99)	11.59 (95% CI: 1.25, 21.93)
Group 2	Established IIH who become pregnant	353.33 (95% CI: 318.29, 388.38)	-1.2 (95% CI: -2.6, 0.21)
Group 3	Pregnancy exclusively occurring prior to IIH diagnosis	354.41 (95% CI: 338.17, 370.66)	-1.8 (95% CI: -2.67, -0.94)
Group 4	IIH patients who were never pregnant	376.19 (95% CI: 359.86, 392.51)	-3.19 (95% CI: -4.09, -2.28)
Macular ganglion cell layer volume, mm^3			
Group 1	IIH diagnosed in pregnancy	0.44 (95% CI: 0.35, 0.54)	0.0023 (95% CI: -0.0001, 0.0048)
Group 2	Established IIH who become pregnant	0.45 (95% CI: 0.42, 0.47)	-0.0004 (95% CI: -0.0008, -0.000047)
Group 3	Pregnancy exclusively occurring prior to IIH diagnosis	0.43 (95% CI: 0.42, 0.44)	-0.0005 (95% CI: -0.0008, -0.0003)
Group 4	IIH patients who were never pregnant	0.45 (95% CI: 0.43, 0.46)	-0.0003 (95% CI: -0.0006, -0.0001)
Headache frequency, days/month			
Group 1	IIH diagnosed in pregnancy	4 (95% CI: -17.56, 25.56)	-0.19 (95% CI: -2.38, 2)
Group 2	Established IIH who become pregnant	14.4 (95% CI: 9.32, 19.48)	-0.27 (95% CI: -0.51, -0.02)
Group 3	Pregnancy exclusively occurring prior to IIH diagnosis	20.47 (95% CI: 17.84, 23.11)	-0.05 (95% CI: -0.22, 0.11)
Group 4	IIH patients who were never pregnant	19.72 (95% CI: 16.95, 22.49)	-0.15 (95% CI: -0.32, 0.02)
Migraine-like headache frequency, days/month			
Group 1	IIH diagnosed in pregnancy	4 (95% CI: -13.58, 21.58)	-0.19 (95% CI: -1.99, 1.61)
Group 2	Established IIH who become pregnant	4.97 (95% CI: -0.09, 10.02)	-0.06 (95% CI: -0.29, 0.18)

Group 3	Pregnancy exclusively occurring prior to IIH diagnosis	11.43 (95% CI: 8.94, 13.93)	-0.12 (95% CI: -0.26, 0.02)
Group 4	IIH patients who were never pregnant	8.91 (95% CI: 6.49, 11.33)	-0.06 (95% CI: -0.2, 0.08)
Headache severity, VAS 0-10			
Group 1	IIH diagnosed in pregnancy	7.05 (95% CI: 0.77, 13.32)	-0.1 (95% CI: -0.73, 0.54)
Group 2	Established IIH who become pregnant	5.45 (95% CI: 3.99, 6.91)	0 (95% CI: -0.08, 0.09)
Group 3	Pregnancy exclusively occurring prior to IIH diagnosis	6.77 (95% CI: 6.06, 7.49)	-0.03 (95% CI: -0.08, 0.02)
Group 4	IIH patients who were never pregnant	5.92 (95% CI: 5.16, 6.67)	0.01 (95% CI: -0.04, 0.07)
HIT-6, score 36-78			
Group 1	IIH diagnosed in pregnancy	-	-
Group 2	Established IIH who become pregnant	59.39 (95% CI: 54.33, 64.45)	0.17 (95% CI: -0.13, 0.46)
Group 3	Pregnancy exclusively occurring prior to IIH diagnosis	61.37 (95% CI: 58.75, 63.99)	-0.06 (95% CI: -0.23, 0.12)
Group 4	IIH patients who were never pregnant	63.02 (95% CI: 60.3, 65.73)	-0.06 (95% CI: -0.26, 0.13)

The LogMAR visual acuity and Humphrey visual field perimetric mean deviation outcomes were similar for the two groups, 2 and 4 (Figure 1A, Supplementary figure 1A). OCT measures showed similar baseline values, although the trajectory of improvement was slower for TRT in those with a pregnancy during the IIH disease course, -1.2 (95% CI: -2.60, 0.21) µm/month versus -3.19 (95% CI: -4.09, -2.28) µm/month (for those never pregnant) (Figure 1C, Table 2) with the difference of 1.99 (95% CI: 0.32, 3.67) µm/month. RNFL showed a similar trajectory to TRT (Figure 1B, Table 2). GCL volume only showed a slight decrease over time for those with established IIH who became pregnant (Figure 1D, Table 2).

