Effect of sleep disturbances on brain structural alterations and cognition, and relationship with obesity and cardiometabolic comorbidities, in normal and Parkinson's populations

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June 2022

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Experimental Medicine.

Table of Contents

1. Abstract

Rationale: Sleep disturbances are a common consequence of aging and their prevalence rises as the proportion of elderly grows in Western populations. They are also frequent amongst individuals with Parkinson's disease (PD). Coinciding with an aging population, is an increasing prevalence of obesity. The interrelations between sleep disturbances, obesity, cardiometabolic disorders, brain structural changes and cognition remain incompletely understood. The effect of sleep disturbances on cognitive performance in PD is also relatively unknown.

Objectives: Investigate the associations between sleep disturbances, obesity, cardiometabolic disorders, brain MRI measures and cognition in a normal population. In addition, investigate the associations between sleep disturbances and cognitive performance in the PD population.

Methods: Structural equation modeling was used to evaluate the associations between Sleep disturbances (focusing on hypersomnolence and snoring), obesity, cardiometabolic disorders, brain structure and cognition in a large sample of normal aging individuals from the UK Biobank. Linear regression modeling was used to evaluate direct associations between sleep disturbances and cognitive performance in the normal aging and PD populations.

Results: In the normal population, sleep disturbances were associated with increased prevalence of obesity, diabetes, dyslipidemia, and inflammation. These cardiometabolic disorders were associated with increased white matter hyperintensities (WMH), that were in turn related to poor cognition. Sleep disturbances were also directly associated with poorer performance in processing speed, fluid intelligence, working memory and executive function, independent of obesity, cardiometabolic disorders and sleep duration. In the PD population,

the presence of snoring and/or obstructive sleep apnea was associated with improved working memory and faster reaction speed.

Conclusion: The association between sleep disturbances and adverse brain health consequences in a normal aging population suggests that interventions targeting sleep health may be beneficial for cognition. In PD, further work on sleep disturbances will be needed to clarify the relationship with cognition.

2. Résumé

Raisons : Les troubles du sommeil sont une conséquence courante de l'âge et leur prévalence augmente avec l'accroissement de la proportion de personnes âgées dans les populations occidentales. Ils sont également fréquents chez les personnes atteintes de la maladie de Parkinson (MP). Coïncidant avec une population vieillissante, il y a une prévalence croissante de l'obésité. Les interrelations entre les troubles du sommeil, l'obésité, les troubles cardiométaboliques, les changements structurels du cerveau et la cognition restent incomplètement comprises. L'effet des troubles du sommeil sur les performances cognitives dans la MP est également relativement inconnu.

Objectifs : D'étudier les associations entre les troubles du sommeil, obésité, les troubles cardiométaboliques, mesures IRM cérébrales et performances cognitives dans une population normale. De plus, les associations entre les troubles du sommeil et la performance cognitive dans la population MP seront étudiées.

Méthode : Le modèle d'équation structurelle a été utilisée pour évaluer les associations entre les troubles du sommeil (en se concentrant sur l'hypersomnolence et le ronflement), obésité, les troubles cardiométaboliques, structure cérébrale et cognition dans un large échantillon d'individus vieillissants normaux de la UK Biobank. La modèle de régression linéaire a été utilisée pour évaluer les associations directes entre les troubles du sommeil et les performances cognitives dans les populations de vieillissement normal et de MP.

Résultat : Dans la population normale, les troubles du sommeil étaient associés avec plus d'obésité, de diabète, de dyslipidémie et d'inflammation. Ces troubles cardiométaboliques étaient associées à des hypersignaux de la substance blanche à l'IRM, qui étaient à leur tour

liées avec une mauvaise cognition. Les troubles du sommeil étaient également directement associés à de pires performances en termes de vitesse de traitement, d'intelligence fluide, de mémoire de travail et de fonction exécutive, indépendamment de l'obésité, des troubles cardiométaboliques et de la durée du sommeil. Dans la population avec MP, la présence de ronflement et/ou d'apnée obstructive du sommeil était associée avec une amélioration de la mémoire de travail et à une vitesse de réaction plus rapide.

Conclusion : L'association entre les troubles du sommeil et les conséquences néfastes sur la santé cérébrale dans une population vieillissante suggère que les interventions ciblant la santé du sommeil peuvent être bénéfiques pour la cognition. Dans la MP, des travaux supplémentaires sur les troubles du sommeil seront nécessaires pour clarifier la relation avec la cognition.

3. Acknowledgements

For the past two years under these extraordinary circumstances, I have had the tremendous support of my supervisor, Dr. Marta Kaminska. She imparted her expertise in epidemiological sleep research, as well as provided guidance as a supervisor to ensure that I would be able to complete my degree on time. Despite setbacks, Dr. Kaminska provided me with opportunities that enriched my experience as a research student. Members of my thesis committee have also been very supportive in these extraordinary times. Dr. Alain Dagher made completing my degree remotely, possible by suggesting a study design, providing access to UK Biobank, and contributing resources and his expertise in neuroscience. Dr. Sushmita Pamidi assisted with the thesis outline and lent her experience in sleep research. Dr. David Labbé aided with the thesis outline and helped plan coursework to ensure credit requirements were met.

Members of Dr. Kaminska's and Dr. Dagher's lab have been invaluable during my time as a student. Dr. Annie Lajoie and Teresa Gomes from Dr. Kaminska's lab contributed their experience and knowledge in sleep research. Dr. Lajoie additionally helped me with transitioning into the projects and aided with administrative tasks. Marianne Gingras, supported the administrative side, helping with the maintenance and submission of REB forms. Dr. Filip Morys from Dr. Dagher's lab contributed greatly to the UK Biobank project: the study design, development of the R statistical software code, and provided guidance in statistical analyses that allowed me to take on a large dataset project.

Lastly, I would like to thank my family and friends who have encouraged and supported my academic endeavours. The past two years was made possible by all the academic and moral support I've received along the way.

4. Contribution of Authors

I, the student, wrote all the chapters of this thesis including the Literature Review (Ch.8), the methods and results of Ch.9 and 10, the methods and predicted results of Ch.11 and Discussion (Ch.12). The student also conducted the statistical analyses and produced the figure and tables from Ch.9 and 10.

Dr. Marta Kaminska contributed to the editorial process for all chapters. Dr. Kaminska, Dr. Alain Dagher and Dr. Filip Morys contributed to the study design of Ch.9 and 10. Dr. Annie Lajoie and Teresa Gomes contributed to the editorial process of Ch.9. Dr. Kaminska, Dr. John Kimoff, Dr. Anne-Louise Lafontaine, Dr. Dagher, and Dr. Lajoie are the investigators of the project outlined in Ch.11 and they contributed to the study design. Dr. Kaminska contributed her expertise and knowledge on sleep research in PD patients for the entirety of Ch.12, Dr. Lajoie contributed her knowledge of OSA and OSA in PD for Ch. 12.1 and 12.2. Additionally, Dr. Dagher, Dr. Morys, Teresa Gomes, and Dr. John Kimoff contributed knowledge of their respective fields to the interpretation of data presented in Ch.12.1.

5. List of Figures and Tables

6. List of Abbreviations

AD: Alzheimer's disease

AHI: Apnea-hypopnea index

BMI: Body mass index

BFP: Body fat percentage

BP: Blood pressure

CFI: Comparative fit index

CRP: C-reactive protein

DBP: Diastolic blood pressure

EF: Executive function

EDS: Excessive daytime sleepiness

ESS: Epworth Sleep Scale

FA: Fractional anisotropy

FI: Fluid intelligence

GDS: Geriatric Depression Scale - Short Form

GM: How hard is it get up in the morning?

HbA1c: Hemoglobin A1c

HDL: High density lipoprotein cholesterol

HTN: Hypertension

MD: Mean diffusivity

MRI: Magnetic resonance imaging

OSA: Obstructive sleep apnea

PD: Parkinson's disease

PSG: Polysomnography

PDSS-2: Parkinson Disease Sleep Scale-2

PM: Prospective memory

RBDSQ: RBD sleep questionnaire

RBD: REM sleep behaviour disorder

REM: Rapid eye movement

RLS: Restless Legs syndrome

RMSEA: Root mean square error of approximation

RT: Reaction time

SBP: Systolic blood pressure

SCOPA-S: Scales for Outcomes in Parkinson's disease – Sleep

SRMR: Standardized root mean squared residual

TG: Triglycerides

VM: Visuospatial memory

WHR: Waist-to-hip ratio

WM: Working memory

WMH: White matter hyperintensities

WMI: White matter integrity

7. Introduction

Sleep disturbances are common in middle-aged and elderly populations and there is emerging evidence that they may be associated with brain structural changes and cognitive decline[1]. As the average age in developed countries continues to increase, the prevalence of sleep disturbances will increase alongside it[2,3]. Common sleep disturbances include obstructive sleep apnea (OSA) and excessive daytime sleepiness (EDS)[4,5], both of which are risk factors of cognitive dysfunction in the middle-aged and elderly[6–9]. Sleep disturbances are also frequent amongst the Parkinson's (PD) population and are linked with additional health consequences[10]. Another concern in public health is the increasing proportion of individuals with obesity in Western populations[11]. Obesity is linked to cardiometabolic consequences, and more recently neurocognitive consequences[12,13]. Obesity is a risk factor of sleep disturbances and conversely, sleep disturbances can be a risk factor for obesity[14–16]. Understanding the effect of sleep disturbances on cognition will support the importance of sleep health, and early detection and treatment may provide beneficial effects for cognitive and cardiometabolic health in an aging population.

The primary objective of this thesis is to investigate the interrelations of sleep disturbances, including hypersomnolence and snoring, with cardiometabolic comorbidities, brain health and cognition in a normal aging population. Secondary objectives include investigating the effects of sleep disturbances on brain structural alterations and cognitive performance in a PD population.

Multiple sleep disturbances occur in aging populations. In the literature review portion of the thesis, we will explore specific sleep disturbances such as OSA (**Ch.8.2**) and EDS (**Ch.8.3**).

We will also review sex-related effects and differences in sleep disturbances (**Ch.8.4**), obesity as a risk factor of sleep disturbances (**Ch.8.5**), and PD and its relationship with sleep disturbances (**Ch.8.6**). Additionally, we explore the beneficial effects of treating OSA in normal and PD populations (**Ch.8.7**). Finally, we will explore the UK Biobank, a large long-term database (**Ch.8.8**) and structural equation model (SEM) (**Ch.8.9**), both of which are important features of the thesis. The results and work done towards the primary objective will be described in **Ch.9,** and **Ch.10** and **11** will explore the results and work done towards the secondary objectives. **Ch.12** discusses the implications of the findings and how it fits in the broader literature. Finally, the thesis concludes with a final summary and conclusion in **Ch.13**.

8. Literature Review

8.1 Sleep and Aging

Sleep is an important aspect of maintaining good health. Sleep has been hypothesized to play a role in many important functions including memory retention and other cognitive functions, emotional regulation, and metabolic functions including removal of CNS metabolic waste[17]. However, chronic poor sleep has become the norm in contemporary society compromising these functions[18]. Lifestyle factors such as the constant exposure to electronic devices like cellphones, computers, and televisions, as well as work culture contribute to poor sleep quality and short sleep duration[19]. Additionally, poor sleep has been linked with negative health outcomes such as obesity[20,21], hypertension[22,23], and cognitive decline[24,25].

Alongside the increasing prevalence of poor sleep is the increasing life expectancy in many developed countries, resulting in a growing proportion of elderly[26]. In 2015, 8.5% of the world's population was 65 years of age or older and by 2050, the proportion is projected to more than double[27]. Aging is associated with increased multimorbidity[28], defined by WHO as multiple ongoing health conditions requiring long-term medical attention[29] and will become a great burden on the health care system[30]. In a large cross-sectional study, it was reported that 64.9% of participants between the ages of 65-84 years old had multimorbidity, rising to 81.5% of participants 85 years and older[28]. Aging is a risk factor for cognitive decline[31,32] as well as neurodegenerative diseases such Alzheimer's disease (AD) and Parkinson's disease (PD)[33,34]. Additionally, aging is associated with increased risk of cardiometabolic disorders including hypertension, diabetes, and cardiovascular disease[35].

Aging also plays a role in poor sleep. With age, it becomes increasingly difficult to fall asleep and stay asleep, leading to shorter sleep duration and sleep fragmentation[36]. Sleep architecture also changes, with older adults experiencing less time in deep sleep (NREM stages 3 and 4), resulting in reduced restorative sleep[37]. These age-related changes in sleep have been hypothesized to be due to changes in circadian modulation, endocrine function, and neural mechanisms of the sleep-wake cycle[37,38]. Furthermore, the frequency of sleep disturbances including insomnia, EDS and OSA increase with age as 40-70% of older adults experience chronic sleep problems[39,40].

8.2 Overview of Obstructive Sleep Apnea and its Consequences

OSA is characterized by episodic partial or complete blockage of the upper airway during sleep due to the collapse of the soft palate resulting in apneas and hypopneas[41]. The prevalence of OSA in adults 65 years and older is estimated to range between 13-32%[42], although it continues to be underdiagnosed[43,44]. OSA is often accompanied by various symptoms such as loud snoring and hypersomnolence, which can affect quality of life in the middle-aged and elderly[41]. Snoring itself is a highly prevalent condition found in 20-40% of the population and it has been reported that snoring, as measured by snoring frequency and intensity, is associated with OSA severity[45]. However, the presence of snoring does not always indicate presence of OSA, especially in individuals with mild snoring and lower BMI[46].

The gold standard for diagnosing OSA is to perform polysomnography (PSG) to measure the apnea-hypopnea index (AHI), the average number of apneas and hypopneas per hour of sleep[47]. Using this method, OSA is diagnosed when AHI is ≥5 with daytime sleepiness symptoms[48]. Disease severity is also measured using AHI: mild OSA is defined as ≥5 and <15

AHI, moderate is ≥15 and <30 AHI, and severe OSA is ≥30 AHI[48]. Differences in scoring criteria can lead to differences in reported prevalence and severity[49,50]. In-lab PSGs can be costly and not easily accessible[51]. Hence the use of screening tools such as the STOP (Snoring, Tiredness, Observed apneas, high blood Pressure), STOP-BANG (STOP and BMI, Age, Neck circumference, Gender) or Berlin questionnaire (which asks about several signs, symptoms and comorbidities of OSA) can be used to more readily determine if individuals are at high risk of OSA[52,53].

There are several risk factors that increase an individual's risk of developing OSA. One of them is male sex; the prevalence of OSA in men is greater than in women, with approximately 10-17% of middle-aged and elderly men diagnosed with OSA compared to 3-9% of women of similar age[54]. OSA prevalence also increases with age. One population study of found an AHI of ≥15/hour in 49.7% of men and 23.4% of women aged 40 and above, and when dividing the participants into <60 years and ≥60 years, prevalence of AHI of ≥15/hour increased significantly in the older age group[55]. Possible mechanisms underlying this sex difference may be differences in body fat distribution[56], anatomical differences of the upper airway and hormonal differences[57,58]. Additional evidence supporting hormonal changes as a key mechanism of developing OSA is that approximately 14.6% of postmenopausal women were screened positive for OSA in comparison to 10.4% of pre-menopausal women[59]. Furthermore, the sex difference between men and women is less pronounced when comparing men with postmenopausal women not on hormone replacement therapy[60].

Obesity is another important risk factor for OSA. The increase in body mass can lead to increased soft tissue mass of the upper airway resulting in it becoming more vulnerable to collapsing during sleep leading to mechanical obstruction or blockage and cessation of

breathing[61]. Around 24-45% of individuals with obesity have OSA[15] and OSA is also strongly associated with increased BMI, waist-to-hip ratio, and neck circumference[62]. Additionally, there is increasing evidence demonstrating that weight loss and bariatric surgery can help reduce OSA severity[15,61,63].

Recent research in OSA has begun to recognize phenotypic subtypes of OSA by classifying individuals based on symptoms[64]. Although, there is no consensus on the exact subtypes, studies have attempted to use symptoms that can be generally categorized as 1) disturbed sleep (insomnia-related), 2) excessively sleepy and 3) minimally symptomatic[65,66]. A novel subtype described as having both symptoms of excessive daytime sleepiness and disturbed sleep[67], was reported to be associated with increased risk of cardiovascular events such as coronary heart disease and heart failure[68].

Hypertension is a common health consequence of OSA. Reports suggest approximately 50% of OSA patients have hypertension[69]. A hypothesized mechanism whereby OSA could lead to hypertension is that apneas and hypopneas induce hypoxemia, causing sympathetic nervous system activation to increase heart rate and blood pressure to re-establish oxygen saturation, which over time results in hypertension[70]. It is also hypothesized that a similar mechanism causes increased risk of diabetes amongst patients with OSA[71]. In addition, OSA-related sleep fragmentation and shorter sleep are also key factors that may lead to increased risk of developing hypertension[72], as well as diabetes due to glucose metabolism dysregulation[71,73].

EDS is a common symptom of OSA and has been reported in 46.5-58.0% of patients[74]. It has been hypothesized that chronic sleep fragmentation and short sleep duration related to

OSA, lead to EDS[75]. OSA combined with EDS has been reported to affect daily function and cognition[75] and significantly increases the risk of cardiovascular events compared to individuals with OSA and minimal symptoms[68]. EDS has its own consequences, independent of OSA, which will be further discussed in the next section (**Ch.8.3**).

Brain structural alterations has been reported in individuals with OSA. Compromised white matter integrity (WMI) has been identified, measured using diffusion tensor imaging (DTI), as reduced fractional anisotropy (FA) and increased mean diffusivity (MD)[76], indicating myelin damage potentially due to hypoxemia from apneas and hypopneas[77,78]. Some magnetic resonance imaging (MRI) studies report grey matter atrophy[79,80], although there are conflicting reports. One MRI study reports of grey mater hypertrophy[81] and reduced MD which may be indicative of compensatory changes[82]. A population-based study found that AHI was associated with increased white matter hyperintensities (WMH) identified from MRI[83], which are associated with increased risk of stroke, dementia, and cognitive decline[84]. These brain structural alterations associated with OSA may exacerbate cognitive decline associated with aging in the middle-aged and elderly[85]. In addition to these brain structural changes, OSA is associated with global cognitive impairment as well as in certain domains such as memory, attention, and executive function[86].

In summary, OSA is associated with many cardiovascular and neurocognitive consequences. Continued research is necessary to help clarify these association. Increased awareness of the risk factors and early signs of OSA are key to properly diagnose and treat OSA to prevent health consequences in the middle-aged and elderly populations.

8.3 Overview of Excessive Daytime Sleepiness and its Consequences

EDS or hypersomnolence, is a common sleep-related complaint reported alongside sleep disorders, neurodegenerative diseases, as well as with non-clinical origins such as with shift work and modern lifestyle[87]. EDS is reported in up to 18% in the general population[88]. A common way to determine EDS is to administer the Epworth Sleepiness Scale (ESS), a questionnaire which measures subjective sleepiness[89]. A score of 11-12 would be considered as mild EDS, a score of 13-15 would be moderate EDS and a score of 16-24 would classify as severe EDS[89]. EDS can also be measured objectively by conducting the multiple sleep latency test (MSLT), that measures how quickly individuals can fall asleep during multiple daytime naps[90] and a mean sleep latency of 8 minutes and less is considered abnormally sleepy[91].

There are many risk factors for EDS, including OSA described in more detail in the previous section (**Ch.8.2**). Additionally, obesity alone is a risk factor for EDS, and will constitute an increasing concern as the proportion of obese individuals continues to grow[92–94]. More details on obesity and its association with sleep disturbances will be described in **Ch. 8.5.** Although OSA and obesity are highly correlated with 26-32% of individuals with both reporting EDS, 18% without OSA also reported EDS, indicating that EDS is associated with obesity independently of OSA[92] as well as independently of diet and physical activity[95]. It has been hypothesized that obesity leads to EDS due to overactivation of the sympathetic nervous system caused by endocrine dysregulation[92,96]. Additionally, weight loss and bariatric surgery in these individuals have been shown to help reduce EDS[97,98].

