OBSTRUCTIVE SLEEP APNOEA (OSA) IN PATIENTS WITH TYPE 1 DIABETES (T1D)

By

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Abstract

There is a high incidence of obstructive sleep apnoea (OSA) in patients with Type 2 diabetes and this is associated with microvascular complications. Despite different aetiology, patients with Type 1 diabetes (T1D) are also at increased risk of diabetes-related vascular complications. Given the lower incidence of T1D, less research has been focussed on it. This research aimed to identify treatable factors which contribute to the morbidity and mortality of T1D. A systematic review, clinical cohort study, and population analysis of GP patient records were conducted to assess the prevalence and development of OSA and associated cardiovascular complications in T1D. This research has shown that OSA is common in T1D and is associated with cardiovascular autonomic neuropathy. It has also shown that T1D increases the incidence of OSA. The main contribution of this study is identifying, for the first time, the risk factors which contribute to the development of OSA in T1D. A further novel finding was that OSA in T1D patients increased the incidence of vascular complications, including heart failure, ischaemic heart disease, peripheral vascular disease, and chronic kidney disease. Better diagnosis and treatment of OSA may help to ameliorate the impact of microvascular complications and heart disease in T1D.

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-List of abbreviations

AASM	American Academy of Sleep Medicine
ACR	Urinary albumin/creatinine ratio
ACTH	Adrenocorticotropic hormone
AHI	Apnoea-hypopnea index
AN	autonomic neuropathy
AXIS	The appraisal tool for cross-sectional studies
BMI	Body mass index
BP	Blood pressure
BQ	Berlin questionnaire
CAN	Cardiovascular autonomic neuropathy
CARTs	Cardiac autonomic reflex tests
CIH	Chronic intermittent hypoxia
CKD	Chronic kidney disease
CPAP	Continuous positive airways pressure
CRF	Case Report Form
CV	Cardiovascular
DAN	Diabetic autonomic neuropathy
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DPN	Diabetic peripheral neuropathy
DR	Diabetic retinopathy
E/I	Exhalation to inhalation
eGFR	Estimated glomerular filtration rate
ESRD	end-stage renal disease
ESS	Epworth Sleepiness Scale
HbA1c	Haemoglobin A1c
HC	Hip circumference
HEFT	Heart of England NHS Foundation Trust
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HPA	hypothalamic-pituitary-adrenal
HRV	Heart Rate Variability
HSAT	Home Sleep Apnoea Testing
IDF	The International Diabetes Federation
IHD	Ischaemic heart disease
IR	Insulin resistance
JBI	Joanna Briggs Institute
LFa	Low-frequency area
MEQ	Morningness-Eveningness questionnaire
MNSI	Michigan Neuropathy Screening Instrument
NC	Neck circumference
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea

PG	Portable polygraph
pNN50	Percentage of differences between adjacent normal R-R intervals that are greater than 50 ms
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PVD	Peripheral vascular disease
QoL	Quality of life
RDI	Respiratory disturbance index
REI	Respiratory events index
REM	Rapid eye movement
RFa	Respiratory frequency area
rmsSD	Square root of the mean of the squares of differences between adjacent normal R-R intervals
ROS	Reactive oxygen species
RP	Retinopathy
SBP	Systolic blood pressure
SDB	Sleep disordered breathing
sdNN	Standard deviation of normal R-R intervals
SF-MPQ-2	Short-form McGill Pain Questionnaire 2
SMI	Serious mental illness
STDR	Sight-threatening diabetic retinopathy
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TIA	Transient ischemic attack
WC	Waist circumference
WHR	Waist−hip ratio
WMD	Weighted mean difference

CHAPTER ONE: GENERAL INTRODUCTION

1.1 Background

Many epidemiological studies have shown that obstructive sleep apnoea (OSA) is very common in patients with Type 2 diabetes (T2D; up to 86% prevalence) (1), which is not surprising considering that OSA and T2D share common risk factors such as obesity and increased age (2). In addition, OSA in patients with T2D is associated with higher blood pressure, worse glycaemic control, and the presence and development of diabetes-related microvascular complications (2). Observational longitudinal studies have also shown that OSA is associated with increased cardiovascular disease and poorer quality of life (3).

Despite the different aetiology, patients with type 1 diabetes (T1D) are also at increased risk of cardiovascular disease and diabetes-related microvascular complications. Given the lower prevalence of T1D, research has often focused on T2D. However, it is important to identify treatable factors that can contribute to the morbidity and mortality of T1D. There is currently little in the literature regarding the prevalence and impact of OSA in patients with T1D and therefore the overall aim of this thesis is to investigate this further.

1.2 Type 1 Diabetes Mellitus

1.2.1 T1D epidemiology

T1D is an unpreventable autoimmune condition. The body's immune system attacks and destroys the insulin-producing cells (beta cells) in the pancreas; the triggers for this are currently unknown. Therefore, people with T1D develop a chronic hyperglycaemia that is characterised by the inability of the pancreas to produce insulin, unlike T2D. Glucose accumulates in the blood instead of being taken up into cells under the hormonal influence of insulin (4).

In contrast to T2D, the majority of T1D cases develop early in life and require immediate medical care (5). People with T1D require life-long insulin treatment and routine glucose level monitoring. At diagnosis, people with T1D are usually not obese, have no or little plasma insulin, and have normal insulin sensitivity (6). People with T2D, on the other hand, are characterised by usually being older, obese, with high plasma insulin, and reduced insulin sensitivity (6). Despite the difference between T1D and T2D in the factors leading to hyperglycaemia, T1D patients are also at increased risk of mortality (7) and cardiovascular disease (8). A population-based study in the UK showed that people with T1D had higher hazard ratio for all-cause mortality and developing major cardiovascular disease (3.6 and 3.7 folds, respectively) as compared to people without diabetes (7, 8).

1.2.2 T1D prevalence

T1D accounts for about 7-12% of all diabetes mellitus (DM) cases in high-income countries (9). According to the England and Wales National Diabetes Audit (2017-2018), more than 250,000 people had T1D (all ages) accounting for about 8% of all those with diabetes. The report also showed that 12,025 people (all ages) were newly diagnosed, of which 58% were males (10). A recent IDF Diabetes Atlas estimated that more than 1.1 million children (<20 years) had T1D globally (11). It was estimated that 26% of children with T1D live in Europe, with the annual increase in prevalence estimated at 3% (12). In the UK, it was estimated that about 40,300 minors (<20 years) had T1D, and about 4,000 new T1D cases (<20 years) were diagnosed per year. Given the increasing prevalence of T1D, it is important to identify treatable factors which might impact on quality of life and the development of complications.

1.2.3 T1D and diabetic-related complications

Although T1D and T2D have different characteristics, both develop similar complications such as cardiovascular autonomic neuropathy (CAN) (13) and insulin resistance (IR) (14, 15), a wide range of micro- and macrovascular complications (see Table 1.1) and endothelial dysfunction (8, 16, 17). In particular, poor glycaemic control is associated with diabetes-related microvascular complications (e.g. retinopathy, nephropathy, and neuropathy) in T1D (18). Although, obesity is typically associated with T2D, many patients with T1D become overweight and/or obese as, due to improvements in care delivered, they live longer. The prevalence of obesity and overweight in T1D youths in the USA is 12.6% and 22.1% respectively as compared to youth without diabetes (16.9% and 16.1% respectively) (19).

Microvascular complications increase the risk of cardiovascular disease and mortality in patients with T1D (20, 21). The mortality rate ratio was about two times higher in T1D patients with diabetic kidney disease or neuropathy compare to T1D patients without microvascular complications (2.20, 95% CI 1.79 to 2.69 and 1.72, 95% CI 1.39 to 2.12, respectively) (20). Increasing the number of microvascular complications increases the risk of cardiovascular complications and mortality (21). As mentioned previously, several epidemiological studies have shown that T1D is a risk factor for cardiovascular outcomes; T1D was associated with increased risk of heart failure, myocardial infarction and ischemic stroke (22).

Table 1.1 Micro- and Macrovascular complications in T1D

Complication	Study name	Cohort characteristics	Prevalence
Retinopathy	DCCT (23)	Diabetes duration <5 years	≈ 44%
	WESDR (25-years cumulative rate) (24)	**At baseline** Age: 24.9±9.3 years Diabetes Duration: 10.7±7.1 years Males: 49.8% HbA1c:10.5±2.0%	83%
	EURODIAB (25)	Age: 32.5±10.0 years Duabetes duration 14.4±9.0 years	Nonproliferative ≈ 36% Proliferative ≈ 11%
Nephropathy	EURODIAB (26)	Age: 32.7±10.2 years Diabetes duration: 14.7±9.3 years HbA1c: 6.7±1.9% Males: 51.3%	Microalbuminuria ≈ 21% Macroalbuminuria ≈ 9%
CAN	EURODIAB (27)	Age: 32.7±10.2 years Diabetes duration: 14.7±9.3 years HbA1c: 6.7±1.9%	36%
	DCCT/EDIC (followed for >23 years) (28)	Median age: 27 years Median diabetes duration: 4 years Median HbA1c: 8.8% Males: 53%	44%
DPN	EURODIAB (29)	Age: 32.7±10.2 years Diabetes duration: 14.7±9.3 years HbA1c: 6.7±1.9% Males: 51.3%	28%
	DCCT/EDIC (followed for >23 years) (28)	Median age: 27 years Median diabetes duration: 4 years Median HbA1c: 8.8% Males: 53%	33%
Hypertension	EURODIAB (30)	Age: 32.7±10.0 years Diabetes duration: 14.7±9.3 years Males: 51%	24%
CVD	EURODIAB (31)	Diabetes duration: 14.7±9.3 years	Overall = 10% By age groups: 15-29 = 6% 30-44 = 8% 45-59 = 25%

Age, diabetes duration, HbA1c were reported as mean ± SD unless specified otherwise. CAN: cardiac autonomic neuropathy; DPN: diabetic peripheral neuropathy; CVD: cardiovascular disease; DCCT: The Diabetes Control and Complications Trial; EDIC: the Epidemiology of Diabetes Interventions and Complications ;WESDR: The Wisconsin Epidemiologic Study of Diabetic Retinopathy; EURODIAB: The EURODIAB IDDM Complications Study

1.2.3.1 T1D and retinopathy:

Diabetes retinopathy (DR) is a serious eye complication in patients with diabetes that might develop into a sight-threatening condition (32). It was reported that about 53% of T1D Indian participants developed retinopathy after about 12 years of diabetes duration (33). A retrospective study in the USA investigated the incidence of diabetic retinopathy in patients diagnosed with diabetes (T1D n=2240; T2D n=1768) under the age of 21 years. 20% of T1D and 7.2% of T2D developed DR over the median of about three years. Also, one unit increase in haemoglobin A1c (HbA1c) increased the hazard by 20% (HR 1.20, 95 % CI 1.06-1.35) (34). In addition, it was reported in a large longitudinal study (followed patients for 20 years in Wisconsin) that the severity of DR increased the cumulative risk of cardiovascular disease and mortality (35).

1.2.3.2 T1D and Kidney Function:

Hadjadj et al. (2016) conducted a large longitudinal study to compare the incidence of all-cause mortality and end stage renal disease (ESRD) between patients with T1D (n=277) and T2D (n=942). The study reported that the rate of death in T2D is about 3.4-fold higher than T1D, whereas ESRD was about 60% less likely in T2D as compared to patients with T1D. These results can be partially explained by some of the differences between the two groups: T2D patients were older, heavier and with a shorter diabetes duration. However, the death rate did not differ between the two groups after adjusting for age, and ESRD became non-significant after adjusting for age, sex and baseline creatinine (36).

In T1D patients with chronic kidney disease (CKD) stages 1 to 3 (eGFR $\geq$ 30 mL/min/1.73 m2), the risk of developing ESRD and death from non-ESDR-related causes (mainly cardiovascular disease) were compared using cohorts from four large cohorts: Joslin (USA),

FinnDiane (Finland), Steno (Denmark), INSERM (France). The study showed that the cohort with the highest risk of ESRD had the lowest risk of death, and cohort with the highest risk of death had the lowest risk of ESRD (37). This authors in this study suggested that death before developing ESRD does not compete with developing ESDR as ESRD and death unrelated to ESRD have different risk factors. Increased eGFR, older age and smoking were the risk factors for mortality. In contrast, higher albumin/creatinine ratio (ACR), lower glomerular filtration rate (eGFR), higher HbA1c, systolic blood pressure, and the smoking were the risk factors for developing ESRD (37). However, many studies have shown that the key cause of this trend is due to competitive risks, including mortality from cardiovascular disease (38, 39). Age and possibly diabetes duration play an essential role in increasing the risk of ESRD. In a US population cohort with predominantly T1D people, it was found that ESRD cases slightly reduced in the age groups below 40 whereas there was an increase in the age group 40-49 (40) despite the advances in renal protective strategies (e.g. controlling glucose level and lowering blood pressure) (41).

1.2.3.3 T1D and Neuropathy

Diabetic neuropathy is a general term used to describe nerve dysfunction or damage in patients with diabetes after exclusion of other possible causes. Diabetes peripheral neuropathy (DPN) is not a homogeneous disorder; indeed, there is a large variation in the clinical course of the disorder and the nerves involved (42, 43). The anatomical distribution of the nerve involvement divided into generalised symmetrical polyneuropathies or focal and multifocal neuropathies (44). Polyneuropathies include autonomic and chronic sensorimotor neuropathies. Focal neuropathies include mononeuropathies involving, for instance, ulnar, radial, and common peroneal nerves (44, 45). Distal symmetric sensorimotor polyneuropathy is the most common form of diabetic neuropathy (46) and involves both small and large fibres (45). Consequently,

its manifestations differ on the basis of the types of nerves involved, from a decreased perception of light touch and temperature to reduced pain perception in feet and loss of ankle reflexes (44, 45).

In addition to age and diabetes duration, glycaemic control is associated with diabetes-related neuropathy. Tesfaye et al. (29) conducted a study involving 3250 insulin-dependent patients with diabetes to identify the potential risk factors for developing diabetic neuropathy (peripheral and autonomic) (29). Neuropathy rates have been found to increase with age, diabetes duration, and HbA1c (29). Increased diastolic blood pressure, weight, height, current smoking, and fasting triglyceride have also been reported to increase the relative risk of neuropathy. Inversely, increased HDL-cholesterol was associated with a reduced relative risk of neuropathy (29).

Diabetic neuropathy is associated with increased morbidity. The same study by Tesfaye et al. (29) has shown an increase in the relative risk of diabetes-related neuropathy in the presence of cardiovascular disease and the progression of both albumin excretion and retinopathy (29).

A large prospective study (EURODIAB) followed-up 1172 patients with T1D for a mean (SD) of 7.3 (0.6) years to explore the incidence of diabetic neuropathy (autonomic and peripheral), and identify the possible risk factors for diabetic neuropathy (47). 276 (23.5%) of patients, who did not have neuropathy at baseline, developed neuropathy. The incidence of abnormal cardiac autonomic function was 17.3%, and the incidence of peripheral neuropathy ranged from 20.4 to 24.4% based on the assessment method. Patients who developed neuropathy were older, with longer diabetes duration, and had poorer HbA1c (47). After adjusting for diabetes duration and HbA1c, the study found total cholesterol, LDL cholesterol, triglycerides, body-mass index, albuminuria (microalbuminuria or macroalbuminuria), history of smoking, hypertension, retinopathy (any), and cardiovascular disease to be risk factors for neuropathy (47).

The EURODIB study, which is a large multicentre study of patients with type 1 diabetes (n=3007), found that cardiac autonomic neuropathy (CAN) was common in T1D with similar prevalence between males and females (35% and 37, respectively) (27). The study also found CAN to be associated with peripheral neuropathy (OR: 4.4; 95% CI: 3.6 to 5.3), severe background retinopathy (OR: 1.4; 95% CI: 1.1 to 1.9), and cardiovascular disease (OR: 1.5; 95% CI: 1.2 to 2.0) (27). The EURODIAB prospective complications study followed-up 956 patients with T1D for a mean (SD) of 7.3 (0.6) years and found that 163 (17%) patients developed CAN (48). The risk factors for the incidence of CAN were age, HbA1c, and feeling faint on standing up. Also, distal symmetrical polyneuropathy and retinopathy were identified as risk factors for incidence of CAN (adjusted OR: 1.9; 95% CI: 1.2 to 3.0 and 1.7; 95% CI: 1.1 to 2.6, respectively) (48).

DPN is common in patients with type 1 diabetes (up to 35%) (29, 42, 49). Distal symmetric sensory polyneuropathy is the most common form of diabetic neuropathy, which can cause a loss of sensation, foot ulceration, and in some cases, can lead to amputation (50-52). This form of peripheral neuropathy may cause painful neuropathy, which has been described by patients in various forms of sensation such as burning, prickling, aching, or cramping, which usually worsens at night (50). Several mechanisms such as peripheral changes in sodium and calcium channel distribution and expression, alter peripheral blood flow, small fibres damage, central sensitisation, and increased glycaemic flux (53) were hypothesised to explain neuropathic pain, but the exact mechanism is still unclear (50, 53). A large community-based study in the UK involving 15,692 patients with diabetes (type 1 [n=1,338]; type 2 [n=14,206]) found that 34% had painful neuropathy whereas 21% had DPN. Compared to type 2 diabetes, both painful neuropathy and DPN were lower in patients with type 1 diabetes (35.0% vs 22.7% and 21.5%

vs 13.4%, respectively). However, patients with T1D were younger and had significantly less clinical neuropathy, foot deformities, and peripheral arterial disease (54).

The Diabetes Control and Complications Trial (DCCT) investigated the impact of intensive insulin therapy on the development of diabetes-related complications compared with conventional therapy in 1441 patients with insulin-dependent diabetes. The study found that intensive insulin therapy had a 60% reduction in the risk of neuropathy (55). Therefore, the conventional therapy group was also encouraged to begin intensive therapy at the end of the DCCT study. The Epidemiology of Diabetes Interventions and Complications (EDIC) study was conducted to follow-up the patients who were enrolled in the DCCT study, and to explore the difference between the two groups following intensive therapy. The EDIC study found people who were on intensive therapy had a lower prevalence of DPN compare with people who were on conventional therapy during DCCT (25% vs35%, respectively) (42). Similarly, people who were on intensive therapy had a lower prevalence of CAN compared with conventional therapy (29% vs 35%, respectively) (42). A Danish study of 339 young T1D patients (age ranges from 12 to 27 years old, and diabetes duration ranges from 9 to 25 years) have shown that about 62% had a reduction in vibration perception threshold (>6.5 V) suggesting that a large number of young T1D patients might start developing peripheral neuropathy early in life without showing clinical symptoms of neuropathy (56).

1.2.4 The pathogenesis of diabetes-related complications

Several genetic and non-genetic factors, such as hyperglycaemia, hypertension, and hyperlipidaemia, may cause or accelerate tissue damage (endothelial dysfunction) in patients with diabetes (57). The Joslin Medalist study (58) and the Golden Years Cohort (59) examined the characteristics of T1D patients with extreme diabetes duration (>50 years) and suggested that genetic factors might promote resistance to complications in their cohorts. This suggestion

was partially supported by linking elevated high-density lipoproteins to the absence of microvascular complications (58, 59). The Joslin Medalist study has also found detectable (0.03-0.2 nmol/l) or sustained (≥0.2 nmol/l) residual C-peptide levels in 67.4% indicating residual functional beta cells and the presence of insulin-producing cells (60).

The C-peptide treatment has been reported to provoke the release of endothelial nitric oxide synthase (eNOS), increased nerve Na+/K+-ATPase activity, and many transcription factors that may enhance the function of nerves and improve nerve structure defects (61). In patients with T1D, C-peptide treatment improved autonomic nerve function (62), microvascular function (63), kidney function (64), and sensory nerve dysfunction (64).

Hyperglycaemia-induced tissue damage tends to primarily occur in tissues where insulin is not required for glucose uptakes such as endothelial tissue, mesangial cells, and neurons (57). This tissue damage may cause end-organ damage such as retinopathy, nephropathy, and neuropathy. The DCCT study (discussed above) has shown the significant role of hyperglycaemia in the development and progression of diabetes-related complications in patients with T1D and how intensive insulin therapy was able to slow the progress of diabetes-related complications (55). Long-term hyperglycaemia is the primary risk factor that causes long-term tissue and organ damage in type 1 and type 2 diabetes (65).

Many pathways have been hypothesised to explain the pathogenesis of vascular complications in patients with diabetes. These pathways are mainly activated due to hyperglycaemia. They include the polyol pathway, protein kinase C (PKC) pathway, advanced glycation end products (AGEs) pathway, hexosamine pathway, and mitochondrial overproduction of superoxide (Figure 1.1) (57).

Long term hyperglycaemia leads to an activation of the polyol pathway. The polyol pathway involves reducing glucose molecules to sorbitol via utilisation of the aldose reductase enzyme. Aldose reductase oxidises NADPH to NADP+ to convert glucose to sorbitol (57). This process consumes the cofactor NADPH, which is required for restoring reduced glutathione (a crucial intracellular antioxidant)(57). Therefore, intracellular oxidative stress can increase due to the reduction in the amount of reduced glutathione (57). Sorbitol dehydrogenase then converts sorbitol to fructose in a process that involves reducing NAD+ to NADH. It is suggested that the rise in cellular glucose leads to an increase in the NADH/NAD+ and decrease in NADPH, which can lead to an accumulation of sorbitol and oxidative stress in the cells especially in retina, kidney, and nerves (57, 66). Sorbitol has high osmotic effects that can cause cell damage when it is accumulated in the microvascular cells (67). Hyperglycaemia-induced polyol flux may cause neuronal damage due to aldose reductase induced oxidative stress (68).

Another pathway that might be activated by hyperglycaemia is the hexosamine pathway. Insulin-independent cells cannot control the amount of glucose transported in them. Therefore, once glucose is in the cell, glycolysis takes place to convert glucose into pyruvate. Most of the glucose metabolised to glucose-6-phosphate is converted into fructose-6 phosphate (57, 67). It is postulated that during sustained hyperglycaemia, some of the fructose-6-phosphate gets redirected to a hexosamine pathway where fructose-6-phosphate is converted to uridine diphosphate N-acetyl glucosamine (57). This substrate can lead to increased pro-inflammatory cytokines activity such as increasing transforming growth factor β and plasminogen activator inhibitor-1 by binding to serine and threonine residues of transcription factors (57, 67). Hyperglycaemia can, therefore, activate the hexosamine pathway leading to many changes in gene expression and protein function that together contribute to the pathogenesis of diabetes-related complications (57, 66, 67).

Hyperglycaemia is also postulated to cause micro- and macrovascular complications in patients with diabetes through the accelerated formation of advanced glycation end-products (AGEs) (69). AGEs are detected both intracellularly and extracellularly; however, intracellular auto-oxidation of glucose is considered to be the primary source of AGEs during hyperglycaemia (69). AGEs are a diverse group of molecules produced from the exposure of proteins, lipids, and nucleic acids to glucose-derived dicarbonyl precursors (such as glyoxal and methylglyoxal) (67, 69). Accumulation of AGEs leads to tissue dysfunction and subsequently, diabetic complications (67, 69). AGEs have been associated with several pathological effects, including altering signalling pathways, increasing endothelial cell permeability, increasing vascular stiffness, decreased eNOS activity, and decreased vessel elasticity (66, 67). Three mechanisms of intracellular AGE precursors have been identified for both intracellular and extracellular damage to cells. The first mechanism is to modify intracellular proteins which may alter protein function, including proteins involved in gene transcription regulation (57, 66, 67). The second mechanism is to modify extracellular matrix molecules and interfere with cell-to-matrix and matrix-to-matrix interactions and therefore cause cell dysfunction (57, 67). The third mechanism is to modify the proteins circulating in the plasma. The binding to and activation of AGE receptors (RAGE) by these AGE-modified proteins mediates the production of reactive oxygen species, growth factors, and inflammatory cytokines leading to pathological changes (57, 67).

Hyperglycaemia is also postulated to activate protein kinase C (PKC) pathway. There are a family of PKC enzymes, and most isoforms can be directly activated by diacylglycerol (DAG). Hyperglycaemia increases the concentration of intracellular diacylglycerol (DAG) in some cells and has been linked to PKC in diabetic animals (66, 67). Increased polyol pathway and RAGE activities during hyperglycaemia can also indirectly activate PKC pathways, possibly through

reactive oxygen species generation (67). PKC induces a number of negative effects, including vascular complications and blood flow abnormalities in retina and renal glomeruli due to decreased eNOS and increased endothelin-1 activity (67, 70). Reducing blood flow to the retina, for example, causes local hypoxia (70). PKC also enhances the expression of vascular endothelial growth factor (VEGF) due to hyperglycaemia, which induces angiogenesis and endothelial permeability (67).

Hyperglycaemia-induced PKC activity also promotes the overexpression of plasminogen activator inhibitor-1, transforming growth factor-β1, type IV collagen, and fibronectin, which contribute to microvascular dysfunction and occlusion (67). Hyperglycaemia-induced PKC activation also promotes the overexpression of plasminogen activator inhibitor-1, transforming growth factor-β1, type IV collagen, and fibronectin, which contribute to microvascular dysfunction and occlusion (67). Pro-inflammatory gene expression and oxidative stress are also increased via increased NF-kB and NADPH oxidase (67).

The mitochondria contribute to diabetes complications by the overproduction of reactive oxygen species. Glucose metabolism continues in the mitochondria via the transport of pyruvate and NADH, which are the products of the cytoplasmic glycolysis (67). In the mitochondria, the tricarboxylic acid (TCA) cycle can oxidise the pyruvate and generate one FADH2 molecule and four NADH molecules plus CO2 and H2O (67). FADH2 and NADH are necessary to generate ATP through the electron transport chain via oxidative phosphorylation (67). NADH donates electrons to complex I and FADH2 donates electrons to complex II in the mitochondrial electron-transport chain (67). Electrons flow from complexes I and II to coenzyme Q which then transfer the electrons to complex III, cytochrome-C, and complex IV to generate a proton (voltage) gradient across the mitochondrial membrane (67). The electrons are then transferred from complex IV to oxygen molecules (O2) that is reduced to H2O (57). The voltage gradient

generates the energy necessary for ATP synthesis. Uncoupled protein 1 (UCP1) allows the protons to return back to the inner mitochondrial membrane in the form of heat to keep the synthesis rate of ATP steady (57). Hyperglycaemia increases the amount of NADH and FADH2 (electron donors) intracellularly (57). The mitochondrial membrane voltage gradient is therefore raised to a critical threshold. This threshold blocks the flow of electrons to complex III and causes electrons to accumulate in coenzyme Q. Coenzyme Q then generates superoxide by donating the backed-up electrons to O2 (57). Hyperglycaemia-induced overproduction of mitochondrial superoxide is found to activate poly(ADP-ribose) polymerase (PARP), which then inhibits glyceraldehyde-3 phosphate dehydrogenase (GAPDH) (71). Activation of PARP and inhibition of GAPDH has been found to activate the alternative metabolic pathways (polyol, PKC, AGEs, and hexosamine) (71).

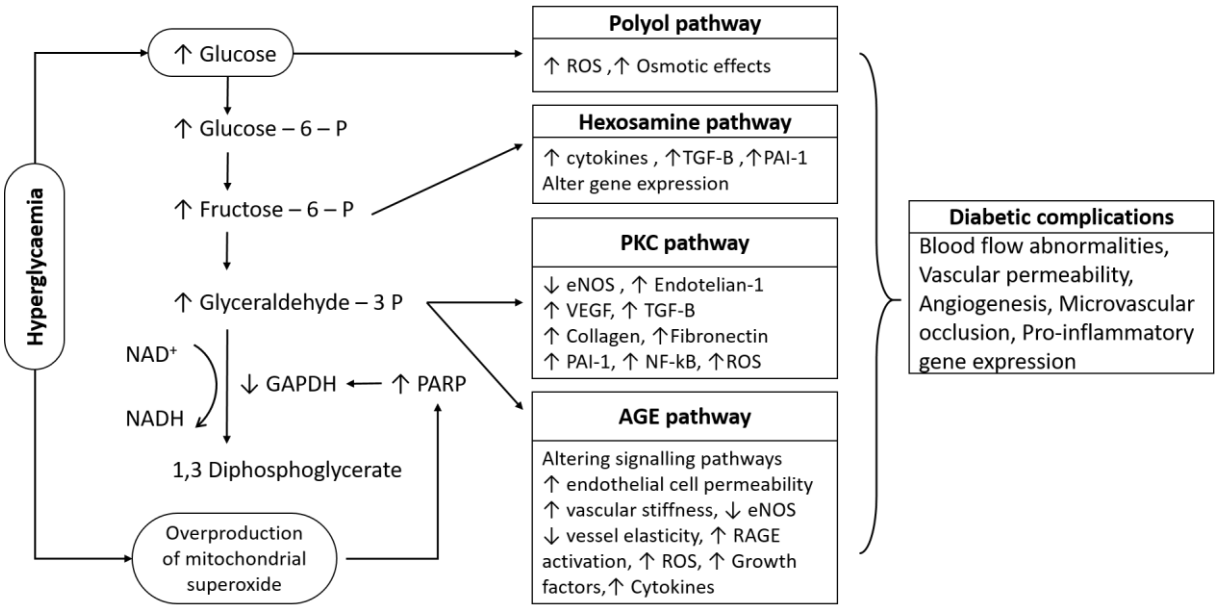


Figure 1.1 Possible mechanisms explaining the development of complications in patients with diabetes (adopted from Brownlee (57)).

1.3 Obstructive Sleep Apnoea

1.3.1 OSA epidemiology

Sleep apnoea is a sleep-disordered breathing (SDB) condition in which a person has recurrent events of breathing cessation during sleep. Obstructive Sleep Apnoea (OSA) is the type of SDB that occurs despite the person's effort to breathe and contrasts with central sleep apnoea, in which the person lacks the central drive for breathing (72). OSA is characterised by upper airway instability resulting in recurrent episodes of complete (apnoea) or near complete (hypopnoea) upper airway obstruction resulting in recurrent episodes of oxygen desaturation and re-saturation (chronic intermittent hypoxia; CIH), cyclical changes in blood pressure, heart rate, and sympathetic activity and disruption to sleep architecture (such as loss of rapid eye movement (REM) and stages 3 and 4 of sleep) (73). OSA is the most common type of sleep-disordered breathing (SDB) (74), and importantly, it often goes undiagnosed (75). The typical night-time symptoms include snoring, witnessed apnoea, nocturnal choking or gasping, and insomnia. Whereas the daytime symptoms include excessive daytime sleepiness, fatigue, memory impairment, and depression (76). Several cross-sectional, longitudinal and interventional studies showed that OSA is associated with increased risk of road traffic accident which was reversible with nocturnal continuous positive airway pressure (CPAP), which is the main treatment for OSA (77, 78).

1.3.2 OSA prevalence:

In middle-aged adults the prevalence of asymptomatic (without hyper-somnolence) OSA (apnoea-hypopnoea index: AHI $\geq$ 5) was estimated to be 24% in men and 9% in women (79). However, the prevalence went down to 4% in men and 2% in women when hyper-somnolence was considered (79). A systematic review of epidemiological studies found that the prevalence

of OSA varies broadly between included studies, and ranged from 9.3 to 71.9% for AHI=>5 (see below). In addition, the review showed that higher BMI, advancing age, and being male increase the prevalence of OSA (80).

1.3.3 OSA scoring:

According to the American Academy of Sleep Medicine (AASM), an apnoea episode is recorded if airflow drops by 90% for 10 seconds or more. A hypopnea episode is recorded if the airflow drops by 30% for 10 seconds or more together with 4% oxygen desaturation from baseline, *or* if the airflow drops by 50% for 10 seconds or more together with 3% oxygen desaturation from baseline. AHI is the way of reporting the severity of sleep apnoea, and it is reported as the number of events per hour (74). AHI is categorised as normal (AHI <5), mild (AHI 5–15), moderate (AHI 15–30), or severe (AHI >30).

1.3.4 OSA and stress

Apnoeic events during sleep could lead to episodes of hypoxia and sleep fragmentation. Hypoxia and sleep fragmentation could act as stressors on the nervous system and activate the hypothalamic-pituitary-adrenal (HPA) axis and the sympathoadrenal system, which are essential components of the response to stress (81). The HPA axis is usually suppressed during normal sleep (81). Intermittent hypoxia and sleep fragmentation in patients with OSA are known to cause stress and alter the HPA axis. The effect of CIH on the HPA axis was investigated on animals by comparing rats exposed to either CIH for 30 days or room air. The rats exposed to CIH showed an increase in HPA axis activity as compared to rats exposed to room air (82). In a human study, it was found that patients with untreated moderate to severe OSA had increased adrenocorticotropic hormone (ACTH) and cortisol pulsatile production and secretory burst half-duration. Indeed, there was a correlation between ACTH secretion and

duration of oxygen below 95%. However, all these parameters were ameliorated after three months of compliance CPAP (83). Cortisol response was increased in healthy subjects after exposure to sleep deprivation compared to participants who had a night of normal sleep, and cortisol response was boosted after exposure to a social stress test in the morning (84). Increase cortisol level leads to an increase in the glucose level in the blood and decrease insulin sensitivity (85). The sympathoadrenal system directly stimulates the adrenal medulla in response to the stressors, which then stimulate the release of catecholamines such as adrenaline and noradrenaline, better known as "fight and flight" response (81).

1.3.5 OSA and quality of life (QoL):

OSA may have serious effects on patients' health and QoL (75). Several studies have linked OSA to impaired health-related quality of life. A large (n=837 men) Australian study recruited people *never been diagnosed with OSA* from the Men Androgen Inflammation Lifestyle Environment and Stress Study to investigate the association between OSA and QoL using the Short Form (36) Health Survey. The study reported impairment of the physical component of the survey in patients who are 40 to 69 years old and had AHI $\geq$ 10, and this impairment was worse for people with severe OSA (AHI $\geq$ 30) despite excessive daytime sleepiness (86). A case-control study in India reported impairment in daily function, social interaction, emotional functioning, and symptoms associated with OSA in patients with OSA compared to controls (87). However, the OSA group were heavier, and females were under-represented (one fifth in the OSA group and one quarter in controls) (87). In Iceland, a large study recruited patients newly diagnosed with moderate to severe OSA who were starting CPAP treatment to examine the effect of OSA treatment on their QoL (88). This study included 822 OSA patients and 742 controls. The physical and mental component scores of the Short Form 12 (SF-12) survey, which is used to assess physical and mental health, were lower in the OSA group compared to

the controls. Two years of CPAP treatment improved both physical and mental component scores compared to their baseline scores, but both scores were still lower than the controls. Interestingly in the OSA group, this study found no relationship between OSA and QoL. Instead, there was a relationship between OSA comorbidities (insomnia and excessive daytime sleepiness) and QoL impairment (88). Given this evidence, it is important to look for associations between T1D and OSA – as early diagnosis of OSA in T1D may help to ameliorate the deterioration in QoL.

1.3.6 OSA and cardiovascular disease

Increased sympathetic activity (89), cellular (90) and systemic oxidative stress (91), and systemic inflammation (92) are all potential mechanisms by which OSA may lead to atherosclerosis and endothelial dysfunction.

The Wisconsin Sleep Cohort Study showed that OSA (even mild) is a risk factor for the development of non-dipping systolic blood pressure (BP) (93) and several RCTs showed that CPAP lowered blood pressure effectively, although this may not be more than other blood pressure lowering treatments (94-96). Furthermore, OSA has been associated with increased risk of cardiovascular disease and that CPAP treatment lowered that risk in observational longitudinal studies (3, 97, 98). RCTs examining the effect of CPAP on cardiovascular (CV) outcome in patients with moderate to severe OSA showed conflicting results (99-101). One RCT, that included patients with ischaemic heart disease, showed a significant delay in the time to the second CV event in the CPAP group, but the total number of events did not differ significantly between the two groups after two years (101). Two RCTs did not show effects on cardiovascular outcomes when an intention-to-treat analysis was used, but the significant impact of CPAP was found when data was adjusted for CPAP adherence (99, 100).

1.3.7 Obstructive sleep apnoea and diabetes mellitus

Many studies have acknowledged OSA as an independent risk factor for abnormal glucose metabolism, hypertension, and cardiovascular diseases (102, 103). Also, it was found that a one unit increase in AHI increased insulin resistance (measured as homeostasis model Assessment of Insulin Resistance (HOMA-IR)) and fasting insulin level by 0.5% (104). Harsch et al. (105) examined the effect of CPAP on insulin resistance on 40 patients (AHI>20; BMI = 32.76 ± 6.92 kg/m^2), and found that insulin sensitivity significantly improved after two days of CPAP use. This improvement persisted after three months of CPAP use (baseline = 5.75 ± 4.20; after 2 days = 6.79 ± 4.91, p=0.003; after 3 months = 7.54 ± 4.84, p=0.001) with no significant change in BMI. This improvement may also indicate that OSA is an independent risk factor for insulin resistance (105).

Several longitudinal studies have shown that OSA is a risk factor for developing T2D independent of confounders including obesity (106, 107). Botros et al. (106) studied whether OSA is an independent risk factor for developing diabetes in 544 patients who were followed-up for about 2.7 years, and they found that patients with an AHI ≥ 8 had adjusted HR of 1.43 (1.10–1.86; P = 0.008) (106).

OSA is very common in patients with T2D, several studies showed an OSA prevalence of 24%-86% in patients with T2D (1, 108-110). The wide range of prevalence is due to variation in the population examined (for example primary care vs secondary care, newly diagnosed vs long term diabetes), the methods of diagnosing OSA (questionnaires vs. portable devices vs. polysomnography) and the criteria used to diagnose OSA (for example AHI vs. oxygen desaturation index (ODI) or different cut offs of AHI such as 5, 10, 15, 30 or considering the presence of excessive daytime sleepiness). Our local data from Birmingham Heartlands

Hospital showed an OSA prevalence of 66% in patients with T2D with higher prevalence in White Europeans compared to South Asians (110).

Several studies showed that OSA is associated with worse glycaemic control in patients with T2D but whether OSA treatment improves glycaemic control is still unclear as two RCTs showed that CPAP had improved HbA1c (111, 112) while one RCT showed that CPAP did not affect HbA1c (113). OSA has been associated with diabetic autonomic neuropathy (114, 115), peripheral neuropathy (116), upper airway neuropathy (117), diabetic retinopathy and chronic kidney disease in patients with T2D (118, 119). A T2D longitudinal study showed an increased odd of sight-threatening DR (STDR) in patients with OSA compared to T2D only (OR 2.3; 95% CI 1.1-4.9; p=0.04) after adjusting for several confounders. Also, patients with OSA had an increased risk of progression of the disease to pre-proliferative or proliferative DR (OR 5.2; 95% CI 1.2-23.0; p=0.03) (120).

Despite the above-mentioned associations of OSA in patients with T2D, the impact of OSA in patients with T1D has received little attention. Patients with T1D might be leaner and younger than patients T2D which might, in part, explain the limited number of studies investigating OSA in T1D.

1.3.8 Obstructive Sleep Apnoea and Diabetic peripheral Neuropathy

OSA has been linked to DPN in patients with T2D. A large T2D study (n=234) found that the prevalence of DPN was significantly higher in T2D with OSA compared to T2D without OSA (60% vs 27%, p <0.001) (110). The presence of sleep apnoea was compared among non-obese T2D with (n=20) and without (n=10) DPN and controls (n=10; healthy age, sex, and BMI match). Sleep apnoea was significantly higher in T2D with DPN than T2D without DPN and controls (T2D with DPN: 40%, without DPN: 10%, controls: 10%)(121). In addition, analysis

of excess daytime sleepiness by multiple sleep latency test tool showed that T2D with DPN had reduced sleep latency compared to T2D without DPN and controls (9.2 ± 4.0 vs 15.1 ± 3.4 vs 16.3 ± 2.2 respectively) (121). Also, T2D with DPN was found to have significantly higher snore and arousal indices (121).

There might be a symptom overlap between painful DPN and OSA. A study of 126 patients found that people with peripheral root or nerve lesions and peripheral neuropathic pain commonly complained about difficulties of sleep (88%) and concentration (76%), as well as lack of energy (86%) and drowsiness (71%) (122). Worse sleep quality was significantly linked to painful DPN. According to clinical observations, neuropathic pain is often worse at night. (123, 124). Analysis of sleep impairment using the Medical Outcomes Study Sleep Scale on 255 patients revealed that patients with painful DPN had worse scores than the general population norm (125). Painful DPN also shows symptoms that overlap with obstructive sleep apnoea. These symptoms include snoring, inadequate sleep leading to tiredness and fatigue upon awakening, and sleepiness during daytime (126). Patients with painful DPN reported difficulties initiating and maintaining sleep (126). Also, a recent review found memory impairment to be common in patients with chronic pain (127).

1.4 Obstructive Sleep Apnoea and Type 1 Diabetes Mellitus

As mentioned above, patients with T1D are leaner and younger than patients with T2D, hence OSA might potentially be less common in patients with T1D compared to T2D and may not necessarily be related to obesity. In addition, the relationship between OSA and glycaemic measures and diabetes-related outcomes might differ in patients with T1D from T2D due to the very long duration of diabetes in patients with T1D and the differences in the pathogenesis of T1D and T2D.

Seven studies have assessed the prevalence of OSA in patients with T1D (109, 114, 128-132) (Table 1.2). One of these studies was questionnaire based (129), three studies were based on oximetry (109, 128, 130), and three studies were based on polygraphy and/or polysomnography (114, 131, 132). Two of these studies were published only in the form of an abstract with no full publication available (130, 132). The reported prevalence of OSA in T1D ranges from 8-46% (109, 128, 131). The more recent studies showed the higher prevalence but the studies were small, with 5 studies having less than 90 patients. However, the OSA prevalence reported in these studies overlap with that reported in patients with T2D although the average BMI was largely within the normal range in these studies but the diabetes duration was very long (Table 1.2). This suggests a mechanism other than obesity may be responsible for OSA in patients with T1D, such as CAN as mentioned above. This is further supported by the finding that in T1D children both the duration of diabetes and the glycaemic control may increase the risk of central apnoea by causing signs of ventilatory dysfunction (133).

Table 1.2 Summary of studies that examined OSA prevalence in patients with T1D

Author	*Mondini et al. (114)*	*Borel et al. (128)*	*Schober et al. (109)*	*van Dijk et al. (129)*	*Iosup et al. (130)*	*Manin et al. (131)*	*Meyer et al. (132)*
Year	1985	2010	2011	2011	2012	2014	2015
N	12	37	58	99	81	67	90
Male (n)	8	25	31	55	41	60	NR
Age	34	43±13	42.4±14.5	43.9±1.3	53.4±14.6	54±10	52±11
BMI	NR	24.7±3	25.4±5.1	24.5±0.3	NR	25.8±4.7	26±4.7
DD	NR	23±14	16.9±14.2	26.9±1.2	23.3±12.9	29±14	28.8±14
Ethnicity	NR	NR	NR	NR	NR	NR	NR
CAN Tested?	Yes	No	No	No	NR	No	No
OSA screening Tool	PG	Oximetry	Airflow & pulse oximetry	Berlin questionnaire	Oximetry	PSG and PG	PSG and PG
Prevalence	8	35	10.3	17.2	27.1	46	43

N: Sample Size; BMI: Body Mass Index; DD: Diabetes Duration; CAN: Cardiac Autonomic Neuropathy; NR: not reported; PSG: Polysomnography; PG: Polygraphy

OSA is accompanied by episode of oxygen desaturation that might also contribute to the development of cardiovascular complications in patients with T1D. Oxygen desaturation index (ODI), lowest O_2 saturation and time spent with oxygen saturation below 90% were all higher in patients T1D and OSA. Micro- and macrovascular complications were also higher in patients with T1D and OSA (128, 131).

The relationship between OSA and glycaemic control in T1D is unclear. In one study by Meyer et al. (132) there was no difference in HbA1c between patients with and without OSA (132). However, the mean HbA1c for the sample was 7.59±1.1% suggesting that in these patients their diabetes is reasonably well controlled; therefore, there may be little room to detect any difference (132). A more recent study found that T1D patients with increased risk of OSA

(based on the Berlin questionnaire) had higher HbA1c than patients with low risk (8.2% ± 0.9 vs. 7.3% ± 0.35, P = 0.03) (134).

The relationship between OSA and diabetes-related vascular disease is poorly explored in patients with T1D. A recent cross-sectional study showed that vascular disorders (based on medical records; OR = 8.28; 95% CI: 1.56–43.97; P = 0.013) and retinopathy (based on retinal images; OR 4.54; 95% CI: 1.09–18.82; P = 0.04) were associated with OSA in T1D, but the confidence intervals were wide so it was difficult to assess the effect size (131). Also, the prevalence of acute coronary syndrome, hypertension, retinopathy, and neuropathy (32%, 87%, 84% and 64.5% respectively) were significantly higher in T1D with OSA as compared to without OSA (3% ($p<0.01$), 47% ($p<0.01$), 31% ($p<0.01$) and 36% ($p=0.03$) respectively) (131). However, these findings were not adjusted for potential confounders.

The role of CAN in OSA in patients with T1D was explored in one small study of 20 lean patients with T1D with (n=9) and without (n=11) CAN; there were no significant differences with regard to HbA1c and duration of diabetes. The two groups were age and BMI matched to 22 healthy controls. OSA was significantly higher in lean T1D patient with CAN than both the patients without CAN and the controls (67%, 23%, and 4.5% respectively; CAN+ vs. CAN-, p = 0.02 and CAN+ vs. Control, p = 0.006) (135).

1.5 Aim and objectives

Given the importance of good glycaemic control in T1D, it is crucial to detect other factors such as OSA that could contribute to reducing diabetes-related complications. OSA is a treatable condition, but it could easily be underdiagnosed (75, 76). Limited small cross-sectional studies have attempted to address this problem. It is, therefore, tempting to speculate that sleep apnoea (possibly central) develops early in the course of T1D (133); however,

diabetes duration and worsening of CAN might lead sleep apnoea to progress to mainly obstructive sleep apnoea. The overall aim of this thesis was to investigate the relationship between OSA and diabetes-related complications in T1D patients. The following are the objectives of the thesis:

1. Chapter 3 aims to conduct a systematic review of the available evidence on the relationship between OSA and diabetes-related complications in adults T1D.
2. Chapter 4 aims to conduct a clinical observational study to examine the relationship between OSA and CAN in patients with T1D.
3. Chapter 5 aims to use the clinical study cohort to assess the relationship between OSA and metabolic profile, presence of DR, CKD, DPN, and quality of life in T1D patients.
4. Chapter 6 aims to conduct a survival analysis to assess the incidence/risk of developing OSA in patients with T1D compared with the general population (without diabetes), and to identify the predictor factors associated with incidence OSA in T1D population.
5. Chapter 7 aims to conduct another survival analysis for patients with T1D only to evaluate the impact of OSA on the macro- and microvascular complications in T1D patients with OSA compared with T1D population without OSA.

1.6 Hypothesis

We hypothesised that OSA is associated with diabetes-related micro- and macrovascular complications (such as cardiovascular disease, cardiac autonomic neuropathy, peripheral neuropathy, nephropathy, and retinopathy) in patients with T1D.

CHAPTER TWO: METHODS

2.1 Overview

In order to explain the previously explained aim, we have conducted four studies. The first study was a systematic review to identify the available studies examining the relationship between OSA and diabetes-related complications in adult patients with T1D (chapter three). The second study was a cross-sectional to investigate the presense and link of OSA to metabolic profile and diabetes-related microvascular complications (chapter four and five). The third and fourth studies were retrospective population-based studies. We conducted a survival analysis in chapter six to assess the incidence of developing OSA in patients with T1D compared to an appropriately matched control population (people without diabetes). In addition, we identified OSA predictor factors in T1D. Then, we conducted another survival analysis, using different dataset, to assess the impact of OSA on the diabetes-related vascular disease in T1D patients with OSA compared to an appropriately matched control T1D population without OSA (chapter seven).

2.2 Systematic review methodology - chapter 3

This review was registered online on PROSPERO (2018: CRD42018094118)(136). This review was reported according to the PRISMA statement, which aims to assist authors enhance the reporting of systematic reviews and meta-analysis. The PRISMA Statement consists of a checklist (27 items) and a flowchart (four phases) (137). The checklist items focus on the essential items for the reporting of clear and transparent systematic review (137). The flowchart illustrates the four phases of the selection process (identification, screening, eligibility, and inclusion) (137, 138).

2.2.1 Search strategy:

The search strategies were developed using index terms and keywords related to type 1 diabetes and obstructive sleep apnoea (see Appendix 2.1 for sample search strategy in Embase). No study design filters were applied. Embase, MEDLINE, CINAHL, and the Cochrane Database of Systematic Reviews were searched on 17 May 2018 for published articles, and repeated on 3 June 2019 to identify recently published articles. PubMed was searched for the last 6 months to capture any studies that have not yet been indexed in MEDLINE. The ISRCTN registry and ClinicalTrials.gov databases were searched for ongoing and recently completed studies. No date or language limitations were applied, and manual scanning of the reference lists of identified papers was carried out to capture additional studies. Experts in the field of diabetes and sleep-disordered breathing were consulted for published and unpublished literature.

2.2.2 Eligibility criteria and screening

The selection of the studies was performed electronically by two independent reviewers, Ziyad Alshehri and Abdulaziz Alzahrani, in two stages. 1) Screening titles and abstracts for inclusion criteria: this was conducted using the Rayyan web application (139). 2) Full-text review. Disagreements in screening were resolved by discussion between the reviewers, and a third independent reviewer CR was invited to facilitate the final decision if needed. A PRISMA flow diagram was used to document the study selection process, and a record kept of reasons for exclusion of studies (see Appendix 2.2). The eligibility criteria are outlined below:

2.2.2.1 Participants:

Adults (>17 years old) with type 1 diabetes and OSA as measured by objective tools (e.g. portable polygraphy, polysomnography). Studies with a mixed diabetes population (type 1 and

type 2) were eligible for inclusion where data could be extracted for the type 1 population separately.

2.2.2.2 Comparator population:

The comparator group were patients with type 1 diabetes but no OSA.

2.2.2.3 Outcomes:

Primary outcomes:

- Prevalence and severity of OSA in patients with T1D.

Secondary outcomes:

- Prevalence and severity of OSA in patients with T1D.
- Diabetes-related complications (peripheral neuropathy, autonomic neuropathy, retinopathy, chronic kidney disease) in patients with T1D with vs. without OSA.
- Measures of glycaemic control such as HbA1c (mmol/mol, %) in T1D patients with and without OSA.
- Total daily dose of insulin (U/kg) in patients with T1D with and without OSA.

2.2.2.4 Studies:

Any primary study that included the relevant population and comparator population and reported at least one of the above-mentioned primary or secondary outcomes was eligible for inclusion in this systematic review.

2.2.2.5 Exclusion criteria

Non-human studies, editorials, guidelines, or reviews. However, reviews were used for citation checking.

2.2.3 Data extraction

Data were extracted on population characteristics (age, BMI, sex, and diabetes duration, HbA1c), study methodology (such as cross-sectional or longitudinal) and results (such as prevalence of OSA, proportion with retinopathy, or autonomic neuropathy). A standardised and piloted data extraction form (Appendix 2.3) was used. Data extraction was performed by one author (ZA) and independently verified by another author (AA). Disagreements were resolved through discussion. Corresponding authors were emailed for additional data if needed for the meta-analysis.

2.2.4 Risk of bias assessment

All included studies were cross-sectional, and the quality and risk of bias were assessed using the appraisal tool for cross-sectional studies (AXIS) (140).

The tool included 20 questions from AXIS (Table 2.1). All of the included articles were evaluated using the questions listed in table 2.1. All questions were answered as either yes or no. Yes in all questions except questions 13 and 19 were coded as number one. No in all questions except 13 and 29 were coded as number zero. There are no cut-offs published with these tools. However, we coded the answers to give a semi-quantitative measure of the studies in line with the assessment tool.

Table 2.1 Quality assessment tool

	Introduction
Q1	Were the aims/objectives of the study clear?
	Methods
Q2	Was the study design appropriate for the stated aim(s)?
Q3	Was the sample size justified?
Q4	Was the target/reference population clearly defined? (Is it clear who the research was about?)
Q5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?
Q6	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?
Q7	Were measures undertaken to address and categorise non-responders?
Q8	Were the risk factor and outcome variables measured appropriate to the aims of the study?
Q9	Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?
Q10	Is it clear what was used to determined statistical significance and/or precision estimates? (e.g. p-values, confidence intervals)
Q11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?
	Results
Q12	Were the basic data adequately described?
Q13	Does the response rate raise concerns about non-response bias?
Q14	If appropriate, was information about non-responders described?
Q15	Were the results internally consistent?
Q16	Were the results presented for all the analyses described in the methods?
	Discussion
Q17	Were the authors' discussions and conclusions justified by the results?
Q18	Were the limitations of the study discussed?
	Other
Q19	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?
Q20	Was ethical approval or consent of participants attained?

2.2.5 Synthesis

Findings related to primary or secondary outcomes in those with and without OSA were narratively described with key results tabulated. Random-effects meta-analysis was performed where at least two studies reported the same outcome. Pooled ORs were presented for complication (autonomic neuropathy, peripheral neuropathy, retinopathy, and/or chronic kidney disease) and pooled weighted mean difference (WMD) was used where studies reported continuous outcomes such as eGFR.