Supplementary Figure 1

a. *Longitudinal LogMAR visual acuity (logunits) from baseline visit for IIH patients categorised by timing of pregnancy in relation to IIH diagnosis/disease, and LOESS smoothers added to show trends across the categories.*
b. *Longitudinal LogMAR visual acuity (logunits) from estimated last menstrual period (LMP) for IIH patients categorised by whether pregnant at time of IIH diagnosis or during IIH disease course. LOESS smoothers added to show trends across the categories.*



To determine outcomes according to the timing of the pregnancy, the data was evaluated from the timing of last menstrual period. Visual function (LogMAR visual acuity and Humphrey visual field perimetric mean deviation) was stable in the patients with pregnancy occurring during their IIH disease course (Figure 2A and Supplementary figure 1B, Table 3). Papilloedema measurements using OCT also remained stable following conception (Figure 2B-D). In group 2 patients (became pregnant during IIH disease course), there was recovery of papilloedema (measured by RNFL) in the 12 months prior to pregnancy (improvement of 22.32µm (95% CI: 11.77, 32.88), from 129.15 to 106.83µm). Macular GCL volume remained stable during pregnancy in those with a pregnancy during IIH disease course (group 2) (Figure 2D, Table 3).

Figure 2 - Longitudinal visual data from estimated last menstrual period (LMP) for IIH patients categorised by whether pregnant at time of IIH diagnosis or during IIH disease course. LOESS smoothers added to show trends across the categories.

a. *Perimetric mean deviation measured by Humphrey visual field 24-2 testing (dB)*
b. *Retinal nerve fibre layer thickness measured on Optical Coherence Tomography (µm)*
c. *Total retinal thickness of optic nerve head measured on Optical Coherence Tomography (µm)*
d. *Macular ganglion cell layer volume measured on Optical Coherence Tomography (mm^3)*

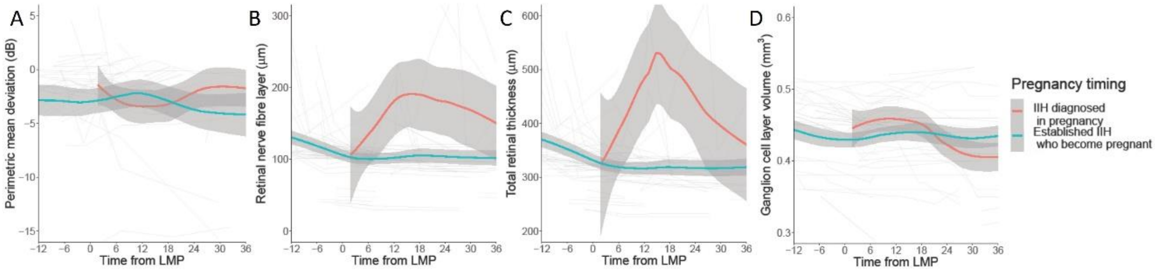


Table 3 – Visual outcomes for pregnant IIH patients by time from last menstrual period (LMP) in relation to IIH diagnosed in pregnancy or established IIH who become pregnant

	Time from LMP (months)	3	6	9	12	24
LogMAR visual acuity, logunits (mean (SD), n)						
Group 1	IIH diagnosed in pregnancy	-0.12 (0.04), 4	-0.09 (0.05), 4	-0.09 (0.05), 4	-0.12 (0.05), 4	-0.16 (0.05), 4
Group 2	Established IIH who become pregnant	-0.02 (0.14), 29	0.01 (0.10), 30	-0.01 (0.10), 20	-0.06 (0.14), 21	-0.02 (0.10), 13
Humphrey visual field perimetric mean deviation, dB (mean (SD), n)						
Group 1	IIH diagnosed in pregnancy	-2.00 (1.06), 2	-3.54 (1.40), 2	-3.66 (1.28), 2	-2.97 (1.47), 2	-2.28 (0.90), 1
Group 2	Established IIH who become pregnant	-1.31 (4.84), 23	-2.85 (3.87), 23	-2.70 (3.70), 15	-1.23 (4.93), 14	-4.49 (3.23), 9
Global peripapillary retinal nerve fibre layer, µm (mean (SD), n)						
Group 1	IIH diagnosed in pregnancy	114.8 (48.16), 3	123.8 (41.47), 3	147.5 (47.9), 3	181.8 (51.3), 3	163.3 (53.6), 4
Group 2	Established IIH who	105.1 (28.87), 25	101.4 (18.58), 28	99.5 (18.49), 18	101.6 (21.14), 19	108.4 (21.87), 15

