ABSTRACT

Sleep apnea is a common cause of somnolence often observed in older men. It is associated with obesity and cardiovascular disease. The association with symptoms other than somnolence is currently unclear. We conducted a cross-sectional study to investigate whether sleep apnea is associated with the symptoms of nocturia and erectile dysfunction as well as with motor vehicle crashes. Data were obtained on 1,010 patients over four years of consecutive referrals with suspected sleep apnea to the Royal Victoria Hospital sleep-disorders clinic.

Of the study population, 48% had polysomnographic sleep apnea. Severe sleep apnea was associated with a two-fold increase in the prevalence of nocturia. Erectile dysfunction among 572 men increased from 17.5% for normal subjects to 29.3% for severe sleep apnea. Sleep apnea as well as daytime somnolence were associated with a higher prevalence of motor vehicle crashes.

Patients with sleep apnea may be at an increased risk of developing nocturia and erectile dysfunction, as well as of being involved in motor vehicle crashes.

RÉSUMÉ

L'apnée du sommeil est souvent présente chez les hommes plus âgés que 40 ans et demeure une cause fréquente d'un syndrôme de somnolence diurne. L'obésité et les maladies cardiovasculaires y sont associées. Les liens entre l'apnée du sommeil et les symptômes autres que la somnolence diurne sont peu étudiés. Une étude transversale a cherché à décrire si l'apnée du sommeil est associée aux symptômes de nocturie et d'impotence sexuelle, ainsi qu' aux accidents de la circulation. Les données de 1010 patients vus pendant 4 ans à la clinique du sommeil de l'Hôpital Royal Victoria ont été analysées.

Quarante-huit pourcent de la population à l'étude a eu l'apnée du sommeil tel que confirmé par polysomnographie. La prévalence de la nocturie était doublée chez les patients avec l'apnée du sommeil sévère par rapport aux patients sans apnée. L'impotence sexuelle parmi 572 hommes a augmenté de 17.5% chez ceux ayant une polysomnographie normale à 29.3% chez ceux démontrant de l'apnée du sommeil sévère. La présence de la respiration perturbée par le sommeil et la somnolence diurne ont été associées avec un taux élévé d'accidents de la circulation.

Les patients avec l'apnée du sommeil peuvent présenter un risque plus élévé de développer la nocturie et l'impotence sexuelle, ainsi que de subir un accident de la circulation.

TO MARIE

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ABBREVIATIONS

AHI:	Apnea-hypopnea index, defined as the total number of apneas and hypopneas divided by the total hours of sleep.
ANP:	Atrial natriuretic peptide.
BMI:	Body mass index defined as: weight (kg)/[height (m)]^2.
CI:	Confidence intervals.
CPAP:	Continuous positive airway pressure. This is the standard treatment of sleep apnea.
CVD:	Cardio-vascular disease.
EDS:	Excessive daytime somnolence.
EEG:	Electroencephalographic.
FAWD:	Falling asleep while driving.
MVC:	Motor vehicle crash.
NIH:	National Institutes of Health (United States).
NPT:	Nocturnal penile tumescence. This is a procedure to objectify and quantify organic erectile dysfunction.
OR:	Odds ratio.
OSAS:	Obstructive sleep apnea syndrome; the combination of *both* the complaint of excessive sleepiness and objectively measured episodes of obstructed breathing during sleep.
REM:	Rapid eye movement, which may also pertain to sleep stage of rapid eye movement sleep.
SD:	Standard deviation.
SDB:	Sleep-disordered breathing, as defined in this thesis as either the presence of habitual snoring or the polysomnographic observation of frequent apneas and hypopneas during sleep.
SWS:	Slow wave sleep, a sleep stage associated with deep sleep.

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During the period of this research project, I have sought the sensible advice of Dr. Jean-François Boivin who was a member of my Thesis Supervisory Committee. He was ever present to provide guidance through the necessary processes involved in graduate research, such as the reshaping of research objectives and participation in grant competitions.

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Prior to my involvement with this project, two doctors in training entered a substantial number of subjects into the numerical datafiles used in the analysis of this project. These are Drs. Rodolfo Denis and Pierre Mayer. Further data entry was done by Frédéric Gaudreau and Véronique Desilets.

During the management of the data, the advice of Miss Odile Sheehy was invaluable.

Finally, I would like to acknowledge the support of the Medical Research Council of Canada for a fellowship supporting my studies at McGill University, and for supporting the research with an operating grant.

PREFACE

This thesis is presented as five chapters, with an introduction, three manuscripts intended for publication, and a summary. The introduction provides definitions and the scope of the relevant aspects of this project, provides a review of the current literature, and declares the study objectives. The three manuscripts report in turn the relationship of degrees of polysomnographic sleep apnea and hypopnea to erectile dysfunction, the association of degrees of polysomnographic sleep apnea and hypopnea to nocturia, and finally the association of sleep disordered breathing with motor vehicle crashes. The fifth chapter summarizes the findings reported in the three manuscripts. Tables and references are provided at the end of each chapter.

Some repetition of material is inevitable in the introductory chapter, the introduction, methods, discussion sections of the manuscripts, and the summary chapter. Nevertheless, the format is necessary to disseminate these findings to the widest audience with reasonable dispatch. Completion of the thesis in this manner has also provided me with the important experience in reporting the results of a study in a way suitable for scientific journal publication. The format is approved by the McGill University Faculty of Graduate Studies and Research.

The following statement must be included in the preface of this thesis:

"Candidates have the option, subject to the approval of the department, of including, as part of the thesis, copies of the text of a paper(s), submitted for publication, or the clearly duplicated text of a published paper(s), provided these copies are bound as integral part of this thesis.

If this option is chosen, connecting texts that provide logical bridges between the different papers are mandatory. The thesis must be written in such a way that it is more than a mere collection of manuscripts; in other words, results of a series of papers must be integrated.

The thesis must still conform to all other requirements of the 'Guidelines for Thesis Preparation'. The thesis must include: a table of contents, abstracts in English and in French, an introduction that clearly states the rationale and objectives of the study, a review of the literature, a final conclusion and summary, and a thorough bibliography and reference list.

Additional material must be provided where appropriate (e.g. in the appendices) and in sufficient detail to allow a clear and precise judgment to be made of the importance and originality of the research reported in the thesis.

In the case of manuscripts co-authored by the candidate and others, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. Supervisors must attest to the accuracy of such statements at the doctoral oral defense. Since the task of the examiners is made

more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers."

AUTHORSHIP

This thesis presents the findings of research initiated by Dr. R. John Kimoff and pursued with Prof. S. Suissa. I formulated current research questions and was responsible for the literature review, the data management, the statistical analysis and the preparation of manuscripts. The co-authors of the manuscripts were members of my Thesis Supervisory Committee who all offered constructive criticism throughout the research project and preparation of manuscripts.

STATEMENT OF ORIGINALITY

To my knowledge, this is the first study to address the consequences of erectile dysfunction, nocturia and motor vehicle crashes as a result of sleep apnea or sleep disordered breathing while accounting for confounding factors and the effect of somnolence where relevant. This was done in the context of a select clinic population recruited consecutively over a defined period of time. Several previous studies have adressed the association of motor vehicle crashes with sleep apnea or sleep disordered breathing, but this study chooses concurrent controls and simultaneously evaluates the important confouding influences of gender, age, cardiovascular disease, alcohol use and the regular use of sedatives.

CHAPTER 1

INTRODUCTION

Sleep apnea is a condition characterized by frequent repeated pauses of breathing during sleep. Once considered a rare condition, population-based estimates have found that sleep apnea is common and has diverse consequences that impact on several domains of morbidity and the risk of mortality. The typical symptoms of sleep apnea are snoring and excessive daytime sleepiness. The most frequent variant of the sleep apnea is obstructive sleep apnea, where the tissues of the tongue and throat repeatedly collapse during sleep, obstructing breathing and causing the breathing pauses, and in turn repeatedly fragmenting sleep with short awakenings or arousals. This phenomenon has been described since 1977. Surgical treatments range from tracheostomy through complex upper airway surgery. Medical therapy includes the lifelong nightly application of oral appliances or continuous positive airway pressure (CPAP). The descriptions and the risk factors for sleep apnea have become better characterized over the past 20 years. The concept of sleep disordered breathing has emerged to include sleep apnea as part of a spectrum of upper airway phenomena during sleep. The impact of sleep apnea has also been better delineated, giving better patient-centered measurements of treatment outcomes.

This thesis sets out to describe three of these consequences perceived by patients with sleep apnea: erectile dysfunction (also known as impotence); nocturia (awakening frequently to urinate) and motor vehicle crashes (also known as car accidents).

1.1 Sleep Apnea, Obstructive Sleep Apnea Syndrome, and Sleep-Disordered Breathing

1.1.1.Definitions

Sleep apnea has been described in the biomedical literature for 21 years. Since then, the terms concerning abnormalities of breathing during sleep vary from publication to publication. 'Sleep apnea', 'sleep apnea syndrome' and 'sleep-disordered breathing' are often used interchangeably, leading to potential confusion unless their definitions are stated in the report. 'Sleep apnea' may refer to the laboratory finding of obstructive sleep apnea or the *syndrome* as defined below; here the term pertains to the polysomnographic observation of frequent apneas and hypopneas during sleep.

The term 'sleep-disordered breathing' (SDB) may be defined broadly as 'any measurable abnormality of breathing occurring during sleep'. This may as a result include not only obstructive sleep apnea , but also include habitual snoring, increased upper airway resistance with respiratory event related arousals, nocturnal alveolar hypoventilation, and central sleep apnea. The use of this term implies the existence of abnormal breathing during sleep regardless of any symptoms. Operational definitions vary widely, but for the purposes of this thesis, the use of the term follows the example of a recent epidemiological study where 'sleep-disordered breathing' denotes either the presence of habitual snoring or the polysomnographic observation of frequent apneas and hypopneas during sleep. [1]

The obstructive sleep apnea *syndrome* (OSAS) is defined by the International Classification of Sleep Disorders Diagnostic and Coding Manual as 'A complaint of

excessive sleepiness or insomnia. Occasionally the patient may be unaware of clinical features that are observed by others. Frequent episodes of obstructed breathing [occur] during sleep. Associated features include: loud snoring; morning headaches; a dry mouth upon awakening; chest retraction during sleep in young children.[...]'[2] This definition has been made operational in epidemiological studies to include the combination of *both* the complaint of excessive sleepiness and objectively measured episodes of obstructed breathing during sleep. This latter definition is the one used in this thesis.

1.1.2.Natural History

Obstructive sleep apnea is believed to exist in an individual for many years prior to symptoms and diagnosis. The current concept postulates a long presymptomatic phase consisting initially of habitual snoring, then frequent hypopneas, then sleep apnea.[3,4] After a variable period of time this finally leads to symptoms or cardiovascular changes. At diagnosis, the individual may have had sleep disordered breathing for several decades, and sleep apnea for five years or more. The symptomatic phase may continue on without diagnosis for years, often decades. Either the patient underestimates the symptoms,[4] or when clearly signalled to a health professional, the syndrome continues unrecognized because patients are rarely examined in their sleep and the health professional may be unfamiliar with the symptoms and signs of sleep apnea syndrome.[5,6]

1.1.3.Epidemiology

Sleep apnea has been found to have a prevalence ranging from 1 to 25% of the population (see Table 1.1).[7-12] Although measurement methods vary, the predominant

reasons for this variability are due to the different definitions as well as demographic and anthropomorphic characteristics of the populations studied.

The most common measurement of sleep apnea is the apnea-hypopnea index (AHI). The consequences of both complete cessation of breathing (apnea) and partial obstruction of breathing (hypopnea) are believed to be similar and are thus usually summed together and divided over the total sleep time (best measured with electroencephalographic monitoring) to calculate the AHI. This has become the metric of sleep apnea breathing severity. The distribution of the AHI is not normal in unselected populations, but displays a zero-heavy skewed distribution (see figure 1.1 for the AHI distribution of the population studied in this thesis).