Depression is an another independent risk factor[99]. Prevalence of EDS in individuals with depression was found to be approximately 50.8%[100]. In addition, the relation between

depression and EDS may be bidirectional as EDS is often an early sign and potential risk factor of depression in the elderly[101,102]. A longitudinal study, using questionnaires to determine EDS, found that older adults with EDS were 2.06 times more at risk of developing depression, independently of sociodemographic and clinical comorbidities[102].

Although EDS is often regarded as a symptom, it may also be a marker for adverse outcomes. EDS is independently associated with cognitive decline in the elderly[6]. In a population-based study of older Italian adults, EDS was the only sleep complaint independently associated with dementia[103]. Additionally, EDS in middle-aged and older adults has been suggested to accelerate brain aging, as EDS was found to be associated with global cortical thinning in cognitively normal elderly[104]. One study found that the presence of EDS in the elderly without dementia is associated with increased β-amyloid accumulation over time, independent of comorbidities such as age, sex, the presence of apolipoprotein E (ApoE) ε4 allele, depression and short sleep duration[105].

Several neurological disorders such as depression, circadian rhythm disorders, epilepsy, and PD share EDS as a common symptom[102,106]. In the PD population, EDS affects approximately 50% of patients and is one of the most common non-motor symptoms[107]. In a 3-year longitudinal study, PD patients had an increase in ESS, in contrast to no changes in healthy controls[108]. Common risk factors of EDS in PD patients include male sex, poor sleep quality, and use of dopamine agonists[109]. In particular, dopaminergic therapy used to treat PD symptoms, has a dose-dependent relationship with EDS[108] and reducing the dosage and discontinuation has been reported to reduce episodes of daytime sleepiness[107,110]. EDS may be related to accelerated PD-related neurodegeneration as an imaging study showed that PD

patients with EDS, but without dementia and hallucinations, have significant grey matter atrophy in many brain areas including frontal, temporal and occipital lobe compared to PD patients without EDS[111]. In addition, a systematic review found that EDS is associated with cognitive decline in PD patients as global cognitive function, executive function, and processing speed were impaired to a greater extent compared to PD patients without EDS[112].

In summary, EDS is a common symptom of obesity, sleep disorders and neurological disorders as well as an independent risk factor for dementia and cognitive decline in the elderly, and an early indicator of neurodegenerative diseases and depression. Screening for EDS should become routine in the middle-aged, elderly, and obese populations for early detection and provide preventative care of underlying disorders.

8.4 Sex-Related Effects and Differences in Sleep Disturbances

There are differences in prevalence of OSA between men and women[55,113,114]. Approximately, 10-17% of middle-aged and elderly men are diagnosed with OSA in contrast to 3-9% of women of similar age[54]. Furthermore, in a study investigating the sex differences of OSA in an elderly French population, the prevalence of undiagnosed women increased with age despite having similar risks compared to their male counterparts[115]. This difference in frequency of diagnosis, may be attributed to differences in presentation and symptoms of sleep disturbances, but also due to biological differences[116]. Men are more likely to report sleep disturbance symptoms related to OSA such as snoring, gasping and observed apnea[113]. In contrast, women are more likely to report symptoms less associated with sleep disturbances such as depression, fatigue, and insomnia[116]. Furthermore, when controlling for age and AHI, men scored higher on the ESS than women[117]. Therefore, it may not be that women are less

susceptible to OSA, but that women are underdiagnosed due to non-specific symptoms[116]. There is also a hypothesis that women are more hesitant to self-report symptoms such as snoring due to social stigma and are consequently referred less to sleep clinics[114].

There is emerging evidence that sleep disturbances differ due to physiological differences between men and women. For similar OSA severity, women were more obese than men and this may be due to sex differences in how adipose tissue is distributed[118,119]. There are also differences in the prevalence of OSA and sleep disturbances between pre- and postmenopausal women[59] as well as between postmenopausal women with hormone replacement therapy compared to those not on treatment[60]. Postmenopausal women not on hormonal replacement have an OSA prevalence closer to their male counterparts of similar age, indicating that sex hormones may play a role in OSA prevalence[60].

Similarly to how there are sex differences in the manifestation of OSA, there are sex differences in the health outcomes associated with them. Women with OSA were more likely to have additional health complications such as depression and hypertension[120,121] as well as white matter alterations[122,123]. Furthermore, one study found that middle-aged and older middle-aged women at high risk of OSA had poorer cognitive function, specifically in episodic memory and executive function, while there were no associations in men[124].

In summary, although prevalence of OSA is still male sex dominated, emerging evidence indicates that women are also at risk of OSA, but they experience different symptoms and are susceptible to different health consequences. Research in female populations with OSA should continue to raise awareness of the differences in clinical presentation to get a proper diagnosis and subsequent treatment.

8.5 Obesity, its Health Consequences, and Relation with Sleep

Coinciding with a growing population of older adults, obesity is a modern epidemic that has been rising in developed countries over the past decades[125]. Obesity is characterized by abnormal or excessive accumulation of adipose tissue and a BMI greater or equal to 30kg/m^2[126,127] . In 2018, 36.3% of Canadian adults were overweight and 26.8% were classified as obese[128]. Obesity is risk factor for many health consequences such as diabetes[129,130], hypertension and cardiovascular disease[131–134], sleep apnea[15,135], and more recently has been shown to be a risk factor for neurocognitive consequences such as brain structural alterations and cognitive decline[13,136].

Obesity is often due to the imbalance of energy intake and expenditure, where lifestyle including poor eating habits and sedentariness are the driving factors[137]. Diet is an important and modifiable risk factor of obesity and recently there has been growing evidence of poor diets altering the gut microbiota leading to increased risk of obesity[138,139]. Lifestyle factors are also key in the rise of obesity as a sedentary and short sleep lifestyle has become more prevalent in developed countries[139]. Poor sleep and short sleep duration can lead to increased daytime sleepiness and reduced subjective energy, contributing to sedentariness increasing the risk of obesity[20,21,139,140]. In one study, short sleep was associated with poor dietary habits via alterations in the neural mechanisms, with unhealthy food activating the brain reward system more while sleep deprived than with normal sleep duration[141]. Obesity can also lead to OSA as described in **8.2 Overview of Obstructive Sleep Apnea**, where increased body weight and adipose tissue increase load on the upper airway making it more vulnerable to collapsing and obstruction[61].

The cardiometabolic consequences of obesity are well documented[142]. Obesity is associated with increased risk of hypertension[131], diabetes[130], and dyslipidemia[143], which in turn increase the risk of cardiovascular diseases such as coronary heart disease and stroke[134]. Furthermore, in a longitudinal study it was reported that severely obese individuals were almost 15 times more at risk of developing cardiometabolic multimorbidity, defined in this study as at least 2 out of stroke, coronary heart disease or diabetes, compared to individuals of healthy BMI, independent of age, sex, and ethnic origin[142].

Recently, there has been increasing evidence that obesity, through its cardiometabolic consequences, also plays a role in brain structural alterations and cognitive decline especially in older adults[13,144]. Obesity has been associated with grey matter atrophy in cognitively normal elderly[144] as well as loss of WMI[145]. Additionally, a recent paper using the UK Biobank dataset found that obesity-related hypertension and diabetes were associated with increased WMH, which in turn was associated with poorer cognitive function[13]. Obesity-related brain structural alteration is hypothesized to be caused by insulin resistance[146], systemic inflammation[147] and vascular dysfunction[148] leading to cognitive dysfunction. Furthermore, these brain structural changes may have a functional impact resulting in accelerated cognitive decline in older adults with obesity compared to those of normal weight[149].

In summary, obesity is a preventable and modifiable risk factor for many sleep-related, cardiometabolic and neurocognitive consequences. Promotion of a healthier lifestyle and awareness of the negative health outcomes of obesity will be key to combat the growing obesity epidemic.

8.6 Parkinson's Disease and Sleep Disturbances

As the proportion of elderly continues to grow, age-related neurodegenerative diseases like PD and AD, will also increase[150]. PD is currently the second most frequently diagnosed neurodegenerative disease and rises in prevalence with age[151,152]. It is often characterized by motor symptoms such as bradykinesia and resting tremor[153], as well as non-motor symptoms such as cognitive dysfunction and dementia[154].

A common non-motor symptom in PD is sleep disturbances including insomnia, hypersomnolence, restless leg syndrome (RLS) and rapid-eye movement (REM) sleep behaviour disorder (RBD)[155], which has been reported in as high as 87% of PD patients[156] and up to 60% have reported OSA[157]. Even before motor symptoms appear, PD patients often present non-motor symptoms[158], with one study suggesting that they can appear more than 10 years before motor symptoms and diagnosis[159]. Questionnaires are often administered to collect information on PD symptoms, some often used are: 1) Parkinson's Disease Sleep Scale 2 (PDSS-2)[160], Scales for Outcomes in Parkinson's Disease – Sleep (SCOPA-Sleep)[161], 3) MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[162].

PD is associated with neuroanatomical changes including degeneration of dopaminergic neurons in the cerebellum resulting in the motor symptoms of PD[163]. With disease progression, there is also global atrophy of the brain in various cortical and subcortical regions leading to reduced brain volume in PD patients[164]. White matter lesions that appear as WMH on MRI are also prevalent in PD patients[165]. Additionally, DTI measures reflecting WMI loss and myelination damage may be potential biomarkers for PD prognosis[166]. These brain

structural alterations are associated with many PD symptoms, especially with cognitive dysfunction and dementia[167,168].

Cognitive decline is another common non-motor symptoms in PD patients[169], including impairments to executive function, visuospatial and memory, and cognitive dysfunction increase the risk of early dementia[151]. Cognitive decline can often precede motor symptoms and even diagnosis[170]. Additionally, in one study, dementia in PD populations is up to 6 times more prevalent compared to similar aged individuals without PD[171]. There are several risk factors of cognitive dysfunction in PD populations including genetics and lifestyle, and recently there has been more evidence implicating OSA as a modifiable risk factor of cognitive impairment in PD[172]. A few studies have reported PD patients with OSA have lower cognitive scores than those without OSA[173,174]. It has been hypothesized that the intermittent hypoxemia and sleep fragmentation due to OSA may exacerbate existing neurodegeneration due to PD, resulting in accelerated cognitive decline[175,176]. The pathophysiology of how OSA may exacerbate PD-related neurodegeneration is still relatively unknown and future research should investigate brain structural changes associated with the presence of OSA in PD populations. Furthermore, continued studies on treating OSA in PD patients are needed to ascertain the effects of treatment on cognition.

8.7 Overview of Treatments for Obstructive Sleep Apnea and Beneficial Effects

There are different management and treatment methods for OSA to help improve symptoms and reduce the impact of negative health outcomes[177]. Lifestyle changes can include weight loss, that has been shown to reduce the severity of OSA, as well as help with management of comorbidities such as hypertension[178]., reduce risk of type 2 diabetes[179] and

cardiovascular events[180]. Weight loss helps alleviate the mechanical obstruction due to excessive adipose tissue, which leads to minimization of snoring, apnea, and hypopnea events[181,182]. A meta-analysis investigating weight loss and severity of OSA reported that although there is heterogeneity in the overall effect, most studies favour weight loss intervention and improvements in AHI following weight loss last for up to 60 months[183].

Continuous positive airway pressure (CPAP) is known as the gold standard for treating moderate-severe OSA[184]. The CPAP machine provides a continuous positive air pressure that keeps the upper airway open to prevent its collapse and obstruction[184]. By preventing the obstruction of the upper airway, CPAP can reduce snoring, daytime sleepiness, and AHI, improving sleep quality[184,185]. Data suggests that CPAP treatment for OSA improves daily function[177], cognitive performance[186], and reduce the risk of cardiovascular events[187] and hypertension[188]. In a large prospective study, individuals with OSA who were ineligible, declined or nonadherent of CPAP were found to have a greater incident of hypertension compared to OSA patients who were treated[188]. However, large randomized controlled trials (RCTs) have consistently failed to demonstrate benefit of CPAP on cardiovascular outcomes, particularly in non-sleepy patients[187,189,190].

Similarly, benefits of CPAP with respect to cognition also remain controversial. A multicentred trial did not find significant cognitive improvement in middle-aged individuals[191]. However, a randomized pilot study involving patients 65 years and older with severe OSA found that after 3 months of treatment, there was improvement in episodic and short-term memory as well as executive function compared to patients received only conservative care[192]. Furthermore, authors found less cortical thinning in patients treated with CPAP[192].

Improvement in cognitive function with the use of CPAP is an important finding given the common occurrence of OSA in older adults[42]. Despite any potential benefits, CPAP treatment has a variable compliance, with studies reporting 40-80% of participants using CPAP regularly and for the prescribed amount of time[193]. Although there have been technological advancements in CPAP treatment to improve adherence, other factors such as psychological and social, continue to impede patients from adhering to the prescribed amount of treatment needed for health benefits[194].

The benefits of treating OSA with CPAP are less well studied in the PD population and there are conflicting reports about the efficacy. One study used CPAP to treat OSA in PD patients for 6 weeks and compared cognitive scores to PD patients with OSA that received a placebo (sham CPAP) for 3 weeks followed by 3 weeks of CPAP and found that CPAP treatment did not rescue cognitive function[174]. In contrast, in a longitudinal observational study, the use of CPAP in PD patients with OSA resulted in improvement in global cognitive function, as well as in other non-motor symptoms at 6- and 12-month follow-up[195]. Specifically, there was improvement in non-motor symptoms such as cognitive function and anxiety in PD patients with good CPAP compliance over 12 months[195]. Moreover, untreated OSA in PD patients was associated with greater motor dysfunction at 12 months, compared with CPAP-treated patients in whom motor function was stabilized[196].

While treating OSA in the general population appears to provide beneficial effects, RCT data, particularly on cardiovascular outcomes, remains disappointing. Patient selection appears to be an important element relating to treatment benefit. Patients with more severe OSA and associated EDS may be more likely to show benefit. Age may also be a factor, especially in

relation to cognition. There are a few promising clinical studies demonstrating improvement of PD-related symptoms following the use of CPAP to treat OSA and future studies should continue to investigate the effects of CPAP in the elderly overall and in PD patients with OSA as well as investigate the effect of CPAP on brain structural degeneration.

8.8 Overview of the UK Biobank

As the global population continues to grow older, long-term databases following the middle-aged and elderly have become an integral part of epidemiological research of aging. These databases provide large sample sizes with a wide range of information collected for each participant longitudinally[197–199]. One such large-scale long-term databases is the UK Biobank, a British research project that aims to recruit and follow approximately 500,000 participants between the ages of 40-69[199]. Beginning in 2006, British citizens registered with the National Health Services (NHS) were recruited to participate in the UK Biobank, where sociodemographic and lifestyle information, physical measurements, medical history, biological samples such as urine and blood samples, and cognitive tests were collected[200].

The database study continues to follow participants longitudinally with online questionnaires on mental health[201] and keep their medical history up to date[200]. One of the largest follow-ups occurred beginning in 2014, where participants were re-recruited to update baseline data, re-perform cognitive tests as well as introduce full body MRI, including abdominal and brain imaging[202]. The UK Biobank anonymizes all data and is open access, allowing researchers from all over the world to conduct research with the goal of improving public health[199,200].

8.9 Overview of Structural Equation Modelling

Structural equation modeling (SEM) is a statistical model that investigates associations between one or multiple independent variables with one or multiple dependent variables[203]. These associations are determined *a priori*, forming the hypothesis, then the model is run to test if these associations are significant[203]. Simple SEMs can be interpreted similarly to multiple linear regression modelling and with a larger sample size, it is possible to test complex models and investigate the interrelations between all the variables[203,204].

SEMs have distinct features, one of which is independent and dependent variables are typically *latent variables*. *Latent variables* can't be observed or measured directly but are composed of *observable variables* or *measured factors*[205]. For example, *cognition* can't be observed or measured directly, however we can define it as combination of *executive function* and *working memory*. Both are *observable variables* that are quantified and measured using cognitive tests[205]. *Observable variables* are represented as boxes and *latent variables* are represented as ellipses in schematic representations of SEMs[203]. Arrows are used to show regression associations between *latent variables* and the *latent variable* on the arrowhead side is the *dependent variable* of that association[206].

To see if the SEM is a good representation of the associations determined *a priori*, evaluation of the SEM is necessary and is known as model fit[205]. There are many model fit indices used to determine if the hypothesized associations of the SEM are good fit in the real data. Chi-square test (χ^2) is used to assess the fit between the hypothesized model and the model with real data; however it is not reliable in very large sample sizes as it will generally always be significant[207,208]. To combat this, other model fit indices are reported alongside Chi-

square test. Root mean square error of approximation (RMSEA) is a measure of poor fit as a value closer to 0 indicates very good fit while a value closer to 1 indicates poor fit[208]. Standardized root mean square residual (SRMR) is similar to RMSEA as the closer the value is to 0, the better the fit[208]. Another model fit index is the comparative fit index (CFI); it is the opposite of RMSEA and SRMR as it measures good fit, with values of closer 0 indicating poor fit while values closer to 1 indicating very good fit[208].

SEMs are not commonly used in epidemiological and medical research[209,210], however there are many advantages to using them over traditional multiple and multivariate linear regressions. Firstly, SEMs allows for the estimation of *latent variables* by combining *observable variables*[203]. In the case of sleep research, specifically OSA; it is known that OSA is underdiagnosed[43,44], therefore using SEMs allow researchers to compile various measurable OSA-related symptoms to compose an OSA surrogate variable. Secondly, SEMs offer the ability to test for both direct and indirect associations[203]. For example, SEMs can determine that *independent variable A* is associated with *dependent variable C*, making a direct association. At the same time, the model can determine that *independent variable A* is associated with *independent variable B,* which is then associated with *dependent variable C*, making an indirect association between *independent variable A* and *dependent variable C*. A disadvantage of SEMs is that it requires a large sample size to produce meaningful results, especially when investigating multiple latent variables and the associations between them[204].

8.10 Conclusions

As the populations in developed countries continue to grow older, the prevalence of sleep disturbances will grow along with it. OSA and EDS are common sleep disturbances that

are risk factors of many negative health outcomes such as cardiometabolic and neurocognitive consequences. Sleep disturbances are also prevalent in PD patients and may exacerbate neurodegeneration and PD symptoms. More clinical studies are needed to understand the impacts of treating OSA on cardiovascular and cognitive outcomes and to define patient populations most likely to benefit. Research in neurodegenerative conditions such as PD is also needed to elucidate if treating OSA may help manage and improve PD symptoms over time. Finally, continued education on the importance of sleep health in middle-aged and older adults is required in public health to act preventatively and mitigate associated health consequences.

9. Associations between sleep disturbances, obesity, cardiometabolic disorders, brain structural alterations and cognition in a normal aging population

The objectives, methods, results, figure, figure caption and tables were adapted from a to-be submitted manuscript, where the student was first author.

9.1 Objectives

The primary objective: investigate the interrelations between sleep disturbances, defined as hypersomnolence and snoring, obesity, cardiometabolic disorders, brain structural alterations and cognition in the normal aging population in a large sample size of the UK Biobank.

Secondary objectives: If a direct association between sleep disturbances and cognition is found, investigate the effect of sleep disturbances on individual cognitive domains, independent of obesity, cardiometabolic covariates and sleep duration. Furthermore, sex as a moderator of the direct associations between sleep disturbances and function in the different cognitive domains will be investigated, as well as possible differences between men and women in those associations.

In the normal aging population of the UK Biobank, we hypothesize that sleep disturbances, focusing on hypersomnolence and snoring, are associated with brain structure alterations and cognitive dysfunction through obesity and its cardiometabolic comorbidities, as well as independently of them. We expect working memory, executive function, and reaction time to be affected. Furthermore, we hypothesize that effect of sleep disturbances on cognitive performance differs between men and women.