The χ^2 test was used to test for heterogeneity, and the I^2 was used to quantify heterogeneity. All meta-analyses except the meta-analysis of OSA proportions were undertaken using Cochrane Review Manager version 5.3 (RevMan). Meta-analysis of OSA proportions were undertaken using MedCalc for Windows version 19.1.3 (MedCalc Software, Ostend, Belgium). MedCalc uses a Freeman-Tukey transformation to calculate the weighted pooled prevalence under the fixed and random effects model (141, 142). Formal assessment of publication bias using funnel plots was performed for the prevalence, however, formal assessment of publication bias using funnel plots and performing meta-regression for diabetic complications were not feasible given the small numbers of studies in the meta-analyses.

2.3 Clinical study methodology (cross-sectional) – chapter 4 and 5

2.3.1 Study Design

This study was an observational cross-sectional study of patients with T1D attending secondary care diabetes clinics in Birmingham.

2.3.2 Study group

Patients with T1D were recruited consecutively from the diabetes clinics at University Hospitals Birmingham NHS Foundation Trust (formerly Heart of England NHS Foundation Trust (HEFT)) by a member of the clinical team.

2.3.3 Study group and recruitment process

Patients were approached and invited to participate in the study by the clinical team during their routine clinical check-ups. The patient information sheet (PIS) was handed to patients by the clinical team, then the PhD student (Mr Alshehri) or a research nurse telephoned the patient after at least 48 hours to check whether the patient was willing to proceed. Patients willing to participate were booked appointments with Mr Alshehri at a time that was convenient for them. During these appointments, patients had the opportunity to ask any questions regarding the study. If patients then agreed to participate, consents were obtained by Mr Alshehri. Following consenting, a copy was given to the patient, a copy was kept in the study file, and a copy was filed in the medical record. Eligibility to participate in the study was checked following the inclusion and exclusion criteria below, and then the data was collected.

2.3.4 Inclusion Criteria:

1. T1D patient aged 18 and above, who was diagnosed more than four years ago.
2. Able to give informed consent.
3. Has sufficient proficiency in English to verbally answer interview questions.

2.3.5 Exclusion Criteria

1. Past medical history of severe respiratory disorders, including treated OSA.
2. Patients using oxygen supplementation.
3. Patients with end-stage renal disease receiving dialysis.

4. Pregnancy.
5. Dementia.
6. End-stage diseases with life expectancy below six months.
7. Patients with implantable devices.
8. Patients with known atrial fibrillation.

2.3.6 Data collected

Mr Alshehri collected study data during a one-to-one interview which lasted 2 to 4 hours. The data was recorded in the case report form (CRF) unless stated otherwise. The CRF was the source of most data, but exceptions are detailed below. The following data were collected:

2.3.6.1 General demographics:

Sex, age, ethnicity, medications (antihypertensive, lipid-lowering, antidepressant, and hypothyroidism), past medical history, diabetes duration, alcohol intake, smoking status, employment, and education. Sex, age, and ethnicity were extracted from the medical records. The remaining information was collected during the interview with the participants to ensure accuracy.

2.3.6.2 Anthropometry:

Weight, height, waist circumference (WC), hip circumference (HC), neck circumference (NC), waist−hip ratio (WHR), body mass index (BMI). BMI, WC, HC and NC were measured twice to ensure accuracy, and the average of the two measurements was used in the analysis. WC was measured at the midpoint between the superior aspect of the iliac crest and the inferior border of the rib cage using a measuring tape (143). Hip circumference was measured horizontally at the widest circumference of the hips (144). NC was measured between the mid-cervical spine and the mid-anterior neck using inelastic tape (145). In men with a laryngeal

prominence (Adam's apple), NC was measured just below the prominence (145). All circumferences were taken with the subjects standing upright, their face directed straight ahead, and shoulders relaxed (145). BMI is used for the measurement of adiposity and the classification of patient's overweight and obesity. People of Asian origins might have an increased risk of obesity-related complications with lower BMI compared to white Europeans (146-148). Some articles suggested using the following cut-offs for Asians: 18.5–22.9 kg/m^2 as normal weight, 23.0–24.9 kg/m^2 as overweight, >25 kg/m^2 as obese (148). In our study, BMI was categorised to normal (<25 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥ 30 kg/m^2), which is the commonly used classification (148).

2.3.6.3 Cardiac Autonomic Neuropathy:

CAN was assessed using heart rate variability (HRV) in response to cardiac autonomic reflex tests. Cardiac data (ECG and blood pressure) was collected and analysed using the ANX-3.0 software (ANSAR Inc., Philadelphia, PA). Using the ECG and R-R intervals, the software analysed frequency domain after respiratory adjustment (low frequency area (LFa), respiratory frequency area (RFa) and LFa/RFa ratio) (13), and time-domain including standard deviation of normal R-R intervals (sdNN), square root of the mean of the squares of differences between adjacent normal R-R intervals (rmsSD), and percentage of differences between adjacent normal R-R intervals that are greater than 50 milliseconds (pNN50) were included (13). HRV and BP were recorded in different positions with the patient in a sitting position during resting, deep breathing, and Valsalva manoeuvre, and in a standing position during postural change (149). Refere to chapter 4 section 4.2.3 for detailed methodology.

2.3.6.4 Metabolic function:

Blood pressure, HbA1c (an indicator of glycaemic control), lipids and thyroid hormone levels were collected for the metabolic function assessment. HbA1c, lipids, and thyroid function were extracted from the patients' electronic records as these are performed as part of routine care. If routine test results were not available, patients were asked to provide samples to be analysed in the NHS Trust laboratories following the interview with me. Blood pressure (BP) was measured twice while the patient was in a seated position with the left arm resting on a table at the level of the heart to ensure accuracy. The measurements were at least 10 minutes apart, and the first measurement was after at least 20 minutes from the start of the research interview to ensure the patient was as relaxed as possible. HbA1c was categorised to three groups (≤58 mmol/mol, 59 – 69 mmol/mol, and ≥ 70 mmol/mol).

2.3.6.5 Nephropathy:

Nephropathy was assessed using estimated glomerular filtration rate (eGFR), and urinary albumin/creatinine ratio (ACR). eGFR, ACR, plasma urea and creatinine levels were extracted from the patients' electronic records. Refer to chapter 5 section 5.2 for more details.

2.3.6.6 Retinopathy:

Retinopathy was assessed using the data obtained from the National Retinopathy Screening Programme. Refer to chapter 5 section 5.2 for more details.

2.3.6.7 Diabetes-related Peripheral Neuropathy (DPN):

For our study, the presence of *DPN* was assessed using the *Michigan Neuropathy Screening Instrument (MNSI). Pain symptoms* were assessed using the *short-form McGill Pain Questionnaire 2 (SF-MPQ-2),* which includes scores for different types of pains, including

neuropathic pain. *Foot insensitivity* was evaluated using the *10g monofilament test*, *large fibre* neuropathy was examined using *biothesiometer*, and *small fibre* neuropathy was assessed using *Neuropad and Sudoscan*. Refer to chapter 5 section 5.2 for more details.

2.3.6.8 Sleep and Obstructive Sleep Apnoea:

Types of sleep study monitors:

There are two categories of sleep monitors: Polysomnography and Polygraphy. Polysomnography (also is known as type 1 study) is a laboratory-based study. This type of study includes several parameters regarding sleep stages and cardio-respiratory function during sleep. Polygraphy (Home Sleep Apnoea Testing (HSAT), also known as unattended or portable sleep monitoring), is designed for monitoring sleep in the comfort of the person's home using portable devices. There are three types of portable sleep monitors (type 2, 3, and 4). The number of parameters that can be collected depends on the type of device that is used. Type 2 devices, also known as portable PSG, collect information of a variety of parameters (e.g. air flow, oxygen saturation, electroencephalogram, electrooculography, electromyography, electrocardiography, and respiratory effort) and most closely replicate the data collected by Type 1 monitoring. Type 4 monitors can only record one or two variables, for example oxygen saturation using oximetry.

Objective assessment:

Screening for the presence and the severity of OSA was performed using a home-based sleep monitor. The home-based sleep monitor is a portable multi-channel respiratory device. The sleep study report was entered into the CRF.

The portable home-based sleep study device was introduced as a simplified, easy to use, inexpensive alternative to the "gold standard" polysomnography (PSG). Portable multi-channel

home-based sleep devices have been used in research as they have the benefit of screening large numbers of patients in the comfort of their own homes and at a minimal cost. In our study, we used the ApneaLink Air (ResMed, USA) device to assess the presence and severity of OSA. The device channels recorded: pulse, oxygen saturation, nasal flow, snoring and respiratory effort. The device was usually returned to me either in person or via taxi the next day, and then sleep data were downloaded to the study computer for analysis (ApneaLink Version 10.20, ResMed, USA; see Figure 2.2). The ApneaLink software uses autoscoring algorithm to detect apnoea and hypopnoea events (150). Compared to the manual scoring of polysomnography, ApneaLink algorithm has shown high sensitivity (92%) and specificity (80%) for identifying SDB at AHI ≥ 5 (150). The sleep studies were scored by a sleep technician and were discussed between different members of the study team. Patients were referred to a sleep clinic for follow-up if needed.

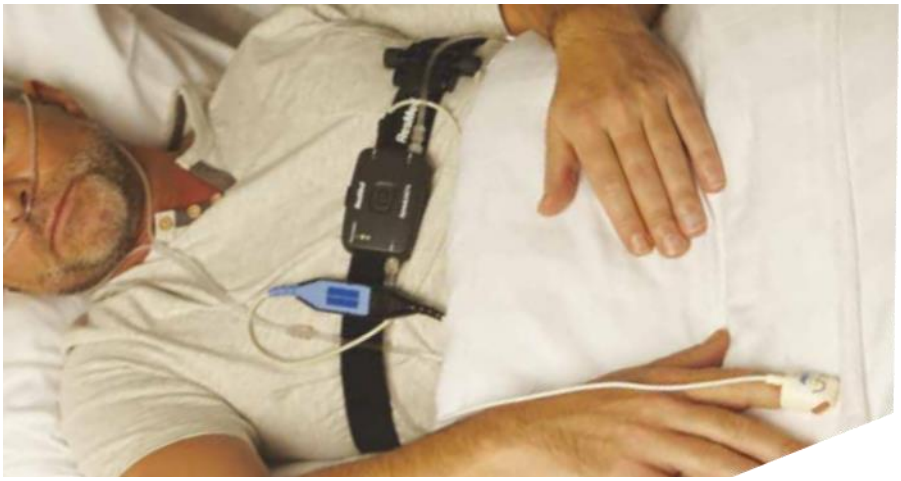


Figure 2.1 ApneaLink Air sleep monitor (source: resmed.com)

If the recording quality was poor, the sleep studies were repeated no more than twice after offering more training, troubleshooting, or changing the device. If persistently poor, then the patient could be referred via the GP to the local NHS sleep clinic (0 patients). The sleep studies

were scored according to the American Academy of Sleep Medicine (AASM) guidelines for Home Sleep Apnoea Testing (HSAT). The apnoea and hypopnea events were scored to calculate the Respiratory Events Index (REI; which is the equivalent of AHI referred to previously) (151). The AASM manual introduced REI term to be used instead of AHI for sleep tests conducted using HSAT or out of centre sleep test (152). Unlike polysomnography, portable sleep monitors usually are not able to detect respiratory events related to arousal as they lack electroencephalography (EEG) channel (153). OSA was diagnosed if the patient had REI ≥ 5 events/hour with involuntary daytime sleepiness (i.e. ESS > 10) or REI ≥ 15 with or without excessive daytime sleepiness (154).

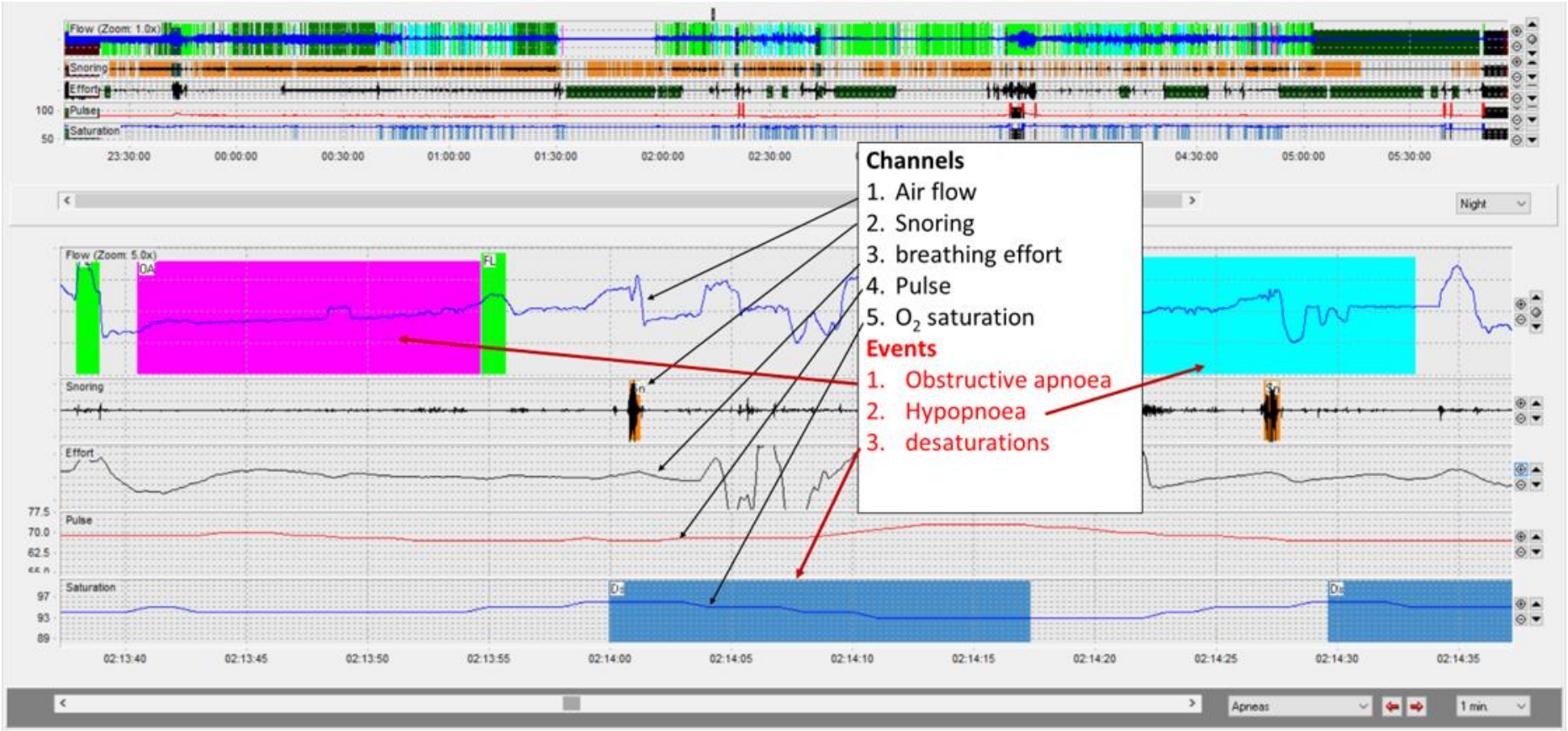


Figure 2.2 A one-minute screen shot of the data downloaded from ApneaLink Air showing evidence of apnoea, hypopnoea, and oxygen desaturation.

Subjective assessment:

Sleepiness was assessed using the Epworth Sleepiness Scale (ESS), and the risk of OSA was collected using the Berlin Questionnaire (BQ). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), and circadian rhythm was assessed using the Morningness-Eveningness (Horne & Ostberg) questionnaire (MEQ). All these questionnaires were validated.

ESS was developed to assess daytime sleep and sleepiness. This questionnaire rates the chances that a participant would 'fall asleep' or 'doze off' when in eight common daily life situations (155). It was initially presented as a tool to distinguish healthy subjects from subjects with various sleep disorders (including obstructive sleep apnoea syndrome, idiopathic hypersomnia, and narcolepsy) (155). It is worth mentioning that ESS does not directly measure OSA; instead, it measures excessive daytime sleepiness which is a common OSA symptom. The test-retest reliability was assessed using the Pearson correlation coefficient between 87 paired scores and the correlation score was $r=0.82$ ($p<0.001$) (156). The reported sensitivity and specificity of ESS (> 10) to detect OSA (AHI $\geq$ 5) are about 66% and 48%, respectively (157). For this study, an ESS > 10 is considered an indication for excessive daytime sleepiness (155).

The Berlin Questionnaire (BQ) was an outcome of the Conference on Sleep in Primary Care in 1996 in Berlin, Germany. Questions were selected from the literature to extract factors or behaviours that consistently predicted the presence of sleep-disordered breathing (158). The questionnaire contains five questions concerning snoring (category 1); four questions addressing daytime sleepiness and sleepiness while driving (category 2); and one question concerning the history of high blood pressure and obesity (158). The results of the BQ are classified as a high or low risk for sleep apnoea. In primary care, the

sensitivity and specificity based on respiratory disturbance index (RDI) > 5 were 86% and 77% respectively, and based on RDI >15 were 54% and 97% respectively (158).

2.3.7 Data handling and record-keeping

We adhered to the Data Protection Act 1998 and the Caldecott principles. The CRF did not include patients' name, date of birth or address. The CRF included a study number. Consents (which included identifiable patient information) were securely stored in the research file and kept at the respective NHS site. The CRFs were stored at the NHS site in a locked cupboard in locked rooms. A copy of the CRF was filed in patients' medical files. The CRFs data were inserted into an Excel spreadsheet which then exported to SPSS (version 25) to perform the statistical analysis. All electronic data were password protected and backed up regularly as they were stored on the University of Birmingham server. The data on the Excel spreadsheet were examined for unusual values, and these were checked and corrected. A sample of the data was cross-validated/examined by the supervisors. The CRFs will be kept for five years from the date of patient recruitment.

The patient's GP was informed (via a letter given to the patient or via post/e-mail) of the patient's participation in the study and patients and GPs were informed of the outcome of the sleep study with further instructions regarding treatment.

2.3.8 Statistical Considerations

2.3.8.1 Sample size calculation

Based on the study by Janovsky et al. (135), the prevalence of OSA in patients with vs without CAN was 66.6% vs 27.2%. Using the Fisher exact test, and in order to achieve a power of 0.8, assuming an α error probability of 0.05, we needed 58 patients. However, Janovsky's study used a very small sample size. So, we calculated the confidence interval

and ran the same test to see the possible sample sizes. We found that the possible sample size needs to be between 14 to 190 patients. So, we aimed to examine the findings after recruiting 60 patients and, we would either continue or stop recruitment based on these findings. Due to challenges with recruiting patients during the time period of the PhD we stopped recruiting after 47 patients. I had restricted time for data collection due to the time it took to secure NHS ethical approval. Therefore, the available time for data collection was about 16 months. Only a small proportion of those patients invited by their healthcare providers to participate in the study were keen to enrol. ClinCalc post-hoc power calculator was used to perform power analysis (159). The power of our study was 81.4% (see Appendix 2.4). Our final sample size therefore fell within the prior calculated limits and was able to achieve a power of 80%.

2.3.8.2 Analysis

Data were summarised as frequencies or mean ± SD or median (IQR or range) depending on data distribution. Data distribution were assessed using histograms and the Shapiro Wilk test. Categorical variables were compared using the Chi-square test. Independent scale variables were compared using the independent t-test or the Mann Whitney U test. For assessing the associations between scale outcomes and potential predictors, multiple linear regressions were used. The assumptions of linear regression were examined, and if violated, the data were transformed accordingly. For dichotomous outcomes, logistic regression was used to assess associations with predictors.

2.3.9 Withdrawal of subjects

Participants were informed that they had the right to withdraw at any time without giving a reason and without compromising their clinical care. The study participants had the

option of withdrawing all the data that were already collected if they decided to withdraw from the study. However, if the research study findings had been published, then data could not be withdrawn.

2.3.10 Ethical Considerations

Ethical approval was obtained from an appropriate NHS ethics committee (REC Ref: 17/WM/0238), and site approvals were obtained from the appropriate NHS Trust R&D department. Patients were consented having been given the opportunity to read the PIS (at least 48 hours) and ask any questions to the investigator. Consents were collected by Mr Ziyad Alshehri (PhD student).

The research raised a potential ethical issue. Patients would need to inform the DVLA and their car insurer if they had OSA. These usually occur after the physician confirmed the diagnosis in the NHS sleep clinic and treatment started if needed. Patients who were compliant with the treatment would keep their license. Although this raised ethical concerns, the fact the patient being screened for a disease that potentially could result in road traffic accidents and then treated if needed, was beneficial to the patients and the public. Patients were informed of the above in the PIS and during the consent process. Also, the decision to inform the DVLA were made after the patient was seen by the sleep physician who might decide to do further tests before confirming the diagnosis of OSA, but patients were advised not to drive when sleepy or tired as per DVLA guidance.

2.3.11 Finance and Insurance

The project was a funded PhD studentship by the Government of Saudi Arabia. Patients still have access to the patient advice and liaison service (PALS) in the NHS.

2.3.12 Reporting and Dissemination

Data reported in the following section have been presented at international and national meetings in the fields of diabetes and sleep apnoea.

2.4 Population-based methodology – chapter 6 and 7

2.4.1 Data source

Datasets for this study were extracted from The Health Improvement Network (THIN), a nationally representative electronic primary care records database that contains anonymised medical records of about 6% of the UK population collected from over 500 practices in the UK (160). The database consists of demographic information, and coded symptoms and medical conditions (Read Codes) (161). The database also provides other data (e.g. HbA1c and blood pressure) recorded using the Additional Health Data (AHD) codes and information about medications using the British National Formulary (BNF) codes.

The THIN database collects patients electronic medical record prospectively from subscribed GP practices. Identifiable information like name, full address, or NHS number are not collected, but each patient is assigned a unique THIN number so that patients can be followed prospectively. Therefore, representative population-based health-related research studies can be carried out.

The Institute of Applied Health Research at the University of Birmingham has a website developed to extract and merge data extracted from the THIN database. Using this website, we defined the following criteria to select a cohort: start and end of the study; inclusion and exclusion criteria; and matching variables. Only data from patients

matching these restrictions were selected. All other variables (e.g. demographics, medications, and diseases) were listed on a different webpage to be extracted and joined to their corresponding selected patient.

All variables registered in the database before the start of this study were categorised as baseline variables. This was performed to exclude patients with OSA at baseline from the patients developing OSA during the follow-up (for the first cohort). This categorisation also enabled us to investigate the baseline predictor variables of developing OSA (Figure 2.3). A spreadsheet of cohort data was generated, and statistical software (Stata version 15) was used for preparation and analysis of the data, as explained below.

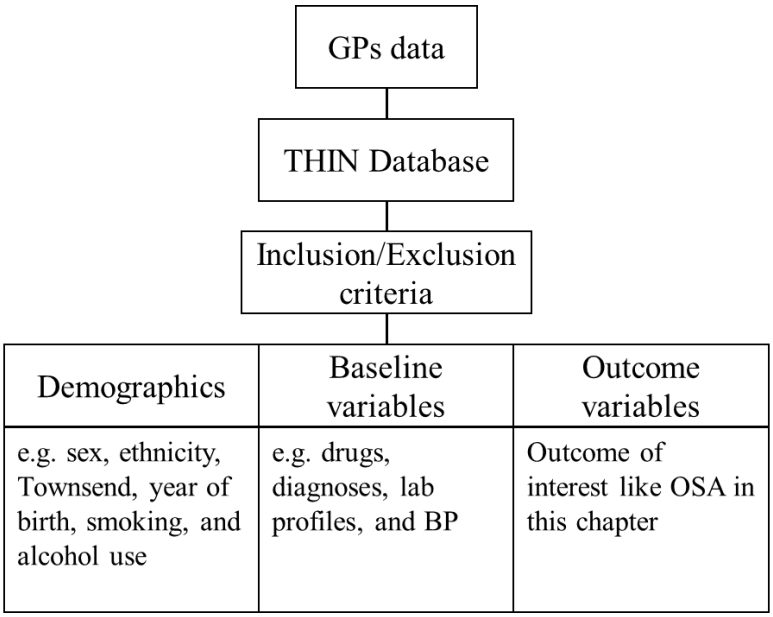


Figure 2.3 diagram of the THIN data extraction for our study

The data preparation included converting and encoding dates to an appropriate format (e.g. text date 2018/11/18 converted to date 18/11/2018), and converting diagnoses and other covariates format from texts to binary or categorical outcomes (e.g. the read code "Fy03.11" for OSA were assigned for patients with OSA, therefore the presence of the

read code was recoded as "1" and the absence of the recoded as "0") so they can be used in statistical analyses.

2.4.2 Population

The primary cohort studies included T1D patients eligible for inclusion between 01 Jan 1990 and 31 Aug 2019. To ensure high-quality data, general practices were eligible for inclusion in the study only 12 months after using electronic medical records and reporting acceptable mortality rates. Patients registered with any of the eligible general practices for at least a year formed the source study population.

2.4.3 Study design

Refer to chapter six and seven for studies' specific methods.

2.4.4 Definitions of covariates for the outcome study

Covariates that may influence the outcomes were selected on the basis of biological plausibility and previous literature. Age, sex, body mass index categories, Townsend quintiles (deprivation measure), smoking status, ethnicity, and drinking status were the covariates of interest to be included in the regression model. Further variables were added to these variables and reported below the analysis. Age at baseline was categorised in an increment of 10 years and all people 70 years old and older were grouped in one group. BMI recorded closest to the index date was analysed. BMI below 14 kg/m^2 and above 75 kg/m^2 was considered implausible. Then BMI was categorised as <18.5 kg/m^2 (underweight), 18.5-25 kg/m^2 (normal weight), 25-30 kg/m^2 (overweight), and >30 kg/m^2 (Obese). Material deprivation is recorded as deprivation quintiles based on the Townsend deprivation index where the 1^{st} quintile indicates the least deprived group and 5^{th} quintile indicates the most deprived group. The Townsend deprivation score is computed using

four census variables (unemployment, overcrowding, non-car, and non-home ownership) which is also linked to postcodes (162). HbA1c below 20 mmol/mol and above 240 mmol/mol were considered implausible. Then HbA1c was categorised as ≤ 47.500 mmol/mol, 47.501-58.500 mmol/mol, 58.501-69.400mmol/mol, and ≥ 69.401mmol/mol. ACR was categorised as <3 (normal to mildly increased), 3 to 30 (moderately increased), and >30 (severely increased) according to NICE guideline. eGFR was calculated using CKD-EPI creatinine equation. eGFR above 200 ml/min/1.73 m² was considered implausible. Then eGFR was categorised as <30 ml/min/1.73 m² (stage 4 and 5), 30-59 ml/min/1.73 m² (stage 3), 60-90 ml/min/1.73 m² (stage 2), and >90 ml/min/1.73 m² (stage1). All implausible data were coded missing. Covariates categorisation are illustrated in Table 2.2.

Table 2.2 illustration of covariates categorisation

BMI categories, kg/m²	Ethnicity	HbA1c, mmol/mol	Townsend
Underweight (<18.5)	White	≤ 47.500	1st (Least deprived)
Normal (18.5-25)	Black	47.501-58.500	2nd Quintile
Overweight (25-30)	South Asians	58.501-69.400	3rd Quintile
Obese (>30)	Others	≥ 69.401	4th Quintile
No data	Mixed-Race	No data	5th (Most deprived)
	No data		No data
Smokers	Drinkers	eGFR, ml/min/1.73 m²	ACR
Non-smokers	Non-drinkers	≥ 60 (≥ Stage 2)	< 3 (Normal to mildly increased)
Discontinued Smoking	Drinkers	30-59 (Stage 3)	3-30 (Moderately increased)
Smokers	Excessive Drinkers	<30 (Stage 4)	> 30 (Severely increased)
No data	No data	No data	No data

2.4.5 Analysis

The baseline covariates were summarised for those exposed and unexposed using appropriate descriptive statistics (e.g. age, sex, BMI, and HbA1c). Categorical variables were presented as frequencies, and continuous variables are presented as mean and

standard deviation (SD). Variables were compared using the Chi-squared ($\chi 2$) test for categorical variables or T-test depending for continuous variables. Crude Hazard Rates (HR) and adjusted Hazard Rates (aHR) and their corresponding 95% confidence intervals (Cis) were calculated using Cox regression. Cox regression was used because it is a commonly used survival analysis method, and the key variable in this analysis is the time to developing OSA. Also, Cox regression is useful in estimating incidence rate even if some of the participants lost to follow-up or did not develop the outcome by the end of the study. All the analyses were performed in Stata IC version 15. Two-sided p- values were obtained, and p-value < 0.05 was considered as statistically significant.

2.4.6 Limitations:

There is a possibility of misdiagnosing the exposure status (T1D) in project 1; we mitigated this issue by excluding patients with a record of T2D. Read codes also may not identify the outcomes accurately on some occasions. We attempted to clarify these limitations in the discussion section.

2.5 Appendices:

Appendix 2.1 sample search strategy (Embase)

1		exp insulin dependent diabetes mellitus/	102607
2		((diabet* or dm) adj4 (type 1 or type1 or type i or type one)).ti,ab,kw.	76711
3		(diabet* adj2 (autoimmun* or auto immun*)).ti,ab,kw.	5287
4		(diabet* adj2 (brittle or labile)).ti,ab,kw.	524
5		(diabet* adj2 (sudden onset or juvenile or childhood)).ti,ab,kw.	4506
6		(diabet* adj2 (insulin depend* or insulin deficien*)).ti,ab,kw.	30603
7		exp sleep disordered breathing/	36973
8		(sleep adj2 (apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea)).ti,ab,kw.	52378
9		1 or 2 or 3 or 4 or 5 or 6	140607
10		7 or 8	63125
11		9 and 10	221

Appendix 2.2 Reasons for excluding studies after full text screening

Author	Reference	Reason for exclusion
Ashour et al., 2013	Ashour, Y., Abou-Hagar, A., El-Shazly, N., Al-Deeb, W., Ahmed, R., El-Kholy, S., & Osama, A. (2013). Sleep apnea in patients with diabetic neuropathy. Egyptian Journal of Neurology, Psychiatry and Neurosurgery, 50(2), 187-193.	No T1D data presented
Barone et al., 2015	Barone, M. T., Wey, D., Schorr, F., Franco, D. R., Carra, M. K., Lorenzi Filho, G., & Menna-Barreto, L. (2015). Sleep and glycemic control in type 1 diabetes. Arch Endocrinol Metab, 59(1), 71-78. doi:10.1590/2359-3997000000013	No patients with OSA?
A. Borel et al., 2010	Borel, A., Benhamou, P., Baguet, J., Halimi, S., Levy, P. A., Mallion, J., & Pepin, J. (2010). High prevalence of sleep apnea syndrome in a type 1 diabetic adult population. American Journal of Respiratory and Critical Care Medicine, 181(1 MeetingAbstracts).	Abstract
A. L. Borel et al., 2010a	Borel, A. L., Benhamou, P. Y., Baguet, J. P., Halimi, S., Levy, P., Mallion, J. M., & PePin, J. L. (2010a). High prevalence of obstructive sleep apnoea syndrome in a Type-1 diabetic adult population: A pilot study. Diabetic Medicine, 27(11), 1328-1329. doi:http://dx.doi.org/10.1111/j.1464-5491.2010.03096.x	Duplicate
A. L. Borel et al., 2010b	Borel, A. L., Benhamou, P. Y., Baguet, J. P., Halimi, S., Levy, P., Mallion, J. M., & Pepin, J. L. (2010b). High prevalence of obstructive sleep apnoea syndrome in a Type 1 diabetic adult population: a pilot study. Diabetic medicine : a journal of the British Diabetic	Duplicate

	Association, 27(11), 1328-1329. doi:https://dx.doi.org/10.1111/j.1464-5491.2010.03096.x	
Bouchard et al., 2014	Bouchard, C. S., Maki, S., Undevia, N., Gaynes, B., Price, R., & Valdez, D. (2014). The association of systemic and ocular disease and the under diagnosis of floppy eyelid syndrome in patients with obstructive sleep apnea. Investigative Ophthalmology and Visual Science, 55(13), 1465.	No patients with T1D?
Chontong, Saetung, & Reutrakul, 2016	Chontong, S., Saetung, S., & Reutrakul, S. (2016). Higher sleep variability is associated with poorer glycaemic control in patients with type 1 diabetes. Journal of Sleep Research, 25(4), 438-444. doi:http://dx.doi.org/10.1111/jsr.12393	Subjective tool for assessment of exposure
Huang et al., 2018	Huang, T. Y., Lin, B., Stampfer, M., Tworoger, S., Redline, S., & Hu, F. (2018). A Population-based Study of the Bidirectional Association Between Sleep Apnea and Diabetes in Three Prospective US Cohorts. Circulation, 137(Supplement 1).	Abstract
Ioja, Chasens, Ng, & Korytkowski, 2016	Ioja, S., Chasens, E. R., Ng, J., & Korytkowski, M. T. (2016). Obstructive sleep apnea in adults with type 1 and type 2 diabetes: Perceptions, practice, and prevalence. Endocrine Reviews, 37(2 Supplement 1). doi:http://dx.doi.org/10.1210/endo-meetings.2016.DGM.19.SAT-699	No eligible outcomes reported
Jauch-Chara, Schmid, Hallschmid, Born, & Schultes, 2008	Jauch-Chara, K., Schmid, S. M., Hallschmid, M., Born, J., & Schultes, B. (2008). Altered neuroendocrine sleep architecture in patients with type 1 diabetes. Diabetes Care, 31(6), 1183-1188. doi:10.2337/dc07-1986	No eligible outcomes reported
Li, Chen, Chen, Shen, & Shen, 2017	Li, C. H., Chen, W. C., Chen, C. Y., Shen, Y. C., & Shen, T. C. (2017). Risk of sleep disorders in patients with type 1 diabetes mellitus: A nationwide population-based cohort study. American Journal of Respiratory and Critical Care Medicine, 195. doi:http://dx.doi.org/10.1164/ajrccm-conference.2017.B80-H	Abstract
Lorenzi-Filho & Drager, 2015	Lorenzi-Filho, G., & Drager, L. F. (2015). Type I diabetes: a new risk factor for obstructive sleep apnea. Revista Portuguesa de Pneumologia, 21(2), 53-54. doi:http://dx.doi.org/10.1016/j.rppnen.2015.02.002	review
H. L. Tan, Babwah, Waheed, & Butt, 2015	Tan, H. L., Babwah, F., Waheed, N., & Butt, M. I. (2015). Obstructive sleep apnoea and type 1 diabetes mellitus. British Journal of Diabetes and Vascular Disease, 15(2), 96-98. doi:http://dx.doi.org/10.15277/bjdvd.2015.020	Case Study
Hiang Leng Tan, Babwah, Waheed, & Imran Butt, 2015	Tan, H. L., Babwah, F., Waheed, N., & Imran Butt, M. (2015). Obstructive sleep apnoea and type 1 diabetes mellitus. British Journal of Diabetes & Vascular Disease, 15(2), 96-98. doi:10.15277/bjdvd.2015.020	Case Study

Appendix 2.3 Data Extraction form.

Study ID					
Extracted by			Reviewed by		
Study Details					
AIM					
Study Type					
Setting					
Country					
Note					
Patients Characteristics					
Population					
Sample size					
Inclusion					
Exclusion					
Method of recruitment					
	Age Years (SD)	BMI Kg/m^2 (SD)	Male N (%)	DD Years(SD)	HbA1c (%)
Total					
OSA+					
OSA-					
Other Characteristics					
Total					
OSA+					
OSA-					
Exposure					
OSA definition					
OSA diagnostic tool					
Manual Scoring					
Cut-off					
Outcomes					
Retinopathy Definition					
Nephropathy Definition					
Peripheral Neuropathy Definition					
Autonomic Neuropathy Definition					
Macro vascular Definition					
Hypertension Definition					
Note					

Results				
OSA n, %				
	OSA +		**OSA -**	
	Events	Total	Events	Total
Retinopathy				
	OSA +		**OSA -**	
	Events	Total	Events	Total
Nephropathy				
	OSA +		**OSA -**	
	Events	Total	Events	Total
Peripheral Neuropathy				
	OSA +		**OSA -**	
	Events	Total	Events	Total
Autonomic Neuropathy				
	OSA +		**OSA -**	
	Events	Total	Events	Total
Macro vascular				
	OSA +		**OSA -**	
	Events	Total	Events	Total
Hypertension				

Other:

	OSA +		**OSA -**	
	Events	Total	Events	Total
	OSA +		**OSA -**	
	Events	Total	Events	Total

Continuous Results:

Outcome	**OSA +**			**OSA -**		
Creatinine (ml/min)	Mean	SD	Total	Mean	SD	Total
Outcome	**OSA +**			**OSA -**		
Microalbuminuria(mg/24h)	Mean	SD	Total	Mean	SD	Total
Outcome	**OSA +**			**OSA -**		
Proteinuria(g/24h)	Mean	SD	Total	Mean	SD	Total

Outcome	**OSA +**			**OSA -**		
HbA1C mmol/mol	Mean	SD	Total	Mean	SD	Total

Outcome	**OSA +**			**OSA -**		
eGFR	Mean	SD	Total	Mean	SD	Total

Appendix 2.4 Post-hoc power calculation

$$Power = \Phi\left\{ \frac{\Delta}{\sqrt{p_1 q_1/n_1 + p_2 q_2/n_2}} - z_{1-\alpha/2} * \frac{\sqrt{\bar{p}\bar{q}(1/n_1 + 1/n_2)}}{\sqrt{p_1 q_1/n_1 + p_2 q_2/n_2}} \right\}$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + k p_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$Power = \Phi\left\{ \frac{0.4012}{\sqrt{0.5625 * 0.4375/16 + 0.1613 * 0.8387/31}} - 1.96 * \frac{\sqrt{0.29788 * 0.70212(1/16 + 1/31)}}{\sqrt{0.5625 * 0.4375/16 + 0.1613 * 0.8387/31}} \right\}$$

$$Power = \Phi(0.892) = 0.814 = 81.4\%\ power$$

p_1 = proportion CAN in T1D with OSA
p_2 = proportion CAN in T1D without OSA
$\Delta = |p_2 - p_1|$
n_1 = sample size for T1D with OSA
n_2 = sample size for T1D without OSA
α = probability of type I error (0.05)
z = critical Z value for a given α
K = ratio of sample size for T1D without OSA to T1D with OSA
$\Phi()$ = function converting a critical Z value to power

Appendix 2.5 Epworth sleepiness scale (ESS)

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in comparison to feeling just tired?

This refers to your usual way of life in recent times.

Even if you have not done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best as you can

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting still in a public place (e.g., a theatre, a cinema or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances allow	___
Sitting and talking to someone	___
Sitting quietly after a lunch without having drunk alcohol	___
In a car or a bus while stopped for a few minutes in traffic	___

THANK YOU FOR YOUR CO-OPERATION

Appendix 2.6 Berlin questionnaire

BERLIN QUESTIONNAIRE

Height (m) _____ Weight (kg)_____ Age_____ Male / Female

Please choose the correct response to each question.

CATEGORY 1

1. **Do you snore?**
   - ☐ a. Yes
   - ☐ b. No
   - ☐ c. Don't know

If you snore:

2. **Your snoring is:**
   - ☐ a. Slightly louder than breathing
   - ☐ b. As loud as talking
   - ☐ c. Louder than talking
   - ☐ d. Very loud – can be heard in adjacent rooms

3. **How often do you snore**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

4. **Has your snoring ever bothered other people?**
   - ☐ a. Yes
   - ☐ b. No
   - ☐ c. Don't Know

5. **Has anyone noticed that you quit breathing during your sleep?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

CATEGORY 2

6. **How often do you feel tired or fatigued after your sleep?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

7. **During your waking time, do you feel tired, fatigued or not up to par?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

8. **Have you ever nodded off or fallen asleep while driving a vehicle?**
   - ☐ a. Yes
   - ☐ b. No

If yes:

9. **How often does this occur?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

CATEGORY 3

10. **Do you have high blood pressure?**
    - ☐ Yes
    - ☐ No
    - ☐ Don't know

Appendix 2.7 Sleep quality assessment (PSQI)

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Scoring

Component 1	#9 Score	C1 _____
Component 2	#2 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3)) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2 _____
Component 3	#4 Score (>7(0), 6-7 (1), 5-6 (2), <5 (3)	C3 _____
Component 4	(total # of hours asleep) / (total # of hours in bed) x 100 >85%=0, 75%-84%=!, 65%-74%=2, <65%=3	C4 _____
Component 5	# sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5 _____
Component 6	#6 Score	C6 _____
Component 7	#7 Score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7 _____

Add the seven component scores together _____ *Global PSQI* _____

A total score of "5" or greater is indicative of poor sleep quality.
If you scored "5" or more it is suggested that you discuss your sleep habits with a healthcare provider

Appendix 2.8 Morningness-Eveningness questionnaire (MEQ)

Instructions:

- Please read each question very carefully before answering.
- Please answer each question as honestly as possible.
- Answer ALL questions.
- Each question should be answered independently of others. Do NOT go back and check your answers.

1. What time would you get up if you were entirely free to plan your day?

5:00 – 6:30 AM	5
6:30 – 7:45 AM	4
7:45 – 9:45 AM	3
9:45 – 11:00 AM	2
11:00 AM – 12 NOON	1
12 NOON – 5:00 AM	0

2. What time would you go to bed if you were entirely free to plan your evening?

8:00 – 9:00 PM	5
9:00 – 10:15 PM	4
10:15 PM – 12:30 AM	3
12:30 – 1:45 AM	2
1:45 – 3:00 AM	1
3:00 AM – 8:00 PM	0

3. If there is a specific time at which you have to get up in the morning, to what extent do you depend on being woken up by an alarm clock?

Not at all dependent	4
Slightly dependent	3
Fairly dependent	2
Very dependent	1

4. How easy do you find it to get up in the morning (when you are not woken up unexpectedly)?

Not at all easy	1
Not very easy	2

Fairly easy	3
Very easy	4

5. How alert do you feel during the first half hour after you wake up in the morning?

Not at all alert	1
Slightly alert	2
Fairly alert	3
Very alert	4

6. How hungry do you feel during the first half-hour after you wake up in the morning?

Not at all hungry	1
Slightly hungry	2
Fairly hungry	3
Very hungry	4

7. During the first half-hour after you wake up in the morning, how tired do you feel?

Very tired	1
Fairly tired	2
Fairly refreshed	3
Very refreshed	4

8. If you have no commitments the next day, what time would you go to bed compared to your usual bedtime?

Seldom or never later	4
Less than one hour later	3
1-2 hours later	2
More than two hours later	1

9. You have decided to engage in some physical exercise. A friend suggests that you do this for one hour twice a week and the best time for him is between 7:00 – 8:00 am. Bearing in mind nothing but your own internal "clock", how do you think you would perform?

Would be in good form	4
Would be in reasonable form	3
Would find it difficult	2
Would find it very difficult	1

10. At what time of day do you feel you become tired as a result of need for sleep?

8:00 – 9:00 PM	5
9:00 – 10:15 PM	4
10:15 PM – 12:45 AM	3
12:45 – 2:00 AM	2
2:00 – 3:00 AM	1

11. You want to be at your peak performance for a test that you know is going to be mentally exhausting and will last for two hours. You are entirely free to plan your day. Considering only your own internal "clock", which ONE of the four testing times would you choose?

8:00 AM – 10:00 AM	4
11:00 AM – 1:00 PM	3
3:00 PM – 5:00 PM	2
7:00 PM – 9:00 PM	1

If you got into bed at 11:00 PM, how tired would you be?

Not at all tired	1
A little tired	2
Fairly tired	3
Very tired	4

12. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which ONE of the following are you most likely to do?

Will wake up at usual time, but will NOT fall back asleep	4
Will wake up at usual time and will doze thereafter	3
Will wake up at usual time but will fall asleep again	2
Will NOT wake up until later than usual	1

One night you have to remain awake between 4:00 – 6:00 AM in order to carry out a night watch. You have no commitments the next day. Which ONE of the alternatives will suite you best?

Would NOT go to bed until watch was over	1
Would take a nap before and sleep after	2
Would take a good sleep before and nap after	3
Would sleep only before watch	4

You have to do two hours of hard physical work. You are entirely free to plan your day and considering only your own internal "clock" which ONE of the following time would you choose?

8:00 AM – 10:00 AM	4
11:00 AM – 1:00 PM	3
3:00 PM – 5:00 PM	2
7:00 PM – 9:00 PM	1

13. You have decided to engage in hard physical exercise. A friend suggests that you do this for one hour twice a week and the best time for him is between 10:00 – 11:00 PM. Bearing in mind nothing else but your own internal "clock" how well do you think you would perform?

Would be in good form	1
Would be in reasonable form	2
Would find it difficult	3
Would find it very difficult	4

14. Suppose that you can choose your own work hours. Assume that you worked a FIVE hour day (including breaks) and that your job was interesting and paid by results). Which FIVE CONSECUTIVE HOURS would you select?

5 hours starting between 4:00 AM and 8:00 AM	5
5 hours starting between 8:00 AM and 9:00 AM	4
5 hours starting between 9:00 AM and 2:00 PM	3
5 hours starting between 2:00 PM and 5:00 PM	2
5 hours starting between 5:00 PM and 4:00 AM	1

15. At what time of the day do you think that you reach your "feeling best" peak?

5:00 – 8:00 AM	5
8:00 – 10:00 AM	4
10:00 AM – 5:00 PM	3
5:00 – 10:00 PM	2
10:00 PM – 5:00 AM	1

16. One hears about "morning" and "evening" types of people. Which ONE of these types do you consider yourself to be?

Definitely a “morning” type	6
Rather more a “morning” than an “evening” type	4
Rather more an “evening” than a “morning” type	2
Definitely an “evening” type	0

CHAPTER THREE: THE RELATIONSHIP BETWEEN OBSTRUCTIVE SLEEP APNOEA AND DIABETES-RELATED COMPLICATIONS IN ADULTS WITH TYPE 1 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Contribution: Ziyad Alshehri contributed to the design of the study, screening, data extraction, analysis, and writing of this chapter. Abdulaziz Alzahrani contributed to the screening and data extraction. I gratefully acknowledge the help and support of Ms Janine Dretzke, a systematic review expert, in the Institute of Applied Health Research, at the University of Birmingham who supported me during the study.

An abstract of the data presented in this chapter was accepted and presented as an oral communication at the Neurodiab conference (2019) in Sitges - Barcelona, Spain (see appendix 3.1).

3.1 Background:

Obstructive Sleep Apnoea (OSA) is the most common type of sleep-disordered breathing (SDB) (74). OSA has been shown to be associated with microvascular complications in patients with type 2 diabetes in cross-sectional studies (110, 163) and predicted the development of advanced retinopathy and decline in estimated glomerular filtration rate (eGFR) in longitudinal studies (119, 120). However, whether similar associations exist in patients with T1D remains unknown.

OSA is characterised by recurrent events of complete or near-complete upper airway obstruction resulting in apnoea, and/or hypopnoea due to upper airway instability. These events lead to cyclic fluctuations in thoracic pressure and oxygen saturation causing changes in blood pressure, heart rate, and sympathetic activity (164). OSA often goes undiagnosed (75) and is associated with serious effects on patients' health (such as cardiovascular disease and Type 2 diabetes) and poor quality of life (3, 75). A much quoted study in this field reported the prevalence of apnoea-hypopnoea index (AHI) ≥ 5 in middle age employees [Wisconsin, USA] to be 24% and 9% in men and women, respectively (79). However, more recent epidemiological studies found the prevalence of AHI ≥ 5 to be 46.5-83.8% in men and 30.5-60.8% in women (165, 166) which is consistent with the increasing prevalence of obesity.

Several epidemiological studies showed that OSA is very common in patients with Type 2 diabetes (T2D; ranges from 23 to 86%) (1, 108-110), which is not surprising considering that OSA and T2D share common risk factors including obesity and increased age (2). OSA in patients with T2D was shown to be associated with higher blood pressure, worse glycaemic control, cardiovascular diseases,

and diabetes-related microvascular complications including autonomic neuropathy, peripheral neuropathy, retinopathy and chronic kidney disease (102, 103, 114-119).

However, the prevalence and impact of OSA in patients with Type 1 diabetes (T1D) remains unclear. This could be in part, due to patients with T1D being leaner and younger. Hence, patients with T1D are perceived to be at lower risk of OSA than patients with T2D, and therefore the risks have not been assessed in this patient group. However, patients with T1D are also at increased risk of cardiovascular disease and diabetes-related microvascular complications and hence it is important to ascertain the risk factors leading to vascular complications in patients with T1D in order to identify new treatment targets and guide screening strategies.

Previous systematic reviews (n=4) examined the relationship between OSA and diabetes-related microvascular complications (167-170). However, these reviews presented the data in patients with T1D and T2D combined (T1D:1.3-6.1%; T2D:93.9-98.7%). Therefore, the interpretation of the results in these reviews is potentially complicated considering the different pathogenesis of T1 and T2 diabetes. These four reviews included either one T1D study (168-170) or two T1D studies (167) in their meta-analyses. These reviews focused on either neuropathy (170), kidney disease (169), or retinopathy (167, 168). But no study focused on the association of OSA and microvascular complications in patients with T1D only. In addition, only one systematic review was specifically about T1D, but this review focussed on sleep characteristics (such as sleep stages, duration, and quality) and the relationship between sleep characteristics and glycaemic control rather than diabetes-related cardiovascular complications (171). Hence, we conducted a systematic review examining the relationship between OSA and diabetes-related complications in patients with T1D.

3.1.1 Aims:

- The primary aim is to determine the prevalence of OSA in in adults with type 1 diabetes.

- The secondary aim is to evaluate the relationship between OSA and diabetic complications.

3.2 Methods:

This review was registered online on PROSPERO (2018: CRD42018094118)(136). This review was reported according to the PRISMA statement for reporting systematic reviews and meta-analyses (137, 138). Fore detailed methods please refer to section 2.2 in the methodology chapter.

In brief, the eligibility criteria are as follow: the poarticipants are the adults (>17 years old) with type 1 diabetes and OSA as measured by objective tools (e.g. portable polygraphy, polysomnography). Studies with a mixed diabetes population (type 1 and type 2) were eligible for inclusion where data could be extracted for the type 1 population separately. The comparator group were patients with type 1 diabetes but no OSA. Any primary study that included the relevant population and comparator population and reported at least one of the above-mentioned primary or secondary outcomes was eligible for inclusion in this systematic review. We excluded non-human studies, editorials, guidelines, or reviews. However, reviews were used for citation checking.

3.2.1.1 Outcomes:

Primary outcomes:

- Prevalence and severity of OSA in patients with T1D.

Secondary outcomes:

- Prevalence and severity of OSA in patients with T1D.
- Diabetes-related complications (peripheral neuropathy, autonomic neuropathy, retinopathy, chronic kidney disease) in patients with T1D with vs. without OSA.

- Measures of glycaemic control such as HbA1c (mmol/mol, %) in T1D patients with and without OSA.
- Total daily dose of insulin (U/kg) in patients with T1D with and without OSA.

3.3 Results

A total of 572 citations were identified and ten studies met the inclusion criteria (see figure 3.1 for the selection process). Reasons for exclusion have been detailed in appendix 2.2.

3.3.1 Study Characteristics

All of the included studies (n=10) were cross-sectional. 492 patients with T1D were included of which 182 were diagnosed with OSA. The study characteristics are shown in Table 3.1. The majority (n=7) of the studies were from Europe, with the remainder from the USA (n=2) and Brazil (n=1). Nine studies used either polysomnography or portable polygraphy (109, 114, 115, 131, 135, 172-175). One study used oximetry to diagnose OSA and then confirmed the results using polysomnography (128).

Participants' characteristics reported in included studies show that participants were adult T1D with more males. Average reported BMI was 23.9 to 28 Kg/m^2, and average diabetes duration was 16.9 to 29 years showing longstanding diabetes. Patients with OSA were older, had higher BMI, and longer diabetes duration (**Table** 3.1). Only one study reported ethnicity (all caucasian) (115).

OSA definitions varied between the different studies (**Table** 3.2) with higher prevalence reported in studies that used lower AHI cut offs to diagnose OSA (**Table** 3.1). Three studies used AHI of 5 as the cut-off, three used 10, and two used 15. Table 3.3 shows the definition of the included studies for the outcomes included in this review.

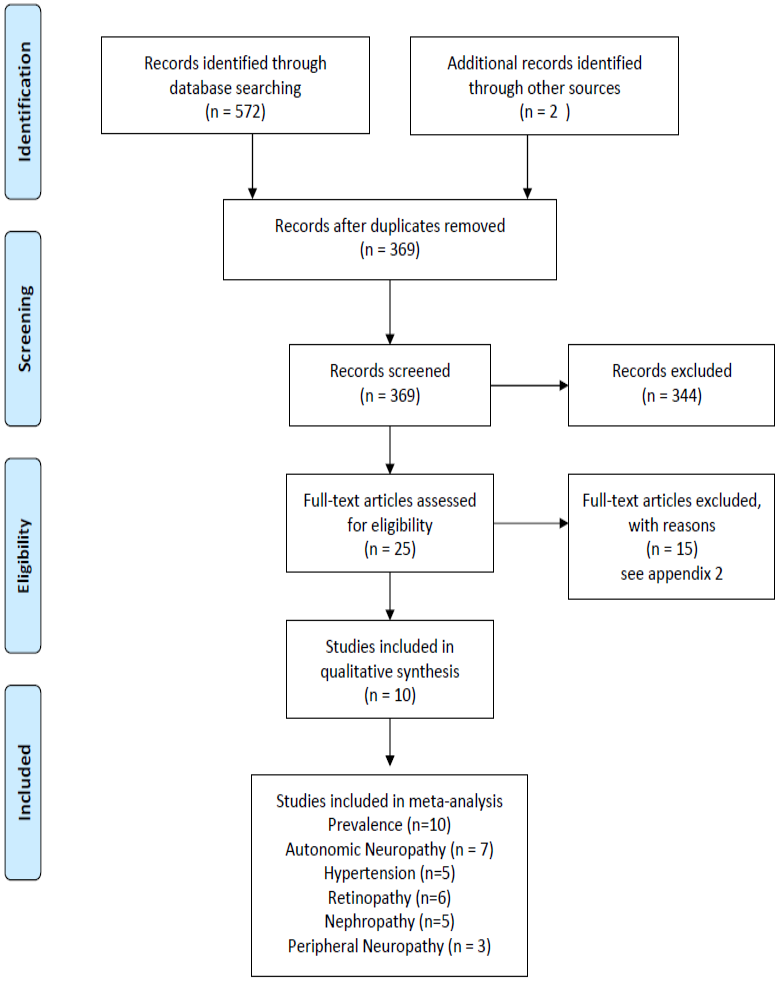


Figure 3.1 PRISMA flow diagram for study inclusion.