Table 1.1:
Prevalences of Sleep Apnea and Obstructive Sleep Apnea Syndrome (OSAS)

Population	Sleep Apnea Prevalence (%)	OSAS Prevalence (%)	Reference
Men, Wisconsin, age 30-60	24	4	7
age 30-39	17	-	
age 40-49	25	-	
age 50-60	31	-	
Women, Wisconsin, age 30-60	9	2	7
age 30-39	6.5	-	
age 40-49	8.7	-	
age 50-60	16	-	
Men, Italy, age 30-39	0.2-1.0	-	8
Men, Italy, age 40-59	3.4-5.0	-	8
Men, Italy, age 60-69	0.5-1.1	-	8
Men, California, age 40-64	11	-	9
Women, California, age 40-64	5.3	-	9
European ethnic	5.6	-	9
Hispanic	16	-	9
African-American	17	-	9
Asian	22	-	9
Men, Canada, adult	25	-	10
Men, Australia, age 40-65	9	-	11
Men, Sweden, age 30-69	0.7-1.9	-	12
Elderly, age 60-95	26-39	5-6	13

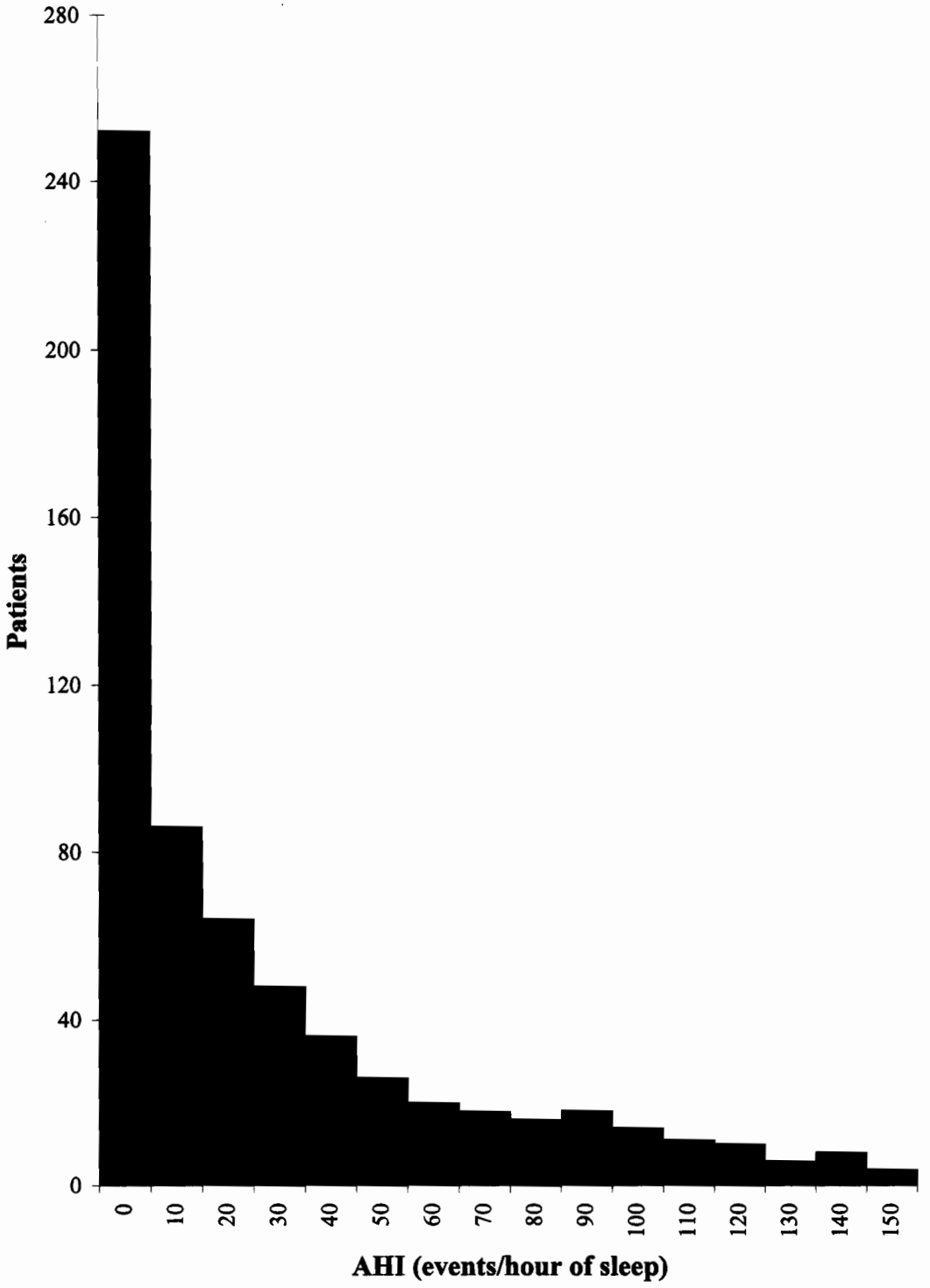

Figure 1.1: Distribution of the apnea-hypopnea index (AHI) in the study sample.

Snoring tends to follow similar prevalence patterns as sleep apnea, but is approximately twice as prevalent in a given population.[7,8,9,14-16] It is believed to be part of the spectrum of sleep-disordered breathing between normal breathing and sleep apnea.[3,15,16] Individuals with sleep apnea usually report habitual snoring.[7,8,9,14,16]

Important demographic characteristics influencing sleep apnea prevalence include gender, age, and ethnic origin. The principle anthropomorphic factors are measures of obesity and cranio-facial characteristics. Body mass index (BMI)[7,8,9,10] and neck circumference[7,16] are consistently predictive of sleep apnea, and are not only associated with the presence of the abnormality but also may be used to estimate the amount of continuous positive airway pressure needed to successfully abolish respiratory arousals.[17] Other measurements that have been found to relate to apnea prevalence are dimensions of the mandible and intraoral anatomy as measured by the length of the soft palate, the intermolar distance and distance from the tongue to the margin of the hard palate in the maximally open mouth.[18]

Any anatomical obstruction of the upper airway may cause sleep apnea; in children, the principle abnormality is adenotonsillar hypertrophy. This is uncommon in adults, as are other tumors of the airway because such abnormalities rarely elude diagnosis for prolonged periods of time. Sleep apnea may also occur in individuals with high upper airway collapsibility independent of obesity, and this may be why sleep apnea is frequently observed (42%) in patients with neurological disease affecting the upper airway.[19]

The reasons why an individual with polysomnographic obstructive sleep apnea develops excessive daytime somnolence (EDS) are poorly characterized. Less than one third of individuals with polysomnographic sleep apnea have subjective EDS[7] although subjective and objective measures of sleepiness often disagree, and

individuals with sleep apnea may underestimate their sleepiness when sleep propensity is objectively measured.[3,16] Sleep-wake habits show only minor variation between the somnolent and the asymptomatic sleep apneics.[20] Brainstem mechanisms, neurohumoral sleep factors, upper airway sensation and afferents of the respiratory system may all potentially contribute. Sleep fragmentation by the repetitive respiratory events leading to repetitive arousals in sleep appears to be important but not itself sufficient, as degree of respiratory effort also appears to explain some of the sleepiness resulting from repetitive respiratory events.[21]

1.1.4.Neuropsychiatric Consequences

The effect of sleep apnea on awake functioning varies widely between individuals. All measures of neuropsychiatric function show considerable overlap with control populations. Self-reported sleepiness as well as objective sleep propensity are high in groups with obstructive sleep apnea syndrome,[7,16,19,22-25] and improve after sufficient treatment.[22-25] Self-reported and objective sleepiness are high in groups with upper airway resistance syndrome, and also improve after treatment.[26] This suggests an important symptomatic burden of sleep disordered breathing beyond that associated with sleep apnea, for which snoring is a proxy obtainable by history.[7,16] This is in the absence of polysomnographic esophageal pressure monitoring, which is considered the gold standard to define the upper airway resistance syndrome.[26]

The subjective and objectively measurable effects of sleep apnea syndrome are more complex than the need to sleep inappropriately in the daytime. Awake vigilance is reduced, especially to monotonous tasks requiring consistent motor output.[27] The prototype standardized task is the driving simulator, where the mean error rate and steering deviation are higher in apneics.[28,29] Other tasks such as the number

connection test and timed decision and dexterity measures tend to be impaired and reveal reduced psychomotor efficiency. [25,30] Repetitive motor skills, attention, concentration and information processing are all involved in the integrated execution of such tasks, which are accomplished with less time-dependent consistency when sleep apnea is present with or without symptoms. It has been recently estimated that an AHI of 15 is equivalent to the decrement in psychomotor efficiency associated with aging 5 additional years.[30] Depressive characteristics are more prominent in the affective profiles of groups with sleep apnea syndrome, correlating with the concentration and integrative cognitive deficits.[31]

Not all measurable deficits improve completely with treatment.[25] The persistence of the abnormal upper airway anatomy for life renders the individual vulnerable to the effects of sleep apnea subsequent to non-compliance with nightly CPAP therapy because disrupted sleep and abnormal daytime function return after one night's sleep without CPAP. [32,33] The role of possible cerebral damage due to chronic intermittent cerebral hypoxia during sleep is presently unclear.

1.1.5.Autonomic Consequences

The autonomic nervous system controls diverse homeostatic processes of the body through reflex regulation. Such functions range from pupillary accommodation in response to changing ambient light to the control of breathing, blood pressure, bladder and erectile function. The classic divisions of these diverse control systems are based upon the neurotransmitters involved; the sympathetic nervous system mediates its functions through the release of adrenergic amines (dopamine, epinephrine, norepinephrine); the parasympathetic nervous system mediates its functions through the release of acetylcholine.

Apneas in sleep produce acute surges in blood pressure with acute arousals, increased sympathetic activity and release of noradrenergic hormones.[34] Chronic hypertension is associated with sleep disordered breathing. [14,16,34-39] This association increases with increasing severity of sleep disordered breathing, applies to 24-hour blood pressure profiles, and persists when accounting for age, BMI, and gender. [39] Early studies suffered from methodologic limitations in blood pressure measurement, choice of controls and handling of confounding variables.[40] Yet the association persists in recent well designed studies, and is supported as in part causal by the common finding of blood pressure reduction with treatment. [39,41,42]

Urinary norepinephrine in apneics is increased during both day and night. [43] Muscle nerve sympathetic activity during wakefulness in patients with obstructive sleep apnea in supine rest is higher compared with controls.[37,44,45] Plasma levels of norepinephrine correlate with resting muscle nerve sympathetic activity. [46] The increased awake sympathetic activity at rest may reflect a pathophysiologic adaptation to hypoxia and hemodynamic changes occurring as a result of repetitive respiratory events during sleep. This hypothesis is supported by the finding that urinary norepinephrine and resting muscle nerve sympathetic activity improve with CPAP therapy. [37,45] Hypoxia from sleep apnea plays an important role in the development of persistent autonomic arousal. Yet the respiratory arousals in the absence of hypoxemia characteristic of the upper airway resistance syndrome are also associated with acute respiratory hypertensive surges, as well as daytime hypertension that is reversible with CPAP. [35,47]

Parasympathetic activity is also intermittently increased. This is most supported by the high rate of nocturnal bradyarrhythmias observed in untreated sleep apnea that fluctuate in a cyclic manner in concert with cyclic apneas.[36,38,48] Cyclic high vagal

output is the presumed mechanism of these arrythmias. These bradyarrhythmias improve promptly and dramatically with CPAP treatment.[48]

Respiratory control abnormalities are frequently observed especially when sleep apnea is associated with significant chronic ventilatory impairment.[49] Examples of this ventilatory impairment include morbid obesity and chronic obstructive pulmonary disease. The reduced ventilatory responses to hypoxia and hypercapnia are at least partially reversible with therapy.[50] Experiments in the animal model of sleep apnea have shown reversible blunting of awake ventilatory responses to hypoxia;[51] the sleep fragmentation alone induces changes similar to sleep apnea in acute respiratory efforts in response to airway occlusion and hypoxia.[52] Hypoxic responses are not only lower in groups with sleep apnea, but also lower among the first-degree relatives of sleep apneics. Respiratory responses to hypercapnia are similar unless resistive loading is also present; in the presence of hypercapnic resistive loading, inspiratory impedance increases with increasing hypercapnia more than in controls.[53] This suggests a familial abnormality of increased upper airway collapsibility as well as blunting of the hypoxic ventilatory response during non-REM sleep.

Other functions of the autonomic nervous system have not been extensively investigated, except for clinical studies of erectile function (see below). Pupillometric responses, which are linked to complex brainstem and higher centers, are significantly altered in the presence of sleep apnea.[54]

1.2 Erectile Dysfunction

1.2.1 Definitions and Classification

Erectile dysfunction is the preferred term for male impotence according to the consensus of the United States National Institutes of Health (NIH) Consensus Panel.[55] This is defined as the consistent inability to attain and maintain a sufficient penile erection to permit satisfactory sexual intercourse. The concept of erectile dysfunction unifies the related processes of sexual desire, erectile failure, orgasm and ejaculation, which can together produce various contributions to overall sexual dysfunction.[56,57]

Usually ascertained through self-report, erectile function can be quantified through various physiologic measurements, the most relevant to this thesis being nocturnal penile tumescence (NPT). The NPT is measured by instrumenting the penis overnight in an attended laboratory, observing changes in dimensions that are expected to physiologically coincide with rapid eye movement (REM) sleep, and having a technician enter the room when erection is present and measure the force (in kilograms) necessary to buckle the fully erect penis.[58] To obtain diagnostically accurate information, at least 2 consecutive nights of recording are necessary to evaluate nocturnal penile tumescence and rigidity without false positive results spuriously suggesting erectile failure.[59] This measurement is reproducible and valid, but measures only one component, the erectile mechanism, of the entire complex of erectile dysfunction. This is the main utility of NPT monitoring, which may distinguish between organic causes of erectile dysfunction (such as nerve damage or vascular compromise) and functional erectile dysfunction (typified by anxiety and excessive psychosocial stress). As may be obvious, NPT is not a practical research tool for studying erectile dysfunction in large samples of the male population. As a result, self-report is the definition of erectile dysfunction for the purposes of this thesis.

1.2.2 Epidemiology and Physiology of Erectile Dysfunction

Erectile dysfunction affects around 30 million North American men.[60] Its prevalence increases with advancing age and is associated with the co-morbid mood disorders, cardiovascular and neurological disease.[55,60] The most complete study of erectile dysfunction was the Massachusetts Male Aging Study, a community based, random sample observational survey of non-institutionalized men 40 to 70 years old.[60] A self-administered sexual activity questions characterized erectile potency. The combined prevalence of all degrees of erectile dysfunction was 52%. The prevalence of complete dysfunction tripled from 5 to 15% over the age range of 40 and 70 years. After adjustment for age, a higher probability of impotence was directly correlated with heart disease, hypertension, diabetes, associated medications, and indexes of anger and

depression, and inversely correlated with serum dehydroepiandrosterone. Diabetes is a risk factor, but usually co-existent vascular or neuropathic damage is clinically evident when erectile dysfunction is persistent. Smoking is a consistent risk factor for erectile dysfunction that is only partially explained by the confounding association with cardiovascular disease. Hypogonadism is relatively uncommon. The effects of medications and alcohol are well known, although alcohol's effect is acute, reversible, and rarely serves as the sole etiology when patients seek medical attention. Antihypertensive medications such as beta blockers can cause chronic erectile dysfunction that may not be mentioned upon prescription and may not be intimated by the patient in follow up visits.