	become pregnant					
Global peripapillary total retinal thickness, µm (mean (SD), n)						
Group 1	IIH diagnosed in pregnancy	349.8 (80.44), 2	319.2 (99.6), 3	351.3 (106.88), 3	485.7 (101.8), 3	430.5 (91.47), 3
Group 2	Established IIH who become pregnant	328.6 (40.52), 25	319.7 (26.17), 28	313.4 (25.81), 19	312.2 (29.03), 18	323.9 (27.66), 14
Macular ganglion cell layer volume, mm^3 (mean (SD), n)						
Group 1	IIH diagnosed in pregnancy	0.45 (0.011), 2	0.46 (0.009), 2	0.46 (0.010), 2	0.46 (0.011), 2	0.42 (0.013), 3
Group 2	Established IIH who become pregnant	0.44 (0.046), 24	0.43 (0.031), 26	0.43 (0.031), 17	0.45 (0.035), 18	0.43 (0.036), 14

5.2.4.3 Visual prognosis in those diagnosed with IIH in pregnancy

IIH was rarely diagnosed for the first time in pregnancy (n=6, 1.6%). Although the numbers are small, these subjects demonstrated a deterioration in PMD, OCT RNFL and TRT following enrolment (Figure 1A-C, Table 3). Outcomes recovered over time. These patients' baseline visits were also whilst pregnant, unlike group 2 where the pregnancy occurred during follow up. There was a statistically significant worse trajectory, towards greater papilloedema, in this cohort (group 1) (as measured by the TRT on OCT) +11.59 µm/month (95% CI: 1.25, 21.93) (Figure 1C, Table 2), compared to the other groups (Groups 2-4) (-1.2 (95% CI: -2.6, 0.21), -1.8 (95% CI: -2.67, -0.94) and -3.19 (95% CI: -4.09, -2.28) respectively) and during pregnancy (Figure 2C) compared to group 2. Other measures were relatively stable over time (Figures 1 and 2, Supplementary figure 1, Table 2).

5.2.4.4 Visual prognostic factors in pregnancy

Prognosis for visual outcomes was principally determined by duration of disease prior to pregnancy. The longer the disease duration, the greater the reduction in papilloedema (RNFL change at baseline of -0.31 (95% CI: -0.53, -0.093) µm per month since diagnostic lumbar puncture and TRT change -0.49 (95% CI: -0.77, -0.21) µm per month).

Baseline BMI was also important with higher BMI indicating a poorer prognosis for visual field PMD (0.092 (0.0083, 0.18) dB per 1kg/m^2). Prognosis was not affected by weight gain during pregnancy, change in BMI during pregnancy or diagnostic lumbar puncture opening pressure.

5.2.4.5 Headache prognosis in IIH according to pregnancy timing

The entire cohort had a high headache morbidity but with marked variability over time. The baseline mean headache frequency (headache days per month) was 14.4 (95% CI: 9.32, 19.48) for those with established IIH who become pregnant (group 2), 20.5 (95% CI: 17.84, 23.11) for those with pregnancy only prior to IIH diagnosis (group 3) and 19.7 (95% CI: 16.95, 22.49) for those never pregnant (group 4) (Figure 3, Table 2). There was insufficient data to comment on group 1, those with IIH diagnosed whilst pregnant (Figure 3, Table 2). Headache frequency improved during pregnancy for those pregnant during the IIH disease course (Figure 4A), whereas the migraine-like headache frequency remained stable (Figure 4B).