Table 3.1. Characteristics of Included Studies

Authors	Study Type	sample size	Location	AHI Cut-off	Tool	OSA in T1D n (%)		Age years (SD)	BMI kg/m^2 (SD)	Male n (%)	Diabetes Duration years (SD)
Guilleminault et al. (172)	CS	4	USA	Not reported	PG	2(50%)	Total:	27(10)	Not reported	4(100%)	Not reported
							OSA-:	29(16)	Not reported	2(100%)	Not reported
							OSA+:	25(6)	Not reported	2(100%)	Not reported
Mondini et al. (114)	CS	12	USA	Not reported	PG	1(8.3%)	Total:	34 (Not reported)	Not reported	Not reported	Not reported
							OSA-:	Not reported	Not reported	Not reported	Not reported
							OSA+:	Not reported	Not reported	Not reported	Not reported
Ficker et al. (115)	CS	22	Germany	AHI ≥ 10	PSG	1(4.5%)	Total:	Not reported	Not reported	Not reported	Not reported
							OSA-	Not reported	Not reported	Not reported	Not reported
							OSA+	Not reported	Not reported	Not reported	Not reported
Borel et al. (128)	CS	37	France	AHI>15	PSG (n=18)[a]	14(37.8%)	Total:	43 (13)	24.7 (3)	25 (68%)	23 (14)
					Oximetry (n=37)		OSA-:	36(11)[C]	24.2(3.1)[C]	14(64%)[C]	17(11)[C]
							OSA+:	53(8) *	25.5(2)	11(73%)	29(13) *
Schober et al. (109)	CS	58	Germany	AHI ≥15/h	PG	6(10.3%)	Total:	42.4(14.5)	25.4 (5.1)	31(53.4%)	16.9(14.2)
							OSA-:	41.3(14.6)	25.1(4.9)	28(53.8%)	16.6(13.9)
							OSA+:	52.0(10.9)	28.1(6.5)	3(50%)	19.6(18.5)

CS: cross-sectional study; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; PG: portable polygraph; PSG: polysomnography; NA: not available; SD: standard deviation (used when mean is reported); IQR: interquartile range (used when median is reported)

[a] :Eighteen out of the 37 participants underwent PSG assessment; [C]: the reported number is calculated by combining two groups (normal and borderline); *: Significant difference between OSA positive group and OSA negative group.

Table 3.1. Characteristics of Included Studies (continue)

Authors	Study Type	sample size	Location	AHI Cut-off	Tool	OSA in T1D n (%)		Age years (SD)	BMI kg/m^2 (SD)	Male n (%)	Diabetes Duration years (SD)
Vale et al. (173)	CS	23	Portugal	AHI >5/h	PSG	13(56.5%)	Total:	38.7(10.7)	28.0 (5.1)	13(56.5%)	17.3(11.7)
							OSA-:	Not reported	Not reported	Not reported	Not reported
							OSA+:	Not reported	Not reported	Not reported	Not reported
Janovsky et al. (135)	CS	20	Brazil	AHI >5/h	PSG	8(40%)	Total:	29.6 (8.0)	23.9 (2.4)	Not reported	Not reported
							OSA-:	Not reported	Not reported	Not reported	Not reported
							OSA+:	Not reported	Not reported	Not reported	Not reported
Manin et al. (131)	CS	67	France	AHI > 10/h	PSG	31(46.3%)	Total:	54 (10)	25.8 (4.7)	40(60%)	29(14)
							OSA-:	53 (10)	25 (4.9)	19(53%)	25(15)
							OSA+:	56 (10)	26.6 (4.3)	21(68%)	34(12) *
Banghoej et al. (175)	CS	199	Denmark	AHI ≥5/h	PG	92(46%)	Total:	53 (15)	25.3 (3.3)	134(67%)	24(14)
							OSA-:	46 (15)	24.4(3.0)	64(60%)	20(13)
							OSA+:	59 (10) *	26.4(3.2) *	70(76.1%) *	28(15) *
Meyer et al. (174)	CS	50	France	AHI >10/h	PG and PSG	14 (28%)	Total:	51 [IQR 20]	25 [IQR 6]	26(52%)	29 [IQR 24]
							OSA-:	46.5[IQR 16]	24.4 [IQR6.5]	16 (44.4%)	26 [IQR 22]
							OSA+:	53 [IQR 16.8]	28.2 [IQR 5.6] *	10 (71.4%)	40 [IQR 12] *

CS: cross-sectional study; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; PG: portable polygraph; PSG: polysomnography; NA: not available; SD: standard deviation (used when mean is reported); IQR: interquartile range (used when median is reported)

[a] **:**Eighteen out of the 37 participants underwent PSG assessment**; [C]:** the reported number is calculated by combining two groups (normal and borderline); ***:** Significant difference between OSA positive group and OSA negative group.

Table 3.2. Apnoea and Hypopnoea Definitions, and Measures

Study	Definitions
Borel et al. (128)	Apnoea and hypopnoea were not defined Cut-off: AHI > 15 ⁄ h
Guilleminault et al. (172)	Referred to standard international criteria by Tassinari et al. (1972). *Reference: Tassinari CA, Dalla-Bernadina B, Cirignotta F, and Ambrosetto G. Apnoeic periods and the respiratory related arousal patterns during sleep in the Pickwickian Syndrome: A polygraphic study. Bull Physiopathol Resp 8:1087-1102, 1972.*
Mondini et al. (114)	Apnoea and hypopnoea: referred to previous study by Guilleminault et al. (1980) Hypopnoea: tidal volume < 300cc. *Reference: Guilleminault C, Cummiskey J, Motca J: Chronic obstructive airflow disease and sleep studies. Am Rev Respir Dis 122:397- 406, 1980*
Schober et al. (109)	Apnoea: airflow reduction ≥ 80% for ≥ 10 s Hypopnoea: airflow reduction of 50%–80% for ≥ 10 s and ≥ 4% drop in oxygen saturation. Minimum sleep time duration 2 h Cut-off: AHI ≥ 15
Vale et al. (173)	Apnoea: cessation of airflow for ≥ 10s Hypopnoea: reduction in thoraco-abdominal movement or airflow ≥ 30% for ≥ 10s and ≥ 3% drop in oxygen saturation. Minimum sleep time duration 4 h Cut-off: AHI> 5
Janovsky et al. (135)	Apnoea: airflow reduction >50% Hypopnoea: airflow reduction of 30–50% Cut-off: AHI >5
Manin et al. (131)	Apnoea: cessation of airflow for ≥ 10s Hypopnoea: airflow reduction ≥ 50 for ≥ 10s and ≥ 3% drop in oxygen saturation. Cut-off: AHI > 10
Banghoej et al. (175)	Apnoea: interruption in airflow ≥ 10 s Hypopnoea: airflow reduction ≥ 10 s and ≥ 3% desaturation cited (American Academy of Sleep Medicine Task Force, 1999). Manual scoring if AHI≤ 30 Minimum sleep time duration 4 h Cut-off: AHI ≥ 5
Ficker et al. (115)	Apnoea: cessation of airflow for ≥ 10s. Hypopnoea: ≥ 50 reduction in thoracoabdominal motion for ≥ 10s associated with ≥ 4% drop in oxygen saturation. Cut-off: AHI ≥ 10
Meyer et al. (174)	Apnoea and hypopnoea: referred to the American Academy of Sleep Medicine (AASM) criteria. Cut-off: AHI ≥ 10

AHI: apnoea hypopnoea index.

Table 3.3. Outcome Definitions

Outcome	Study	Definition
Nephropathy	Manin et al. (131)	Microalbuminuria ≥ 30 mg/24 h and/or a creatinine clearance < 60 ml/min.
	Banghoej et al. (175)	Microalbuminuria (urinary albumin/creatinine ratio 30–300 mg/g) or macroalbuminuria (urinary albumin/creatinine ratio > 300 mg/g).
	Meyer et al. (174)	Reported but not defined
	Borel et al. (128)	Reported but not defined
	Schober et al. (109)	Reported but not defined
Peripheral Neuropathy	Manin et al. (131)	• Pin prick, vibration and/or toes position sensation abnormalities. • Absence of osteotendinous reflexes. • Monofilament examination score < 6 of 9)
	Mondini et al. (114)	Clinical symptoms supported by electrophysiological studies
	Banghoej et al. (175)	Using biothesiometry (> 25 V is abnormal)
	Meyer et al. (174)	Reported but not defined
	Schober et al. (109)	Reported but not defined
Retinopathy	Manin et al. (131)	By retinal photography, ophthalmologic examination and/or previous laser therapy
	Banghoej et al. (175)	Based on digital fundus photography.
	Guilleminault et al. (172)	Reported but not defined
	Meyer et al. (174)	Reported but not defined
	Schober et al. (109)	Reported but not defined
	Borel et al. (128)	Reported but not defined
Autonomic Neuropathy	Manin et al. (131)	Orthostatic hypotension (reduction of ≥ 20 mm Hg in SBP or ≥ 10 mm Hg in DBP) and/or documented gastroparesis. (not reported whether possible or definite)
	Mondini et al. (114)	Heart rate variability (cold pressor test, deep breathing, Valsalva, and Müller's Manoeuvres) (not reported whether possible or definite)
	Banghoej et al. (175)	Heart rate variability measures (E:I, 30:15, and Valsalva manoeuvre) using Vagus™ device (Definite CAN (≥ 2 indices are abnormal)
	Guilleminault et al. (172)	Heart rate variability measures (cold stress, deep breathing and Valsalva manoeuvre) (definite CAN)
	Ficker et al. (115)	Heart rate variability measures (normal breathing, deep breathing, and standing manoeuvres; Definite CAN (≥ 3 indices are abnormal)
	Janovsky et al. (135)	Heart rate variability measures (E:I, 30:15, and Valsalva manoeuvre) and orthostatic hypotension (Definite CAN (≥ 2 indices are abnormal))
	Meyer et al. (174)	• Measuring sweat gland dysfunction using Sudoscan. • CAN risk calculated from Sudoscan result (possible CAN).
Hypertension	Banghoej et al. (175)	Treated for hypertension
	Meyer et al. (174)	Reported but not defined
	Borel et al. (128)	Reported but not defined
	Manin et al. (131)	SBP ≥ 135 mm Hg, DBP ≥ 85 mm Hg, or undergoing treatment for high blood pressure
	Schober et al. (109)	Not defined

SBP: systolic blood pressure; DBP: diastolic blood pressure; CAN: cardiac autonomic neuropathy; AN: autonomic neuropathy.

3.3.2 Quality assessment:

The quality of the included studies varies as shown in
Figure 3.2. All of the included studies were cross-sectional. Two studies were published as research letters (128, 174). The sample sizes were not justified in any of the included studies. Patients were recruited from diabetes clinics or centres in all studies except for the one study that included 10 patients with autonomic nervous system dysfunction (172), and four of those 10 patients had T1D. However, the selection process in all studies was convenience sampling (consecutive recruitment), which is not the optimal method of selection. This type of sampling might introduce a potential selection bias. All of the included studies measured at least one of the outcomes we were interested in, using instruments that were published previously. The statistical methods and significance were not reported in two studies (114, 172) as they reported the raw data for the patients with OSA. No measures were undertaken to address non-responders in all studies, however, four out of ten studies provided some information about non-responders (non-participants). Most of the included studies (8 out of 10) might potentially introduce a risk of non-response bias as they reported no or limited information about non-responders. Although three studies stated strategies to deal with confounding factors (131, 174, 175), one study reported adjusted results (175).

The basic data were adequately described in all the studies except for two (114, 135). It is also important to state that one study, published as a research letter does not have a methods section, however, the statistical analysis is written in the characteristics table legend (128).

The discussions and conclusions in all studies were justified by their results, however, only half the studies addressed the study limitations (128, 131, 173-175). It is important

to note that three studies received funding from companies that manufacture the instruments used to collect data for the studies (109, 174, 175).

	Guilleminault et al. (172)	Mondini et al. (114)	Borel et al. (128)	Schober et al. (109)	Ficker et al. (115)	Janovsky et al. (135)	Vale et al. (173)	Manin et al. (131)	Banghoej et al. (175)	Meyer et al. (174)
	Aim and Methodology									
Q1	1	1	1	1	1	1	1	1	1	1
Q2	1	1	1	1	1	1	1	1	1	1
Q3	0	0	0	0	0	0	0	1	1	0
Q4	0	1	1	1	1	1	1	1	1	1
Q5	0	0	1	1	1	0	1	1	1	1
Q6	0	0	0	0	0	0	0	0	0	0
Q7	0	0	0	0	0	0	0	0	0	0
Q8	1	1	1	1	1	1	1	1	1	1
Q9	1	1	1	1	1	1	1	1	1	1
Q10	0	0	1	1	1	1	1	1	1	1
Q11	1	1	1	1	1	1	1	1	1	1
	Result									
Q12	1	0	1	1	1	0	1	1	1	1
Q13	0	0	0	1	0	0	0	0	1	0
Q14	0	0	0	1	1	0	0	1	1	0
Q15	1	1	1	1	1	0	1	1	1	1
Q16	1	1	1	1	1	1	1	1	1	1
	Discussion									
Q17	1	1	1	1	1	1	1	1	1	1
Q18	0	0	0	1	0	0	1	1	1	1
	Other									
Q19	1	1	1	0	1	1	1	1	0	1
Q20	0	1	1	1	1	1	1	1	1	1
Total	10	11	14	16	15	11	15	17	17	15

Figure 3.2 Quality assessment of the included studies

3.3.3 Prevalence of OSA

The range of reported OSA proportions in T1D studies varies widely (Table 3.4). The pooled prevalence ranged from 20.6% to 43.7%, but the pooled prevalence showed significant statistical heterogeneity (I^2 = 84.6%; Table 3.4A). A subgroup analysis of five (5/10) studies defining OSA as AHI ≥ 10 showed lower estimated prevalence ranging from 10.6% to 37.9% (I2 = 85.1%; Table 3.4B). The funnel plot illustrated symmetrical distribution, with this suggestive of low publication bias across the included studies (n=10; Figure 3.3).

Table 3.4 estimated prevalence of OSA for all included studies (n=10) of patients with T1D and subgroup estimation for studies using AHI ≥ 10 as cut-off for diagnosing OSA

A) AHI ≥ 5

Study	Sample size	Proportion (%)	95% CI	Weight (%) Random effect
A) AHI ≥ 5				
Guilleminault et al. (172)	4	50.0%	6.8 to 93.2	5.0
Mondini et al. (114)	12	8.3%	0.2 to 38.5	8.1
Ficker et al. (115)	22	4.5%	0.1 to 22.8	9.7
Borel et al. (128)	37	37.8%	22.5 to 55.2	10.8
Schober et al. (109)	58	10.3%	3.9 to 21.2	11.5
Vale et al. (173)	23	56.5%	34.5 to 76.8	9.8
Janovsky et al. (135)	20	40.0%	19.1 to 63.9	9.5
Manin et al. (131)	67	46.3%	34.0 to 58.9	11.7
Banghoej et al. (175)	199	46.2%	39.2 to 53.4	12.6
Meyer et al. (174)	50	28.0%	16.2 to 42.5	11.3
Total (random effects)	**492**	**31.5%**	**20.6 to 43.7**	**100**
B) Subgroup (AHI ≥ 10; n=5/10)				
Mondini et al. (114)	12	8.3%	0.2 to 38.5	13.13
Ficker et al. (115)	22	4.5%	0.1 to 22.8	15.51
Borel et al. (128)	37	37.8%	22.5 to 55.2	17.09
Schober et al. (109)	58	10.3%	3.9 to 21.2	18.1
Manin et al. (131)	67	46.3%	34.0 to 58.9	18.36
Meyer et al. (174)	50	28.0%	16.2 to 42.5	17.8
Total (random effects)	**246**	**22.7%**	**10.6 to 37.9**	**100**

A) Test of Heterogeneity: Cochran's Q = 58.4, df = 9 (p<0.01), I^2 = 84.6%
B) Test of Heterogeneity: Cochran's Q = 33.5, df = 5 (p<0.01), I^2 = 85.1%

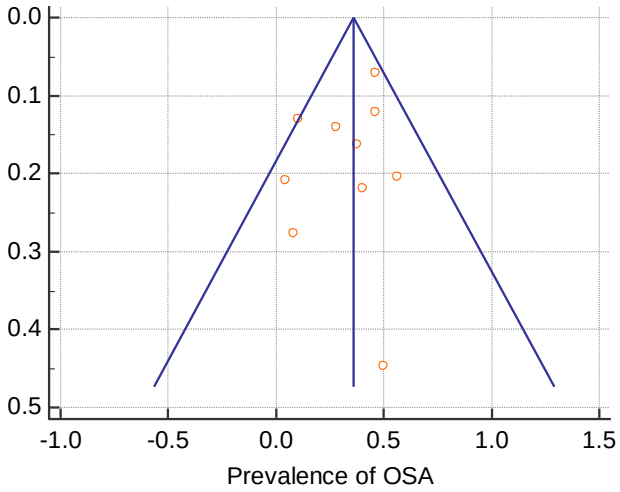


Figure 3.3 Funnel plot of standard error by prevalence of OSA in patients with T1D (n=10). *Each circle represents one of the included studies.*

3.3.4 Glycaemic control (HbA1c)

HbA1c in T1D with (n=144) and without (n=217) OSA was reported in four out of ten studies. The pooled HbA1c in Figure 3.4 did not show any significant difference between T1D with and without OSA, WMD 0.19 (95% CI: -2.13-2.93). We found no heterogeneity between studies for HbA1c.

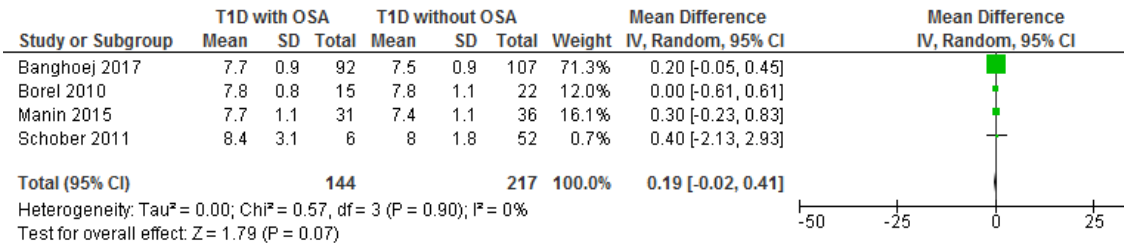


Figure 3.4. There is no association between OSA and HbA1c in patients with T1D. *T1D: type 1 diabetes; OSA: obstructive sleep apnoea; SD: standard deviation; IV: inverse variance; CI: confidence interval; Chi^2 = chi-square; df = degrees of freedom; P: p-value; I^2: I-square heterogeneity statistic; Z: Z-value.*

3.3.5 Autonomic Neuropathy:

Autonomic neuropathy in T1D with (n=181) and without (n=260) OSA was reported in seven out of ten studies (114, 115, 131, 135, 172, 174, 175). Five studies diagnosed autonomic neuropathy using heart rate variability (HRV) (114, 115, 135, 172, 175), one study indirectly measured CAN risk using Sudoscan (174), and one study reported orthostatic hypotension and gastroparesis (131). However, the last one reported orthostatic hypotension and gastroparesis separately.

All seven studies were included in the meta-analysis (Figure ***3.5***a). Autonomic neuropathy was significantly higher in the group with OSA with an odds ratio (OR) of 4.06 (95% CI: 2.01-8.19). The heterogeneity of these studies was very low (I^2 = 0%). Meta-analysis reported in Figure ***3.5***b shows the pooling of results from studies which used cardiac autonomic reflex tests to assess autonomic neuropathy.

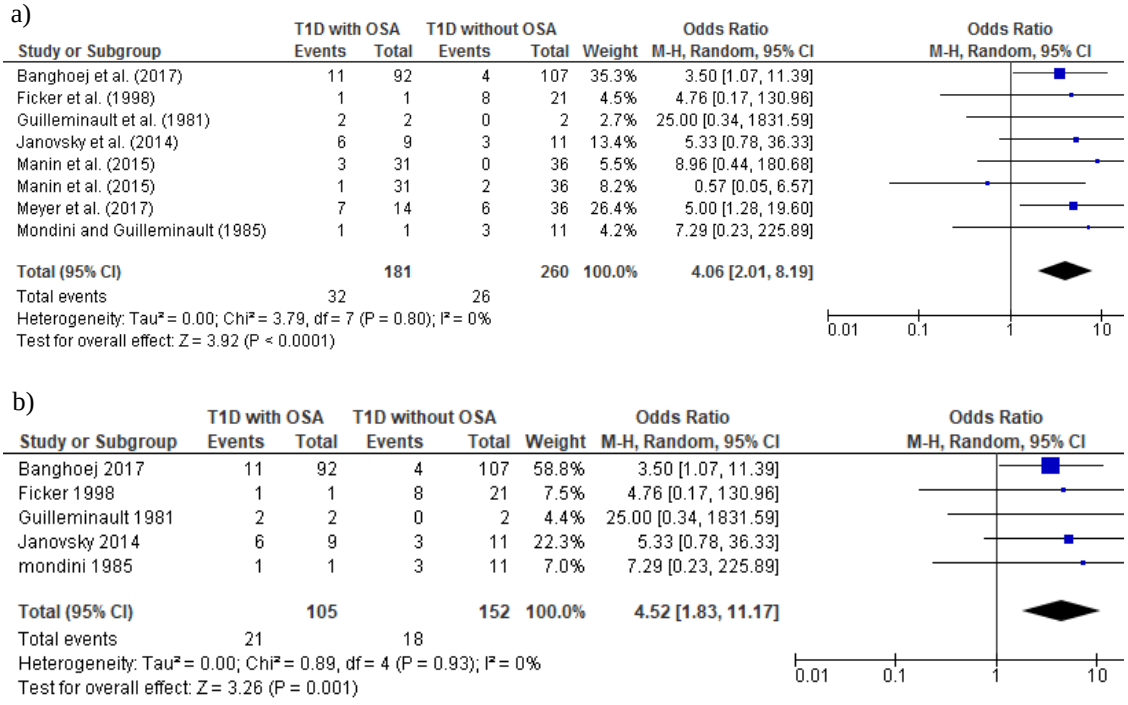


Figure 3.5. There is an association between OSA and autonomic neuropathy in patients with T1D. *a) meta-analysis of all the studies which reported autonomic neuropathy as an outcome; b) sub-analysis meta-analysis of the studies which used HRV analysis (cardiac autonomic reflex tests). T1D: type 1 diabetes; OSA: obstructive sleep apnoea; M-H: Mantel-Haenszel test; Random: random-effects model; CI: confidence interval; Chi² = chi-square; df = degrees of freedom; P: p-value; I²: I-square heterogeneity statistic; Z: Z-value*

3.3.6 Hypertension

Hypertension in T1D with (n=158) and without (n=253) OSA was reported in five out of ten studies (109, 128, 131, 174, 175). Three studies did not define hypertension (109, 128, 174). One study defined it as treated for hypertension (175). The last one defined hypertension as either treated for hypertension, having systolic BP ≥ 135 mm Hg, or diastolic BP ≥ 85 mm Hg (131).

All five studies were pooled in the forest plot in Figure ***3.6***. Hypertension was significantly higher in the OSA group with an OR of 4.42 (95% CI: 2.36-8.29). The heterogeneity of these studies was I^2 = 31%.

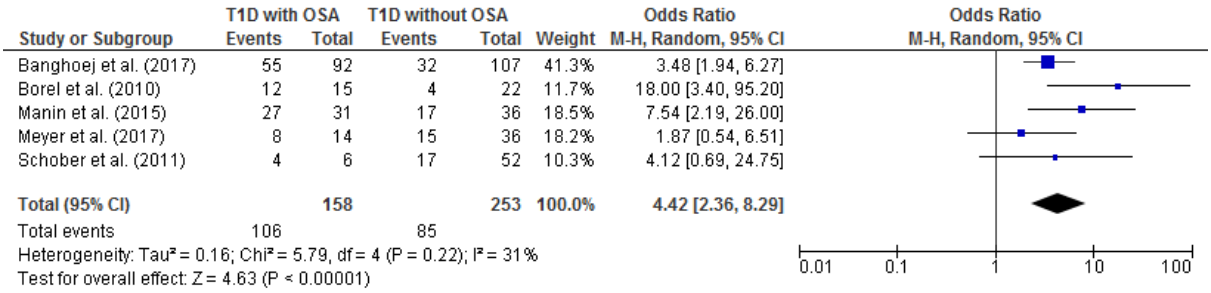


Figure 3.6. There is an association between OSA and hypertension in patients with T1D. *T1D: type 1 diabetes; OSA: obstructive sleep apnoea; M-H: Mantel-Haenszel test; Random: random-effects model; CI: confidence interval; Chi^2 = chi-square; df = degrees of freedom; P: p-value; I^2: I-square heterogeneity statistic; Z: Z-value.*

3.3.7 Retinopathy

Retinopathy in T1D with (n=160) and without (n=255) OSA was reported in six out of ten studies (109, 128, 131, 172, 174, 175). Four studies did not define retinopathy (109, 128, 172, 174). One study diagnosed retinopathy based on fundus images (175). One study based the diagnosis on retinal images, ophthalmologic examination, and/or previous laser therapy (131).

All six studies were pooled in the forest plot in Figure ***3.7***. Retinopathy was associated with OSA with an OR of 2.44 (95% CI: 1.01-5.89). The heterogeneity of these studies was high (I^2 = 58%). Only two studies reported proliferative retinopathy which was not pooled due to the small number of studies (131, 175). Both studies show significant increase in the odds of proliferative retinopathy in T1D with OSA 2.36 (1.03-5.41) and 6.53 (2.24-19.10) in Banghoej et al. (175) and Manin et al. (131) studies, respectively.

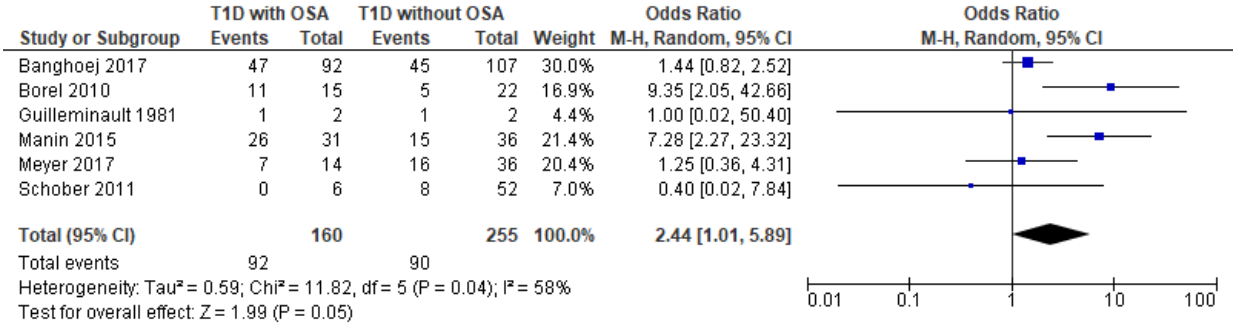


Figure 3.7. There is an association between OSA and retinopathy in patients with T1D. *T1D: type 1 diabetes; OSA: obstructive sleep apnoea; M-H: Mantel-Haenszel test; Random: random-effects model; CI: confidence interval; Chi^2 = chi-square; df = degrees of freedom; P: p-value; I^2: I-square heterogeneity statistic; Z: Z-value.*

3.3.8 Nephropathy

Nephropathy in T1D with (n=158) and without (n=253) OSA was reported in five out of ten studies (109, 128, 131, 174, 175). Three studies did not define nephropathy (109, 128, 174). One study diagnosed nephropathy based on albumin/creatinine ratio (175). One study diagnosed nephropathy based on microalbuminuria and/or creatinine clearance (131). All five studies were pooled in the forest plot in Figure ***3.8***. Nephropathy was significantly higher in the OSA group with OR 2.46 (95% CI: 1.21-4.98). The heterogeneity of these studies was low (I^2 = 21%).

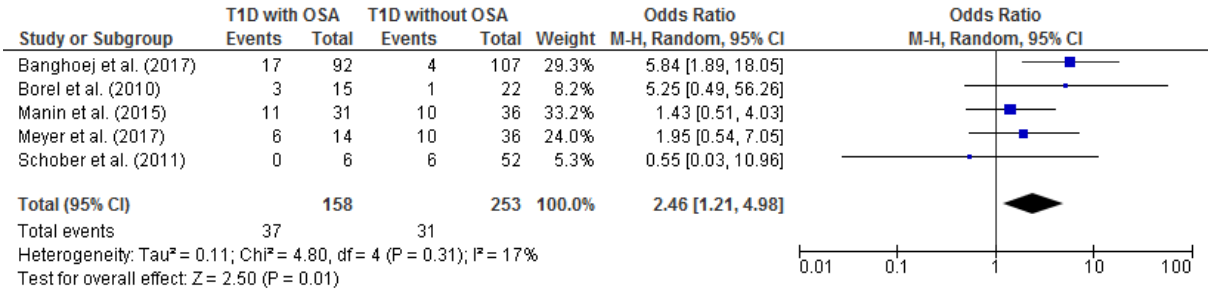


Figure 3.8. There is an association between OSA and nephropathy outcome in patients with T1D. *T1D: type 1 diabetes; OSA: obstructive sleep apnoea; M-H: Mantel-Haenszel test; Random: random-effects model; CI: confidence interval; Chi^2 = chi-square; df = degrees of freedom; P: p-value; I^2: I-square heterogeneity statistic; Z: Z-value.*

3.3.9 Peripheral Neuropathy

Peripheral neuropathy was assessed in five of the ten studies (109, 114, 131, 174, 175). Only three studies reported peripheral neuropathy in T1D with (n=137) and without (n=179) OSA (131, 174, 175). Two studies reported a clear definition of peripheral neuropathy (131, 175), whereas one study reported the results of separate assessments that were used in assessing peripheral neuropathy (174). We used the result of the neurological examination to include in the meta-analysis.

The three studies were pooled in the forest plot in Figure ***3.9***. Peripheral neuropathy was significantly higher in the OSA group (OR: 3.30, 95% CI: 2.06-5.31). The heterogeneity of these studies was very low (I^2 = 0%).

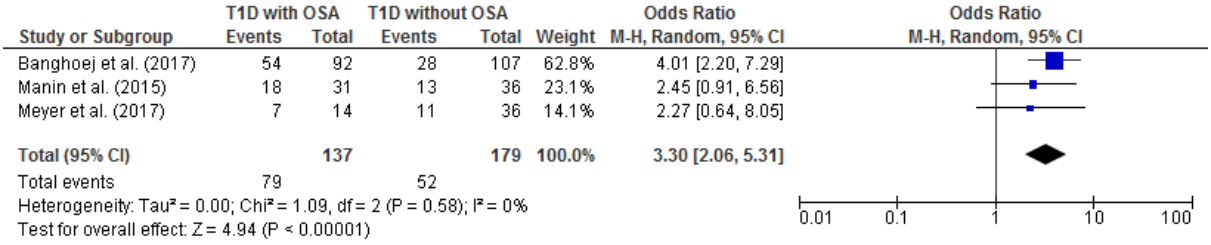


Figure 3.9. There is an association between OSA and peripheral neuropathy in patients with T1D*. T1D: type 1 diabetes; OSA: obstructive sleep apnoea; M-H: Mantel-Haenszel test; Random: random-effects model; CI: confidence interval; Chi² = chi-square; df = degrees of freedom; P: p-value; I²: I-square heterogeneity statistic; Z: Z-value.*

3.4 Discussion:

Key points:

- OSA was common in patients with T1D
- OSA was associated with hypertension in patients with T1D
- OSA was associated with microvascular complications (CAN, retinopathy, nephropathy, and peripheral neuropathy) in patients with T1D

This systematic review was conducted to assess the relationship between OSA and diabetes-related complications (hypertension, autonomic neuropathy, peripheral neuropathy, nephropathy, and retinopathy) in adult patients with T1D, and we found that these complications were higher in patients with OSA and T1D vs T1D without OSA despite similar HbA1c. However, patients with OSA were older, had longer diabetes duration and higher BMI which might contribute to the associations described in this meta-analysis. We also noted the lack of any cohort or interventional study and hence we cannot ascertain the direction of the relationship between OSA and diabetes-related complications in patient with T1D. It is recommended to use a fixed-effects model if two assumptions are met. Firstly, there is a good reason to assume that all included studies are functionally identical. Secondly, we are aiming to calculate the common effect size (176). So, we used a random-effects model because we found some heterogeneity between studies (table 3.2 and table 3.3), but the studies have enough in common to consider conducting a meta-analysis (176). It has been reported also that I^2 can be imprecise in small meta-analyses (177).

The prevalence of OSA in patients with T1D

Different studies identified different prevalences. The prevalence of OSA (AHI ≥ 5) in patients with T1D ranged from 20.6% to 43.7%. The wide variation in prevalence between studies might be explained by the variation of the AHI definitions and cut-offs used, the sampled population, the ages of the studied participants, and the examination tool used. The improvement in the technology might also contribute to the variation as recent studies tend to report higher OSA prevalence (178). However, the definition of hypopnoea has changed over the years, which is shown on the AHI definition table (table 2.3). Deciding the reduction in airflow and the drop in oxygen saturation cut-offs accounted for a significant part of the AHI score (179). Several studies have shown that changing these cut-offs had a great impact on hypoxia index and therefore AHI (179, 180). A study compared the scoring of 100 sleep recording using the two AASM criteria (2007 and 2012) (180). 2007 guideline defines hypopnoea as a reduction of ≥ 30% in airflow and a drop of ≥ 4% in oxygen saturation (180). Alternatively, a reduction of ≥ 50% in airflow and a drop of ≥3% in oxygen or arousal (180). 2012 guideline defines hypopnoea as a reduction of ≥ 30% in airflow and a drop of ≥ 3% drop in oxygen or arousal (180). The study found that the 2012 guideline is looser than 2007 guideline and score higher AHI as compare to the two definitions in 2007 guideline (180). Similarly, a study of 328 sleep recording shows that using a stricter drop in oxygen cut-off (≥4% vs ≥3%) reduces the total number of hypopnoea events per hours and therefore the AHI (179).

The association between OSA and hypertension in patients with T1D

Our results suggest a significant association between OSA and hypertension in T1D. These findings are consistent with the large body of evidence showing that OSA is

associated with hypertension (including resistant hypertension) in patients with and without diabetes and that CPAP lowers blood pressure (181-183). The links between OSA and hypertension might be in part related to sympathetic activation as a recent study found that beta-blocker (Nebivolol) was better than a diuretic in treating hypertension in patients with OSA (184), and that renal denervation reduced both blood pressure and the AHI in patients with moderate to severe OSA (185).

The association between OSA and microvascular complications in patients with T1D

Our results suggest a significant association between OSA and autonomic neuropathy. The links between OSA and sympathetic activation (which occurs at the termination of the apnoea/hypopnea episodes) is well established and is the basis for the recent use of peripheral arterial tonometry to diagnose OSA (186, 187). CPAP has also been shown to lower sympathetic tone within days (187, 188). However, in patients with diabetes, due to the hyperglycaemia and the long diabetes duration, it is plausible that OSA can be associated with parasympathetic as well as sympathetic dysfunction (particularly sympathetic withdrawal which is assessed by HRV in the studies included in this meta-analysis). A previous study in patients with Type 2 diabetes also showed that OSA was associated with autonomic dysfunction and parasympathetic withdrawal (189). It is not clear whether OSA is leading to CAN or CAN is leading to OSA in patients with diabetes, particularly that both directions of the relationship are plausible biologically (oxidative stress, impaired upper airway control, changes to chemoreceptors sensitivity). In addition, it is plausible that obesity might contribute to these observed links. However, a previous study of patients with diabetes (T1D=1, T2D=17) found a significantly higher AHI (39.5±13 vs 15.8±12; $p<0.01$) in patients with diabetes and autonomic neuropathy compared to patients with higher BMI but without autonomic neuropathy (35 ± 4 vs.37 ±

5) (190). This suggests that autonomic neuropathy might play a role in the development of OSA in patients with diabetes and that the relationship is potentially bidirectional.

Our results suggest a significant association between OSA and retinopathy. We found the odds of retinopathy to be 2.4 times higher in T1D with OSA as compared to T1D only. A similar association between OSA and retinopathy was reported in a T2D longitudinal study. The study found an independent association (OR= 2.3) between OSA and sight-threatening diabetic retinopathy (120). OSA was also a predictor of worsening retinopathy in T2D (120).

Our results suggest a significant association between OSA and peripheral neuropathy. We found the odds of peripheral neuropathy to be 3.3 times higher in T1D with OSA as compared to T1D only. An independent association between OSA and peripheral neuropathy was reported in T2D, and this was explained by the presence of a higher level of oxidative stress in patients with OSA vs without OSA and in patients with peripheral neuropathy vs those without (110).

Our results show that the odds of nephropathy is 2.5 times higher in the OSA group. A recent systematic review shows that OSA is associated with a decline in kidney function in both patients with and without diabetes (191). An observational study found that patients who were diagnosed with OSA before admission to an intensive care unit had about a 53% increase risk of acute kidney injury (192). A meta-analysis suggested a relationship between OSA and diabetic kidney disease in T2D (169). In a T2D cohort study, OSA was identified as a predictor of decline in kidney function (119). Intermittent hypoxia might be a risk factor for kidney dysfunction as it was reported that an increase in the oxygen desaturation index was independently associated with a decrease in kidney function in patients with diabetes (193).

Possible mechanisms linking OSA to diabetes-related complications in T1D

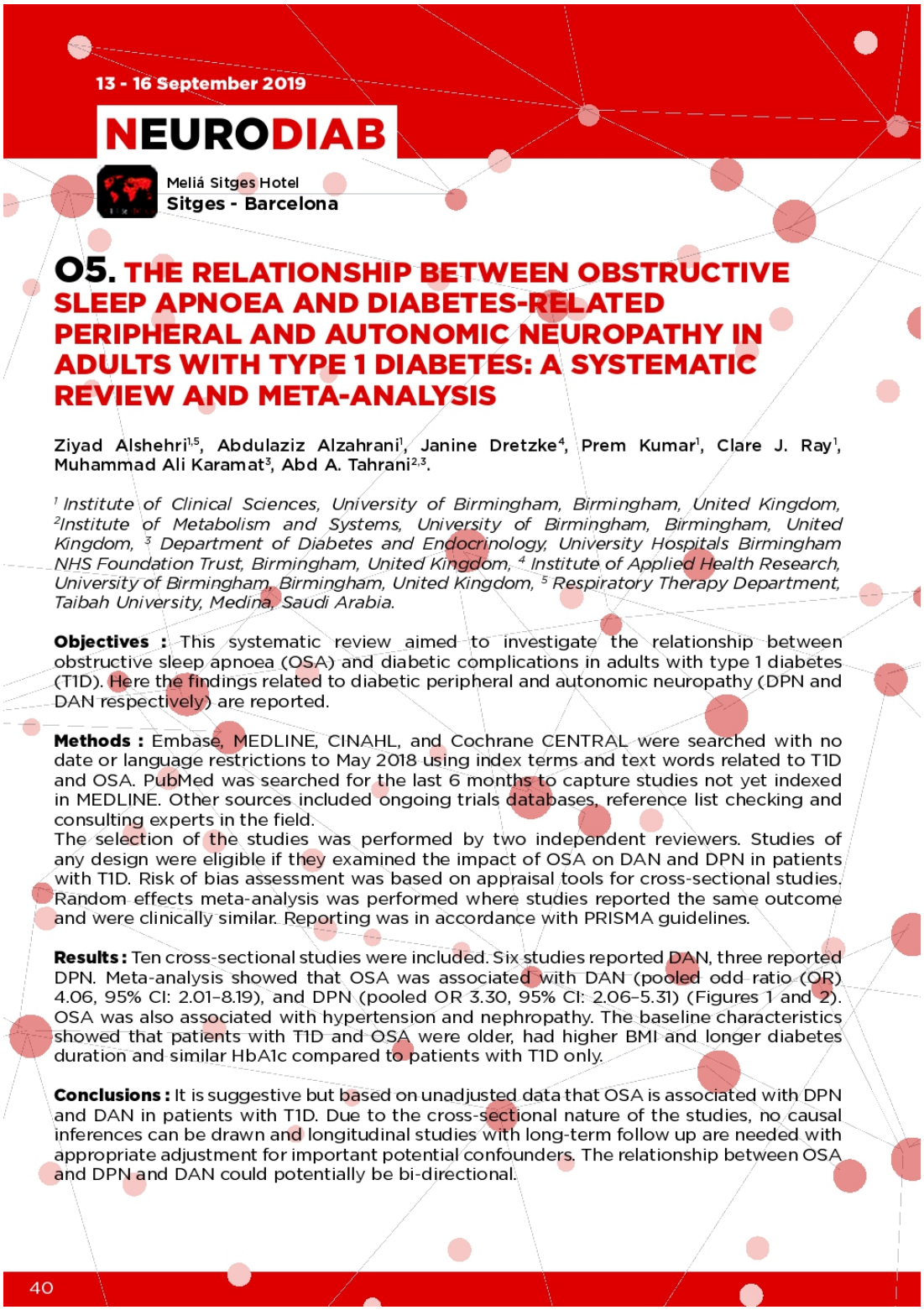
Hyperglycaemia in patients with diabetes is known to activate pathways such as polyol, advanced glycation end-products (AGEs), protein kinase C (PKC), and hexosamine pathways (57). Theses pathways has been linked to increased oxidative stress, cellular dysfunction and microvascular complications (57). OSA might contribute to diabetes complication by worsening the oxidative stress and sympathetic imbalance (194-196) which is discussed in details in the general discussion.

.The limitations of this review include the inability to run sub-analyses due to the limited number of studies pooled for each outcome. Some of the included studies did not define all of the reported outcomes. However, these outcomes are the number or percentage of patients with specific conditions, so it is likely those studies extracted the outcomes from patients' medical records. However, kidney disease might differ based on the definition used. So, as an effort to control for the variation caused by undefined outcomes, we pooled only studies that reported their results as nephropathy. However, we recommend reporting the diagnostic methods for all reported results to help future reviews control for methodological variation. Our results show a wide range of prevalence. The number of participants, OSA definitions, including minimum analysed sleep time might influence the variation in reported OSA prevalence seen between studies. Also, improvement to the sensitivity of the sleep monitor might justify this variation. Due to the small number of included studies in the meta-analyses, it was unfeasible to conduct sub-analysis based on AHI. Age and diabetes duration are highly correlated in patients with T1D, as diabetes in T1D usually occurs early in life. As expected, both are higher in the OSA group, and for the same reason mentioned above, it was unfeasible to run sub-analysis by age or diabetes duration.

In summary, this review shows that autonomic neuropathy, hypertension, retinopathy, nephropathy, and peripheral neuropathy are associated with the presence of OSA in patients with T1D. However, we could not analyse the effect of the possible confounder factors such as age, diabetes duration, and BMI due to the limited number of included studies. Therefore, future studies should control for possible confounding factors. Also, large longitudinal studies with long-term follow up are needed to assess the possible bi-directional mechanisms between OSA and T1D. Therefore, we conducted cross-sectional and longitudinal studies in the following chapters to address these issues.

3.5 Appendices:

Appendix 3.1 abstract presented on the Neurodiab conference (13/9/19)



13 - 16 September 2019

NEURODIAB

Meliá Sitges Hotel
Sitges - Barcelona

O5. THE RELATIONSHIP BETWEEN OBSTRUCTIVE SLEEP APNOEA AND DIABETES-RELATED PERIPHERAL AND AUTONOMIC NEUROPATHY IN ADULTS WITH TYPE 1 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objectives : This systematic review aimed to investigate the relationship between obstructive sleep apnoea (OSA) and diabetic complications in adults with type 1 diabetes (T1D). Here the findings related to diabetic peripheral and autonomic neuropathy (DPN and DAN respectively) are reported.

Methods : Embase, MEDLINE, CINAHL, and Cochrane CENTRAL were searched with no date or language restrictions to May 2018 using index terms and text words related to T1D and OSA. PubMed was searched for the last 6 months to capture studies not yet indexed in MEDLINE. Other sources included ongoing trials databases, reference list checking and consulting experts in the field.
The selection of the studies was performed by two independent reviewers. Studies of any design were eligible if they examined the impact of OSA on DAN and DPN in patients with T1D. Risk of bias assessment was based on appraisal tools for cross-sectional studies. Random effects meta-analysis was performed where studies reported the same outcome and were clinically similar. Reporting was in accordance with PRISMA guidelines.

Results : Ten cross-sectional studies were included. Six studies reported DAN, three reported DPN. Meta-analysis showed that OSA was associated with DAN (pooled odd ratio (OR) 4.06, 95% CI: 2.01–8.19), and DPN (pooled OR 3.30, 95% CI: 2.06–5.31) (Figures 1 and 2). OSA was also associated with hypertension and nephropathy. The baseline characteristics showed that patients with T1D and OSA were older, had higher BMI and longer diabetes duration and similar HbA1c compared to patients with T1D only.

Conclusions : It is suggestive but based on unadjusted data that OSA is associated with DPN and DAN in patients with T1D. Due to the cross-sectional nature of the studies, no causal inferences can be drawn and longitudinal studies with long-term follow up are needed with appropriate adjustment for important potential confounders. The relationship between OSA and DPN and DAN could potentially be bi-directional.

CHAPTER FOUR: OBSTRUCTIVE SLEEP APNOEA AND CARDIAC AUTONOMIC NEUROPATHY

Contribution: Ziyad Alshehri contributed to the design of the study, recruitment, cardiac autonomic neuropathy assessment, data collection, all statistical analyses and writing of this chapter. I would like to acknowledge the valuable help provided by Dr Muhammad Ali Karamat MD, Dr Quratul-ain Altaf MD, and Helen Jenner (research practitioner) at Heartlands hospital. Matthew Nicholls (sleep technician) manually scored the sleep recording for sleep apnoea.

An abstract of the data presented in this chapter was accepted and presented as an oral communication at the Neurodiab conference (2019) in Sitges - Barcelona, Spain (see Appendix 4.1*).*

Another abstract of the data presented in this chapter has been accepted for a poster presentation at the Diabetes UK Professional Conference (2020) and will be presented on March 2020

4.1 Background

Neuropathy is a common complication in patients with diabetes. Nerve damage that is related to diabetes is called diabetic neuropathy. Diabetic peripheral neuropathy (DPN) refers to the nerve damage or dysfunction of the nerves supplying the extremities leading to loss of sensation, pain, muscle weaknesses, or ulceration. Diabetic autonomic neuropathy (DAN) refers to damage or dysfunction of the nerves supplying visceral organs, blood vessels, or smooth muscles. The heart is innervated by both the sympathetic and parasympathetic branches of the autonomic nervous system and therefore, damage or dysfunction of these nerves is called cardiac autonomic neuropathy (197).

Cardiac autonomic function can be assessed using cardiac autonomic reflex tests. These tests include a deep breathing manoeuvre, blowing into an occluded tube (Valsalva manoeuvre), and a standing manoeuvre (198). Although cardiac autonomic reflex tests (CARTs) are not direct measures for the autonomic nervous system, it is accepted as the gold standard for CAN diagnosis. Heart rate responses (based on time-domain) are usually assessed in response to CARTs such as deep breathing, Valsalva, or changes in posture. One abnormal result is usually considered early or borderline CAN, but two or more abnormal results are considered confirmed CAN (199).

Spectral analysis (frequency domain) of heart rate variability (HRV) can be used to measure autonomic function non-invasively. Frequencies between 0.04Hz and 0.12Hz are defined as

low frequency (LF) on the frequency domain, and frequencies between 0.15Hz and 0.40Hz are identified as high frequency (HF; Figure 4.1). These indices are used to evaluate sympathetic and parasympathetic modulation. There are two methods to transform ECG recordings and compute the frequency domain indices of HRV; fast Fourier transformation (FFT) and continuous wavelet transformation (CWT). FFT spectral analysis of HRV does not take into consideration the effect of respiration on autonomic activity. Indeed, one of the weaknesses of using FFT is that some of the HF overlap with parts of the LF during slow breathing which then leads to a false increase in LF (Figure 4.1; (200)). CWT transform ECG and simultaneously analyse the frequency domain in the context of the on-going respiratory activity (Figure 4.2).

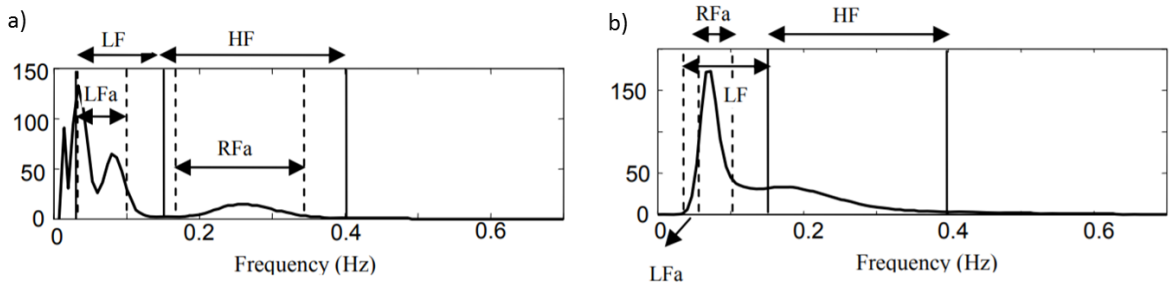

Figure 4.1 Spectral analysis of HRV showing the reference lines for the frequency parameters. *The solid lines show fixed reference lines for LF and HF using FFT. Dashed lines show and compare the enhanced reference lines for low-frequency area (LFa), and respiratory-frequency area (RFa) relocated in context respiratory activity between a) normal breathing and b) deep breathing. This figure was adopted from (Aysin & Aysin, 2006)(200).*

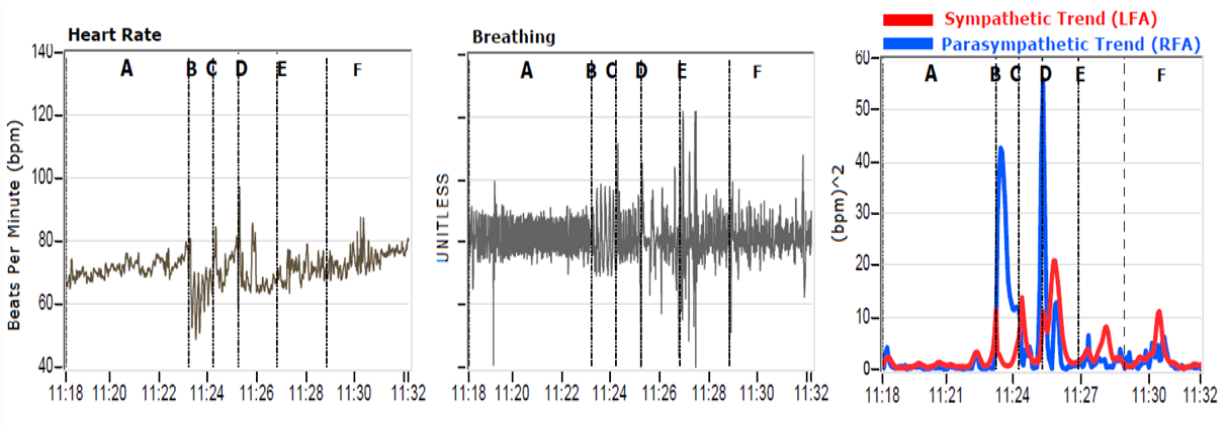

Figure 4.2 Simultaneous analysis of the frequency domain (LFa and RFa) in the context of the on-going respiratory activity. *HRV on the left, respiratory activity on the middle, and simultaneously analysed LFa and RFa on the right during different cardiac autonomic reflexes; A: baseline period; B: deep breathing period C: recovery period from deep breathing; D: Valsalva period; E: recovery period from Valsalva; F: standing period.*

Few studies have investigated OSA in patients with T1D. The prevalence of OSA reported in these patients ranged from 8% up to 46% (109, 128, 131). The average BMI of the patients included in these studies were not in the obese range, but despite that reported prevalences were similar to those reported for obese T2D. This observation suggests that factors other than obesity play an important role in the relationship between OSA and T1D. These factors may include autonomic neuropathy.

The role of CAN in OSA in patients with T1D was explored in one small study of 20 lean patients with T1D with (n=9) and without (n=11) CAN; there were no significant differences concerning HbA1c and duration of diabetes. The two groups were age and BMI matched to 22 healthy controls. OSA was significantly higher in lean T1D patients with CAN than both the patients without CAN and the controls (67%, 23%, and 4.5% respectively; CAN+ vs CAN-, p = 0.02 and CAN+ vs Control, p = 0.006) (135).