A physician survey demonstrated that 6 in 10,000 men are specifically treated each year indicating that this common affliction is rarely treated.[60] The desire for treatment is demonstrated by the high volume of sales in 1998 of an effective oral

treatment for erectile dysfunction. Sildafinil (Viagra, Pfizer) in 10 weeks was filled in 2.7 million U.S. prescriptions, with $411 million in sales, in an unprecedented volume of sales at launch dubbed a pharmaceutical industry milestone.[61]

The physiology of erectile function requires a receptive psychological environment, an intact nervous system, adequate arterial supply, a functional veno-occlusive mechanism, and an anatomically intact penis.[57] Pelvic sympathetic nerves enter the spinal cord at thoracic nerve roots 11 and 12, as well as lumbar roots 1 and 2. The parasympathetic, and somatic axons of the pudendal nerve enter the spinal cord through sacral roots 2, 3 and 4. These all synapse with the spinal erection center, which in turn connects to the brain. Sleep induces erections during REM periods with a mechanism that is poorly understood.[58] In complete erectile dysfunction requiring penile prosthesis surgery, vascular lesions are discernible on pathologic examination only 52% of the time. Neuropathic and other anatomic lesions are often present, but do not account for the entire remainder.[62] Occult causes of complete erectile dysfunction remain despite extensive evaluation. These individuals are often prescribed palliative therapies based upon physician judgment and patient preference.

1.2.3 Links with Sleep Apnea and Sleep-Disordered Breathing

The preponderance of erectile dysfunction in patients with sleep apnea has been noted in a small case series[63] and by clinical experience.[16] Sleep apnea has also been found in a high percentage of patients referred for NPT testing with concomitant polysomnography.[64] The pathophysiology of the associated erectile dysfunction is not well described. It may be due to comorbid cardiovascular disease (CVD) such as hypertension, stroke and heart disease,[14,38] or their medical management.[60,65,67]

Neuropsychiatric or autonomic dysfunction from sleep fragmentation may also have causal roles in any link between sleep apnea and erectile dysfunction.

In a recent report, treatment for sleep apnea with continuous positive airway pressure (CPAP) improved erectile dysfunction in one third of the cases studied; the factors associated with failure of efficacy were not clearly delineated.[68] A population based prevalence study of sleep disordered breathing found that erectile dysfunction was not significantly associated with sleep disordered breathing after a multiple correlation analysis that controlled for age, CVD and excessive daytime sleepiness.[9] Thus, the relationship between sleep apnea and erectile dysfunction remains uncertain. The role of several interrelated factors have yet to be assessed in studying this potential manifestation of sleep apnea. The primary respiratory disturbance (apneas and hypopneas) must be studied while accounting for the effects of age, cardiovascular disease, diabetes, and obesity.

1.3 Nocturia

1.3.1 Definitions

Nocturia may be defined as "excessive urination at night".[69] This qualitative definition has posed problems, in as much that the actual number of times habitually needed to void throughout a night's sleep has varied in published studies from any voiding to three times or more. Many prevalence studies cited below use voiding twice a night as the definition of nocturia. A well conducted epidemiological study has defined a habitual frequency of three or more times a night as definitely abnormal.[70] This self reported information has been found to be highly accurate when validated by 24-hour urine metering.[71]

1.3.2 Epidemiology and Impact

Nocturia has been considered an annoying symptom of aging. The range of operational definitions may explain the wide range of prevalences found for nocturia, as population based studies estimate prevalences of nocturia from 11 to 40% of adults.[70,72-75] Despite these limitations, studies have repeatedly shown that nocturia increases in prevalence with age from near 5% at age 30 to 30% or more at 65 years old. This increase is not entirely paralleled by bladder outlet problems in men,[72,75] nor is it clearly paralleled by stress or urge incontinence symptoms in women.[73,75]

It has been found through qualitative research that the process of emptying one's bladder repeatedly at night is not simple when coexistent conditions are present.[76,77] Examples include night blindness, mobility problems from skeletal or neurological disorders, postural hypotension, and cardiorespiratory diseases that limit exercise tolerance. It requires little imagination to see the risk posed to an individual who must rise three times a night to use a walker, turn on a light, negotiate the distance and any obstacles on the way to the bathroom, to enter, use the toilet, leave the bathroom, and return, often in a sleepy state. This illustrates that nocturia may not only be inconvenient but also risky. Nocturia rarely occurs in isolation, as a cross-sectional study in a geriatric clinic has found that nocturia often coexists with other chronic disease states, as well as the chronic use of one or multiple medications.[78] It is not surprising that nocturia is a risk factor for falls requiring medical attention.[79] This study of falls also attempted to link nocturia to fractures, but the power of the study was insufficient. Over the past decade, surveys from several community based samples have found that nocturia is associated with non-restorative sleep, frequent awakenings, and awakening due to breathing difficulties.[80,81] Furthermore, there was found to be an

incremental association of the number of times usually needed to void throughout a night's sleep and excessive daytime sleepiness. General well-being is less and quality of life suffers.[80,82] Nocturia is a common reason for seeking outpatient care,[75] as a survey of general practitioners recorded this as a complaint 1.7% of visits, and community surveys suggest that two thirds of individuals with nocturia to the point of dissatisfaction did not seek medical attention. Patients seek emergency room care for nocturia at a frequency similar to seeking such care for heart diseases, asthma, renal disorders, psychiatric problems and headaches.[83]

The accepted etiologies of nocturia vary, and include nocturnal drinking and alcohol use, benign prostatic hypertrophy, bladder detrusor muscle instability, edematous states, and the side effect of diuretic use.[84] At times, this is ascribed to the aging process itself. One explanation is that the circadian rhythm of antidiuretic hormone secretion is attenuated with age, resulting in an inappropriate nocturnal diuresis. Clinical evaluation seeks these causes with an unquantified accuracy or effect on outcome in general practice. When both nocturia and benign prostatic hypertrophy are present and prostatic resection is performed to relieve symptoms, two thirds of individuals 3 months post-operatively remain with significant nocturia, implying that the resection may not be addressing the specific etiology of the complaint. These procedures were done in the context of a university based teaching hospital and a prospective outcomes research protocol where the majority of the prostatism-related symptoms improved dramatically.[85]

1.3.3 Links with Sleep Apnea and Sleep-Disordered Breathing

What is the relationship with sleep apnea? A recent polysomnographic study found that awakenings after episodes of obstructive apnea often resulted in nocturia, and that 79% of episodes of nocturia in the sleep laboratory were immediately

preceded by an apnea and an arousal with a subsequent awakening to urinate. Only one subject ascribed the awakening to a breathing problem, while the rest perceived that the full bladder woke them up.[86] This symptom has been linked with sleep apnea in case reports[87] and has been found to occur 28% of the time in a survey of patients with sleep apnea.[16] Without comparison to a control group, it may be argued that this symptom is no more prevalent in individuals with compared to those without sleep apnea.

The reasons for nocturia occurring in sleep apnea may stem from noradrenergic neuro-humoral responses to the sleep disordered breathing which may increase renal perfusion. Renal responsiveness to atrial natriuretic peptide (ANP) may increase despite no clear elevation in measured serum ANP levels because urinary cyclic guanosine monophosphate (the renal second messenger of ANP) levels are elevated during sleep with apnea.[88,89] The natriueresis that occurs with sleep apnea appears to normalize in response to therapy with continuous positive airway pressure (CPAP).[90]

Our hypothesis is that sleep apnea as measured by the apnea-hypopnea index (AHI) is related to nocturia and that this relation is not explained by the confounding factors of age, gender and comorbid disease that are believed to predispose to this symptom.

1.4 Motor Vehicle Crashes

1.4.1 Definitions and Classification

Motor vehicle crashes (MVC) have a wide range of definition when studied in epidemiological research, from any contact unintentionally occurring between a car and another object, to fatal collisions. The importance of the varying degrees of

crashes ranges over a spectrum ranging from costly inconvenience to death involving the driver and others. Most studies have been concerned with crashes that either incur an insurance claim, require a police report, or cause injury. Many of these operational definitions will underestimate crash rates, as many crashes that are potentially dangerous but with minimal consequence are rendered benign and are not counted because of factors beyond the driver's control.[91] For example, driving off the road is potentially fatal on a bridge, but usually without consequence on a flat field. A crash reported by the driver is the definition used for this thesis.

1.4.2 Epidemiology

Motor vehicle crashes comprise the largest fraction of all accidents in Canada and Québec. In 1987, 1.4 million accidents were reported to Statistics Canada. Of these, 33% in Canada and 35% in Québec were MVCs. The regional age-standardized crash rates were 84 and 60 per thousand population respectively.[92] Injury resulted from 42% of these MVCs. An in-patient stay in hospital resulted from 7% of all MVCs. The injuries sustained tended to involve multiple body sites (32% of all injuries) and 19% resulted in head injuries (37% of all head injuries).

Accidents are the fifth leading cause of mortality in Québec , Canada and the United States.[93-96] In Québec during 1993, the age-standardized mortality rate for men was 20 per 100,000 population, and 8 for women.[95] In Canada during 1996, the mortality rate was 12.1.[94] In the United states, similar patterns emerge, with an age-adjusted death rate of 16.2 deaths per 100,000 population in 1996.[97] If only licensed individuals are considered in the denominator, 6.8% per year are involved in a police reported crash, and the mortality rate is 31/100,000 drivers. This is despite a consistent trend in declining mortality in north America. Despite being the fifth leading cause of mortality, it is the leading cause of potential years of life lost before age 75, with a mean loss of 41 years in Québec.[95]

The economic impact among the survivors is considerable. In 1987, it was estimated that 58% of all direct accident related expenses incurred by individuals were due to MVCs, totaling 647 million dollars. An additional 238 million was required for direct hospital costs.[92]

From a perspective of injury control, the current dominant analytic paradigm is the Haddon matrix. This essentially classifies into twelve sets the categories of relevant study and intervention. The matrix is constructed by factoring the three temporal phases (pre-event, event, post-event) with four domains (human factors, agent or vehicle, physical environment, socio-cultural environment). The focus of this thesis is related to pre-event human factors.

Males are involved more frequently in all types of accidents, including MVCs.[92,97-99] The gender association with MVCs may be entirely explained by the increased number of miles driven per year by men.[97-99] Age is a strongly associated factor in drivers sustaining MVCs. The highest rates of MVC are consistently seen in drivers under age 25.[92,95,97,99] Rates then decline slightly with age to approximately age 65. With further advancing age, drivers between the ages of 75 and 84 have a four to six times higher risk of MVC per distance driven.[100] Yet their population risk usually remains the same or only slightly elevated because of less distance driven. Household income has been found to be associated in a graded manner with standardized MVC rates, with 71 per 1000 population with the lowest household income bracket to 114 per 1000 in the highest bracket.[92] The putative explanation for this is the increased rate of personal vehicle ownership with increasing income.

Regular alcohol use has been associated with higher frequency of all accidents, as well as MVCs.[92,98,101] In Canada, this effect quadruples the MVC rate from 51 per 1000 non-drinkers to 198 per 1000 drinking 14 or more drinks per week.[92] This effect appears predominantly in the 15-24 year old age group, but not in older age groups. This age-alcohol interaction has also been observed in the United States.[102] Mortality from the crash has also been repeatedly linked to excessive driver blood-alcohol levels[101,102] leading to widespread legislation discouraging drunk driving[103] and a subsequent decline in MVC mortality.[95,97]

More distance driven per year would be expected to expose a driver to more risk of a crash. Yet drivers with more experience have less crashes per mile driven, and drive more miles per year. In a telephone survey of 7634 current drivers in Montreal whose crash histories were all ascertained with government records, crash rate per mile driven increased among the less frequent drivers, but the overall crash rate per driver-year quadrupled from the least to the most categories of miles driven per year.[98] Other studies with less power did not find this association[104] but recent large population-based studies confirm the association of distance driven per year as a proportional risk factor for fatal crashes.[97,99]

Medical conditions considered important in increasing MVC risk include both diseases and their treatments. Conditions include cardiovascular disease,[105] specific neurological disease, diabetes,[106] visual and hearing impairments,[100] major limb amputation or severe mobility impairment from arthritis.[107] Treatments may also affect driving performance, including recent anesthesia,[100] neuroleptic and sedative prescription, and use of opiates.[107-110] Adiposity has been found to be associated with MVC risk.[98,111] Drowsiness is found to be a risk factor in MVC. Sleep deprivation is the most common cause, often resulting from lifestyle or shift work, and drowsiness

interacts with other factors associated with MVC. For example, driving more and more often was an independent risk factor, as was younger drivers and male gender. [112]

1.4.3 Links with Sleep Apnea and Sleep-Disordered Breathing

Between 1 and 23% of MVC's requiring a police report are considered to be due to sleepiness while driving, with the lower boundary of these estimates being considered conservative.[113-116] When an MVC is attributed to sleepiness, it more often involves a higher speed collision and more severe injury, in a manner similar to MVC's associated with alcohol consumption.[114] Both sleep disordered breathing and OSAS have been associated with an increased risk of MVC. [111,117-124] Many of the demographic and medical risk factors for MVC are also associated with SDB, which confounds the relationship of SDB and OSAS with MVC.