Figure 3 - Longitudinal headache data from baseline visit for IIH patients categorised by timing of pregnancy in relationship to IIH disease course, and LOESS smoothers added to show trends across the categories.

a. *Headache frequency (days per month)*
b. *Migraine-like headache frequency (days per month)*
c. *Headache mean severity of predominant headache (0-10 numerical rating scale)*
d. *Headache Impact Test 6 (HIT6) (quality of life measure score 36-78)*

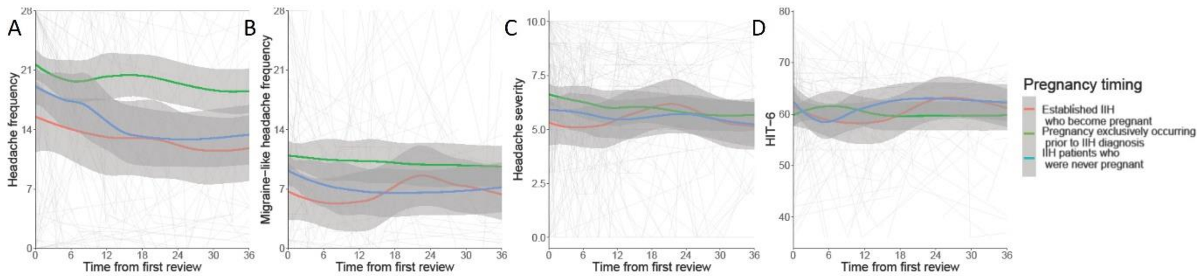
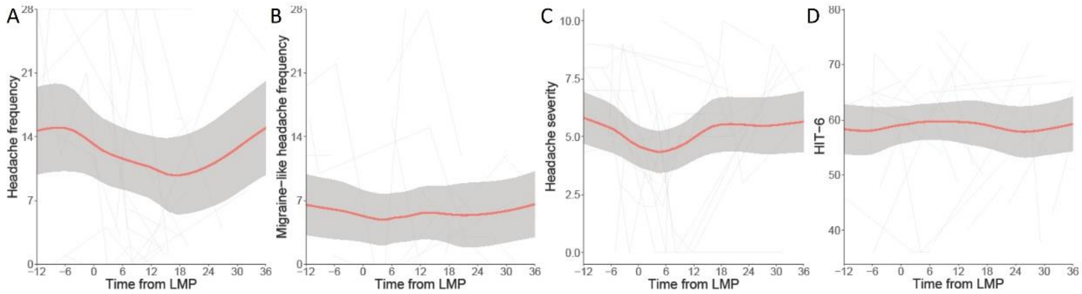


Figure 4 - Longitudinal headache data from estimated last menstrual period (LMP) for IIH patients pregnant during IIH disease course. LOESS smoothers added to show trends across the categories.

- *a. Headache frequency (days per month)*
- *b. Migraine-like headache frequency (days per month)*
- *c. Headache mean severity of predominant headache (0-10 numerical rating scale)*
- *d. Headache Impact Test 6 (HIT6) (quality of life measure score 36-78)*



Headache severity was moderate intensity; rated 5.5 out of 10 (95% CI: 3.99, 6.91) for those pregnant during their IIH disease course (Group 2), 6.8 (95% CI: 6.06, 7.49)) for those with pregnancy only prior to IIH diagnosis (Group 3) and 5.9 (95% CI: 5.16, 6.67) for those never pregnant (Group 4) (Figure 3C, Table 2). Severity appeared to improve prior to pregnancy slightly with relative stability during pregnancy (Figure 4C).

Headache burden, measured by HIT-6 score, was comparable between these three groups (Figure 3D, Table 2) with a moderate to severe impact (59-63 out of 78), with relative stability during pregnancy (Group 2) (Figure 4D). There was no difference in trajectory (Table 2) between any of the pregnancy groups and it remained stable.

Daily headache at baseline visit was the main prognostic factor for headache frequency and severity outcomes, with previous migraine history and disease duration having a lesser but statistically significant effect on headache frequency.

5.2.5 Discussion

This is the largest prospective study to assess the impact of pregnancy on IIH outcomes. Pregnancy at the time of IIH diagnosis is rare but characterised by worsening of visual field function and papilloedema measured by OCT imaging during the pregnancy with subsequent recovery after the pregnancy. Despite a seemingly more severe disease course none of this subset required surgical intervention for sight threatening papilloedema. For those with established IIH, becoming pregnant did not adversely affect visual outcomes. Headache outcomes in the long term showed marked variability and no relationship was found to the timing of pregnancy.

