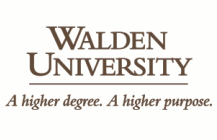

2017

Association Between Age-Related Macular Degeneration and Sleep-Disordered Breathing

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This is to certify that the doctoral dissertation by

Jeffrey Nau

has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
the review committee have been made.

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2017

Abstract

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by

Jeffrey A. Nau

Master's Medical Science, MCP Hahnemann University, 2002

BS Biology, Stony Brook University, 1997

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

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Abstract

Age-related macular degeneration (AMD) is a chronic, irreversible disease that robs individuals of vision, quality of life, and independence. It is the leading cause of blindness in industrialized countries. Sleep-disordered breathing (SDB) is a condition characterized by repeated episodes of apnea and/or hypopnea, insomnia, short sleep duration, and/or sleep disturbances (snoring, gasping, etc.). Because SDB has been shown to cause chronic hypoxia resulting in oxidative stress on the retina, it has been proposed that SDB may be associated with AMD. Based on the life course theory of chronic disease, this quantitative, cross-sectional study used data from the 2005–2008 National Health and Nutrition Examination Survey to study whether there was an association between SDB and AMD, including neovascular AMD and geographic atrophy in adults 40 years and older. Descriptive statistics and logistic regression analyses were used. The results suggest that AMD is associated with diagnosed sleep disorders, including sleep apnea and insomnia, as well as sleep apnea symptoms of gasping snoring, snorting, and stopping breathing. The findings of this study highlight the importance of diagnostic screening and therapeutic intervention to treat SDB. Early diagnosis and therapy for SDB could address not only the comorbidities associated with SDB, but could also prevent or slow the progression of AMD. In turn, this would yield lower rates of vision loss, reduced comorbidities associated with vision loss, and reduced impact of AMD on the health care system and social and financial costs to society.

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Chapter 1: Introduction to the Study

Introduction

The World Health Organization (WHO) ranks age-related macular degeneration (AMD) as the third leading cause of blindness globally behind cataracts and glaucoma and the leading cause of blindness in industrialized countries (World Health Organization [WHO], 2015). . By the year 2050, the estimate of people with AMD is expected to more than double from 2.07 million to 5.44 million (National Eye Institute, 2016a). Although the clinical understanding of AMD is continually evolving, the precise etiology of the disease remains elusive. A recently emerging area of interest is the impact of sleep and/or sleep-disordered breathing (SDB) on the development and treatment of AMD (Khurana et al., 2016). Currently, there exists a knowledge gap which this research was designed to address.

SDB is a condition whereby episodes of cessation of breathing or apnea are repeated and/or an abnormally shallow rate of respiration (hypopnea) occurs (Peppard et al., 2013) . This disruption can be caused by complete or partial obstructions to the airway, known as obstructive sleep apnea, or by disorders such as chronic sinusitis, allergies, and obesity (Balachandran & Patel, 2014). It is estimated that 14% of males and 5% of females in the United States meet the Medicare criteria for obstructive sleep apnea, which is an apnea/hypopnea score greater than 5, plus symptoms of daytime sleepiness (Peppard et al., 2013). Systematic monitoring of SDB is not currently performed in the United States because it is costly and time-consuming (Peppard et al., 2013). Therefore,

the prevalence of SDB may be underestimated and undiagnosed subjects may be at risk for its serious long-term complications.

Findings of this research could reinforce the need for diagnostic screening and therapeutic intervention to treat SDB. Early diagnosis and initiation of therapy for SDB would not only address the comorbidities associated with SDB, but may also prevent or slow the progression of AMD. Preventing or slowing the progression of AMD may result in lower rates of vision loss and reduced comorbidities associated with vision loss. In turn, this would help reduce the impact of AMD on the health care system and overall costs to society.

In this chapter, I describe the following components of the study: background; problem statement; purpose; research questions and hypotheses; nature of the study; conceptual framework; assumptions, scope and delimitations, limitations; and significance.

Background

AMD is a disease of the retina that causes photoreceptor degeneration (W. Wong et al., 2014). Currently, there are few effective preventive measures available to patients, for example, dietary supplements and smoking cessation, (Glaser et al., 2015). It was estimated in the year 2000 that AMD affected 1.75 million individuals in the United States (Friedman et al., 2004). This number has increased to 2.07 million in the decade since (NEI, 2016a). AMD exists in both dry and wet forms. The dry form is characterized by a slow degeneration of photoreceptors and the wet or neovascular AMD (nAMD)

form identified by the formation of new blood vessels in an area of the retina that is normally avascular (Leibowitz et al., 1980). Data from the 2005–2008 National Health and Nutrition Examination Survey (NHANES) estimated that the overall prevalence of AMD in the U.S. population was 6.5% (Klein et al., 2011). Joachim, Mitchell, Burlutsky, Kifley, and Wang (2015) provided estimates from the Blue Mountain Eye Study in Australia. They wrote that the 15-year incidence was 22.7% for early AMD and 6.8% for late (neovascular) AMD in subjects older than 49 years. Currently, the only therapy shown to have a preventive benefit for dry AMD is a combination of antioxidant supplements (Age-Related Eye Disease Study 2 Research Group, 2013). Treatment for the neovascular form of AMD was thought to have been revolutionized by the advent of anti-vascular endothelial growth factor (VEGF) therapy, although long-term outcomes have shown that the therapy is not sustainable and most patients do not achieve functional vision outcomes (Brown et al., 2006; Heier et al., 2012; Kaiser et al., 2007; Rasmussen et al., 2013; Schmidt-Erfurth et al., 2014).