Considering the importance of achieving reasonable glycaemic control in patients with T1D in order to reduce the burden and the complications of the disease, it is essential to understand the factors that contribute to the development of diabetes-related complications. OSA is potentially a treatable contributor to the burden of T1D but only a small number of studies, some of which have significant methodological limitations, with small numbers of patients, have tried to address this issue. Nonetheless, OSA can easily be undiagnosed for years (75, 76) and one small (n=7) early study suggested that sleep apnoea might start even during childhood in patients with T1D, although this was mostly mild central rather than obstructive apnoea, but glycaemic control correlated with the severity of the apnoea (133). This finding makes it tempting to speculate that in patients with T1D, sleep apnoea starts very early in the course of the disease as central sleep apnoea that then progresses, with the worsening of CAN, longer diabetes duration and the increased weight over the decades, to a mixed obstructive/central sleep apnoea. So, we hypothesised that CAN is associated with OSA in patients with T1D.

4.1.1 Aim

This study aimed to evaluate the relationship between OSA and CAN in patients with T1D.

4.2 Methods

4.2.1 Study Design

This study was an observational cross-sectional study of patients with T1D attending secondary care diabetes clinics in Birmingham at University Hospitals Birmingham NHS Foundation Trust.

4.2.2 Study group

Patients with T1D were recruited consecutively from the diabetes clinics at University Hospitals Birmingham NHS Foundation Trust (formerly Heart of England NHS Foundation Trust

(HEFT)) by a member of the clinical team. Please refer to chapter 2 section 2.3 for detailed methodology.

4.2.3 Data collected

Below in detail is the specific methodology for collecting the cardiac autonomic neuropathy data.

4.2.3.1 Cardiac Autonomic Neuropathy:

CAN was assessed using heart rate variability (HRV) in response to cardiac autonomic reflex tests. Cardiac data (ECG and blood pressure) was collected and analysed using the ANX-3.0 software (ANSAR Inc., Philadelphia, PA). Using the ECG and R-R intervals, the software analysed frequency domain after respiratory adjustment (low frequency area (LFa), respiratory frequency area (RFa) and LFa/RFa ratio) (13), and time-domain including standard deviation of normal R-R intervals (sdNN), square root of the mean of the squares of differences between adjacent normal R-R intervals (rmsSD), and percentage of differences between adjacent normal R-R intervals that are greater than 50 milliseconds (pNN50) were included (13). HRV and BP were recorded in different positions with the patient in a sitting position during resting, deep breathing, and Valsalva manoeuvre, and in a standing position during postural change (149).

A three-lead ECG was used to collect the data required for analysing HRV. The right arm (RA) electrode was placed below the right clavicle bone in the midclavicular point, the left arm (LA) electrode was placed below the left clavicle bone in the midclavicular point, and the left limb (LL) electrode was placed on the lower edge of the left rib cage (Figure 4.3). The blood pressure cuff was placed on the left upper arm (Figure 4.3).

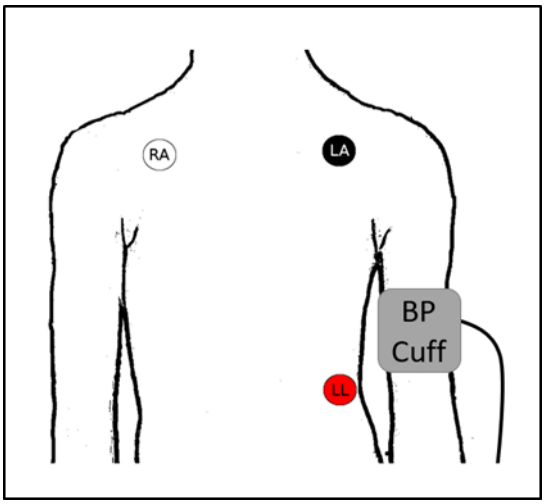

Figure 4.3 Placement of ECG leads and BP cuff

Patients were then seated with their arm rested at heart level on a desk to perform cardiac autonomic reflex tests (Figure 4.4). Patients were asked to keep quiet and minimise movement for five minutes to record baseline HRV before starting the cardiac autonomic challenges. For deep breathing patients were asked to perform slow and deep breaths (five seconds inhalation and five seconds exhalation) for one minute to increase the parasympathetic tone. Patients were then asked to blow into an occluded tube for 15 seconds (Valsalva manoeuvre) to increase sympathetic activity by increasing the thoracic pressure then breathe normally for 15 seconds. This first Valsalva manoeuvre was followed by four short Valsalva manoeuvres (10 seconds blowing into the occluded tube and 5 seconds normal breathing). This challenge was cancelled if the patient had retinopathy or complained of chest pain. Finally, the patients were asked to stand for five minutes, and PhD student held the patients' arms horizontally at the level of the heart to avoid the hydraulic effect.

Figure 4.4 The timeline of the cardiac autonomic reflex tests; bpm=breaths per minute

Cardiac autonomic reflex tests are considered the "gold standard" to diagnose CAN. Deep breathing manoeuvre accentuates the variation in R-R intervals between exhalation (long R-R intervals) and inhalation (short R-R intervals). The exhalation to inhalation (E/I) ratio is estimated by dividing the average longest R-R intervals by the average shortest R-R intervals to assess the sympathovagal response (autonomic function) to deep breathing. Valsalva manoeuvre leads to changes in heart rate due to increasing the intrathoracic pressure and mechanical straining the heart. Straining the heart for 15 seconds leads to a drop in blood pressure and tachycardia (short R-R intervals). Releasing the strain leads to an increase in blood pressure and bradycardia (long R-R intervals). Valsalva ratio is estimated by dividing the longest R-R interval (after releasing the strain) by the shortest R-R interval (during the strain) to assess the sympathovagal response to Valsalva manoeuvre. Standing manoeuvre leads to an immediate increase in heart rate that usually reaches a maximum at the 15th beat (shortest R-R intervals) — followed by a decrease in heart rate that becomes stable at 30th beat (longest R-R interval). Standing ratio (30:15 ratio) is estimated by dividing the longest R-R interval at the 30th beat by the shortest R-R interval at the 15th beat to assess the sympathovagal response to standing. Also, we recorded blood pressure at baseline and after standing to calculate blood response to standing. Normal age-related values are defined as previously reported (198). A diagnosis of CAN for this study was made when two or more of the following tests were abnormal: E/I ratio, 30:15 ratio,

Valsalva ratio, and postural drop in BP by 20mmHg in systolic (13). Data were securely stored on the laptop, which was used to perform the test.

4.3 Results:

4.3.1 Study characteristics

47 patients were included (women 75%, insulin pumps 66%, mean (SD): age 44.9 years (13.4), diabetes duration 29.6 years (13.0); median [IQR]: BMI 26.2 kg/m^2 [23.1-29.2], HbA1c 8.2% [7.3-9.1]). The majority of participants were white (96%), and neither of the two non-white participants had OSA. There was no statistical difference regarding gender between T1D patients with OSA and patients with T1D only (p=0.29). Patients with and without OSA had similar age, gender, diabetes duration, and HbA1c. Patients with OSA had higher BMI 28.7 kg/m^2 [25.1 - 33.5] vs 25.11 kg/m^2 [22.6 - 28.2], p=0.03. Waist circumference and waist-hip ratio were significantly higher in patients with T1D and OSA (Table 4.1). Also, T1D patients with and without OSA had similar use of antihypertensive, lipid-lowering, antidepressant, thyroid replacement hormone (Table 4.2).

Table 4.1 Patients characteristics in relation to OSA status in patients with T1D

	Total	OSA-	OSA+	p
Age *years, M(SD)*	44.9 (13.4)	44.4(13.9)	45.9(12.8)	0.72
Female, *n (%)*	35 (74.5%)	25 (80.6%)	10 (62.5%)	0.29
White, *n (%)*	45 (95.7%)	29 (93.5%)	16 (100%)	0.43
Insulin pump, *n (%)*	31 (66.0%)	20 (64.5%)	11 (68.8%)	0.77
DD years, *M(SD)*	29.6 (13.0)	27.7(13.2)	33.1(12.4)	0.18
Drink Alcohol, *n (%)*	36 (76.6%)	22 (71.0%)	14 (87.5%)	0.29
Alcohol *unit/week, Mdn [IQR]*	2 [0.1-6.0]	2.0 [0.0 – 6.0]	2.0 [0.2- 19.3]	0.37
Smoking				0.01
Current, *n (%)*	4 (8.5%)	0 (0.0%)	4 (25.0%)	
Ex, *n (%)*	11 (23.4%)	6 (19.4%)	5 (31.3%)	
Never, *n (%)*	32 (68.1%)	25 (80.6%)	7 (43.8%)	
Insulin dose *unit/day, Mdn[IQR]*	40.0 [30.0 -50.0]	38 [30.0 – 45.0]	46.5 [38.0 – 63.8]	0.08
BMI *kg/m^2, Mdn[IQR]*	26.2 [23.1-29.2]	25.1 [22.6 - 28.2]	28.7 [25.1 - 33.5]	0.05
BMI categories				0.02
Normal weight, *n (%)*	17 (36.2%)	14 (45.2%)	3 (18.8%)	
Overweight, *n (%)*	20 (42.6%)	14 (45.2%)	6 (37.5%)	
Obese, *n (%)*	10 (21.3%)	3 (9.7%)	7 (43.8%)	
Weight *kg, Mdn[IQR]*	73.5 [61.4 – 83.1]	72.0 [58.4 - 81.8]	81.3 [70.5 - 99.8]	0.03
Height cm, *M(SD)*	167.5 (8.5)	167.3 (8.1)	167.9 (9.6)	0.83
Nick circ. *cm, M(SD)*	36.5 (4.2)	35.6 (3.3)	38.2 (5.2)	0.08
Waist circ. *cm, M(SD)*	94.3 (13.5)	90.4 (11.6)	102.0 (13.9)	0.01
Hip circ. *cm, M(SD)*	107.0 (9.4)	105.5 (8.7)	110.0 (10)	0.13
WHR, *Mdn[IQR]*	0.88 [0.84 – 0.93)	0.87 [0.81 - 0.90]	0.90 [0.86 - 1.00]	0.01
HbA1c *mmol/mol, Mdn[IQR]*	66.0 [56.0 – 76.0]	64.0 [55.0 – 71.0]	70.5[61.3 – 82.8]	0.07
HbA1c %, *Mdn[IQR]*	8.2[7.3-9.1]	8.0 [7.2-8.7]	8.6[7.8-9.7]	0.07
SBP, *Mdn[IQR]*	122 [115 – 131]	118 [112 - 131]	124 [115 - 133]	0.36
DBP, *M(SD)*	71 (7)	70 (7)	72 (8)	0.40

Data is present as n (%) for categorical variables, and mean (standard deviation) or median [interquartile range] for continuous variables. Chi-square test was run on categorical variables. Independent T-test or Mann-Whitney U test was run on continuous variables. P<0.05 was considered to represent a significant difference between patients with and without OSA. M: mean; SD: standard deviation; Mdn: median; IQR: interquartile range; DD: Diabetes Duration; BMI: body mass index; circ: circumference; WHR: waist-hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 4.2 Relationship between drug used and OSA status in patients with T1D

	Total	OSA- (n=31)	OSA+ (n=16)	p-value
Antihypertensive, *n (%)*	19 (40.4%)	10 (32.3%)	9 (56.3%)	0.11
Lipid Lowering, *n (%)*	23 (48.9%)	13 (41.9%)	10 (62.5%)	0.18
Antidepressant, *n (%)*	11 (23.4%)	5 (16.1%)	6 (37.5%)	0.15
Thyroid hormone, *n (%)*	12 (25.5%)	9 (29%)	3 (18.8%)	0.51

Data is present as n (%). Chi-square test was run on categorical variables. P<0.05 was considered to represent a significant difference between patients with and without OSA. Antihypertensive drugs include sympatholytics, diuretics, vasodilators, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers)

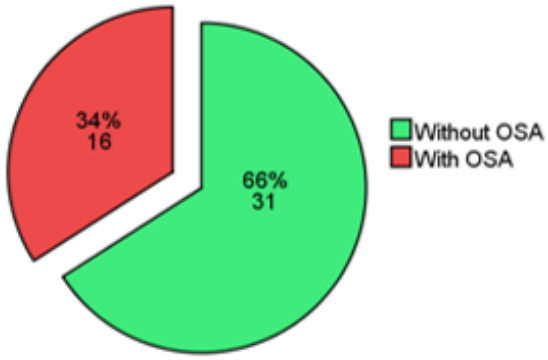

Figure 4.5 Percentage and number of cases with and without OSA . Patients with OSA (red; REI≥15 or REI≥5 with ESS≥11) and without OSA (green; REI<15 with ESS<11 or REI<5). n= 47.

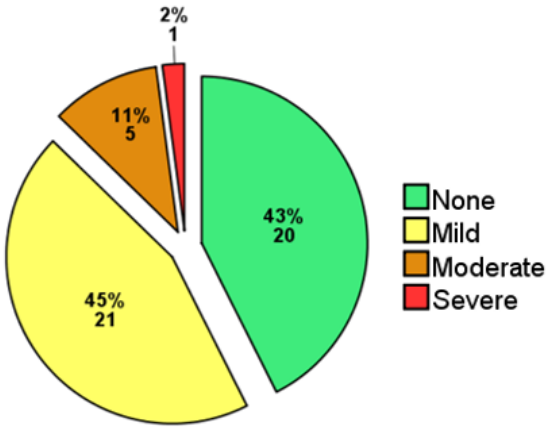

Figure 4.6 Percentage and number of cases in relation to the severity of REI. *Patients with no OSA (green; REI<5) and patients with mild: REI 5-15 (yellow), moderate (orange; REI 15-30), and severe (red; REI>30) OSA. n=47*

4.3.2 Obstructive sleep apnoea

57.4% (n=27) had REI ≥ 5 (Figure 4.6) and OSA prevalence was 34.0% (n=16; Figure 4.5). Sleep parameters show no difference in median [IQR] sleep duration between T1D with and without OSA (440 [346.8 - 484.8] vs 420 [322 - 484], respectively; p=0.85). Also, parameters show that OSA status are based on respiratory event and obstructive-apnoea indices, but not central-apnoea or mixed apnoea indices (Table 4.3). Nadir nocturnal O_2 saturation median [IQR] was similar between patients with OSA compared to patients without OSA (OSA+ 83% [80 - 86] vs OSA- 87% [82 - 89]; p=0.6), however, percentage of time spent with O_2 < 90% median [IQR] was significantly more in patients with OSA (OSA+ 3.5% [1.3 - 13.3] vs without OSA 0.0% [0.0 – 3.0]; p=0.01).

Table 4.3 Sleep and sleep apnoea parameters in relation to OSA status in patients with T1D

Sleep parameters	OSA- (n=31)	OSA+ (n=16)	P value
Respiratory events index, *Mdn[IQR]*	3.7 [2.2 - 6.2]	10.9 [6.5 - 16.1]	<0.01
Obstructive apnoea index, *Mdn[IQR]*	0.2 [0 - 0.5]	0.7 [0.2 - 2]	<0.01
Central apnoea index, *Mdn[IQR]*	0 [0 - 0.2]	0.1 [0 - 0.6]	0.28
Mixed apnoea index, *Mdn[IQR]*	0 [0 - 0]	0 [0 - 0]	0.3
ODI, *Mdn[IQR]*	4 [2.3 - 6.6]	12 [6.5 - 16.2]	<.01
Nadir nocturnal O_2, *Mdn[IQR]*	87% [82 - 89]	83% [80 - 86]	0.06
Time O_2 < 90% *mins, Mdn [IQR]*	2 [0 - 13]	17 [4.5 - 57.5]	0.01
% time O_2 < 90%, *Mdn[IQR]*	0.0% [0.0 – 3.0]	3.5% [1.3 - 13.3]	0.01
Sleep duration in minutes, *Mdn[IQR]*	420 [322 - 484]	440 [346.8 - 484.8]	0.85

Data is present as median [IQR]. Mann-Whitney U test was run, and. P<0.05 was considered to represent a significant difference between patients with and without OSA; Mdn: median; IQR: interquartile range; ODI: oxygen desaturation index.

Twenty-one (45%) participants were at high risk of OSA based on the Berlin questionnaire. It was found that 14 (30%) of the participants had excessive daytime sleepiness, and 31 (68%) had poor quality of sleep. MEQ results showed that none of the participants scored a definite morning type, 15 (32%) were “moderate morning”, 23 (49%) were “intermediate”, 7 (15%) “moderate evening”, and 2 (4%) were “definite evening”. Only Berlin and ESS questionnaires were significantly different between the two groups. However, ESS was part of the OSA definition. Therefore, ESS is expected to be significant.

Table 4.4 Subjective sleep characteristics in T1D patients with (OSA+) and without OSA (OSA-):

Sleep Questionnaires	OSA- (n=31)	OSA+ (n=16)	p-value
High risk of OSA (Berlin)	10 (32%)	11 (69%)	0.02
Excessive daytime sleepiness (ESS)	3 (10%)	11 (69%)	0.00
Poor sleep quality (PSQI)	20 (65%)	12 (75%)	0.47
Circadian rhythm (MEQ)			0.36
Definite Morning	0 (0%)	0 (0%)	
Moderate Morning	12 (39%)	3 (19%)	
Intermediate	15(48%)	8 (50%)	
Moderate Evening	3 (10%)	4 (25%)	
Definite Evening	1 (3%)	1 (6%)	

Data was presented as n (%). Chi-square test was run on categorical variables. P<0.05 was considered to represent a significant difference between patients with and without OSA.

4.3.3 Heart rate variability and obstructive sleep apnoea:

4.3.3.1 Frequency domain and obstructive sleep apnoea:

Patients with OSA and T1D had lower frequency domain indices compared to patients with T1D only (Table 4.5). Baseline LFa and RFa were lower in T1D with OSA versus T1D only (Median (IQR)): 0.54 (0.18-0.83) vs 0.99 (0.48-2.34); p<0.01, and 0.28 (0.16-0.38) vs 0.79 (0.34-2.87); p<0.01 respectively (Figure 4.7 a & b). However, due to reductions in both parameters there was no significant difference in LFa/RFa ratio (sympathovagal balance; p=.11; Figure 4.7 c). The respiratory frequency area during deep breathing was lower in patients with T1D and OSA (Median (IQR)): 10.18 (0.82-19.49) vs 14.94 (8.60-44.93); p=0.02 (Figure 4.7 e). Valsalva LFa and RFa were lower in T1D with OSA versus T1D only (Median (IQR)): 9.11 (1.04-36.80) vs 45.26 (17.17-67.31); p<0.01, and 0.83 (0.29-2.37) vs 4.03 (1.85-8.22); p<0.01 respectively (Figure 4.7 g & h).

Table 4.5 Frequency domain analysis during baseline, deep breathing, Valsalva, and standing manoeuvres in T1D patients with OSA (OSA+) compared to T1D only (OSA-).

Mdn [IQR]	Reference	OSA-	OSA+	p value
Baseline		*n=31*	*n=16*	
LFa bpm^2	1.0 < LFa <10.0	0.99 [0.48 - 2.34]	0.54 [0.18 - 0.83]	< 0.01
RFa bpm^2	1.0 < RFa <10.0	0.79 [0.34 - 2.87]	0.28 [0.16 - 0.39]	< 0.01
LFa/RFa Ratio	0.4 < Ratio <3.0	1.16 [0.56 - 2.08]	1.77 [0.98 - 3.25]	0.11
Deep Breathing		*n=31*	*n=16*	
LFa bpm^2		0.98 [0.42 - 2.03]	0.7 [0.26 - 1.32]	0.36
RFa bpm^2	About 50-fold increase	14.94 [8.60 - 44.93]	10.18 [0.82 - 19.49]	0.02
LFa/RFa Ratio		0.06 [0.03 - 0.17]	0.12 [0.06 - 0.42]	0.04
Valsalva		*n=25*	*n=13*	
LFa bpm^2	About 50-fold increase	45.26 [17.17 - 67.31]	9.11 [1.04 - 36.8]	< 0.01
RFa bpm^2	Up to 60% increase	4.03 [1.85 - 8.22]	0.83 [0.29 - 2.37]	< 0.01
LFa/RFa Ratio		9.56 [7.21 - 14.98]	11.37 [3.98 - 24.38]	0.79
Standing		*n=30*	*n=16*	
LFa bpm^2	Increase	1.625 [0.63 - 6.29]	0.77 [0.32 - 2.79]	0.09
RFa bpm^2	Decrease	0.51 [0.19 - 1.56]	0.215 [0.11 - 1.13]	0.12
LFa/RFa Ratio		3.105 [1.91 - 6.09]	2.855 [1.52 - 8.25]	0.61

Data is present as median [IQR]. Mann-Whitney U test was run, and. P<0.05 was considered to represent a significant difference between patients with and without OSA; Mdn: median; IQR: interquartile range; LFa: low-frequency area; RFa: respiratory frequency area. Deep breathing, Valsalva, and standing references are in relation to the initial baseline measurement.

Spearman's rho correlation coefficient was also used to assess the relationship between OSA parameters and the frequency domain parameters (LFa, RFa, and LFa/RFa) of the HRV. At baseline, the results show that LFa decreases as the following OSA parameters increase: REI (r_s (47) = -0.31, p = 0.03), ODI (r_s (47) = -3.0, p = 0.04), time (r_s (47) = -0.33, p = 0.02), and percentage (r_s (47) = -0.3, p = 0.04) of time spent with oxygen saturation below 90%. The results also show that RFa decreases as the following OSA parameters increase: REI (r_s (47) = -0.35, p = 0.02), ODI (r_s (47) = -0.32, p = 0.03), time (r_s (47) = -0.41, p < 0.01), and percentage (r_s (47) = -0.36, p = 0.01) of time spent with oxygen saturation below 90%. In addition, lower nocturnal

nadir oxygen saturation correlated with lower LFa and RFa (r_s (47) = 0.31, p = 0.03 and r_s (47) = -0.33, p = 0.02, respectively) (Table 4.6).

During deep breathing, we found that low RFa correlates (Spearman's rho) with lower nocturnal nadir oxygen saturation (rs (47) = 0.31, p = 0.03), and increased time spent with oxygen saturation below 90% (rs (47) = -31, p = 0.03) (Table 4.7).

During Valsalva, the results (Spearman's rho) show that LFa and RFa decreases as the following OSA parameters increase: REI (LFa: r_s (38) = -0.40, p = 0.01 and RFa: r_s (38) = -0.42, p = 0.01), obstructive apnoea index (OAI) (LFa: r_s (38) = -0.48, p < 0.01 and RFa: r_s (38) = -0.54, p < 0.01), ODI (LFa: r_s (38) = -0.36, p = 0.03 and RFa: r_s (38) = -0.40 p = 0.01), time (LFa: r_s (38) = -0.43, p < 0.01 and RFa: r_s (38) = -0.37, p = 0.02), and percentage (LFa: r_s (38) = -0.45, p < 0.01 and RFa: r_s (38) = -0.36, p = 0.03) of time spent with oxygen saturation below 90%. Nocturnal nadir oxygen saturation correlated only with RFa (r_s (38) = -0.37, p = 0.02) (Table 4.8).

During Standing, the results show that only LFa correlate (Spearman's rho) with the following OSA parameters: REI (r_s (46) = -0.30, p = 0.04), nocturnal nadir oxygen saturation (r_s (46) = 0.33, p = 0.03), time (r_s (46) = -0.37, p = 0.01), and percentage (r_s (46) = -0.31, p = 0.04) of time spent with oxygen saturation below 90%. Nocturnal nadir oxygen saturation correlated only with RFa (r_s (38) = -0.37, p = 0.02) (Table 4.9).

Table 4.6 Correlations between OSA parameters and baseline frequency-domain parameters in patients with T1D (n=47).

		Baseline LFa	Baseline RFa	Baseline LFa/RFa Ratio
Respiratory events index	r	-0.31	-0.35	0.16
	p-value	***0.03***	***0.02***	*0.29*
Obstructive-apnoea index	r	-0.11	-0.2	0.2
	p-value	*0.45*	*0.19*	*0.17*
Central-apnoea index	r	-0.05	0.12	-0.26
	p-value	*0.76*	*0.41*	*0.08*
Mixed-apnoea index	r	-0.08	0.05	-0.12
	p-value	*0.61*	*0.76*	*0.43*
Oxygen desaturation index	r	-0.3	-0.32	0.12
	p-value	***0.04***	***0.03***	*0.43*
Nadir oxygen saturation	r	0.31	0.33	-0.15
	p-value	***0.03***	***0.02***	*0.3*
Time spent with oxygen saturation < 90%	r	-0.33	-0.41	0.26
	p-value	***0.02***	***< 0.01***	*0.08*
% time spent with oxygen saturation < 90%	r	-0.3	-0.36	0.23
	p-value	***0.04***	***0.01***	*0.11*

r: correlation coefficient; analysed using Spearman's rho correlation coefficient

Table 4.7 Correlations between OSA parameters and deep breathing frequency-domain parameters in patients with T1D (n=47).

		DB LFa	DB RFa	DB LFa/RFa Ratio
Respiratory events index	r	-0.03	-0.30	0.28
	p-value	*0.86*	***0.04***	*0.06*
Obstructive-apnoea index	r	-0.14	-0.26	0.11
	p-value	*0.36*	*0.08*	*0.48*
Central-apnoea index	r	-0.06	-0.10	0.00
	p-value	*0.68*	*0.50*	*0.99*
Mixed-apnoea index	r	-0.05	0.00	-0.12
	p-value	*0.71*	*0.98*	*0.41*
Oxygen desaturation index	r	-0.03	-0.23	0.20
	p-value	*0.83*	*0.12*	*0.17*
Nadir oxygen saturation	r	0.27	0.31	-0.19
	p-value	*0.07*	***0.03***	*0.20*
Time spent with oxygen saturation < 90%	r	-0.30	-0.31	0.10
	p-value	***0.04***	***0.03***	*0.50*
% time spent with oxygen saturation < 90%	r	-0.26	-0.28	0.11
	p-value	*0.08*	*0.06*	*0.47*

r: correlation coefficient; analysed using Spearman's rho correlation coefficient

Table 4.8 Correlations between OSA parameters and Valsalva frequency-domain parameters in patients with T1D (n=38).

		Valsalva LFa	Valsalva RFa	Valsalva LFa/RFa Ratio
Respiratory events index	r	-0.40	-0.42	0.02
	p-value	**0.01**	**0.01**	0.89
Obstructive-apnoea index	r	-0.48	-0.54	0.01
	p-value	**< 0.01**	**< 0.01**	0.98
Central-apnoea index	r	-0.07	-0.10	-0.27
	p-value	0.66	0.56	0.11
Mixed-apnoea index	r	-0.06	-0.04	-0.19
	p-value	0.72	0.83	0.26
Oxygen desaturation index	r	-0.36	-0.40	0.08
	p-value	**0.03**	**0.01**	0.64
Nadir oxygen saturation	r	0.23	0.39	-0.14
	p-value	0.17	**0.02**	0.42
Time spent with oxygen saturation < 90%	r	-0.43	-0.37	-0.16
	p-value	**< 0.01**	**0.02**	0.35
% time spent with oxygen saturation < 90%	r	-0.45	-0.36	-0.19
	p-value	**< 0.01**	**0.03**	0.25

r: correlation coefficient; analysed using Spearman's rho correlation coefficient

Table 4.9 Correlations between OSA parameters and Standing frequency-domain parameters in patients with T1D (n=46).

		Standing LFa	Standing RFa	Standing LFa/RFa Ratio
Respiratory events index	r	-0.30	-0.26	-0.04
	p-value	**0.04**	0.08	0.79
Obstructive-apnoea index	r	-0.25	-0.19	-0.10
	p-value	0.09	0.21	0.52
Central-apnoea index	r	-0.09	0.03	-0.16
	p-value	0.57	0.84	0.30
Mixed-apnoea index	r	-0.03	0.04	-0.04
	p-value	0.85	0.77	0.78
Oxygen desaturation index	r	-0.28	-0.24	-0.04
	p-value	0.06	0.12	0.79
Nadir oxygen saturation	r	0.33	0.22	0.15
	p-value	**0.03**	0.15	0.31
Time spent with oxygen saturation < 90%	r	-0.37	-0.21	-0.25
	p-value	**0.01**	0.17	0.10
% time spent with oxygen saturation < 90%	r	-0.31	-0.16	-0.23
	p-value	**0.04**	0.31	0.13

r: correlation coefficient; analysed using Spearman's rho correlation coefficient

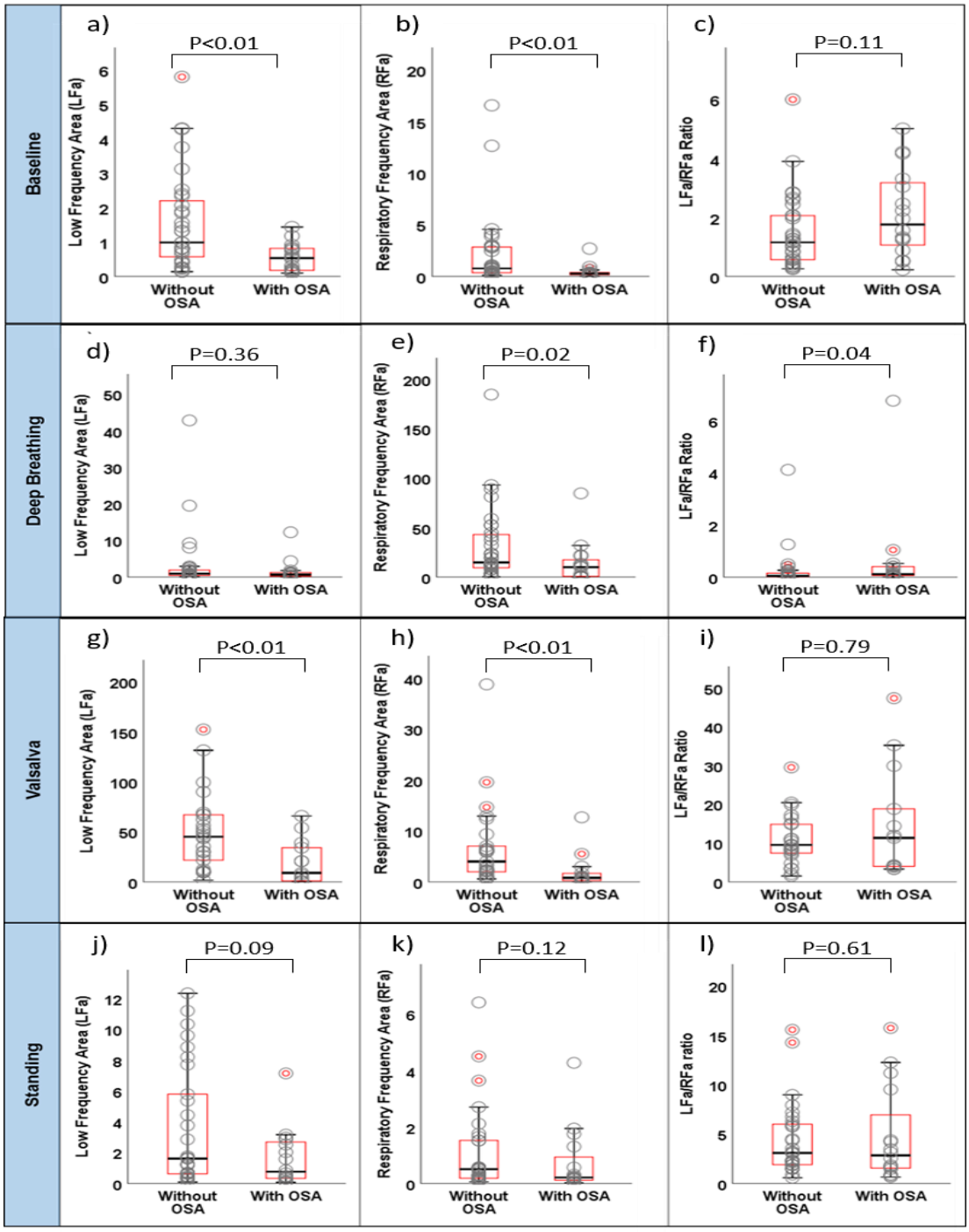

Figure 4.7 Frequency-domain indices in T1D patients with and without OSA. *Circles show individual patients; Whisker box plots show the median, and upper and lower quartiles; Mann-Whitney U test was run, and. P<0.05 was considered to represent a significant difference between patients with and without OSA.*

4.3.3.2 Time-domain and obstructive sleep apnoea:

Similar to the frequency-domain, patients with OSA and T1D had lower time-domain indices compared to patients with T1D only (Table 4.10). At baseline, sdNN, rmsSD, and pNN50 were lower in T1D with OSA versus T1D only ($p<0.01$). During deep breathing and Valsalva manoeuvres, sdNN and pNN50 were significantly lower in patients with OSA ($p<0.05$), but during standing, only sdNN was significantly lower in patients with OSA ($p<0.05$;Table 4.10).

Spearman's rho correlation coefficient was also used to assess the relationship between OSA parameters and the time domain parameters (sdNN, rmsSD, and pNN50). The analysis found OSA parameters that correlated with some of time domain parameters of the HRV. Time spent with oxygen saturation below 90% negatively correlated with baseline sdNN ($r_s(38) = -0.33$, $p = 0.03$), and rmsSD ($r_s(47) = -0.30$, $p = 0.04$). OAI negatively correlated with Valsalva sdNN ($r_s(38) = -0.39$, $p = 0.01$), rmsSD ($r_s(38) = -0.35$, $p = 0.03$), and pNN50 ($r_s(38) = -0.37$, $p = 0.02$).

Table 4.10 Time-domain analysis during baseline, deep breathing, Valsalva, and standing manoeuvres in T1D patients with OSA (OSA+) compared to T1D only (OSA-).

	OSA-	OSA+	p value
Baseline	*n=31*	*n=16*	
sdNN *msec, Mdn [IQR]*	34 [23 - 40]	21 [13 - 28]	< 0.01
rmsSD *msec, Mdn [IQR]*	20 [15 - 30]	12 [9 - 16]	< 0.01
pNN50 *%, Mdn [IQR]*	1 [1 - 10]	0 [0 - 1]	< 0.01
Deep Breathing	*n=31*	*n=16*	
sdNN *msec, Mdn [IQR]*	67 [53 - 98]	50 [16 - 64]	0.02
rmsSD *msec, Mdn [IQR]*	44 [28 - 64]	31 [13 - 50]	0.09
pNN50 *%, Mdn [IQR]*	23 [9 - 33]	7 [0 - 23]	0.02
Valsalva	*n=25*	*n=13*	
sdNN *msec, Mdn [IQR]*	93 [71 - 116]	57 [32 - 85]	< 0.01
rmsSD *msec, Mdn [IQR]*	43 [28 - 60]	33 [20 - 47]	0.05
pNN50 *%, Mdn [IQR]*	18 [7 - 23]	8 [2 - 16]	0.02
Standing	*n=30*	*n=16*	
sdNN *msec, Mdn [IQR]*	40 [27 - 52]	24 [16 - 39]	0.02
rmsSD *msec, Mdn [IQR]*	15 [10 - 21]	10 [7 - 20]	0.13
pNN50 *%, Mdn [IQR]*	1 [0 - 2]	0 [0 - 1]	0.15

Data is present as median [IQR]. Mann-Whitney U test was run, and. P<0.05 was considered to represent a significant difference between patients with and without OSA; Mdn: median; IQR: interquartile range. sdNN: standard deviation of normal R-R intervals; rmsSD: square root of the mean of the squares of differences between adjacent normal R-R intervals; pNN50: percentage of differences between adjacent normal R-R intervals that are greater than 50 ms.

4.3.3.3 Change in HRV parameters in response to cardiac reflex manoeuvres

The response to sympathetic modulation via Valsalva manoeuvre shows that patients with OSA had depressed power as compared to participants without OSA. Further analysis to the median power in response to Valsalva shows lower power in participants with OSA (Figure 4.8 a), and this median was even lower in participants with higher REI score (REI≥15; Figure 4.8 b).

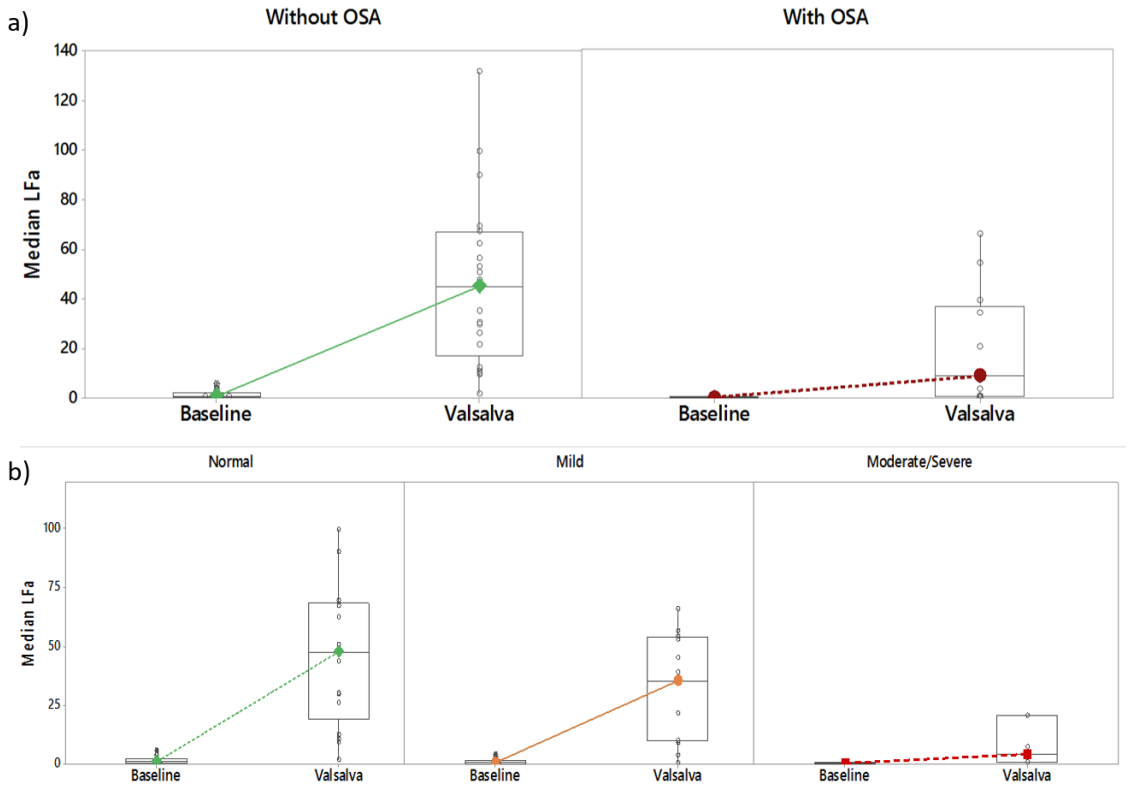

Figure 4.8 Comparing individual data points and median low frequency area (LFa) response to Valsalva between patients with and without OSA *The lines connect the median points during the baseline (sitting, relaxed, and breathing normally) recording to corresponding points during Valsalva; each coloured shape represent median; a) compare the medians according to the presence (REI≥15, or REI≥ and ESS≥11) or absence (REI 5-14.9 but ESS<11, or REI<5) of OSA; b) compare the medians according the severity of the REI (Normal <5, mild 5-14.9, moderate/severe ≥15).*

Similar to sympathetic modulation, the response to parasympathetic modulation via the deep breathing manoeuvre shows that patients with OSA had depressed power as compared to participants without OSA. Further analysis to the median power in response to deep breathing shows lower power in participants with OSA (Figure 4.9 a), and this median was even lower in participants with higher REI score (REI ≥ 15; Figure 4.9 b).

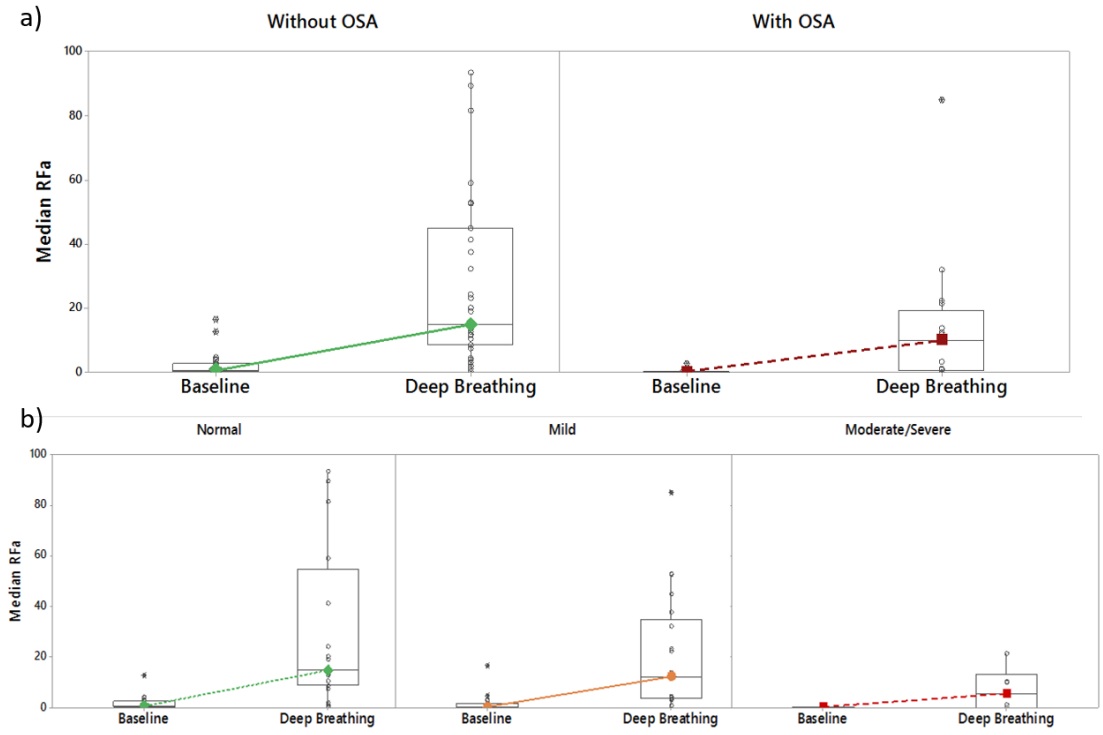

Figure 4.9 Comparing individual data points and median respiratory frequency area (RFa) response to deep breathing between patients with and without OSA. *The lines connect the median points during the baseline (sitting, relaxed, and breathing normally) recording to corresponding points during deep breathing; each coloured shape represent median; a) compare the medians according to the presence (REI≥15, or REI≥ and ESS≥11) or absence (REI 5-14.9 but ESS<11, or REI<5) of OSA; b) compare the medians according the severity of the REI (Normal <5, mild 5-14.9, moderate/severe ≥15).*

The sdNN parameter of the time domain shows a lower median in the participants with OSA as compared to participants without OSA (Figure 4.10a). Further analysis using REI score severity shows that participants with moderate to severe REI recorded lower than participants with normal or mild REI. Also, participants with mild REI recoded similar to participants with normal REI (Figure 4.10b).

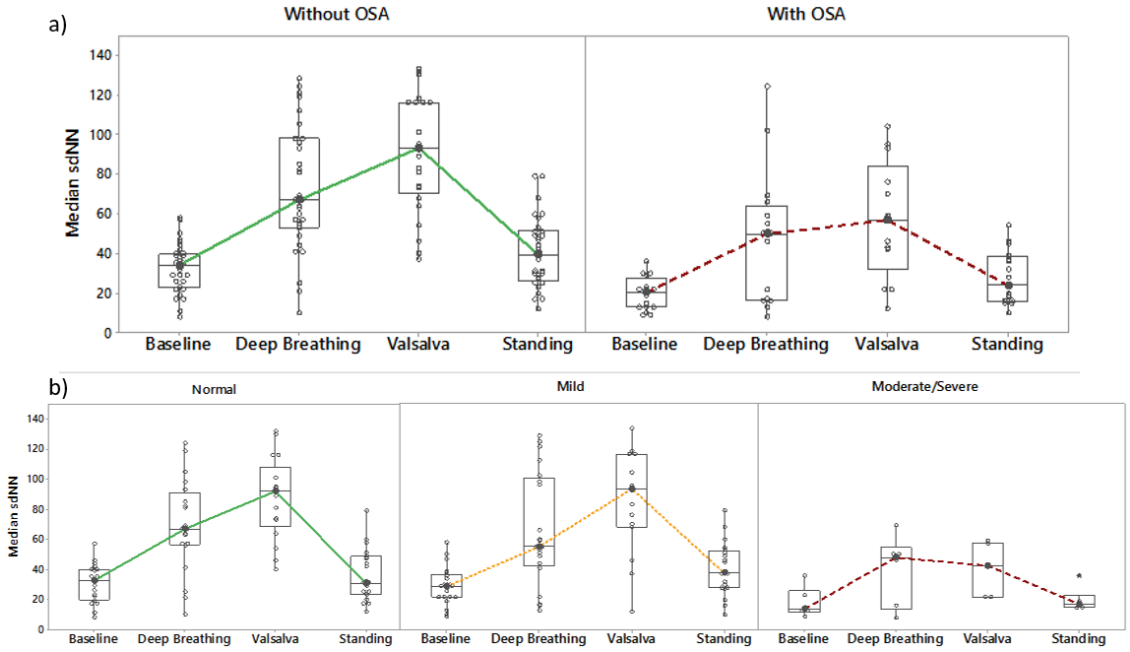

Figure 4.10 Comparing change of median sdNN during baseline, deep breathing, Valsalva, and standing. *The dark circles represent the median points and the lines link each category during cardiac reflex manoeuvres;the white circles represent individual patients; a) compare the medians according to the presence (REI≥15, or REI≥ and ESS≥11) or absence (REI 5-14.9 but ESS<11, or REI<5) of OSA; b) compare the medians according the severity of the REI (Normal <5, mild 5-14.9, moderate/severe ≥15).*

4.3.3.4 Time-domain ratios, orthostatic hypotension, and obstructive sleep apnoea

Individual time-domain ratios (E/I ratio, Valsalva ratio, 30:15 ratio, and orthostatic hypotension [drop in systolic BP by ≥ 20mmHg]) were analysed. Nine participants (19%) did not complete the Valsalva manoeuvre (eight had retinopathy, and one became light-headed during the test). One participant did not complete the standing manoeuvre. The analysis of these parameters in relation to the presence of OSA shows that participants with OSA had a higher percentage of abnormal E/I but not statistically significant (37.5% vs 12.9%; p=0.07). The percentages of abnormal Valsalva and 30:15 ratios were higher and statistically significant in the OSA group as compared to participants with T1D only ([61.5% vs 24.0%; p=0.04], and [56.3% vs 23.3%; p=0.03], respectively; Figure 4.11). The percentage of participants with orthostatic hypotension

were not different between the participants with OSA and participants with T1D only (12.5 [n=2/16] vs 6.7% [n=2/30]; p=0.60).

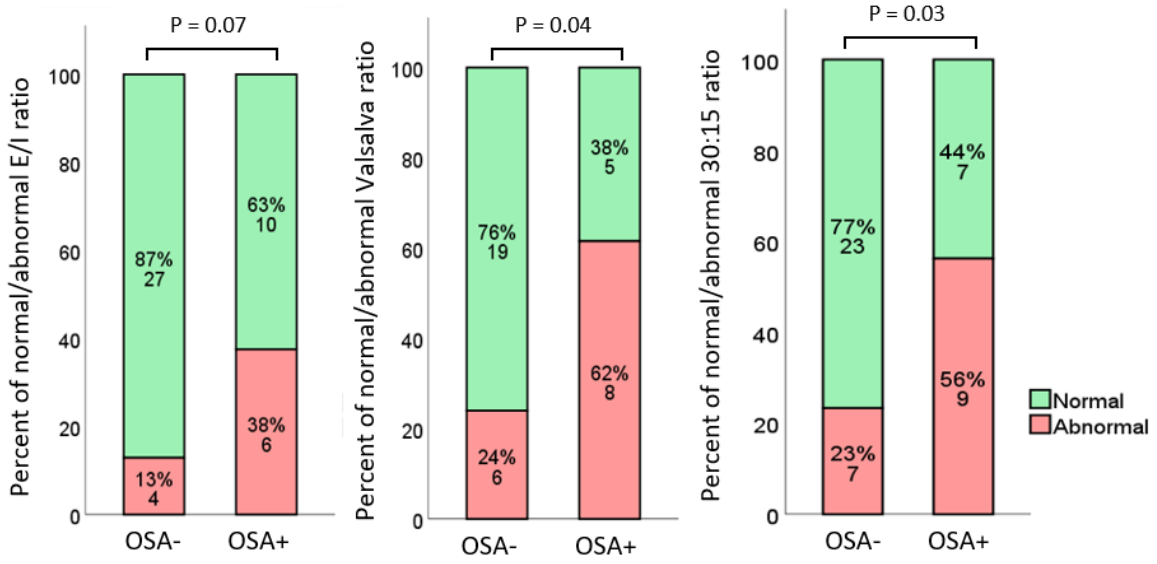

Figure 4.11 Comparing the percentage of cases with normal or abnormal standardised time-domain ratios in relation to OSA. *The percentage and number of cases with normal (green) and abnormal (red) E/I ratio[a], Valsalva ratio[b], and 30:15 ratio[c] for patients with (OSA+) and without OSA (OSA-); [a] p=0.07 (Fisher's exact test comparing proportion of the abnormal E/I ratio by the presence and absence of OSA); [b] p<0.05 (Fisher's exact test comparing proportion of the abnormal Valsalva ratio by the presence and absence of OSA) ; [c] p<0.01 (Chi-Square test comparing proportion of the abnormal 30:15 ratio by the presence and absence of OSA).*

Spearman's rho correlation coefficient was used to assess the relationship between sleep apnoea parameters and the time-domain ratios of the HRV. There was a negative correlation between E/I ratio and time spent with oxygen saturation below 90% (r_s (47) = -0.31, p = 0.03). There was also negative correlation between Valsalva ratio and REI (r_s (38) = -0.43, p =0.01), OAI (r_s (38) = -0.48, p < 0.01), and ODI (r_s (38) = -0.35, p = 0.03) (Table 4.11***).***

Table 4.11 Correlations between OSA parameters and time-domain ratios (E/I ratio, Valsalva ratio, and 30:15 ratio) in patients with T1D.

		E/I ratio (n=47)	Valsalva ratio (n=38)	30:15 ratio (n=47)
Respiratory events index	r	-0.26	-0.43	-0.26
	p-value	*0.08*	***0.01***	*0.07*
Obstructive-apnoea index	r	-0.21	-0.48	-0.2
	p-value	*0.15*	***<0.01***	*0.17*
Central-apnoea index	r	-0.12	-0.01	0.17
	p-value	*0.44*	*0.94*	*0.25*
Mixed-apnoea index	*r*	-0.05	0.04	-0.06
	p-value	*0.76*	*0.8*	*0.67*
Oxygen desaturation index	*r*	-0.21	-0.35	-0.21
	p-value	*0.16*	***0.03***	*0.15*
Nadir oxygen saturation	*r*	0.25	0.14	0.19
	p-value	*0.09*	*0.41*	*0.20*
Time spent with oxygen saturation < 90%	*r*	-0.31	-0.14	-0.26
	p-value	***0.03***	*0.39*	*0.07*
% time spent with oxygen saturation < 90%	*r*	-0.29	-0.19	-0.22
	p-value	*0.05*	*0.26*	*0.14*

r: correlation coefficient; analysed using Spearman's rho correlation coefficient

4.3.3.5 Cardiac autonomic neuropathy and obstructive sleep apnoea

CAN was diagnosed in 29.8% (n=14) T1D based on two or more abnormal CAN Tests (E/I ratio, 30:15 ratio, Valsalva ratio, and postural drop in systolic BP by 20 mmHg). Patients with and without CAN had similar mean (SD) age (49.9 (12.9) vs 43.3 (13.1); p=0.12), diabetes duration (34.9 (12.8) vs 27.4 (12.9); p= 0.07), median [IQR] BMI (26.3 [22.7-30.5] vs 25.6 [22.7-28.7]; p=0.70), and HbA1c (8.6% [7.2-9.4] vs 8.1% [7.3-8.7]; p=0.54). However, more males were diagnosed with CAN compared to females (58.3% (n=7) males vs 20.6% (n=7) females; p=0.03). CAN was more common in patients with OSA vs without OSA (56.3% (n=9) vs 16.7% (n=5), p=0.01; Figure ***4.12***). Patients with OSA were 6.4 times more likely to have CAN (Nagelkerke R^2=0.22; OR 6.43; 95% 1.62 – 25.49; p<0.01) and this association remained significant after adjusting for age, sex, BMI, and diabetes duration (Nagelkerke R^2=0.37; OR

7.77; 95% 1.36 – 44.44; p=0.02). Patients with OSA and T1D had lower frequency and time domain parameters compared to patients with T1D only (Table 4.5 &Table 4.10).