Self-reported fertility problems were reported by 22% of our cohort. It is noteworthy that 31% of participants reported that IIH had affected their contraception choice and a concern that 7% stated that a pregnancy resulted from inadequate contraception due to changes made as result of their IIH diagnosis. This observation highlights the need to modernise the education of physicians particularly for those who manage contraceptive prescriptions as there are no contraindicated contraceptives in IIH, although the usual contraindications and recommendations for patients with migraine would apply in IIH with migrainous headache.[12]

The proportion of patients diagnosed with IIH whilst pregnant is lower (1.6%) than previously reported in other smaller studies 3.3%-8.4%.[29, 30] This could be due to variation between global IIH populations and sample sizes. Although a diagnosis of IIH diagnosed in pregnancy (Group 1) was a rare occurrence, the disease should be closely monitored throughout pregnancy considering the more severe papilloedema here when diagnosed during pregnancy. In group 1 we also noted a trend towards declining perimetric mean deviation and worsening papilloedema measured by OCT imaging (Figure 2). We have previously shown that acute IIH has more severe papilloedema than chronic IIH,[37] so there is the possibility that newly diagnosed IIH in pregnancy would have more severe papilloedema than those with more chronic IIH who become pregnant. Those patients with IIH diagnosed in pregnancy (Group 1) were interesting in that papilloedema worsened during the 12 months following diagnosis. This contrasts with newly diagnosed IIH patients who are not pregnant who gradually improve over time.[37] This poses a significant treatment dilemma as in pregnancy there are more limited treatment options, including the potential teratogenicity of carbonic anhydrase inhibitors,[12] although one study showed safety of acetazolamide in pregnancy.[38] The mechanism to explain why new onset IIH may deteriorate during pregnancy is not known. Hypertestosteronism has been demonstrated in IIH and linked to driving CSF secretion and ICP elevation.[24] It is also known that during pregnancy testosterone levels increase.[39] Thus, a potential mechanism might be the increased testosterone in pregnancy upregulating CSF secretion causing increased intracranial pressure and a worsening of the papilloedema observed here during pregnancy.

The longitudinal outcomes for established IIH patients who became pregnant (Group 2) are comparable to those IIH patients who were never pregnant (Group 4), and those with pregnancies only prior to an IIH diagnosis (Group 3). This is a constructive result and highlights that pregnancy should not be avoided in all IIH patients, although control of the disease should be optimised before planned pregnancies where possible.[29, 30] Papilloedema improved in the 12 months before conception (Figure 2B-C) reflecting disease optimisation targeting ocular remission before planned pregnancies, although it could also reflect the natural disease course seen in IIH patients with active disease.[37] The current recommendation is to optimise IIH control prior to pregnancy[12] and this may additionally help reduce the previously demonstrated increased risk of gestational diabetes mellitus and pre-eclampsia.[28] This may also reflect the worse visual outcomes seen in those diagnosed in pregnancy (Group 1) as they may have not had the opportunity to have the disease optimised before conception. For this group avoidance of excessive gestational weight gain would be considered as important.[12, 17]

This study did not demonstrate pregnancy relevant modifiable visual prognostic factors, of either gestational bodyweight or BMI gain, although this may reflect the difficulty in differentiating normal gestational weight gain from excessive gestational weight gain. Weight management is the only disease modifying therapy in IIH[5, 9, 10] however, this is more challenging in pregnancy especially given the differing distributions of adiposity seen in pregnancy and IIH.[13, 14] Routine weight monitoring during pregnancy is not presently recommended in the UK according to the National Institute for Heath and Care excellence (NICE), although IIH would be a condition in which it should be monitored due to the risks of high gestational weight gain.[40] An individualised approach is recommended, discussed in a sensitive manner avoiding obesity stigmatising language.[12] Disease duration was a prognostic marker likely reflecting a longer time from elevated intracranial pressure detected and therefore more likely to be in ocular remission. This highlights that targeting disease remission before pregnancy has improved long term outcomes.