Research into risk factors associated with AMD has provided information on a number of variables that include age, smoking (Myers et al., 2014; Thornton et al., 2005; Velilla et al., 2013), race and/or ethnicity (Klein, Li, et al., 2013; W. Wong et al., 2014), family history (Seddon, Cote, Page, Aggen, & Neale, 2005), obesity (Clemons et al., 2005), and a growing number of genetic mutations (Kanda et al., 2007; Klein, Myers, et al., 2013; Seddon et al., 2007; Triebwasser et al., 2015; van Lookeren Campagne, LeCouter, Yaspan, & Ye, 2014). Genetic studies have shown that inheritable mutations

may account for up to 70% of the risk for AMD and those that have been shown to be most strongly associated include the complement factor H (*CFH*) and the age-related maculopathy susceptibility 2/High Temperature Requirement A Serine Peptidase 1 (ARMS2/HTRA1) genes (Kanda et al., 2007; Seddon et al., 2007)

The landmark Wisconsin Sleep Cohort study estimated the prevalence of SDB in 30–60-year-old subjects , who were currently employed at 9% in women and 24% in men (T. Young et al., 1993). The Wisconsin Sleep Cohort study has since been followed longitudinally to estimate the prevalence of SDB in the United States during the periods of 1988-1994 and 2007-2010 (Peppard et al., 2013). The prevalence of SDB in 2007-2010 was 10% among 30-49 year old men; 17% among 50-70 year old men; 3% among 30-49 year old women; and 9% among 50-70 year old women (Peppard et al., 2013). The authors estimated that prevalence since the period 1988-1994 has increased between 14% and 55%, depending upon the specific gender/age subgroup under study (Peppard et al., 2013).

SDB has been shown to cause disrupted sleep patterns, intermittent hypoxia, abnormal heart rhythms, hypertension, and increased intrathoracic pressure (Somers et al., 2008). Population based studies have illustrated an association between SDB and cardiovascular disease (Shahar et al., 2001); metabolic syndrome (Kawada, Otsuka, Nakamura, & Kon, 2015); hypertension (Geiger & Shankar, 2015); cognitive function (Addison-Brown et al., 2014; Blackwell et al., 2015); liver disease (Trzepizur et al.,

2016); kidney disease (Molnar et al., 2015); quality of life; genetic mutations, specifically apolipoprotein epsilon 4 (Gottlieb et al., 2004); and mortality (Gami et al., 2013).

There is a gap in the knowledge about the association between AMD and SDB. Currently, Retina Specialists and Ear Nose and Throat (ENT) Specialists do not routinely co-manage patients. Recently, there has been an increased interest in understanding the association between these two chronic diseases. A statistically significant association (OR=3.3; 95% CI 1.32-8.27) between short sleep duration and neovascular AMD (Perez-Canales, Rico-Sergado, & Perez-Santonja, 2016). Similar findings have been shown with OSA and AMD (Keenan, Goldacre, & Goldacre, 2016). Sleep duration may also be associated with geographic atrophy (Khurana et al., 2016).

The current study has potential implications for positive social change. The resulting data may provide health care providers and patients a better understanding of how to better manage both AMD and SDB from a multi-disciplinary approach and could support the creation of public health interventions to improve screening, prevention and/or treatment of SDB, ultimately resulting in better AMD outcomes. Patients and physicians do not currently see vision loss as a consequence of SDB. But fear of vision loss could increase patients' impetus for getting screened for SDB, improving compliance with therapies, such as continuous positive airway pressure (CPAP), and adding to the cost-effectiveness argument with payers for covering screening and prevention. A more detailed discussion of the data on AMD and SDB is provided in Chapter 2.

Problem Statement

Age-related eye disease is a growing public health problem throughout the world (Pascolini & Mariotti, 2012) The human retina requires a significant amount of energy to keep its photoreceptors at an optimum functioning state and when oxygen is removed a significant increase in lactate ensues (Ames, Li, Heher, & Kimble, 1992). Based on this high-energy demand, nature has given it the greatest blood flow of any organ in the body relative to its size (Blasiak, Petrovski, Vereb, Facsko, & Kaarniranta, 2014; Boltz et al., 2010; Remsch, Spraul, Lang, & Lang, 2000). This places the retina in a precarious state when oxygen levels in the blood drop. Chronic apnea/hypopnea episodes during SDB can lead to damage from ischemia and hypoxia. In some cases, chronic apnea/hypopnea episodes may lead to pathological changes and/or irreversible damage to the retina (Blasiak et al., 2014).

SDB is shown to be commonly underdiagnosed or misdiagnosed, and subsequently untreated (Gibson, 2004; T. Young, Evans, Finn, & Palta, 1997). SDB can be treated effectively with CPAP, although many patients are poorly compliant with the therapy (Weaver & Grunstein, 2008). Based on the combination of underdiagnosis,-misdiagnosis, and poor compliance, a significant portion of patients experience regular apneas and hypopneas during sleep (Peppard et al., 2013). Researching the possible association between AMD and SDB addresses a current gap in the literature; research could lead to additional understanding and thus promote awareness, screening, and improved adherence to preventive therapy.

Purpose of the Study

The purpose of this quantitative, cross-sectional study was to evaluate the association between SDB and AMD in noninstitutionalized U.S. adults using the 2005–2008 NHANES dataset. Based on nationally representative data, I investigated whether respondents with SDB (independent variable) had an increased prevalence of AMD (dependent variable). The intent of the study was to address the gap in understanding whether SDB is associated with the development of AMD and to add to the current literature on the association between the two diseases. using data from the 2005–2008 NHANES retinal fundus photograph evaluation and sleep disorder questionnaire (CDC, 2016a). I selected this dataset due to the availability of AMD data based on masked central grading of retinal fundus photographs unique to this NHANES sampling period.

Research Questions and Hypothesis

The research questions and associated hypotheses that will guide this study are as follows:

Research Question 1: Is there an association between self-reported SDB and fundus photography identified AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI?

H_01: There is no association between self-reported SDB and fundus photography identified AMD among adults 40 years and older who

participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI.

$H_1 1$: There is an association between self-reported SDB and fundus photography identified AMD among adult 40 years and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI.

Research Question 2: Is there an association between self-reported SDB and fundus photography identified neovascular AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI?

$H_0 2$: There is no association between self-reported SDB and fundus photography identified neovascular AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI.