The relative influence of all these factors on MVC risk is unclear. The effect of SDB on MVC risk varies by gender[1] which in turn may be due to gender differences in the mileage driven per year with difference opportunities for MVC.[97,99] Alcohol may have a synergistic effect with sleep apnea on driving performance.[125] Irregular schedules and insufficient sleep can worsen SDB and sleep apnea severity,[126] are common in commercial truck drivers, who also have a high prevalence of undiagnosed sleep apnea;[127] the interaction of these two factors on sleepiness and driving performance is potentially dangerous but as yet unquantified.

Varying degrees of cognitive dysfunction are found in patients with untreated OSAS or asymptomatic SDB. [22-25,27-31] Chronic excessive daytime somnolence is considered the main factor that renders individuals with OSAS at more risk of MVC. [111,118,119,123] This somnolence varies in a graded manner whether measured electroencephalographically or behaviorally from full awake vigilance to sleep. When individuals with OSAS are awake, their driving simulator performance indicates an impairment when untreated,[28,29] which improves with treatment.[128,129] Among patients compliant with prolonged study protocols, their reported MVC rates improve

with continuous CPAP use by as much as a factor of 5.[129,130] Select patients treated with surgery (uvulopalatopharyngoplasty) and who are compliant with long term study protocols also reduce their subsequent MVC rate to a similar degree.[131]

All of the studies except for two[1,111] selected the individuals with obstructive sleep apnea syndrome or sleep disordered breathing, and whose selection may have involved MVC history and coincident neuropsychological dysfunction. None have accounted for comorbid conditions or alcohol use, and few account for age or gender. We propose that confounding factors account for at least some of the association of obstructive sleep apnea syndrome and sleep disordered breathing with MVC, and that sleep disordered breathing is independently associated with MVC risk.

1.5 Study Objectives and Presentation of Articles

The overall unifying hypothesis is that sleep apnea is related to several clinical consequences beyond excessive daytime sleepiness. These consequences include erectile dysfunction, nocturia and motor vehicle crashes. This was approached through the evaluation of these three symptoms or consequences at presentation for specialized diagnostic opinion.

Our first hypothesis was that sleep apnea is related to erectile dysfunction while accounting for the clinical and physiologic factors that are known to affect this symptom. Our secondary hypotheses were that the consequent sleep fragmentation as measured by decreased fraction s of REM and slow wave sleep (SWS) would potentially mediate this association. The other clinical consequences of sleep apnea such as cardio-vascular disease and excessive daytime somnolence may confound or mediate the association.

Our second major hypothesis was that sleep apnea is related to nocturia and that this relation is not explained by the confounding factors of age, gender and comorbid disease that are believed to predispose to this symptom.

The third major hypothesis is that sleep apnea or sleep-disordered breathing affects MVC risk while taking into account other variables known to predispose to MVC. We also sought to evaluate this across the spectrum of three risky events from falling asleep at the wheel while driving, having had an MVC, and having repeated MVC's, as these outcomes span increasing levels of risk of harm to self and others.

The first article (Chapter 2) approaches the hypothesis that sleep apnea is related to erectile dysfunction. The second article (Chapter 3) proceeds to evaluate the relationship with nocturia. The third article (Chapter 4) evaluates the relationship of sleep-disordered breathing with motor vehicle crash history.

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CHAPTER 2

SLEEP APNEA AND ERECTILE DYSFUNCTION

2.1 Preface to the manuscript

This manuscript presents the study describing the relationship between sleep apnea and erectile dysfunction. Limitations of previous studies were due to the absence of a control group or selection of affected individuals and controls, and the narrow definition of erectile dysfunction by one night's measurement of nocturnal penile tumescence, and the lack of adjustment or inappropriate adjustment for confounding variables.

The introduction of the article summarizes the prevalence and shared risk factors for erectile dysfunction and sleep apnea, and the available literature on the relationship between erectile dysfunction and sleep apnea. The methods section describes the methods of measurement, the crossectional design as well as the categorization of sleep apnea and age. Note that the sample is smaller than the samples described in chapters 3 and 4 because of the analysis was performed while data entry was still in progress. The sample is also smaller because women are excluded.

The results for the crude and adjusted odds ratios are discussed in the light of the current accepted causes of erectile dysfunction, the potential patho-physiological links with sleep apnea, as well as the assessment of confounding in future treatment studies of erectile dysfunction associated with sleep apnea.

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Baltzan MA, Kimoff RJ, Suissa S. Sleep apnea and erectile dysfunction. Unpublished manuscript. Montreal: Department of Epidemiology and Biostatistics, McGill University, 1998.

2.2 Abstract

Erectile dysfunction and sleep apnea are prevalent disorders that share several risk factors. To assess whether sleep apnea as quantified by the apnea-hypopnea index (AHI) is related to erectile dysfunction, a cross-sectional hospital-based case series was carried out in a tertiary care sleep-disorders clinic. Consecutive patients were referred for polysomnography with a suspected diagnosis of snoring or sleep apnea between April 1, 1990 and October 31, 1993. Clinical examination, questionnaire and attended polysomnography were performed on all subjects. Self-reported erectile dysfunction was the outcome.

There were 572 men with a mean age of 49.8 ± 6.5 years. Of these, 47% had normal polysomnography, 26% had mild sleep apnea and the remaining 27% had severe sleep apnea. The prevalence of erectile dysfunction increased from 17.5% for normal subjects to 22.6% for mild and 29.3% for severe sleep apnea. Age, the presence of cardiovascular disease and excessive daytime somnolence were strongly associated with erectile dysfunction. After controlling for age and cardiovascular disease, the odds ratio of erectile dysfunction was 1.2 (95% CI: 0.8-2.1) and 1.3 (95% CI: 1.1-1.5) respectively for mild and severe subjects relative to normals. Further adjustment for excessive daytime somnolence abolished this association. Erectile dysfunction is associated with sleep apnea independently of age and the presence of cardiovascular disease. Excessive daytime somnolence may mediate this relation.

2.3 Introduction

Erectile dysfunction affects around 30 million North American men[1,2] while sleep apnea affects 3.6 to 22 million men between the ages of 30 and 60 in North America.[3-5] The prevalences of both conditions increase with advancing age and are associated with several co-morbid conditions, including mood disorders, cardiovascular and neurological disease.[1,2,5,6] The preponderance of erectile dysfunction in patients with sleep apnea has been noted in a small case series[7] and by clinical experience.[6] Sleep apnea has also been found in a high percentage of patients referred for nocturnal penile tumescence (NPT) testing with concomitant polysomnography.[8-10] The pathophysiology of the associated erectile dysfunction is not well described. It may be due to comorbid cardiovascular disease (CVD) such as hypertension, stroke and heart disease,[11,12] or their medical management.[2,9,13] Neuropsychiatric[14-18] or autonomic dysfunction[19-23] from sleep fragmentation may also play a causal role between sleep apnea and erectile dysfunction.

In a recent report, treatment for sleep apnea with continuous positive airway pressure (CPAP) improved erectile dysfunction in one third of the cases studied; the factors associated with failure of efficacy were not clearly delineated.[24] A population based prevalence study of sleep disordered breathing found that erectile dysfunction was not significantly associated with sleep apnea after a multiple correlation analysis that controlled for age, CVD and excessive daytime sleepiness.[25] Thus, the relationship between sleep apnea and erectile dysfunction remains uncertain. The role of several interrelated factors must be assessed in studying and managing this manifestation of sleep apnea. The primary respiratory disturbance (apneas and hypopneas), its cardiovascular consequences, and its neuropsychiatric consequences must be studied while accounting for the effects of age, cardiovascular disease, diabetes,[2] and obesity.

In this study, we assessed whether sleep apnea is related to erectile dysfunction independently of the clinical and physiologic factors that are known to affect these conditions. We also studied whether the consequent alterations in sleep stages could affect this association along with CVD and excessive daytime somnolence.

2.4 Methods

We addressed these questions using consecutive patients referred to a tertiary sleep disorders center. Patients were studied with attended polysomnography and completed a health status questionnaire.

2.4.1 Sources of Data

The Sleep Laboratory of the Royal Victoria Hospital is one of the three major clinical sleep laboratories in the Province of Québec, Canada. Patients are referred from general practitioners and specialists. Clinical variables which are obtained upon presentation to the clinic are age, gender, body mass index, comorbid disease, subjective excessive daytime somnolence, and suspected diagnosis. Since April 1, 1990 all patients are asked to complete a questionnaire on their first visit. Most patients in this clinic presenting with possible SAHS are subsequently studied with polysomnography.

Between April 1, 1990 and October 31, 1993, 1196 consecutive patients seen in the Sleep Disorders Clinic underwent polysomnography. Only subjects with clinical diagnoses of normal physiologic sleep, snoring, and obstructive sleep apnea are included from this population. We therefore excluded patients with other illnesses such as: chronic lung disease on home oxygen (59), epilepsy (2), narcolepsy (19), parasomnias (25), periodic leg movements (51), and other neuromuscular diseases (21). We also excluded patients who did not fill out a questionnaire (42) and those who underwent daytime diagnostic polysomnography or split night diagnostic and CPAP titration studies (159) because of the effect these techniques have upon sleep stages and the measurement of sleep apnea-hypopnea syndrome.[26, 27] This excludes a

total of 478 patients, with 818 remaining for study. Of these 818 subjects, 572 were men.

2.4.2 Measurements

Polysomnography was performed on all patients presenting with a possibility of sleep apnea. The degree of sleep apnea was quantified by the apnea-hypopnea index (AHI). It was calculated from the total number of apneas (total cessation of breathing for over 10 seconds associated with oxygen desaturation) plus the total number of hypopneas (decrease in airflow to 50% or less for over 10 seconds associated with oxygen desaturation of at least 4% from baseline) throughout the night divided by the total hours of electroencephalographic (EEG) sleep.[28]

Sleep stages were defined by conventional criteria[29] and manually scored by qualified technicians of sleep. Stages 3 and 4 are here referred to as "slow wave sleep" (SWS). The sleep stages SWS and REM are expressed as percentages of total sleep time. Arousals were scored as 'movement arousals' defined by Rechtschaffen and Kales.[29]

The presence or absence of erectile dysfunction was assessed from the questionnaire. The definition was symptomatic in order to include both functional and organic forms of erectile dysfunction. Erectile dysfunction was defined for the purpose of study as a positive answer to the question: 'Do you have sexual problems? Impotency?' Obesity was measured by the body mass index (BMI), also known as the Quetelet index and defined as: weight (kg)/[height (m)]^2. Diabetes was operationally defined as diabetes requiring medication. Cardiovascular disease (CVD) was considered present if one or more of the following conditions was found on initial consultation: hypertension requiring medication, previous myocardial infarction,

angina requiring medication, or congestive heart failure, or if the following medications were prescribed: beta blockers, calcium channel blockers, diuretics, nitrates and acetyl salicylic acid preparations in once daily dosing. Excessive daytime somnolence was defined by response to a validated series of 9 questions regarding habitually falling asleep in the context of a range of common daytime activities.

2.4.3 Data Analysis

The dependent variable (outcome) in all analyses was erectile dysfunction. The primary determinant under study was the AHI as the measure of sleep apnea. Confounding variables included age, body mass index, presence of CVD, excessive daytime somnolence and the markers of disturbed sleep architecture: movement arousal index, percentages of REM sleep and slow wave sleep.

Standard methods for the analysis of binary data were used to describe the relationship of all variables with erectile dysfunction. The odds ratio was used for all analyses. Continuous variables were partitioned at the median to form 2 x 2 tables and into quartiles to assess linearity with logit plots. For the AHI, subjects were partitioned at cutpoints of 15 and 40 as these have been used in the literature as clinically significant definitions of normal (15 or less), 'mild' (>15 to 40) and 'severe' (>40) sleep apnea respectively.[30] Alternate cut points including an AHI below 5 to define normal did not change the results presented below. Separate analyses with the movement arousal index instead of AHI did not change the results presented. Stratified analyses of the relationship between AHI and erectile dysfunction were performed within the covariate strata to assess the possible effect modifying roles these covariates may play. Standard logistic regression analysis was used for all analyses.[31] Modeling with stepwise forward and backwards variable selection was performed based upon the model improvement found by including sequential variables with a p-

value of 0.05 or less. Interaction variables were presented for modeling if they could be justified by a finding in this or previous studies compatible with effect modification. 'Best fit' models were chosen based upon the hypotheses and the degree of fit the model displayed for the data. The Hosmer-Lemeshow goodness-of-fit statistic with at least eight degrees of freedom was used to assess model fit, where a lower test statistic and a p-value closer to 1.00 denote better fit. All analyses were performed on SAS 6.12 statistical software (Cary, N.C.).