Headache burden in IIH is a significant problem even after the disease comes into ocular remission[41] and while recently headache morbidity appears to be correlated with raised intracranial pressure, the mechanisms driving headache once the intracranial pressure has settled remain unclear.[42, 43] This data shows marked variability in headache outcomes, which reflects what has been found in the IIH population as a whole.[37] Headache frequency was high at baseline (Figure 3) in groups 2, 3 and 4 with either mild improvement or stability over time (Table 2). This plateau was also seen for migraine-like headache frequency, headache severity and HIT-6 score, and highlights the need for new treatment options for the management of persistent post IIH headache which has been called for by patients and physicians.[41, 44] Headache treatments are limited in pregnancy and these are mainly based around acute medications rather than prophylactics.[12] The prognostic factors in this cohort were daily headache at diagnosis and a personal migraine history. This is helpful clinically as it could signpost those people who require escalation of headache treatment and referral to specialist services.

This was a prospectively collected real-world clinical practice study and has inherent limitations such as missing data. For example, missing data exists for those patients seen at other institutions before referral to UHB. Attempts were made to minimise this by obtaining prior clinical noting however some data were omitted. As a tertiary neuro-ophthalmology referral centre, initial visits may have occurred at other hospitals in the country before subsequent referral and therefore baseline data could have been at a different point in their disease course. To reduce this bias, we defined disease duration as being the time from first diagnostic lumbar puncture to the first encounter in our clinic (baseline visit), however lead-time bias may have an impact on the accuracy of this data. There are currently no studies evaluating exact start of symptoms that confirm a diagnosis of IIH, as defining disease onset. The maternal health questionnaire was self-reported and recall bias could exist here. An unavoidable limitation is the sample size for those diagnosed with IIH in pregnancy, however for the first time illustrated that this should be studied further. Use of medications are limited in pregnancy and therefore may partially explain some of the worsening in papilloedema seen in those diagnosed in pregnancy, although would not explain fully the differences as those with subsequent pregnancies did not deteriorate. Some outcomes were missing due to patient preference and others as OCT imaging protocols changed after the start of the study. Some patients were in ocular remission from an IIH perspective when pregnancy occurred and therefore the changes seen reflect a real-world cohort rather than what occurs in active IIH during pregnancy. As per clinical practice some individuals were discharged to other institutions for local follow-up whilst others in remission were discharged completely leading to reduced numbers longitudinally followed-up. In this analysis we also did not have a control group without IIH, although to control for pregnancy we included patients who had never been pregnant.

5.2.6 Conclusions

Diagnosing IIH in pregnancy is rare with worsening of perimetric mean deviation and papilloedema measurements noted during pregnancy. Established IIH with subsequent pregnancies occurs more frequently and has a good visual outcome. Headache outcomes showed marked variability with similar long-term outcome between all groups. Monitoring of people with IIH during their pregnancy is important and particularly needed in those diagnosed with IIH at the time of pregnancy. Our data suggests that in those with well controlled IIH prior to pregnancy, the pregnancy did not exacerbate IIH.

5.2.7 References

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Chapter 6: Overall Conclusions

6.1 Summary

The primary objectives of this doctoral thesis were to investigate the impacts of Idiopathic Intracranial Hypertension (IIH), with a particular focus on women of childbearing age. The longitudinal outcomes have been demonstrated in a medically managed IIH cohort, in those with 'atypical' presentations, in those with comorbid PCOS and in pregnancy. Notably, this research provided pioneering insights into the implications of IIH on pregnancy, specifically regarding gestational complications.

My research has revealed that people with IIH were adversely affected by the first COVID-19 lockdown. Overall IIH has been found to be negatively influenced by papilloedema severity, daily headache at presentation and a personal migraine history, but positively improved by weight loss. The longitudinal outcomes were unaffected by comorbid PCOS, asymptomatic presentations, presentation with a healthy weight BMI or pregnancies occurring during the IIH disease course.

The prevalence of comorbid PCOS in our cohort was 20% and it was associated with an increased incidence of self-reported fertility problems. IIH was also shown to impact fertility, preeclampsia risk, gestational diabetes risk and caesarean section rates. IIH outcomes were impacted when IIH was diagnosed in pregnancy but not in those with established IIH who had a subsequent pregnancy. This body of work has furthered the literature with these new findings of adverse maternal health associations, outlined the spectrum of IIH, and highlighted the neutral influence of pregnancy for the majority of women living with IIH.

6.2 Main conclusions

The cessation of outpatient IIH and neuro-ophthalmology services during the coronavirus pandemic had a detrimental impact on the recognition of papilloedema and outcomes for patients. The impact was seen most acutely in the massive rise in surgical interventions following the first lockdown. The mental health of our patients was also affected. As a result, throughout the subsequent waves of COVID-19, an emergency papilloedema outpatient service has been maintained to limit further negative effects on our patients. This highlighted the importance of hospital services both for the detection of papilloedema and its ongoing management.