$H_1 2$: There is an association between self-reported SDB and fundus photography identified neovascular AMD among adult 40 years and older who participated in the 2005–2008NHANES survey before and after controlling for age, smoking, and BMI.

Research Question 3: Is there an association between self-reported SDB and fundus photography identified geographic atrophy among adults 40 years

and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI?

H_03: There is no association between self-reported SDB and fundus photography identified geographic atrophy among adults 40 years and older who participated in the 2005–2008 NHANES survey.

H_13: There is an association between self-reported SDB and fundus photography identified geographic atrophy among adult 40 years and older who participated in the 2005–2008 NHANES survey.

Theoretical Framework

Life course theory, or the life course approach, is based on an interdisciplinary framework for guiding research on health, human development, and aging (D. Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003). The approach is applicable to chronic disease, infectious disease, and a number of other areas of public health (Ben-Shlomo & Kuh, 2002; D. Kuh et al., 2003; Lynch & Smith, 2005). The theory can help explain how biological, behavioral, environmental, and psychosocial processes that operate across an individual's life course, or across generations, may influence the development of disease risk (D. Kuh et al., 2003). The time factor for the development of AMD is important within the context of this framework. AMD has a predictably long latency period and exposures—for example, recurrent hypoxic episodes during SDB which are likely to occur earlier in life—may promote late disease progression (Lynch & Smith, 2005). Although the study collected data on SDB from a single point in time due to the cross-

sectional design, it is likely that the SDB data represent an ongoing condition. Evidence from the literature on the development of AMD implicated a number of risk factors: age, smoking (Myers et al., 2014; Thornton et al., 2005; Velilla et al., 2013), race and/or ethnicity (Klein, Li, et al., 2013; W. Wong et al., 2014), family history (Seddon, Cote, et al., 2005), obesity (Clemons et al., 2005), and a number of genetic mutations (Kanda et al., 2007; Klein, Myers, et al., 2013; Seddon et al., 2007; Triebwasser et al., 2015; van Lookeren Campagne et al., 2014). As previously stated, genetic studies have shown that inheritable mutations may account for up to 70% of the risk for AMD (Seddon, Cote, et al., 2005; van Lookeren Campagne et al., 2014). The mutations, present from birth, may represent the first "hit" that occurs with the life-course progression of AMD. Although the genetic associations are strong for AMD, the penetrance of the disease varies with some individuals who present with mild signs of disease, such as drusen, a yellowish deposit under the retina, alone, others with the non-neovascular form of AMD, and finally 10% of patients progressing to severe AMD, including choroidal neovascularization and geographic atrophy (Friedman et al., 2004; Klein et al., 2011). This evidence suggests that additional factor(s) can influence AMD patients in addition to their genetic predisposition and thus cause their disease to progress later in life. These represent additional hits that may increase the risk of developing AMD. Figure 1 illustrates a life course theory model applied to the study of AMD pathogenesis and incorporating the hypothesis of a potential association with SDB.

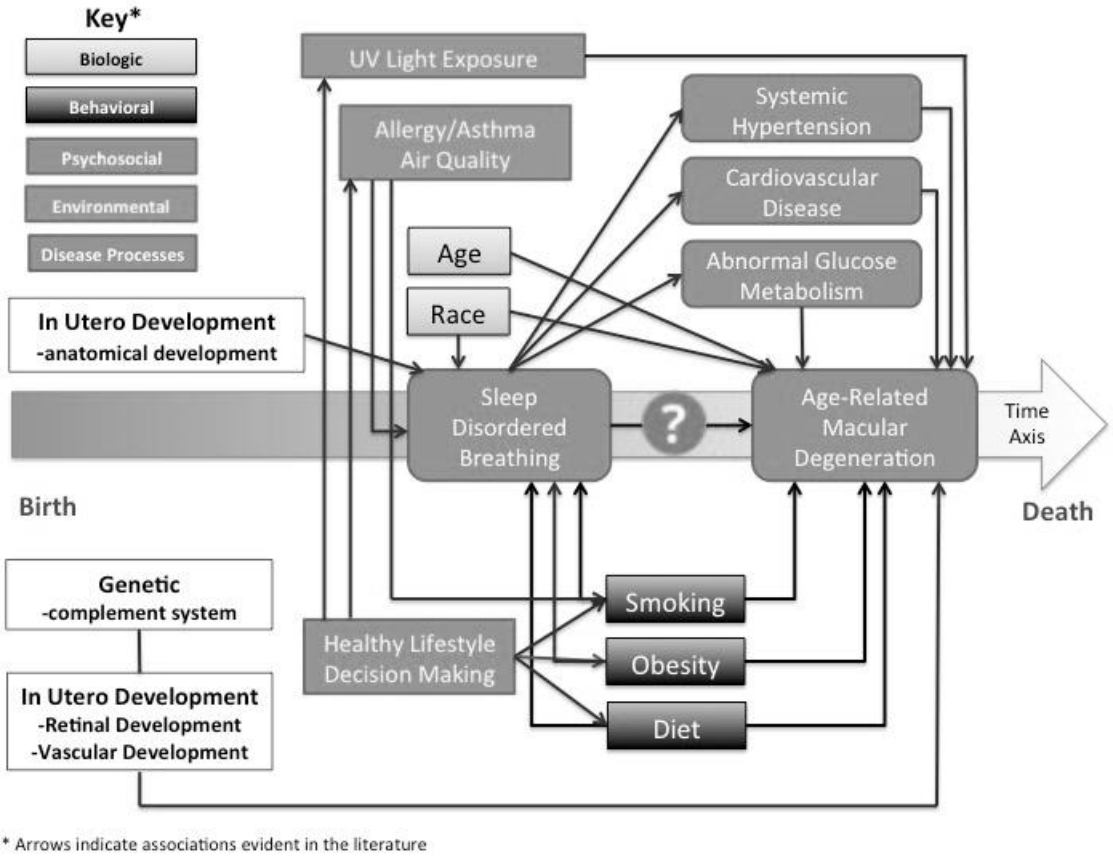

Figure 1. Life course theory model of AMD pathogenesis incorporating the hypothesis of a potential association with SDB.