9.2 Methods

Study Population

In this study, we used data from the UK Biobank, a long-term database that began initial assessments in 2006 and collected a wide range of health information on participants such as physical measurements, biological samples, lifestyle questionnaires, cognitive tests and imaging[211]. Following Morys et al.[13], we only included participants with available brain imaging data (n=38,346) and then excluded individuals with a diagnosis of neurological illness (n=1966). For analyses, we used data collected at two-time points; initial assessment (obesity measures, blood markers, and confounders) and imaging visit (brain magnetic resonance imaging (MRI), sleep disturbances measures, cognitive tests, and confounders), approximately 8 years later. All participants signed informed consent forms prior to participating in the UK Biobank that was approved by the North-West Multi-Centre Research Ethics Committee. This research was conducted using the UK Biobank Resource under Application Number 35605.

Sleep disturbances

Sleep disturbances were measured using four sleep behavior questions self-reported at the imaging visit: I) "Does your partner or a close relative or friend complain about your snoring?", with answers yes or no; II) "How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g., when working, reading or driving)" with possible answers 1) Never/rarely, 2) Sometimes, 3) Often, 4) All the time; III) "Do you have a nap during the day?" with possible answers 1) Never/rarely, 2) Sometimes, or 3) Usually; and IV) "On an average day, how easy do you find getting up in the morning?" with possible answers 1) Not at all easy, 2) Not very easy, 3) Fairly easy, 4) Very easy.

Obesity

Obesity measures included body mass index (BMI), body fat percentage (BFP) and waist-to-hip ratio (WHR). BMI and BFP measures were provided by the UK Biobank, WHR was calculated by dividing waist circumference by hip circumference.

Cardiometabolic comorbidities

Hypertension was defined using self-reported diagnosis, and from resting systolic and diastolic blood pressure (BP) collected at initial assessment (mean of two measurements). Diabetes was defined with self-reported diagnosis and serum glucose and hemoglobin A1c (HbA1c) levels. Serum C-reactive protein (CRP) was used as a measure of inflammation[212] and dyslipidemia was defined using high-density lipoprotein cholesterol (HDL) and serum triglycerides (TG) levels. All blood markers were collected non-fasting.

Brain imaging

Four brain MRI variables that were pre-processed by the UK Biobank, were investigated[213]. Cortical thickness was derived with FreeSurfer by Desikan-Killiany-Tourville (DKT) atlas (thickness of all DKT parcels)[214,215], cortical volume derived from T1 brain structural imaging (a global measure for total volume of peripheral grey matter), and subcortical volume was derived with FreeSurfer by automatic subcortical segmentation (Aseg; a global measure for total volume of subcortical grey matter)[214,216]. Volume of WMH was derived from T1 and T2-FLAIR imaging and calculated using Brain Intensity AbNormality Classification Algorithm (BIANCA; global measure for total volume of WMH)[217].

Cognition

Cognition was measured using six cognitive tests conducted at the imaging visit via touchscreen interface. Although the UK Biobank did not administer validated cognitive tests, the cognitive tasks correspond well with their validated counterparts that measure similar cognitive abilities[218]. The six cognitive measures were: 1) Visuospatial memory (VM), as average number of incorrect matched pairs; 2) Processing speed as mean reaction time (RT); 3) Prospective memory (PM), as total number of times an intention was forgotten on the PM task; 4) Fluid intelligence (FI), as total score on a set of reasoning tasks; 5) Working memory (WM), as total number of digits recalled correctly and 6) Executive function (EF), as the total number of puzzles solved correctly in a tower rearranging task. Higher scores in VM, RT and PM indicated worse cognitive performance. Loading of the six cognitive factors into a single latent variable resulted in *higher* cognition scores being indicative of greater cognitive *dysfunction*.

Statistical Analyses

A structural equation model (SEM) was used to test for associations determined *a priori*. Prior to analyses, volumes of cortical and subcortical grey matter, and WMH were corrected for intracranial volume. Secondly, WMH, BMI, CRP, TG, HDL, HbA1c and glucose levels were log-transformed. All continuous measures were normalized. Furthermore, since lower levels of HDL are indicative of a healthier constitution, we multiplied HDL by -1 for ease of interpretation. Next, we pairwise excluded outliers that were 2.2 interquartile range below 1st or above 3rd quartile, resulting in a sample size of 36,468. Finally, we residualized all measured variables in the SEM to control for confounders (list found in **Confounders** section).

The lavaan package[219] in R[220] was used to test the SEM with eleven latent variables: 1) sleep disturbances (the four self-reported sleep measures), 2) obesity (BMI, BFP, WHR), 3) hypertension (hypertension diagnosis, systolic and diastolic BP), 4) inflammation (CRP levels), 5) diabetes (diabetes diagnosis, glucose and HbA1c levels), 6) dyslipidemia (TG and HDL levels), 7) cortical thickness (mean thickness of all parcels weighted by surface area of each hemisphere), 8) cortical volume, 9) subcortical volume, 10) WMH, and 11) cognition (the six cognitive measures). Since the latent variable dyslipidemia was composed of two measures (TG and HDL), we constrained the loading factors of both so that they would be weighed equally. We allowed for residual correlations between cortical thickness, cortical and subcortical volume and between similar metabolic syndromes: WHR and hypertension, diabetes, and dyslipidemia. The model used maximum likelihood estimation (ML) with robust standard errors and excluding pairwise missing values, Model fit was assessed using comparative fit index (CFI), root mean square of error approximation (RMSEA) and standardized root mean square residual (SRMR).

To investigate the association between sleep disturbances and each cognitive domain, we used multiple linear regression models. To extract sleep disturbances scores for each participant to be used in the linear regression models, we created a simpler SEM (not shown) with only the sleep disturbances latent variable and each cognitive test as its own latent variable. This simpler SEM used ML estimation with standard errors and used full information maximum likelihood (FIML) to deal with missing values, allowing us to obtain sleep disturbances scores regardless of the completeness of their cognitive data. We adjusted for the same confounders as the main SEM with the addition of obesity measures (BMI and waist-to-hip ratio) and cardiometabolic comorbidities (list found in Confounders section). Note that each

regression had varying numbers of participants as not all participants completed all the cognitive tests.

Additional linear regression models evaluating association between sleep disturbance and cognitive domains were constructed to analyze for sex interaction and for stratification by sex. Finally, we assessed the effect of specific sleep symptoms on cognitive outcomes by using individual sleep items as predictors in separate linear regression models. Correction for multiple comparisons was applied to all linear regression models using the false discovery rate (FDR) Benjamini-Hochberg procedure.[221]

Confounders

For all analyses, we controlled for age, sex, average household income, Townsend Deprivation Index, highest level of education attained, depression, frequency of alcohol intake, number of days per week of 10 minutes or more of vigorous physical activity, smoking status, and self-reported sleep duration by residualizing the variables of interest. Age, income, physical activity, smoking status, and sleep duration were collected at both visits; therefore, we matched those confounders to the same visit as when the measure of interest was collected.

In our multiple linear regression model and moderation analyses, we additionally controlled for obesity measures (BMI and WHR), and dichotomized cardiometabolic comorbidities. A participant was marked hypertensive if they had a HTN diagnosis, systolic BP $\geq$140mm/Hg, and/or diastolic BP $\geq$90 mm/Hg[222]. A participant was marked diabetic if they had a diabetes diagnosis, HbA1c levels $\geq$48 mmol/mol, and/or glucose levels $\geq$11 mmol/L[223,224] A participant was marked with dyslipidemia if they had TG levels $\geq$2.3 mmol/L[225], and/or HDL

levels ≤1.2 mmol/L[226]. Lastly, participants were marked with inflammation if they had CRP levels ≥10 mg/L[227,228].

9.3 Results

Demographic Characteristics

The study population was comprised of 36,468 individuals, 46.7% male with a mean age of 63.6 ± 7.5 years at the imaging visit (Table 1). Only 0.6% of the sample self-reported a diagnosis of OSA, in contrast to 33.8% self-reported loud snoring. The average BMI (26.5 ± 4.2) indicated a slightly overweight study population. The mean Townsend deprivation index, a socioeconomic measure, was -1.91 ± 2.7, which suggests participants were on average from affluent areas of the UK.

Sleep disturbances are directly associated with cognitive dysfunction, and through pathways involving obesity, cardiometabolic comorbidities and brain structure alterations

In the main SEM, we investigated associations between sleep disturbances, obesity, cardiometabolic comorbidities, brain imaging variables and cognition (Figure 1). Sleep disturbances were associated with increased prevalence of obesity, diabetes, dyslipidemia, and inflammation, and with lower prevalence of hypertension (Table 2). In turn, obesity, diabetes, and dyslipidemia were associated with increased WMH, and WMH were positively related to cognitive dysfunction. Note that a higher cognitive score represents greater cognitive dysfunction. Furthermore, dyslipidemia and WMH were associated with increased subcortical volume that was in turn associated with cognitive dysfunction. We found that hypertension, diabetes, inflammation, and WMH were all associated with reduced cortical thickness. Reduced cortical thickness was associated with cognitive dysfunction. Sleep disturbances were

also directly associated with increased WMH, reduced cortical volume, and reduced subcortical volume. In addition, we found that sleep disturbances, hypertension, diabetes, inflammation, dyslipidemia, WMH and increased subcortical volume were directly associated with reduced cognitive function. The SEM also showed that sleep disturbances defined as self-reported snoring and hypersomnolence were directly associated with cognitive dysfunction. The model produced the following fit indices: $\chi^2(253)=7088.121$, $p<0.001$; CFI=0.952; RMSEA=0.027; SRMR=0.027, indicating a good fit.

We performed a sensitivity analysis using definitions from inpatient records and/or self-reported diagnoses for hypertension and diabetes. There were no differences from the main model in significant associations (results not shown).

Sleep disturbances are associated with cognitive deficits in several domains

Using multiple linear regression, sleep disturbances were associated with slower reaction times, and lower scores in fluid intelligence, working memory and executive function, independently of obesity and cardiometabolic disorders (Table 3). Sleep disturbances were not significantly associated with visuospatial and prospective memory.

Sex does not moderate associations between sleep disturbances and cognitive deficits

Analyses with sex as a moderator did not find any significant moderating effects (interactions) of sex on the associations between sleep disturbances and any of the cognitive domains (Table 4). When stratifying by sex, the magnitudes of the beta point estimate indicated that males performed worse compared to females, especially in fluid intelligence and working memory, however confidence intervals overlapped considerably (Table 5).

Specific sleep symptoms have different cognitive implications

We also investigated the relations between each sleep measure (snoring, daytime sleepiness, likelihood to nap during the day and difficulty getting up in the morning) and each cognitive domain (Table 6). Snoring was not significantly associated with any cognitive domain. Daytime sleepiness was associated with slower reaction times and poorer executive function. Likelihood to nap was associated with poorer visuospatial memory, fluid intelligence, working memory, executive function, and slower reaction times. Difficulty getting up in the morning was associated with poorer fluid intelligence and working memory.

9.4 Figure and figure caption

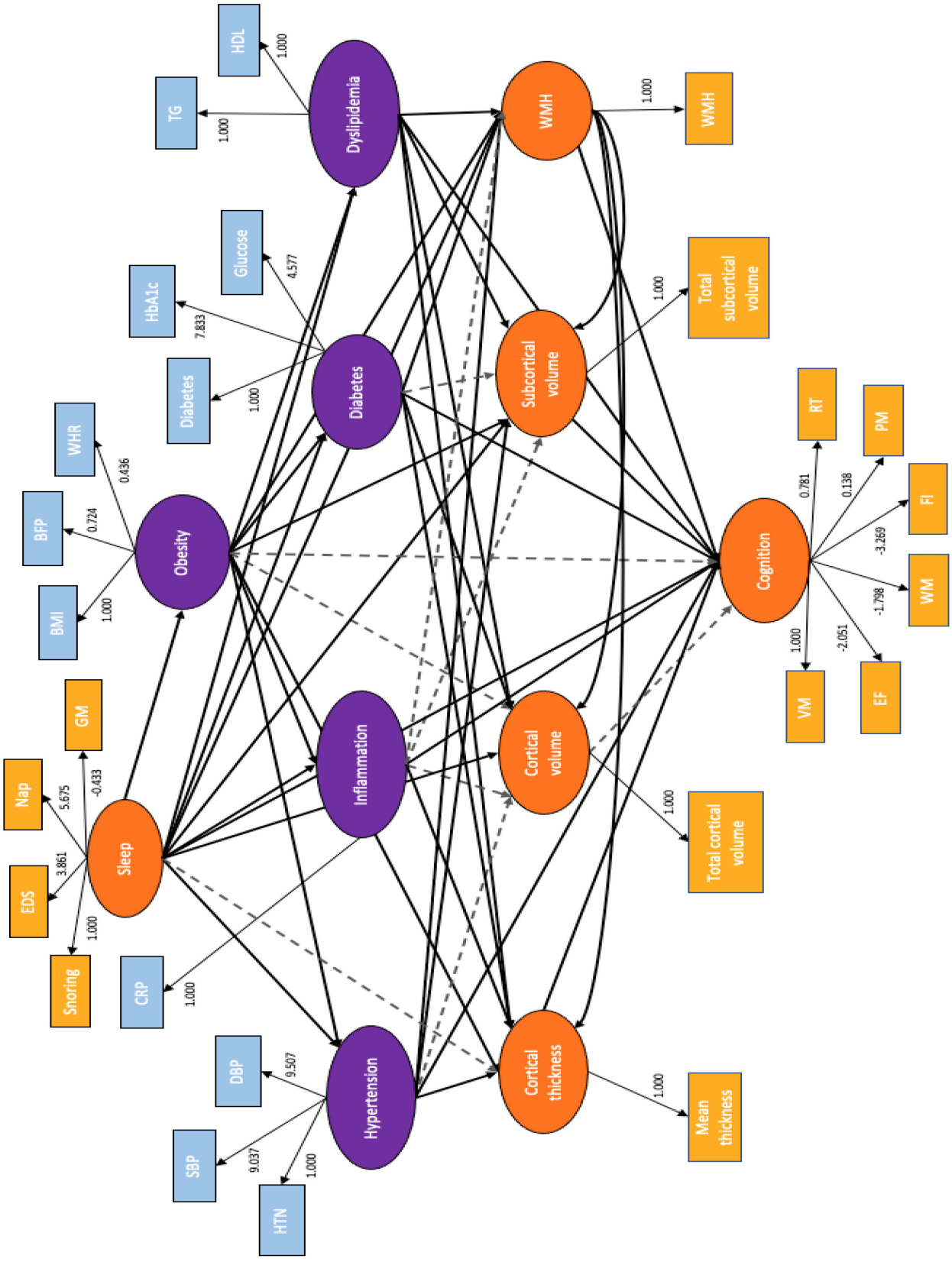

Figure 1: Sleep disturbances are associated with cognitive dysfunction through cardiometabolic comorbidities and brain imaging changes. Associations between latent variables were adjusted for age, sex, income, Townsend Deprivation Index, education, depression, alcohol intake, physical activity, smoking status, and sleep duration. Magnitudes of each association are listed in Table 2. Bolded lines represent significant associations at $p<0.05$ and dashed lines represent nonsignificant associations. Variables highlighted in blue and purple were measured at initial visit and variables highlighted in orange and yellow represent measures at 8-year follow-up. EDS: excessive daytime sleepiness, Nap: likelihood to nap, GM: how easy to get up in the morning, BMI: body mass index, BFP: body fat percentage, WHR: waist-to-hip ratio, HbA1c: hemoglobin A1c, TG: triglycerides, HDL: high density lipoprotein, SBP: systolic blood pressure, DBP: diastolic blood pressure, CRP: c-reactive protein, VM: visuospatial memory, EF: executive function, WM: working memory, FI: fluid intelligence, PM: prospective memory, RT: reaction time.

9.5 Tables

Table 1: Demographic characteristics of the normal aging population in the UK Biobank.

Characteristics	All (n=36,468)	Female (n=19,444)	Male (n=17,021)
Age (years)	63.6 (7.5)	63.0 (7.4)	64.3 (7.6)
Sex (n male, %)	17,021 (46.7)	-	-
Body mass index (kg/m^2)	26.5 (4.2)	26.0 (4.5)	27.1 (3.7)
Waist-to-hip ratio	0.85 (0.09)	0.80 (0.07)	0.92 (0.06)
Education qualifications (n, %)*			
College/University degree	17,735 (48.6)	9244 (47.5)	8491 (49.9)
A levels/AS levels or equivalent	4401 (12.1)	2479 (12.7)	1922 (11.3)
O levels/GCSEs or equivalent	6432 (17.6)	3749 (19.3)	2683 (15.8)
CSEs or equivalent	1378 (3.8)	746 (3.8)	632 (3.7)
NVQ/HND/HNC or equivalent	2126 (5.8)	714 (3.7)	1412 (8.3)
Other professional qualifications (e.g. nursing, teaching)	1813 (5.0)	1162 (6.0)	651 (3.8)
Alcohol consumption (n, %)*			
Never	1703 (4.7)	1141 (5.9)	562 (3.3)
Monthly or less	3079 (8.4)	2143 (11.0)	936 (5.5)
2-4 times a month	4730 (13.0)	2826 (21.5)	1904 (11.2)
2-3 times a week	7970 (21.9)	4188 (21.5)	3782 (22.2)
4 or more times a week	7769 (21.3)	3546 (18.2)	4223 (24.8)
Smoking status (n, %)*			
Past smoker	12,108 (33.2)	5939 (30.5)	6169 (36.2)
Current smoker	1243 (3.4)	563 (2.9)	680 (4.0)
Never	22,764 (62.4)	12,743 (65.5)	10,021 (58.9)
Townsend deprivation index	-1.91 (2.7)	-1.87 (2.7)	-1.95 (2.7)

Income (£ / n, %)*			
Less than 18,000	3974 (10.9)	2464 (12.7)	1510 (8.9)
18,000 – 30,999	8850 (24.7)	4903 (25.2)	3947 (23.2)
31,000 – 51,999	9960 (27.3)	4997 (25.7)	4963 (29.2)0
52,000 – 100,000	7611 (20.9)	3509 (18.1)	4102 (24.1)
>100,000	2443 (6.7)	1068 (5.5)	1375 (8.1)
Depression (n, %)	5144 (14.1)	3420 (17.6)	1723 (10.1)
Hypertension (n, %)	6602 (18.1)	2985 (15.4)	3617 (21.3)
Diabetes (n, %)	893 (2.5)	328 (1.7)	565 (3.3)
Sleep duration (hours)	7.1 (1.1)	7.1 (1.1)	7.2 (1.1)
Obstructive sleep apnea (n, %)	209 (0.6)	46 (0.2)	163 (1.0)
Snoring (n, %)	12,212 (33.5)	5072 (26.1)	7140 (41.9)
Daytime sleepiness (n, %)*			
Never/rarely	27,945 (76.6)	15,428 (79.3)	12,517 (73.5)
Sometimes	7414 (20.3)	3494 (18.0)	3920 (23.0)
Often	826 (2.3)	381 (2.0)	445 (2.6)
All the time	0	0	0
Likelihood to nap (n, %)*			
Never	20,859 (57.2)	12,472 (64.1)	8387 (49.3)
Sometimes	13,377 (36.7)	6238 (32.1)	7139 (41.9)
Usually	1986 (5.5)	605 (3.1)	1381 (8.1)
How easy to get up in the morning (n, %)*			
Not at all easy	877 (2.4)	652 (3.4)	225 (1.3)
Not very easy	3738 (10.3)	2458 (12.6)	1279 (7.5)
Fairly easy	16,632 (48.4)	9714 (50.0)	7918 (46.5)
Very easy	13,962 (38.3)	6483 (33.3)	7477 (43.9)

Legend: GSCEs: General Certificate of Secondary Education, CSEs: Certificate of Secondary Education, NVQ: National Vocational Qualification, HND: Higher National Diploma, HNC: Higher National Certificate; *Percentages may not add up to 100% as participants had the option to answer “Prefer not to answer” or “I don’t know”

Table 2: Associations between latent variables from SEM represented in Figure 1.