This research in this thesis has established that the longitudinal outcomes in medically treated IIH patients are good. However, those with the most severe papilloedema, more likely to require surgical intervention, had the worst visual outcomes as measured by visual fields and macular ganglion cell layer imaging. This provides evidence for optimising disease control early to minimise the risk of permanent visual loss. Optical coherence tomography papilloedema measurements of average global peripapillary retinal nerve fibre layer thickness and total retinal thickness are a better measures of disease activity than either visual acuity or visual fields and should be integrated into IIH care nationally. This could be further enhanced if the total retinal thickness of the optic nerve head could be calculated accurately and automatically, especially in severe papilloedema where current automated segmentation is more inaccurate.

Weight loss is the key positive prognostic marker for visual outcomes over time. This research has added to current literature, and IIH patients need better community and specialist weight management services to achieve this difficult task. Headache outcomes were demonstrated to be influenced by daily headache at presentation and a personal migraine history, with a marked variability in frequency and severity in our dataset. There is an unmet clinical need for effective prophylaxis, especially in patients with persistent post-IIH headache, and further research in this area is recommended.

Asymptomatic IIH and healthy weight BMI at presentation was uncommon and required closer monitoring. Of note, two thirds of asymptomatic participants became symptomatic over the course of follow up and patients with a healthy weight BMI at baseline are potentially harder to manage as the only disease modifying treatment currently is weight loss.

PCOS occurred more commonly in patients with IIH but not as frequently as initially reported. The clinical benefit of detecting this would be to identify and manage patients at higher risk of fertility problems, as highlighted by the self-reported maternal health questionnaire, although fertility was also shown to be affected in IIH in the absence of PCOS. The reduced fertility rates in IIH without comorbid PCOS demonstrated have several potential causes including hyperandrogenism, obesity, and the metabolic syndrome, although additional currently unidentified mechanisms may also be driving this. The presence of comorbid PCOS was not shown to affect the visual and headache prognosis. It is reassuring that despite both affecting patients' metabolic profiles, the different androgen signatures previously demonstrated might mean that there was no enhanced CSF secretion, illustrated by similar outcomes. Further research is warranted to evaluate the impact on metabolic outcomes such as cardiovascular disease of dual pathology.

The increased risk of gestational complications in IIH have been demonstrated for the first time, over that of a non-IIH and non-PCOS control group. The risk of pre-eclampsia was even higher than in a PCOS population, which shares an obesity phenotype. This new finding is of clinical importance as increased obstetric surveillance in IIH beyond ocular monitoring would be recommended to enable early treatment of pre-eclampsia and gestational diabetes. There is an increased need for multi-disciplinary working between obstetric, neurology and ophthalmology teams. The prospective cohort study illustrated that IIH diagnosed during pregnancy was rare but associated with a worsening of papilloedema measurements during the pregnancy and therefore warrants close supervision. It could have reflected a more acute disease course with limited treatment options. However, pregnancy does not need to be avoided in the majority of known IIH cases as subsequent pregnancies did not adversely affect long term visual and headache outcomes. Therefore, targeting disease remission before a planned pregnancy and avoidance of excessive gestational weight gain would be recommended in IIH to reduce the risk of exacerbations and complications.

6.3 Strengths

My research has contributed to the neurological field, as it has established important markers for predicting visual loss, illustrated the benefits of integrating optical coherence tomography imaging into IIH care to monitor visual function and identified the expected progression in variety of comorbid diseases and presentations. This has answered some of the top 10 priorities for IIH research.[1]

I have addressed some of the main concerns within women's health and IIH, including PCOS and pregnancy. Further to my thesis, in collaboration with my supervisors, I have published practical advice for the management of IIH in pregnancy.[2] This research can better inform healthcare consultations through highlighting the importance of targeting IIH remission prior to planning pregnancies, management during pregnancy (not just IIH but also earlier recognition of pregnancy complications) and the delivery of babies to mothers with IIH. Furthermore, the research has highlighted the need to identify comorbid PCOS due to the individual and combined risks of fertility problems. There is a need to integrate some of the identified prognostic markers into IIH care, as they have the potential to indicate a need for more rapid escalation of treatment, including peripapillary retinal nerve fibre layer thickness >300µm for visual outcomes and daily headache at presentation for headache outcomes.