A number of the criteria for causation proposed by Bradford Hill (1965) are relevant to AMD and SDB. As discussed, there is biological plausibility that ischemia and hypoxia play a role in AMD (Blasiak et al., 2014; Grunwald, Metelitsina, Dupont, Ying, & Maguire, 2005). Coherence exists in that the cause-and-effect association of ischemia and hypoxia with the disease fit the natural history of the disease (Grunwald et al., 2005). There is a temporal relationship between the peak presentation of SDB and the presentation of signs associated with early AMD (Bixler, Vgontzas, Ten Have, Tyson, &

Kales, 1998; Bourne et al., 2014). This study and its inherent research questions attempted to add to the data related to causality by providing evidence of consistency, strength of association, and biological gradient. A more detailed discussion of the life course theory of chronic disease is presented in Chapter 2.

One other conceptual model, the chronic care model (CCM), was assessed for this study (Wagner et al., 2001). The CCM was initially developed by Wagner et al. in 1996 and its' aim was to "transform the daily care for patients with chronic illnesses from acute and reactive to proactive, planned, and population-based" (Wagner, Austin, & Von Korff, 1996, p. 13). The CCM addresses the shortcomings of the current delivery of care to chronic diseases, as they are often managed much the same way as an acute condition. This model does not integrate well with the research question of this study as it does not take into account the events over the course of the patients' lifetime that may have contributed to disease. For this reason, the life course theory was chosen as the theoretical framework for this study.

Nature of the Study

In this study, I used a quantitative, cross-sectional approach to understand whether SDB characteristics are associated with early or late AMD. Quantitative data are most appropriate to investigate this association with appropriate inferential testing. Data from the 2005–2008 NHANES retinal fundus photograph evaluation, and sleep disorder questionnaire were used in this analysis (CDC, 2016a). Because the NHANES survey is a national survey that includes a representative sampling of the U.S. population, with

oversampling of certain underrepresented groups (including the elderly as it pertains to this study), the data will enable extrapolation to the U.S. population (CDC, 2011). The surveys from the years 2005-2006 and 2007-2008 contain data from a retinal fundus photograph evaluation (choroidal neovascularization, geographic atrophy, AMD severity), and sleep disorder questionnaire (SDB severity based on questions about sleep apnea, insomnia, short sleep duration, and other sleep disturbances). Retinal fundus photography from these sampling frames was graded by masked graders at the Wisconsin Epidemiological Grading Center (CDC, 2005). This combination of survey and examination methodology was appropriate for answering this research question because it allowed me to use data from the U.S. population that included individuals who may have AMD but are unaware and/or undiagnosed. Grading of fundus photographs by a central reading center reduces misclassification bias by categorizing participants based on photography findings and not relying upon participant recall. Participants who were not aware, or had not been formally diagnosed with AMD, were identified by trained independent graders (CDC, 2005).

To answer the research questions, I conducted a chi-square test for association to determine any differences in the distribution of AMD across sociodemographic, lifestyle, and sleep characteristics. Cumulative odds ordinal logistic regression (OLR) with proportional odds (ordinal dependent variable with responses no AMD, early AMD, late AMD) regression and binomial logistic regression modeling (dependent variable with responses no choroidal neovascularization, choroidal neovascularization present; no

geographic atrophy, geographic atrophy present) were fit to understand the association between AMD and sleep parameters after adjustment for sociodemographic and lifestyle factors. Survey specific sampling design variables and sampling weights were incorporated in the analyses to account for the complex multistage sampling design of NHANES. Definitions for early and late AMD with the 2005–2008 dataset have been previously defined (Klein et al., 1991) and operationalized from this same dataset looking at AMD prevalence (Klein et al., 2011). OLR allowed me to use the robust data provided from the masked reading of fundus images. Logistic regression was performed to determine whether the presence of AMD could be predicted by self-reported SDB, categorized by the definitions of Chen, Redline, Shields, Williams, & Williams (2014). Additional covariates were included in the model: age, race/ethnicity, smoking history, body mass index (BMI), and diabetes status. ORs with 95% confidence intervals are reported.

Definition of Terms

AMD): A degenerative disease of the retina that primarily impacts the macular region and is currently the leading cause of blindness in industrialized countries (NEI, 2016b; WHO, 2015)

*Choroidal neovascularization**:*** Often termed neovascular AMD (nAMD) or wet AMD, choroidal neovascularization is the formation of new and/or abnormal blood vessels from the choroid layer of the retina. In choroidal neovascularization, the vessels grow underneath the macula region of the retina, which under normal conditions is

avascular. These vessels, due to their immaturity, leak fluid, lipid, and proteins into the surrounding tissues. Ultimately, this process results in scar formation in the central portion of the retina that negatively impacts vision (NEI, 2016b).

Continuous Positive Airway Pressure: A mechanical ventilation device that is placed over the nose and/or mouth during sleep to provide positive airway pressure that opens the area of obstruction and allows for improved oxygen saturation. Although highly effective, most subjects are non-compliant with the treatment modality (Weaver & Grunstein, 2008).

Drusen: Drusen are yellowish deposits under the retina that are present and can be seen in early AMD. Components of drusen include lipid, inflammatory proteins, and photoreceptor breakdown products (Mullins, Russell, Anderson, & Hageman, 2000).

Geographic Atrophy: Defined as the late stage of dry AMD. Geographic atrophy consists of areas of retina devoid of the retinal pigment epithelial layer with subsequent loss of the overlying photoreceptor layer (NEI, 2016).

OSA: A condition that occurs during sleep where a subjects tongue falls back against his or her soft palate, causing the soft palate and uvula fall back against the back of the throat, mechanically closing the airway (American Sleep Apnea Association, 2016).