2.5 Results

There were 572 men in the cohort of 818 eligible subjects. The mean age of these men was 49.8 ± 6.5 years, with 126 (22%) reporting erectile dysfunction. Seventeen percent had cardiovascular disease (CVD) and 33% had excessive daytime somnolence. Of the 100 subjects with CVD, 93 had hypertension, 28 chronic stable angina, 23 a previous myocardial infarction and 19 stable congestive heart failure; twenty-two subjects had 2 or more CVD diagnoses, usually hypertension combined with one of the other diseases. More than half had a BMI less than 30 kg/m^2, with a mean BMI of 29.7 ± 6.5 kg/m^2. The mean AHI was 27.1 ± 28.4 events/hour. Eleven subjects (1.9%) were found to have more central apneas than obstructive apneas when the AHI was >15. Diabetes was found to be infrequent as only 3% of the cohort were prescribed medications, and was not considered further in the analysis. Abnormal sleep architecture was frequently demonstrated, with the mean (SD) percentage of REM sleep being 13.2 ± 6.8% and SWS percentage 11.8 ± 10.2%.

The prevalence of erectile dysfunction increased by increasing categories of sleep apnea (see figure 2.1). Univariate analyses shown in table 2.1 indicate that the crude odds ratio of erectile dysfunction increased with the AHI. Relative to normal AHI, mild AHI subjects had an odds-ratio (OR) of 1.4 (95% CI: 0.8-2.3), while for the severe AHI subjects it was 2.0 (95% CI: 1.2-3.1). This relationship demonstrated a significant trend (chi-squared of 8.1, p-value 0.017). The prevalence of erectile dysfunction also increased with age with ORs of 2.0 (95% CI: 1.1-3.6) and 2.3 (95% CI: 1.2-4.2) for ages 40-59 and over 60 respectively relative to subjects less than 40 years of age. The body mass index demonstrates a weak but significant relationship (BMI $\geq$ 28.5 kg/m^2 compared to less than 28.5: OR = 1.5, 95% CI 1.0 to 2.2). The presence of CVD (OR 5.5; 95% CI: 3.6 to 8.5) and excessive daytime somnolence (OR 4.1; 95% CI: 2.7 to 6.0) are both strongly associated with an increased rate of erectile

dysfunction. Neither the lack of REM sleep or SWS were found to have a significant relation with erectile dysfunction. Examination of the confounding variables revealed that CVD, excessive daytime somnolence and age were all positively correlated (data not shown).

Logistic regression analysis was performed to control for the effects of covariant factors. Table 2.2 shows that, after controlling for age, the effect of AHI on erectile dysfunction was reduced but remained present with odds ratios of 1.2 (95% CI: 0.8-2.1) and 1.3 (95% CI: 1.1-1.5) respectively for mild and severe subjects. When further adjusted for CVD as well as age, the AHI remained similarly associated with erectile dysfunction. When, in addition to age and CVD, further adjustment for excessive daytime somnolence was performed, the AHI was no longer significantly associated with erectile dysfunction (Table 2.3). The odds ratios for mild and severe conditions became respectively 0.9 (95% CI: 0.5-1.4) and 1.0 (95% CI: 0.8-1.2).

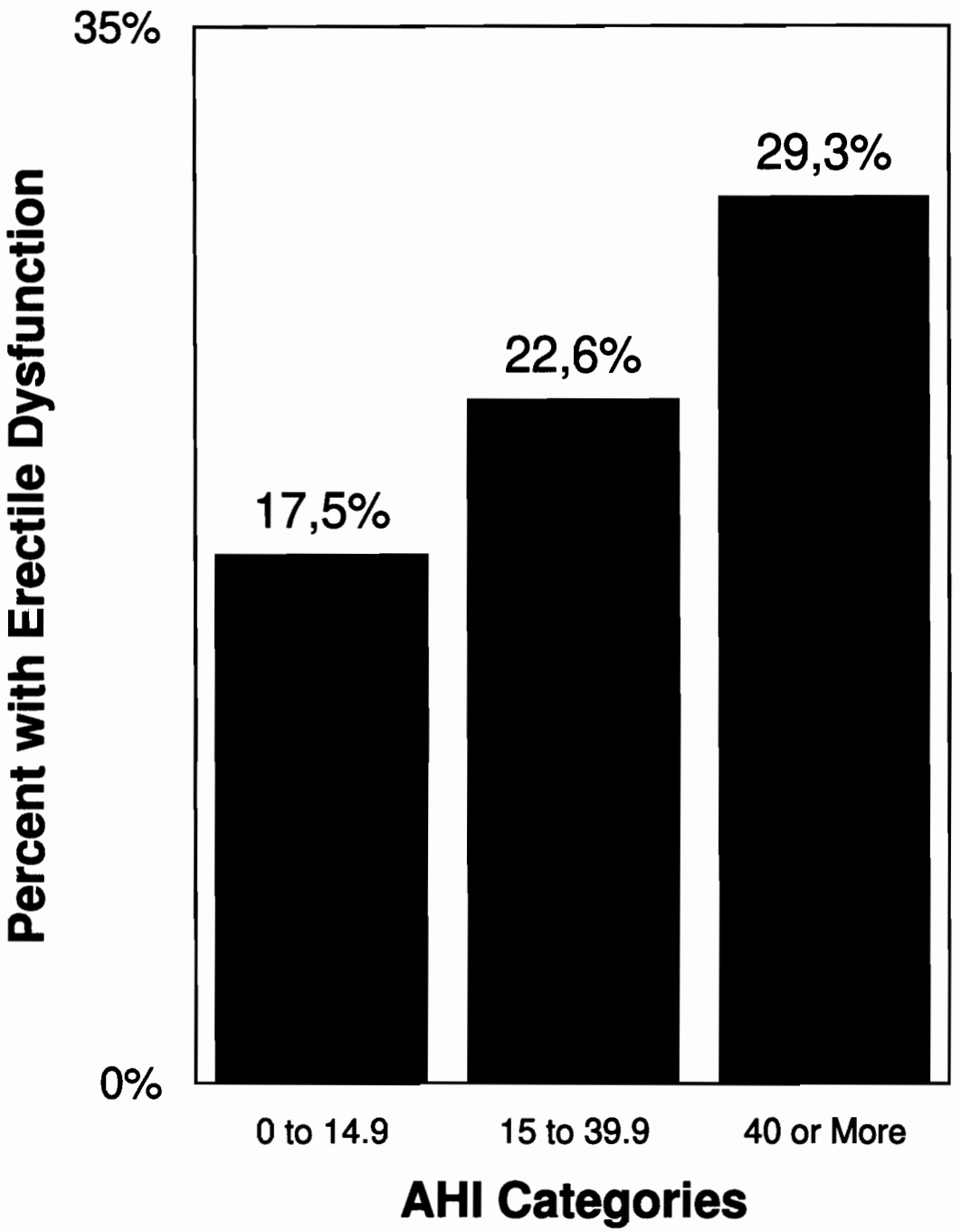

Figure 2.1: Frequency of erectile dysfunction by category of sleep apnea.

Abbreviation: AHI: apnea-hypopnea index.

Table 2.1: Crude Associations with Erectile Dysfunction

Risk Factor	Erectile Dysfunction	No Erectile Dysfunction	OR	95%CI
Apnea-Hypopnea Index (events/hour)				
0 to 14.9	47	222	1.0	referent
15 to 39.9	33	113	1.4	0.8 to 2.3
40 or more	46	111	2.0	1.2 to 3.1
Age (in years)				
20 to 39	17	110	1.0	referent
40 to 59	69	222	2.0	1.1 to 3.6
60 or more	40	114	2.3	1.2 to 4.2
Excessive Sleepiness				
Absent	52	330	1.0	referent
Present	74	116	4.1	2.7 to 6.0
Cardio-vascular Disease				
Absent	75	397	1.0	referent
Present	51	49	5.5	3.6 to 8.5
Body Mass Index (in kg/m^2)				
< 28.5	53	233	1.0	referent
≥ 28.5	73	213	1.5	1.0 to 2.2
Rapid Eye Movement Sleep (% of total sleep time)				
$\geq 13.4\%$	67	218	1.0	referent
$< 13.4\%$	59	228	0.8	0.6 to 1.3
Slow Wave Sleep (% of total sleep time)				
$\geq 10.4\%$	61	223	1.0	referent
$< 10.4\%$	65	223	1.1	0.7 to 1.6

Abbreviation: 95% CI: 95% confidence interval.

Table 2.2:

Effect of AHI on Erectile Dysfunction Adjusted for Age

Risk Factor	Odds Ratio	95% CI
Apnea-Hypopnea Index (events/hour)		
0 to 14.9	1.0	referent
15 to 39.9	1.2	0.8 to 2.1
40 or more	1.3	1.1 to 1.5
Age (in Years)		
20 to 39	1.0	referent
40 to 59	1.8	1.0 to 3.3
60 or more	1.5	1.1 to 2.0

Abbreviation: 95% CI: 95% confidence interval.

Table 2.3:

Effect of AHI on Erectile Dysfunction
Adjusted for Age, Cardio-vascular Disease and Excessive Daytime Somnolence

Risk Factor	Odds Ratio	95% CI
Apnea-Hypopnea Index (events/hour)		
0 to 14.9	1.0	referent
15 to 39.9	0.9	0.5 to 1.4
40 or more	1.0	0.8 to 1.2
Age (in Years)		
20 to 39	1.0	referent
40 to 59	1.5	1.1 to 2.2
60 or more	2.2	1.2 to 1.7
Cardio-vascular Disease		
Present	2.7	1.6 to 4.6
Excessive Daytime Somnolence		
Present	6.4	3.8 to 10.6

Abbreviation: 95% CI: 95% confidence interval.

2.6 Discussion

The presence of an association between erectile dysfunction and sleep apnea is supported by the findings of this study. This association is reduced but persists after accounting for the influence of age and pre-existing cardiovascular disease. However, when adjusted further for the presence of excessive daytime somnolence, this association is entirely eliminated.

We feel that adjusting for the presence of daytime somnolence when studying the relationship of sleep apnea with erectile dysfunction is inappropriate since it represents an over adjustment for a factor potentially in the causal pathway.[32] Such over adjustment may account for the null association of sleep-disordered breathing with erectile problems found on multiple partial correlation analysis where both erectile dysfunction and several measures of somnolence were included in a multivariate model.[25] There is observational evidence that excessive daytime somnolence due to chronic sleep fragmentation is an intermediate factor. Erectile dysfunction has been found to be associated with other disorders of excessive somnolence of diverse etiologies which all result in sleep fragmentation.[33] Sleep-disordered breathing causes somnolence and associated neuropsychiatric dysfunction, which may in turn contribute to functional erectile dysfunction by reduced libidinal drive with or without reduced libidinal expression. These may in turn result in fewer attempts at sexual intercourse. These relationships have yet to be clearly documented and present a realm requiring more research. The biological effect of sleep apnea reducing organic erectile function (the ability of a subject to attain normal penile tumescence without the influence of conscious factors such as anxiety) is documented by the frequent observation of low or absent penile tumescence in REM sleep of individuals with sleep apnea.[8-10] This occurs frequently with or without the presence of hypertension or antihypertensive therapy.[9] Nevertheless, studies with experimental induction of sleep fragmentation and somnolence and documenting the organic and

functional effects on erectile dysfunction are needed in order to support any hypothesis that sleep apnea causes erectile dysfunction.

We believe that the association between sleep apnea and erectile dysfunction may be causal. Evidence of causation includes the dose response between sleep apnea severity and erectile dysfunction. Moreover, erectile dysfunction is also rapidly reversible when CPAP successfully eliminates sleep apnea.[24] The relatively weak relationship (odds ratio generally less than 2) suggest that this relationship may be the result of confounding and not causation, population inhomogeneity or inhomogenous effects.

Our study confirms that both advancing age and CVD are associated with erectile dysfunction. The age dependent increase in erectile dysfunction has been known for decades, and has been confirmed in large population based studies.[2] The strong association with CVD has also been previously demonstrated in men with hypertension[2,9] and heart disease.[2]

There are limitations to this study. The cross-sectional design cannot distinguish the sequence of association, namely which of sleep-disordered breathing and erectile dysfunction occurs first. The length-biased sampling which may occur in such a study would tend to underestimate the frequency of self-limited functional erectile dysfunction (cases with a short duration), and over represent cases of chronic persistent erectile dysfunction (cases with a long duration).[33] The current etiologic concept that sleep apnea is largely a structural disease with a long natural history spanning years if not decades before diagnosis[36] supports the utility of this design for studying associations with chronic complaints. Self-reported daytime sleepiness may correlate poorly with objective somnolence as measured by multiple sleep latency or maintenance of wakefulness testing, but generally underestimates objectively measured somnolence and may be more clinically relevant to the individual in the context of usual daily activities. The estimation of somnolence used in this study was sufficient

to negate the dose-related association of sleep-disordered breathing with erectile dysfunction. Erectile dysfunction was assessed by a questionnaire only, and may have led to the reporting of diverse sexual problems. Such lack of precision in the principal measure of outcome will likely have resulted in an underestimation of the strength of the association examined. The association of sleep apnea with objective decreases in penile tumescence has been demonstrated previously in small series of selected patients.[8,9]

In summary, we found that erectile dysfunction was related to the AHI, after adjustment for age and the presence of cardiovascular disease. The preponderance of excessive daytime somnolence in the subjects with both conditions suggests that both erectile dysfunction and somnolence are related to sleep disordered breathing in a similar fashion. This finding may aid in guiding further research into the mechanisms and management of erectile dysfunction in the context of sleep apnea-hypopnea syndrome. At least, the study identifies sleep apnea-hypopnea syndrome as a modifiable risk factor for erectile dysfunction.

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CHAPTER 3

SLEEP APNEA AND NOCTURIA

3.1 Preface to the manuscript

This manuscript presents the second study describing the relationship between sleep apnea and nocturia. Limitations of previous studies were due to the absence of a control group, inconsistent or vague definitions of nocturia, and no assessment of confounding variables.