Predictors and outcomes	**Regression coefficient**
Sleep disturbances impact on:	
Obesity	1.468 ***
Hypertension	-0.050 ***
Inflammation	0.285 ***
Diabetes	0.058 ***
Dyslipidemia	0.787 ***
Cortical thickness	-0.012
Cortical volume	-0.228 ***
Subcortical volume	-0.362 ***
WMH	0.311 ***
Cognitive dysfunction	0.144 ***
Obesity impact on:	
Hypertension	0.022 ***
Inflammation	0.532 ***
Diabetes	0.017 ***
Dyslipidemia	0.362 ***
Cortical thickness	0.016 *
Cortical volume	-0.011
Subcortical volume	-0.058 ***
WMH	0.030 ***
Cognitive dysfunction	0.001
Hypertension impact on:	
Cortical thickness	-0.270 ***
Cortical volume	0.011
Subcortical volume	0.546 ***
WMH	1.563 ***
Cognitive dysfunction	0.051 ***
Inflammation impact on:	
Cortical thickness	-0.014 **

Cortical volume	0.003
Subcortical volume	0.005
WMH	0.004
Cognitive dysfunction	0.005 ***
Diabetes impact on:	
Cortical thickness	-1.056 ***
Cortical volume	-0.693 ***
Subcortical volume	0.063
WMH	1.087 ***
Cognitive dysfunction	0.143 ***
Dyslipidemia impact on:	
Cortical thickness	0.042 ***
Cortical volume	0.076 ***
Subcortical volume	0.072 ***
WMH	0.035 ***
Cognitive dysfunction	0.007 *
WMH impact on:	
Cortical thickness	-0.112 ***
Cortical volume	-0.188 ***
Subcortical volume	0.077 ***
Cognitive dysfunction	0.012 ***
Cortical thickness impact on:	
Cognitive dysfunction	-0.004 **
Cortical volume impact on:	
Cognitive dysfunction	-0.002
Subcortical volume impact on:	
Cognitive dysfunction	0.009 ***

Legend: * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$

Table 3: Cognitive performance in specific domains in association with sleep disturbances

	Beta (95% CI)[1]
Visuospatial memory† (n=23,748)	0.0056 (-0.0071, 0.0183)
Reaction time† (n=23,658)	0.0422 (0.0299, 0.0545) ***
Prospective memory† (n=23,739)	0.0039 (-0.0087, 0.0164)
Fluid intelligence (n=23,392)	-0.0272 (-0.0403, -0.0141) ***
Working memory (n=16,879)	-0.0312 (-0.0460, -0.0164) ***
Executive function (n=16,145)	-0.0713 (-0.0866, -0.0559) ***

Legend: * = p<0.05, ** = p<0.01, *** = p<0.001; †higher score signifies worse performance; [1]Adjusted for age, sex, BMI, waist-to-hip ratio, income, Townsend Deprivation Index, education, depression, alcohol intake, physical activity, smoking status, sleep duration, hypertension, diabetes, inflammation, and dyslipidemia; Benjamini-Hochberg corrected for multiple comparison

Table 4: Sex as a moderator of sleep disturbances on cognitive performance

	Beta (95% CI)[1] for interaction Sleep disturbances x Sex
Visuospatial memory† (n=23,748)	-0.0152 (-0.0099, 0.0402)
Reaction time† (n=23,658)	-0.0070 (-0.0312, 0.0172)
Prospective memory† (n=23,739)	0.0052 (-0.0196, 0.0299)
Fluid intelligence (n=23,392)	-0.0211 (-0.0468, 0.0046)
Working memory (n=16,879)	-0.0211 (-0.0503, 0.0080)
Executive function (n=16,145)	-0.00002 (-0.0302, 0.0301)

Legend: * = p<0.05, ** = p<0.01, *** = p<0.001; †higher score signifies worse performance; [1]Adjusted for age, BMI, waist-to-hip ratio, income, Townsend Deprivation Index, education, depression, alcohol intake, physical activity, smoking status, sleep duration, hypertension, diabetes, inflammation, and dyslipidemia; Benjamini-Hochberg corrected for multiple comparison

Table 5: Cognitive performance in association with sleep disturbances for females and males.

Associations	Beta (95% CI)[1]
Female - Sleep disturbances and	
Visuospatial memory† (n=12,965)	-0.0015 (-0.0185, 0.0156)
Reaction time† (n=12,915)	0.0416 (0.0252, 0.0580) ***
Prospective memory† (n=12,959)	0.0004 (-0.0164, 0.0172)
Fluid intelligence (n=12,777)	-0.0188 (-0.0364, -0.0012)
Working memory (n=9,260)	-0.0227 (-0.0427, -0.0028)
Executive function (n=8,868)	-0.0689 (-0.0895, -0.0482) ***
Male - Sleep disturbances and	
Visuospatial memory† (n=10,783)	0.0118 (-0.0070, 0.0306)
Reaction time† (n=10,743)	0.0441 (0.0257, 0.0625) ***
Prospective memory† (n=10,780)	0.0093 (-0.0093, 0.0278)
Fluid intelligence (n=10,615)	-0.0345 (-0.0535, -0.0152) ***
Working memory (n=7,619)	-0.0387 (-0.0605, -0.0169) ***
Executive function (n=7,277)	-0.0728 (-0.0954, -0.0502) ***

Legend: * = p<0.05, ** = p<0.01, *** = p<0.001; †higher score signifies worse performance; [1]Adjusted for age, BMI, waist-to-hip ratio, income, Townsend Deprivation Index, education, depression, alcohol intake, physical activity, smoking status, sleep duration, hypertension, diabetes, inflammation, and dyslipidemia; Benjamini-Hochberg corrected for multiple comparison.

Table 6: Cognitive performance in association with subjective sleep measures

Associations	Snoring - Beta (95% CI)[1]	Daytime Sleepiness - Beta (95% CI)[1]	Likelihood to nap - Beta (95% CI)[1]	Difficulty getting up - Beta (95% CI)[1]
Visuospatial memory† (n=23,748)	0.0122 (-0.0149, 0.0394)	-0.0099 (-0.0361, 0.0161)	0.0275 (0.0064, 0.0487)*	-0.0108 (-0.0283, 0.0067)
Reaction time† (n=23,658)	-0.0040 (-0.0302, 0.0221)	0.0432 (0.0179, 0.0684)**	0.0279 (0.0074, 0.0483)*	-0.0185 (-0.0354, -0.0016)
Prospective memory† (n=23,739)	0.0041 (-0.0308, 0.0226)	0.0074 (-0.0183, 0.0332)	-0.0033 (-0.0242, 0.0176)	-0.0075 (-0.0249, 0.0097)
Fluid intelligence (n=23,392)	-0.0225 (-0.0503, 0.0053)	-0.0115 (-0.0383, 0.0153)	-0.0304 (-0.0521, -0.0087)*	-0.0278 (-0.0458, -0.0099)**
Working memory (n=16,879)	-0.0015 (-0.0332, 0.0302)	-0.0190 (-0.0495, 0.0114)	-0.0393 (-0.0639, -0.0146)***	-0.0351 (-0.0557, -0.0144)**
Executive function (n=16,145)	0.0134 (-0.0197, 0.0464)	-0.0693 (-0.1009, -0.0377)***	-0.0522 (-0.0778, -0.0266)***	-0.0069 (-0.0283, 0.0145)

Legend: * = p<0.05, ** = p<0.01, *** = p<0.001; †higher score signifies worse performance; [1]Adjusted for age, sex, BMI, waist-to-hip ratio, income, Townsend deprivation Index, education, depression, alcohol intake, physical activity, smoking status, sleep duration, hypertension, diabetes, inflammation, and dyslipidemia; Benjamini-Hochberg corrected for multiple comparison.

10. Associations between sleep disturbances and cognitive performance in a Parkinson's population

10.1 Objectives

The primary objective of this study was, in the PD population of the UK Biobank, to investigate the effect of sleep-disordered breathing, defined as OSA and/or self-reported loud snoring, on cognitive performance. The secondary objective was to investigate the effect of EDS, a common consequence of PD, on cognitive performance, independent of known covariates such as hypertension and depression.

In the PD population of the UK Biobank, we hypothesize that sleep-disordered breathing, defined as snoring and/or OSA, are associated with poorer cognitive performance, and that subjective EDS is associated with poorer cognitive performance.

10.2 Methods

Study Population

Data collected at the initial assessment of the UK Biobank was used, which included demographic, lifestyle, and biological data from approximately 500,000 participants. We only included participants with an inpatient record of PD and/or self-reported PD and no other neurological disorders (n=2111). We then excluded participants with missing data for snoring or EDS (n=235). All participants signed informed consent forms prior to participating in the UK Biobank project, which was approved by the North-West Multi-Centre Research Ethics Committee. This research was conducted using the UK Biobank Resource under Application Number 35605.

Sleep disturbances

We investigated 2 different definitions of sleep disturbances: 1) an OSA diagnosis from inpatient records and/or self-reported snoring by answer "yes" to "Does your partner or a close relative or friend complain about your snoring"; and 2) self-reported EDS variable by answering "How likely are you to doze off or fall asleep during the daytime when you don't meant to?" with i) Never/rarely, ii) Sometimes, iii) Often, or iv) All the time. We dichotomized the EDS variable by grouping participants who answered "Sometimes", "Often" and "All the time" into "EDS" and participants who answered "Never/rarely" were categorized as "no EDS".

Cognitive Tests

Cognition was measured using the same tests described in **Ch. 9.2 Methods – Cognition**. The tower rearranging task used to measure executive function was not tested during initial assessment, therefore was excluded in this chapter's analyses.

Statistical Analyses

We used R and the base package[220] to perform all statistical analyses. Student's T-test was used with continuous variables and Chi-square test was used with categorical variables to evaluate the differences in demographic characteristics between PD patients with OSA and/or snoring and patients without OSA or snoring. Univariable linear regression modeling was performed to investigate relationships between each baseline characteristics and cognitive performance.

Multiple linear regression modeling was used to evaluate the associations between the 2 definitions of sleep disturbances, 1) OSA and/or snoring and 2) EDS, with each cognitive test, respectively. We investigated an unadjusted model, model 2 adjusted for age, sex, BMI and

education, and model 3 adjusted for model 2 covariates in addition to hypertension, diabetes, depression, and EDS. We also investigated the association between EDS and cognitive outcomes using multiple linear regression model and similarly evaluated an unadjusted model, model 2 and model 3 confounders, except we removed EDS as covariate in model 3.

10.3 Results

Demographic Characteristics

We identified 1,876 individuals with PD in the UK Biobank, with 39.8% reporting OSA and/or snoring (Table 7). Of the PD patients reporting OSA and/or snoring, 71.9% were male. There was also a significantly larger proportion of those with OSA and/or snoring having hypertension and higher BMI and WHR. Participants who had neither OSA or snoring had longer PD duration and interestingly, EDS was not significantly different between both groups.

Age, BMI, education, hypertension, depression, and EDS were associated with changes in cognitive performance

Univariable linear regression showed that years of education was associated with better working memory, fluid intelligence and faster processing speed (Table 8). Age was associated with poorer visuospatial memory and slower processing speed. Male sex was associated with faster processing speed. Hypertension was associated with poorer performance in fluid intelligence, visuospatial memory, and slower processing speed. Depression was associated with poorer working memory, fluid intelligence, and visuospatial memory as well as slower reaction time. Finally, EDS was associated with poorer performance in fluid intelligence and slower reaction time.

WHR, PD duration, past smoking, current smoking, diabetes, and stroke were not significantly associated with any of the cognitive tests.

OSA and/or snoring was associated with better working memory and faster processing speed

In the unadjusted model, OSA and/or snoring was associated with better working memory and faster processing speed (Table 9). In model 2, after adjusting for age, sex, BMI, and education, OSA and/or snoring was still significantly associated with improved working memory, but no longer associated with reaction time. In model 3, OSA and/or snoring was significantly associated with faster reaction time and no longer associated with working memory, independent of model 2 covariates in addition to hypertension, diabetes, depression, and EDS.

We performed a sensitivity analysis using only OSA diagnosis as the exposure and there were no significant associations with any of the cognitive tests, possibly due to reduced sample size.

EDS was associated with slower processing speed, independent of covariates

In the unadjusted model, EDS was associated with poorer performance in fluid intelligence and slower reaction time (Table 10). After adjusting for the covariates of model 2, EDS was only associated with slower reaction time. Similarly, in model 3, EDS was only associated with slower reaction time.

10.4 Tables

Table 7: Demographic characteristics of the PD population in the UK Biobank (N=1,876)

	OSA and/or snoring (n=747)	No OSA or snoring (n=1129)	p-value*
Age (years)	62.8 (5.1)	62.9 (5.7)	ns
Sex (n male, %)	537 (71.9)	640 (56.7)	<0.001
Body mass index (kg/m^2)	28.3 (4.4)	27.1 (4.6)	<0.001
Waist-to-hip ratio	0.92 (0.08)	0.89 (0.09)	<0.001
Parkinson's disease duration (years)	10.4 (6.1)	11.3 (6.7)	0.001
Education (years)	12.4 (2.6)	12.6 (2.5)	ns
Ever smoked (n, %)	451 (60.4)	630 (55.8)	ns
Current smoker (n, %)	51 (6.8)	65 (5.8)	ns
Hypertension (n, %)	387 (51.8)	509 (45.1)	0.005
Diabetes (n, %)	56 (7.5)	98 (8.7)	ns
Stroke (n, %)	19 (2.5)	27 (2.4)	ns
Heart attack (n, %)	29 (3.9)	50 (4.4)	ns
Depression (n, %)	126 (16.9)	193 (17.1)	ns
Excessive daytime sleepiness (n, %)	331 (44.3)	457 (40.4)	ns

*Student's T-test was used for continuous variables and Chi-square test was used for categorical variables; ns = nonsignificant at $p \geq 0.05$.

Table 8: Univariable analyses of baseline characteristics in association with cognitive outcomes in individuals with PD.

Characteristics	Working memory (n=171) - Beta	Fluid intelligence (n=519) - Beta	Prospective memory † (n=560) - Beta	Visuospatial memory† (n=1846) - Beta	Processing speed† (n=1809) - Beta
Age	0.030	-0.032	0.0059	0.041***	3.68***
Sex (male)	0.51	0.31	-0.036	0.069	-25.9***
Body Mass Index	-0.016	-0.060**	0.0085	0.0003	0.54
Waist-to-hip ratio	1.153	-1.55	0.30	0.80	-7.9
PD duration	-0.0043	-0.020	-0.0009	0.013	0.3
Education (years)	0.13**	0.26***	-0.011	-0.027	-5.2***
Ever smoked	0.10	0.21	-0.022	-0.094	0.66
Current smoker	-0.04	-0.11	0.021	-0.13	0.87
Hypertension	0.22	-0.43*	0.073	0.26*	26.5***
Diabetes	-0.88	-0.46	0.075	0.16	2.3
Stroke	-0.59	0.30	-0.16	-0.35	-42.35
Heart Attack	-0.97	0.47	0.057	-0.28	16.1
Depression	-0.57*	-0.61*	0.0087	0.30*	28.8**

Legend: * = p<0.05, ** = p<0.01, *** = p<0.001; †higher score signifies worse performance

Table 9: Cognitive performance in association with snoring and/or OSA in individuals with PD.

Associations	Unadjusted – Beta (95%CI)	Model 2[a] – Beta (95%CI)	Model 3[b] – Beta (95%CI)
Working memory (n=171)	0.56 (0.15, 0.97)**	0.45 (0.033, 0.86)*	0.39 (-0.025, 0.81)
Fluid intelligence (n=519)	0.28 (-0.094, 0.66)	0.29 (-0.085, 0.67)	0.32 (-0.063, 0.69)
Prospective memory† (n=560)	-0.027 (-0.11, 0.060)	-0.30 (-0.12, 0.060)	-0.033 (-0.12, 0.060)
Visuospatial memory† (n=1846)	-0.15 (-0.35, 0.047)	-0.14 (-0.34, 0.065)	-0.14 (-0.34, 0.061)
Reaction time† (n=1809)	-20.61 (-35.8, -5.4)**	-15.27 (-30.7, 0.19)	-16.77 (-32.1, -1.3)*

Legend: * = p<0.05, ** = p<0.01, *** = p<0.001; †higher score signifies worse performance. [a]Model 2 adjusted for age, sex, BMI, and education, [b]Model 3 adjusted as for model 2 and for hypertension, diabetes, depression, and EDS

Table 10: Cognitive performance in association with EDS in individuals with PD.

Associations	Unadjusted – Beta (95%CI)	Model 2[a] – Beta (95%CI)	Model 3[b] – Beta (95%CI)
Working memory (n=171)	-0.16 (-0.58, 0.27)	-0.28 (-0.69, 0.14)	-0.18 (-0.60, 0.24)
Fluid intelligence (n=519)	-0.40 (-0.79, -0.023)*	-0.30 (-0.67, 0.068)	-0.29 (-0.66, 0.081)
Prospective memory† (n=560)	0.023 (-0.064, 0.11)	0.0023 (-0.087, 0.092)	0.0016 (-0.088, 0.091)
Visuospatial memory† (n=1846)	0.058 (-0.14, 0.26)	0.045 (-0.15, 0.24)	0.39 (-0.16, 0.24)
Reaction time† (n=1809)	29.8 (14.7, 44.8)***	29.7 (14.5, 44.9)***	29.7 (14.5, 44.8)***

Legend: * = p<0.05, ** = p<0.01, *** = p<0.001; †higher score signifies worse performance. [a]Model 2 adjusted for age, sex, BMI, and education, [b]Model 3 adjusted as for model 2 and for hypertension, diabetes, and depression.

11. White Matter Integrity in Patients with Parkinson's Disease and Obstructive Sleep Apnea – A Pilot Study

11.1 Objectives

The primary objective of this pilot study includes using a sample PD population from the Quebec Parkinson's Network (QPN) to compare white matter integrity (WMI) in individuals with and without OSA based on the STOP-BANG questionnaire. Another objective is to investigate the associations between objective measures of OSA and WMI in a subset of PD patients, as well as collecting pilot subjective sleep measures using sleep-related questionnaires.

In the PD population of the QPN, we hypothesize that OSA contributes to the loss of WMI, independent of age, sex, PD duration, depression, and cardiometabolic comorbidities.

11.2 Methods

Study Population

Participants will be recruited from the QPN, that have collected participants' lifestyle and clinical data including PD information such as responses to PD-related questionnaires. The QPN is an open-access longitudinal repository with sociodemographic and clinical data on PD patients in Quebec, with over 1,400 PD patients registered in 2019[229]. The QPN provides a resource for clinicians and researchers to perform studies with the goal of better understanding the mechanisms of PD and develop potential treatments[229]. Participants of QPN, are also invited to participate in Clinical Biological Imaging and Genetic repository (C-BIGR), which is another open-access repository that collects clinical, biological, imaging and genetic data on patients with neurological diseases and healthy controls[230]. Inclusion criteria include 1) a diagnosis of Parkinson's disease confirmed by a neurologist, based on the Clinical Diagnostic

Criteria of the Movement Disorder Society[162], 2) sufficient knowledge of English or French to complete questionnaires and 3) available neuroimaging data within the C-BIG Repository. Exclusion criteria are 1) other major neurological disorder or 2) receiving treatment for OSA at the time of study or within 1 month prior to the brain MRI. Participants will receive an electronic informed consent form via REDCap prior to participation. The project is approved by the McGill University Health Care Centre (MUHC) Research Ethics Board.

OSA-related and sleep-related questionnaires

Screening for OSA will be done using STOP-BANG[53], a validated questionnaire that is highly sensitive for OSA in the general population. Our lab has previously found STOP-BANG to be adequately sensitive in detecting OSA in PD patients[231]. Sleep measures will be collected using the following tools: 1) Epworth Sleep Scale (ESS) to measure EDS[89] 2) Parkinson's Disease Sleep Scale – 2 (PDSS-2) to measure sleep quality related to PD[160] 3) Scales for Outcomes in Parkinson's disease – Sleep (SCOPA-S) to measure PD-related insomnia[161] 4) Geriatric Depression Scale (GDS) will be used to screen for depression[232] and lastly 5) REM Sleep Behaviour Disorder (RBD) Questionnaire (RBDSQ) to screen for RBD[233].