Polysomnography : Also commonly called a sleep study, is a clinical procedure that records brain activity, the oxygen level of the blood, heart rate and breathing, and

documents eye and leg movements during the overnight study (Weaver & Grunstein, 2008)

SDB: Refers to a number of conditions that impact the overall quality of sleep for an individual that include but are not limited to a formal diagnosis of sleep apnea. In the context of the 2005–2008 NHANES data, this includes patient reported sleep apnea; sleep apnea symptoms such as habitual snoring, snorting, or stopping breathing; insomnia; short sleep duration; and any sleep disorder diagnosed by a physician or other health professional (Chen et al., 2014).

Assumptions

The 2005–2008 NHANES dataset was used for this study. I assumed that the sample I analyzed was representative of noninstitutionalized adults over 40 years in the United States. In addition, I assumed that the NHANES Digital Grading Protocol for evaluating fundus photographs was followed (CDC, 2005). Similar grading and staging systems for AMD have been shown to have high reliability compared to standard clinical examination (Bird et al., 1995; Seddon, Sharma, & Adelman, 2006). Masked grading of the retina fundus images was important to this study in order to provide reliable categorization of AMD status.

Scope and Delimitations

The 2005–2008 NHANES dataset was chosen for this study because it represented a unique cross-sectional dataset with masked grading of fundus photography for retinal disease. While SDB was based on participants' self-report of disease, masked

grading of AMD severity removed this need and minimized recall and/or report bias. In addition, the severity grading of AMD allowed for additional information about the disease to be incorporated into the analyses. A simple dichotomous answer from patient self-report as to whether disease is present or absent would limit the amount of information available for analyses and potentially introduce additional recall bias.

The NHANES dataset is a purposive sample from which an approximation of the U.S. population was developed. This study was delimited to the population of the United States in which the NHANES dataset was collected. Thus, the results are valid and generalizable to the U.S. population where the survey was conducted. The results may not be generalized to other non-U.S. populations. NHANES used oversampling to improve the precision of estimates of health status indicators for population subgroups of particular public health interest (Johnson et al., 2013). In 2005–2006, people aged 70 and over were oversampled, while in 2007–2008 people aged 80 and over were oversampled (Johnson et al., 2013). As AMD prevalence increased significantly with increasing age, additional sampling of any subjects over the age of 40 will improve the precision of estimating AMD prevalence in those subgroups (W. Wong et al., 2014).

Limitations

This study was subject to several limitations. First, given my use of cross-sectional data I could not make a causal inference as to whether SDB leads to the development of late or early AMD. Based on the limitations of the study design, this study could only elucidate a better understanding of the association between these two

conditions. It is possible that my findings could be explained by an underlying mechanism that affects both AMD and SDB—there are a number of shared confounders that include age, gender, obesity, diabetes status, and past and current smoking status (see Chapter 2). Future research should be aimed at understanding and elucidating whether SDB can cause AMD.

Second, SDB variables were assessed by self-reported questionnaire and thus were subject to measurement and/or report bias. At the same time, however, multiple questions surrounding SDB could also be a strength in that the variables collected in the NHANES sleep questionnaire represented a wide range of questions on the topic of SDB. Important information collected using the questionnaire might be lost if there were only information on the absence/presence of SDB as diagnosed by polysomnography.

Third, there are inherent limitations to the NHANES sampling methodology (CDC, 2011). The main limitation is that the survey incorporates only noninstitutionalized U.S. citizens. As AMD presents primarily in the elderly population, a significant number of potential participants could have been in nursing homes, hospitals, and long-term care facilities (Klein et al., 2011). In addition, a small number of participants opted out of, or were excluded from, undergoing digital fundus photography. Also excluded were participants having no light perception, severe visual impairment in both eyes, or an infection in at least one eye (CDC, 2005). Finally, the NHANES survey data might not contain a representative sample of certain underrepresented age and/or ethnic groups (Johnson et al., 2013).

Fourth, a number of biases are inherent in survey research (Choi & Pak, 2005). Nonresponse bias is a possibility in surveys such as NHANES as answers of participants may differ from the potential answers of those participants who did not answer. There is variability in the number of participants completing each specific questionnaire (demographics, diabetes, sleep, etc.). Survey research such as the NHANES is subject to recall bias from self-reported health outcomes that can ultimately result in subsequent misclassification bias (Szklo & Nieto, 2014). The NHANES survey has been compared to other surveys (Behavioral Risk Factor Surveillance System, National Health Interview Survey, and National Survey on Drug Use) using self-reported public health data and is found to have comparable predictive validity with these instruments (Li et al., 2012; Pierannunzi, Hu, & Balluz, 2013). Additionally, the dependent variable in these analyses was obtained from centralized masked grading of fundus photographs, which eliminates this bias.

Significance

In this study, I examined whether insufficient sleep or sleep disturbances (SDB) are associated with AMD using a sample of the U.S. population. U.S. Census Bureau projections have estimated that the number of Americans over 65 years of age will more than double to 87 million by the middle of this century (United States Census Bureau, 2015b). Thus, the number of persons with AMD is estimated to double by 2050, from 2.07 to 5.44 million patients (NEI, 2015). The public health impact of AMD is significant, not only due to the increase in population blindness, but to the number of

physical and mental comorbidities associated with visual impairment (Court, McLean, Guthrie, Mercer, & Smith, 2014).

The results from this study are expected to add to the current body of literature on the association between SDB and AMD. This additional understanding may have important public health implications for promoting improved screening and treatment of SDB in order to reduce the impact of AMD on the health of those older than 40 years. In addition, an improved preventative treatment for AMD would decrease its costs in the healthcare system. CPAP therapy has been shown to be effective in reducing morbidity and mortality, although patients are highly noncompliant (Weaver & Grunstein, 2008). In a poll conducted by Research!America and the Alliance for Eye and Vision Research (AEVR), the fear of blindness was one of the top four "worst things that could happen to you" for all respondents, including cancer, Alzheimer's disease, and Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome () (Association for Research and Vision in Ophthalmology, 2014). The fear of blindness can be harnessed during discussions between providers and patients; the fear of losing vision may promote compliance with CPAP therapy. Conversely, for those patients who present with signs of AMD, the retina specialist may provide referral to a sleep clinic for SDB diagnosis. Early diagnosis and initiation of therapy for SDB could address not only the comorbidities associated with SDB, but they could also prevent or slow the progression of AMD. This, in turn, would lower the rates of vision loss, reduce comorbidities associated with vision

loss, and reduce the impact of AMD on the health care system and on the overall cost to society.