The introduction of the article summarizes the scope and impact of nocturia, and the available literature on the relationship between nocturia and sleep apnea. The methods section describes the methods of measurement, the cross-sectional design as well as the categorization of sleep apnea and age. Note that the sample is larger because of the longer time period of consecutive subjects entered for analysis, as well as the inclusion of women.

The results for the crude and adjusted odds ratios are discussed in the light of the current accepted causes of nocturia, as well as the assessment of outcomes in treatment studies of sleep apnea.

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3.2 Abstract

Nocturia is a common symptom with important clinical impact. This predisposes to falls, is associated with poor sleep, and has often been ascribed to sleep apnea. We sought to study if sleep apnea as quantified by the apnea-hypopnea index (AHI) is related to nocturia while accounting for various clinical and physiologic factors that may also affect this symptom. A cross-sectional study was performed in a tertiary care sleep-disorders clinic. Consecutive patients were referred for polysomnography for a suspected diagnosis of snoring or sleep apnea. Nocturia was defined as habitually awakening more than twice to urinate. Demographic and anthropomorphic characteristics as well as comorbid diseases and polysomnographic sleep variables were gathered on all patients.

The mean age (±SD) of the 1010 patients was 51.0 ± 12.9 years, with 236 (23%) women,169 (17%) reporting nocturia and 485 (48%) with an AHI >15. The prevalence of nocturia increased with increasing sleep apnea. The prevalences were 9.7% if the AHI was 15 or less, 19.7% with an AHI of >15 to 40, and 28.4% if the AHI was >40. Age (compared to age 20 to 39, age 40 to 59, OR = 1.6 95%CI 0.9 to 2.6; age >60 OR = 2.7 95%CI 1.6 to 4.6) and the presence of cardiovascular disease (OR = 3.8 95%CI 2.6 to 5.4) were associated with nocturia. A lower percentage of slow wave sleep was associated with nocturia, while REM sleep demonstrated no association. Logistic regression analysis demonstrated that the AHI remained associated with nocturia when age, gender, CVD and slow wave sleep were considered simultaneously.

Nocturia occurs with increasing frequency as sleep apnea severity increases. Age and CVD are significant confounding factors. When nocturia is reported by a patient, sleep apnea should also be considered in the differential diagnosis.

3.3 Introduction

Nocturia has been considered an annoying side effect of diuretic use or a symptom of the aging uro-genital tract.[1] It is a clear risk factor for falls requiring medical attention[2] and is associated with non-restorative sleep.[3,4] Nocturia is a very common reason for seeking outpatient[5] and emergency room care.[6] A recent polysomnographic study found that awakenings after episodes of obstructive apnea often resulted in nocturia.[7] This symptom has been associated with sleep apnea in case reports[8] and has been found to occur 28% of the time in a survey of patients with sleep apnea.[9] Without comparison to a control group, it may be argued that this symptom is no more prevalent in individuals with compared to those without sleep apnea, as population based studies estimate prevalences of nocturia from 11 to 40% of adults.[10,11] The reasons for nocturia to occur with sleep apnea syndrome may stem from neuro-humoral responses to the sleep apnea[12,13] which appear to normalize in response to therapy with nasal continuous positive airway pressure (CPAP).[14]

Our hypothesis was that sleep apnea is related to nocturia and that this relation is not explained by the confounding factors of age, gender and comorbid disease that may predispose to this symptom.

3.4 Methods

We investigated this hypothesis using a cohort of consecutive patients referred to a tertiary sleep disorders center. Patients were studied with attended polysomnography and completed a questionnaire.

3.4.1 Source of Data

The Sleep Laboratory of the Royal Victoria is one of the three major clinical sleep laboratories in the province of Québec, Canada. Patients are referred from general practitioners and specialists.

Between April 1, 1990 and December 31, 1994, all patients who underwent a first polysomnography were screened for inclusion. Only subjects with diagnoses of normal physiologic sleep, snoring, and obstructive sleep apnea are included. This study was approved by the hospital research ethics board.

3.4.2 Measurements

The standard measurement of sleep apnea was the apnea-hypopnea index (AHI) calculated from the total number of apneas (total cessation of breathing for over 10 seconds) plus the total number of hypopneas (decrease in airflow by 50% or less for over 10 seconds associated with oxygen desaturation of at least 2% from baseline) divided by the total hours of electroencephalographic sleep.[15] Subjects who underwent only daytime diagnostic or split-night diagnostic/titration studies were excluded because of the effect these techniques have upon sleep stages and AHI measurement.[16,17]

Sleep stages were defined by conventional criteria [18] and manually scored by qualified technicians of sleep. Stages 3 and 4 are referred to as "slow wave sleep" (SWS). The sleep stages SWS and rapid eye movement sleep (REM) are expressed as

percentages of total sleep time. Alternate analyses using total time in these stages did not change the results presented.

The presence or absence of nocturia was assessed by response to the questionnaire. Nocturia was defined as an answer of more than 2 to the question: 'How many times do you get up to urinate at night?' This number of habitual nocturnal void episodes has been defined as abnormal.[19] The regular use of alcohol prior to bedtime was also asked, and any regular quantity of one or more drinks per night was considered a positive answer. Obesity was measured by the body mass index (BMI) defined as: weight(kg)/[height(m)]^2. Diabetes was operationally defined as diabetes requiring medication. Cardiovascular disease was considered present if one or more of the following conditions was found on initial consultation: hypertension requiring medication, previous myocardial infarction, angina requiring medication, or congestive heart failure, or if the following medications were prescribed: beta blockers, calcium channel blockers, diuretics, nitrates and acetyl salicylic acid preparations.

3.4.3 Data Analysis

The outcome in all analyses was nocturia. The primary determinant under study was the AHI. Confounding variables included age, gender, regular alcohol use before bedtime, body mass index, presence of CVD, and presence of diabetes mellitus. The markers of disturbed sleep architecture were the arousal index as well as the percentages of REM sleep and slow wave sleep.

Standard methods for the analysis of binary data were used to describe the relationship of all variables with nocturia. The odds ratio was used for all analyses. Continuous variables were partitioned at the median to form 2 x 2 tables and into quartiles to assess linearity with logit plots. For the AHI, groups were partitioned at cutpoints of 15 and 40 as these have been used in the literature as definitions of

clinically significant 'mild' and 'severe' sleep apnea respectively.[20] Standard logistic regression analysis was performed. All analyses were performed on SAS 6.12 statistical software (Cary, N.C.).

3.5 Results

A total of 1424 subjects underwent a first polysomnography. Subjects were excluded because of chronic hypoxemic lung disease (59), epilepsy (5), narcolepsy (21), parasomnias (25), periodic leg movements (68), and other neuromuscular diseases (23). Excluded were also subjects who did not fill out a questionnaire (42) and those who underwent daytime diagnostic polysomnography or split night diagnostic and NCPAP titration studies (171). This excludes a total of 414 patients, with 1010 (71%) remaining for study.

Of those remaining, the mean age (±SD) was 51.0 ± 12.9 years, with 236 (23%) women and 169 (17%) reporting nocturia. One-hundred and sixty-four (16%) had cardio-vascular disease (CVD) and 381 (38%) had excessive daytime somnolence. Of the 164 subjects with any CVD, 130 (79%) had hypertension, 38 (23%) chronic stable angina, 24 (14%) a previous myocardial infarction and 20 (11%) stable congestive heart failure; twenty-two subjects had 2 or more CVD diagnoses, usually hypertension combined with one of the other diseases. More than half had a BMI less than 30 kg/m^2, with a mean BMI of 29.5 ± 7.6 kg/m2. The mean AHI was 25.6 ± 29.3 events/hour. An AHI more than 15 events/hour was found in 485 (48%). Diabetes was found to be infrequent in this cohort as only 30 (3%) of the cohort were prescribed medications, and it was excluded as a factor in this analysis. Abnormal sleep architecture was frequently demonstrated, with the mean percentage of REM sleep being 12.8 ± 6.9% and SWS percentage 13.8 ± 11.4%.

The prevalence of nocturia increased with increasing categories of sleep-disordered breathing. The prevalences were 9.7% if the AHI was 15 or less, 19.7% with an AHI of >15 to 40, and 28.4% if the AHI was >40. This relationship demonstrated a significant trend (chi-squared of 45.2, p-value less than 0.001). Age

was also associated in a graded manner (Table 3.1). Male gender and body mass index demonstrated weak but significant associations. The presence of CVD was strongly associated with nocturia. A lower percentage of slow wave sleep was associated with nocturia, while REM sleep demonstrated no association. Alcohol use was not associated with nocturia as defined; if the definition was changed to 'waking more than once nightly to urinate', then alcohol use became significant.

Logistic regression analysis was performed to estimate the independent effect of each factor. Table 3.2 shows that the AHI remains associated with nocturia when age, gender, CVD and slow wave sleep are considered simultaneously. Gender, body mass index, and SWS no longer remained associated with nocturia. Age and the presence of CVD contributed independently to the probability of nocturia. Separate analyses with the arousal index instead of AHI did not change these findings.

Table 3.1: Crude Associations with Nocturia

Risk Factor	Nocturia	No Nocturia	OR	95%CI
Age (in years)				
20 to 39	20	172	1.0	referent
40 to 59	83	458	1.6	0.9 to 2.6
60+	66	211	2.7	1.6 to 4.6
Gender				
Female	25	211	1.0	referent
Male	144	630	1.9	1.2 to 3.0
Apnea-Hypopnea Index (events/hour)				
0 to 15	51	474	1.0	referent
>15 to 40	45	183	2.3	1.5 to 3.5
> 40	73	184	3.7	2.5 to 5.3
Cardio-vascular Disease				
Absent	110	736	1.0	referent
Present	59	105	3.8	2.6 to 5.4
Bedtime Alcohol Use				
Absent	131	739	1.0	referent
Present	8	27	1.7	0.7 to 3.7
Body Mass Index (in kg/m^2)				
< 28.5	66	439	1.0	referent
≥ 28.5	103	402	1.7	1.2 to 2.4
Rapid Eye Movement Sleep (% of total sleep time)				
≥ 13.1%	94	418	1.0	referent
< 13.1%	75	423	0.8	0.6 to 1.1
Slow Wave Sleep (% of total sleep time)				
≥ 12.2%	104	408	1.0	referent
< 12.2%	65	433	0.6	0.4 to 0.8

Abbreviation: 95% CI: 95% confidence interval.

Table 3.2:
Adjusted Effect of AHI on Nocturia
for Age, Gender, Alcohol Use and Cardio-vascular Disease

Risk Factor	Odds Ratio	95% Confidence
Apnea-Hypopnea Index (events/hour)		
0 to 15	1.0	referent
>15 to 40	1.8	1.5 to 2.2
> 40	2.2	1.4 to 3.5
Age (in years)		
20 to 39	1.0	referent
40 to 59	1.1	0.6 to 1.8
60+	1.4	1.1 to 1.9
Gender		
Female	1.0	referent
Male	0.9	0.5 to 1.6
Cardio-vascular Disease		
Absent	1.0	referent
Present	3.3	2.2 to 6.0
Slow Wave Sleep (% of total sleep time)		
≥ 12.2%	1.0	referent
< 12.2%	0.9	0.6 to 1.5

Abbreviation: 95% CI: 95% confidence interval.

3.6 Discussion

Sleep disordered breathing is clearly related to nocturia. This is supported by both the crude and adjusted findings of this study. Nocturia occurs with increasing frequency with increasing severity of sleep apnea. Age and CVD are confounding factors.

This association may in part explain the finding that nocturia has been related to nocturnal thirst, poor sleep quality and daytime sleepiness.[4] The daytime sleepiness and fatigue observed with sleep apnea has been ascribed to chronic sleep fragmentation. From the patient's point of view, the nocturia and its accompanying awakening may be the apparent culprit, especially if this is accompanied by difficulty in resuming sleep. Patients with sleep apnea rarely report that their nocturnal awakenings are due to respiratory events, but attribute these awakenings to the need to void.[7] As a result, the bothersome nocturia may become the patient's focus, and lead not only to an evaluation for prostatism but to empirical medical therapy. When nocturia is reported by a patient, sleep apnea should also be considered in the differential diagnosis.

Nocturia is generally not regarded as an outcome in the evaluation of treatment of sleep apnea syndrome unless the study is specifically designed to investigate urinary parameters. Whether the increased nocturnal urine output that accompanies the disturbed renin and atrial natriuretic profiles in sleep apnea is a precursor to hypertension is at present unclear. From the patient's point of view, nocturia may be underestimated by the physician until it is related to a nocturnal fall and possibly fracture.[2] The reduction in nocturia resulting from CPAP therapy may be valued by the patient, a point that once understood may aid in improving adherence with CPAP.

We chose our definition of nocturia based on a published survey defining abnormal nocturnal urinary frequency. [19] We believe that a uniform definition of nocturia (more than twice a night) be used in reporting investigations in the future, as this is likely why prevalence estimates vary widely.

In summary, nocturia is related to sleep disordered breathing. This symptom is more prevalent with more severe sleep apnea and is not explained by confounding factors of aging and CVD. The diagnosis of sleep apnea syndrome should be seriously considered whenever a patient reports awakenings more than twice a night to urinate.