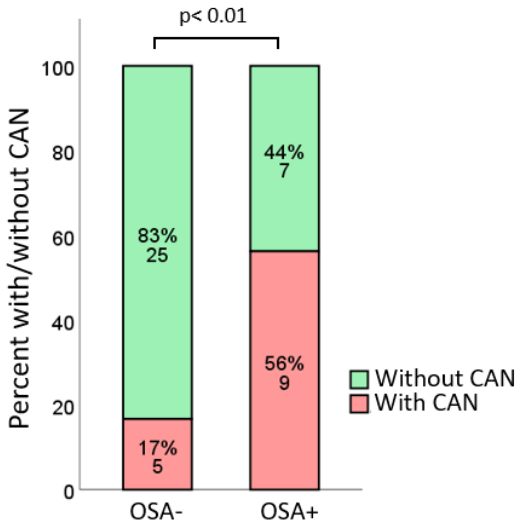

Figure 4.12 CAN is more prevalent in patients with OSA. *The percentage [b] and number of cases with and without CAN in relation to the presence or absence of OSA. This figure reported the proportion of cases with and without CAN for each OSA group; [b] p<0.01 (Fisher's exact test comparing the proportion of the presence of CAN by the presence and absence of OSA).*

We analysed and compared sleep parameters for patients with CAN compared to patients without CAN to assess the influence of OSA parameters on CAN. OSA parameters showed significantly higher REI and obstructive apnoea index (OAI) in patients with CAN compared to patients without CAN (REI: 10.7 [4.0 - 16.8] vs 5.0 [2.7 - 9.0] and OAI:0.8 [0.4 - 2.1] vs 0.2 [0.0 - 0.5]; p <0.01). Nocturnal lowest (nadir) oxygen saturation was significantly lower in patients with CAN (82% [71 - 88] vs 86% [82 – 89]; p=0.04). Although time and percentage of time spent with oxygen saturation below 90% were higher in patients with CAN, the differences were not statistically significant (Table 4.12).

Table 4.12 Sleep and sleep apnoea parameters in relation to the presence (CAN+) or absence (CAN-) of cardiac autonomic neuropathy in patients with T1D (n=46)

	CAN- (32)	CAN+ (14)	P-value
Respiratory events index, *Mdn [IQR]*	5.0 [2.7 - 9.0]	10.7 [4.0 - 16.8]	**0.02**
Obstructive apnoea index, *Mdn [IQR]*	0.2 [0.0 - 0.5]	0.8 [0.4 - 2.1]	**<0.01**
Central apnoea index, *Mdn [IQR]*	0 [0 - 0.35]	0.0 [0.0- 0.4]	0.64
Mixed apnoea index, *Mdn [IQR]*	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.52
ODI, *Mdn [IQR]*	5.3 [3.5 - 9.4]	10.2 [3.0 - 17.2]	0.08
Nadir nocturnal O_2, *Mdn [IQR]*	86% [82 – 89]	82% [71 - 88]	**0.04**
Time O_2 < 90% *mins, Mdn [IQR]*	2.0 [0.0 - 15.3]	18.5 [1.0 - 69.5]	0.09
% time O_2 < 90%, *Mdn [IQR]*	0.5% [0.0 – 3.0]	4.5% [0.0 – 15.0]	0.07

Data is present as median [IQR]. Mann-Whitney U test was run, and. P<0.05 was considered to represent a significant difference between patients with and without OSA; Mdn: median; IQR: interquartile range; ODI: oxygen desaturation index.

4.4 Discussion

Key points:

- OSA was common in T1D
- OSA was associated with CAN
- OSA was associated with reduced HRV parameters

Using inclusive criteria for recruitment to avoid limiting the study to a subgroup of T1D and using rigorous methodology, we studied the association between OSA and CAN in patients with T1D. We found that about one-third of the participants had OSA, and OSA was associated with increased risk of CAN.

Study characteristics

Similar to previous studies of OSA in T1D (109, 131, 174), our T1D patients with OSA and without OSA had similar age and gender distribution. T1D with OSA had a higher BMI; however, our cohort showed a similar diabetes duration between patients with and without OSA. The majority of our population were white (96%). This was greater than the percentage of white T1D in England (around 73% (10)) and the white population in the West Midlands region (79%; Office of National Statistics (201)). Unlike previous studies (109, 131, 174, 175), the majority of participants in this study were females (75%). According to the national diabetes audit, there are around 56.7% males and 43.3% females with T1D in England (10). It is important to note that several landmark OSA studies reported more than double prevalence of OSA in males than the prevalence of OSA in females (202, 203). However, a previous study of the prevalence of OSA in the severely obese population (BMI=49±8 kg/m^2; n=308) from the same region (West Midland) reported similar percentages of white (87.3%) and females

(71.1%) (204) compared to this study. This over-representation might suggest that females and white were more willing to volunteer for clinical studies.

We have analysed the distribution of drugs used by patients with and without OSA as medications such as antihypertensive and lipid-lowering drugs might affect HRV. We found that T1D with and without OSA had a similar use of antihypertensive and lipid-lowering drugs (see Table 4.2). There is a discrepancy in the effect of antihypertensive drugs (such as ACE inhibitors and CCB) on the HRV. 24-h HRV analyses of 27 patients with mild to moderate essential hypertension who are treated with amlodipine or fosinopril and followed-up for six months showed a decrease in BP with no effect on the time or frequency domain of the HRV (205). Another three-way randomised crossover study of 20 patients, who were treated for essential hypertension, underwent three 4-week periods of no drug, amlodipine, or nifedipine retard. Compared with no drugs, both amlodipine and nifedipine reduced BP, but only nifedipine retard reduced LF and HF and increased the natural log of LF/HF (206).

Similarly, the effect of lipid-lowering drugs (statin) on HRV was not consistent. A 6-weeks treatment with simvastatin on 25 patients with non-ischemic dilated cardiomyopathy did not show a significant difference in RFa response to deep breathing and LFa response to Valsalva compared to their baseline before treatment (207). Nevertheless, a double-blind, placebo-controlled, cross-over study of ten patients with coronary artery disease showed that atorvastatin drugs improved the sympathovagal balance (LF/HF ratio) compared to placebo (208). Therefore, drugs used by the patients in our study are likely to have a minimal effect on our analysis of the relationship between OSA and CAN as there was no significant difference between the two groups.

Obstructive sleep apnoea:

Despite requiring a symptom (excessive day time sleepiness) to classify mild REI (≥5) as OSA positive, we have found that sixteen (34%) participants were diagnosed with OSA. The obstructive sleep apnoea health economics report (2014) estimated that the total population of adults with OSA in the UK to be 1.5 million, and only about 330,000 adults were diagnosed or treated for OSA (209). We found that 57% of all participants had mild to severe (REI>5) and 13% of all participants had moderate to severe (REI>15) REI which was consistent with the findings of previous T1D studies (109, 173, 175). Table 4.3 above shows that the respiratory events in our participants with OSA were mainly obstructive. Also, these events were accompanied by higher desaturation events and longer time with O_2 below 90%, which might lead to oxidative stress due to the intermittent hypoxia. Interestingly, the study mentioned above of severely obese patients reported an OSA prevalence (AHI ≥ 5) of 68.5% which is close to our finding of 57.4% (REI ≥ 5), but our population were not obese (median BMI 26.2 kg/m^2 [23.1-29.2]). Two T1D studies in Portugal (n=23) and Denmark (n=199) reported that 57% and 46% of T1D had AHI ≥ 5, respectively (131, 173). A multicentre study in Germany reported that about 10% of T1D participants (n=58) had moderate to severe (>15) AHI (109). Most of the studies regarding OSA in T1D were conducted in white populations. Therefore, further studies are needed to investigate the prevalence and impact of OSA on a diversity of ethnic groups.

Cardiac autonomic neuropathy and obstructive sleep apnoea:

In this study, we found a significant association between OSA and CAN in T1D, and this association remained significant after adjusting for several risk factors of OSA such as sex, age, and BMI (210). This finding is consistent with the results in chapter 2, and consistent with previous studies in patients with diabetes, both obese (190) and non-obese (211). A previous study of non-obese patients with diabetes (20 T1D and 6 T2D) found higher AHI in patients

with diabetes and autonomic neuropathy (n=18) compared to patients with diabetes but without autonomic neuropathy (n=8) (211). The same group conducted another study on obese patients with diabetes (1 T1D and 17 T2D) and found that likewise, obese patients with diabetes and autonomic neuropathy (n=8) had significantly higher AHI compared to obese patients without diabetic autonomic neuropathy (190).

CAN is a common diabetes-related neuropathy in T1D. A prospective study recruited 956 T1D (age at baseline= 31.3±8.9) without CAN at baseline from the EURODIAB Prospective Complications Study (31 European clinics). Seventeen per cent (n=163) of these participants developed CAN over 7.3±0.6 years follow-up. Witte et al. found that age and HbA1c increased the risk of developing CAN by 30% and 20%, respectively (212). Unlike the Witte et al. study, our study did not show significant differences in age or HbA1c between people with or without CAN. One of the possible reasons for the disparity may be that the sample size of our study could not detect the difference between patients with and without CAN. Another possible reason is that our patients with and without CAN had sub-optimal HbA1c (8.6% [7.8-9.7] vs 8.0 % [7.2-8.7], respectively) compared to a well-controlled HbA1c in Witte's cohort of patients who developed CAN and those who did not (6.9% ± 1.8 vs 6.4% ± 1.8, respectively). However, HbA1c on our cohort is more typical of T1D patients. In our study also, there was no significant difference in HbA1c between people with and without OSA. Similar results regarding HbA1c were reported by other T1D studies (109, 128, 131, 175), which is also consistent with the pooled HbA1c result of our meta-analysis in chapter 2.

We found a reduction in HRV (time- and frequency-domains) in T1D with OSA compared to T1D without OSA. Some studies reported a reduction of HRV and sympathovagal imbalance in patients with T1D (213). These studies proposed that hyperglycaemia in T1D reduces parasympathetic modulation and increases sympathetic modulation (213). However, our

analysis of the frequency-domain showed that LFa and RFa were suppressed in T1D with OSA with no significant difference in the sympathovagal balance. There was similar reduction in both sympathetic and parasympathetic modulation in people with OSA (without diabetes) compared to people without OSA (214). Our findings have shown that LFa and RFa correlated with OSA severity and hypoxia (cumulative time with O_2 <90%) during sleep, suggesting an association between worsening in autonomic function and worsening OSA and hypoxemia. sdNN and rmsSD also correlated with the amount of hypoxemia time during sleep (cumulative time with O_2 <90%). It is also clear from figures 4.8, 4.9, and 4.10 that sympathovagal response to the provocative challenges were supressed more in T1D with moderate to severe REI compared to T1D with mild or normal REI.

Therefore, our findings suggest that the high frequency of CAN in our study might be related to the presence of OSA. This is because CAN is frequent in patients with OSA despite the similarity between the groups with and without OSA in age, gender, diabetes duration, and HbA1C. In addition, provoking the sympathetic and parasympathetic responses by deep breathing, Valsalva, or standing presented more abnormal results in the OSA group. Therefore, we inferred that the impairment of the autonomic function could be multifactorial, and OSA played an essential role in this relation. This inference was supported by the increased of REI, OAI, and decreased nadir oxygen saturation in patients with CAN.

Several studies reported an alteration in the autonomic function in OSA. OSA might affect the autonomic function via the intermittent hypoxia and hypercapnia, or arousal. Similar to our findings, HRV was assessed in 74 obese (BMI>30) adults without diabetes and found that OSA patients had reduced time and frequency domains. Besides, AHI was associated with time-domain after adjusting for age, gender, blood pressure cholesterol levels, and HbA1c (215).

Another large retrospective study (n=168) of non-obese adults found correlations between OSA indices (AHI, ODI, and micro-arousals), and HRV indices (216).

Although hypoglycaemia worsens the autonomic function predisposing patients to increased risk of cardiovascular events, the coincident of hypoxia and hypoglycaemia leads to further exacerbation of the autonomic dysfunction. A clinical trial examined the effect of hypoxia and hypoglycaemia combined in T1D (n=13; diabetes duration =17±5 years; HbA1c = 7.5% ± 0.3) patients' HRV and spontaneous cardiac baroreflex sensitivity (sCBRS). The study found that HRV and sCBRS were reduced during hypoglycaemic events, and both were further reduced during hypoxia compared with normoxia (217). However, CPAP treatment increased plasma nitric oxide and reduced 24-h urinary noradrenaline after one night of CPAP. Also, CPAP improved baroreflex sensitivity index after three-month CPAP treatment (218).

Oxidative stress had been reported in both T1D and OSA. Therefore, the mechanism linking OSA to CAN might be increased oxidative stress. Hyperglycaemia in patients with diabetes is linked to several complications and is expected to damage the nerves via several pathways. Neurons and Schwann cells in peripheral nerves do not require insulin to move glucose into the cells (57). Therefore, accumulation of glucose in these cells activates alternative metabolic pathways, including polyol, AGEs, PKC, and hexosamine pathways (57). These mechanisms will be discussed in detail in the general discussion. Hyperglycaemia also leads to overproduction of reactive oxygen species (ROS) such as hyperglycaemia-induced superoxide (57, 66). OSA, on the other hand, leads to increase ROS level due to the redox effects caused by CIH (194). Increased level of ROS to the level that the body’s antioxidant mechanisms cannot deal with leads to oxidative stress (57). A previous laboratory study has shown that an increased level of glucose in endothelial tissue increases the production of ROS via

mitochondrial electron transport chain complex II. Also, inhibition of electron transport chain complex II not only inhibits ROS production but also inhibited the pathways mentioned above (219). This suggestion is supported by the correlations between HRV indices and hypoxia parameters, including nadir oxygen saturation, and percentage of time spent with oxygen saturation below 90% during sleep.

The strength of this study is the rigorous methods used in assessing the autonomic function of patients and the inclusive inclusion criteria used on recruitment to the study. Also, we have a detailed assessment of the parameters associated with OSA and CAN. The tool we used for the assessment of HRV considers the effect of respiration on the frequency domain, especially during deep breathing. Also, patients with and without OSA had similar age, diabetes duration, and HbA1c. As with previous T1D studies, we have some limitations. Although the main limitation was that this was a cross-sectional study and with a relatively small sample size, we were able to find significant association between OSA and CAN that was adjusted for several confounding factors. However, causality and direction cannot be established. Although we observed the coexistence of OSA and CAN in patients with T1D, we could not establish which of these two conditions is a risk factor for the other.

We could not investigate the direction of the relationship between OSA and CAN. However, the relationship might be bi-directional where CAN reduces the patency of the airway leading to increase the airway collapsibility. OSA and hypoxemia, on the other hand, reduces the autonomic function and the airway patency leading to worsening in OSA (see General Discussion).

In summary, OSA was frequent in patients with T1D (34%), and OSA was associated with CAN after adjusting for age, sex, diabetes duration, and BMI. Also, CAN indices correlated

with OSA and hypoxia. These results are discussed in the general discussion in the context of the other studies in this thesis

4.5 Appendices

Appendix 4.1 Abstract presented on the Neurodiab conference (16/9/19)

ORAL ABSTRACT

O37. OBSTRUCTIVE SLEEP APNOEA AND CARDIAC AUTONOMIC NEUROPATHY IN PATIENTS WITH TYPE 1 DIABETES: A CROSS-SECTIONAL STUDY

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Objectives : Obstructive sleep apnoea (OSA) is associated with sympathetic activation in the general population. However, little is known about the relationship between OSA and cardiac autonomic function in patients with Type 1 diabetes (T1D). Previous studies have shown a high prevalence of OSA in patients with T1D despite the absence of obesity, suggesting factors other than obesity might contribute to OSA in these patients, such as cardiac autonomic neuropathy (CAN). We aimed to assess the relationship between OSA and CAN in patients with T1D.

Methods : Adults with T1D without known OSA or end stage renal disease were recruited from a single secondary diabetes centre in the UK. OSA was defined as an apnoea hypopnea index (AHI) ≥ 15 or an AHI 5-14.9 with excessive daytime sleepiness (based on Epworth Sleepiness Scale (ESS) ≥ 11). The AHI was measured using polygraphy (ApneaLink Air, Resmed, USA). CAN was defined as >= 2 abnormal tests (E/I, Valsalva, & 30:15 ratios, or postural drop in blood pressure). Cardiac autonomic reflex tests and heart rate variability were assessed using ANX 3.0 (ANSAR inc, Philadelphia, PA).

Results : 42 patients were included (men 24%, insulin pumps 69%, mean (SD) age 46.8 (12.6), diabetes duration 30.9 (13.1), median [IQR] BMI 26.1 [23.0 - 29.2], Hb1Ac 8.1% [7.3 – 8.7]). 57.1% (n=24) had AHI >=5 and OSA prevalence was 36% (n=15), Patients with and without OSA had similar age, gender, diabetes duration, and Hb1Ac. Patients with OSA had higher BMI (28.7 (25.0 - 32.4) vs 25.1 (22.6 – 28.1), p=0.047).
CAN prevalence was 33.3% (n=14). CAN was more common in patients with OSA vs without OSA (60% (n=9) vs. 18.5% (n=5), p=0.01) which remained significant after adjusting for age, sex, BMI, and diabetes duration (Nagelkerke R^2=0.37; OR 6.97; 95% 1.18 – 41.29; p=0.033). AHI was also associated with CAN after similar adjustments (Nagelkerke R^2=0.42; OR 1.30; 95% 1.03 – 1.63; p=0.024). Patients with OSA and T1D had lower frequency and time domain parameters compared to patients with T1D only (Table 1).

Conclusions : CAN is associated with OSA in patients with T1D. OSA is associated with sympathetic and parasympathetic withdrawal. Whether OSA has an impact on diabetes-related outcomes such as hypoglycaemia and vascular disease remain to be examined. CAN might contribute to the development of OSA in patients with T1D in the absence of obesity, but longitudinal studies are needed.

CHAPTER FIVE: OBSTRUCTIVE SLEEP APNOEA AND OTHER DIABETES-RELATED COMPLICATIONS IN PATIENTS WITH TYPE 1 DIABETES

Contribution: Ziyad Alshehri contributed to the design of the study, recruitment, peripheral neuropathy assessment, data collection, all statistical analyses and writing of this chapter. I would like to acknowledge the valuable help provided by Dr Muhammad Ali Karamat MD, Dr Quratul-ain Altaf MD, and Helen Jenner (research practitioner) at Heartlands hospital. Matthew Nicholls (sleep technician) manually scored the sleep recording for sleep apnoea.

Two abstracts of the data presented in this chapter were accepted and presented at the Neurodiab conference (2019) in Sitges - Barcelona, Spain (see Appendix 5.3 & Appendix 5.4*).*

5.1 Introduction

Several epidemiological studies in T1D have identified hyperglycaemia as a critical driver for the development of diabetes-related microvascular complications, including diabetic retinopathy, nephropathy, neuropathy (220, 221). Compared to conventional therapy, a landmark RCT of more than 1400 T1D patients found that intensive glycaemic control reduced the risk of developing diabetic retinopathy (DR) by 76% (95% CI: 62-85), the progression of DR by 54% (95% CI: 39-66), the occurrence of microalbuminuria by 39% (95% CI: 21-52), and clinical neuropathy by 60% (95% CI: 38-74). However, the downside of this intensive intervention was the two- to three-times increased risk of severe hypoglycaemia (18).

Diabetes complications and hyperglycaemia have been linked to increased mortality in T1D (222-224). The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) analysed the association between HbA1c level and cardiovascular mortality in a cohort of 879 T1D who were not diagnosed with cardiovascular complications or end-stage renal disease at baseline. The study found that patients with HbA1c $\geq$ 12.1% had 3.3 times greater (95% CI: 1.8-6.1) relative risk of cardiovascular mortality compared to patients with HbA1c $\leq$ 9.4% (222).

5.1.1 Metabolic function

Different obesity measures such as BMI, waist circumference, and waist to hip ratio are associated with the risk of metabolic dysfunction (225) and OSA(226, 227) in the general population. The increase in these measures increases the risk of morbidity and mortality. Previous studies have shown that OSA patients with systematic (228) or resistant (229) hypertension were heavier and had larger neck and waist circumferences (228, 229). In the

USA, 19 combined prospective studies including more than 1.4 million white adults showed a significant increase in the hazard ratio of mortality in people with a BMI below and above 22.5 to 24.9 kg/m^2. This result was similar even when the analysis was limited to healthy subjects who never smoked (230).

In addition, Drager et al., (228) investigated the predictors of OSA in 99 patients with systematic hypertension. The study found that patients with OSA were heavier (median [IQR] BMI: 26.9 [24.1 – 29.9] vs 30.9 [27.9 – 34.1]), had larger neck (median [IQR]: 36 [33 – 40] vs 41 [37 – 43]) and waist circumferences (median [IQR]: 90 [82 – 97] vs 104 [93 – 109]), higher blood glucose (median [IQR] fasting glucose: 94 [88 – 98] vs 100 [92 – 116]) and triglycerides (median [IQR]: 98 [69 – 146] vs 152 [102 – 204]), and lower HDL (median [IQR]: 46 [38 – 52] vs 40 [34 – 47]) (228).

After adjusting for age, BMI, smoking, and alcohol consumption, a UK-based study found an increased risk of metabolic syndrome (OR: 9.1; 95% CI 2.6-31.2; $p<0.01$) in patients newly diagnosed with OSA (n=61) compared to 43 patients without OSA. After the same adjustment, OSA was also associated with higher BP, glucose, insulin, triglycerides, and lower HDL (231).

5.1.2 Retinopathy

DR is a serious diabetes-related complication that has been linked to cardiovascular morbidity and mortality in patients with T1D (35, 232, 233). DR is a progressive complication in patients with diabetes. If left untreated, this complication can progress to sight-threatening or blindness (25).

In the European population, the EURODIAB Study reported a prevalence of 26%, 10%, and 11% for mild non-proliferative, moderate-severe non-proliferative, and proliferative retinopathy, respectively (25). In the USA, a population-based study, which combined data

from the New Jersey 725 study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy, estimated that about 86% T1D American (≥18 years old) had DR, and about 42% had sight-threatening DR (223). The cumulative rate of DR development was 83% in the Wisconsin Epidemiologic Study of Diabetic Retinopathy based on 25 years T1D follow-up (24), which is lower than the 14 years cumulate rate in the same population (86%) (234). This reduction suggested that the progression of DR might be preventable; therefore, identifying treatable risk factors, such as OSA, is vital to help reduce the progression of complications such as retinopathy in T1D.

Similar to T1D patients (235), OSA was associated with retinal nerve fibre layer thickness (236) compared with control groups. A study of 124 patients who underwent a sleep study found an independent inverse association between the severity of OSA and the reduction in nasal retinal nerve fibre layer thickness (237). Also, AHI has been positively linked to wider retinal venules regardless of age, gender, BMI, hypertension, diabetes and lipid level according to the Wisconsin Sleep Cohort Study (n=476) (238).

Several T2D studies have found an association between OSA and retinopathy (163, 239, 240). Kosseifi et al.(240) found that nocturnal O_2 desaturation was associated with retinopathy. However, another study found no link between OSA and retinopathy in T2D patients, but lowest O_2 saturation was an independent predictor for Maculopathy only (241). A recent T2D study found that OSA was linked to STDR and independent predictor of retinopathy progression. Also, CPAP therapy reduced the progression to advanced DR (120).

A limited number of studies reported inconsistent findings of the relationship between OSA and T1D (109, 128, 131, 172, 174, 175), presented in chapter 2. However, the two studies which found an association between OSA and retinopathy did not adjust for the possible confounding factors and did not examine the correlation with OSA parameters (128, 131).

5.1.3 Nephropathy and kidney function

Diabetes-related nephropathy was associated with severe morbidity and mortality (242). According to the national diabetes audit, in 2015/16, the prevalence of chronic kidney disease (CKD) stage 1, stage 2, and stages 3-5 were 17.9%, 35.6% and 11.3%, respectively (243). Also, in 2014/15, it was found that 1.1% of T1D patients had end-stage renal disease (ESRD) (243). As stated in the UK renal registry 20th annual report, the most common cause of renal replacement therapy-treated renal failure remained diabetic nephropathy (28.6%) (244). The incidence rate of ESRD in French T1D adults with proteinurea at baseline was estimated to be 47.1 (95% CI: 38.4 to 55.9) per 1,000 patient-years after about 12 years follow-up time (36).

OSA was associated with patients with CKD irrespective of diabetes. A recent study of 395 with stages three and four CKD in china were examined for the presence of OSA and the effect of nasal CPAP treatment on their kidney functions. The study found that about 45% of the study population had OSA and that OSA parameters such as higher AHI and lower O_2 saturation were associated with lower estimated glomerular filtration rate (eGFR). Also, this study found that treating OSA using CPAP could minimise progression of kidney dysfunction (eGFR decline) (245).

A recent study of 69 patients without known comorbidities (e.g. diabetes, hypertension, kidney disease, and respiratory disease) were recruited after referral to sleep clinic. This research involved mainly males (79.2 %) and found that OSA was linked to renal dysfunction biomarkers (cystatin C and neutrophil gelatinase-associated lipocalin) (246).

Another study of 40 snorer patients (83% males) without sonorities such as diabetes, hypertension, and renal dysfunction examined the link between OSA and CKD. Severe OSA (AHI>30/h) accounted for about 70% of participants, and kidney function was linked to OSA

parameters. AHI was independently associated with urine ACR, and ODI was independently associated with eGFR (247).

Although limited studies of T1D patients investigated the relationship between OSA and nephropathy, their results lack agreement (109, 131, 175).

5.1.4 Peripheral neuropathy

Diabetic neuropathy in T1D is a common diabetes-related complication. Diabetes leads to microvascular impairment and reduction in capillary blood flow which then reduces the adequate perfusion of nerves. This reduction in perfusion leads to a decline in nerve function. In patients with T1D and T2D, it was found that nerve conduction velocity correlated with tissue perfusion and oxygenation in the peroneal (248) and sural (249) nerves.

The EURODIAB Study investigated the prevalence of diabetic peripheral neuropathy (DPN) in 3250 randomly selected T1D patients from 16 European countries, including the UK. The EURODIAB study found that 28 % had diabetic neuropathy and that the prevalence of diabetic neuropathy increased with increasing age, diabetes duration, or HbA1c (29). Similarly, a large UK multicentre study of 2414 T1D patients found that 22.7% had DPN, and that age and diabetes duration increased the risk of DPN (49). DPN is a heterogeneous condition due to the differences in the nerves involved, such as mono or poly, small or large, and proximal or distal nerves. Therefore, the prevalence of DPN differs based on several factors such as the population studied, the assessment tools, and the cut-offs used.

According to the SEARCH study, DPN was studied using the Michigan Neuropathy Screening Instrument, and it was found that 8.5% of 1720 young adults and adolescencents with T1D developed DPN after a mean (SD) diabetes duration of 7.9 (1.9) years (250). In the Danish population study of T1D, DPN was assessed using vibration perception threshold (>6.5 V), and

the prevalence of DPN was 62% (56). The Finnish Diabetic Nephropathy study analysed the mortality rate of 4,201 T1D adults for a median of 7 years follow-up. The study found a 3.6 (95% CI: 3.2- 4.0) higher mortality rate compared to the age- and sex- matched general population (224).

The most common form of diabetic neuropathy is distal symmetric sensorimotor polyneuropathy (46). Distal symmetric sensorimotor polyneuropathy manifestations can range widely, based on the types of nerves involved, from a decreased perception of light touch and temperature to reduced pain perception in feet (44). Distal symmetric polyneuropathy was associated with serious conditions such as coronary artery disease (251) and lower-extremity arterial calcification (252).

OSA was associated with peripheral nerves dysfunction in patients without diabetes (253). It was observed that OSA patients had lower sensory nerve action potential amplitudes compared with age and BMI patients without OSA (253). After six months of OSA treatment, the same study found an average 2.6 μV increase in amplitudes (253). The severity of peripheral nerve dysfunction in OSA patients can be related partially to nocturnal hypoxemia (254).

There is little evidence about the relationship of OSA and DPN in patients with T1D, and whether OSA may worsen the diabetes-related effects on the peripheral nerves. Only three studies reported the rate of DPN in T1D with and without OSA, as indicated in chapter 2. However, more insight into the relationship between OSA and DPN was detected in T2D study. In the T2D study, OSA was associated with DPN (OR:2.8; 95% CI, 1.4 to 5.5; P< 0.01) independent of several possible confounding factors such as sex, BMI, HbA1c, diabetes duration, and eGFR (110). Also, T1D patients with OSA had even more ulcers and loss of sensation and ankle reflexes (110). Tahrani et al., (110) suggested oxidative and nitrosative stress as the mechanism to lower tissue perfusion, and linking OSA to DPN. This argument is

backed by a case study series showing that severe OSA can prevent the healing of diabetic foot ulcers (255).

5.1.5 Quality of life

In general, quality of life (QoL) assessment is a measure of a person's well-being. This assessment explores different aspects of an individual's life like mental, social and physical aspects. Different instruments are available to assess health-related QoL. General instruments are intended to assess general health aspects and therefore theoretically suitable for a variety of patient groups and populations. Specific QoL tools are intended to assess how a disease or a medical condition affects the patients QoL like Stroke Specific Quality of Life (256), Diabetes-Specific Quality-of-Life Scale (257), and Calgary Sleep Apnea Quality of Life Index (258).

Chronic diseases have been associated with reduced QoL. A large USA survey (n= 340,575) found that people with chronic conditions like diabetes, arthritis, and heart disease were two times more likely to report dissatisfaction with their life compared to participants without these conditions (259). Dissatisfaction, on the other hand, was strongly associated with impairment in several health-related QoL aspects like insufficient sleep, depressive and anxiety symptoms, physical and mental function, and pain perception after adjusting for several demographic variables (259).

OSA is also linked to QoL impairment. A study recruited 223 patients referred to a sleep clinic for investigation of sleep-disordered breathing (SDB). Included patients assessed for SDB based on oxygen desaturation events and underwent QoL assessment using the short form-36 survey. The study showed that patients with OSA requiring CPAP treatment score lower in the dimensions of the survey as compared with reference general public scores; and the worse scores were on the vitality and social dimensions of the survey. However, CPAP treatment was associated with ameliorating QoL in all dimensions (260). Similarly, a recent large study that

evaluated QoL of 2,027 SDB patients using general QoL questionnaire (EQ-5D) and SDB specific questionnaire (FOSQ). Both questionnaires showed an improvement in QoL after positive airway pressure therapy (261).

However, the associations of OSA and quality of life (QOL) in patients with longstanding T1D are unknown.

5.1.6 Aims

Assess the relationship between OSA and metabolic profile (weight, BP, lipids, HbA1c) in T1D.

Evaluate the relationship between OSA and the presence of DR, CKD, and DPN in T1D patients.

Assess the relationship between OSA and QOL in patients with T1D.

5.2 Methods:

The cohort in this chapter is the same as studied in the previous chapter and the general section of the methodology is explained in chapter two section 2.3. Following are the specific methods for this chapter.

5.2.1.1 Nephropathy:

Nephropathy was assessed using estimated glomerular filtration rate (eGFR), and urinary albumin/creatinine ratio (ACR). eGFR, ACR, plasma urea and creatinine levels were extracted from the patients' electronic records. If routine test results were not available, patients were asked to provide samples to be analysed in the NHS Trust laboratories following the interview with me. Microalbuminuria is defined as albumin excretion of ≥ 30 mg/day, and this is viewed as an initial and early sign of diabetic nephropathy. ACR ≥ 3.5 mg/mmol in women and >2.5 mg/mmol in men is consistent with microalbuminuria (262). eGFR was calculated using the 4-variable modification of diet in renal disease (MDRD) equation (263). CKD is diagnosed if eGFR < 60 mL/min/1.73 m^2 or albuminuria is present (119).

5.2.1.2 Retinopathy:

Retinopathy was assessed using the data obtained from the National Retinopathy Screening Programme. Patients with diabetes usually have two retinal images obtained per eye at least once a year. These images are analysed and scored according to the National Screening Programme guidelines by trained retinal graders with a robust system for quality control. The grades from the most recent images (whether before or after the sleep study) were taken as the data entered in the CRF. The retinopathy grades were obtained from the patients' electronic records or local retinal screening services.

5.2.1.3 Diabetes-related Peripheral Neuropathy (DPN):

For our study, the presence of *DPN* was assessed using the *Michigan Neuropathy Screening Instrument (MNSI). Pain symptoms* were assessed using the *short-form McGill Pain Questionnaire 2 (SF-MPQ-2),* which includes scores for different types of pains, including neuropathic pain. *Foot insensitivity* was evaluated using the *10g monofilament test*, *large fibre* neuropathy was examined using *biothesiometer*, and *small fibre* neuropathy was assessed using *Neuropad and Sudoscan*.

The *MNSI* consists of two components (questionnaire and foot examination) that help with the early diagnosis of DPN (Appendix 5.1) (264). The questionnaire part (MNSIq) includes 15 yes or no questions seeking to identify the symptoms of DPN. Subjects scored one point for each of the following questions 1-3, 5-6, 8-9, 11-12, 14-15 if the participants answered *"yes"*. Items 7 and 13 were counted as one point each if answered *"No"*. For the examination, I inspected patients' feet for abnormalities, including dry skin, ulceration, or deformities. I then examined the patients' ability to sense the vibration of 128 Hz tuning fork on the great toes. Holding the tuning fork with two fingers on patients' great toes, I asked them to tell me when they stopped

feeling the vibration. Vibration sensation was scored present (the time difference between patients ceasing to feel the vibration on their toes and me ceasing to feel the vibration on my fingers <10 seconds), reduced (time difference ≥10 seconds), or absent (patients did not feel the vibration). I examined the patients' ankle reflex using a reflex hammer. If reflexes were found, then they were recorded as *"present"*. If not found, patients were asked to hook their hands together and pull (Jendrassic manoeuvre) during the examination. Reflexes found with the manoeuvre were recorded *"present with reinforcement"*. Reflexes marked *"absent"* if not present even with reinforcement. The MNSI questions have been validated against several diagnostic tests such as quantitative vibration testing, autonomic function testing, and nerve conductions. In the original article, the sensitivity and the specificity of the examination part (MNSIe) for score > 2 were 80% and 95%, respectively (264). For this study, DPN was diagnosed if the examination score is >2 or the questionnaire score is ≥ 7.

SF-MPQ-2 is a questionnaire used to measure patients' sensations and descriptions of pain (Appendix 5.2). SF-MPQ-2 is an updated version of SF-MPQ. This questionnaire measures neuropathic and non-neuropathic pain by giving 22 descriptors of pain, and the patient has to describe the severity of pain on a scale from 0 to 10 (265).

The 10g monofilament (Baileys Instruments Co., Chorlton, Manchester, UK; Figure 5.1*) test* was performed on ten sites on each foot (one on the dorsum and nine on the plantar surface) as a test for foot insensitivity (266). In this study, the cut-off for the abnormal monofilament test is < 8 correct responses (267). A systematic review to look at the validity of monofilament as a tool for peripheral neuropathy found that the sensitivity and specificity ranged from 41-93% and 68-100%, respectively (268).

Figure 5.1 Bailey 10 g monofilament

Vibration perception threshold (VPT) is used to assess large fibres for early detection of DPN. VPT was measured using a Horwell neurothesiometer (Scientific Laboratory Supplies, Nottingham, U.K.) bilaterally on the great toes (Figure 5.2). This test was repeated three times, and the mean of the three results was recorded for the analysis (269).

Figure 5.2 Horwell neurothesiometer device

Neuropad is a non-invasive indicator used to assess sudomotor dysfunction. The Neuropad is used to evaluate small fibre rather than large fibre function. The Neuropad was stuck on the

plantar region of the foot for 10 minutes. The diagnosis was categorised based on changing of cobalt (II) chloride solution colour (270). The Neuropad result was recorded as complete (change from blue to pink), partial (patchy pink), or no change (remain blue) (Figure 5.3). For our study, we considered the results *normal* if we had a complete change in colour in 10 minutes.

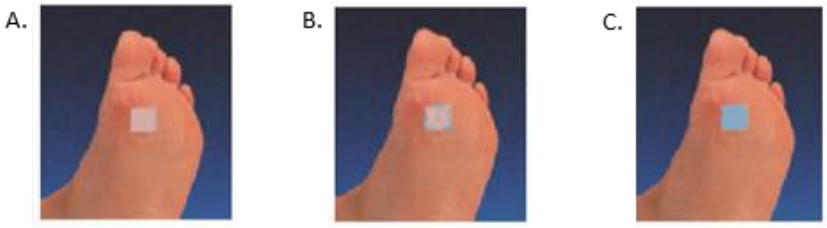

Figure 5.3 Neuropad.A) complete change of colour; B) partial change of colour; C) no change in colour.

Sudoscan (Impeto Medical, Paris France) is another non-invasive method to measure sudomotor function by measuring electrochemical skin conductance (ESC) of foot soles and hand palms (Figure 5.4 & Figure 5.5). Patients were asked to stand barefooted on a stainless-steel plate and place their palms on other plates. These plates had electrodes that would stimulate sweat glands using low-level voltage and sensors that measured the conductance resulting from this electrochemical reaction. This test produced a quantitative result reported in microsiemens (µS). Sudoscan has shown to have a sensitivity of 87.5% and a specificity of 76.2% for identifying DPN (271).

Figure 5.4 Sudoscan device

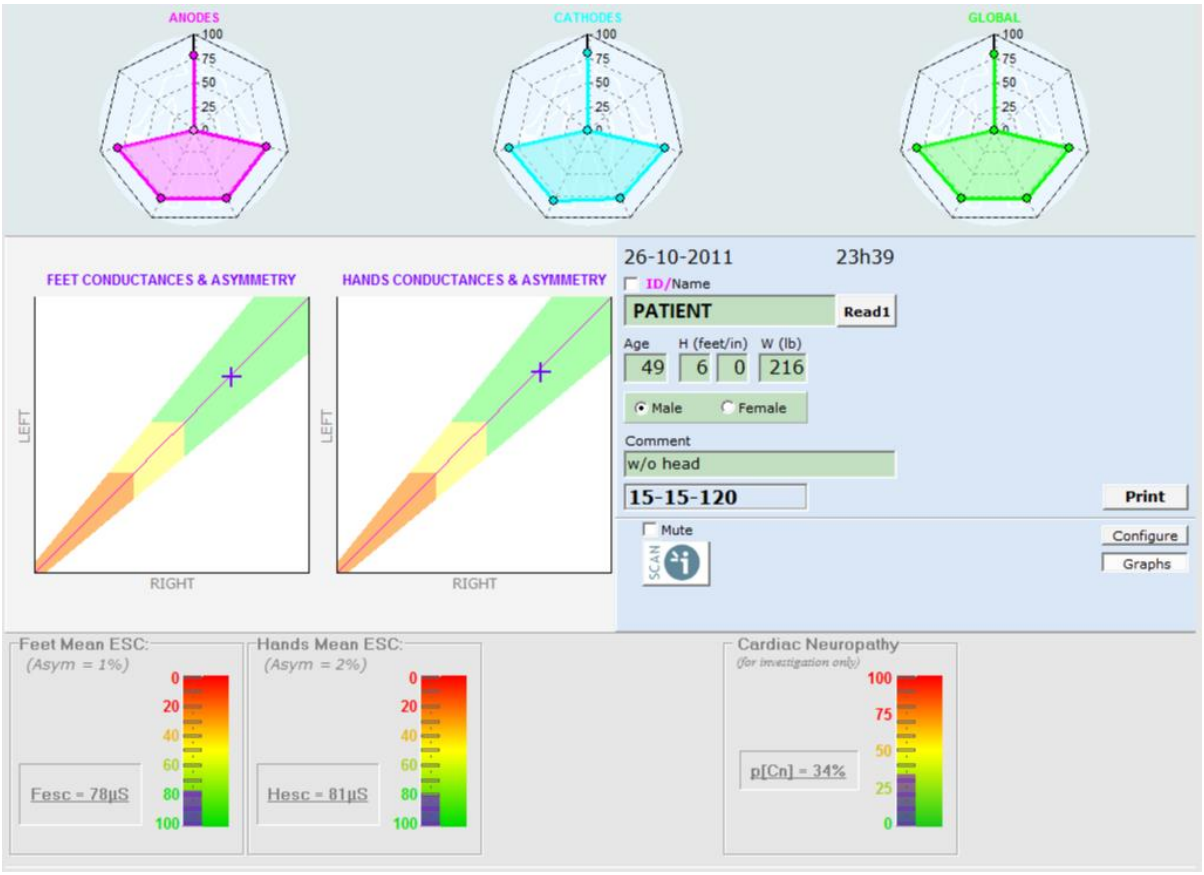

Figure 5.5 sample sudoscan result in patients with normal sudomotor function.

5.2.1.4 Quality of Life (QoL):

QoL was assessed using the *EQ-5D-5L questionnaire*. EQ-5D-5L is used to assess health status, and it is an updated version of EQ-5D-3L which was developed by the EuroQol Group to improve its sensitivity and reliability while maintaining feasibility and possibly reducing ceiling effects (272). The discriminative power of EQ-5D-5L was tested on patients with diabetes in Singapore, and it was more discriminative than the older version (273). The EQ-5D-5L consists of 2 pages – descriptive system and the EQ Visual Analogue scale (EQ-VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems (272).

5.3 Results:

47 patients were included (women 75%, insulin pumps 66%, mean (SD) age 44.9 years (13.4), diabetes duration 29.6 years (13.0), median [IQR] BMI 26.2 kg/m^2 [23.1-29.2], HbA1c 8.2% [7.3-9.1]). 57.4% (n=27) had REI ≥ 5 and OSA prevalence was 34.0% (n=16). Patients with and without OSA had similar age, gender, diabetes duration, and HbA1c. Patients with OSA had higher BMI 28.7 [25.1 - 33.5] vs 25.11 [22.6 - 28.2], p=0.03. Waist circumference and waist-hip ratio were significantly higher in patients with T1D and OSA (chapter 4: Table 4.1).

5.3.1 Metabolic function

Patients with OSA were heavier and had larger central adiposity. Mean (SD) waist circumference (WC) in T1D with OSA was 102 cm (14) compared with 90 cm (12) in T1D without OSA. Median [IQR] waist to hip ratio (WHR) in patients with OSA was 0.90 [0.86 to 1.00] compared with 0.87 [0.81 - 0.90] in patients without OSA (chapter 4: Table 4.1).

However, metabolic parameters including glycated haemoglobin (HbA1c), circulating lipids (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein) SBP, DBP, and thyroid-stimulating hormone (TSH) did not statistically differ between T1D with and without OSA (Table 5.1).

Table 5.1 Metabolic parameters in patients with OSA and T1D (OSA+) compared to patients with T1D only (OSA-)

	OSA-	OSA+	P-value
HbA1c (mmol/mol), *Mdn [IQR]*	64.0 [55.0 - 71.0]	70.5 [61.3 - 82.8]	0.07
HbA1c %, *Mdn [IQR]*	8% [7.2 - 8.7]	8.6% [7.8 - 9.7]	0.07
HbA1c categories			0.29
≤58 mmol/mol, *n (%)*	12 (38.7%)	3 (18.8%)	
59 – 69 mmol/mol, *n (%)*	8 (25.8%)	4 (25.0%)	
≥ 70 mmol/mol, *n (%)*	11 (35.5%)	9 (56.3%)	
Total cholesterol, *Mdn [IQR*]	4.4 [3.6 - 5.2]	4.8 [3.9 - 5.2]	0.44
Triglycerides, *Mdn [IQR*]	0.8 [0.6 - 0.9]	0.9 [0.7 - 1.2]	0.08
HDL, *Mdn [IQR*]	1.6 [1.4 - 1.9]	1.5 [1.3 - 1.9]	0.54
LDL, *Mdn [IQR*]	2.4 [1.7 - 2.9]	2.6 [2.0 - 3.3]	0.32
TSH, Mdn [IQR]	1.5 [1.0 - 2.3]	1.5 [1.3 - 2.8]	0.61

Data is present as median [IQR] for continuous variables and as n (%) for categorical variables. Mann-Whitney U test was run on continuous variables, and chi-square was run on categorical variables; Mdn: median; IQR: interquartile range; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TSH: thyroid-stimulating hormone

Spearman's rho correlation coefficient was also used to assess the relationship between OSA parameters and metabolic parameters (HbA1c, diabetes duration, insulin dosage, total cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, and TSH). Our findings show that HbA1c positively correlated with central apnoea index: CAI (r_s (47) = 0.39, p = 0.01). Diabetes duration correlated with obstructive apnoea index: OAI (r_s (47) = 0.37, p = 0.01), lowest nocturnal O_2 saturation (r_s (47) = 0.31, p = 0.04), time and percent of time spent with O_2 < 90% r_s (47) = 0.31, p = 0.03 and r_s (47) = 0.30, p = 0.04, respectively. Insulin dosage inversely correlated with sleep duration (r_s (47) = -0.29, p = 0.05), and positively correlated with REI and ODI (r_s (47) = 0.32, p = 0.03 and r_s (47) = 0.30, p = 0.04, respectively).

In addition, all obesity measures (BMI, NC, WC, HC, and WHR) positively correlated with REI, and ODI (Table 5.2). However, only WHR correlated with OAI. WHR and NC inversely correlated with sleep duration (Table 5.2).

Table 5.2 Correlations between OSA parameters and Obesity measures in T1D (n=47).

		BMI	NC	WC	HC	WHR
Respiratory events index	r	0.46	0.42	0.51	0.32	0.47
	P-value	**0.00**	**0.00**	**0.00**	**0.03**	**0.00**
Sleep Duration in minutes	r	-0.09	-0.33	-0.20	-0.17	-0.29
	P-value	0.53	**0.02**	0.18	0.27	0.05
Obstructive-apnoea index	r	0.19	0.28	0.27	0.07	0.30
	P-value	0.21	0.06	0.07	0.62	**0.04**
Central-apnoea index	r	0.00	0.05	0.08	0.09	0.01
	P-value	0.98	0.75	0.57	0.56	0.93
Mixed-apnoea index	r	-0.32	-0.31	-0.29	-0.26	-0.25
	P-value	**0.03**	**0.03**	0.05	0.08	0.09
Oxygen desaturation index	r	0.47	0.40	0.50	0.33	0.43
	P-value	**0.00**	**0.00**	**0.00**	**0.02**	**0.00**
Nadir oxygen saturation	r	-0.14	-0.18	-0.20	-0.05	-0.26
	P-value	0.33	0.22	0.18	0.75	0.07
Time spent with oxygen saturation < 90%	r	0.28	0.14	0.25	0.13	0.26
	P-value	0.06	0.34	0.09	0.40	0.08
% time spent with oxygen saturation < 90%	r	0.25	0.13	0.22	0.11	0.22
	P-value	0.09	0.39	0.13	0.46	0.14

r: correlation coefficient; analysed using Spearman's rho correlation coefficient

5.3.2 Retinopathy

Fifteen participants had no diabetic retinopathy (33.3%), 20 participants had background retinopathy (R1: 44.4%), two had pre-proliferative retinopathy (R2: 4.4%), and eight had proliferative retinopathy (R3: 17.8%) (Table 5.3). Patients with OSA and T1D had a higher proportion of retinopathy (R1, R2, or R3) 87.5% (n=14) as compared to 55.2% (n=16; p=0.03)

of patients with T1D only (*Figure 5.6*). Only six (13.3%) patients had maculopathy of which only one patient (6.3%) had OSA and T1D, and five patients (17.2%) had T1D only, but the difference between the group was not significant (p=0.65). Ten (21.7%) patients had photocoagulation. 37.5% (n=6) of patients with OSA and T1D had photocoagulation compared to 13.3% (n=4) of patients with T1D only. Although a higher proportion of patients with T1D and OSA had photocoagulation laser treatment, the difference was not significant (p=0.07).

Patients with OSA were 5.7 times more likely to have retinopathy (R1, R2, or R3) (Nagelkerke R^2=0.16; OR 5.68; 95% 1.09 – 29.69; p<0.04) this association did not remain significant after adjusting for age, sex, BMI, and diabetes duration (Nagelkerke R^2=0.49; OR 2.77; 95% 0.42 – 18.30; p=0.29).

Spearman's rho correlation coefficient was used to assess the relationship between sleep apnoea parameters and retinopathy grades. There was positive correlation between REI and retinopathy grades (r_s (45) = 0.34, p = 0.02). Stronger correlations were found between E/I ratios and retinopathy grades (r_s (45) = -0.44, p < 0.01), laser treatment (r_s (46) = -0.41, p < 0.01), and STDR (r_s (46) = -0.38, p < 0.01). Also, retinopathy grades correlated with WC (r_s (45) = 0.31, p = 0.04), WHR (r_s (45) = 0.43, p < 0.01), and diastolic BP (r_s (45) = 0.30, p = 0.05). STDR correlated with HbA1c (r_s (46) = 0.33, p = 0.03), WHR (r_s (46) = 0.30, p = 0.04), and diastolic BP (r_s (46) = 0.30, p = 0.04). Retinopathy also inversely correlated with several baseline and deep breathing parameters.

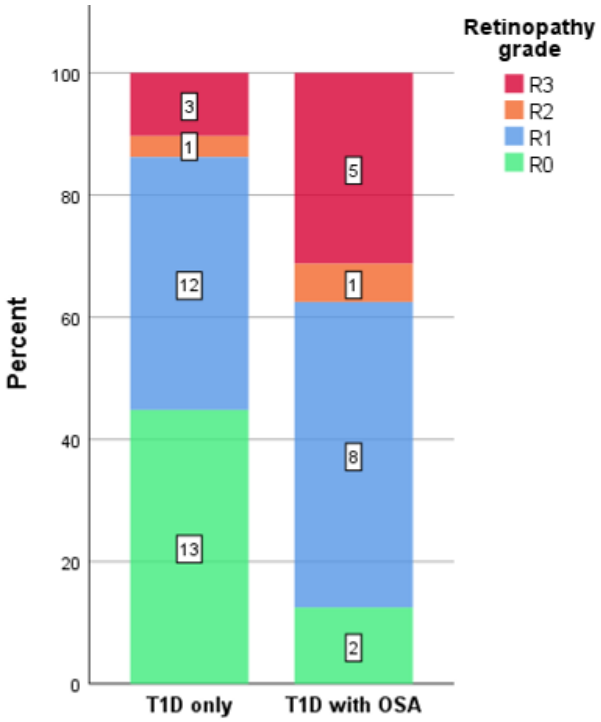

Figure 5.6 Retinopathy grades in T1D with OSA compared to patients with T1D only. *R0: no retinopathy; R1: background retinopathy; R2: pre-proliferative retinopathy; R3: proliferative retinopathy*

Table 5.3 The relationship between OSA and retinopathy, maculopathy, and laser treatment in T1D with OSA (OSA+) and T1D only (OSA-)

		Total	OSA-	OSA+	p-value
Retinopathy Grades	cases, n	45	29	16	0.09
	R0	15 (33.3%)	13 (44.8%)	2 (12.5%)	
	R1	20 (44.4%)	12 (41.4%)	8 (50%)	
	R2	2 (4.4%)	1 (3.4%)	1 (6.3%)	
	R3	8 (17.8%)	3 (10.3%)	5 (31.3%)	
Maculopathy	cases, n	45	30	16	
	M1	6 (13.3%)	5 (17.2%)	1 (6.3%)	0.40
Laser Tx	cases, n	46	31	16	
	Photocoagulation	10 (21.7%)	4 (13.3%)	6 (37.5%)	0.07
Any Retinopathy	cases, n	45	29	16	
	R1,R2, or R3	30 (66.7%)	16 (55.2%)	14 (87.5%)	0.03
STDR	cases, n	46	30	16	
		14 (30.4%)	8 (26.7%)	6 (37.5%)	0.51

Data presented as n (%); Chi-square test was run on categorical variables; R0: no retinopathy; R1: background retinopathy; R2: pre-proliferative retinopathy; R3: proliferative retinopathy; M1: Maculopathy. Tx: treatment; STDR: sight-threatening diabetic retinopathy (R2, R3, M1, or laser treatment).

5.3.3 Kidney function

CKD based on ACR and/or eGFR found that six patients had CKD. CKD was observed in three (18.8%) patients with OSA and T1D compare to three (9.7%) patients with T1D only, but this difference was not statistically significant (p=0.40).

eGFR showed that 15 (31.9%) had normal eGFR ≥ 90 ml/min (stage 1), 29 (61.7%) had slightly reduced eGFR 60 to 89 ml/min (stage 2), and three (6.4%) had reduced eGFR 30 to 59 ml/min (stage 3). Median [IQR] eGFR was slightly lower in patients with OSA but not statistically significant (78.5 [73.3 - 102.2] vs 83.0 [77.0 - 109.0]; p=0.20).

Microalbuminuria based on ACR results were found in three (18.8%) patients with OSA and T1D compare to two (6.5%) patients with T1D only, but this difference was not statistically significant (p=0.32).

Spearman's rho correlation coefficient was also used to assess the relationship between OSA parameters and kidney function parameters (eGFR, ACR, creatinine, and plasma urea). The results have shown that eGFR had inverse correlation with sleep duration (r_s (47) = - 0.20, p = 0.05) and positive correlation with CIA (r_s (47) = 0.35, p = 0.02) and mixed apnoea index: MAI (r_s (47) = 0.30, p = 0.04). Creatinine also was inversely correlated with MAI (r_s (47) = -0.34, p = 0.02). However, plasma urea , and ACR showed no correlation with OSA parameters.