Summary

AMD represents a serious global public health problem. With an aging population and increasing life expectancy, AMD is expected to have a greater public health impact in the future. Although in recent years, data has emerged that elucidate a strong genetic association with AMD, the incomplete penetrance of the disease suggests that underlying mechanisms are still poorly understood. SDB represents a potentially important variable in the pathway of AMD pathogenesis (Figure 1).

In this chapter, I discussed the epidemiology of AMD and SDB, presented a brief overview of the extant literature on these conditions and their potential relationship. I presented the problems associated with an aging population and the consequences of AMD and suggested this research is needed to further explore SDB as a risk factor for this condition. I specified the research questions related to this research and the quantitative methodology I used to address them. I also justified the use of the life course theory as a framework for this research. An overview of the assumptions, scope and limitations, including those based on the use of secondary data, of the study was provided. Lastly, I concluded with a discussion on the significance of the current study and implications for positive social change.

A detailed review of the literature on AMD and SDB is presented in Chapter 2. In Chapter 3 I describe the research methodology, including the dependent, independent,

and confounding variables, and the statistical testing was used to answer the research questions. The results of this study are reported in Chapter 4; the summary, discussion, and conclusions are presented in Chapter 5.

Chapter 2: Literature Review

Introduction

The purpose of this quantitative, cross-sectional study was to evaluate the association between SDB and AMD in noninstitutionalized U.S. adults based on NHANES 2005-2008. Findings from this study will add to the current understanding of the associations between these two chronic diseases.

The association between AMD and SDB is not well understood. (Keenan et al., 2016; Perez-Canales et al., 2016) suggest that there is an association; Khurana et al. (2016) does not. Khurana et al. (2016) have also shown an association between SDB and late AMD (geographic atrophy) alone.

AMD is the third leading cause of blindness globally behind cataracts and glaucoma; it is the leading cause of blindness in developed countries (WHO, 2015). Because AMD is a disease that presents later in life, the elderly population is disproportionately affected (WHO, 2015). The United Nations (UN) (2015) estimates that globally, the population over 60 years of age is the fastest growing and is expected to increase by 45% by the middle of the century. Thus, in the United States, the U.S. Census Bureau projects that 1 in 5 Americans will be over the age of 65 by 2050 (United States Census Bureau, 2015b). Given that AMD is age related, it is likely that as the population grows older AMD will become a major public health problem. Wong et al. (2014) performed a systematic review and meta-analysis of all population-based studies [on what exactly?] that used retinal photographs and standardized grading classifications

to determine the presence of disease. By their estimation, AMD is prevalent in approximately 9% of the global population, which suggests that 196 million people will have AMD by the year 2020 (W. Wong et al., 2014). The cause(s) of AMD remain elusive. Data suggest a strong genetic association as well as a number of risk factors , including age, smoking (Myers et al., 2014; Thornton et al., 2005; Velilla et al., 2013), race and/or ethnicity (Klein, Li, et al., 2013; W. Wong et al., 2014), family history (Seddon, Cote, et al., 2005), obesity (Clemons et al., 2005), and a number of genetic mutations (Kanda et al., 2007; Klein, Myers, et al., 2013; Seddon et al., 2007; Triebwasser et al., 2015; van Lookeren Campagne et al., 2014). Despite a significant amount of data supporting risk factors, the cause of AMD remains elusive. SDB causality on the other hand is characterized with a higher degree of certainty.

SDB is defined as a number conditions, including central sleep apnea (CSA), OSA, and sleep-related hypoventilation or hypoxemic syndromes (American Academy of Sleep Medicine, 2014). During breathing-impaired sleep, the retina does not receive appropriate oxygenation and nutrition, and thus is at risk for chronic and irreversible damage. There is mounting evidence that SDB may be associated with AMD pathogenesis and with retinal disorders in general (Barak, Sherman, & Schaal, 2012; Boland et al., 2004; Boltz et al., 2010; Huseyinoglu et al., 2014; Perez-Canales et al., 2016)This literature review covers the epidemiology of AMD and SDB, the risk factors for each disease, the impact of SDB on the treatment of AMD, and finally the association between AMD and SDB. There is also a review of the literature on the association

between the two diseases and their relationship to the systemic and retinal vascular system.

Literature Search Strategy

PubMed and Google Scholar were used to identify cohort or cross-sectional studies that investigated the possibility of an association between AMD and SDB The following Medical Subject Heading (MeSH) terms were used: *age-related macular degeneration, macular degeneration, choroidal neovascularization, GA, SBD, OSA,* and *sleep apnea*. The searches yielded more than 15,000 articles on these two chronic diseases. To whittle down this number, the peer-reviewed articles were selected only if (a) they were published after 1993, in English and in full text, and only if (b) the subjects were over the age of 18 or they used the measure of Apnea-Hypopnea Index (AHI), Respiratory Disturbance Index (RDI), self-reported physician diagnoses, or self-reported sleep duration were included in the review. This narrowed down the total to about 300 articles.