6.4 Limitations

The limitations for my thesis have been discussed throughout my thesis in the research chapters. The main limitation for the longitudinal datasets is that they were based on data from one large tertiary IIH service rather than national data, therefore may not be generalisable to a national IIH population, although counteracting this is that the IIH service in Birmingham is one of the main IIH centres internationally with national tertiary referrals. Due to the real-world nature of the data, I adjusted for the decreasing longitudinal sample sizes, which resulted from patient care returning closer to the patient's home, and follow-up intervals determined by clinical characteristics. There is also a need to establish how the longitudinal outcomes are influenced by intracranial pressure lowering medications, as there was not a significant effect noted in our cohort. Long term medication use is often limited by side effects therefore potentially only providing a temporary benefit, whereas other factors provide longer lasting benefits such as lifestyle changes and weight management. My research includes the largest prospective IIH studies to date and raises important questions for further research as well as providing strong research evidence.

6.5 Recommendations

Based on these conclusions, medical professionals should be aware when a patient's trajectory is different from the expected thus potentially warranting treatment escalation, in particular if optical coherence tomography measures are worsening. Identification and management of poor prognostic factors earlier may modify the longer-term outcomes seen in these studies. There is a need for doctors to be aware of the increased risk of metabolic complications in IIH and to discuss weight management in a sensitive manner with appropriate referral to specialist services. Better education is needed for all professionals who manage IIH patients particularly surrounding contraceptive choices and discussion of appropriate delivery options when IIH patients are pregnant.

Patients can also benefit from this research as this adds to the evidence base for weight management approaches in IIH, although marked weight loss is hard to achieve and to maintain with dietary measures alone.[3] With regards to pregnancies, I would recommend optimising disease control prior to planned pregnancies where this is possible. However, there is also reassurance in the finding that the longer-term outcomes were similar between patients with known IIH who had subsequent pregnancies and those who were never pregnant. Although comorbid PCOS can make weight management more challenging, and is associated with self-reported fertility problems, it was not associated with worse IIH outcomes. These patients would potentially benefit from endocrinology review due to the dual pathology.

As for NHS service provision there is a need for better access to tertiary weight management services, headache specialists, and the development of integrated multidisciplinary services nationally. There is also a need to make bariatric surgery available for IIH patients at the obesity related disease threshold of $35kg/m^2$.

Future research in IIH is needed to understand the pathophysiological mechanisms underlying the illustrated increased risks of pre-eclampsia, gestational diabetes, fertility problems and debilitating headaches. Regarding pre-eclampsia, my recommendations would be to investigate the role of hyperandrogenism and obesity as these are the most likely potential drivers in IIH. Similarly, these should be evaluated for gestational diabetes. The underlying fertility mechanisms have not been investigated in IIH and warrant further endocrinological research both to confirm my findings as well as establishing mechanisms. Further investigations are needed into why some IIH patients present either in an asymptomatic fashion or without the classical obesity phenotype and whether the metabolic implications arising differ from those with a classical presentation. Headache burden is high in IIH even after the cessation of elevated intracranial pressure, potentially through central sensitization and activation of the trigeminovascular system, and better treatment options are needed both in the acute and chronic phases of the disease. There should be a focus on treatments that minimise cognitive side effects, associated weight gain and can be used safely in pregnancy.

6.6 Final conclusions

People with IIH were adversely affected by the first COVID-19 national lockdown. Overall IIH has been found to be negatively influenced by papilloedema severity, daily headache at presentation and a personal migraine history, but positively improved by weight loss. While it was found there was a 20% comorbid PCOS prevalence and self-reported fertility problems in this IIH cohort; these were not associated with longer-term adverse outcomes. IIH was also shown to impact fertility, preeclampsia risk, gestational diabetes risk and caesarean section rates. IIH outcomes were impacted when IIH was diagnosed in pregnancy but not in those with established IIH who had a subsequent pregnancy. This body of work has furthered the literature with these new findings of adverse maternal health associations, outlined the spectrum of IIH, and highlighted the neutral influence of pregnancy for most women living with IIH.

6.7 References

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Thank you for reading my thesis.