Table 5.4 Kidney function parameters in patients with OSA and T1D (OSA+) compared to patients with T1D only (OSA-)

	OSA-	OSA+	P-value
CKD, *n (%)*	3 (9.7%)	3 (18.8%)	0.40
Microalbuminuria, *n (%)*	2 (6.5%)	3 (18.8%)	0.32
eGFR mL/min/1.73 m^2, Mdn [IQR]	83.0 [77.0 - 109.0]	78.5 [73.3 - 102.2]	0.20
eGFR stages			0.75
Stage 1 (>90), *n (%)*	11 (35.5%)	4 (25.0%)	
Stage 2 (60-89), *n (%)*	18 (58.1%)	11 (68.8%)	
Stage 3 (30-59), *n (%)*	2 (6.5%)	1 (6.3%)	
Plasma urea	4.7 [3.9 - 6.1]	4.9 [4.1 - 5.6]	0.72
Creatinine, *Mdn [IQR]*	68.0 [63.0 - 77.0]	74.5 [67.5 - 87.8]	0.12

Data is present as n (%) for categorical variables, and median [interquartile range] for continuous variables. Chi-square test was run on categorical variables. Mann-Whitney U test was run on continuous variables. P<0.05 was considered to represent a significant difference between patients with and without OSA. Mdn: median; IQR: interquartile range; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

5.3.4 Peripheral neuropathy

Based on MNSI, twenty-six (55%) patients had DPN. Small fibre neuropathy based on Neuropad and Sudoscan were 26 (55.3%) and 17 (40.5%), respectively. Large fibre neuropathy was present in 7 (14.9%), Foot insensitivity was present in 4 (8.5%). However, there was no significant difference between patients with and without OSA (Table 5.5)

Although there was no between-group difference in all peripheral nerves' assessments, Table 5.5 showed that OSA group had significantly higher median MNSI questionnaire (1.5 [1.0-3.0] vs 1.0 [0.0-2.0]; p=0.03) and examination (3.0 [2.5-4.4] vs 2.5 [2.0-3.5]; p=0.02) scores. Similarly, right and left VPT measurement were higher in T1D with OSA compared with T1D without OSA (RT VPT: 10 [6-14] vs 7 [4-9]; LT VPT: 11 [6-13] vs 7 [4-10]; RT and LF: p<0.05). Futher analyses have shown that there has been a gradual increase in DPN (40%, 57%, and 100%; p=0.01) based on OSA severity (no OSA, mild, and moderate/severe). After adjusting for age, sex, BMI categories, diabetes duration and HbA1c categories, the association between OSA severity and DPN remained significant (Nagelkerke R^2=0.38; OR 3.81; 95% 1.11 – 13.11; p=0.03).

T1D with OSA median [IQR] total pain score on short-form McGill pain questionnaire were significantly higher than T1D without OSA (0.69 [0.52-1.91] vs 0.23 [0.09-0.68]; p<0.01). In addition, median [IQR] neuropathic and continuous pain scores were higher in OSA group compared with T1D without OSA (1.42 [0.54-2.42] vs 0.17 [0.00-0.67]; p<0.01 and 1.00 [0.58-1.67] vs 0.33 [0.00-1.17]; p=0.02, respectively). Although continuous and neuropathic pain descriptors were both significantly higher in the OSA group, neuropathic pain shows the largest median difference of all pain subscales (Table 5.6).

After adjusting for age, sex, BMI categories, diabetes duration and HbA1c categories, the association between OSA and neuropathic pain score remained significant (Nagelkerke R^2=0.61; OR 6.06; 95% 1.46 – 25.15; p=0.01). The association between OSA and total mean pain score became borderline following the same adjustment (Nagelkerke R^2=0.49; OR 2.87; 95% 0.96 – 8.55; p=0.06; Table 5.7).

Table 5.5 peripheral nerves assessments in relation to the presence (OSA+) or absence (OSA-) of obstructive sleep apnoea in patients with T1D (n=47)

	Total	OSA- (n=31)	OSA+ (n=16)	p-value
Abnormal MNSI, *n (%)*	26 (55.3%)	15 (48.4%)	11 (68.8%)	0.18
MNSIq, *Mdn [IQR]*	1.0 [0.0-2.0]	1.0 [0.0-2.0]	1.5 [1.0-3.0]	**0.03**
MNSIe, *Mdn [IQR]*	3.0 [2.5-4.0]	2.5 [2.0-3.5]	3.0 [2.5-4.4]	**0.02**
Abnormal NeuroPad, *n (%)*	26 (55.3%)	19 (61.3%)	7 (43.8%)	0.25
Abnormal monofilament test, *n (%)*	4 (8.5%)	1 (3.2%)	3 (18.8%)	0.11
Abnormal Sudoscan, *n (%)*	17 (40.5%)	9 (33.3%)	8 (53.3%)	0.21
Hands conductance, *Mdn [IQR]*	70 [61-78]	69 [63-78]	71 [44-80]	0.87
Hands asymmetry, *Mdn [IQR]*	4% [1-6]	3% [1-6]	4% [2-6]	0.49
Feet conductance, *Mdn [IQR]*	75 [68-80]	75 [68-80]	75 [56-80]	0.68
Hands asymmetry, *Mdn [IQR]*	2% [1-4]	2% [1-4]	2% [1-5]	0.77
Abnormal VPT, *n (%)*	7 (14.9%)	3 (9.7%)	4 (25%)	0.21
Right VPT, *Mdn [IQR]*	7.7 [5-10.5]	7 [4-9]	10 [6-14]	**0.04**
Left VPT, *Mdn [IQR]*	8 [5-11.3]	7 [4-10]	11 [6-13]	**0.03**

Data is present as n (%) for categorical variables, and median [interquartile range] for continuous variables. Chi-square test was run on categorical variables. Mann-Whitney U test was run on continuous variables. P<0.05 was considered to represent a significant difference between patients with and without OSA. Mdn: median; IQR: interquartile range; MNSI: Michigan Neuropathy Screening Instrument; MNSIq: MNSI questionnaire; MNSIe: MNSI examination. VPT: vibration perception threshold.

Table 5.6 short-form McGill pain questionnaire in relation to the presence (OSA+) or absence (OSA-) of obstructive sleep apnoea in patients with T1D (n=47)

	Total	OSA- (n=31)	OSA+ (n=16)	p-value
Total pain score, *Mdn [IQR]*	0.45 [0.14-1.00]	0.23 [0.09-0.68]	0.69 [0.52-1.91]	**<0.01**
Continuous, *Mdn [IQR]*	0.50 [0.00-1.50]	0.33 [0.00-1.17]	1.00 [0.58-1.67]	**0.02**
Intermittent, *Mdn [IQR]*	0.00 [0.00-0.33]	0.00 [0.00-0.17]	0.00 [0.00-1.18]	0.12
Neuropathic, *Mdn [IQR]*	0.33 [0.00-1.50]	0.17 [0.00-0.67]	1.42 [0.54-2.42]	**<0.01**
Affective, *Mdn [IQR]*	0.00 [0.00-1.25]	0.00 [0.00-0.75]	0.50 [0.00-2.75]	0.25

Data is present as median [interquartile range] for continuous variables. Mann-Whitney U test was run on continuous variables. P<0.05 was considered to represent a significant difference between patients with and without OSA. Mdn: median; IQR: interquartile range.

Table 5.7 Univariate and multivariate logistic regression analysis for the association between pain and obstructive sleep apnoea

	Univariate	model 1	model 2	model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Total pain	2.73 (1.10-6.76)*	2.61 (1-6.77)*	3.02 (1.05-8.71)*	2.87 (0.96-8.55)
Continuous	1.53 (0.91-2.57)	1.43 (0.87-2.35)	1.73 (1.01-2.96)*	1.61 (0.94-2.76)
Intermittent	2.94 (0.84-10.35)	3.3 (0.72-15.2)	2.77 (0.79-9.68)	2.38 (0.74-7.7)
Neuropathic	2.36 (1.18-4.74)*	3.36 (1.32-8.56)*	4.76 (1.4-16.14)*	6.06 (1.46-25.15)*
Affective	1.45 (0.91-2.30)	1.44 (0.9-2.32)	1.58 (0.97-2.57)	1.58 (0.94-2.63)

Univariate: Unadjusted

Model 1 : adjusted for age, gender, and diabetes duration

Model 2: model 1 plus BMI categories

Model 3: model 2 plus HbA1c categories

OR: odds ratio; CI: confidence interval; *: $p<0.05$; **:$p<0.01$

In relation to OSA parameters, DPN based on MNSI and MNSI examination score positively correlated with REI and OAI. MNSI assessment score only correlated with ODI and time spent below 90% saturation. Right and left VPT scores individually positively correlated with REI. Sudoscan correlated with REI and ODI. However, the severity (abnormal, borderline, or normal) of hands conductance abnormality inversely correlated with lowest O_2 saturation (Table 5.8).

Table 5.8 Correlations between OSA parameters and peripheral nerves assessments in patients with T1D (n=47).

		REI	Sleep Duration	OAI	CAI	MAI	ODI	Lowest O_2 Sat	Time < 90%	% time < 90%
MNSI history score	r	0.18	0.17	0.07	0.03	0.14	0.12	-0.02	0.17	0.14
	p-value	0.23	0.26	0.66	0.87	0.35	0.41	0.90	0.25	0.34
MNSI assessment score	r	0.37	0.12	0.36	-0.08	-0.18	0.33	-0.01	0.29	0.22
	p-value	**0.01**	0.42	**0.01**	0.57	0.24	**0.02**	0.96	**0.05**	0.13
MNSI, (A/N)	r	0.29	0.04	0.33	-0.04	-0.02	0.22	0.03	0.20	0.19
	p-value	**0.05**	0.77	**0.03**	0.79	0.90	0.14	0.83	0.18	0.21
Monofilament, (A/N)	r	0.24	-0.03	0.20	-0.11	-0.06	0.19	0.02	0.05	-0.02
	p-value	0.11	0.82	0.18	0.45	0.67	0.21	0.88	0.75	0.88
NEUROPAD, (A/N)	r	-0.02	-0.10	-0.01	-0.18	0.19	0.02	-0.08	0.12	0.10
	p-value	0.90	0.49	0.95	0.24	0.20	0.92	0.59	0.43	0.50
Hands Conductance, (A/B/N)	r	0.03	0.13	-0.03	-0.02	0.12	0.05	-0.34	0.15	0.15
	p-value	0.86	0.38	0.83	0.88	0.44	0.76	**0.02**	0.31	0.30
Feet Conductance, (A/B/N)	r	0.27	-0.17	0.09	-0.06	0.13	0.26	-0.19	0.08	0.09
	p-value	0.07	0.25	0.54	0.71	0.38	0.08	0.19	0.59	0.54
Sudoscan, (A/N)	r	0.32	-0.06	0.14	0.07	0.04	0.31	-0.24	0.09	0.09
	p-value	**0.04**	0.72	0.38	0.67	0.81	**0.05**	0.13	0.58	0.57
RT VPT score	r	0.34	0.05	0.30	0.02	-0.05	0.27	0.00	0.21	0.12
	p-value	**0.02**	0.75	**0.04**	0.89	0.72	0.07	0.98	0.17	0.42
LT VPT score	r	0.30	0.04	0.26	0.07	-0.04	0.23	-0.02	0.25	0.18
	p-value	**0.04**	0.77	0.08	0.63	0.79	0.13	0.91	0.09	0.22
VPT (A/N)	r	0.23	0.16	0.20	0.19	-0.09	0.19	0.22	-0.03	-0.12
	p-value	0.12	0.29	0.18	0.21	0.56	0.19	0.14	0.82	0.41

(A/N): abnormal/normal; (A/B/N): abnormal/borderline/normal; r: correlation coefficient; analysed using Spearman's rho correlation coefficient

5.3.5 Quality of life

Patients with OSA and T1D had lower QOL compared to those with T1D only (EQ-5D-5L VAS: 75% [63 - 84] vs 85% [80 - 90]; p<0.01; EQ-5D-5L Index: 0.77 [0.74 - 0.85] vs 1.00

[0.88 – 1.00]; p<0.01; Table 5.9). After adjusting for age, sex, BMI categories, diabetes duration and HbA1c categories, EQ-5D-5L VAS (Nagelkerke R^2=0.52; OR 0.88; 95% 0.79 – 0.98; p=0.02), and EQ-5D-5L index (Nagelkerke R^2=0.67; OR 0.000; 95% 0.000 – 0.003; p<0.01) remained significantly associated with OSA (Table 5.10) showing that OSA was associated with worse QOL.

Further analyses of the distribution of QoL dimension responses have shown that the OSA group had significantly poorer QoL in pain/discomfort and anxiety/depression (Table 5.12). In relation to OSA parameters, both EQ-5D-5L VAS and EQ-5D-5L index related to REI and nocturnal hypoxemia (Table 5.11).

Table 5.9 Quality of life in relation to the presence (OSA+) or absence (OSA-) of obstructive sleep apnoea in patients with T1D (n=47)

	Total	OSA-	OSA+	p-value
EQ-5D-5L INDEX	0.88 [0.77-1.00]	1.00 [0.88-1.00]	0.77 [0.74-0.85]	<0.01
EQ-VAS	85% [75-90]	85% [80-90]	75% [63-84]	<0.01

Data is present as median [interquartile range] for continuous variables. Mann-Whitney U test was run on continuous variables. P<0.05 was considered to represent a significant difference between patients with and without OSA. Mdn: median; IQR: interquartile range

Table 5.10 Univariate and multivariate logistic regression analysis for the association of quality of life with obstructive sleep apnoea

	Univariate	model 1	model 2	model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
EQ-5D-5L index	0 (0-0.005)**	0 (0-0.007)**	0 (0-0.003)**	0 (0-0.003)**
EQ-VAS	0.89 (0.81-0.96)**	0.88 (0.81-0.97)**	0.89 (0.80-0.98)*	0.88 (0.79-0.98)*

Univariate: Unadjusted

Model 1 : adjusted for age, gender, and diabetes duration

Model 2: model 1 plus BMI categories

Model 3: model 2 plus HbA1c categories

OR: odds ratio; CI: confidence interval; *: p<0.05; **:p<0.01

Table 5.11 Correlations between OSA parameters and quality of life in patients with T1D (n=47).

		REI	OAI	ODI	TIME < 90%	% time < 90%
	cases, n	47	47	47	47	47
EQ-5D-5L index	*r*	-0.31	-0.30	-0.30	-0.417	-0.40
	p-value	**0.03**	**0.04**	**0.04**	**<0.01**	**0.01**
EQ-5D-5L VAS	*r*	-0.33	-0.22	-0.36	-0.25	-0.29
	p-value	**0.02**	0.14	**0.01**	0.10	**0.05**

r: correlation coefficient; analysed using Spearman's rho correlation coefficient

Table 5.12 Distribution of EQ-5D-5L dimension responses in patients with and without OSA

	Total	OSA-	OSA+	p-value
Mobility, *n (%)*				0.12
No problems	39 (83%)	28 (90.3%)	11 (68.8%)	
Slight problems	7 (14.9%)	3 (9.7%)	4 (25%)	
Moderate problems	1 (2.1%)	0 (0%)	1 (6.3%)	
Severe problems	0 (0%)	0 (0%)	0 (0%)	
Unable to walk about	0 (0%)	0 (0%)	0 (0%)	
Self-care, *n (%)*				0.34
No problems	46 (97.9%)	31 (100%)	15 (93.8%)	
Slight problems	1 (2.1%)	0 (0%)	1 (6.3%)	
Moderate problems	0 (0%)	0 (0%)	0 (0%)	
Severe problems	0 (0%)	0 (0%)	0 (0%)	
Unable to wash or dress	0 (0%)	0 (0%)	0 (0%)	
Usual activity, *n (%)*				0.1
No problems	39 (83%)	28 (90.3%)	11 (68.8%)	
Slight problems	8 (17%)	3 (9.7%)	5 (31.3%)	
Moderate problems	0 (0%)	0 (0%)	0 (0%)	
Severe problems	0 (0%)	0 (0%)	0 (0%)	
Unable to do usual activities	0 (0%)	0 (0%)	0 (0%)	
Pain/discomfort, *n (%)*				**0.01**
No pain/discomfort	34 (72.3%)	27 (87.1%)	7 (43.8%)	
Slight pain/discomfort	12 (25.5%)	4 (12.9%)	8 (50%)	
Moderate pain/discomfort	1 (2.1%)	0 (0%)	1 (6.3%)	
Severe pain/discomfort	0 (0%)	0 (0%)	0 (0%)	
Extreme pain/discomfort	0 (0%)	0 (0%)	0 (0%)	
Anxiety/depression, *n (%)*				**0.03**
Not anxious/depressed	30 (63.8%)	24 (77.4%)	6 (37.5%)	
Slight anxious/depressed	10 (21.3%)	5 (16.1%)	5 (31.3%)	
Moderate anxious/depressed	6 (12.8%)	2 (6.5%)	4 (25%)	
Severe anxious/depressed	1 (2.1%)	0 (0%)	1 (6.3%)	
Extremely anxious/depressed	0 (0%)	0 (0%)	0 (0%)	

Data is present as n (%). Chi-square test was run on categorical variables. $P<0.05$ was considered to represent a significant difference between patients with and without OSA.

5.4 Discussion

Key points:

- It was unclear if OSA was associated with metabolic dysfunction, but T1D with OSA had increased insulin usage compared with T1D alone
- There was an association between OSA and retinopathy in general but not with STDR
- We found no evidence of the association between OSA and reduced kidney function.
- QoL was worse in patients with T1D and OSA compared with T1D alone

5.4.1 Metabolic function:

For T1D with OSA, the central adiposity was higher compared to patients without OSA, which is consistent with data gathered for T2D (110, 120) and other populations (104, 226, 246). In contrast to earlier findings in T2D studies, we found that the increased obesity measures in the OSA group were not reflected in patients circulating lipids. A possible explanation for this might be that our patients were less obese than the participants in T2D studies (110, 120), and this is supported by other T1D studies (109, 128, 131, 175). Consequently, possible interference of circulating lipids in other complications can be reduced to a minimum or ruled out for this cohort.

Similar to previous T1D (128, 131, 174, 175) and T2D (119, 120) studies, our patients with and without OSA had similar HbA1c. A possible explanation for this similarity might be the awareness of healthcare providers of the importance of controlling blood glucose level to reduce diabetes-related complications. This explanation is supported by the high and similar proportions of insulin pumps users, as shown in chapter 4, table 4.1. However, the increased insulin use in the OSA group, as shown in the positive relation between insulin used and OSA (REI and ODI), might explain the effect of OSA on glucose metabolism. Diabetes duration, on

the other hand, was related to REI and nocturnal hypoxemia. Long-term diabetes, therefore, possibly leads to OSA. OSA affects the metabolism of glucose, which increases insulin need.

5.4.2 Retinopathy

Two-thirds of our cohort had retinopathy, and the retinopathy was significantly higher in the OSA group. Manin et al. (131) reported similar proportions of retinopathy in their cohort of T1D. Our findings became non-significant after adjustment. However, a previous large T2D study observed a significant association between OSA and STDR after adjustment for possible confounding factors, and CPAP reduced the progression of retinopathy (120).

In the present study, retinopathy grades were related to REI but not nocturnal hypoxia. Retinopathy was also inversely correlated to autonomic dysfunction. Autonomic dysfunction was also related to OSA in chapter 3. Previous studies of patients with diabetes (T1D and T2D) have noted the relationship between retinopathy and autonomic dysfunction (274, 275).

A possible explanation is that OSA worsens the autonomic function. Then reduced autonomic function leads to progression in retinopathy. A study of 154 T1D with normal albumin urea showed a reduced autonomic function in T1D with retinopathy compared to T1D without retinopathy (276). Another possible explanation comes from the high proportions of retinopathy in this study and previous literature, observing that the high percentage of retinopathy after an average of 7.5 years follow-up indicates early manifestation of microvascular complications in T1D. (33, 34). Larger studies are probably needed to examine the adjusted relationship between OSA and retinopathy in T1D.

5.4.3 Kidney Function

We found no difference in CKD between T1D and OSA group compared with T1D only group. Previous studies of T1D patients reported similar findings (109, 128, 131, 174); and similar to

our studies, the OSA group and non-OSA group had similar age, gender, BMI, and HbA1c. One study (n=199), however, reported significantly higher diabetic nephropathy and plasma creatinine level in T1D with OSA compared with T1D without OSA (175). However, this study was different from our study in many aspects. Unlike Banghoej et al. (175), our groups had similar age, sex, and diabetes duration. Our cohort reported similar lower systolic blood pressure with no difference between groups. Banghoej et al. (175) cohort, on the other hand, reported higher systolic blood pressure that was also significantly higher in the OSA group. One last thing is that the majority of participants were females, whereas Banghoej et al. (175) study included mostly males. However, Banghoej et al. (175) found the association between OSA and nephropathy to remain significant after multivariate analysis that included age, gender, BMI, hypertension, nephropathy, and neuropathy. Our study also showed no correlation between ACR, plasma urea, or eGFR with OSA specific parameters.

5.4.4 Peripheral neuropathy

We found an association between OSA severity and DPN based on MNSI. However, this association was not observed when we compared DPN in patients with and without OSA. Limited studies have investigated the relationship between OSA and DPN in patients with T1D (131, 174, 175). However, the only study reported an increased DPN was based on VPT in T1D with OSA compared with T1D only (175). As mentioned above, unlike our cohort, this study had significantly different characteristics between patients with and without OSA. Therefore, the association became non-significant after adjusting for possible confounding factors. Also, this study overlooked the association between DPN and OSA severity. Another study which included T1D and T2D, showed a relationship between OSA severity and DPN (109). However, the weakness of the study is the failure to analyse the relationship based on the type of diabetes because it has been reported that the mechanism of the development of DPN differs between

T1D and T2D (277). A previous study compared patients with severe OSA but without diabetes (n=23) to age and BMI matched control (n=23) and showed reduced sensory nerve action potential amplitudes in the OSA group. Also, this study has found an improvement in sensory nerve action potential amplitudes after six months of CPAP (253). Therefore, the effect of OSA on peripheral nerve function may be more prominent in severe OSA if other factors like age and BMI are controlled.

5.4.5 Quality of life

In our study, patients with T1D and OSA had worse QoL score for both the index score and the self-rated score (EQ-5d-5l VAS). These scores correlated with the number of events and nocturnal hypoxemia. Also, these variables maintained the relationship with OSA after adjustment for possible confounding factors suggesting that the coexistence of OSA and T1D worsen the impairment on patients QoL.

Although breathing abnormalities in OSA patients occur at night, the consequence of these events impairs the person's daytime mental and physical function mainly due to sleepiness (278). The prevalence of depression and anxiety on T1D were estimated to be 20% and 25%, respectively (279). Depression and anxiety in patients with T1D can be related to diabetes-related complications (280-282). Pain results on EQ-5D-5L and McGill pain questionnaire (Table 5.12 and Table 5.6) suggest that painful neuropathy might play an essential role in QoL impairment.

In summary, OSA is associated with painful DPN and worse quality of life in patients with long-standing T1D. Besides, severe OSA might have an additive effect on the eye and kidney complications, even in patients with reasonable metabolic control. Whether OSA treatment can improve diabetic peripheral neuropathy, retinopathy, neuropathy pain, and quality of life need to be examined in a randomised controlled trial.

5.5 Appendices

Appendix 5.1 Michigan Neuropathy Screening Instrument

A. History (To be completed by the person with diabetes)

Please take a few minutes to answer the following questions about the feeling in your legs and feet. Check yes or no based on how you usually feel. Thank you.

1. Are you legs and/or feet numb?	☐ Yes	☐ No
2. Do you ever have any burning pain in your legs and/or feet?	☐ Yes	☐ No
3. Are your feet too sensitive to touch?	☐ Yes	☐ No
4. Do you get muscle cramps in your legs and/or feet?	☐ Yes	☐ No
5. Do you ever have any prickling feelings in your legs or feet?	☐ Yes	☐ No
6. Does it hurt when the bed covers touch your skin?	☐ Yes	☐ No
7. When you get into the tub or shower, are you able to tell the hot water from the cold water?	☐ Yes	☐ No
8. Have you ever had an open sore on your foot?	☐ Yes	☐ No
9. Has your doctor ever told you that you have diabetic neuropathy?	☐ Yes	☐ No
10. Do you feel weak all over most of the time?	☐ Yes	☐ No
11. Are your symptoms worse at night?	☐ Yes	☐ No
12. Do your legs hurt when you walk?	☐ Yes	☐ No
13. Are you able to sense your feet when you walk?	☐ Yes	☐ No
14. Is the skin on your feet so dry that it cracks open?	☐ Yes	☐ No
15. Have you ever had an amputation?	☐ Yes	☐ No

B. Physical Assessment (To be completed by health professional)

1. Appearance of Feet

	Right	Left
a. Normal	☐ 0 Yes ☐ 1 No	Normal ☐ 0 Yes ☐ 1 No
b. If no, check all that apply:		If no, check all that apply:
Deformities	☐	Deformities ☐
Dry skin, callus	☐	Dry skin, callus ☐
Infection	☐	Infection ☐
Fissure	☐	Fissure ☐
Other	☐	Other ☐
specify:	_____	specify: _____

	Right		Left	
	Absent	Present	Absent	Present
2. Ulceration	☐ 0	☐ 1	☐ 0	☐ 1

	Right			Left		
	Present	Present/ Reinforcement	Absent	Present	Present/ Reinforcement	Absent
3. Ankle Reflexes	☐ 0	☐ 0.5	☐ 1	☐ 0	☐ 0.5	☐ 1

	Right			Left		
	Present	Decreased	Absent	Present	Decreased	Absent
4. Vibration perception at great toe	☐ 0	☐ 0.5	☐ 1	☐ 0	☐ 0.5	☐ 1

Appendix 5.2 Short-Form McGill Pain Questionnaire-2

Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2)

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms. Please put an **X** through the numbers that best describe the intensity of each of the pain and related symptoms you felt during the past week. Use 0 if the word does not describe your pain or related symptoms.

1. Throbbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
2. Shooting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
3. Stabbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
4. Sharp pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
5. Cramping pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
6. Gnawing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
7. Hot, burning pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
8. Aching pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
9. Heavy pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
10. Tender	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
11. Splitting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
12. Tiring, exhausting	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
13. Sickening	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
14. Fearful	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
15. Punishing, cruel	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
16. Electric shock pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
17. Cold, freezing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
18. Piercing	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
19. Pain caused by light touch	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
20. Itching	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
21. Tingling or "pins and needles"	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
22. Numbness	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*

Appendix 5.3 Abstract presented on the Neurodiab conference (16/9/19)

13 - 16 September 2019

NEURODIAB

Meliá Sitges Hotel
Sitges - Barcelona

P3. VARIATION IN DIABETES PERIPHERAL NEUROPATHY (DPN) PREVALENCE AND LACK OF AGREEMENT BETWEEN NEUROPAD, SUDOSCAN, VIBRATION PERCEPTION THRESHOLD AND THE MICHIGAN NEUROPATHY SCREENING INSTRUMENT IN DIAGNOSING DPN IN PATIENTS WITH LONGSTANDING TYPE 1 DIABETES

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Objectives : Diabetes peripheral neuropathy (DPN) is common in patients with Type 1 diabetes (T1D). Currently available tools to diagnose DPN vary in its ability to detect large vs small fibre neuropathy. Hence the prevalence of DPN might vary according to the method used. In this cross-sectional study we aimed to assess the prevalence of DPN in patients with longstanding T1D based on Neuropad, Sudoscan, vibration perception threshold (VPT) and the Michigan Neuropathy Screening Instrument (MNSI). We also aimed to compare the agreement between these methods

Methods : Adults with T1D without known OSA or end stage renal disease were recruited from a single secondary diabetes centre in the UK. Neuropad test was classified as normal if there was a total change in the colour of the plaster, while patchy or no change was considered abnormal. Sudoscan test was interpreted in line of the paper by Vinik et al. (2015) based on ethnicity. MNSI was considered abnormal if MNSI questionnaire scored more than 7 or MNSI examination scored ≥ 2.5. VPT was measured using a neurothesiometer (Scientific Laboratory Supplies Limited, Nottingham, UK) with an average of three measurements ≥ 15 volts on either great toe considered abnormal.

Results : 42 patients were included (Caucasian 95%, men 24%, insulin pumps 69%, mean (SD) age 46.8 (12.6), diabetes duration 30.9 (13.1), median [IQR] BMI 26.1 [23.0 - 29.2], Hb1Ac 8.1% [7.3 – 8.7]). The prevalence of DPN was 60% (n=25), 36% (n=15), 14% (n=6), 60% (n=25) based on Neuropad, Sudoscan, VPT and MNSI respectively.

There was poor agreement in detecting DPN between the examined methods.

Out of 25 patients with abnormal Neuropad, 56% (n=14), 16% (n=4), 60% (n=15) had abnormal Sudoscan, VPT, and MNSI respectively. Out of 15 patients with abnormal Sudoscan, 93% (n=14), 20% (n=3), 67% (n=10) had abnormal Neuropad, VPT, and MNSI respectively.

Appendix 5.4 Abstract presented on the Neurodiab conference (14/9/19)

13 - 16 September 2019

NEURODIAB

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P8. OBSTRUCTIVE SLEEP APNOEA IS ASSOCIATED WITH PAINFUL PERIPHERAL NEUROPATHY AND WORSE QUALITY OF LIFE IN PATIENTS WITH LONGSTANDING TYPE 1 DIABETES

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Objectives : Obstructive sleep apnoea (OSA) is common in patients with type 1 diabetes (T1D). However, the associations of OSA and painful diabetes peripheral neuropathy (PDPN) and quality of life (QOL) in patients with longstanding T1D are unknown. The aim of this study was to assess the relationship between OSA and PDPN and QOL in patients with T1D.

Methods : Adults with T1D without known OSA or end stage renal disease were recruited from a single secondary diabetes centre in the UK. OSA was defined as an apnoea hypopnea index (AHI) ≥ 15 or an AHI 5-14.9 with excessive daytime sleepiness (based on Epworth Sleepiness Scale (ESS) ≥ 11). The AHI was measured using polygraphy (ApneaLink Air, Resmed, USA). PDPN was assessed using the Short Form McGill Pain Questionnaire 2 (SF-MPQ-2), and QOL was assessed using the EQ-5D-5L questionnaire.

Results : 42 patients were included (men 24%, insulin pumps 69%, mean (SD) age 46.8 (12.6), diabetes duration 30.9 (13.1), median [IQR] BMI 26.1 [23.0 - 29.2], Hb1Ac 8.1% [7.3 - 8.7]). 57.1% (n=24) had AHI >=5 and OSA prevalence was 36% (n=15), Patients with and without OSA had similar age, gender, diabetes duration, and Hb1Ac. Patients with OSA had higher BMI (28.7 (25.0 - 32.4) vs 25.1 (22.6 – 28.1), p=0.047).
The prevalence of OSA was 36%. Patients with OSA and T1D had higher total mean pain score (0.64 [0.5 - 2.05] vs 0.23 [0.05 - 0.64]; p<0.01) and neuropathic pain score (1.5 [0.5 - 2.67] vs 0 [0 - 0.67]; p<0.01) compared to patients with T1D without OSA. Patients with OSA and T1D had lower QOL compared to those with T1D only (EQ-5D-5L Scale: 75% [60 - 85] vs 86% [80 - 90]; p<0.01; EQ-5D-5L Index: 0.77 [0.74 - 0.85] vs 1 [0.85 - 1]; p<0.01).
After adjusting for age, sex, BMI, diabetes duration and HbA1c the association between OSA and neuropathic pain score remained significant (Nagelkerke R^2=0.66; OR 7.59; 95% 1.40 – 41.04; p=0.02). The association between OSA and total mean pain score became borderline following adjustment (Nagelkerke R^2=0.48; OR 4.21; 95% 0.92 – 19.34; p=0.06).
After similar adjustment, EQ-5D-5L scale (Nagelkerke R^2=0.64; OR 0.86; 95% 0.76 – 0.98; p=0.02), and EQ-5D-5L index (Nagelkerke R^2=0.67; OR 0.00; 95% 0.00 – 0.07; p=0.02) remained significantly associated with OSA showing that OSA was associated with worse QOL.

Conclusions : OSA is associated with PDPN and worse quality of life in patients with long standing T1D. Whether OSA treatment can improve pain and quality of life needs to be examined in a randomised controlled trial.

CHAPTER SIX: THE INCIDENCE/RISK OF DEVELOPING OSA IN PATIENTS WITH T1D – A POPULATION-BASED RETROSPECTIVE COHORT STUDY

Contribution: Ziyad Alshehri contributed to the design of the study. I gratefully acknowledge the support of Dr Krish Nirantharakumar team (Anuradhaa Subramanian, Krishna Gokhale, and Nicola Adderley) from Institute of Applied Health Research who helped me with the initial stages of the study. They carried out the data extraction from the THIN database. I carried out the data cleaning and performed the data analysis with help advice provided by Miss Anuradhaa Subramanian, and writing this chapter.

6.1 Background

A detailed overview of OSA is given in the general introduction (see Chapter 1), but in summary OSA has been associated with T1D and diabetic complications in chapter 2 and 3. However, little is known about the direction of this relationship. Therefore, in this chapter, we aimed to investigate the whether T1D increases the risk developing of OSA or not, and the possible predictor factors of OSA.

OSA and Cardiovascular Disease

OSA has been associated with increased risk of mortality and multiple comorbidities, including Type 2 diabetes (T2D) and cardiovascular disease, as well as poor quality of life (283-287). OSA increases the risk of premature death, especially from cardiovascular events. It has been found that untreated severe OSA in men increases the risk of both fatal (OR: 2.87; 1.17–7.51; p=0.025) and non-fatal (OR: 3.17; 1.12–7.51; p=0.001) cardiovascular events which can be reduced by CPAP (3). Several studies have identified the relationship between OSA and hypertension (288, 289). Large epidemiological population-based studies showed that patients with OSA are at increased risk of developing hypertension (289) which, multiple meta-analyses of RCTs have shown, is responsive to CPAP treatment (94, 182).

After adjusting for several metabolic and cardiovascular confounders, Yaggi et al. (290) found that the hazard ratio, of all-cause mortality or stroke in patients with OSA, to be 1.97 (1.12-3.48; P=0.01). A large South Korean retrospective study compared the standardised mortality ratio (SMR) of patients with severe OSA to the general population. The study found that the SMR of cardiovascular mortality in patients with severe OSA is higher than the general population (1.79; 1.15 –2.67; $p < 0.05$) (291). A meta-analysis of prospective studies concluded

that severe obstructive sleep apnoea is an independent predictor of cardiovascular mortality with an estimated hazard ratio (HR) of 2.65 (1.82-3.85; P=0.000) (292).

Several epidemiological studies have found that OSA is very common in people with T2D, with a prevalence of up to 86% (1). Several cross-sectional studies suggested an association between OSA and diabetes-related vascular disease (110, 118-120). Some cohort studies suggested OSA as an independent risk factor for diabetic-related complications such as diabetic nephropathy (119) and proliferative diabetic retinopathy (120). The high prevalence of OSA in T2D is not surprising considering that obesity is a major risk factor for both conditions. However, several small studies in patients with T1D also showed a high prevalence of OSA in patients with T1D (109, 175), although these patients were leaner than patients with T2D.

Our systematic review (see Chapter 2) looking at the impact of OSA on diabetic-complications in patients with T1D found seven studies (all cross-sectional) assessing the impact of OSA in patients with T1D (131, 174). All the studies identified in the systematic review were of small sample size (< 100 patients) (167, 169); hence the true prevalence of OSA in T1D is still unknown. There is a need to examine whether patients with T1D are at increased risk of OSA similar to patients with T2D and to examine the relationship between OSA and diabetes-related complications in patients with T1D. Several mechanisms might make patients with T1D at increased risk of OSA despite the lack of obesity and the younger age, including the presence of autonomic neuropathy (135) which can affect ventilatory drive and upper airway stability during sleep (293).

Therefore, we aimed to assess:

1. The incidence/risk of developing OSA in patients with T1D compared to an appropriately matched control population.
2. The predictors of incident OSA in T1D population.

6.2 Methods

6.2.1 Study Design

Age, gender, GP practice and BMI matched controlled retrospective cohort study to estimate the risk of *developing* OSA among T1D patients compared to controls (without T1D). Further analysis to determine risk factors for OSA in the T1D exposed population. Refer to chapter 2 section 2.4 for general detailed methodology.

6.2.2 Exposed Cohort

The exposed cohort was identified as patients with T1D. T1D diagnosis was based on the presence of T1D Read Codes (Appendix 6.2) in the THIN database and the absence of any record of Type 2 Diabetes Mellitus (Appendix 6.3).

6.2.3 The unexposed cohort for the outcomes study

For each exposed patient, up to four controls were randomly selected from age, gender, GP practice, and BMI matched pool of patients without a record of diabetes (both type 1 and type 2). Multiple controls can be matched to each case to help increase the statistical power in order to increase the ability to detect an association if one exists. It was reported that the statistical power was greatly increased by including up to four controls per case; however, there is a little gain from having more than four controls per case (294-297). A two-step process achieved the exclusion of Type 2 patients in control and exposed groups. Firstly, we used type 2 diabetes read codes (Appendix 6.3) as an exclusion criterion during the selection process; therefore, any patient with these codes would be excluded. Secondly, during the preparation of the extracted data for analysis, we identified and removed patients (along with their matched controls) potentially with T2D rather than T1D in the exposed group as patients who are not using insulin and/or are using type 2 diabetes drugs (include Acarbose, DPP-4 inhibitors, Glitazones, Glinides, GLP-1 analogues, Sulphonylureas, or SGLT2 inhibitor). In addition, we identified

potential T2D patients in the control group as patients using insulin treatment and/or T2D drugs. Then we removed the identified T2D patients from the control group without removing the matched exposed because up to four controls were matched to each exposed patient (Appendix 6.2). We also removed controls with HbA1c > 47.5.

6.2.4 Follow-up period (the first cohort)

Index dates for T1D patients were the latest of the following: date of T1D diagnosis, or 12 months after the registration date of the patients with the practice, or 12 months after practice reporting the acceptable mortality rating (AMR), or 12 months after the VISION system implementation date. These conditions were used to ensure that the data extracted were of good quality. The unexposed patients were assigned the same index date as their corresponding exposed patient to avoid immortal time bias. The T1D and control patients were followed from the index date until the earliest of the following endpoints: OSA date, death date, the date they leave the practice, the date the practice ceases contributing to the database and the study end date.

Further validation measures of the index and exit dates were performed to ensure data quality. Before analysing the data, A) we ensured that registration dates, AMR dates, and computerisation of the GP dates were all before the index dates and B) that collection dates, death dates, and transfer dates were all after the index dates.

6.2.5 Outcomes

The primary outcome was OSA identified during follow-up based on Read Codes (Appendix 6.1). Patients with OSA at baseline were excluded from the outcome analysis of this study as the aim of this study was to look at the risk of *developing* OSA in patients with T1D.

6.3 Results:

6.3.1 Population characteristics:

This population-based study included 163,550 patients (34,147 T1D (cases) and 129,403 controls) who were not treated for T2D and were not diagnosed with OSA at or before the start of the study (Figure 6.1). Males account for 56.9% of the population. The mean (SD) age and BMI of this cohort were 38.39 years (17.62) and 25.82 kg/m^2 (4.33) at baseline, respectively. The exposed group (T1D; diagnosed on or before their index date) included 34,147 patients whereas the control group (without T1D) included 129,403 patients. The exposed and control groups were matched based on age, BMI, gender, and GP practice. Patients' sex, age, and BMI presented in Table 6.1 illustrate the successful matching of the two groups (exposed and control). Males in the control and exposed group were both slightly higher than females (56.88% and 56.91%, respectively; Table 6.1).

The two groups had similar proportions of smokers and Townsend score, but the control had a higher proportion of drinkers (Table 6.2). Even though ethnicity is missing more than half of the study population, more than 90% of the reported ethnicity were white European (Table 6.2).

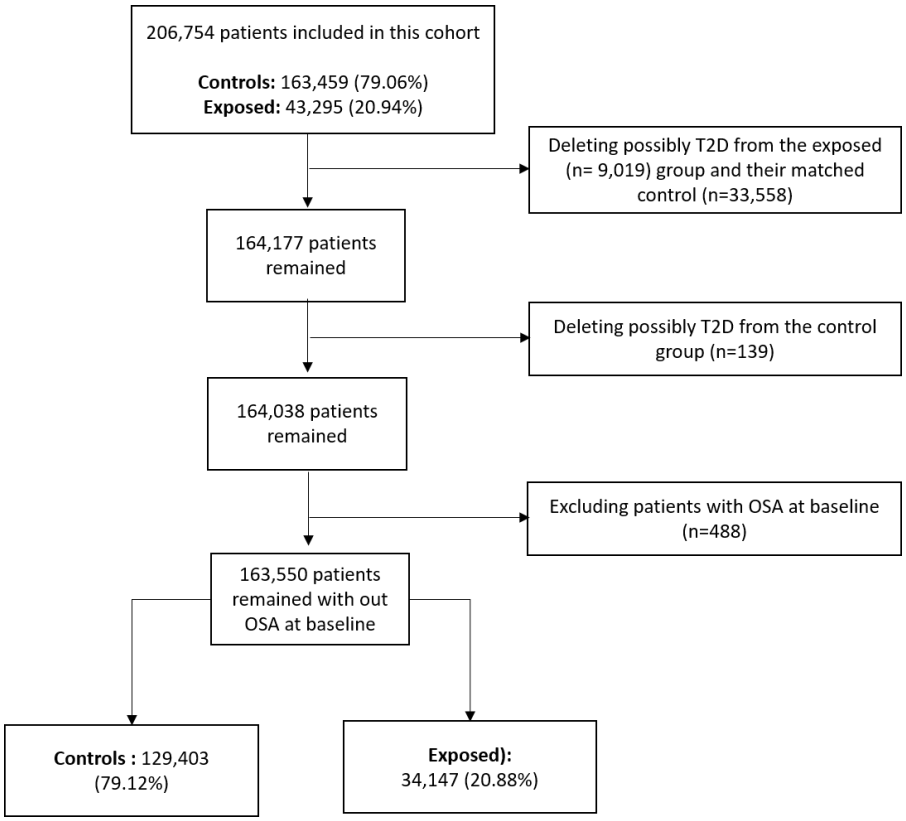

Figure 6.1 Flowchart of the data preparation to compare the incident of OSA in patients with and without T1D

Table 6.1. Baseline matched demographic variables in patients with T1D (exposed) and patients without T1D (control).

	Control	Exposed	Total
	129403 (79.12%)	34147 (20.88%)	163550 (100%)
Age (years), mean (SD)	38.34 (17.56)	38.59 (17.86)	38.39 (17.62)
Male, n (%)	73599 (56.88%)	19434 (56.91%)	93033 (56.88%)
BMI (kg/m2), mean (SD)	25.75 (4.18)	26.10 (4.82)	25.82 (4.33)
BMI categories, n (%)			
Underweight (<18.5)	796 (0.62%)	357 (1.05%)	1153 (0.70%)
Normal Weight (18.5-25)	47715 (36.87%)	12079 (35.37%)	59794 (36.56%)
Overweight (25-30)	38217 (29.53%)	9715 (28.45%)	47932 (29.31%)
Obese (>30)	15550 (12.02%)	4919 (14.41%)	20469 (12.52%)
No data	27125 (20.96%)	7077 (20.73%)	34202 (20.91%)

Data are reported as mean (SD; standard deviation) or number (n) of cases (%; percentage); BMI: body mass index.

Table 6.2. Baseline unmatched demographics in patients with T1D (exposed) and patients

	Control	Exposed	Total
	129403 (79.12%)	34147 (20.88%)	163550 (100%)
Smokers, n (%)			
Non-smokers	61750 (47.72%)	16851 (49.35%)	78601 (48.06%)
Discontinued Smoking	16873 (13.04%)	5033 (14.74%)	21906 (13.39%)
Smokers	28660 (22.15%)	7641 (22.38%)	36301 (22.20%)
No data	22120 (17.09%)	4622 (13.54%)	26742 (16.35%)
Alcohol intake, n (%)			
Non-Drinkers	15523 (12.00%)	5754 (16.85%)	21277 (13.01%)
Drinkers	73803 (57.03%)	17928 (52.50%)	91731 (56.09%)
Excessive Drinkers	4534 (3.50%)	1532 (4.49%)	6066 (3.71%)
No data	35543 (27.47%)	8933 (26.16%)	44476 (27.19%)
Townsend, n (%)			
1st (Least deprived)	27382 (21.16%)	6372 (18.66%)	33754 (20.64%)
2th Quintile	24078 (18.61%)	6042 (17.69%)	30120 (18.42%)
3th Quintile	24004 (18.55%)	6387 (18.70%)	30391 (18.58%)
4th Quintile	21513 (16.62%)	5929 (17.36%)	27442 (16.78%)
5th (Most deprived)	14828 (11.46%)	4313 (12.63%)	19141 (11.70%)
No data	17598 (13.60%)	5104 (14.95%)	22702 (13.88%)
Ethnicity, n (%)			
White	45504 (35.16%)	15750 (46.12%)	61254 (37.45%)
Black[1]	1267 (0.98%)	362 (1.06%)	1629 (1.00%)
South Asians	1850 (1.43%)	365 (1.07%)	2215 (1.35%)
Others[2]	419 (0.32%)	139 (0.41%)	558 (0.34%)
Mixed-Race	808 (0.62%)	130 (0.38%)	938 (0.57%)
No data	79555 (61.48%)	17401 (50.96%)	96956 (59.28%)

Data are reported as mean (SD; standard deviation) or number (n) of cases (%; percentage); Townsend: material deprivation score; [1]: Black including African and Caribbean [2]: Others including Chinese, Middle-Eastern.

6.3.2 Type 1 diabetes and the hazard ratio of OSA:

219 (0.64%) T1D and 531 (0.41%) control developed OSA by the end of the study. The unadjusted incidence rate was 10.37 in T1D and 6.10 in patients without T1D per 10,000

person-years. The Median [IQR] follow-up years were 4.81[1.80-9.59] and 5.60[2.32-10.24] for the exposed and control, respectively. Unadjusted hazard ratio (HR) in the primary cohort was 1.71 (95% CI: 1.46-2.00; p<0.001). Adjusted HR (aIRR) was 1.67 (95% CI: 1.42-1.95; p<0.001) adjusted for age, sex, body mass index categories, Townsend quintiles, and smoking status at baseline (model 1). Alcohol intake and Ethnicity had large percentages of unknown data. Therefore, their effects on regression model were tested (Model 2 and 3, respectively). Further adjustments were performed by including the variables in model 1 plus cardiovascular disease (CVD), hypertension, and atrial fibrillation at baseline (model 4). Model 4 adjustment had similar results to model 1 (HR: 1.67; 95% CI: 1.42-1.96; p<0.001). We found that median [IQR] diabetes duration in T1D with OSA was higher than T1D without OSA (19.36 [7.42-28.11] and 10.47 [2.56-21.17], respectively).

6.3.3 Sub-analysis:

A sub-analysis limited to patients who were less than 60 years old showed aHR of 1.61 (95% CI: 1.36-1.91; p<0.001). We further limited the analysis to patients less than 60 years old and diagnosed with diabetes before the age of 40 years old along with their corresponding control. The aHR then increased to 1.69 (95% CI: 1.41-2.02; p<0.001). Then we limited the analysis to people less than 40 years old, and the aHR dropped to 1.35 (95% CI: 1.03-1.76; p=0.03; Table 6.3).

Table 6.3 Cox proportional hazards models for the risk of T1D in developing OSA

	Total	No. of OSA	LH chi^2	HR	95% CI	p-value
Unadjusted	163,550	750	40.93	1.71	1.46-2.00	0.00
Model 1	163,550	750	698.08	1.67	1.42-1.95	0.00
Model 2	163,550	750	709.83	1.69	1.44-1.98	0.00
Model 3	163,550	750	708.62	1.64	1.40-1.92	0.00
Model 4	163,550	750	702.34	1.67	1.42-1.96	0.00
Sub-analysis						
Model 1A	142,875	669	695.40	1.61	1.36-1.91	0.00
Model 1B	129,292	568	609.58	1.69	1.41.2.02	0.00
Model 1C	94,742	286	348.17	1.35	1.03-1.76	0.03

Model 1: adjusted for age, sex, BMI categories, Townsend quintiles, smoking status; Model 2: Model 1 and alcohol intake; Model 3: Model 1 and ethnicity; Model 4: Model 1 plus CVD, hypertension, and atrial fibrillation; A: limited analysis to people who were < 60 years old at index date; B: limited analysis to the population who were < 60 years old at index date, and people diagnosed with T1D before the age of 40 along with their matched control; C: limited analysis to people who were <40 years old at the start. No: number; OSA: obstructive sleep apnoea; LH: likely-hood chi squired; CI: confidence interval.

6.3.4 Baseline HbA1c:

As HbA1c is used as an index of glycaemic control, as expected, this data was not available for about 98% of the control group. Interestingly, despite HbA1c being part of the routine monitoring of patients with T1D, this data was only available for 28% of the exposed group. The largest proportion of the exposed group was in the highest HbA1c level category (36%) (Table 6.4). By analysing HbA1c categories of the reported data for the exposed group, we found that 50% of the available HbA1c was in the highest level group (indicating poor glycaemic control) (Figure 6.2).

Table 6.4. Baseline HbA1c (glycaemic control) in patients with T1D (exposed) and patients without T1D (control)

	Control 129500 (79.13%)	Exposed 34147 (20.87%)	Total 163647 (100%)
HbA1c, n (%)			
≤ 48 mmol/mol	2643 (2.04%)	1911 (5.60%)	4554 (2.78%)
48-59 mmol/mol	0 (0%)	4664 (13.66%)	4664 (2.85%)
59-69 mmol/mol	0 (0%)	5755 (16.85%)	5755 (3.52%)
≥ 69 mmol/mol	0 (0%)	12331 (36.11%)	12331 (7.54%)
No data	126760 (97.96%)	9486 (27.78%)	136246 (83.31%)

Data are reported as number (n) of cases (%: percentage); HbA1c: Haemoglobin A1c.

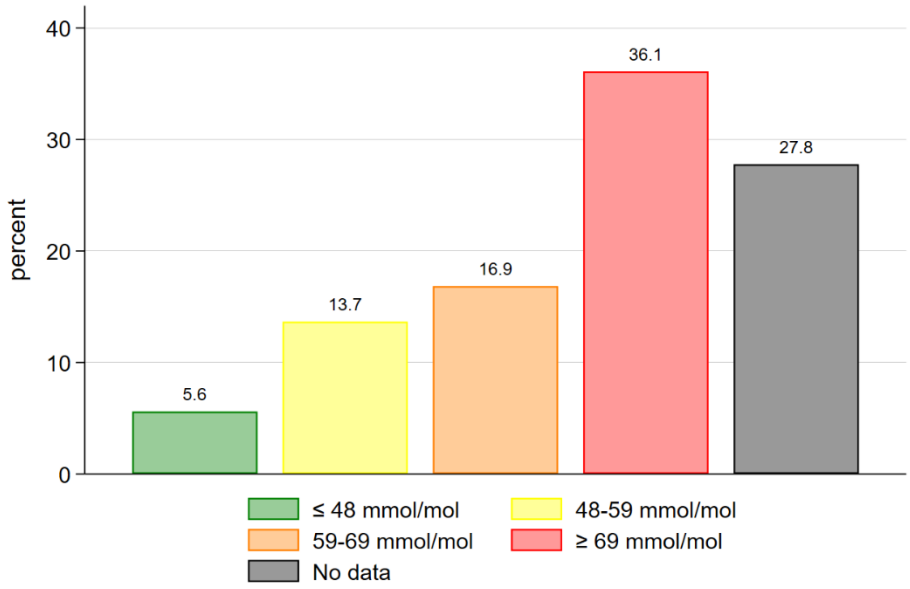

Figure 6.2 Categories of HbA1c (glycaemic control) for the exposed (T1D) This figure presents the data for T1D alone. The green bar represents low HbA1c. Bar colours change gradually as HbA1c level increases. Red bar represents high HbA1c, and the grey bar represent the missing data. Number on the top of the bars are reported in percent (%).

6.3.5 Baseline kidney function:

About 99% and 71% of ACR and eGFR data (respectively) were not reported for the control group, and again this is expected as patients without diabetes do not have their kidney function checked routinely. Even though ACR and eGFR are also part of the routine care for T1D, a large amount of data was missing (Table 6.4 and Table 6.5). About three-quarters of ACR data and a third of eGFR data were not reported for T1D (Figure 6.3 and Figure 6.4). The majority of the available data for ACR and eGFR reported normal ACR (0.37% and 18.45%) and eGFR (15.26% and 40.32%) in control and exposed respectively (Table 6.5).

Table 6.5 Baseline kidney function in patients with T1D (exposed) and patients without T1D (control).

		Control 129403 (79.12%)	Exposed 34147 (20.88%)	Total 163550 (100%)
ACR, n (%)				
	< 3	484 (0.37%)	6301 (18.45%)	6785 (4.15%)
	3 - 30	189 (0.15%)	1331 (3.90%)	1520 (0.93%)
	> 30	102 (0.08%)	334 (0.98%)	436 (0.27%)
	No data	128628 (99.40%)	26181 (76.67%)	154809 (94.66%)
eGFR, n (%)				
	>90 (Stage 1)	19744 (15.26%)	13769 (40.32%)	33513 (20.49%)
	60-90 (Stage 2)	15366 (11.87%)	7409 (21.70%)	22775 (13.93%)
	30-59(Stage 3)	2209 (1.71%)	1849 (5.41%)	4058 (2.48%)
	<30 (Stage 4)	137 (0.11%)	436 (1.28%)	573 (0.35%)
	No data	91947 (71.05%)	10684 (31.29%)	102631 (62.75%)

Data are reported as number (n) of cases (%; percentage); ACR: Albumin/creatinine ratio; eGFR: estimated glomerular filtration rate.