The questionnaires were developed in electronic form and responses will be collected using REDCap: a web-based platform for research studies to collect data remotely[234,235]. Participants will be contacted via email or phone call. An email will then be sent to interested individuals with a link to complete the informed consent document, as approved by the Research Ethics Board of MUHC. After completion of the consent form, a unique link will be sent allowing participants to answer the questionnaires on their own time and at their own pace. Two reminders will be sent if no answer is received at 2-weekly intervals.

Polysomnography

Polysomnography (PSG) data of a subset of participants were collected from other projects within our group that followed standard PSG protocols[236].

Neuroimaging

MRI data is available through the C-BIGR. Neuroimaging will be used for brain structure variables including fractional anisotropy (FA) and mean diffusivity (MD) as measures of WMI changes.

Statistical analyses

From the QPN phone and email recruitment, assuming a response rate of 25%, we expect 350 questionnaire responses. The C-BIGR currently has over 150 participants who have undergone brain MRI and recruitment is still ongoing. We expect approximately a 40% response rate in this group resulting in recruitment of 60 PD patients with brain imaging data, with 20 of them having PSG data through other studies in our lab. As of 2020, 12 participants in our lab's sleep research database were also registered with C-BIGR.

Student T-test or chi-square test will be used to evaluate differences in demographic data between patients at low compared at high risk of OSA, as determined by STOP-BANG. Univariable linear regression modeling will be performed to investigate the associations of covariates such as age, sex, BMI, and comorbidities with WM changes. Multiple linear regression model will be used to evaluate the association between OSA and WM measures while controlling for covariates determined from the univariate models. In the subset of participants with PSG data, we will evaluate the association between presence of OSA and questionnaire scores. In addition, the association of OSA variables such AHI and RDI, as well as

intermittent hypoxemia and sleep fragmentation measures, with WM changes will be investigated using similar statistical models.

11.3 Predicted Outcomes

Differences between PD patients at high risk and low risk of OSA

We predict that PD patients at high risk of OSA will be predominantly male, with hypertension, and greater age, BMI, and neck size. We also predict that PD duration, symptomatic subtypes categorized using subjective sleep questionnaires and medication will have an effect on the risk of OSA, as determined by STOP-BANG. Determining the effects of the covariates and sleep-related variables will be preliminary data in fine-tuning the methodology for future studies using STOP-BANG to assess OSA in PD populations.

WM integrity changes are more extensive in PD patients at high risk of OSA

We predict that PD patients at high risk of OSA have poorer WMI. Patients categorized at high risk of OSA, as determined by STOP-BANG, will have lower FA and greater MD compared to PD patients categorized as low risk of OSA. Similarly, we predict that PD patients with a higher AHI, respiratory disturbance index (RDI), and oxygen desaturation index (ODI) as determined by PSG, are associated with lower FA and greater MD. We will also explore effects of different sleep architecture changes on MRI findings.

Subjective sleep quality is compromised in the PD population

We predict that within our PD population, those at high risk of OSA as determined by STOP-BANG, we will observe greater frequency of participants reporting poorer subjective sleep quality as determined by ESS, PDSS-2, and SCOPA-S questionnaires compared to participants at low risk of OSA . Furthermore, the frequency of PD participants reporting depression

determined by GDS and RBD determined by RBDSQ, will also be greater compared to PD participants at low risk of OSA.

12. Discussion

This thesis investigated the interrelations of sleep disturbances, obesity and its cardiometabolic consequences, brain structural alterations and cognition an aging population of the UK Biobank, as well as the associations between sleep disturbances and cognitive performance in a PD population of the UK Biobank. Additionally, a project to investigate the effects of OSA on WMI in PD patients was described.

12.1 Effects of sleep disturbances in a normal aging population

In the normal aging population, we found that sleep disturbances defined using questions on daytime sleepiness, napping, difficulty getting up in the morning and disturbing snoring, were associated with poorer cognitive performance directly as well as indirectly through obesity, diabetes, dyslipidemia, inflammation, reduced cortical thickness and increased WMH. Furthermore, sleep disturbances were directly associated with slower reaction times and poorer performance in fluid intelligence, working memory and executive function. Sex did not moderate the associations between sleep disturbances and individual cognitive domains and the magnitude of these associations did not differ significantly between sex.

Firstly, our SEM model provided novel evidence that sleep disturbances, defined as hypersomnolence and loud snoring, were directly associated with brain structural alterations such as reduced cortical and subcortical volume and increased WMH, and directly associated with global cognitive dysfunction, using a large cohort within a single model also assessing cardiometabolic comorbidities and independently of sleep duration. Our findings fill the lack of evidence on the relations between sleep disturbances and neurocognitive consequences, previously only found in separate models and smaller studies[76,79,83,103].

Secondly, our results found sleep disturbances to be positively associated with diabetes, inflammation, and dyslipidemia. It has been previously known that sleep disturbances such as OSA and short sleep duration were associated with increased risk of metabolic and cardiovascular disease[237]. We expand on this by demonstrating these associations in a large sample size, independently of sleep duration and with a focus on sleepy-related symptoms. Moreover, the hypersomnolence aspect of our sleep disturbances definition support EDS as a risk factor of increased incidence of cardiovascular disease, morbidity and mortality using a large cohort[238,239]. However, contrary to studies that found EDS to be associated with hypertension[240–242], we found that sleep disturbances were negatively associated with hypertension. A previous study has similarly found that normotensives reported subjective EDS more frequently than hypertensives[243]. These conflicting results may be due to the heterogeneity of the underlying mechanism causing hypertension. For example, both hypertension and insomnia can be related to a hyperarousal state with increased sympathetic nervous system activation[244].

We identified sleep disturbances, defined as daytime sleepiness and loud snoring, to be associated with poorer fluid intelligence, working memory and executive function, as well as slower reaction times. This parallels a previous study that found OSA to be associated with poorer memory, attention, and executive function[86]. Our findings using a definition of sleep disturbances that includes EDS, support reports of significant cognitive differences being identified between OSA patient with and without EDS[245]. Additionally, we found that EDS symptoms are associated with poorer cognitive performance specifically in visuospatial memory, processing speed, fluid intelligence, working memory and executive function,

independent of sleep duration, obesity and cardiometabolic comorbidities. EDS is believed to be a marker for adverse effects of OSA, both with respect to cardiovascular and cognitive outcomes[95,103,104]. Our findings provide novel evidence in a large cohort that hypersomnolence symptoms are a key factor associated with poorer cognition function.

One of the possible links between sleep disturbances and cognitive dysfunction is inflammation[246]. We have found levels of the inflammatory marker CRP to be involved in the pathway between sleep disturbances and cognitive outcomes. However, pathways not involving inflammation were also identified. This would suggest that markers other than CRP might be more relevant in the process, or that inflammation is not the only mechanism involved. Alternatively, the role of CRP may be sex-related as a previous study found CRP levels moderated the effects of OSA on cognitive performance in females, but not in males[124].

Using our definition of sleep disturbances, we have found in a large population sample, that sleep disturbances were associated with increased WMH. WMH are an indicator of cerebrovascular disease and increased risk of stroke, dementia, and cognitive dysfunction[247,248]. Others have found WMH to be associated with sleep disturbances assessed through various methods, e.g. the Sleep Disturbance Symptom Questionnaire (SDSQ), actigraphy-assessed sleep changes and subjective symptoms of sleep-disordered breathing[249–251]. Data on the relationship between OSA and WMH are conflicting. Some have found an association[83,252]. In a recent study however, OSA severity measures were not associated with WMH, but EDS was not assessed[253]. Meanwhile, EDS alone in older adults has been associated with WMH[254]. Longer sleep duration has also been reported to be associated with increased WMH[255], however our results found that sleep disturbances with EDS symptoms was

associated with increased WMH, independently of sleep duration. This may implicate EDS as predisposing OSA patients to an increased risk of developing WMH. Furthermore, genetic predisposition, such as ApoE ε4 genotype, has been reported to be associated with increased of WMH[256,257]. The ApoE ε4 genotype is also a risk factor of OSA[258] and of sleep disturbances independent of AD[259]. Therefore, perhaps it is not the OSA that leads to increased WMH, but OSA-associated factors that have a greater impact.

Our definition of sleep disturbances was associated with reduced cortical thickness indirectly via diabetes, inflammation and WMH, independent of sleep duration. Furthermore, we found an association between increased WMH and reduced cortical thickness, that is in turn associated with poor cognition. These associations have been reported in smaller clinical cohorts[260,261] and we were able to provide novel evidence in a large sample size and within a single model.

When stratifying by sex, our study did not find sex as a moderating factor on the association between sleep disturbances and cognition, nor were there significant differences in cognitive performance between men and women. In contrast, a large population study found that middle-aged women at high risk of OSA (determined with STOP questionnaire), had poorer performance in episodic memory and executive function compared to middle-aged men[124]. This study further noted that inflammation mediated this association in women[124]. The conflicting results may be due to differences in defining sleep disturbances as well as adjusting for different confounders.

There is evidence that snoring is a strong predictor of OSA[45,46] and because OSA is known to be largely underdiagnosed[43,44], we used loud snoring along with questions

pertaining to hypersomnolence to define sleep disturbances. When looking at individual symptoms separately, self-reported loud snoring was not associated with changes in cognitive performance. This is in contrast to OSA studies that have found OSA to be associated with poorer cognitive outcomes[7,262,263]. There is a lack of information on the prevalence of OSA in snorers, however a pilot study reported about 75% of 273 snorers have moderate-severe OSA as determined by PSG[264].

Our findings suggest that sleep disturbances, defined as hypersomnolence and snoring, have cardiometabolic and neurocognitive consequences in the middle-aged and elderly. Next steps should be to investigate the mechanisms of these associations as well as evaluating if treating sleep disturbances may improve health consequences.

12.2 Effects of sleep disturbances on cognition in a Parkinson's population

In the PD population, using multiple linear regression, we found that the presence of OSA and/or loud snoring, was significantly associated with better working memory and faster reaction time. Depending on the confounders adjusted for in the models, sleep-disordered breathing, defined as an OSA diagnoses and/or self-reported loud snoring, were only significantly associated with better working memory, independent of age, sex, BMI, and education. However, sleep-disorder breathing was only significantly associated with faster reaction times, when we additionally adjusted for hypertension, diabetes, depression, and EDS. Investigating EDS on its own, it was associated with slower reaction times and worse fluid intelligence, although only slower reaction times remained significantly associated after adjustments.

A previous clinical study investigating OSA in PD had reported that global cognition, as measured by the Montreal Cognitive Assessment (MoCA), was poorer in PD patients with OSA compared to those without[174]. A meta-analysis on observational studies, similarly found that OSA was associated with increased PD-related global cognitive dysfunction[175]. Additionally, another meta-analysis found that several cognitive domains, such as verbal recall and recognition and executive functions were affected by poor sleep in PD patients[265]. Our results differing from previous literature were unexpected. A possible explanation may be the inclusion of self-reported snoring in our definition of sleep-disordered breathing, due to low number of OSA diagnosed in the PD population in the UK Biobank. This would have increased sensitivity, but reduced specificity for OSA. Moreover, the relationship between snoring and OSA may differ in PD patients compared with the general population[176]. We were unable to ascertain any treatment of OSA. Moreover, the self-report of snoring would require another person to be bothered by the snoring, and so might be confounded by marital status or other factors. Furthermore, we were not able to take into consideration medication use, which may have affected cognition[266–268].

Interestingly, our univariable analyses found several baseline characteristics to be associated with better cognitive performance in the PD population of the UK Biobank. Notably, higher BMI was associated with faster reaction time. As PD progresses, patients typically begin to lose weight[269], therefore higher BMI may be indicative of early PD when psychomotor activity has yet to be significantly impaired as a result of motor and non-motor symptoms. Greater number of years of education was also associated with faster reaction times as well as with better working memory and fluid intelligence. More years of education may be protective

against PD-related cognitive impairment as similar findings were reported in healthy normal middle-aged and elderly individuals, where more years of education was associated with better cognitive performance in several domains[270,271].

We investigated the associations of EDS and cognitive performance in PD patients and found that EDS was associated with poorer fluid intelligence and slower reaction times, but only the latter remained significant after adjusting for confounders. This corroborates with a systematic review that found PD patients with EDS had greater deficits in processing speed[112]. The review also reported poorer global cognition and executive function in PD patients with EDS compared to patients without[112]. However, objective rather than subjective sleepiness has been found to be more clearly related to cognitive dysfunction including attention, semantic verbal fluency and processing speed[272].

Our findings showing better cognitive performance in association with sleep-disordered breathing defined as OSA and/or snoring in PD patients warrants further work. Objective testing will be needed to confirm the associations between specific sleep disturbances with cognitive performance. Longitudinal studies will also be needed to determine causality, if any.

12.3 Potential Effects of OSA on White Matter Integrity in a Parkinson's Population

The pilot study aims to investigate the associations between subjective and objective sleep measures and WMI. This study will collect subjective and objective measures in the PD population of the QPN. Questionnaire, PSG, and MRI data will be aggregated. The findings will provide pilot data that may shine some light on the pathophysiological changes of the brain of PD patients in association with OSA.

A previous study investigated brain structural and cognitive changes in PD patients with general sleep disturbances as measured by SCOPA-nighttime scale[273]. Specifically for WM changes, they found that PD patients with sleep disturbances experienced poorer WMI compared to PD patients without[273]. However, there is little known about the WMI changes associated with OSA in PD patients. A recent population-based study on middle-aged individuals with OSA, but without PD reported that AHI and ODI were associated with WMH volume, independent of WMH risk factors[83]. Moreover, a clinical study found that prior to CPAP treatment, OSA patients without psychiatric disorders experienced cognitive impairment and increased sleepiness associated with compromised WMI[274]. CPAP treatment for 12 months was able to reverse affected regions in OSA patients that were compliant and had significant improvement in memory, attention, and executive function[274].

These findings in non-PD patients with OSA may give insight on how OSA may accelerate WM deterioration in PD patients. It may also support the notion that CPAP treatment for PD patients with OSA may be able to slow OSA-related cognitive impairment. Our study aims to fill this gap in knowledge and provide evidence supporting the importance of investigating and treating OSA to maintain sleep health in PD patients, which may provide benefits such as slowing neurodegeneration and cognitive decline.

12.4 Limitations

This thesis has many strengths such as large sample size and pre-processed brain imaging for analyses of the aging population of the UK Biobank. There were also different cognitive tests available to measure cognitive domains individually. An overarching limitation for **Ch.9** and **Ch.10**, was that we used subjective sleep measures from questionnaires as there

were no objective sleep measures and there was a small number of participants diagnosed with OSA. Furthermore, there is no information in the UK Biobank on whether participants receive treatments such as CPAP, for their sleep disturbances. The UK Biobank study population has been noted to be overall healthier and to have higher socioeconomic status than the general UK population[275]. Socioeconomic status, including education and income, is associated with cognitive status[276–278]. As such, we controlled for education, household income, and the Townsend deprivation Index in **Ch.9.** In **Ch. 10,** given the smaller sample size, we controlled for education.

A limitation from **Ch.9** was that we used self-reported hypertension and diabetes, which may result in misclassification bias. However, we increased sensitivity by including objective measures of SBP and DBP for hypertension, and glucose and Hb1Ac levels for diabetes in our definitions. A limitation from **Ch.10**, is that it is unknown what criteria were used for diagnosing PD in the UK Biobank. Although we used both self-reported and inpatient hospital records to determine PD diagnosis, there is an uncertainty of the method and if it was consistent for all diagnoses. Additionally, due to the small sample size of PD patients in the UK Biobank, we were unable to conduct a similar SEM analysis in this population and there was an even smaller number of PD patients with available brain imaging data. A limitation from **Ch. 11**, is that due to the extraordinary world circumstances over the past 2 years, there has been many delays in getting the study started. Therefore, the time interval between when a PD patient undergoes a brain MRI and when they answer sleep-related questionnaires has become longer than expected and may affect cross-sectional analyses. This project will also be limited due to small

sample size. Moreover, there may have been a delay between the PSG and the MRI. However, it is a pilot project with the aim of gathering preliminary data to help guide future studies.

12.5 Future Directions

In the normal aging population of the UK Biobank, the next steps could be investigating *brain age* as the outcome, replacing imaging and cognitive measures. *Brain age* is a relatively new and upcoming measure of how old an individual's brain is using machine learning based on neuroimaging data[279]. *Brain age* has been shown to be associated with cognitive and physiological aging of the brain as well as be able to predict risk of neurodegenerative disorders[279]. Understanding the associations between sleep disturbances, obesity, cardiometabolic consequences and *brain age*, may provide new evidence on the importance of sleep health in the middle-aged and elderly. Additionally, the UK Biobank has genetic information, such as genotyping, and future work should investigate for genetic predisposition.

In the PD population of the UK Biobank, as the database continues to perform brain imaging, it may become possible to have a large enough sample size to conduct analyses using brain imaging measures as outcomes. Moreover, similar to the next steps for the normal aging population, investigation using *brain age* as an outcome in the PD population may provide new information on the effect of sleep disturbances on brain health of PD patients. Genotyping data should also be considered to investigate the role of genetics in these associations.

Based on the predicted results in **Ch.11.3**, observational and interventional studies investigating how treating OSA in PD patients could alter WMI should be conducted and could provide evidence on the importance of sleep health in PD evolution.

13. Final Conclusion and Summary

The primary objective of **Ch.9**, investigating the interrelations between sleep disturbances, defined as hypersomnolence and snoring, obesity, cardiometabolic disorders, brain structural alterations and cognition in a normal aging population of the UK Biobank, was met by conducting SEM analysis. Since a direct association between sleep disturbances and cognition was found in the SEM, the secondary objectives related to the normal aging population were conducted. Investigation of the associations between sleep disturbances and specific cognitive domains was met by conducting multiple linear modelling with 6 cognitive tests as outcomes. Furthermore, moderation analyses were conducted to meet the objective of evaluating sex-related effects on the associations between sleep disturbances and cognitive performances.

The primary objective of **Ch.10**, investigating the effect of sleep-disordered breathing, defined as an OSA diagnosis and/or self-reported loud snoring, on cognitive performance in the PD population of the UK Biobank, was met by conducting multiple linear regression with 5 different cognitive tests as outcomes. Another objective we investigated was the effect of subjective EDS on cognitive performance. This objective was met by conducted multiple linear regression with the 5 cognitive tests as outcomes and was able to evaluate which cognitive domains were associated with EDS in PD patients.

The primary objective of **Ch.11** will be to investigate differences in WMI, measured as FA and MD, in PD populations at high-risk and at low-risk of OSA as determined by STOP-BANG questionnaire. Multiple linear regression modelling will be used to conduct research on these associations. In addition, investigating the associations between objective sleep measures and

WMI measures will be conducted in a subset of PD patient with PSG data and MRI data and multiple linear regression modelling will be used to obtain pilot data on these associations. Finally, subjective sleep quality data collected via sleep-related questionnaires, will be conducted to better understand how sleep is affected in PD patients

In conclusion, the findings described in this thesis provide evidence that sleep plays an important role on the overall health of middle-age and elderly individuals, including those with neurodegenerative conditions like PD. The findings demonstrate that sleep disturbances, such as loud snoring, EDS and/or OSA, have health consequences beyond poor sleep quality and short sleep duration. In the normal aging population, the findings emphasize the need to routinely investigate and subsequently treat sleep disturbances, which may be key to slowing down cognitive decline. In the PD population, the findings suggest more research is needed to ascertain the relationship of OSA and subjective loud snoring with cognitive function, as well as emphasize EDS as a notable symptom of PD.