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Theoretical Foundation

The WHO has adopted the life course approach as one of its overarching principles in the *Global Action Plan for the Prevention and Control of Noncommunicable Diseases* (WHO, 2013). The life course theoretical model is based on an interdisciplinary framework for guiding research on health, human development and aging (Diana Kuh &

Ben-Shlomo, 2004). The origin of this theory can be traced back to research investigating the impact of the Great Depression of the 1930s on individual and family pathways (Elder, 1974). Elder (1974) used data from longitudinal studies to investigate the impact of this time period on the long-term development of children born in the 1920s. As Kuh et al. (2004) stated, the life course approach to epidemiology is more than the mere collection of longitudinal data for analysis or associated with a particular research methodology. Important components of the theoretical model are the temporal relationships of the exposures and the relationships between these exposures. A challenge that is often faced by practitioners of life-course epidemiology is how to translate the findings into public health interventions as the biological, social and/or environmental exposures have happened in the past. There are three main life-course models: the cumulative exposure model, the chains of risk model, and the critical period model (Diana Kuh & Ben-Shlomo, 2004). The models are not necessarily discreet and it is possible that they may exist simultaneously or as slight variations with aspects of multiple models (D. Kuh et al., 2003). The critical period model (Figure 2a) is based on the premise that exposure(s) acting during a specific period (in utero for example) can impart lifelong effects on the structure and/or function of organs and tissues in the body (Nishi et al., 2015). These exposures can exert effects independently or in concert with other exposures (Figure 2a). The chains of risk model (Figure 2b) posits that a sequence of linked exposures act in a way such that a harmful exposure results in an exposure to a subsequent harmful event, thus increasing risk (Nishi et al., 2015). The cumulative risk

model is based on the accumulation of a number of types of risks that lead to long-term damage and disease development (Nishi et al., 2015). This model differs from the chains of risk model in that the exposures can work independently from one another. The cumulative risk model (Figure 2c) was proposed as the most appropriate to explain the relationship with SDB and AMD.

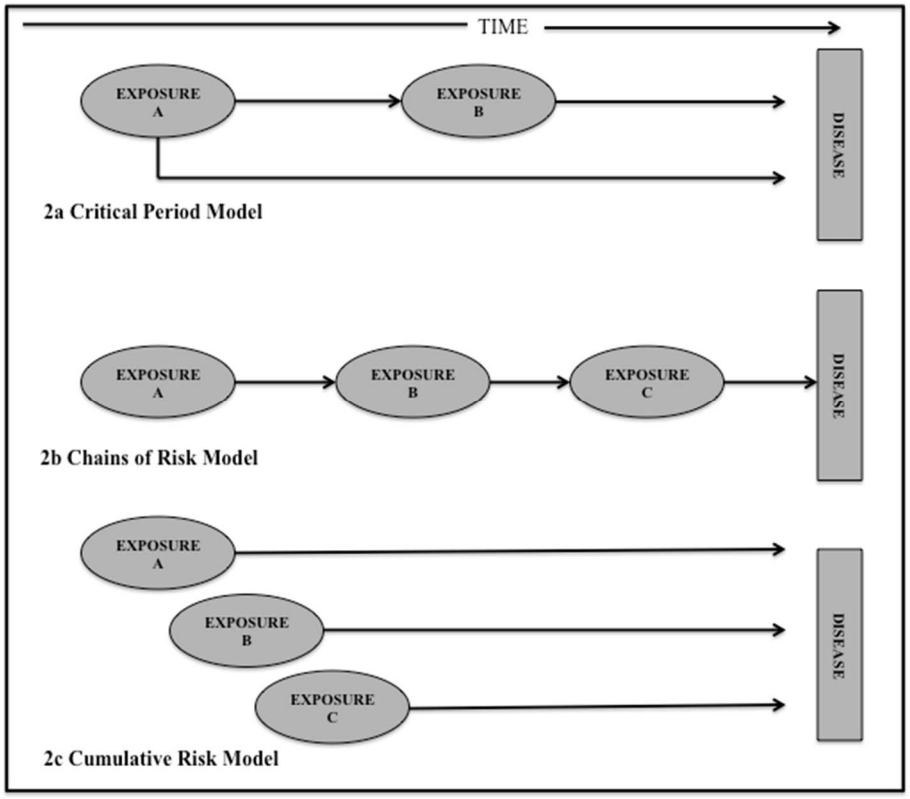

Figure 2. Life course causal models. Adapted with permission (Appendix A) from A Life Course Approach to Chronic Disease Epidemiology (Page 10), by D. Kuh, 2004, New York: Oxford University Press. Copyright 2004 by the Oxford University Press.

A cumulative risk model of AMD is illustrated in Figure 3.