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CHAPTER 4

SLEEP DISORDERED BREATHING AND MOTOR VEHICLE CRASHES

4.1 Preface to the manuscript

This manuscript presents the results of the third study which describes the relationship of sleep apnea and sleep disordered breathing with self-reported motor vehicle crashes. Limitations of previous studies were due to selection of affected individuals and controls, vague definitions of sleep apnea or sleep apnea syndrome, and inconsistent assessment of confounding variables.

The introduction of the article summarizes the scope and impact of motor vehicle crashes, with special reference to sleepiness-related crashes and sleep apnea or sleep disordered breathing. The methods section describes the methods of measurement, the cross-sectional design as well as the categorization of sleep apnea and sleep disordered breathing.

The results for the crude and adjusted odds ratios are discussed in the light of the current accepted risk factors for motor vehicle crash.

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Baltzan MA, Kimoff RJ, Suissa S. Sleep disordered breathing and motor vehicle crashes. Unpublished manuscript. Montreal: Department of Epidemiology and Biostatistics, McGill University, 1998.

4.2 Abstract

Sleep apnea is a prevalent cause of somnolence and morbidity and is associated with age, gender, obesity and cardiovascular disease. The independent association with motor vehicle crashes (MVC) is complex. A cross-sectional investigation of MVC in association with polysomnographic sleep apnea was undertaken. Data were obtained on 996 patients over four years of consecutive referrals with suspected sleep apnea to the Royal Victoria Hospital sleep-disorders clinic.

Of entire study population, 68% had at least minimal polysomnographic sleep apnea. Prior MVC was associated with sleep apnea when habitual snorers were removed from the referent group. Chronic self-perceived daytime somnolence was strongly associated with crashes. Other known risk factors were found to be associated with MVC, including age, gender, presence of cardiovascular disease, alcohol consumption and habitual sedative use. Multiple MVC and falling asleep while driving were also associated with the same risk factors in a similar manner. Multiple logistic regression analysis revealed that the presence of sleep disordered breathing (SDB) remained associated with MVC independent of confounding factors (OR 4.1, 95%CI 2.5 to 6.8). This relation was reduced but not eliminated when excessive daytime somnolence was added into the model (OR 2.3, 95%CI 1.2 to 4.7).

This is the first study of which we are aware that sleep disordered breathing is independently associated with motor vehicle crashes in the face of other well-known confounding variables.

4.3 Introduction

Motor vehicle crashes (MVC) are the leading cause of death and hospitalization by unintentional injury in North America with an age-adjusted death rate of 16.2 deaths per 100,000 in 1996.[1-3] Between 1 to 23% of MVC's requiring a police report are considered to be due to sleepiness while driving.[4-7] When an MVC is attributed to sleepiness, it more often involves a higher speed collision and more severe injury, in a manner similar to MVC's associated with alcohol consumption.[5] Obstructive sleep apnea syndrome (OSAS) defined as unexplained excessive daytime somnolence in association with sleep disordered breathing (SDB), is a prevalent and treatable cause of chronic excessive daytime somnolence (EDS).[8-11] Both sleep disordered breathing and OSAS have been associated with an increased risk of MVC.[12-19] Other factors are also well accepted to be associated with MVC, such as male gender,[2,5,20,21] age,[2,5,20-23] obesity,[18,20] cardio-vascular disease (CVD),[23] alcohol consumption,[2,20,24] and the use of long-acting sedatives.[25,26] Many of these risk factors for MVC are also associated with SDB, which confounds the relationship of SDB and OSAS with MVC.

The relative size of effect of all these factors on MVC risk is unclear. The effect of SDB on MVC risk varies by gender[12] which in turn may be due to gender differences in the mileage driven per year with different opportunities for MVC.[20,21] Alcohol may have a synergistic effect with sleep apnea on driving performance.[27]

Varying degrees of cognitive dysfunction are found in patients with untreated OSAS or asymptomatic SDB.[28,29] Chronic excessive daytime somnolence is considered the main factor that renders individuals with OSAS at more risk of MVC.[13,14,18,19] This somnolence varies in a graded manner whether measured electroencephalographically or behaviorally from full awake vigilance to sleep. Even when behaviorally awake, continuous measures of cortical executive functions and

simulator driving performance indicate an impairment in untreated OSAS. [30,31] Measurable brain dysfunction may persist in OSAS after apparently adequate treatment. [32]

We sought to study the effect of SDB on MVC risk while taking into account other variables known to predispose to MVC. We also sought to elucidate factors that may be different between falling asleep at the wheel while driving, having had an MVC, and having repeated MVC's, as these outcomes span increasing levels of risk of harm to others.

4.4 Methods

We investigated this hypothesis using a cohort of consecutive patients referred to a tertiary sleep disorders center. Patients were studied with attended polysomnography and completed a health status questionnaire.

4.4.1 Sources of Data

The Sleep Laboratory of the Royal Victoria is one of the three major clinical sleep laboratories in the province of Québec, Canada. Patients are referred from general practitioners and specialists. Clinical variables which are obtained upon presentation to the clinic are age, gender, body mass index, comorbid disease, subjective excessive daytime somnolence, and suspected diagnosis. Since April 1, 1990 all patients are asked to complete a questionnaire on their first visit. Patients in this clinic presenting with possible OSAS are subsequently studied with polysomnography.

Between April 1, 1990 and December 31, 1994, 1424 consecutive patients seen in the Sleep Disorders Clinic underwent a first polysomnography with at least 3 hours of sleep. Only subjects with clinical diagnoses of normal physiologic sleep, snoring, and obstructive sleep apnea are included from this population. Other illnesses such as chronic lung disease on home oxygen (59), epilepsy (5), narcolepsy (21), parasomnias (25), periodic leg movements (68), and other neuromuscular diseases (23) were excluded from this cohort. Excluded are also patients who did not sufficiently fill out a questionnaire (56) and those who underwent daytime diagnostic polysomnography or split night diagnostic and CPAP titration studies(171) because of the effect these techniques have upon sleep stages and AHI measurement.[33,34] This excludes a total of 428 patients, with 996 (70%) remaining for study.

4.4.2 Measurements

Polysomnography was performed on all patients presenting with a possibility of OSAS. The apnea-hypopnea index was calculated from the total number of apneas (total cessation of breathing for over 10 seconds associated with oxygen desaturation) plus the total number of hypopneas (decrease in airflow by 50% or less for over 10 seconds associated with oxygen desaturation of at least 4% from baseline) throughout the night divided by the total hours of electroencephalographic (EEG) sleep. [35]

The number of previous motor vehicle accidents was asked of each patient. Sedative use was gathered, and the use of a benzodiazepine or barbituate more than once weekly to sleep was considered regular use. The usual consumption of alcohol prior to bedtime was also asked, and any regular quantity of one or more drinks per night was considered regular use. Obesity was measured by the body mass index (BMI), also known as the Quetelet index and defined as: weight (kg)/[height (m)]^2. Cardiovascular disease was considered present if one or more of the following conditions was found on initial consultation: hypertension requiring medication, previous myocardial infarction, angina requiring medication, or congestive heart failure, or if the following medications were prescribed: beta blockers, calcium channel blockers, diuretics, nitrates and acetyl salicylic acid preparations. The individual's usual sleep duration was estimated in hours per major sleep episode. Excessive daytime somnolence was assessed by response to 9 questions regarding falling asleep in daytime situations. The scores range from 0 to 11, where 2 or more may be considered abnormal. The responses have been found to quantify the sleepiness in OSAS, correlates with the Epworth sleepiness scale with a rho of 0.56, and responds as expected to therapy of OSAS. [36] The response to the question "Do you fall asleep while driving?" was analyzed as a separate outcome.

4.4.3 Data Analysis

The primary outcome in the analyses was any MVC, with falling asleep while driving and multiple MVC analyzed as secondary outcomes. The primary determinant under study was SDB which uses a history of habitual snoring and the apnea-hypopnea index (AHI) to categorize SDB as used previously.[12] Confounding variables included age, gender, regular alcohol or sedative use at bedtime, reported usual sleep duration, body mass index, and presence of CVD.

Standard methods for the analysis of binary data were used to describe the relationship of all variables with erectile dysfunction. The odds ratio was used for all analyses. Continuous variables were partitioned at the median to form 2 x 2 tables and into quartiles to assess linearity with logit plots. Standard logistic regression analysis was performed.[37] Logistic modeling for the primary outcome of MVC was performed with stepwise forward and backwards variable selection based upon the model improvement found by including sequential variables with a p-value of 0.1 or less. 'Best fit' models were chosen based upon the hypotheses and the degree of fit the model displayed for the data. The Hosmer-Lemeshow goodness-of-fit statistic with at least seven degrees of freedom was used to assess model fit. All analyses were performed on SAS 6.12 statistical software (Cary, N.C.).

4.5 Results

The mean age (±SD) was 51.3 ± 12.9 years, with 233 (23%) women. Of the 996 subjects, 335 (34%) reported motor vehicle crashes, 217 (22%) more than one MVC, and 117 of 817 (14%) reported falling asleep at the wheel. One-hundred and sixty-eight (17%) had cardiovascular disease (CVD) and 313 (33%) had excessive daytime somnolence. Of the 168 subjects with any CVD, 134 (80%) had hypertension, 39 (23%) chronic stable angina, 26 (15%) a previous myocardial infarction and 21 (13%) stable congestive heart failure; 35 subjects had 2 or more CVD diagnoses, usually hypertension combined with one of the other diseases. The mean reported sleep duration was 6.8 ± 1.3 hours per night, with 62 (6.2%) taking sedatives regularly and 36 (3.6%) using nightly alcohol. Half had a BMI less than 27.6 kg/m^2, with a mean BMI of 29.3 ± 7.5 kg/m2. The mean AHI was 25.9 ± 29.4 events/hour. An AHI more than 5 events/hour was found in 677 (68%), and 15 events/hour or more was found in 479 (48%). Of those with an AHI of less than 15 events/hour, 311 (60%) did not snore habitually and 206 (40%) snored habitually. Abnormal sleep architecture was frequently demonstrated, with the mean percentage of REM sleep being 12.8 ± 7.1% and slow wave sleep percentage 14.2 ± 11.9%.

The MVC was associated with sleep-disordered breathing, but not in linear manner (table 4.1). This relationship demonstrated a significant trend (chi-squared of 19.5, p-value less than 0.001). No categorization of SDB based solely on AHI was associated with MVC. Age was associated in a graded manner where older age tended to be associated with less MVC. Male gender, presence of CVD, nightly alcohol consumption, and regular sedative use all demonstrated strong associations. Body mass index and reported nightly sleep duration demonstrated no association with MVC. The strongest association was excessive daytime somnolence (score of 2 or

more) with MVC, with an odds ratio (95% confidence interval) of 13.6 (9.9 to 18.6). As the sleepiness score increased, there was no increment in the rate of MVC.

Table 4.1: Crude Associations with Motor Vehicle Crash

Risk Factor		MVC	No MVC	OR	95%CI
Non-snorers	AHI < 5	33	165	1.0	referent
Snorers	AHI < 5	69	52	6.6	4.0 to 10.9
	AHI 5 to 15	60	137	2.2	1.4 to 3.5
	AHI > 15	173	307	2.8	1.9 to 4.2
Age (in years)					
20 to 39		76	115	1.0	referent
40 to 59		187	346	0.8	0.9 to 1.8
60 or more		72	200	0.5	0.4 to 0.8
Gender					
Female		33	200	1.0	referent
Male		302	461	4.0	2.7 to 5.9
Sleepiness Score					
0 to 1		50	456	1.0	referent
2		40	58	13.2	8.6 to 20.4
3 to 4		72	111	14.1	9.7 to 20.4
5 or more		65	94	13.2	9.0 to 19.4
Cardio-vascular Disease					
Absent		243	593	1.0	referent
Present		92	68	3.3	2.3 to 4.7
Body Mass Index (in kg/m^2)					
< 27.5		168	314	1.0	referent
≥ 27.5		167	347	0.9	0.7 to 1.2
Nightly Alcohol Consumption					
Absent		270	597	1.0	referent
Present		21	11	4.2	2.0 to 8.9
Nightly Sedative Use					
Absent		187	570	1.0	referent
Present		34	26	4.0	2.3 to 6.8
Reported Usual Sleep Duration (hours/night)					
≤ 6.5		121	76	1.0	referent
> 6.5		180	137	0.8	0.6 to 1.2

Abbreviations: 95% CI: 95% confidence interval; MVC: Motor Vehicle Crash.

Multiple logistic regression analysis was performed to estimate the independent effect of each factor (table 4.2). Sleep-disordered breathing was recategorized as either present or absent based on the findings shown in table 4.1. Sleep disordered breathing remains associated with MVC when age, gender, CVD, nightly alcohol consumption and regular sedative use are considered simultaneously. All odds ratios remain similar in magnitude to the univariate analyses. When the presence of EDS was included (table 4.3), the odds ratios for SDB, CVD and regular sedative use were all reduced, with CVD and regular sedative use no longer significantly associated with MVC. No significant interaction was found between regular alcohol use and SDB.

Multiple motor vehicle crashes were reported by 218 (22%). When the risk factors for multiple MVC were examined (table 4.4), a pattern of associations emerged similar to that found with any MVC (table 4.1). Multiple MVC were again associated with sleep-disordered breathing in a non-linear manner. Male gender, CVD, nightly alcohol consumption, and regular sedative use all demonstrated strong associations similar to those in table 4.1 (results not shown). Body mass index and nightly sleep duration again demonstrated no association. The strongest association again was with EDS, with an odds ratio of 8.8 (6.1 to 12.6). Falling asleep at the wheel demonstrated similar associations (table 4.4). Falling asleep at the wheel occurred rarely in the absence of other signs of daytime somnolence, resulting in a very high odds ratio when excessive daytime somnolence was present (odds ratio > 100).