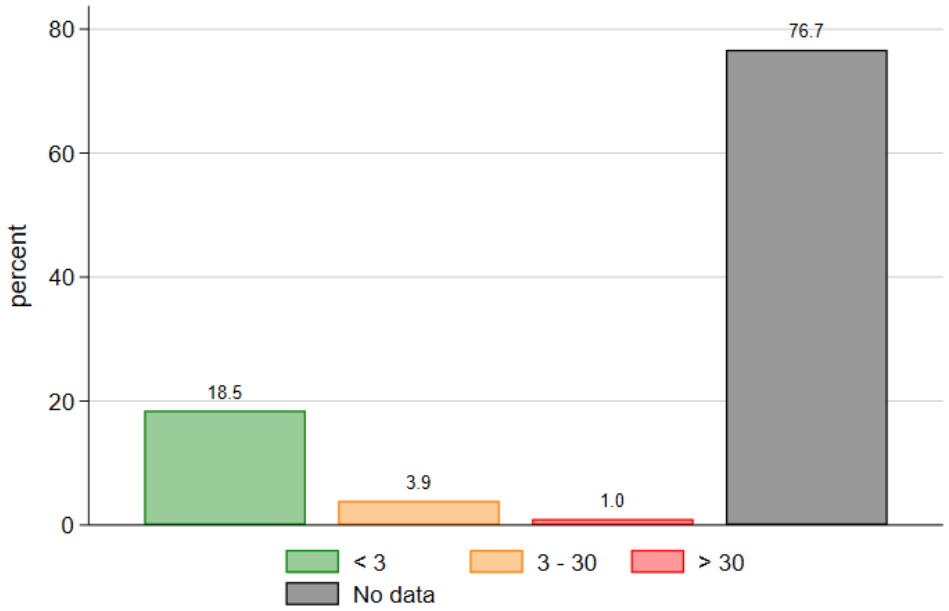

Figure 6.3 Categories distribution of ACR for the exposed (T1D) This figure presents the data for T1D alone. The green bar represents low ACR. Bar colours change gradually as ACR level increases. Red bar represents high ACR, and the grey bar represent the missing data. Number on the top of the bars are reported in percent (%).

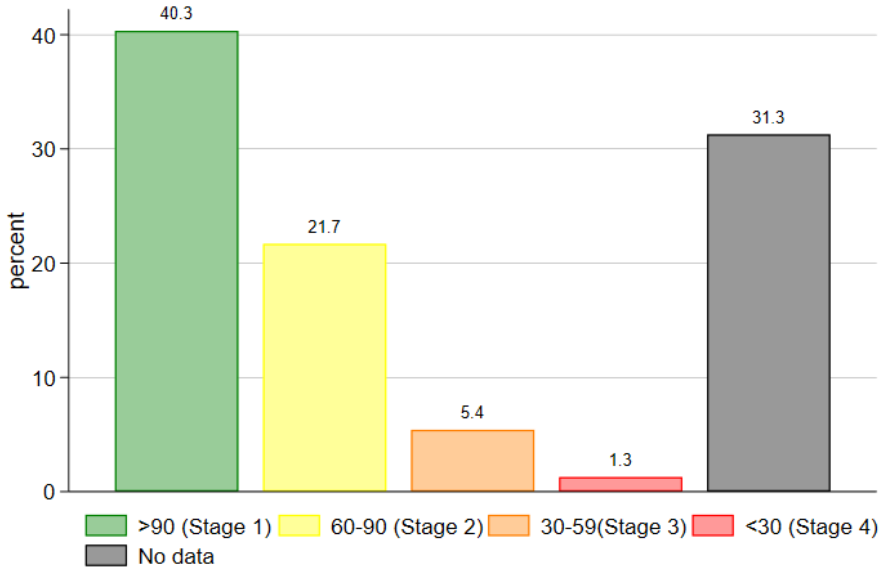

Figure 6.4 Categories distribution of eGRF for the exposed (T1D) This figure presents the data for T1D alone. The green bar represents high eGFR. Bar colours change gradually as eGFR level decreases. Red bar represents low eGFR, and the grey bar represent the missing data. Number on the top of the bars are reported in percent (%).

6.3.6 Baseline Drug use:

No patient in the cohort was using T2D drugs at baseline except metformin (1.46% of the cohort; Table 6.6), as T1D patients sometimes use it (298). Also, as shown in Table 6.6, there were higher percentages in the exposed group of patients who were using an ACE inhibitor, lipid-lowering, and primary antihypertension drugs at baseline (24.42% vs 5.38%, 25.38% vs 4.87%, and 31.55% vs 16.50%, respectively; p<0.001).

Table 6.6. Drugs used at baseline in patients with T1D (exposed) and patients without T1D (control).

	Control 129403 (79.12%)	Exposed 34147 (20.88%)	Total 163550 (100%)
Insulin	0 (0.00%)	34147 (100%)**	34147 (20.88%)
Metformin	201 (0.16%)	2181 (6.39%)**	2382 (1.46%)
Other DM drugs	0 (0.00%)	0 (0.00%)	0 (0.00%)
ACE inhibitor	6957 (5.38%)	8340 (24.42%)**	15297 (9.35%)
Lipid Lowering	6305 (4.87%)	8666 (25.38%)**	14971 (9.15%)
Antihypertensives	21354 (16.50%)	10774 (31.55%)**	32128 (19.64%)

Data are reported as number (n) of cases (%; percentage); Other DM Drugs include Acarbose, DPP-4 inhibitors, Glitazones, Glinides, GLP-1 analogues, Sulphonylureas, SGLT2 inhibitor. **: p <0.01; *: p <0.05.

6.3.7 Baseline comorbidities:

The percentage of baseline cardiovascular disease among T1D was double the percentage in the control group (7.70% vs 3.45%, respectively; p<0.001). Out of the list of cardiovascular diseases, we found that baseline heart failure, ischaemic heart disease (IHD), and stroke/TIA were more than two times higher in the exposed group as compared to the control. Hypoglycaemia, retinopathy, and foot disease are frequent in patients with diabetes. So, it is not surprising to see higher percentages in the exposed group. Baseline mental health conditions

show that anxiety and serious mental illness (SMI) did not differ much between the groups, but depression was slightly more in the exposed (Table 6.7). Hypertension at baseline was higher in the exposed group (16.87% vs 7.90%; p<0.001). However, the distribution of the baseline systolic and diastolic blood pressure were similar between exposed and controls (Table 6.8).

Table 6.7. Baseline comorbidities in patients with T1D (exposed) and patients without T1D (control)

	Control 129403 (79.12%)	Exposed 34147 (20.88%)	Total 163550 (100%)
cardiovascular disease	4461 (3.45%)	2629 (7.70%)**	7090 (4.34%)
Heart failure	561 (0.43%)	459 (1.34%)**	1020 (0.62%)
IHD	3050 (2.36%)	1798 (5.27%)**	4848 (2.96%)
Stroke and TIA	1459 (1.13%)	950 (2.78%)**	2409 (1.47%)
Hypertension	10221 (7.90%)	5761 (16.87%)**	15982 (9.77%)
Atrial fibrillation	945 (0.73%)	300 (0.88%)**	1245 (0.76%)
Hypoglycaemia	106 (0.08%)	5422 (15.88%)**	5528 (3.38%)
Retinopathy (RP)**			
No RP	128478 (99.29%)	29725 (87.05%)	158203 (96.73%)
R2, R3, M1	184 (0.14%)	2239 (6.56%)	2423 (1.48%)
Blindness, Laser, or Vitreous Injection	741 (0.57%)	2183 (6.39%)	2924 (1.79%)
Foot Disease	1112 (0.86%)	4104 (12.02%)**	5216 (3.19%)
Mental Health			
Anxiety	12990 (10.04%)	3172 (9.29%)**	16162 (9.88%)
Depression	19369 (14.97%)	6199 (18.15%)**	25568 (15.63%)
SMI	1497 (1.16%)	447 (1.31%)*	1944 (1.19%)

Data are reported as number (n) of cases (%; percentage); IHD: Ischaemic heart disease; TIA: transient ischemic attack; SMI: serious mental illness; According to NSC-UK grading, R2 is pre-proliferative, R3 is proliferative, M1 is maculopathy. Foot disease includes limb amputation, foot ulcer, gangrene, peripheral Neuropathy, and peripheral Vascular Disease. **: p <0.01; *: p <0.05.

Table 6.8. Baseline blood pressure level in patients with T1D (exposed) and patients without T1D (control).

	Control 129403 (79.12%)	Exposed 34147 (20.88%)	Total 163550 (100%)
Diastolic BP, n (%)			
< 50	900 (0.70%)	192 (0.56%)	1092 (0.67%)
50 - 59	2032 (1.57%)	1068 (3.13%)	3100 (1.90%)
60 - 69	15533 (12.00%)	5897 (17.27%)	21430 (13.10%)
70 - 79	35980 (27.80%)	11567 (33.87%)	47547 (29.07%)
80 - 89	37058 (28.64%)	9326 (27.31%)	46384 (28.36%)
90 - 99	8931 (6.90%)	2020 (5.92%)	10951 (6.70%)
100 - 109	1673 (1.29%)	332 (0.97%)	2005 (1.23%)
110 - 119	242 (0.19%)	68 (0.2%)	310 (0.19%)
120 - 129	49 (0.04%)	8 (0.02%)	57 (0.03%)
130 - 140	6 (0.00%)	6 (0.02%)	12 (0.01%)
No data	26999 (20.86%)	3663 (10.73%)	30662 (18.75%)
Systolic BP, n (%)			
< 80	612 (0.47%)	66 (0.19%)	678 (0.41%)
80 - 99	2287 (1.77%)	801 (2.35%)	3088 (1.89%)
100 - 119	28766 (22.23%)	8116 (23.77%)	36882 (22.55%)
120 - 139	48542 (37.51%)	13877 (40.64%)	62419 (38.17%)
140 - 159	18326 (14.16%)	5893 (17.26%)	24219 (14.81%)
160 - 179	3144 (2.43%)	1381 (4.04%)	4525 (2.77%)
180 <	744 (0.57%)	350 (1.02%)	1094 (0.67%)
No data	26982 (20.85%)	3663 (10.73%)	30645 (18.74%)

Data are reported as number (n) of cases (%; percentage); BP: blood pressure.

6.3.8 Risk factors for OSA in the T1D exposed population:

Further analysis was undertaken to determine risk factors at *baseline* for OSA in the T1D exposed population (Table 6.9). We found that one-year increase in age at diagnosis with T1D decreases the HR of developing OSA by 2%. Compared to people aged 20 to 30 years, HR is about 1.8 and 2.4 times higher in people who are 30 to 40 years old and 40 to 50 years old,

respectively. Males have 2.7 times increase in the hazard of developing OSA compared to their female counterparts. Overweight and obese had higher (1.8 and 6.2 folds, respectively) risk than underweight/normal weight in developing OSA. People using lipid-lowering drugs and antihypertensive drugs had 2.0 and 1.5 times increase the risk of developing OSA, respectively. People with atrial fibrillation and depression at baseline had 3.0 and 1.9 times, respectively, increase the risk for OSA (Figure 6.5).

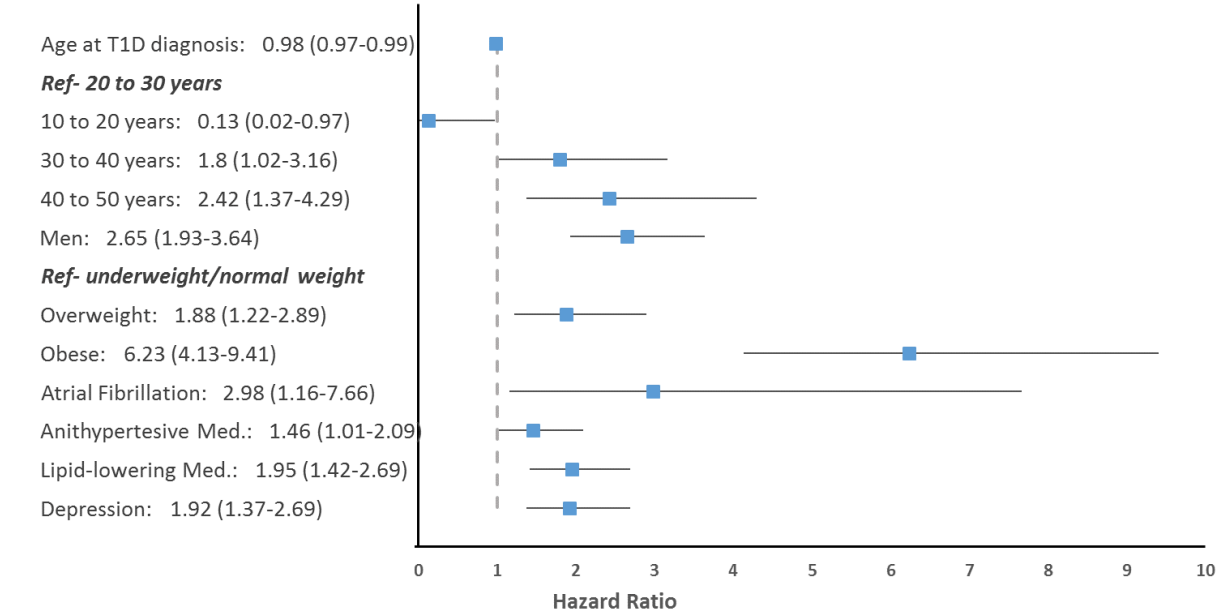

Figure 6.5 The predictors for OSA in the T1D exposed population. *The square present the HR point and the line illustrate the confidence interval. The vertical dotted line is the HR reference line of no effect. This figure presents the significant predictors. For a complete list see Table* ***6.9***

Table 6.9 The risk factors for OSA in the T1D exposed population

Predictors		HR	95% CI	P-value
Age at diagnosis		0.98	0.97-0.99	**0.001**
Age groups	20-30	Ref		
	0-10 years	0.51	0.11-2.38	0.395
	10 -20 years	0.13	0.02-0.97	0.047
	30 - 40 years	1.80	1.02-3.16	**0.042**
	40 - 50 years	2.42	1.37-4.29	**0.002**
	50 - 60 years	1.86	0.98-3.54	0.069
	60 - 70 years	1.91	0.90-4.03	0.092
	70 - max years	1.02	0.31-3.39	0.974
Sex	Female	Ref		
	Male	2.65	1.93-3.64	**0.000**
BMI Categories	Normal weight (< 25)	Ref		
	Overweight (25-30)	1.88	1.22-2.89	**0.004**
	Obese (>30)	6.23	4.13-9.41	**0.000**
	No data	1.83	1.04-3.22	**0.037**
Townsend	1st quintile	Ref		
	2	0.86	0.56-1.31	0.479
	3	0.79	0.51-1.22	0.286
	4	0.88	0.56-1.37	0.571
	5	0.94	0.56-1.53	0.797
	No data	1.25	0.81-1.93	0.319

Table 6.9 The risk factors for OSA in the T1D exposed population continued

Predictors		HR	95% CI	P-value
Hypoglycaemia		0.84	0.58-1.21	0.340
Foot Disease		1.04	0.72-1.49	0.843
RP Categories	No RP	Ref		
	R2, R3, M1	1.03	0.65-1.64	0.891
	Blind/Laser/ Vitreous injection	1.13	0.73-1.75	0.580
Lipid-lowering drugs		1.95	1.42-2.69	**0.000**
Antihypertensive drugs		1.46	1.01-2.09	**0.042**
Hear failure		1.59	0.54-4.71	0.405
IHD		0.71	0.40-1.24	0.224
Stroke and TIA		0.74	0.32-1.70	0.474
Hypertension		1.01	0.71-1.43	0.956
Atrial fibrillation		2.98	1.16-7.66	**0.024**
Depression		1.92	1.37-2.69	**0.000**
Anxiety		0.95	0.61-1.47	0.803
Serious mental illness (SMI)		1.12	0.45-2.81	0.803

Adjusted hazard ratios (aHR) and their corresponding 95% confidence intervals (Cis) were calculated using Cox regression.

6.4 Discussion:

Key points:

- T1D increases the incidence of OSA compared with the general population.
- The possible predictors of OSA in patients with T1D were younger age at T1D diagnosis, middle age, male gender, obesity, lipid-lowering and antihypertensive drugs, atrial fibrillation, and depression at baseline.

In this study, we examined the role of T1D in the incidence of OSA. We found that T1D leads to a 1.67-fold increase in the hazard of developing OSA compared to the general population, independent of potential confounding factors. Our estimated hazard was similar to the risk of

OSA in Taiwanese T1D patients (HR:1.65; 95% CI: 1.45-1.86) (299). Also, our results showed higher hazard of OSA in T1D (adjusted HR: 1.67; 95% CI: 1.46-2.00) compared with the hazard of OSA in T2D (adjusted IRR 1.36 (95% CI:1.30-1.42; p<0.001) as reported in a recently published UK population-based study (181).

As the early-onset of T1D usually occurs before the age of 40, we have conducted sensitivity analyses to investigate the effect of age at diagnosis on the incidence rate ratio of OSA (Table 6.3). Interestingly, the hazard ratio of OSA did not change when we limited the analysis to patients who were diagnosed with T1D before the age of 40, and their age was less than 60 years old — showing that patients with early-onset T1D had a higher risk of OSA. When we limited the analysis to patients who were less than 40 years old we found that hazard ratio was still significantly higher than controls but there was about 32% reduction compared to the unlimited analysis. In the risk factors analysis, the HR peaks in the 40 to 50 age group, and limiting the analysis to <40 years old excluded people with higher risk. So, this might explain the reduction in the risk. Both sensitivity analyses confirmed the essential role of long-lasting diabetes in developing OSA.

Baseline predictors

The results also identified possible predictors at baseline for developing OSA in T1D patients. These predictors added that younger age at diagnosis of diabetes, middle-age (30-50 years old), male sex, overweight and obesity, atrial fibrillation, depression, lipid-lowering drugs, and antihypertensive drugs increase the hazard of developing OSA in patients with T1D. Similarly, age, male sex, obesity, and depression were also identified as predictors for increasing the risk of OSA in T2D (181). Age, male sex, and BMI are established risk factors for OSA (300). There are also other risk factors including neck circumference, alcohol consumption (301), tonsil size, and Mallampati score (302) that has been reported to be stronger than age, sex, and BMI. These

airway measurements were not available in this study. However, we observed no relationship between alcohol consumption and incidence OSA even in excessive drinker group (Table 6.9).

Baseline depression

In our study, depression was the only mental illness which was an independent predictor for OSA in T1D. Several mental illnesses have been associated with OSA. A large USA retrospective study investigated the association between OSA and psychiatric disorders in 118,105 OSA out of more than 4 million records included in their study (303). According to this study, depression was the most common (22%) mental disorder in patients with OSA. The other mental disorders like anxiety, posttraumatic stress disorder, psychosis, and bipolar disorders were less common (17%, 12%, 5%, and 3%, respectively) (303). A systematic review has found that major depressive disorder is associated with increased prevalence of OSA (304). Another systematic review found that patients assessed pre- and post- CPAP therapy have shown that treating OSA had a significant improvement in depression, anxiety, excessive daytime sleepiness, and QoL (305). This association might also explain the reduced quality of life in our clinical cohort with OSA compared with T1D without OSA (see chapter 4: Table 5.9). OSA and depression shared similar symptoms such as daytime sleepiness, loss of energy, and poor concentration (306). Some studies suggested that OSA and depression were derived from similar mechanisms (305). These mechanisms include oxidative stress, HPA disturbance and neurotransmitter imbalance (83-85, 307-310).

Baseline atrial fibrillation:

We found that AF was a strong predictor of OSA in patients with T1D. The risk of AF was higher in patients with T1D (n=36258) than the general population in Sweden (n=179980), and the risk was higher in women (HR: 1·50; 95% CI: 1.30-1.72; p<0·01) than men (HR: 1.13; 95%

CI: 1.01–1.25; p=0·03) (311). Sleep disturbance has been linked to AF despite the presence or absence of OSA, and this link was suggested to be mediated by the decrease in rapid eye movement sleep based on three large USA databases (312). Several studies have reported a high prevalence of OSA in patients with AF (up to 85%) (313-316). OSA in patients with AF was associated with increased risk of hospitalisation (HR: 1.12; 95% CI; 1.03-1.22; P = 0.01) (313). Compared with treated OSA patients, untreated OSA group was associated with an increased risk of AF recurrence (317). A large study of more than 10,000 patients with AF found that CPAP reduced AF progression (HR: 0.66; 95% CI: 0.46-0.94; P = 0.02) (313). Also, a meta-analysis of 8 studies showed that CPAP treatment was associated with a 44% reduction of AF recurrence (318).

Several studies identified OSA as an independent risk factor for increased mortality and morbidity both in T2D and patients without diabetes. OSA has been found to increase fatal and non-fatal CVD (3, 288, 289) which were responsive to CPAP treatment (94, 182). Other studies had suggested OSA as an independent risk factor for diabetes-related complications (119, 120). The small number of T1D observational studies found that diabetic complications are associated with the presence of OSA. Therefore, it is probable that the relationship between OSA and diabetes-related complications in T1D people are a circular relationship where the presence of the complication makes the OSA worse, and the presence of OSA makes the complications worse.

Strengths and weakness

Our study is the first longitudinal study to investigate the role of T1D in the incidence of OSA in the UK population. Also, it is the first study that identified predictors of OSA in T1D patients. The strength of our study is that we used a rigorous methodology to identify the risk of developing OSA in T1D patients. Also, we used a strict process to exclude T2D patients from

both T1D group and controls because T2D might be a confounding factor to OSA and diabetes-related complications. We matched for common risk factors for OSA (age, sex, and BMI). We also matched GP practices to ensure that patients in the exposed and control groups receive similar health care. The weakness of this study is that we rely on diagnoses codes entered by GP practices. Therefore, we could not analyse the severity of OSA nor examine the other sleep study parameters.

In summary, we found an increased risk of incidence OSA in patients with T1D compared with the general population. We also found that younger age at T1D diagnosis, middle age, male gender, obesity, lipid-lowering and antihypertensive drugs, atrial fibrillation, and depression at baseline were predictors of OSA in patients with T1D. Further longitudinal studies are needed to investigate the effect of OSA on the development of cardiovascular diseases. Therefore, we have conducted a retrospective study in chapter 6 to assess the association between OSA and cardiovascular complications in patients with T1D.

6.5 Appendices:

Appendix 6.1. Read Codes used to identify patients with obstructive sleep apnoea.

Read code	Description
Fy03.00	Sleep apnoea
Fy03.11	Obstructive sleep apnoea
Fy04.11	Ondine's curse
H5B..00	Sleep apnoea
H5B0.00	Obstructive sleep apnoea
R005100	[D]Insomnia with sleep apnoea
R005300	Hypersomnia with sleep apnoea
R005311	[D]Sleep apnoea syndrome
R005312	[D]Syndrome sleep apnoea
R060400	[D]Apnoea

Appendix 6.2. Read Codes used to identify patients with type 1 diabetes

Read Codes	description
C100000	Diabetes mellitus, juvenile type, no mention of complication
C100011	Insulin dependent diabetes mellitus
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
C104000	Diabetes mellitus, juvenile type, with renal manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C106000	Diabetes mellitus, juvenile, + neurological manifestation
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C107300	IDDM with peripheral circulatory disorder
C108.00	Insulin dependent diabetes mellitus
C108.11	IDDM-Insulin dependent diabetes mellitus
C108.12	Type 1 diabetes mellitus
C108.13	Type I diabetes mellitus
C108000	Insulin-dependent diabetes mellitus with renal complications
C108011	Type I diabetes mellitus with renal complications
C108012	Type 1 diabetes mellitus with renal complications
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C108111	Type I diabetes mellitus with ophthalmic complications
C108112	Type 1 diabetes mellitus with ophthalmic complications
C108200	Insulin-dependent diabetes mellitus with neurological comps
C108211	Type I diabetes mellitus with neurological complications
C108212	Type 1 diabetes mellitus with neurological complications
C108300	Insulin dependent diabetes mellitus with multiple complicatn

Read Codes	description
C108311	Type I diabetes mellitus with multiple complications
C108312	Type 1 diabetes mellitus with multiple complications
C108400	Unstable insulin dependent diabetes mellitus
C108411	Unstable type I diabetes mellitus
C108412	Unstable type 1 diabetes mellitus
C108500	Insulin dependent diabetes mellitus with ulcer
C108511	Type I diabetes mellitus with ulcer
C108512	Type 1 diabetes mellitus with ulcer
C108600	Insulin dependent diabetes mellitus with gangrene
C108611	Type I diabetes mellitus with gangrene
C108612	Type 1 diabetes mellitus with gangrene
C108700	Insulin dependent diabetes mellitus with retinopathy
C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C108800	Insulin dependent diabetes mellitus - poor control
C108811	Type I diabetes mellitus - poor control
C108812	Type 1 diabetes mellitus - poor control
C108900	Insulin dependent diabetes maturity onset
C108911	Type I diabetes mellitus maturity onset
C108912	Type 1 diabetes mellitus maturity onset
C108A00	Insulin-dependent diabetes without complication
C108A11	Type I diabetes mellitus without complication
C108A12	Type 1 diabetes mellitus without complication
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C108B11	Type I diabetes mellitus with mononeuropathy
C108B12	Type 1 diabetes mellitus with mononeuropathy
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
C108C11	Type I diabetes mellitus with polyneuropathy
C108C12	Type 1 diabetes mellitus with polyneuropathy
C108D00	Insulin dependent diabetes mellitus with nephropathy
C108D11	Type I diabetes mellitus with nephropathy
C108D12	Type 1 diabetes mellitus with nephropathy
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E11	Type I diabetes mellitus with hypoglycaemic coma
C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
C108F00	Insulin dependent diabetes mellitus with diabetic cataract
C108F11	Type I diabetes mellitus with diabetic cataract
C108F12	Type 1 diabetes mellitus with diabetic cataract
C108G00	Insulin dependent diab mell with peripheral angiopathy
C108G11	Type I diabetes mellitus with peripheral angiopathy
C108G12	Type 1 diabetes mellitus with peripheral angiopathy
C108H00	Insulin dependent diabetes mellitus with arthropathy
C108H11	Type I diabetes mellitus with arthropathy

Read Codes	description
C108H12	Type 1 diabetes mellitus with arthropathy
C108J00	Insulin dependent diab mell with neuropathic arthropathy
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C10C.12	Maturity onset diabetes in youth type 1
C10E.00	Type 1 diabetes mellitus
C10E.11	Type I diabetes mellitus
C10E.12	Insulin dependent diabetes mellitus
C10E000	Type 1 diabetes mellitus with renal complications
C10E011	Type I diabetes mellitus with renal complications
C10E012	Insulin-dependent diabetes mellitus with renal complications
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E200	Type 1 diabetes mellitus with neurological complications
C10E211	Type I diabetes mellitus with neurological complications
C10E212	Insulin-dependent diabetes mellitus with neurological comps
C10E300	Type 1 diabetes mellitus with multiple complications
C10E311	Type I diabetes mellitus with multiple complications
C10E312	Insulin dependent diabetes mellitus with multiple complicat
C10E400	Unstable type 1 diabetes mellitus
C10E411	Unstable type I diabetes mellitus
C10E412	Unstable insulin dependent diabetes mellitus
C10E500	Type 1 diabetes mellitus with ulcer
C10E511	Type I diabetes mellitus with ulcer
C10E512	Insulin dependent diabetes mellitus with ulcer
C10E600	Type 1 diabetes mellitus with gangrene
C10E611	Type I diabetes mellitus with gangrene
C10E612	Insulin dependent diabetes mellitus with gangrene
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10E800	Type 1 diabetes mellitus - poor control
C10E811	Type I diabetes mellitus - poor control
C10E812	Insulin dependent diabetes mellitus - poor control
C10E900	Type 1 diabetes mellitus maturity onset
C10E911	Type I diabetes mellitus maturity onset
C10E912	Insulin dependent diabetes maturity onset
C10EA00	Type 1 diabetes mellitus without complication
C10EA11	Type I diabetes mellitus without complication
C10EA12	Insulin-dependent diabetes without complication
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10EB11	Type I diabetes mellitus with mononeuropathy

Read Codes	description
C10EB12	Insulin dependent diabetes mellitus with mononeuropathy
C10EC00	Type 1 diabetes mellitus with polyneuropathy
C10EC11	Type I diabetes mellitus with polyneuropathy
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
C10ED00	Type 1 diabetes mellitus with nephropathy
C10ED11	Type I diabetes mellitus with nephropathy
C10ED12	Insulin dependent diabetes mellitus with nephropathy
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE11	Type I diabetes mellitus with hypoglycaemic coma
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10EF00	Type 1 diabetes mellitus with diabetic cataract
C10EF11	Type I diabetes mellitus with diabetic cataract
C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
C10EG11	Type I diabetes mellitus with peripheral angiopathy
C10EG12	Insulin dependent diab mell with peripheral angiopathy
C10EH00	Type 1 diabetes mellitus with arthropathy
C10EH11	Type I diabetes mellitus with arthropathy
C10EH12	Insulin dependent diabetes mellitus with arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C10EJ11	Type I diabetes mellitus with neuropathic arthropathy
C10EJ12	Insulin dependent diab mell with neuropathic arthropathy
C10EK00	Type 1 diabetes mellitus with persistent proteinuria
C10EK11	Type I diabetes mellitus with persistent proteinuria
C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
C10EL11	Type I diabetes mellitus with persistent microalbuminuria
C10EM00	Type 1 diabetes mellitus with ketoacidosis
C10EM11	Type I diabetes mellitus with ketoacidosis
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C10EN11	Type I diabetes mellitus with ketoacidotic coma
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10EQ00	Type 1 diabetes mellitus with gastroparesis
C10EQ11	Type I diabetes mellitus with gastroparesis
C10P000	Type I diabetes mellitus in remission
C10P011	Type 1 diabetes mellitus in remission
C10y000	Diabetes mellitus, juvenile, + other specified manifestation
C10z000	Diabetes mellitus, juvenile type, + unspecified complication

Appendix 6.3. Read Codes used to identify patients with type 2 diabetes

List of type 2 diabetes Read Codes						
C100100	C109112	C109900	C109F11	C10F111	C10FB11	C10FM00
C100112	C109200	C109911	C109F12	C10F200	C10FC00	C10FM11
C101100	C109211	C109912	C109G00	C10F211	C10FC11	C10FN00
C102100	C109212	C109A00	C109G11	C10F300	C10FD00	C10FN11
C103100	C109300	C109A11	C109G12	C10F311	C10FD11	C10FP00
C104100	C109311	C109A12	C109H00	C10F400	C10FE00	C10FP11
C105100	C109312	C109B00	C109H11	C10F411	C10FE11	C10FQ00
C106100	C109400	C109B11	C109H12	C10F500	C10FF00	C10FQ11
C107100	C109411	C109B12	C109J00	C10F511	C10FF11	C10FR00
C107400	C109412	C109C00	C109J11	C10F600	C10FG00	C10FR11
C109.00	C109500	C109C11	C109J12	C10F611	C10FG11	C10P100
C109.11	C109511	C109C12	C109K00	C10F700	C10FH00	C10P111
C109.12	C109512	C109D00	C10D.00	C10F711	C10FH11	C10y100
C109.13	C109600	C109D11	C10D.11	C10F811	C10FJ00	C10z100
C109000	C109611	C109D12	C10F.00	C10F900	C10FJ11	
C109011	C109612	C109E00	C10F.11	C10F911	C10FK00	
C109012	C109700	C109E11	C10F000	C10FA00	C10FK11	
C109100	C109711	C109E12	C10F011	C10FA11	C10FL00	
C109111	C109712	C109F00	C10F100	C10FB00	C10FL11	

CHAPTER SEVEN: THE IMPACT OF OBSTRUCTIVE SLEEP APNOEA IN PATIENTS WITH TYPE 1 DIABETES: A POPULATION-BASED RETROSPECTIVE COHORT STUDY

Contribution: Ziyad Alshehri contributed to the design of the study. I gratefully acknowledge the support of Dr Krish Nirantharakumar team (Anuradhaa Subramanian, Krishna Gokhale, and Nicola Adderley) from Institute of Applied Health Research who helped me with the initial stages of the study. They carried out the data extraction from the THIN database. I carried out the data cleaning and performed the data analysis with help advice provided by Miss Anuradhaa Subramanian, and writing this chapter.

7.1 Background

As detailed in previous chapters, OSA was common in patients with T1D and associated with cardiovascular complications. Our systematic review (chapter 2) shows an association between OSA and several diabetes-related microvascular complications such as diabetic autonomic neuropathy, retinopathy, nephropathy and peripheral neuropathy. In chapter 3 and 4, we used rigorous methodology and OSA definition (respiratory evets index: REI ≥ 5 events/hour with involuntary daytime sleepiness or REI ≥ 15 with or without excessive daytime sleepiness). Our findings such as cardiac autonomic neuropathy (adjusted OR: 7.8; 95% 1.4 – 44.4; p=0.02) agreed with the published literature explored in chapter 2 (the systematic review), but contradicted the findings with regards to peripheral neuropathy, nephropathy, and retinopathy.

We found in chapter 5 that T1D increased the risk of incidence OSA. However, no study has investigated the impact of OSA on type 1 diabetes-related vascular diseases. As previously discussed (see chapter 5), OSA has been associated with an increased risk of fatal and non-fatal cardiovascular complications in people without diabetes. Hence there is a need to examine the relationship between OSA and diabetes-related complications in patients with T1D. We hypothesised that OSA has an impact on the diabetes-related micro- and macro- vascular complications in T1D.

Therefore, we aimed to assess:

- The impact of OSA on the diabetes-related vascular disease (macro and micro) in T1D patients with OSA compared to an appropriately matched control T1D population without OSA.

A secondary outcome would be mental health as we found in chapter 4 and 5 an association between OSA and depression and anxiety.

7.2 Methods

7.2.1 Study Design

This is a retrospective cohort study. This study was developed to estimate the risk of *developing* vascular outcomes among concurrently diagnosed T1D and OSA patients compared to T1D patients without OSA. Refer to chapter 2 section 2.4 for general detailed methodology.

7.2.2 Exposed Cohort

The exposed cohort was identified as patients with a **concurrent** diagnosis of T1D *and* OSA without the concern of their temporality. In the previous chapter we were looking for T1D who then developed OSA, which contrasts with what we are looking for here which is the development of vascular complications in patients with OSA and T1D, no matter what order they were developed, compared with T1D alone. T1D and OSA were identified using Read Codes (appendices 5.1 and 5.2 in chapter 5).

7.2.3 Unexposed cohort for the outcomes study

For each exposed patient, up to four controls were randomly selected from age, gender, and BMI matched pool of T1D patients *without* a record of OSA. Patients with potential T2D rather than T1D were excluded using the process explained in the previous chapter.

7.2.4 Follow-up period

The index date for the exposed cohort was the latest of T1D and OSA diagnosis because we required the exposed group to have both diabetes and OSA at the start of the study. Therefore, the order of the diagnosis is not important for this project. The unexposed diabetes patients were assigned the same index date as their corresponding case. Follow-up was until the earliest of

following endpoints: outcome under consideration, death date, the date they left the practice, the date the practice ceased contributing to the database and the study end date.

7.2.5 Outcomes

The primary outcome was a composite of any cardiovascular disease (ischaemic heart disease, stroke or TIA, and heart failure). Secondary outcomes included each of the cardiovascular disease outcomes separately and microvascular complications, such as sight-threatening retinopathy, nephropathy and peripheral neuropathy separately. Read Codes used to indentify baseline and outcome variables were listed in Appendix 7.1. All outcomes were part of disease registers general practices are expected to maintain as per the Quality Outcome Framework. For each of the outcome analyses, patients with outcomes at baseline were excluded.

7.3 Results:

7.3.1 Patients' characteristics:

This population-based study included 1,622 patients (483 T1D with OSA (exposed) and 1,139 (controls); Figure 7.1). The exposed and control groups were matched based on age, BMI, and sex. Patients' sex, age, and BMI, presented in Table 7.1, illustrate the successful matching of the two groups (exposed and control). Both groups were not treated for T2D. Males accounted for 79.4% of the population and did not differ between study groups. The mean (SD) age and BMI of this cohort were 49.6 years (13.9) and 31.6 kg/m^2 (6.1) at baseline, respectively (Table 7.1). Age and BMI mean differences were –2.3 years and – 2.8 kg/m^2 between groups ($p<0.01$). However, this was expected as the variation fell within the variation limit (± 3 units) we used when we matched for age and BMI. Although the slight difference in the large dataset could show a significant statistical difference, we found that diabetes duration, HbA1c, Townsend score, ethnicity, and drinking status were similar between groups (Table 7.2 and Table 7.3). Although about half the study did not report ethnicity, the majority of those who reported ethnicity were white European.

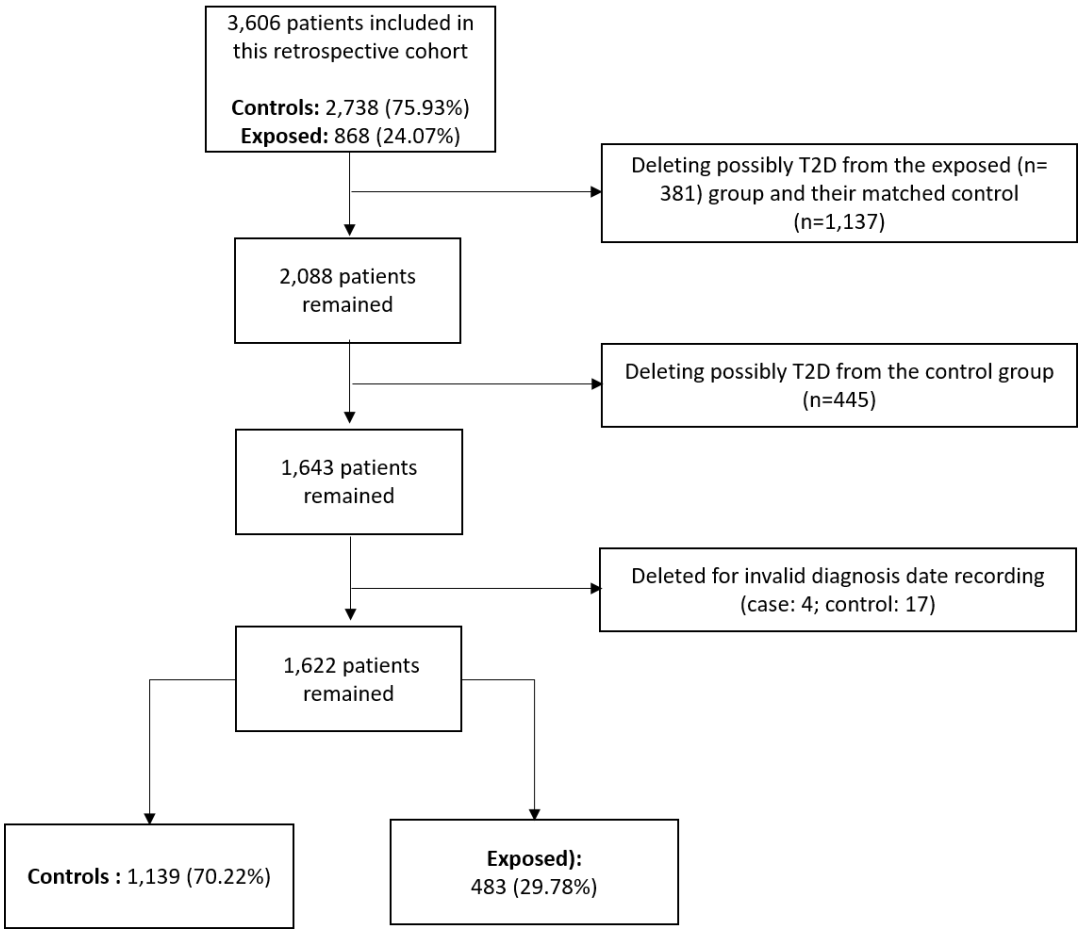

Figure 7.1 Flowchart of the data preparation to compare the impact of OSA in patients with T1D.

Table 7.1. Baseline matched demographic variables in T1D with OSA (exposed) and patients with T1D only (control).

	Control 1,139 (70.22%)	Exposed 483 (29.78%)	Total 1,622 (100%)
Age (years), mean (SD)**	48.9 (13.7)	51.3 (14.3)	49.6 (13.9)
Male, n (%)	913 (80.2%)	374 (77.4%)	1,287 (79.4%)
BMI (kg/m^2), mean (SD) **	30.8 (5.3)	33.6 (7.3)	31.6 (6.1)
BMI categories, n (%) **			
Underweight (<18.5)	3 (0.3%)	1 (0.2%)	4 (0.3%)
Normal Weight (18.5-25)	138 (12.1%)	37 (7.7%)	175 (10.8%)
Overweight (25-30)	371 (32.6%)	118 (24.4%)	489 (30.2%)
Obese (>30)	564 (49.5%)	286 (59.2%)	850 (52.4%)
No data	63 (5.5%)	41 (8.5%)	104 (6.4%)

Data are reported as mean (SD; standard deviation) or number (n) of cases (%; percentage); BMI: body mass index.

Table 7.2. Baseline unmatched demographics in T1D with OSA (exposed) and patients with T1D only (control)

	Control 1,139 (70.2%)	Exposed 483 (29.8%)	Total 1,622 (100%)
Diabetes Duration median [IQR]	18.5 (13.3)	19.0 (15.1)	18.7 (13.9)
Smokers, n (%)*			
Non-smokers	575 (50.5%)	228 (47.2%)	803 (49.5%)
Discontinued Smoking	306 (26.9%)	167 (34.6%)	473 (29.2%)
Smokers	209 (18.4%)	69 (14.3%)	278 (17.1%)
No data	49 (4.3%)	19 (3.9%)	68 (4.2%)
Alcohol intake, n (%)			
Non-drinkers	26 (2.3%)	19 (3.9%)	45 (2.8%)
Drinkers	174 (15.3%)	82 (17.0%)	256 (15.8%)
Excessive Drinkers	82 (7.2%)	31 (6.4%)	113 (7.0%)
No data	857 (75.2%)	351 (72.7%)	1208 (74.5%)
Townsend, n (%)			
1st (Least deprived)	248 (21.8%)	90 (18.6%)	338 (20.8%)
2th Quintile	218 (19.1%)	92 (19.1%)	310 (19.1%)
3th Quintile	226 (19.8%)	80 (16.6%)	306 (18.9%)
4th Quintile	177 (15.5%)	82 (17.0%)	259 (16.0%)
5th (Most deprived)	127 (11.2%)	59 (12.2%)	186 (11.5%)
No data	143 (12.6%)	80 (16.6%)	223 (13.8%)
Ethnicity, n (%)			
White	530 (46.5%)	248 (51.4%)	778 (48.0%)
Black[1]	11 (1.0%)	7 (1.5%)	18 (1.1%)
South Asians	7 (0.6%)	8 (1.7%)	15 (0.9%)
Others[2]	1 (0.1%)	0 (0%)	1 (0.1%)
Mixed-Race	6 (0.5%)	4 (0.8%)	10 (0.6%)
No data	584 (51.3%)	216 (44.7%)	800 (49.3%)

Data are reported as mean (SD; standard deviation) or number (n) of cases (%; percentage); Townsend: material deprivation score; [1]: Black including African and Caribbean [2]: Others including Chinese, Middle-Eastern.

7.3.2 Baseline clinical measures and comorbidities:

Unlike the previous chapter, there was better reporting of HbA1c in this dataset. HbA1c was available for more than 86% of the cohort, and there was no significant difference between exposed and control groups (Table 7.3). However, more than one-third of the control and exposed groups has HbA1c ≥ 69.4 mmol/mol.

Insulin use and other DM drugs confirmed the success in excluding patients who might have T2D. Compared with control, we also found that more patients in the exposed group were on

Metformin (25.8% vs 36.9%; p<0.001), lipid-lowing (67.2% vs 73.3%; p=0.015), ACE-inhibitor (56.4% vs 66.9%; p<0.001), and antihypertensive drugs (62.4% vs 74.3%; P<0.001; Table 7.3).

Not all microvascular complications were associated with OSA at baseline. Baseline CKD stages based on eGFR calculation showed that more than 76% of the population were on stage 2 or above (normal to mild CKD) at baseline (Table 7.3). Pearson chi^2 test showed significant differences between eGFR stages between T1D with and without OSA (p<0.01). However, we ran a test of proportions to identify the stages where the two groups differ, and we found that more controls had eGFR ≥ 60 (Stage 2 or better) compare with exposed (78.7% vs 68.9%; p<0.01). The other stages were similar between groups.

Similarly, the percentage of control with ACR < 3 were 41.6% compared with 34.0% in the exposed group (Table 7.3). Baseline ACR categories were significantly different between the two groups using Pearson chi^2 test (p<0.01), however, the test of proportions to identify the exact categories with significant difference showed no significant statistical difference between groups in all categories.

Baseline CKD (stages 3 to 5) based on read codes was higher in patients with T1D and OSA (Table 7.4), and the odds of baseline CKD (stages 3 to 5) were about two times higher for the OSA group (OR:1.9; 95% CI: 1.4-2.7; p<0.001).

Baseline peripheral neuropathy and sight-threatening retinopathy were present in 25.1% and 29.0% of the population, respectively (Table 7.4). The exposed group had increased risk of baseline peripheral neuropathy (OR: 1.29; 95% CI: 1.02-1.64; p=0.036) compared with controls. However, baseline sight-threatening retinopathy was not different between T1D with and without OSA.

Baseline cardiovascular disease, including heart failure, ischemic heart disease (IHD), stroke and transient ischemic attack (TIA) were increased in T1D with OSA (Table 7.4). Baseline heart failure, IHD, and stroke/TIA results were combined in one cardiovascular variable to assess the association of cardiovascular disease in the presence and absence of OSA. The odds of baseline cardiovascular disease in T1D with OSA was two times higher than T1D without OSA (OR: 2.0; 95% CI: 1.5-2.6; p<0.001). Baseline assessment of each cardiovascular disease showed that the OSA group had higher risk of heart failure (OR: 1.9; 95% CI: 1.1-3.3; p=0.028), IHD (OR: 1.8; 95% CI: 1.3-2.4; p<0.001), and stroke/TIA (OR: 2.4; 95% CI: 1.5-3.7; p<0.001) compared to patients with T1D without OSA.

Baseline hypertension and atrial fibrillation were also higher in patients with T1D and OSA (Table 7.4). The odds of baseline hypertension and atrial fibrillation were 1.6 (95% CI: 1.3-2.0; p<0.001) and 3.1 (95% CI: 1.7-5.6; p<0.001) in T1D with OSA, respectively.

Diabetic foot disease was identified if patients had either limb amputation, foot ulcer, or gangrene diagnoses. As shown in Table 7.4 baseline diabetic foot disease was present in 9.1% of the population, and it was higher in T1D with OSA compared with T1D without OSA, and the odds of diabetic foot disease was 1.8 (95% CI: 1.2-2.6; p=0.002) higher in patients with T1D and OSA.

Baseline mental health shows that anxiety and depression present in 7.8% and 19.9% of the population, and it was higher in T1D with OSA compared to T1D without OSA (Table 7.4). The odds of baseline anxiety and depression were 2.1 (95% CI: 1.4-3.0; p<0.001) and 2.2 (95% CI: 1.7-2.8; p<0.001) in T1D with OSA, respectively. Serious mental illness (SMI), however, was present in 2.6%, and it was similar in T1D with and without OSA.

Table 7.3 baseline clinical measures in patients with T1D and OSA (exposed) and patients with T1D only (control)

	Control 1,139 (70.2%)	Exposed 483 (29.8%)	Total 1,622 (100%)
HbA1c, n (%)			
≤ 48 mmol/mol	84 (7.4%)	27 (5.6%)	111 (6.8%)
48-59 mmol/mol	210 (18.4%)	84 (17.4%)	294 (18.1%)
59-69 mmol/mol	277 (24.3%)	117 (24.2%)	394 (24.3%)
≥ 69 mmol/mol	415 (36.4%)	186 (38.5%)	601 (37.1%)
No data	153 (13.4%)	69 (14.3%)	222 (13.7%)
eGFR, n (%) **			
≥ 60 (≥ Stage 2)	896 (78.7%)	333 (68.9%)	1229 (75.8%)
30-59(Stage 3)	99 (8.7%)	66 (13.7%)	165 (10.2%)
<30 (Stage 4)	33 (2.9%)	21 (4.4%)	54 (3.3%)
No data	111 (9.8%)	63 (13.0%)	174 (10.7%)
ACR, n (%) **			
< 3	474 (41.62%)	164 (33.95%)	638 (39.33%)
3-30	93 (8.17%)	60 (12.42%)	153 (9.43%)
> 30	39 (3.42%)	19 (3.93%)	58 (3.58%)
No data	533 (46.8%)	240 (49.69%)	773 (47.66%)
Insulin	1139 (100%)	483 (100%)	1622 (100%)
Metformin	294 (25.8%)	178 (36.9%) **	472 (29.1%)
Other DM drugs	0 (0%)	0 (0%)	0 (0%)
Lipid Lowering	765 (67.2%)	354 (73.3%) *	1119 (69.0%)
ACE-inhibitor	642 (56.4%)	323 (66.9%) **	965 (59.5%)
Antihypertensive	711 (62.4%)	359 (74.3%) **	1070 (66.0%)

Data are reported as number (n) of cases (%; percentage); HbA1c: Haemoglobin A1c; eGFR: estimated glomerular filtration rate; ACR: albumin/creatinine ratio; Other DM Drugs include Acarbose, DPP-4 inhibitors, Glitazones, Glinides, GLP-1 analogues, Sulphonylureas, SGLT2 inhibitor. **: $p < 0.01$; *: $p < 0.05$.

Table 7.4. Baseline comorbidities in T1D with OSA (exposed) and patients with T1D only (control)

	Control 1,139 (70.2%)	Exposed 483 (29.8%)	Total 1,622 (100%)
cardiovascular disease	164 (14.4%)	120 (24.8%) **	284 (17.5%)
Heart failure	28 (2.5%)	22 (4.6%) *	50 (3.1%)
IHD	127 (11.2%)	89 (18.4%) **	216 (13.3%)
Stroke and TIA	45 (4.0%)	43 (8.9%) **	88 (5.4%)
Hypertension	449 (39.4%)	246 (50.9%) **	695 (42.9%)
Atrial fibrillation	20 (1.8%)	25 (5.2%) **	45 (2.8%)
PVD	46 (4.0%)	28 (5.8%)	74 (4.6%)
Hyperthyroidism	27 (2.4%)	11 (2.3%)	38 (2.3%)
Hypoglycaemia	240 (21.1%)	97 (20.1%)	337 (20.8%)
Peripheral Neuropathy	269 (23.6%)	138 (28.6%) *	407 (25.1%)
Sight-threatening RP	332 (29.2%)	139 (28.8%)	471 (29.0%)
CKD (stages 3 to 5)	91 (8.0%)	69 (14.3%) **	160 (9.9%)
Diabetic Foot Disease	89 (7.8%)	59 (12.2%) **	148 (9.1%)
Mental Health			
Anxiety	69 (6.1%)	57 (11.8%) **	126 (7.8%)
Depression	181 (15.9%)	141 (29.2%) **	322 (19.9%)
SMI	26 (2.3%)	16 (3.3%)	42 (2.6%)

Data are reported as number (n) of cases (%; percentage); IHD: Ischaemic heart disease; TIA: transient ischemic attack; SMI: serious mental illness; Foot disease includes amputations, ulcers, and gangrenes. **: $p < 0.01$; *: $p < 0.05$.

7.3.3 Risk of incident CVD in T1D with and without OSA

Cardiovascular disease (CVD) here is the combination of heart failure, ischemic heart disease (IHD), and stroke/TIA combined into one variable. The date associated with the earliest event was used to calculate the follow-up time if a patient had more than one of these complications.

Cardiovascular disease (CVD)

1,275 (27.4% had T1D and OSA) patients were included for this analysis after excluding 284 patients with CVD at baseline and 63 patients with invalid data. Median [IQR] follow-up time was 3.13 years [1.27-6.01]. The crude incidence rate of CVD was higher in T1D with OSA (30.4 incidence rate per 1,000 person-years) compared with T1D without OSA (14.0 incidence rate per 1,000 person-years). T1D patients with OSA had about 80% increase in the risk of incidence CVD (adjusted HR: 1.76; 95% CI: 1.16 to 2.67; $p = 0.008$) after adjusting for

potential baseline confounding characteristics (including age categories, sex, BMI categories, smoking status, Townsend categories, diabetes duration, HbA1c categories, and eGFR categories), drug used (lipid-lowering, ACE-inhibitor, and antihypertensive drugs), and comorbidities (hypertension and atrial fibrillation; Table 7.5).

Table 7.5 Crude and adjusted hazard ratio for association of cardiovascular disease (CVD) with obstructive sleep apnoea in patients with T1D

	CVD	
	Exposed	Unexposed
No. of patients	349 (27.37%)	926 (72.63%)
Outcome events, n (%)	45	57
Person-years	1481.05	4080.45
Incidence rate of CVD per 1,000 person-years	30.38 (22.69 to 40.69)	13.97 (10.78 to 18.11)
Hazard ratio (95% CI)		
Unadjusted:	2.17 (1.47 to 3.22); P-value <0.001	
Model 1:	1.84 (1.21 to 2.78); P-value =0.004	
Model 2:	1.82 (1.20 to 2.75); P-value =0.005	
Model 3:	1.76 (1.16 to 2.67); P-value =0.008	

Model 1: adjusted for baseline age categories, sex, BMI categories, smoking status, Townsend categories, diabetes duration, HbA1c categories, and eGFR categories.
Model 2: model 1 plus baseline use of lipid-lowering, ACE-inhibitor, and antihypertensive drugs.
Model 3: model 2 plus baseline hypertension and atrial fibrillation.