14. Reference List

1. Spira AP, Chen-Edinboro LP, Wu MN, Yaffe K. Impact of Sleep on the Risk of Cognitive Decline and Dementia. *Curr Opin Psychiatry*. 2014;27(6):478-483. doi:10.1097/YCO.0000000000000106

2. Olivari BS, French ME, McGuire LC. The Public Health Road Map to Respond to the Growing Dementia Crisis. Albert SM, ed. *Innov Aging*. 2020;4(1):igz043. doi:10.1093/geroni/igz043

3. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-Analysis of Quantitative Sleep Parameters From Childhood to Old Age in Healthy Individuals: Developing Normative Sleep Values Across the Human Lifespan. *Sleep*. 2004;27(7):1255-1273. doi:10.1093/sleep/27.7.1255

4. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev*. 2017;34:70-81. doi:10.1016/j.smrv.2016.07.002

5. Hayley AC, Williams LJ, Kennedy GA, Berk M, Brennan SL, Pasco JA. Prevalence of excessive daytime sleepiness in a sample of the Australian adult population. *Sleep Med*. 2014;15(3):348-354. doi:10.1016/j.sleep.2013.11.783

6. Jaussent I, Bouyer J, Ancelin ML, et al. Excessive Sleepiness is Predictive of Cognitive Decline in the Elderly. *Sleep*. 2012;35(9):1201-1207. doi:10.5665/sleep.2070

7. Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. *Respirol Carlton Vic*. 2013;18(1):61-70. doi:10.1111/j.1440-1843.2012.02255.x

8. Stranks EK, Crowe SF. The Cognitive Effects of Obstructive Sleep Apnea: An Updated Meta-analysis. *Arch Clin Neuropsychol*. 2016;31(2):186-193. doi:10.1093/arclin/acv087

9. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of Sleep-Disordered Breathing With Cognitive Function and Risk of Cognitive Impairment. *JAMA Neurol*. 2017;74(10):1237-1245. doi:10.1001/jamaneurol.2017.2180

10. Menza M, Dobkin RD, Marin H, Bienfait K. Sleep disturbances in Parkinson's disease. *Mov Disord*. 2010;25(S1):S117-S122. doi:10.1002/mds.22788

11. Bancej C, Jayabalasingham B, Wall RW, et al. Trends and projections of obesity among Canadians. *Health Promot Chronic Dis Prev Can Res Policy Pract*. 2015;35(7):109-112.

12. Apovian CM. Obesity: Definition, Comorbidities, Causes, and Burden. *Am J Manag CARE*. 2016;22(7):10.

13. Morys F, Dadar M, Dagher A. Association Between Midlife Obesity and Its Metabolic Consequences, Cerebrovascular Disease, and Cognitive Decline. *J Clin Endocrinol Metab*. 2021;106(10):e4260-e4274. doi:10.1210/clinem/dgab135

14. Marks R, Landaira M. Sleep, Disturbances of Sleep, Stress and Obesity: A Narrative Review. *J Obes Eat Disord*. 2015;1(2). doi:10.21767/2471-8203.100006

15. Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK. Interactions Between Obesity and Obstructive Sleep Apnea: Implications for Treatment. *Chest*. 2010;137(3):711-719. doi:10.1378/chest.09-0360

16. Jehan S, Zizi F, Pandi-Perumal SR, et al. Obstructive Sleep Apnea and Obesity: Implications for Public Health. *Sleep Med Disord Int J*. 2017;1(4):00019.

17. Vyazovskiy VV. Sleep, recovery, and metaregulation: explaining the benefits of sleep. *Nat Sci Sleep*. 2015;7:171-184. doi:10.2147/NSS.S54036

18. Colten HR, Altevogt BM, Research I of M (US) C on SM and. *Extent and Health Consequences of Chronic Sleep Loss and Sleep Disorders*. National Academies Press (US); 2006. Accessed April 30, 2022. https://www.ncbi.nlm.nih.gov/books/NBK19961/

19. Shochat T. Impact of lifestyle and technology developments on sleep. *Nat Sci Sleep*. 2012;4:19-31. doi:10.2147/NSS.S18891

20. Beccuti G, Pannain S. Sleep and obesity. *Curr Opin Clin Nutr Metab Care*. 2011;14(4):402-412. doi:10.1097/MCO.0b013e3283479109

21. Ogilvie RP, Patel SR. The epidemiology of sleep and obesity. *Sleep Health*. 2017;3(5):383-388. doi:10.1016/j.sleh.2017.07.013

22. Calhoun DA, Harding SM. Sleep and Hypertension. *Chest*. 2010;138(2):434-443. doi:10.1378/chest.09-2954

23. Bansil P, Kuklina EV, Merritt RK, Yoon PW. Associations Between Sleep Disorders, Sleep Duration, Quality of Sleep, and Hypertension: Results From the National Health and Nutrition Examination Survey, 2005 to 2008. *J Clin Hypertens*. 2011;13(10):739-743. doi:10.1111/j.1751-7176.2011.00500.x

24. Benitez A, Gunstad J. Poor Sleep Quality Diminishes Cognitive Functioning Independent of Depression and Anxiety in Healthy Young Adults. *Clin Neuropsychol*. 2012;26(2):214-223. doi:10.1080/13854046.2012.658439

25. Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol*. 2014;13(10):1017-1028. doi:10.1016/S1474-4422(14)70172-3

26. Mathers CD, Stevens GA, Boerma T, White RA, Tobias MI. Causes of international increases in older age life expectancy. *The Lancet*. 2015;385(9967):540-548. doi:10.1016/S0140-6736(14)60569-9

27. He W, Goodkind D, Kowal P. *An Aging World: 2015.*; 2016. doi:10.13140/RG.2.1.1088.9362

28. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet*. 2012;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2

29. World Health Organization. *Multimorbidity*. World Health Organization; 2016. Accessed May 17, 2022. https://apps.who.int/iris/handle/10665/252275

30. Hazra NC, Rudisill C, Gulliford MC. Determinants of health care costs in the senior elderly: age, comorbidity, impairment, or proximity to death? *Eur J Health Econ*. 2018;19(6):831-842. doi:10.1007/s10198-017-0926-2

31. Deary IJ, Corley J, Gow AJ, et al. Age-associated cognitive decline. *Br Med Bull*. 2009;92(1):135-152. doi:10.1093/bmb/ldp033

32. Hugo J, Ganguli M. Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment. *Clin Geriatr Med*. 2014;30(3):421-442. doi:10.1016/j.cger.2014.04.001

33. Rossini PM, Rossi S, Babiloni C, Polich J. Clinical neurophysiology of aging brain: From normal aging to neurodegeneration. *Prog Neurobiol*. 2007;83(6):375-400. doi:10.1016/j.pneurobio.2007.07.010

34. Hou Y, Dan X, Babbar M, et al. Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol*. 2019;15(10):565-581. doi:10.1038/s41582-019-0244-7

35. Costantino S, Paneni F, Cosentino F. Ageing, metabolism and cardiovascular disease. *J Physiol*. 2016;594(8):2061-2073. doi:10.1113/JP270538

36. Pace-Schott EF, Spencer RMC. Chapter 5 - Age-related changes in the cognitive function of sleep. In: Green AM, Chapman CE, Kalaska JF, Lepore F, eds. *Progress in Brain Research*. Vol 191. Enhancing Performance for Action and Perception. Elsevier; 2011:75-89. doi:10.1016/B978-0-444-53752-2.00012-6

37. Mander BA, Winer JR, Walker MP. Sleep and Human Aging. *Neuron*. 2017;94(1):19-36. doi:10.1016/j.neuron.2017.02.004

38. Espiritu JRD. Aging-Related Sleep Changes. *Clin Geriatr Med*. 2008;24(1):1-14. doi:10.1016/j.cger.2007.08.007

39. Ancoli-Israel S. Sleep and its disorders in aging populations. *Sleep Med*. 2009;10:S7-S11. doi:10.1016/j.sleep.2009.07.004

40. Miner B, Kryger MH. Sleep in the Aging Population. *Sleep Med Clin*. 2017;12(1):31-38. doi:10.1016/j.jsmc.2016.10.008

41. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population—a review on the epidemiology of sleep apnea. *J Thorac Dis*. 2015;7(8):1311-1322. doi:10.3978/j.issn.2072-1439.2015.06.11

42. Glasser M, Bailey N, McMillan A, Goff E, Morrell MJ. Sleep apnoea in older people. *Breathe*. 2011;7(3):248-256. doi:10.1183/20734735.021910

43. Gibson GJ. Obstructive sleep apnoea syndrome: underestimated and undertreated. *Br Med Bull*. 2004;72(1):49-64. doi:10.1093/bmb/ldh044

44. Sia CH, Lee CH, Tan CY, et al. Awareness and knowledge of obstructive sleep apnea in the general population. *Eur Respir J*. 2016;48(suppl 60). doi:10.1183/13993003.congress-2016.PA2322

45. Sowho M, Sgambati F, Guzman M, Schneider H, Schwartz A. Snoring: a source of noise pollution and sleep apnea predictor. *Sleep*. 2020;43(6):zsz305. doi:10.1093/sleep/zsz305

46. Myers KA, Mrkobrada M, Simel DL. Does This Patient Have Obstructive Sleep Apnea?: The Rational Clinical Examination Systematic Review. *JAMA*. 2013;310(7):731-741. doi:10.1001/jama.2013.276185

47. Rundo JV, Downey R. Chapter 25 - Polysomnography. In: Levin KH, Chauvel P, eds. *Handbook of Clinical Neurology*. Vol 160. Clinical Neurophysiology: Basis and Technical Aspects. Elsevier; 2019:381-392. doi:10.1016/B978-0-444-64032-1.00025-4

48. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep*. 1999;22(5):667-689.

49. Redline S, Kapur VK, Sanders MH, et al. Effects of Varying Approaches for Identifying Respiratory Disturbances on Sleep Apnea Assessment. *Am J Respir Crit Care Med*. 2000;161(2):369-374. doi:10.1164/ajrccm.161.2.9904031

50. Ruehland WR, Rochford PD, O'Donoghue FJ, Pierce RJ, Singh P, Thornton AT. The New AASM Criteria for Scoring Hypopneas: Impact on the Apnea Hypopnea Index. *Sleep*. 2009;32(2):150-157.

51. Corral J, Sánchez-Quiroga MÁ, Carmona-Bernal C, et al. Conventional Polysomnography Is Not Necessary for the Management of Most Patients with Suspected Obstructive Sleep

Apnea. Noninferiority, Randomized Controlled Trial. *Am J Respir Crit Care Med*. 2017;196(9):1181-1190. doi:10.1164/rccm.201612-2497OC

52. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med*. 1999;131(7):485-491. doi:10.7326/0003-4819-131-7-199910050-00002

53. Chung F, Abdullah HR, Liao P. STOP-Bang Questionnaire: A Practical Approach to Screen for Obstructive Sleep Apnea. *Chest*. 2016;149(3):631-638. doi:10.1378/chest.15-0903

54. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased Prevalence of Sleep-Disordered Breathing in Adults. *Am J Epidemiol*. 2013;177(9):1006-1014. doi:10.1093/aje/kws342

55. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med*. 2015;3(4):310-318. doi:10.1016/S2213-2600(15)00043-0

56. Simpson L, Mukherjee S, Cooper MN, et al. Sex Differences in the Association of Regional Fat Distribution with the Severity of Obstructive Sleep Apnea. *Sleep*. 2010;33(4):467-474.

57. Bonsignore MR, Saaresranta T, Riha RL. Sex differences in obstructive sleep apnoea. *Eur Respir Rev Off J Eur Respir Soc*. 2019;28(154):190030. doi:10.1183/16000617.0030-2019

58. Perger E, Mattaliano P, Lombardi C. Menopause and Sleep Apnea. *Maturitas*. 2019;124:35-38. doi:10.1016/j.maturitas.2019.02.011

59. Zolfaghari S, Yao C, Thompson C, et al. Effects of menopause on sleep quality and sleep disorders: Canadian Longitudinal Study on Aging. *Menopause*. 2020;27(3):295-304. doi:10.1097/GME.0000000000001462

60. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):608-613. doi:10.1164/ajrccm.163.3.9911064

61. Cowan DC, Livingston E. Obstructive Sleep Apnoea Syndrome and Weight Loss: Review. *Sleep Disord*. 2012;2012:163296. doi:10.1155/2012/163296

62. Lim YH, Choi J, Kim KR, et al. Sex-specific characteristics of anthropometry in patients with obstructive sleep apnea: neck circumference and waist-hip ratio. *Ann Otol Rhinol Laryngol*. 2014;123(7):517-523. doi:10.1177/0003489414526134

63. Castriotta RJ, Chung P. Cutting for Cures: Bariatric Surgery and Obstructive Sleep Apnea. *J Clin Sleep Med*. 2019;15(10):1391-1392. doi:10.5664/jcsm.8008

64. Zinchuk A, Yaggi HK. Phenotypic Subtypes of OSA: A Challenge and Opportunity for Precision Medicine. *Chest*. 2020;157(2):403-420. doi:10.1016/j.chest.2019.09.002

65. Ye L, Pien GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J*. 2014;44(6):1600-1607. doi:10.1183/09031936.00032314

66. Keenan BT, Kim J, Singh B, et al. Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. *Sleep*. 2018;41(3):zsx214. doi:10.1093/sleep/zsx214

67. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom Subtypes of Obstructive Sleep Apnea Predict Incidence of Cardiovascular Outcomes. *Am J Respir Crit Care Med*. 2019;200(4):493-506. doi:10.1164/rccm.201808-1509OC

68. Allen AJH, Jen R, Mazzotti DR, et al. Symptom subtypes and risk of incident cardiovascular and cerebrovascular disease in a clinic-based obstructive sleep apnea cohort. *J Clin Sleep Med*. Published online April 25, 2022. doi:10.5664/jcsm.9986

69. Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive Sleep Apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension*. 2011;58(5):811-817. doi:10.1161/HYPERTENSIONAHA.111.179788

70. Bisogni V, Pengo MF, Maiolino G, Rossi GP. The sympathetic nervous system and catecholamines metabolism in obstructive sleep apnoea. *J Thorac Dis*. 2016;8(2):243-254. doi:10.3978/j.issn.2072-1439.2015.11.14

71. Reutrakul S, Mokhlesi B. Obstructive Sleep Apnea and Diabetes. *Chest*. 2017;152(5):1070-1086. doi:10.1016/j.chest.2017.05.009

72. Zhao J, Wang W, Wei S, Yang L, Wu Y, Yan B. Fragmented Sleep and the Prevalence of Hypertension in Middle-Aged and Older Individuals. *Nat Sci Sleep*. 2021;13:2273-2280. doi:10.2147/NSS.S337932

73. Reutrakul S, Van Cauter E. Interactions between sleep, circadian function, and glucose metabolism: implications for risk and severity of diabetes. *Ann N Y Acad Sci*. 2014;1311(1):151-173. doi:10.1111/nyas.12355

74. Bjorvatn B, Lehmann S, Gulati S, Aurlien H, Pallesen S, Saxvig IW. Prevalence of excessive sleepiness is higher whereas insomnia is lower with greater severity of obstructive sleep apnea. *Sleep Breath*. 2015;19(4):1387-1393. doi:10.1007/s11325-015-1155-5

75. Lal C, Weaver TE, Bae CJ, Strohl KP. Excessive Daytime Sleepiness in Obstructive Sleep Apnea. Mechanisms and Clinical Management. *Ann Am Thorac Soc*. 2021;18(5):757-768. doi:10.1513/AnnalsATS.202006-696FR

76. Koo DL, Kim HR, Kim H, Seong JK, Joo EY. White matter tract-specific alterations in male patients with untreated obstructive sleep apnea are associated with worse cognitive function. *Sleep*. 2020;43(3). doi:10.1093/sleep/zsz247

77. Soares J, Marques P, Alves V, Sousa N. A hitchhiker's guide to diffusion tensor imaging. *Front Neurosci*. 2013;7. Accessed May 14, 2022. https://www.frontiersin.org/article/10.3389/fnins.2013.00031

78. Huang W, Li H, Li H, Huang T, Yuan S, Lü T. White matter lesions are associated with obstructive sleep apnea hypopnea syndrome. *Neurol Res*. 2022;44(5):423-428. doi:10.1080/01616412.2021.2000823

79. Joo EY, Tae WS, Lee MJ, et al. Reduced Brain Gray Matter Concentration in Patients With Obstructive Sleep Apnea Syndrome. *Sleep*. 2010;33(2):235-241.

80. Huang X, Tang S, Lyu X, Yang C, Chen X. Structural and functional brain alterations in obstructive sleep apnea: a multimodal meta-analysis. *Sleep Med*. 2019;54:195-204. doi:10.1016/j.sleep.2018.09.025

81. Baril AA, Gagnon K, Brayet P, et al. Gray Matter Hypertrophy and Thickening with Obstructive Sleep Apnea in Middle-aged and Older Adults. *Am J Respir Crit Care Med*. 2017;195(11):1509-1518. doi:10.1164/rccm.201606-1271OC

82. Baril AA, Martineau-Dussault MÈ, Sanchez E, et al. Obstructive Sleep Apnea and the Brain: a Focus on Gray and White Matter Structure. *Curr Neurol Neurosci Rep*. 2021;21(3):11. doi:10.1007/s11910-021-01094-2

83. Zacharias HU, Weihs A, Habes M, et al. Association Between Obstructive Sleep Apnea and Brain White Matter Hyperintensities in a Population-Based Cohort in Germany. *JAMA Netw Open*. 2021;4(10):e2128225. doi:10.1001/jamanetworkopen.2021.28225

84. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010;341:c3666. doi:10.1136/bmj.c3666

85. Ayalon L, Ancoli-Israel S, Drummond SPA. Obstructive Sleep Apnea and Age A Double Insult to Brain Function? *Am J Respir Crit Care Med*. 2010;182(3):413-419. doi:10.1164/rccm.200912-1805OC

86. Krysta K, Bratek A, Zawada K, Stepańczak R. Cognitive deficits in adults with obstructive sleep apnea compared to children and adolescents. *J Neural Transm*. 2017;124(Suppl 1):187-201. doi:10.1007/s00702-015-1501-6

87. Slater G, Steier J. Excessive daytime sleepiness in sleep disorders. *J Thorac Dis*. 2012;4(6):608-616. doi:10.3978/j.issn.2072-1439.2012.10.07

88. Swanson LM, Arnedt JT, Rosekind MR, Belenky G, Balkin TJ, Drake C. Sleep disorders and work performance: findings from the 2008 National Sleep Foundation Sleep in America poll. *J Sleep Res*. 2011;20(3):487-494. doi:10.1111/j.1365-2869.2010.00890.x

89. Johns MW. A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. *Sleep*. 1991;14(6):540-545. doi:10.1093/sleep/14.6.540

90. Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal RB. The clinical use of the MSLT and MWT. *Sleep*. 2005;28(1):123-144. doi:10.1093/sleep/28.1.123

91. Littner MR, Kushida C, Wise M, et al. Practice Parameters for Clinical Use of the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. *Sleep*. 2005;28(1):113-121. doi:10.1093/sleep/28.1.113

92. Panossian LA, Veasey SC. Daytime Sleepiness in Obesity: Mechanisms Beyond Obstructive Sleep Apnea—A Review. *Sleep*. 2012;35(5):605-615. doi:10.5665/sleep.1812

93. Slater G, Pengo MF, Kosky C, Steier J. Obesity as an independent predictor of subjective excessive daytime sleepiness. *Respir Med*. 2013;107(2):305-309. doi:10.1016/j.rmed.2012.10.013

94. Mokhber S, Zargham Ravanbakhsh P, Jesmi F, Pishgahroudsari M, Ghanbari Jolfaei A, Pazouki A. Comparing the Excessive Daytime Sleepiness of Obese and Non-obese Patients. *Iran Red Crescent Med J*. 2016;18(7):e21964. doi:10.5812/ircmj.21964

95. Maugeri A, Medina-Inojosa JR, Kunzova S, et al. Sleep Duration and Excessive Daytime Sleepiness Are Associated with Obesity Independent of Diet and Physical Activity. *Nutrients*. 2018;10(9):1219. doi:10.3390/nu10091219

96. Thorp AA, Schlaich MP. Relevance of Sympathetic Nervous System Activation in Obesity and Metabolic Syndrome. *J Diabetes Res*. 2015;2015:e341583. doi:10.1155/2015/341583

97. Sareli AE, Cantor CR, Williams NN, et al. Obstructive Sleep Apnea in Patients Undergoing Bariatric Surgery—A Tertiary Center Experience. *Obes Surg*. 2011;21(3):316-327. doi:10.1007/s11695-009-9928-1