Table 4.2:

Multivariate Model of Risk Factors for Motor Vehicle Crash

Risk Factor	Odds Ratio	95% CI
Sleep Disordered Breathing	4.1	2.5 to 6.8
Age (in years)		
20 to 39	1.0	referent
40 to 59	0.5	0.3 to 0.8
60 or more	0.7	0.4 to 0.8
Male Gender	2.8	1.6 to 5.1
Cardio-vascular Disease	3.4	2.0 to 6.0
Nightly Alcohol Consumption	3.8	1.4 to 10.7
Nightly Sedative Use	3.4	1.8 to 6.5

Abbreviation: 95% CI: 95% confidence interval.

Table 4.3:

Multivariate Model of Risk Factors for Motor Vehicle Crash Including Excessive Daytime Somnolence

Risk Factor	Odds Ratio	95% CI
Sleep Disordered Breathing	2.3	1.2 to 4.7
Age (in years)		
20 to 39	1.0	referent
40 to 59	0.6	0.4 to 1.2
60 or more	0.7	0.5 to 1.1
Male Gender	2.8	1.4 to 6.4
Cardio-vascular Disease	1.2	0.6 to 2.4
Nightly Alcohol Consumption	7.7	2.0 to 34.3
Nightly Sedative Use	2.0	0.8 to 5.0
Excessive Daytime Somnolence	18.0	10.1 to 33.1

Abbreviations: 95% CI: 95% confidence interval.

Table 4.4: Associations of Sleep Disordered Breathing with Falling Asleep While Driving (FAWD) and Multiple Motor Vehicle Crashes (MVC)

Sleep Disordered Breathing		FAWD	No FAWD	OR	95%CI
Non-snorers	AHI < 5	9	180	1.0	referent
Snorers	AHI < 5	24	56	8.6	4.1 to 17.8
	AHI 5 to 15	18	140	2.6	1.2 to 5.
	AHI > 15	66	324	4.1	2.1 to 8.0
		Multiple MVC	**1 or 0 MVC**	**OR**	**95%CI**
Non-snorers	AHI < 5	21	177	1.0	referent
Snorers	AHI < 5	78	43	4.6	2.7 to 8.1
	AHI 5 to 15	35	162	1.8	1.0 to 3.2
	AHI > 15	119	361	2.8	1.7 to 4.5

Abbreviations: 95% CI: 95% confidence interval; MVC: Motor vehicle crash; FAWD: Falling asleep while driving.

4.6 Discussion

Sleep disordered breathing is clearly related to MVC. The severity of SDB does not appear to affect the association with MVC. Age, gender, CVD, alcohol and sedative use are significant confounding factors. This confounding does not account for the association of SDB with MVC. Chronic EDS may account for some of the association. This is the first study of which we are aware that sleep disordered breathing is independently associated with motor vehicle crashes in the face of the other well-known confounding variables of age, gender, alcohol and sedative use. It is also the first study to demonstrate an independent relationship with self-perceived excessive daytime somnolence.

Excessive daytime somnolence has been linked to MVC risk. The present finding of the very strong association of EDS with MVC supports the causative role of chronic EDS in excess MVC risk. This causative role is supported by the published findings of elevated MVC risk with diverse other causes of EDS, such as narcolepsy,[13,14] shift work,[38,39] and the physiologic circadian tendency to sleep.[4,5,40] The findings that countermeasures designed to reduce somnolence improve driving performance[41,42] and that specific treatment for OSAS improves driving simulator performance[31,43] further support this causative link. The previous finding of no association of MVC with EDS as measured by mean sleep onset latency of the multiple sleep latency test (MSLT)[12] may be due to the limitations of the MSLT such as the motivational influences affecting this measurement[44] and the insensitivity of standard scoring methods for detecting the onset of states of reduced vigilance prior to the onset of consolidated sleep.[45] The same study[12] found no correlation of Epworth sleepiness scores with MVC; this may be due to a non-linear relation of perceived chronic sleepiness and MVC.

Sleep disordered breathing, and not polysomnographic sleep apnea, was found to be related to MVC. This may relate to the strong dependence of MVC risk on

excessive daytime somnolence. In population-based study of the relation of polysomnographic sleep apnea, excessive sleepiness remains strongly related to snoring even when sleep apnea has been excluded.[8] Subsequent study has determined that this is due to the upper airway resistance syndrome.[46] This is where individuals without polysomnographic sleep apnea but who have excessive daytime sleepiness and frequently snoring demonstrate repetitive and frequent arousals from sleep after episodes of crescendo snoring or partial obstruction to breathing without hypopneas or apneas. Monitoring for the upper airway resistance syndrome was not routine; indeed, it was described in 1994.[46] The definition of sleep disordered breathing used here and elsewhere takes advantage of the fact that snoring is a good if imperfect marker for upper airway resistance syndrome.[46] Conversely, the absence of loud habitual snoring is useful for excluding cases of the upper airway resistance syndrome from the reference group. This reduces the misclassification of affected individuals as 'normal' in the reference group, and a consequent underestimation of association.

Our outcome measures were self-reports of falling asleep at the wheel and MVC. The accuracy of these may be questioned, as it may be suspected that individuals may underestimate their number of MVC in the face of a potential diagnosis of a disability. Moreover, the period over which these MVCs were reported may have varied across subjects. Despite this possibility, we found plausible accident rates, similar or above those expected as reported in Québec during this period.[47] Many accidents occur which never incur a police report. The effect of SDB on MVC risk is in line with previously published reports.[12-19] The relative effect of confounding factors was also in line with previous reports, such as 3-fold increase in MVC risk comparing men to women,[21] age strata throughout our population's range,[2,21] and the effect of regular reported alcohol use.[2] The fact that the spectrum of outcomes examined (falling asleep while driving, any MVC, multiple MVC) gave similar profiles of risk factors also lends credence to the robustness of our findings.

In summary, MVC is related to sleep disordered breathing. The relation of MVC's is not affected by the severity of SDB and is not explained by confounding factors of age, gender, regular alcohol or sedative use and CVD. The diagnosis of obstructive sleep apnea syndrome should be seriously considered whenever a patient reports a motor vehicle crash and unexplained excessive daytime somnolence.

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CHAPTER 5

SUMMARY, CONCLUSION AND IMPLICATIONS FOR FUTURE STUDY

5.1 Summary

This cross-sectional study describes the relationships of sleep apnea or sleep disordered breathing with erectile dysfunction, nocturia, and motor vehicle crashes (MVC). It was carried out in a tertiary care clinic population with suspected sleep apnea. The total of 1010 subjects with a spectrum of sleep apnea severity made it possible to analyze the relationships with apnea severity as well as the roles of many confounding variables.

Erectile dysfunction was common in this population, and increased with increasing apnea severity. The prevalence rose from 17.5% with an apnea-hypopnea index (AHI) of 15 or less to 29.3% if the AHI was more than 40. This association was attenuated when adjusted for the confounding variables of age and cardio-vascular disease, and was entirely eliminated when excessive daytime somnolence was included in the multiple logistic model. Excessive daytime somnolence was independently strongly associated with erectile dysfunction, with an odds ratio of 6.4 (95% confidence intervals: 3.8 to 10.6). We propose that chronic somnolence may be an intervening variable in the link between sleep apnea and erectile dysfunction.

Nocturia was found to be prevalent in our population, ranging from 9.7% with an AHI of 15 or less to 28.4% if the AHI was more than 40. This graded relationship remained after adjusting for confounding variables. Age and cardio-vascular disease were both positively associated with nocturia, and remained so on multivariate

analysis. Excessive daytime somnolence was again strongly associated with nocturia, with an odds ratio of 15.0 (95% confidence intervals: 9.6 to 23.4).

Motor vehicle crash rate, as well as rates of falling asleep at the wheel and multiple motor vehicle crash, were all related to sleep disordered breathing. Yet unlike erectile dysfunction and nocturia, this relationship was not associated in a graded manner with sleep apnea, and was only significant when snorers were excluded from the reference group. A similar relationship between sleep disordered breathing and MVC has been found in a population based study.[1] Despite the potential limitations of the self-reported outcome measurement, other known risk factors for MVC such as age, gender, use of alcohol or sedatives were found to display relationships with MVC rates in keeping with previously published studies. Subjective excessive daytime somnolence was strongly associated with MVC, with an odds ratio of 15.0 (95% confidence intervals: 9.6 to 23.4).

5.2 Conclusion

The three clinical consequences of erectile dysfunction, nocturia, and motor vehicle crashes were all found to be related to the occurrence of sleep apnea or sleep disordered breathing. Erectile dysfunction and nocturia demonstrated associations that increased with increasing severity of the sleep apnea. The roles of the confounding variables were found to be important in each case, with odds ratios for the confounding variables that were often greater in magnitude than severe sleep apnea. Excessive daytime somnolence was strongly associated with all three outcomes. The common confounding variables of age and cardio-vascular disease were also related to each of the three outcomes.

5.3 Implications for Future Study

5.3.1 Syndrome Definition with Sleep Disordered Breathing

The obstructive sleep apnea syndrome definition is currently undergoing revision by a task force of the American Sleep Disorders Association.[2] The proposed new definition requires a complaint of unexplained excessive daytime somnolence in the context of an elevated respiratory disturbance index. The respiratory disturbance index proposed will include not only the AHI as described here, but also respiratory event related arousals which have been found to occur with high frequency in the upper airway resistance syndrome, which in turn is proposed to be included as part of the spectrum of the proposed newly defined obstructive sleep apnea syndrome. This definition, if accepted, will supersede the definition currently used and quoted in chapter 1 of this thesis.[3] The definitions used in this thesis must not only reflect the rapidly growing scientific understanding in this field, but also address the limitations in measurements made from 1990 to 1994. The upper airway resistance syndrome was not described until 1994.[4] The definition of sleep disordered breathing used here and elsewhere takes advantage of the fact that snoring is a good if imperfect marker for the upper airway resistance syndrome,[4] or conversely that the absence of loud habitual snoring excludes potential misclassification of cases of the upper airway resistance syndrome in the reference group.

Erectile dysfunction and nocturia are both related to sleep apnea. This may add important considerations to future definitions of the obstructive sleep apnea syndrome, especially if these findings are corroborated by other studies. Motor vehicle crashes may be related to somnolence, but their potential catastrophic importance merit special consideration, and may also be arguably included in any future syndrome definition. If

a syndrome is taken as 'a sum of signs of any morbid state',[5] then these aspects of a patient's history add to the symptom complex that formally defines the syndrome. Such complaints may also be the basis for further inquiry by a health professional into the possibility of sleep apnea, as well as goals guiding the management of patients with known or suspected sleep disordered breathing.

5.3.2 Quality of Life With Sleep Apnea and Sleep Disordered Breathing

Sleep apnea is associated with reduced self-rated quality of life, and its treatment improves quality of life despite considerable inconvenience and cost[6] The consequences other than somnolence (erectile dysfunction, nocturia and MVC) each most likely play their role in affecting the quality of life of an individual with obstructive sleep apnea sydrome. These considerations are partially taken into account in the only currently published quality of life scale specific for sleep disorders.[7] One domain of this specific quality of life measure is dedicated to intimacy and sexual relationships, and another (vigilance) relies heavily on the ability to drive without fighting sleep. No mention is made, however, of nocturia, which regardless of etiology has been clearly related to inconvenience, dissatisfaction, and poor general quality of life in studies from 3 continents.[8-12] Thus the findings of this thesis could potentially broaden knowledge regarding the impact of sleep disordered breathing on quality of life.

5.3.3 Risk Stratification of Drivers With Suspected Sleep Apnea

The implications of this research are important in terms of public health and injury prevention. Driver sleepiness is a causative factor in 1% to 23% of all MVC.[13-16] Surveys of the prevalence of driving while sleepy and crashes attributed to

sleepiness suggest that sleepiness may be a more common cause of highway crashes than is reflected by the lower boundary of these estimates. [17] About 96% of sleep-related crashes involve passenger vehicle drivers and 3% involve drivers of large trucks. [17] Risk factors include youth, shift work, alcohol use, medications, and sleep disorders. Any sleep disordered breathing appears to be sufficient to be a marker of increased MVC risk[1] independent of confounding factors. This 'all-or none' finding may be due to the concept that sleep fragmentation from chronic and frequent cortical arousals from sleep may be sufficient to impair daytime function regardless of the amount of desaturation per breathing episode or the actual count of respiratory events per hour of sleep. Driving requires consistency of performance, and MVC risk may reflect the inconsistency, whether a result of inexperience, alcohol or fragmented sleep.

Yet the prevalences of sleep disordered breathing and sleep apnea are high (1 to 25%), and the cumulative accident rate is approximately 6 to 7% per year per driver. Preventive efforts regarding MVC injury must be able to focus their resources on groups at higher risk rather than simply on the presence or absence of sleep disordered breathing or sleep apnea. [18-20]

The findings of this study simultaneously compare the relative strengths of association of sleep disordered breathing and sleep apnea with other known risk factors for MVC. This information may be employed in the future derivation of an appropriately weighted MVC risk stratification index in order to better guide efforts at injury prevention in the field of sleep disorders. This sort of risk stratification has been both derived and successfully applied in order to effectively focus interventions in the medical prevention of perioperative myocardial infarction.[21]

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