Heart failure

In a separate analysis of heart failure, 1,503 (29.5% had T1D and OSA) patients were included for this analysis after excluding 50 patients with heart failure at baseline and 69 patients with invalid data. Median [IQR] follow-up time was 3.46 years [1.49-6.64]. The crude incidence rate of heart failure was higher in T1D with OSA (13.6 incidence rate per 1,000 person-years) compared with T1D without OSA (4.2 incidence rate per 1,000 person-years). T1D patients with OSA had about 2.4 times increase in the risk of incident heart failure (adjusted HR: 2.34; 95% CI: 1.26 to 4.36; p =0.008) after adjusting for same potential confounding factors described above (Table 7.6).

Table 7.6 Crude and adjusted hazard ratio for association of heart failure with obstructive sleep apnoea in patients with T1D

	Heart failure	
	Exposed	Unexposed
No. of patients	443 (29.47%)	1,060 (70.53%)
Outcome events, n (%)	27	20
Person-years	1981.89	4784.93
Incidence rate of heart failure per 1,000 person-years	13.62 (9.34 to 19.87)	4.18 (2.7 to 6.48)
Hazard ratio (95% CI)		
Unadjusted:	3.23 (1.81 to 5.76); P-value <0.001	
Model 1:	2.59 (1.41 to 4.76); P-value =0.002	
Model 2:	2.40 (1.29 to 4.47); P-value =0.006	
Model 3:	2.34 (1.26 to 4.36); P-value =0.007	

Model 1: adjusted for baseline age categories, sex, BMI categories, smoking status, Townsend categories, diabetes duration, HbA1c categories, and eGFR categories.
Model 2: model 1 plus baseline use of lipid-lowering, ACE-inhibitor, and antihypertensive drugs.
Model 3: model 2 plus baseline hypertension and atrial fibrillation.

Ischaemic heart disease (IHD)

Regarding IHD, 1,338 (28.2% had T1D and OSA) patients were included for this analysis after excluding 216 patients with IHD at baseline and 68 patients with invalid data. Median [IQR] follow-up time was 3.34 years [1.40-6.35]. Similar to the above cardiovascular complications, the crude incidence rate of IHD was higher in T1D with OSA (18.2 incidence rate per 1,000 person-years) compared with T1D without OSA (7.3 incidence rate per 1,000 person-years). T1D patients with OSA had about two times increase in the risk of incidence IHD (adjusted HR: 1.95; 95% CI: 1.13 to 3.34; p =0.016) after adjusting for same potential confounding described above (Table 7.7).

Table 7.7 Crude and adjusted hazard ratio for association of ischemic heart disease (IHD) with obstructive sleep apnoea in patients with T1D

	IHD	
	Exposed	Unexposed
No. of patients	377 (28.18%)	961 (71.82%)
Outcome events, n (%)	30	31
Person-years	1652.72	4239.15
Incidence rate of IHD per 1,000 person-years	18.15 (12.69 to 25.96)	7.31 (5.14 to 10.4)
Hazard ratio (95% CI)		
Unadjusted:	2.50 (1.51 to 4.14); P-value <0.001	
Model 1:	2.09 (1.22 to 3.56); P-value =0.007	
Model 2:	2.03 (1.19 to 3.47); P-value =0.009	
Model 3:	1.95 (1.13 to 3.34); P-value =0.016	

Model 1: adjusted for baseline age categories, sex, BMI categories, smoking status, Townsend categories, diabetes duration, HbA1c categories, and eGFR categories.
Model 2: model 1 plus baseline use of lipid-lowering, ACE-inhibitor, and antihypertensive drugs.
Model 3: model 2 plus baseline hypertension and atrial fibrillation.

Stroke or transient ischemic attack (TIA)

Regarding stroke or TIA, 1,468 (28.9% had T1D and OSA) patients were included for this analysis after excluding 88 patients with stroke or TIA at baseline and 66 patients with invalid data. Median [IQR] follow-up time was 3.41 [1.14-5.51]. Our data showed a similar incidence rate of stroke or TIA in T1D with or without OSA (7.2 vs 7.5 incidence rate per 1,000 person-years; p=0.457, respectively). Unlike the above cardiovascular complications, unadjusted Cox regression analysis showed that OSA did not affect the hazard of incident stroke or TIA in patients with T1D (unadjusted HR: 0.97; 95% CI: 0.52 to 1.80; p =0.918).

7.3.4 Risk of incidence of other cardiovascular complications in T1D with and without OSA

Hypertension

874 (25.6% had T1D and OSA) patients were included for this analysis after excluding 695 patients with hypertension at baseline and 53 patients with invalid data. Median [IQR] follow-up time was 3.09 years [1.27-5.83]. 68 patients in the control and 19 patients in the exposed developed hypertension. Interestingly, our data showed no significant difference in the incidence rate of hypertension between T1D with or without OSA (20.0 vs 25.8 incidence rate per 1,000 person-years; p=0.164, respectively). This was also supported using the Cox regression analysis. Unadjusted Cox regression analysis showed that OSA did not affect the hazard of incidence hypertension in patients with T1D (unadjusted HR: 0.79; 95% CI: 0.48 to 1.32; p =0.368).

Atrial fibrillation (AF)

1,503 (29.2% had T1D and OSA) patients were included for this analysis after excluding 45 patients with AF at baseline and 68 patients with invalid data. Median [IQR] follow-up time was 3.47 [1.53-6.67]. The crude incidence rate of AF was higher in T1D with OSA (7.02 incidence rate per 1,000 person-years) compared with T1D without OSA (3.1 incidence rate per 1,000 person-years). Unadjusted HR showed an increased risk of OSA (unadjusted HR: 2.30; 95% CI: 1.11 to 4.76; P-value =0.025). The HR remained high, but no longer significant after adjusting for baseline age categories, sex, BMI categories, smoking status, Townsend categories, ethnicity, diabetes duration, HbA1c categories, ACR categories, drinking status, and eGFR categories (p=0.06; Table 7.8).

Table 7.8 Crude and adjusted hazard ratio for association of atrial fibrillation (AF) with obstructive sleep apnoea in patients with T1D

	AF	
	Exposed	Unexposed
No. of patients	440 (29.16%)	1,069 (70.84%)
Outcome events, n (%)	14	15
Person-years	1993.4	4817.2
Incidence rate of AF per 1,000 person-years	7.02 (4.16 to 11.86)	3.11 (1.88 to 5.17)
Hazard ratio (95% CI)		
Unadjusted:	2.30 (1.11 to 4.76); P-value =0.025	
Model 1:	2.11 (0.97 to 4.61); P-value =0.060	

Model 1: adjusted for baseline age categories, sex, BMI categories, smoking status, Townsend categories, diabetes duration, HbA1c categories, and eGFR categories.

Peripheral vascular disease (PVD)

1,479 (29.6% had T1D and OSA) patients were included for this analysis after excluding 74 patients with PVD at baseline and 69 patients with invalid data. Median [IQR] follow-up time was 3.47 years [1.51-6.63]. The crude incidence rate of PVD was higher in T1D with OSA (8.5 incidence rate per 1,000 person-years) compared with T1D without OSA (2.6 incidence rate per 1,000 person-years). We found that OSA increased the hazard of incidence PVD in patients with T1D patients with OSA after adjustment for several confounding factors listed in Table 7.9. The adjusted HR for incidence PVD was 2.73 (95% CI: 1.24 to 5.99; p =0.012).

Table 7.9 Crude and adjusted hazard ratio for association of peripheral vascular disease (PVD) with obstructive sleep apnoea in patients with T1D

	PVD	
	Exposed	Unexposed
No. of patients	437 (29.55%)	1,042 (70.45%)
Outcome events, n (%)	17	12
Person-years	1996.1	4685.4
Incidence rate of PVD per 1,000 person-years	8.52 (5.29 to 13.70)	2.56 (1.45 to 4.51)
Hazard ratio (95% CI)		
Unadjusted:	3.23 (1.54 to 6.79); P-value =0.002	
Model 1:	2.81 (1.30 to 6.10); P-value =0.009	
Model 2:	2.63 (1.21 to 5.73); P-value =0.015	
Model 3:	2.73 (1.24 to 5.99); P-value =0.012	

Model 1: adjusted for baseline age categories, sex, BMI categories, smoking status, Townsend categories, diabetes duration, HbA1c categories, and eGFR categories.
Model 2: model 1 plus baseline use of lipid-lowering, ACE-inhibitor, and antihypertensive drugs.
Model 3: model 2 plus baseline hypertension and atrial fibrillation.

Diabetic foot disease

Diabetic foot disease which includes ulcers, gangrenes and amputation were also assessed. 1,408 (28.9% had T1D and OSA) patients were included for this analysis after excluding 148 patients with diabetic foot disease at baseline and 66 patients with invalid data. Median [IQR] follow-up time was 3.28 years [1.36-6.33]. Sixty-one patients in the control and 29 patients in the exposed developed diabetic foot during the follow-up time. Interestingly, our data showed no significant difference in the incidence rate of diabetic foot disease between T1D with or without OSA (15.5.0 vs 13.8 incidence rate per 1,000 person-years; p=0.301, respectively). Unadjusted Cox regression analysis showed that OSA did not affect the hazard of incidence diabetic foot in patients with T1D (unadjusted HR: 1.10; 95% CI: 0.70 to 1.71; p =0.687).

7.3.5 Risk of incident microvascular complications in T1D with and without OSA

Chronic kidney disease (CKD) stages 3 to 5 based on Read Codes

1,397 (28.5% had T1D and OSA) patients were included for this analysis after excluding 160 patients with CKD stages 3 to 5 at baseline and 65 patients with invalid data. Median [IQR] follow-up time was 3.21 [1.35-6.07]. The crude incidence rate of CKD was higher in T1D with OSA (27.5 incidence rate per 1,000 person-years) compared with T1D without OSA (16.4 incidence rate per 1,000 person-years). OSA increased the risk of incident CKD in patients with T1D (HR: 1.54; 95% CI: 1.00 to 2.15; P-value =0.049) after adjusting for baseline age categories, sex, BMI categories, smoking status, Townsend categories, diabetes duration, HbA1c categories, and eGFR categories. The hazard remained significant after adding baseline AF to the Cox model (HR: 1.47; CI 95%: 1.00 to 2.14; P-value = 0.049). However, HR was no longer significant after including the use of ACE-inhibitor, antihypertensive, and lipid-lowering drugs (Table 7.10).

Table 7.10 Crude and adjusted hazard ratio for association of chronic kidney disease (CKD) stages 3 to 5 with obstructive sleep apnoea in patients with T1D

	CKD	
	Exposed	Unexposed
No. of patients	398 (28.49%)	999 (71.51%)
Outcome events, n (%)	48	72
Person-years	1743.2	4390.3
Incidence rate of CKD per 1,000 person-years	27.54 (20.75 to 36.54)	16.40 (13.02 to 20.66)
Hazard ratio (95% CI)		
Unadjusted:	1.69 (1.17 to 2.43); P-value =0.005	
Model 1:	1.47 (1.00 to 2.15); P-value =0.049	
Model 2:	1.37 (0.88 to 1.90); P-value =0.196	
Model 3:	1.43 (0.97 to 2.10); P-value =0.069	
Model 3a:	1.47 (1.00 to 2.14); P-value =0.049	

Model 1: adjusted for baseline age categories, sex, BMI categories, smoking status, Townsend categories, diabetes duration, HbA1c categories, and eGFR categories.
Model 2: model 1 plus baseline use of lipid-lowering, ACE-inhibitor, and antihypertensive drugs.
Model 3: model 1 plus atrial fibrillation and hypertension.
Model 3a: model 1 plus atrial fibrillation.

Sight-threatening retinopathy

1,107 (25.6% had T1D and OSA) patients were included for this analysis after excluding 471 patients with sight-threatening retinopathy at baseline and 44 patients with invalid data. Median [IQR] follow-up time was 2.78 [1.49-6.57]. Interestingly, our analysis showed no significant difference in the incidence rate of sight-threatening retinopathy between T1D with or without OSA (40.0 vs 31.0 incidence rate per 1,000 person-years; p=0.064, respectively). This was also supported using the Cox regression analysis. Unadjusted Cox regression analysis showed that OSA did not affect the hazard of incident sight-threatening retinopathy in patients with T1D (unadjusted HR: 1.29; 95% CI: 0.93 to 1.78; p =0.129).

7.3.6 Risk of incident depression and other mental health disorders in T1D with and without OSA

1,250 (26.7% had T1D and OSA) patients were included for this analysis after excluding 322 patients with depression at baseline and 50 patients with invalid data. Median [IQR] follow-up time was 3.13 years [1.36-6.12]. The crude incidence rate of depression was higher in T1D with OSA (19.2 incidence rate per 1,000 person-years) compared with T1D without OSA (10.6 incidence rate per 1,000 person-years). We found that OSA increased the hazard of incident depression in patients with T1D patients with OSA after adjustment for several confounding factors listed in Table 7.11. The proportional-hazards assumption test showed a violation of the Cox models for analysing depression ($p<0.05$). Therefore, these violations were corrected by stratifying the age groups using *strata* function on STATA ($p=0.853$). The average adjusted HR for incidence depression was 1.80 (95% CI: 1.09 to 2.98; $p =0.023$; Table 7.11). We also analysed anxiety and serious mental illness. However, found no increased risk of incidence anxiety (unadjusted HR: 1.63; 95% CI: 0.85 to 3.15; $p=0.142$) and serious mental illness (unadjusted HR: 1.59; 95% CI: 0.45 to 5.65; $p=0.470$) in T1D with and without OSA.

Table 7.11 Crude and adjusted hazard ratio for association of depression with obstructive sleep apnoea in patients with T1D

	Depression	
	Exposed	Unexposed
No. of patients	334 (26.72%)	916 (73.28%)
Outcome events, n (%)	28	43
Person-years	1456.2	4072.7
Incidence rate of CKD per 1,000 person-years	19.23 (13.28 to 27.85)	10.56 (7.83 to 14.24)
Hazard ratio (95% CI)		
Unadjusted:	1.84 (1.15 to 2.97); P-value =0.012	
Model 1s:	1.88 (1.14 to 3.10); P-value =0.013	
Model 2s:	1.87 (1.13 to 3.07); P-value =0.014	
Model 3s:	1.80 (1.09 to 2.98); P-value =0.023	

Model 1: adjusted for baseline age categories, sex, BMI categories, smoking status, Townsend categories, diabetes duration, HbA1c categories, and eGFR categories.
Model 2: model 1 plus baseline use of lipid-lowering, ACE-inhibitor, and antihypertensive drugs.
Model 3: model 2 plus baseline hypertension and atrial fibrillation.
s: stratified (all models stratified by age categories).

7.4 Discussion:

Key points

- Patients with T1D and OSA had worse health and QoL at baseline than patients with T1D alone.
- Patients with T1D and OSA had an increased risk of incidence of CVD compared with T1D alone.
- Patients with T1D and OSA had an increased risk of incidence of microvascular complications compared with T1D alone.
- Patients with T1D and OSA had an increased risk of incidence of depression compared with T1D alone.

We have investigated the impact of OSA on diabetes-related vascular disease using a large GP database (THIN) to produce a longitudinal study. We have used a rigorous methodology to ensure we could perform a good quality analysis that could be generalised to patients with T1D. We have excluded patients with possible T2D, as explained in the previous chapter (see chapter 5), as these co-morbidities have already been thoroughly investigated and presence of T2D is linked to several vascular diseases (319-322). We have found that OSA in patients with T1D was associated with several comorbidities at baseline, and we explored the directional relationship between OSA and vascular complications and mental health. These finding are discussed below.

One of the strengths of our study is the number of similar characteristics between exposed and control groups that could otherwise influence the results. Although we matched for age, BMI, and sex, the two groups also had similar diabetes duration, HbA1C, Townsend score, ethnicity, and drinking status.

Baseline characteristics

As mentioned above, baseline analysis presented many characteristics that were similar between exposed (T1D and OSA) and control groups (T1D only) including diabetes duration, HbA1c, sex, and hypoglycaemia. Some of these characteristics, such as diabetes duration and HbA1c are known to increase the risk of diabetes-related complications in T1D (24, 49, 56, 234). Although the exposed group were slightly older and had higher BMI, this was not concerning for a few reasons. We were trying to match up to four controls for each exposed, and it was impossible to find four exact matches based on age and BMI. Therefore, we have used a code to look up control matches who were three units higher or lower than the exposed (see Table 7.1). Surprisingly, about 30% and 52% of the study population were overweight and obese, respectively which could indicate an increase in the levels of obesity among T1D.

Baseline comorbidities and vascular complications

More people in the exposed group had diabetes-related complications (including macrovascular and microvascular complications) than controls at baseline. The percentage of people with CVD, neuropathy, CKD, diabetic foot disease, atrial fibrillation, and hypertension was higher in the exposed group. As mentioned above diabetes duration and hyperglycaemia were linked to several diabetes-related complications. However, our two groups had similar diabetes duration and HbA1c despite having long-lasting diabetes and large proportion of them had high HbA1c (37% had HbA1c $\geq$ 69mmol/mol; see Table 7.3). So, this suggests that OSA may independently increase the risk of developing diabetes-related complications.

It was expected to find more people in the exposed group using antihypertensive, lipid-lowering, and ACE-inhibitor drugs. Therefore, many of these drugs, HbA1c, and diabetes duration were part of the variables included to the regression models for the incidence analysis. Interestingly, more people in the exposed used metformin compared with controls (37% vs

26%, respectively). Increased use of metformin could suggest an association between OSA and insulin resistance. This suggestion agreed with increased use of insulin dosages we found in the clinical study (see chapter 4).

In addition, we did not find any difference in STDR between the exposed and control groups at baseline which is consistent with our finding in chapter 4. There might be an impact of OSA on retinopathy as we observed a correlation between retinopathy and OSA parameters in chapter 4. However, early intervention due to the routine eye examination for T1D and early diagnosis of retinopathy that might reduce the progression of retinopathy to Sight-threatening retinopathy.

Baseline Mental health

Interestingly, at baseline, the exposed group was associated with anxiety and depression suggesting worse QoL. Four findings are consistent with recently published findings of the National Survey on Drug Use and Health in the USA. This study examined the mental health of 264,653 participants (3.3% had sleep apnoea), and found that people with sleep apnoea had increased odds of anxiety (OR: 2.9; 95% CI: 2.6 to 3.2) and depression (OR: 3.1; 95% CI: 2.8 to 3.5) (323). However, many studies have linked anxiety and depression to T1D (324, 325). Therefore, it is surprising to find worse mental health in the exposed group which suggest an additional negative impact of OSA on T1D mental health.

Incidences of vascular complications:

Before discussing the results pertaining to the incidence of various comorbidities in the two study groups, it is important to highlight that patients who had the outcome of interest (e.g. heart failure, IHD etc) at baseline were excluded from the analysis to make sure only patients that *developed* the outcome of interest after study the study commenced were included in the analysis. Our study has shown that, over a relatively short follow up duration (~3+ years), OSA was associated with several vascular complications.

Cardiovascular complications:

OSA was associated with increasing the risk of incidence of CVD in T1D patients. After excluding patients with CVD at baseline, we found that OSA increased the hazard of incident CVD by 78% compared with T1D without OSA. Interestingly, further analysis of CVD elements according to our definition (see the methods) showed that the risk of heart failure and IHD increase by 2.4 and 2.0-fold, respectively, after adjusting for all potential confounding factors. Having similar association between OSA and IHD and heart failure is not surprising as IHD is the most common cause of heart failure. However, contrary to this, we found no association with stroke and TIA.

OSA also led to increased incidence of PVD in T1D. Both IHD and PVD share common risk factors such as hyperglycaemia, hypertension, obesity, and dyslipidaemia, and inflammation (326-329). However, we have adjusted for many of these risk factors and more (see Table 7.7 & Table 7.9). Similar to IHD, PVD is characterised by narrowing of vascular lumen leading to reduction blood flow and therefore reduction in oxygen supply (326). The increased risk of IHD and PVD highlights the damaging role of OSA to vasculature of the heart and the peripheral extremities.

Although many mechanisms are proposed to explain the relationship between OSA and cardiovascular complications such as oxidative stress, sympathetic activation, and altering intrathoracic pressure (330), intrathoracic pressure change during apnoea episodes likely play an important role in the development of heart diseases. In an animal study to examine the impact of OSA on left ventricular performance, four dogs underwent tracheostomy to stimulate airway occlusion during sleep. It was found that left ventricular ejection fraction decreased from 58% ±3 before airway occlusions to 51%±3 ($p< 0.05$) (331), which is suggestive of a mechanical

effect of the apnoeas on the heart performance. Also, a one month CPAP treatment plus medical therapy for patients with OSA and reduced left ventricular ejection fraction (n=12) compared with medical therapy only (n=12) showed that CPAP group had an increased left ventricular ejection fraction and reduced blood pressure and heart rate; where patients located on medical therapy only had no statistical change (332). Further discussion of the mechanisms by which T1D and OSA precipitate cardiovascular disease can be found in the final chapter of this thesis (see General Discussion).

Despite finding an association between OSA and atrial fibrillation at baseline, unadjusted incidence of atrial fibrillation was significantly higher in the exposed group. However, this relationship did not remain significant after adjusting for potential confounding factors. Compared to the general population, T1D has been found to increase the risk of atrial fibrillation according to recent large Swedish population study (311). Also, several studies have described the relationship between OSA and atrial fibrillation. OSA has been found to be common among patients with atrial fibrillation (62-88%) (316, 333). Indeed, patients with severe sleep-disordered breathing (RDI $\geq$ 30) had about a four-fold increase in the risk of nocturnal atrial fibrillation compared with patients without normal sleep breathing (RDI<5) (334); and CPAP treatment was linked to lower atrial fibrillation recurrence (317). Therefore, it is possible OSA events induce sleep cardiac arrhythmia via nocturnal hypoxemia or the alteration in intrathoracic pressure.

We found no difference in the incidence of hypertension between T1D with and without OSA despite having a high proportion of hypertensive patients at baseline and the high incidence rates of hypertension in both T1D and OSA patients. At baseline, 66% were on antihypertensive drugs, and about 43% were diagnosed with hypertension. Also, about 10% developed hypertension during the follow-up period. Hypertension is an important risk factor for

cardiovascular disease (335-337). A large cross-sectional study of 422 patients with resistant hypertension found that 82% had AHI ≥ 5 and 56% had AHI ≥ 15. A recent study of 47 patients with untreated OSA found that the severity of OSA correlated with serum matrix metalloproteinase-9 (MMP-9), which is a marker of extracellular matrix degradation (338). In a study of non-hypertensive people (n=595), it was found that people with detectable MMP-9 had approximately a two-fold risk of progressing to the higher blood pressure category (339). These results suggest that OSA might play a role in vasculature remodelling.

It is also proposed that a chronic increase in blood pressure exerts a force on the vascular system leading to compromised vasodilatory function or reduced lumen, due to issues such as endothelial dysfunction or lipid accumulation; these changes result in tissue damage (340). Therefore, it is important to emphasise that we controlled for both baseline hypertension and antihypertensive drugs in model 2 of the Cox analysis to correct for the impact of hypertension on the other vascular complications.

Microvascular complications

Incidence of CKD (stages 3 to 5) was about 47% higher in exposed group compared with control. The adjusted regression model remained significant, however, the regression model became no longer significant after adding antihypertensive, ACE-inhibitors, and lipid-lowering drugs to the regression model. Unlike the incidence of CKD, the incidence of sight-threatening retinopathy was similar between the exposed and control. As OSA was linked to the remodelling of the coronary and peripheral vascular, it is possible that OSA alters the blood vessels supplying the kidney leading to the development or progression to advanced stages of CKD (341).

In summary, this is the first study to determine the directional impact of OSA in T1D patients with regard to the development of heart failure, IHD, PVD, and CKD. We also determined the

impact of OSA in the incidence of depression. At baseline, we observed increased micro- and macrovascular complications and worse mental health which indicates that OSA is associated with worse health and QoL in T1D. Further longitudinal studies are needed to investigate the impact of treating OSA in reducing the risk of vascular complications onsets in patients with T1D and this is discussed further in the final chapter of this thesis.

7.5 Appendices:

Appendix 7.1 list of Read codes

Variable	Code list												
Anxiety	1466	8CAZ000	8HHp.00	E200.00	E200000	E200200	E200300	E200400	E200500	E200z00	E202.12	E292000	E2D0.00
	E2D0z00	Eu05400	Eu34114	Eu40.00	Eu40y00	Eu40z00	Eu41.00	Eu41000	Eu41100	Eu41111	Eu41112	Eu41113	Eu41200
	Eu41211	Eu41300	Eu41y00	Eu41y11	Eu41z00	Eu41z11	Eu51511	Eu93000	Eu93100	Eu93200	Z4L1.00	E200100	E200111
	E202.00	E202.11	E202000	E202100	E202200	E202D00	E28..00	E280.00	E281.00	E282.00	E283.00	E283z00	E284.00
	E28z.00	Eu4..00	Eu40000	Eu40011	Eu40012	Eu40100	Eu40112	Eu41011	Eu41012	Eu42.11	Eu42.12	Eu43.00	Eu43000
	Eu43012	Eu43y00	Eu43z00	Z522600	146G.00	1B1H.11	1Bb..00	E202300	E202400	E202500	E202600	E202700	E202800
	E202900	E202A00	E202B00	E202C00	E202E00	E202z00	E227z11	E28z.11	E28z.12	E2D0100	Eu22y11	Eu40111	Eu40200
	Eu40211	Eu40212	Eu40213	Eu40214	Eu40300	Eu40z11	Eu40z12	Eu45212	Eu45215	Z481.00	Z522400	Z522700	E2...00
	E20..00	E204.00	E20y.00	E20y200	E20y300	E20yz00	E20z.00	E20z.11	E21..11	E210.00	E283100	E28z.13	Eu34111
	Eu34113	Eu60000	Eu60011	Eu60600									
AF	3272	3273	14AN.00	3272	G573.00	G573000	G573200	G573300	G573400	G573500	G573z00	14AR.00	3273
	G573100	G573600											
Stroke/TIA	G65..00	G64..12	G66..11	G65..12	G66..00	G65z.00	G64z.00	G61z.00	G61..00	G64z111	G64..11	G64z.12	G66..13
	G64..13	G66..12	G61..11	G667.00	G614.00	G663.00	G64..00	G64z200	G64z300	G668.00	G613.00	G641.00	G64z.11
	G65zz00	G65z100	G640.00	G669.00	G664.00	G61..12	G660.00	G61X100	G662.00	G661.00	G65y.00	G63y000	G63y100
	G64z000	G64z400	G641000	G61X000	G616.00	G617.00	G61X.00	G610.00	G665.00	G6X..00	G641.11	G640000	G676000
	G611.00	G6W..00	G653.00	G612.00	G64z100	G654.00	G666.00	Gyu6400	G65z000	G618.00	G615.00	Gyu6500	Gyu6300
	Gyu6600	Gyu6G00	Gyu6F00	ZV12D00									

Appendix 7.1 list of Read codes (continues)													
Variable	Code list												
ST retinopathy	7276	7272012	7272013	7272300	7272500	7272600	7272800	7272900	2BBk.00	2BBl.00	2BBO.00	5B4..11	Z6F..11
	5B42.00	ZV52200	ZV43000	ZV43100	FyuL.00	F49z.11	F490900	F495A00	F491.00	F491500	F492300	F492500	F491700
	F491800	F492400	F491600	F490400	F490300	F490200	F490700	F490800	F490600	F490500	F491100	F492100	F491300
	F491400	F492200	F491200	8F62.00	8F6..11	8F61.00	ZN56800	F49..00	F490z00	F490.00	F49A.00	F495000	F490100
	668C.00	Fy1..00	F4H7300	Fy1..12	ZN56A00	Fy1..11	9m08.00	2BBr.00	F49..11	ZK74.00	F494.00	F496500	F496600
	F496400	F495500	F495600	F495400	F495800	F495900	F495700	F496200	F496300	F496100	F495200	F495300	F495100
	F49..12	F492.00	F492z00	F492000	F496.00	F496z00	F496000	F498.00	F49C.00	2B7A.11	2B6A.11	22E6.11	22E6.00
	22E6.12	22EF.00	2B7B.00	2B7C.00	2B7T.00	2B7V.00	2B7W.00	2B7X.00	2B7S.00	2B7Q.00	2B7R.00	2B7P.00	2B6S.00
	2B6Q.00	2B6R.00	2B6P.00	2B7L.00	2B6L.00	22E6.13	2B6B.00	2B6C.00	2B6T.00	2B6V.00	2B6W.00	2B6X.00	2B7E.00
	2B78.00	2B6E.00	2B68.00	2B79.00	2B69.00	2B7A.00	2B6A.00	F491000	F491z00	Z9E2.00	F49..13	F495z00	F495.00
	Z96..00	Z9E5400	Z9E1100	Z962.00	Z9E5100	Z961.00	Z9E3200	Z9E3400	Z9E3300	Z9E3100	Z9E5.00	Z9E4.00	Z9E3.00
	Z9E1200	Z9E3500	8HlE.00	6689	6688.11	6688	6689.11	668D.00	8D36.00	9Nfb.00	9NfB.00	9Nfc.00	9Nfa.00
	F497.00	F49B.00	F49..14	F490000	1a00000	F49D.00	F493.00	F49y.00	F404200	F404100	Z9E3900	Z9E3C00	Z9E3D00
	Z9E3800	Z9E3B00	9NlD.00	1B75.00	1B77.00	2BBr.00	2BBL.00	2BBm.00	2BBn.00	2BBW.00	2BBX.00	F425900	F42y900
	C10EP00	C10EP11	C10FQ00	C10FQ11	F420300	7272900	F420400	2BBY.00	2BBo.00	F420200	2BBR.00	2BBS.00	F420800
	7272300	7272600	7272012	7272013	F420500	2BBO.00	2BBO.00	5B4..11	Z6F..11	2BBk.00	2BBl.00	F420100	F420700
	F422z00	F422.00	FyuF700	2BBT.00	2BBV.00	7272500	7272800	2BB7.00	2BB8.00	7276	F420500	F422y00	F4K2800
	FyuH400	2BB8.00	7270D00	7270z00	7270300	7274800	727C200	7270D00	7L19E00	727C100	7270200	7277600	7270C00
	727C100	7270400	727Cy00	727Cz00	7273000	727C000	7270y00	7270800	7270900	7270A00	7270411	7270500	7270600
	7270200	7270300	7270400	7270	7270100	F4K2800	FyuH400	2BB8.00					
SMI	E....00	E0...00	E00..00	E00..11	E00..12	E000.00	E001.00	E001000	E001100	E001200	E001300	E001z00	E002.00
	E002000	E002100	E002z00	E003.00	E004.00	E004.11	E004000	E004100	E004200	E004300	E004z00	E00y.00	E00y.11
	E00z.00	E01..00	E010.00	E010.11	E010.12	E011.00	E011000	E011100	E011200	E011z00	E012.00	E012.11	E012000

	E013.00	E014.00	E014.11	E015.00	E01y.00	E01y000	E01yz00	E01z.00	E02..00	E020.00	E021.00	E021000	E021100
	E021z00	E022.00	E023.00	E02y.00	E02y000	E02y100	E02y200	E02y300	E02y400	E02yz00	E02z.00	E03..00	E030.00

Appendix 7.1 list of Read codes (continues)													
Variable	Variable												
	E030.11	E030.12	E030000	E030100	E030200	E030300	E030400	E030z00	E031.00	E031.11	E031000	E031100	E031200
	E031300	E031400	E031z00	E03y.00	E03y000	E03y100	E03y200	E03y300	E03yz00	E03z.00	E04..00	E040.00	E040.11
	E041.00	E042.00	E04y.00	E04z.00	E0y..00	E0z..00	E1...00	E10..00	E100.00	E100.11	E100000	E100100	E100200
	E100300	E100400	E100500	E100z00	E101.00	E101000	E101100	E101200	E101300	E101400	E101500	E101z00	E102.00
	E102000	E102100	E102200	E102300	E102400	E102500	E102z00	E103.00	E103000	E103100	E103200	E103300	E103400
	E103500	E103z00	E104.00	E104.11	E105.00	E105000	E105100	E105200	E105300	E105400	E105500	E105z00	E106.00
	E106.11	E107.00	E107.11	E107000	E107100	E107200	E107300	E107400	E107500	E107z00	E10y.00	E10y.11	E10y000
	E10y100	E10yz00	E10z.00	E11..00	E11..11	E11..12	E11..13	E110.00	E110.11	E110000	E110100	E110200	E110300
	E110400	E110500	E110600	E110z00	E111.00	E111000	E111100	E111200	E111300	E111400	E111500	E111600	E111z00
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	E114000	E114100	E114200	E114300	E114400	E114500	E114600	E114z00	E115.00	E115.11	E115000	E115100	E115200
	E115300	E115400	E115500	E115600	E115z00	E116.00	E116000	E116100	E116200	E116300	E116400	E116500	E116600
	E116z00	E117.00	E117000	E117100	E117200	E117300	E117400	E117500	E117600	E117z00	E118.00	E11y.00	E11y000
	E11y100												
PVD	G73z000	G73zz00	G73z.00	G73..00	662U.00								
IHD	G3...00	G3...11	G3...12	G3...13	G30..00	G30..11	G30..12	G30..13	G30..14	G30..15	G30..16	G30..17	G300.00
	G301.00	G301000	G301100	G301z00	G302.00	G303.00	G304.00	G305.00	G306.00	G307.00	G307000	G307100	G308.00
	G309.00	G30A.00	G30B.00	G30X.00	G30X000	G30y.00	G30y000	G30y100	G30y200	G30yz00	G30z.00	G31..00	G310.00
	G310.11	G311.00	G311.11	G311.12	G311.13	G311.14	G311000	G311011	G311100	G311200	G311300	G311400	G311500

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	G33z700	G33zz00	G34..00	G340.00	G340.11	G340.12	G340000	G340100	G341.00	G341.11	G341000	G341100	G341111
	G341200	G341300	G341z00	G342.00	G343.00	G344.00	G34y.00	G34y000	G34y100	G34yz00	G34z.00	G34z000	G35..00
	G350.00	G351.00	G353.00	G35X.00	G36..00	G360.00	G361.00	G362.00	G363.00	G364.00	G365.00	G366.00	G37..00

Appendix 7.1 list of Read codes (continues)													
Variable	Variable												
	G38..00	G380.00	G381.00	G382.00	G383.00	G384.00	G38z.00	G39..00	G3y..00	G3z..00	Gyu3.00	Gyu3000	Gyu3100
	Gyu3200	Gyu3300	Gyu3400	Gyu3500	Gyu3600								
hypertension	G2...00	G2...11	G20..00	G20..11	G20..12	G200.00	G201.00	G202.00	G203.00	G20z.00	G20z.11	G21..00	G210.00
	G210000	G210100	G210z00	G211.00	G211000	G211100	G211z00	G21z.00	G21z000	G21z011	G21z100	G21zz00	G22..00
	G22..11	G220.00	G221.00	G222.00	G22z.00	G22z.11	G23..00	G230.00	G231.00	G232.00	G233.00	G234.00	G23z.00
	G24..00	G240.00	G240000	G240z00	G241.00	G241000	G241z00	G244.00	G24z.00	G24z000	G24z100	G24zz00	G25..00
	G25..11	G250.00	G251.00	G26..00	G26..11	G27..00	G28..00	G2y..00	G2z..00	Gyu2.00	Gyu2000	Gyu2100	
Heart failure	G580.00	G581.00	G58..11	G58..00	G580.11	G58z.00	G581000	G581.13	G580.14	1O1..00	G580.12	G580.13	G580300
	G58z.12	Q48y100	G232.00	G1yz100	G581.11	Q490.00	G580000	G580200	G582.00	G580100	G581.12	G234.00	
Diabetic foot	14F6.00	14F6.00	14F7.00	14F7.00	2G48.00	2G4E.00	2G54.00	2G55.00	2G5H.00	2G5L.00	2G5S.00	2G5T.00	2G5V.00
	2G5W.00	2G64.00	8CMT.00	8CS3.00	8CT1.00	8CV2.00	C108500	C108511	C108512	C109400	C109411	C109412	C10E500
	C10E511	C10E512	C10F400	C10F411	M271.00	M271.11	M271.12	M271.13	M271.14	M271.15	M271000	M271100	M271100
	M271200	M271300	M271400	M271700	M271700	M273.00	M274.00	R054200	R054300	R054200	R054300	G732000	G732100
	A3A0F00	14N4.00	14N4.11	14N4100	14N4Z00	2G42.00	2G43.00	2G44.00	2G45.00	2G46.00	2G47.00	2G4A.00	2G4B.00
	2G56.00	2G57.00	2G61.00	2G62.00	7L06.00	7L06000	7L06011	7L06012	7L06013	7L06014	7L06015	7L06016	7L06017
	7L06100	7L06111	7L06112	7L06200	7L06211	7L06212	7L06300	7L06311	7L06312	7L06313	7L06314	7L06315	7L06316
	7L06317	7L06318	7L06319	7L06400	7L06411	7L06412	7L06413	7L06y00	7L06z00	7L07.00	7L07000	7L07011	7L07012

	7L07100	7L07111	7L07200	7L07211	7L07212	7L07213	7L07300	7L07311	7L07312	7L07y00	7L07z00	7L07z11	7L08.00
	7L08.11	7L08000	7L08011	7L08100	7L08200	7L08300	7L08400	7L08500	7L08y00	7L08z00	7L08z11	Z6P3100	Z6X2.00
	14N4.00	14N4.11	14N4100	14N4Z00	2G42.00	2G43.00	2G44.00	2G45.00	2G46.00	2G47.00	7L06.00	7L06000	7L06011
	7L06012	7L06013	7L06014	7L06015	7L06016	7L06017	7L06100	7L06111	7L06112	7L06200	7L06211	7L06212	7L06300
	7L06311	7L06312	7L06313	7L06314	7L06315	7L06316	7L06317	7L06318	7L06319	7L06400	7L06411	7L06412	7L06413
	7L06y00	7L06z00											

Appendix 7.1 list of Read codes (continues)													
Variable	Variable												
Depression	E2B..00	Eu32z11	E112.14	E200300	E135.00	E204.00	E290.00	2257	1B17.00	E204.11	1465	62T1.00	Eu32z00
	E2B0.00	Eu32z12	Eu33.00	E2B1.00	Eu32.00	1B17.11	Eu53012	E112.11	Eu32z14	E113700	E112.12	Eu32y00	E113.11
	E112.13	E112z00	Eu32.13	Eu34113	Eu41211	Eu34100	Eu34111	Eu33.15	Eu33.11	Eu33.13	Eu32.11	E11z200	Eu32100
	Eu32200	1B1U.00	1BT..00	1B1U.11	E211200	E112.00	Eu32400	Eu32y11	E118.00	Eu33212	Eu33211	Eu32000	Eu41200
	9H91.00	9H90.00	Eu53011	E113200	E113.00	E112200	E112300	Eu34114	E112100	E291.00	Eu32.12	Eu3y111	212S.00
	Eu33.12	E002100	Eu33400	Eu32212	E113z00	E113300	E11y200	E001300	Eu32z13	Eu33.14	E113100	Eu33100	Eu33000
	9H92.00	8CAa.00	8HHq.00	Eu92000	Eu33200	E112000	E113000	E290z00	Eu33z11	Eu32211	9HA0.00	E004300	E112500
	Eu33z00	9HA1.00	Eu33y00	E113600	E113500	Eu32y12	E112600	Eu32213	Eu33214				
CKD stages 3 to 5	1Z12.00	1Z13.00	1Z14.00	1Z15.00	1Z16.00	1Z1a.00	1Z1b.00	1Z1B.00	1Z1B.11	1Z1c.00	1Z1C.00	1Z1C.11	1Z1d.00
	1Z1D.00	1Z1D.11	1Z1e.00	1Z1E.00	1Z1E.11	1Z1f.00	1Z1F.00	1Z1F.11	1Z1G.00	1Z1G.11	1Z1H.00	1Z1H.11	1Z1J.00
	1Z1J.11	1Z1K.00	1Z1K.11	1Z1L.00	1Z1L.11	1Z1T.00	1Z1V.00	1Z1W.00	1Z1X.00	1Z1Y.00	1Z1Z.00	K05..12	K050.00

General discussion

Evidence from the literature suggests that T1D people have higher cardiovascular and mortality risks compared with diabetes-free people (7, 8). Similar to T2D, T1D is associated with several diabetes-related complications including endothelial dysfunction, microvascular and macrovascular complications, and this is the case, despite the improvement in diabetes treatment and management (18, 41). Based on this knowledge, it is important to identify treatable comorbidities, which when addressed, may reduce the risk of diabetes-related complications and improve patient's quality of life.

The overall aim of this thesis was to explore the relationship between obstructive sleep apnoea and type 1 diabetes. To explore this relationship, a systematic review was conducted to evaluate the available data in this area of study and to identify important areas worthy of further study to help identify treatable factors, which contribute to the development of comorbidities. Following from this, a clinical cross-sectional study was carried out primarily to examine the prevalence of OSA in T1D and its link to cardiac autonomic neuropathy, but also to the other diabetes-related microvascular complications as secondary outcomes. To complement this clinical study a retrospective population-based study was carried out examining whether T1D could lead to OSA. We also showed that, the presence of OSA in T1D increases the risk of diabetes-related vascular complications such as heart failure, ischaemic heat disease, sight-threatening retinopathy, and chronic kidney disease.

8.1 A summary of the main findings of this thesis

The main significant findings of this research are that:

- OSA is common in patients with T1D.
- T1D increases the incidence of OSA compared with the general population.
- OSA in T1D patients increases the incidence of vascular complications.

- OSA in T1D patients is associated with CAN.

8.1.1 OSA is common in patients with T1D

The first significant finding is that OSA is common in patients with T1D. This is a significant finding as OSA is a disease that can be treated relatively easily using CPAP (342). As discussed in chapter three, our study cohort were not obese and about three-quarters were females which supposedly puts them at lower risk of OSA, and we also considered mild REI (5-14.9 events/h) as OSA positive only if it was associated with excessive daytime sleepiness. However, we found high prevalence of OSA (34.0%) despite being at low risk according to the traditional risk factors for OSA. It has been reported that OSA is linked to several changes in the upper airway muscles and nerves that could reduce the integrity of the upper airway (343). It is possible that in the T1D patients, similar mechanisms to those discussed below, which have been implicated in the development of microvascular complications, may be damaging the muscles and nerves that maintain the upper airway patency. For example, the formation of advanced glycation end products (AGEs) has been compared among OSA patients without diabetes (n=119), age-matched healthy subject (n=234), and T2D patients (n=134). It was found that AGEs formation in OSA patients without diabetes was higher than the healthy group, but lower than T2D group (3.68 unit per mL ± 0.39, 3.22 ± 0.54, and 4.11 ± 0.99, respectively) (344). In OSA subjects without diabetes, AGEs also were positively correlated with AHI severity (345) and nocturnal desaturation duration (344); however, CPAP treatment ameliorated AGEs formation (345).

It appears that OSA is overlooked in patients with T1D. Despite recruiting patients for the clinical study who had never been diagnosed or treated for OSA, about a third were diagnosed with OSA as a result of this study. Interestingly, no one was excluded for having previously

been diagnosed with OSA. The results of this study suggest that healthcare providers should consider screening T1D for OSA as part of routine clinical care. It might not be feasible to screen all T1D patients using a full night sleep study, such as the one used in this thesis. Therefore, there is a need to develop a T1D-specific tool (e.g. questionnaire) that may help to identify the T1D at higher risk of OSA. This might include questions from the sleep questionnaires that we have used in this study (see chapter 4:Table 4.4).

8.1.2 T1D leads to the development of OSA

The second significant finding, from the first THIN population-study, is that T1D may lead to the development of OSA (increased incidence of OSA compared with the general population). The incidence HR of this study was higher than the incidence rate ratio reported for T2D by using the same database and adjusting for similar confounding factors (1.67 in our study vs 1.36 in T2D; see chapter five). Given the finding of the clinical study, it is likely that the numbers of OSA cases in the THIN study are likely to be a large underestimate given the number of cases of undiagnosed OSA we uncovered in that study. The systemic review (see chapter 2) showed that even in studies where the cut-off for OSA was ≥ 5, there was an association between OSA and microvascular complications. So, there is a need to identify T1D who are at risk of OSA as treating OSA might improve their health, reduce their complications, and improve their quality of life.

This study has identified for *the first time* the risks factor that contribute to the development of OSA in patients with T1D (see chapter 5). These risk factors included younger age at T1D diagnosis, increased age, overweight and obesity, use of lipid-lowering and antihypertensive drugs, atrial fibrillation, and depression. These risk factors might be helpful in the development of a new, tailored screening tool to stratify the risk of OSA in patients with T1D.

8.1.3 OSA in TID leads to increased vascular complications

The third significant finding is that OSA in T1D patients increased the incidence of vascular complications. It is possible that OSA contribute to the development of vascular complications by increased ROS due to CIH, exaggerated oscillations of intrathoracic pressure due to apnoea events, and increased sympathetic activity (346). Our findings show increased incidence of IHD and PVD which commonly occur due to reduction in the diameter of the lumen of blood vessels. This reduction could be caused by plaque build-up, vascular stiffness, or vasoconstriction (347-349). Many studies have explored the impact of oxidative stress on atherosclerosis and have shown that increased ROS oxidize LDL which then leads to plaque formation in the vessels(350). ROS might also reduce the bioavailability of nitric oxide leading to cellular damage and endothelial dysfunction (350). These changes in the blood vessels reduces the amount of oxygen reaching the end organ such as the heart and the kidney (351, 352). Therefore, theses organs become at risk of ischaemic damage in addition to the direct impact of OSA.

Further to the discussion in chapter 6, the oscillation in the intrathoracic pressure due to apnoeas would increase the demand for oxygen of the heart, as it is having to cope with hemodynamic changes associated with the apnoeic events. However, this increased demand could not be met if the vessels supplying the heart were damaged. Therefore, it is really important for patients with vascular complications, specially heart failure, IHD, and PVD, to be assessed for OSA as untreated OSA could contribute to a faster deterioration.

8.1.4 OSA in T1D is associated with CAN

The fourth significant finding is that OSA in T1D patients was associated with CAN. The significance of this finding is that it might provide an explanation for the increased incidence of OSA in T1D, and the increased incidence of vascular complications in these patients. CAN was associated with OSA after adjusting for age, sex, diabetes duration, and BMI (see chapter 3). From this study, it is not possible to conclude whether CAN causes OSA or, vice versa, OSA causes CAN. We know that patients with OSA had lower sympathetic and parasympathetic activity. We also know the responses to cardiac autonomic reflex tests in patients with T1D and OSA was lower than the responses in T1D alone. It is also possible that autonomic neuropathy due to long-lasting diabetes reduces the patency of the upper airways, and thus leads to OSA. OSA, on the other hand, may contribute to the damaging or suppression the function of the autonomic nervous system including leading to the development of CAN. The CAN may then lead to damage or worsen the damage to the vascular system and the end-organs such as the heart and the kidney caused by T1D.

8.2 Possible mechanisms linking OSA to diabetes-related complications in T1D

Evidence from the literature regarding the mechanisms, which underlie the development of diabetes-related complications and the complications that arise from OSA, might help us to understand the mechanisms which result in the worse outcomes defined in this thesis in patients with both T1D and OSA.

Diabetes is characterised by hyperglycaemia. Some cells, such as retina cells, renal glomerulus cells, and neurons, are not insulin-dependent cells (57). Unlike insulin-dependent cells, insulin-independent cells move glucose from the extracellular to the intracellular space by diffusion

(353). Therefore, hyperglycaemia activates alternative metabolic pathways to breakdown glucose within the cells. Several pathways are proposed to explain the link between hyperglycaemia and diabetic microvascular complications. The major pathways are the polyol pathway, advanced glycation end-products (AGEs) pathway, protein kinase C (PKC), and hexosamine pathway (57). The activation of these pathways leads to alteration in extracellular molecules and circulating proteins, cellular dysfunction, and effects on gene expression. These changes then lead to the development of microvascular complications (57). A potential link between these alternative glucose metabolic pathways and the vascular damage, is the production of reactive oxygen species (ROS) (66).

Importantly, CIH is a feature of OSA that leads to increased ROS levels due to the redox effect and therefore also causes oxidative stress (194). Oxidative stress might lead to a chronic inflammatory response in OSA patients, which leads to cellular dysfunction, including potential to the vasculature and to autonomic nerves. In addition to this, studies have suggested that sleep fragmentation also leads to sympathetic activation. A large cohort study (n=901) found that arousal index also had a stronger relation to sympathetic over-activity than AHI (354). Similar results in healthy elderly suggested that sympathetic arousal increases the risk of hypertension (89). This evidence may help to explain the worse CAN that was observed in patients with T1D and OSA.

Another explanation for the worsening CAN in T1D with OSA may be explained by alterations in carotid body function. Studies on rats showed that CIH enhances carotid chemoreceptors response to hypoxia (196), and decreases carotid baroreceptors response to increased carotid sinus pressure (355). Importantly, a recent review might provide an explanation for the consequences of having both T1D and OSA in the control of the cardiovascular system. Both CIH (a feature of OSA) and hypoglycaemia (commonly encountered in T1D) elevate the level

of circulating adrenaline. Adrenaline, in turn, enhances CB activity (356). These changes are associated with sympathovagal imbalance (autonomic dysfunction) caused by enhanced sympathetic and blunted vagal tone (195, 196). Two studies that investigated OSA in type 1 diabetes reported blunted or absent heart rate response to apnoeic events (114, 172). This reduced heart rate response might be related to the sympathovagal imbalance, although a study on patients with congestive heart failure who underwent CB removal did not show a change in heart rate response to hypoxia (357). Also, it was found that autonomic dysfunction precedes hypertension in rat models after exposure to IH (195). Stimulation of apnoeic episodes in awake healthy subjects using Mueller manoeuvre shows fluctuations in BP and sympathetic nerve activity (358). This response might be the feedback of carotid chemoreceptors to the autonomic system in response to the hypoxia (359), leading to systematic hypertension (360). Therefore, it is likely treating OSA might improve the cardiovascular autonomic function, which then ameliorate or reduce further progression in vascular complications.

Importantly, both carotid chemoreceptor and baroreceptor functions were restored after treating rats with antioxidants (196, 355). In addition, it was reported that one month CPAP treatment improves arterial stiffness in the kidney and endothelial dysfunction, leading to better renal perfusion (361), and reduction in the progression of proliferative retinopathy (120). It was also found that long-term (2 years) CPAP treatment improved autonomic balance during sleep (362). These findings are important as it means that identifying OSA in T1D is a treatable factor which will ameliorate the development of cardiovascular and other diabetes-related complications in these patients leading to a reduction in the burden of cardiovascular disease and autonomic dysfunction, other diabetic complications and to an improvement in patient quality of life.

8.3 Future directions:

We have found that T1D increases the risk of OSA. However, it is not clear whether CAN precedes OSA or not. Therefore, longitudinal studies are needed to investigate this relationship. The study needs to recruit age, sex and BMI matched T1D with and without CAN, and then follow them over time to compare the incidence of OSA between the groups. The study needs to control for known and potential cardiovascular and metabolic risk factors such as diabetes duration, dyslipidemia, hypertension, and atrial fibrillation.

To investigate the pathological mechanisms that might contribute to the relationship between OSA and T1D an observational study to explore the association between OSA and several biomarkers that might help understand how OSA contribute to the vascular complications needs to be performed. Therefore, T1D with and without OSA need to be recruited in ordered to examine the possible mechanism leading to cardiovascular complications such as inflammatory markers, oxidative stress and nitrosative stress. A comparison of alternative metabolic pathways including polyol, AGEs, PKC, and hexosamine pathway, also needs to be performed.

Health professionals and policymakers interested in T1D should be aware of the link between T1D and OSA. They should also be aware of the increased diabetes-related complications associated with the presence of OSA such as CAN and CVD. As shown previously, both CAN and OSA were underdiagnosed and closely linked. Therefore, we recommend that health policies and guidelines for the management of T1D patients should include routine screening for CAN and OSA.

There are different methods to treat OSA such as oral devices or CPAP to keep the airway open during sleep, or surgically removing excess tissue, but the most common treatment is CPAP. The most important future study is to investigate whether treating OSA in T1D reduces the risk

of cardiovascular complications. Therefore, a prospective study is needed to examine the impact of treating OSA on cardiovascular complications. The study needs to recruit patients with OSA and offer them CPAP treatment. Then follow them over time. Data must be collected at baseline and then repeated at intervals (e.g. 1, 3, 6, and 12 months) to monitor the progression of disease. The study needs to assess the following outcomes: HbA1c, insulin use, ACR, eGFR, oxidative stress, CAN, and retinopathy. For this study, it is important assess the CPAP compliance and to encourage the participants to use the CPAP most of the night. Also, it is important to conduct a sub-analysis on compliant participants alone.

In summary, this research has shown that OSA is common in T1D and is associated with CAN. It has also shown that T1D increases the incidence of OSA. This study has shown, for the first time, the risk factors which contribute to the development of OSA in T1D. A further novel finding was that OSA in T1D patients increased the incidence of vascular complications, including heart failure, ischaemic heart disease, peripheral vascular disease, and chronic kidney disease. Better diagnosis and treatment of OSA may help to ameliorate the impact of microvascular complications and heart disease in T1D.

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