98. Fernandez-Mendoza J, Vgontzas AN, Kritikou I, Calhoun SL, Liao D, Bixler EO. Natural History of Excessive Daytime Sleepiness: Role of Obesity, Weight Loss, Depression, and Sleep Propensity. *Sleep*. 2015;38(3):351-360. doi:10.5665/sleep.4488

99. Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A. Excessive Daytime Sleepiness in a General Population Sample: The Role of Sleep Apnea, Age, Obesity, Diabetes, and Depression. *J Clin Endocrinol Metab*. 2005;90(8):4510-4515. doi:10.1210/jc.2005-0035

100. Hein M, Lanquart JP, Loas G, Hubain P, Linkowski P. Prevalence and risk factors of excessive daytime sleepiness in major depression: A study with 703 individuals referred for polysomnography. *J Affect Disord*. 2019;243:23-32. doi:10.1016/j.jad.2018.09.016

101. Zhang D, Zhang Z, Li H, Ding K. Excessive Daytime Sleepiness in Depression and Obstructive Sleep Apnea: More Than Just an Overlapping Symptom. *Front Psychiatry*. 2021;12. Accessed May 9, 2022. https://www.frontiersin.org/article/10.3389/fpsyt.2021.710435

102. Jaussent I, Bouyer J, Ancelin ML, et al. Insomnia and Daytime Sleepiness Are Risk Factors for Depressive Symptoms in the Elderly. *Sleep*. 2011;34(8):1103-1110. doi:10.5665/SLEEP.1170

103. Merlino G, Piani A, Gigli GL, et al. Daytime sleepiness is associated with dementia and cognitive decline in older Italian adults: A population-based study. *Sleep Med*. 2010;11(4):372-377. doi:10.1016/j.sleep.2009.07.018

104. Carvalho DZ, St. Louis EK, Boeve BF, et al. Excessive daytime sleepiness and fatigue may indicate accelerated brain aging in cognitively normal late middle-aged and older adults. *Sleep Med*. 2017;32:236-243. doi:10.1016/j.sleep.2016.08.023

105. Carvalho DZ, St Louis EK, Knopman DS, et al. Association of Excessive Daytime Sleepiness With Longitudinal β-Amyloid Accumulation in Elderly Persons Without Dementia. *JAMA Neurol*. 2018;75(6):672-680. doi:10.1001/jamaneurol.2018.0049

106. Maestri M, Romigi A, Schirru A, et al. Excessive daytime sleepiness and fatigue in neurological disorders. *Sleep Breath*. 2020;24(2):413-424. doi:10.1007/s11325-019-01921-4

107. Knie B, Mitra MT, Logishetty K, Chaudhuri KR. Excessive Daytime Sleepiness in Patients with Parkinson's Disease. *CNS Drugs*. 2011;25(3):203-212. doi:10.2165/11539720-000000000-00000

108. Amara AW, Chahine LM, Caspell-Garcia C, et al. Longitudinal assessment of excessive daytime sleepiness in early Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2017;88(8):653-662. doi:10.1136/jnnp-2016-315023

109. Zhu K, van Hilten JJ, Marinus J. Course and risk factors for excessive daytime sleepiness in Parkinson's disease. *Parkinsonism Relat Disord*. 2016;24:34-40. doi:10.1016/j.parkreldis.2016.01.020

110. Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. *Lancet Neurol*. 2009;8(10):929-937. doi:10.1016/S1474-4422(09)70225-X

111. Kato S, Watanabe H, Senda J, et al. Widespread cortical and subcortical brain atrophy in Parkinson's disease with excessive daytime sleepiness. *J Neurol*. 2012;259(2):318-326. doi:10.1007/s00415-011-6187-6

112. Jester DJ, Lee S, Molinari V, Volicer L. Cognitive deficits in Parkinson's disease with excessive daytime sleepiness: a systematic review. *Aging Ment Health*. 2020;24(11):1769-1780. doi:10.1080/13607863.2019.1660852

113. Lozo T, Komnenov D, Badr MS, Mateika JH. Sex differences in sleep disordered breathing in adults. *Respir Physiol Neurobiol*. 2017;245:65-75. doi:10.1016/j.resp.2016.11.001

114. Lin CM, Davidson TM, Ancoli-Israel S. Gender Differences in Obstructive Sleep Apnea and Treatment Implications. *Sleep Med Rev*. 2008;12(6):481-496. doi:10.1016/j.smrv.2007.11.003

115. Sforza E, Chouchou F, Collet P, Pichot V, Barthélémy JC, Roche F. Sex differences in obstructive sleep apnoea in an elderly French population. *Eur Respir J*. 2011;37(5):1137-1143. doi:10.1183/09031936.00043210

116. Ye L, Pien GW, Weaver TE. Gender differences in the clinical manifestation of obstructive sleep apnea. *Sleep Med*. 2009;10(10):1075-1084. doi:10.1016/j.sleep.2009.02.006

117. Wang X, Li W, Zhou J, et al. Smoking and sleep apnea duration mediated the sex difference in daytime sleepiness in OSA patients. *Sleep Breath*. 2021;25(1):289-297. doi:10.1007/s11325-020-02109-x

118. Kritikou I, Basta M, Tappouni R, et al. Sleep apnoea and visceral adiposity in middle-aged male and female subjects. *Eur Respir J*. 2013;41(3):601-609. doi:10.1183/09031936.00183411

119. Harada Y, Oga T, Chihara Y, et al. Differences in Associations between Visceral Fat Accumulation and Obstructive Sleep Apnea by Sex. *Ann Am Thorac Soc*. 2014;11(3):383-391. doi:10.1513/AnnalsATS.201306-182OC

120. Heinzer R, Marti-Soler H, Marques-Vidal P, et al. Impact of sex and menopausal status on the prevalence, clinical presentation, and comorbidities of sleep-disordered breathing. *Sleep Med*. 2018;51:29-36. doi:10.1016/j.sleep.2018.04.016

121. Greenberg-Dotan S, Reuveni H, Simon-Tuval T, Oksenberg A, Tarasiuk A. Gender Differences in Morbidity and Health Care Utilization Among Adult Obstructive Sleep Apnea Patients. *Sleep*. 2007;30(9):1173-1180. doi:10.1093/sleep/30.9.1173

122. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-Disordered Breathing, Hypoxia, and Risk of Mild Cognitive Impairment and Dementia in Older Women. *JAMA*. 2011;306(6):613-619. doi:10.1001/jama.2011.1115

123. Macey PM, Kumar R, Yan-Go FL, Woo MA, Harper RM. Sex Differences in White Matter Alterations Accompanying Obstructive Sleep Apnea. *Sleep*. 2012;35(12):1603-1613. doi:10.5665/sleep.2228

124. Thompson C, Legault J, Moullec G, et al. Association between risk of obstructive sleep apnea, inflammation and cognition after 45 years old in the Canadian Longitudinal Study on Aging. *Sleep Med*. 2022;91:21-30. doi:10.1016/j.sleep.2022.02.006

125. Bleich SN, Cutler D, Murray C, Adams A. Why Is the Developed World Obese? *Annu Rev Public Health*. 2008;29(1):273-295. doi:10.1146/annurev.publhealth.29.020907.090954

126. CDC. Defining Adult Overweight and Obesity. Centers for Disease Control and Prevention. Published May 3, 2022. Accessed May 14, 2022. https://www.cdc.gov/obesity/basics/adult-defining.html

127. Obesity. Accessed May 14, 2022. https://www.who.int/health-topics/obesity

128. Government of Canada SC. Overweight and obese adults, 2018. Published June 25, 2019. Accessed May 10, 2022. https://www150.statcan.gc.ca/n1/pub/82-625-x/2019001/article/00005-eng.htm

129. Hossain P, Kawar B, El Nahas M. Obesity and Diabetes in the Developing World — A Growing Challenge. *N Engl J Med*. 2007;356(3):213-215. doi:10.1056/NEJMp068177

130. Verma S, Hussain ME. Obesity and diabetes: An update. *Diabetes Metab Syndr Clin Res Rev*. 2017;11(1):73-79. doi:10.1016/j.dsx.2016.06.017

131. Jiang SZ, Lu W, Zong XF, Ruan HY, Liu Y. Obesity and hypertension. *Exp Ther Med*. 2016;12(4):2395-2399. doi:10.3892/etm.2016.3667

132. Zalesin KC, Franklin BA, Miller WM, Peterson ED, McCullough PA. Impact of Obesity on Cardiovascular Disease. *Endocrinol Metab Clin North Am*. 2008;37(3):663-684. doi:10.1016/j.ecl.2008.06.004

133. Ortega FB, Lavie CJ, Blair SN. Obesity and Cardiovascular Disease. *Circ Res*. 2016;118(11):1752-1770. doi:10.1161/CIRCRESAHA.115.306883

134. Bastien M, Poirier P, Lemieux I, Després JP. Overview of Epidemiology and Contribution of Obesity to Cardiovascular Disease. *Prog Cardiovasc Dis*. 2014;56(4):369-381. doi:10.1016/j.pcad.2013.10.016

135. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and Obstructive Sleep Apnea. *Proc Am Thorac Soc*. 2008;5(2):185-192. doi:10.1513/pats.200708-137MG

136. Prickett C, Brennan L, Stolwyk R. Examining the relationship between obesity and cognitive function: A systematic literature review. *Obes Res Clin Pract*. 2015;9(2):93-113. doi:10.1016/j.orcp.2014.05.001

137. Hill JO, Wyatt HR, Peters JC. Energy Balance and Obesity. *Circulation*. 2012;126(1):126-132. doi:10.1161/CIRCULATIONAHA.111.087213

138. Clarke SF, Murphy EF, Nilaweera K, et al. The gut microbiota and its relationship to diet and obesity. *Gut Microbes*. 2012;3(3):186-202. doi:10.4161/gmic.20168

139. Hruby A, Manson JE, Qi L, et al. Determinants and Consequences of Obesity. *Am J Public Health*. 2016;106(9):1656-1662. doi:10.2105/AJPH.2016.303326

140. Chaput JP. Sleep patterns, diet quality and energy balance. *Physiol Behav*. 2014;134:86-91. doi:10.1016/j.physbeh.2013.09.006

141. St-Onge MP, Wolfe S, Sy M, Shechter A, Hirsch J. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. *Int J Obes*. 2014;38(3):411-416. doi:10.1038/ijo.2013.114

142. Kivimäki M, Kuosma E, Ferrie JE, et al. Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe. *Lancet Public Health*. 2017;2(6):e277-e285. doi:10.1016/S2468-2667(17)30074-9

143. Vekic J, Zeljkovic A, Stefanovic A, Jelic-Ivanovic Z, Spasojevic-Kalimanovska V. Obesity and dyslipidemia. *Metabolism*. 2019;92:71-81. doi:10.1016/j.metabol.2018.11.005

144. Raji CA, Ho AJ, Parikshak NN, et al. Brain structure and obesity. *Hum Brain Mapp*. 2009;31(3):353-364. doi:10.1002/hbm.20870

145. Kullmann S, Schweizer F, Veit R, Fritsche A, Preissl H. Compromised white matter integrity in obesity. *Obes Rev*. 2015;16(4):273-281. doi:10.1111/obr.12248

146. Ekblad LL, Rinne JO, Puukka P, et al. Insulin Resistance Predicts Cognitive Decline: An 11-Year Follow-up of a Nationally Representative Adult Population Sample. *Diabetes Care*. 2017;40(6):751-758. doi:10.2337/dc16-2001

147. Spyridaki EC, Avgoustinaki PD, Margioris AN. Obesity, inflammation and cognition. *Curr Opin Behav Sci*. 2016;9:169-175. doi:10.1016/j.cobeha.2016.05.004

148. Tanaka H, Gourley DD, Dekhtyar M, Haley AP. Cognition, Brain Structure, and Brain Function in Individuals with Obesity and Related Disorders. *Curr Obes Rep*. 2020;9(4):544-549. doi:10.1007/s13679-020-00412-y

149. Bischof GN, Park DC. Obesity and Aging: Consequences for Cognition, Brain Structure and Brain Function. *Psychosom Med*. 2015;77(6):697-709. doi:10.1097/PSY.0000000000000212

150. Zheng JC, Chen S. Translational Neurodegeneration in the era of fast growing international brain research. *Transl Neurodegener*. 2022;11(1):1. doi:10.1186/s40035-021-00276-9

151. Aarsland D, Batzu L, Halliday GM, et al. Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primer*. 2021;7(1):1-21. doi:10.1038/s41572-021-00280-3

152. Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: A systematic review and meta-analysis. *Mov Disord*. 2014;29(13):1583-1590. doi:10.1002/mds.25945

153. Moustafa AA, Chakravarthy S, Phillips JR, et al. Motor symptoms in Parkinson's disease: A unified framework. *Neurosci Biobehav Rev*. 2016;68:727-740. doi:10.1016/j.neubiorev.2016.07.010

154. Pagonabarraga J, Kulisevsky J. Cognitive impairment and dementia in Parkinson's disease. *Neurobiol Dis*. 2012;46(3):590-596. doi:10.1016/j.nbd.2012.03.029

155. Pfeiffer RF. Non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord*. 2016;22:S119-S122. doi:10.1016/j.parkreldis.2015.09.004

156. Kurtis MM, Rodriguez-Blazquez C, Martinez-Martin P. Relationship between sleep disorders and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord*. 2013;19(12):1152-1155. doi:10.1016/j.parkreldis.2013.07.026

157. Zeng J, Wei M, Li T, et al. Risk of Obstructive Sleep Apnea in Parkinson's Disease: A Meta-Analysis. *PLOS ONE*. 2013;8(12):e82091. doi:10.1371/journal.pone.0082091

158. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. *J Neurochem*. 2016;139(S1):318-324. doi:10.1111/jnc.13691

159. Pont-Sunyer C, Hotter A, Gaig C, et al. The Onset of Nonmotor Symptoms in Parkinson's disease (The ONSET PD Study). *Mov Disord*. 2015;30(2):229-237. doi:10.1002/mds.26077

160. Trenkwalder C, Kohnen R, Högl B, et al. Parkinson's disease sleep scale—validation of the revised version PDSS-2. *Mov Disord*. 2011;26(4):644-652. doi:10.1002/mds.23476

161. Marinus J, Visser M, van Hilten JJ, Lammers GJ, Stiggelbout AM. Assessment of Sleep and Sleepiness in Parkinson Disease. *Sleep*. 2003;26(8):1049-1054. doi:10.1093/sleep/26.8.1049

162. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease: MDS-PD Clinical Diagnostic Criteria. *Mov Disord*. 2015;30(12):1591-1601. doi:10.1002/mds.26424

163. Wu T, Hallett M. The cerebellum in Parkinson's disease. *Brain*. 2013;136(3):696-709. doi:10.1093/brain/aws360

164. Biundo R, Formento-Dojot P, Facchini S, et al. Brain volume changes in Parkinson's disease and their relationship with cognitive and behavioural abnormalities. *J Neurol Sci*. 2011;310(1):64-69. doi:10.1016/j.jns.2011.08.001

165. Bohnen NI, Albin RL. White matter lesions in Parkinson disease. *Nat Rev Neurol*. 2011;7(4):229-236. doi:10.1038/nrneurol.2011.21

166. Zhang Y, Burock MA. Diffusion Tensor Imaging in Parkinson's Disease and Parkinsonian Syndrome: A Systematic Review. *Front Neurol*. 2020;11:531993. doi:10.3389/fneur.2020.531993

167. Hall JM, Ehgoetz Martens KA, Walton CC, et al. Diffusion alterations associated with Parkinson's disease symptomatology: A review of the literature. *Parkinsonism Relat Disord*. 2016;33:12-26. doi:10.1016/j.parkreldis.2016.09.026

168. Zheng Z, Shemmassian S, Wijekoon C, Kim W, Bookheimer SY, Pouratian N. DTI correlates of distinct cognitive impairments in Parkinson's disease. *Hum Brain Mapp*. 2014;35(4):1325-1333. doi:10.1002/hbm.22256

169. Aarsland D, Creese B, Politis M, et al. Cognitive decline in Parkinson disease. *Nat Rev Neurol*. 2017;13(4):217-231. doi:10.1038/nrneurol.2017.27

170. Fengler S, Liepelt-Scarfone I, Brockmann K, Schäffer E, Berg D, Kalbe E. Cognitive changes in prodromal Parkinson's disease: A review. *Mov Disord*. 2017;32(12):1655-1666. doi:10.1002/mds.27135

171. Perez F, Helmer C, Foubert-Samier A, Auriacombe S, Dartigues JF, Tison F. Risk of dementia in an elderly population of Parkinson's disease patients: A 15-year population-based study. *Alzheimers Dement*. 2012;8(6):463-469. doi:10.1016/j.jalz.2011.09.230

172. Lajoie AC, Lafontaine AL, Kimoff RJ, Kaminska M. Obstructive Sleep Apnea in Neurodegenerative Disorders: Current Evidence in Support of Benefit from Sleep Apnea Treatment. *J Clin Med*. 2020;9(2):297. doi:10.3390/jcm9020297

173. Mery VP, Gros P, Lafontaine AL, et al. Reduced cognitive function in patients with Parkinson disease and obstructive sleep apnea. *Neurology*. 2017;88(12):1120-1128. doi:10.1212/WNL.0000000000003738

174. Harmell AL, Neikrug AB, Palmer BW, et al. Obstructive Sleep Apnea and Cognition in Parkinson's disease. *Sleep Med*. 2016;21:28-34. doi:10.1016/j.sleep.2016.01.001

175. Elfil M, Bahbah EI, Attia MM, Eldokmak M, Koo BB. Impact of Obstructive Sleep Apnea on Cognitive and Motor Functions in Parkinson's Disease. *Mov Disord*. 2021;36(3):570-580. doi:10.1002/mds.28412

176. Kaminska M, Lafontaine AL, Kimoff RJ. The Interaction between Obstructive Sleep Apnea and Parkinson's Disease: Possible Mechanisms and Implications for Cognitive Function. *Park Dis*. 2015;2015:e849472. doi:10.1155/2015/849472

177. Chaiard J, Weaver TE. Update on Research and Practices in Major Sleep Disorders: Part I. Obstructive Sleep Apnea Syndrome. *J Nurs Scholarsh*. 2019;51(5):500-508. doi:10.1111/jnu.12489

178. Fantin F, Giani A, Zoico E, Rossi AP, Mazzali G, Zamboni M. Weight Loss and Hypertension in Obese Subjects. *Nutrients*. 2019;11(7):1667. doi:10.3390/nu11071667

179. Hamman RF, Wing RR, Edelstein SL, et al. Effect of Weight Loss With Lifestyle Intervention on Risk of Diabetes. *Diabetes Care*. 2006;29(9):2102-2107. doi:10.2337/dc06-0560

180. Clifton PM, Keogh JB. Effects of Different Weight Loss Approaches on CVD Risk. *Curr Atheroscler Rep*. 2018;20(6):27. doi:10.1007/s11883-018-0728-8

181. Tuomilehto H, Seppä J, Uusitupa M. Obesity and obstructive sleep apnea – Clinical significance of weight loss. *Sleep Med Rev*. 2013;17(5):321-329. doi:10.1016/j.smrv.2012.08.002

182. Chang HP, Chen YF, Du JK. Obstructive sleep apnea treatment in adults. *Kaohsiung J Med Sci*. 2020;36(1):7-12. doi:10.1002/kjm2.12130

183. Mitchell LJ, Davidson ZE, Bonham M, O'Driscoll DM, Hamilton GS, Truby H. Weight loss from lifestyle interventions and severity of sleep apnoea: a systematic review and meta-analysis. *Sleep Med*. 2014;15(10):1173-1183. doi:10.1016/j.sleep.2014.05.012

184. Cao MT, Sternbach JM, Guilleminault C. Continuous positive airway pressure therapy in obstuctive sleep apnea: benefits and alternatives. *Expert Rev Respir Med*. 2017;11(4):259-272. doi:10.1080/17476348.2017.1305893

185. Sánchez AI, Martínez P, Miró E, Bardwell WA, Buela-Casal G. CPAP and behavioral therapies in patients with obstructive sleep apnea: Effects on daytime sleepiness, mood, and cognitive function. *Sleep Med Rev*. 2009;13(3):223-233. doi:10.1016/j.smrv.2008.07.002

186. Seda G, Matwiyoff G, Parrish JS. Effects of Obstructive Sleep Apnea and CPAP on Cognitive Function. *Curr Neurol Neurosci Rep*. 2021;21(7):32. doi:10.1007/s11910-021-01123-0

187. McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med*. 2016;375(10):919-931. doi:10.1056/NEJMoa1606599

188. Marin JM, Agusti A, Villar I, et al. Association Between Treated and Untreated Obstructive Sleep Apnea and Risk of Hypertension. *JAMA*. 2012;307(20):2169-2176. doi:10.1001/jama.2012.3418

189. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med*. 2020;8(4):359-367. doi:10.1016/S2213-2600(19)30271-1

190. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial. *Am J Respir Crit Care Med*. 2016;194(5):613-620. doi:10.1164/rccm.201601-0088OC

191. Kushida CA, Nichols DA, Holmes TH, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: The Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep*. 2012;35(12):1593-1602. doi:10.5665/sleep.2226

192. Dalmases M, Solé-Padullés C, Torres M, et al. Effect of CPAP on Cognition, Brain Function, and Structure Among Elderly Patients With OSA. *Chest*. 2015;148(5):1214-1223. doi:10.1378/chest.15-0171

193. Virk JS, Kotecha B. When continuous positive airway pressure (CPAP) fails. *J Thorac Dis*. 2016;8(10):E1112-E1121. doi:10.21037/jtd.2016.09.67

194. Weaver TE, Sawyer AM. Adherence to Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea: Implications for Future Interventions. *Indian J Med Res*. 2010;131:245-258.

195. Kaminska M, Mery VP, Lafontaine AL, et al. Change in Cognition and Other Non-Motor Symptoms With Obstructive Sleep Apnea Treatment in Parkinson Disease. *J Clin Sleep Med*. 2018;14(05):819-828. doi:10.5664/jcsm.7114

196. Meng L, Benedetti A, Lafontaine AL, et al. Obstructive sleep apnea, CPAP therapy and Parkinson's disease motor function: A longitudinal study. *Parkinsonism Relat Disord*. 2020;70:45-50. doi:10.1016/j.parkreldis.2019.12.001

197. Cook DA, Andriole DA, Durning SJ, Roberts NK, Triola MM. Longitudinal Research Databases in Medical Education: Facilitating the Study of Educational Outcomes Over Time and Across Institutions. *Acad Med*. 2010;85(8):1340-1346. doi:10.1097/ACM.0b013e3181e5c050

198. Raina P, Wolfson C, Kirkland S, et al. Cohort Profile: The Canadian Longitudinal Study on Aging (CLSA). *Int J Epidemiol*. 2019;48(6):1752-1753j. doi:10.1093/ije/dyz173

199. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLOS Med*. 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779

200. Allen N, Sudlow C, Downey P, et al. UK Biobank: Current status and what it means for epidemiology. *Health Policy Technol*. 2012;1(3):123-126. doi:10.1016/j.hlpt.2012.07.003

201. Davis KAS, Coleman JRI, Adams M, et al. Mental health in UK Biobank – development, implementation and results from an online questionnaire completed by 157 366 participants: a reanalysis. *BJPsych Open*. 2020;6(2):e18. doi:10.1192/bjo.2019.100

202. Littlejohns TJ, Holliday J, Gibson LM, et al. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nat Commun*. 2020;11(1):2624. doi:10.1038/s41467-020-15948-9

203. Ullman JB, Bentler PM. Structural Equation Modeling. In: *Handbook of Psychology, Second Edition*. John Wiley & Sons, Ltd; 2012. doi:10.1002/9781118133880.hop202023

204. Wolf EJ, Harrington KM, Clark SL, Miller MW. Sample Size Requirements for Structural Equation Models: An Evaluation of Power, Bias, and Solution Propriety. *Educ Psychol Meas*. 2013;76(6):913-934. doi:10.1177/0013164413495237

205. Fan Y, Chen J, Shirkey G, et al. Applications of structural equation modeling (SEM) in ecological studies: an updated review. *Ecol Process*. 2016;5(1):19. doi:10.1186/s13717-016-0063-3

206. Shaheen F, Ahmad N, Waqas M, Waheed A, Farooq O. Structural Equation Modeling (SEM) in Social Sciences & Medical Research: A Guide for Improved Analysis. *Int J Acad Res Bus Soc Sci*. 2017;2017:5. doi:10.6007/IJARBSS/v7-i5/2882

207. Alavi M, Visentin DC, Thapa DK, Hunt GE, Watson R, Cleary M. Chi-square for model fit in confirmatory factor analysis. *J Adv Nurs*. 2020;76(9):2209-2211. doi:10.1111/jan.14399

208. Peugh J, Feldon DF. "How Well Does Your Structural Equation Model Fit Your Data?": Is Marcoulides and Yuan's Equivalence Test the Answer? *CBE—Life Sci Educ*. 2020;19(3):es5. doi:10.1187/cbe.20-01-0016

209. Beran TN, Violato C. Structural equation modeling in medical research: a primer. *BMC Res Notes*. 2010;3:267. doi:10.1186/1756-0500-3-267

210. Amorim LDAF, Fiaccone RL, Santos CAST, et al. Structural equation modeling in epidemiology. *Cad Saude Publica*. 2010;26(12):2251-2262. doi:10.1590/s0102-311x2010001200004

211. Allen NE, Sudlow C, Peakman T, Collins R, UK Biobank. UK biobank data: come and get it. *Sci Transl Med*. 2014;6(224):224ed4. doi:10.1126/scitranslmed.3008601

212. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. *Front Immunol*. 2018;9:754. doi:10.3389/fimmu.2018.00754

213. Alfaro-Almagro F, Jenkinson M, Bangerter NK, et al. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *NeuroImage*. 2018;166:400-424. doi:10.1016/j.neuroimage.2017.10.034

214. Fischl B. FreeSurfer. *NeuroImage*. 2012;62(2):774-781. doi:10.1016/j.neuroimage.2012.01.021

215. Klein A, Tourville J. 101 Labeled Brain Images and a Consistent Human Cortical Labeling Protocol. *Front Neurosci*. 2012;6:171. doi:10.3389/fnins.2012.00171

216. Fischl B, Salat DH, Busa E, et al. Whole Brain Segmentation. *Neuron*. 2002;33(3):341-355. doi:10.1016/S0896-6273(02)00569-X

217. Griffanti L, Zamboni G, Khan A, et al. BIANCA (Brain Intensity AbNormality Classification Algorithm): A new tool for automated segmentation of white matter hyperintensities. *NeuroImage*. 2016;141:191-205. doi:10.1016/j.neuroimage.2016.07.018

218. Fawns-Ritchie C, Deary IJ. Reliability and validity of the UK Biobank cognitive tests. *PLoS ONE*. 2020;15(4):e0231627. doi:10.1371/journal.pone.0231627

219. Rosseel Y. lavaan: An R Package for Structural Equation Modeling. *J Stat Softw*. 2012;48:1-36. doi:10.18637/jss.v048.i02

220. R Core Team. Published online 2021. https://www.R-project.org/

221. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc Ser B Methodol*. 1995;57(1):289-300.

222. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020;75(6):1334-1357. doi:10.1161/HYPERTENSIONAHA.120.15026

223. *Glycated Haemoglobin (HbA1c) for the Diagnosis of Diabetes*. World Health Organization; 2011. Accessed June 2, 2022. https://www.ncbi.nlm.nih.gov/books/NBK304271/

224. Riemsma R, Ramos IC, Birnie R, et al. *Conversion Tables for Glycated Haemoglobin and Glucose Values*. NIHR Journals Library; 2016. Accessed May 27, 2022. https://www.ncbi.nlm.nih.gov/books/NBK348987/

225. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*. 1992;85(1):37-45. doi:10.1161/01.CIR.85.1.37

226. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106

227. Pearson TA, Mensah GA, Alexander RW, et al. Markers of Inflammation and Cardiovascular Disease. *Circulation*. 2003;107(3):499-511. doi:10.1161/01.CIR.0000052939.59093.45

228. Kushner I, Rzewnicki D, Samols D. What Does Minor Elevation of C-Reactive Protein Signify? *Am J Med*. 2006;119(2):166.e17-166.e28. doi:10.1016/j.amjmed.2005.06.057

229. Gan-Or Z, Rao T, Leveille E, et al. The Quebec Parkinson Network: A Researcher-Patient Matching Platform and Multimodal Biorepository. *J Park Dis*. 2020;10(1):301-313. doi:10.3233/JPD-191775

230. Das S, Abou-Haidar R, Rabalais H, et al. The C-BIG Repository: an Institution-Level Open Science Platform. *Neuroinformatics*. Published online May 18, 2021. doi:10.1007/s12021-021-09516-9

231. Gomes T, Benedetti A, Lafontaine AL, et al. Validation of STOP, STOP-BANG, STOP-BAG, STOP-B28 and GOAL screening tools for identification of obstructive sleep apnea in patients with Parkinson's disease. Submitted 2022.

232. Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull*. 1988;24(4):709-711.

233. Stiasny-Kolster K, Mayer G, Schäfer S, Möller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire--a new diagnostic instrument. *Mov Disord Off J Mov Disord Soc*. 2007;22(16):2386-2393. doi:10.1002/mds.21740

234. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010

235. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. doi:10.1016/j.jbi.2019.103208

236. Iber C, Ancoli-Israel S, Chesson A, Quan S. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. 1st ed. American Academy of Sleep Medicine; 2007.

237. Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. *J Sleep Res*. 2012;21(4):427-433. doi:10.1111/j.1365-2869.2011.00990.x

238. Olszowka M, Held C, Hadziosmanovic N, et al. Excessive daytime sleepiness, morning tiredness and major adverse cardiovascular events in patients with chronic coronary syndrome. *J Intern Med*. 2021;290(2):392-403. doi:10.1111/joim.13294

239. Newman AB, Spiekerman CF, Enright P, et al. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. The Cardiovascular Health Study Research Group. *J Am Geriatr Soc*. 2000;48(2):115-123. doi:10.1111/j.1532-5415.2000.tb03901.x

240. Lindberg E, Berne C, Franklin KA, Svensson M, Janson C. Snoring and daytime sleepiness as risk factors for hypertension and diabetes in women—A population-based study. *Respir Med*. 2007;101(6):1283-1290. doi:10.1016/j.rmed.2006.10.015

241. Ren R, Li Y, Zhang J, et al. Obstructive Sleep Apnea With Objective Daytime Sleepiness Is Associated With Hypertension. *Hypertension*. 2016;68(5):1264-1270. doi:10.1161/HYPERTENSIONAHA.115.06941

242. Kapur VK, Resnick HE, Gottlieb DJ, for the Sleep Heart Health Study Group. Sleep Disordered Breathing and Hypertension: Does Self-Reported Sleepiness Modify the Association? *Sleep*. 2008;31(8):1127-1132. doi:10.5665/sleep/31.8.1127

243. Martynowicz H, Skomro R, Gać P, et al. The influence of hypertension on daytime sleepiness in obstructive sleep apnea. *J Am Soc Hypertens*. 2017;11(5):295-302. doi:10.1016/j.jash.2017.03.004

244. Li Y, Vgontzas AN, Fernandez-Mendoza J, et al. Insomnia With Physiological Hyperarousal Is Associated With Hypertension. *Hypertension*. 2015;65(3):644-650. doi:10.1161/HYPERTENSIONAHA.114.04604

245. Zhou J, Camacho M, Tang X, Kushida CA. A review of neurocognitive function and obstructive sleep apnea with or without daytime sleepiness. *Sleep Med*. 2016;23:99-108. doi:10.1016/j.sleep.2016.02.008

246. Li Y, Vgontzas AN, Fernandez-Mendoza J, et al. Objective, but Not Subjective, Sleepiness is Associated With Inflammation in Sleep Apnea. *Sleep*. 2016;40(2):zsw033. doi:10.1093/sleep/zsw033

247. Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are White Matter Hyperintensities Made of? *J Am Heart Assoc*. 2015;4(6):e001140. doi:10.1161/JAHA.114.001140

248. Sharma R, Sekhon S, Cascella M. White Matter Lesions. In: *StatPearls*. StatPearls Publishing; 2022. Accessed January 12, 2022. http://www.ncbi.nlm.nih.gov/books/NBK562167/

249. Rostanski SK, Zimmerman ME, Schupf N, et al. Sleep Disordered Breathing and White Matter Hyperintensities in Community-Dwelling Elders. *Sleep*. 2016;39(4):785-791. doi:10.5665/sleep.5628

250. Thurston RC, Wu M, Aizenstein HJ, et al. Sleep characteristics and white matter hyperintensities among midlife women. *Sleep*. 2020;43(6):zsz298. doi:10.1093/sleep/zsz298

251. Cheng CY, Tsai CF, Wang SJ, Hsu CY, Fuh JL. Sleep disturbance correlates with white matter hyperintensity in patients with subcortical ischemic vascular dementia. *J Geriatr Psychiatry Neurol*. 2013;26(3):158-164. doi:10.1177/0891988713493503

252. Del Brutto OH, Mera RM, Zambrano M, Castillo PR. Relationship between obstructive sleep apnea and neuroimaging signatures of cerebral small vessel disease in community-dwelling older adults. The Atahualpa Project. *Sleep Med*. 2017;37:10-12. doi:10.1016/j.sleep.2017.06.009

253. Schammel NC, VandeWater T, Self S, et al. Obstructive sleep apnea and white matter hyperintensities: correlation or causation? *Brain Imaging Behav*. Published online February 26, 2022. doi:10.1007/s11682-022-00642-9

254. Zhao J, Kong Q, Wang M, et al. Association of Excessive Daytime Sleepiness with Cerebral Small Vessel Disease in Community-Dwelling Older Adults. *Nat Sci Sleep*. 2022;14:765-773. doi:10.2147/NSS.S357586

255. Ramos AR, Dong C, Rundek T, et al. Sleep Duration is Associated with White Matter Hyperintensity Volume in Older Adults: The Northern Manhattan Study. *J Sleep Res*. 2014;23(5):524-530. doi:10.1111/jsr.12177

256. Rojas S, Brugulat-Serrat A, Bargalló N, et al. Higher prevalence of cerebral white matter hyperintensities in homozygous APOE-ε4 allele carriers aged 45-75: Results from the ALFA study. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab*. 2018;38(2):250-261. doi:10.1177/0271678X17707397

257. Sudre CH, Cardoso MJ, Frost C, et al. APOE ε4 status is associated with white matter hyperintensities volume accumulation rate independent of AD diagnosis. *Neurobiol Aging*. 2017;53:67-75. doi:10.1016/j.neurobiolaging.2017.01.014

258. Uyrum E, Balbay O, Annakkaya AN, Balbay EG, Silan F, Arbak P. The Relationship between Obstructive Sleep Apnea Syndrome and Apolipoprotein E Genetic Variants. *Respiration*. 2015;89(3):195-200. doi:10.1159/000369560

259. Blackman J, Love S, Sinclair L, Cain R, Coulthard E. APOE ε4, Alzheimer's disease neuropathology and sleep disturbance, in individuals with and without dementia. *Alzheimers Res Ther*. 2022;14(1):47. doi:10.1186/s13195-022-00992-y

260. Mayer C, Frey BM, Schlemm E, et al. Linking cortical atrophy to white matter hyperintensities of presumed vascular origin. *J Cereb Blood Flow Metab*. 2021;41(7):1682-1691. doi:10.1177/0271678X20974170

261. Rizvi B, Narkhede A, Last BS, et al. The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. *Neurobiol Aging*. 2018;64:25-32. doi:10.1016/j.neurobiolaging.2017.12.006

262. Bucks RS, Olaithe M, Rosenzweig I, Morrell MJ. Reviewing the relationship between OSA and cognition: Where do we go from here? *Respirol Carlton Vic*. 2017;22(7):1253-1261. doi:10.1111/resp.13140

263. Bawden FC, Oliveira CA, Caramelli P. Impact of obstructive sleep apnea on cognitive performance. *Arq Neuropsiquiatr*. 2011;69(4):585-589. doi:10.1590/S0004-282X2011000500003

264. Keropian B, Murphy N. The prevalence of OSA in snorers presenting with various chief complaints: a pilot study. *Cranio J Craniomandib Pract*. 2014;32(3):217-218. doi:10.1179/0886963414Z.00000000032

265. Pushpanathan ME, Loftus AM, Thomas MG, Gasson N, Bucks RS. The relationship between sleep and cognition in Parkinson's disease: A meta-analysis. *Sleep Med Rev*. 2016;26:21-32. doi:10.1016/j.smrv.2015.04.003

266. Ikeda M, Kataoka H, Ueno S. Can levodopa prevent cognitive decline in patients with Parkinson's disease? *Am J Neurodegener Dis*. 2017;6(2):9-14.

267. Morrison CE, Borod JC, Brin MF, Hälbig TD, Olanow CW. Effects of levodopa on cognitive functioning in moderate-to-severe Parkinson's disease (MSPD). *J Neural Transm*. 2004;111(10):1333-1341. doi:10.1007/s00702-004-0145-8

268. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive Effects of Long-Term Benzodiazepine Use. *CNS Drugs*. 2004;18(1):37-48. doi:10.2165/00023210-200418010-00004

269. Cersosimo MG, Raina GB, Pellene LA, Micheli FE, Calandra CR, Maiola R. Weight Loss in Parkinson's Disease: The Relationship with Motor Symptoms and Disease Progression. *BioMed Res Int*. 2018;2018:e9642524. doi:10.1155/2018/9642524

270. Small BJ, Dixon RA, McArdle JJ. Tracking Cognition–Health Changes From 55 to 95 Years of Age. *J Gerontol Ser B*. 2011;66B(suppl_1):i153-i161. doi:10.1093/geronb/gbq093

271. Parisi JM, Rebok GW, Xue QL, et al. The Role of Education and Intellectual Activity on Cognition. *J Aging Res*. 2012;2012:e416132. doi:10.1155/2012/416132

272. Bolitho SJ, Naismith SL, Salahuddin P, Terpening Z, Grunstein RR, Lewis SJG. Objective Measurement of Daytime Napping, Cognitive Dysfunction and Subjective Sleepiness in Parkinson's Disease. *PLOS ONE*. 2013;8(11):e81233. doi:10.1371/journal.pone.0081233

273. Chung SJ, Choi YH, Kwon H, et al. Sleep Disturbance May Alter White Matter and Resting State Functional Connectivities in Parkinson's Disease. *Sleep*. 2017;40(3):zsx009. doi:10.1093/sleep/zsx009

274. Castronovo V, Scifo P, Castellano A, et al. White Matter Integrity in Obstructive Sleep Apnea before and after Treatment. *Sleep*. 2014;37(9):1465-1475. doi:10.5665/sleep.3994

275. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *Am J Epidemiol*. 2017;186(9):1026-1034. doi:10.1093/aje/kwx246

276. Farah MJ. The Neuroscience of Socioeconomic Status: Correlates, Causes, and Consequences. *Neuron*. 2017;96(1):56-71. doi:10.1016/j.neuron.2017.08.034

277. Zhang M, Gale SD, Erickson LD, Brown BL, Woody P, Hedges DW. Cognitive function in older adults according to current socioeconomic status. *Aging Neuropsychol Cogn*. 2015;22(5):534-543. doi:10.1080/13825585.2014.997663

278. Basta NE, Matthews FE, Chatfield MD, Brayne C, MRC-CFAS. Community-level socio-economic status and cognitive and functional impairment in the older population. *Eur J Public Health*. 2008;18(1):48-54. doi:10.1093/eurpub/ckm076

279. Cole JH, Franke K. Predicting Age Using Neuroimaging: Innovative Brain Ageing Biomarkers. *Trends Neurosci*. 2017;40(12):681-690. doi:10.1016/j.tins.2017.10.001