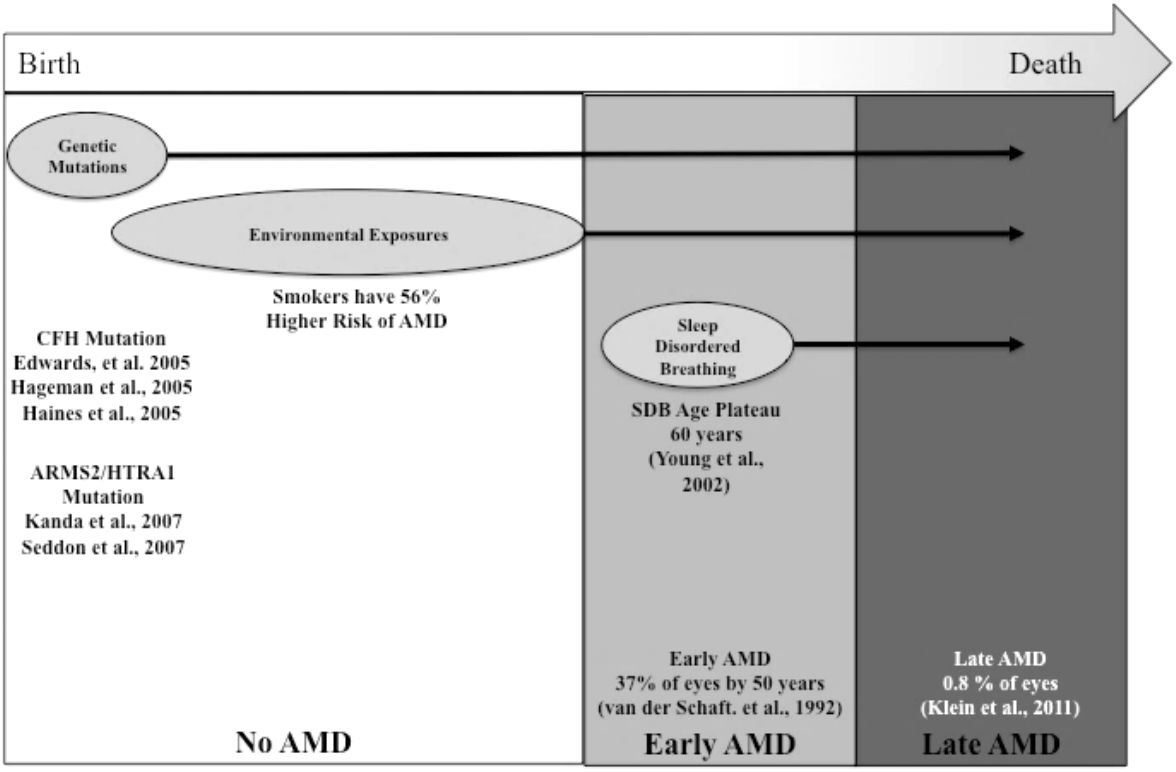

Figure 3. Life Course Cumulative Risk Model for AMD with SDB as a potential exposure.

Time is an integral component of life course theory and is an undercurrent exposure in the cumulative risk model of AMD. Age-related changes in the eye are not specifically called out as a discrete exposure, but should be considered an exposure that continually exists in the background of the model. Numerous studies have shown that increasing age is associated with increasing risk of disease (Tomany et al., 2004). There are several temporally associated exposures that have been shown to highly related to the development of AMD. AMD has been associated with a number of genetic mutations, most specifically with the genes that code for CFH and the ARMS2/HTRA1 gene (Kanda et al., 2007; Seddon et al., 2007). The CFH gene has been shown to regulate the

Complement system and keep Complement mediated inflammation under control (Zipfel, Lauer, & Skerka, 2010). Mutation of the gene removes the protective effect and increases inflammatory response in the retina. Both CFH and ARMS2/HTRA1 mutations have been shown to be associated with drusen formation and progression of AMD (Dietzel et al., 2014). These early exposures present at births represent the first in a series of potential exposures as shown in Figure 3.

Although the reduction in smoking is one of the most successful Public Health victories in the United States, exposure in early adult life and continued smoking for the current >40 age group is still significant (Holford, Levy, & Meza, 2016). It has been shown that compared to nonsmokers, past and current smokers develop late stage AMD a mean of 4.9 and 7.7 years sooner, respectively ($p < 0.001$ for both) (Lechanteur et al., 2015). When risk alleles for CFH and ARMS2/HTRA1 mutations and smoking are taken into account, late stage AMD develops 12.2 years sooner, on average, then those with no risk alleles ($p < 0.001$) (Lechanteur et al., 2015).

SDB represents a third, and potentially important exposure that may add to the cumulative risk of developing AMD with hypoxia placing additional oxidative stress on the already exposed retina (Barak et al., 2012; Keenan et al., 2016; Khurana et al., 2016; Perez-Canales et al., 2016). Blasiak et al. (2014) have implicated hypoxia and oxidative stress as important factors in the pathogenesis of AMD. Although the authors did not speculate on the specific causes of hypoxia, their opinion was that anything that can impair the blood supply to the retina might lead to hypoxia, oxidative stress, and cellular

dysfunction. Chronic hypoxic episodes due to SDB could be a potential initiator of this cascade.

AMD

AMD is a degenerative retinal disease primarily affecting the photoreceptor and retinal pigment epithelium tissue layers leading to a progressive loss of vision. Early AMD presents as lipid rich deposits called drusen and/or mild pigmentary changes in the retina, normally without corresponding vision loss (Lim, Mitchell, Seddon, Holz, & Wong, 2012). Vision loss from AMD usually is caused by one of two progressive degenerative processes termed choroidal neovascularization (wet AMD); neovascular AMD (nAMD) or geographic atrophy (dry AMD). Choroidal neovascularization constitutes abnormal blood vessel formation in the sub-retinal pigment epithelial and subretinal spaces (Lim et al., 2012). This form of AMD can cause dramatic reductions in visual acuity due to exudation, pigment epithelial layer detachment (PED), retina pigment epithelium tears, and ultimately leads to scarring of the retina (van Lookeren Campagne et al., 2014; Yonekawa, Miller, & Kim, 2015). Geographical atrophy is characterized by loss of the choriocapillaris layer of the retina and subsequent atrophy of the overlying retinal pigment epithelial layer (Lim et al., 2012). This loss of critical tissue layers that keep rods and cones healthy and functioning causes photoreceptor loss and subsequent decline in visual acuity. Although this process is generally results in more gradual visual acuity loss as compared to an acute decline with choroidal neovascularization, both

processes can be equally detrimental to quality of life and independence for patients (Coleman et al., 2010).

Patients with nAMD usually present to general ophthalmologists in their late 60s or 70s, with a complaint of varying degrees of vision loss and/or metamorphopsia (Klein et al., 2011; Ryan, 2013). The defining feature of nAMD is the presence choroidal neovascularization, primarily diagnosed based on fluorescein angiography (Lim et al., 2012). Choroidal neovascularization is the presence of a new blood vessel that originates in the choroidal circulation of the retina and can be found underlying or penetrating Bruchs membrane, violating the structural integrity of the blood retina barrier. This new vessel emerges within the normally avascular macula region and due to its immature morphology leaks serous and/or blood exudates into the surrounding retina tissue (Ryan, 2013; van Lookeren Campagne et al., 2014; Yonekawa et al., 2015). The end product of this disease process is fibrous scarring of the retina and irreversible vision loss (Lim et al., 2012). Subjects can be affected unilaterally or bilaterally (NEI, 2016b). Having choroidal neovascularization in one eye predicts a higher risk for development of choroidal neovascularization in the fellow eye (Silva et al., 2011). Current therapy for nAMD consists of regular intraocular injections of anti-VEGF medications (Lim et al., 2012). At the present time there are no preventive therapies available for nAMD.

Dry AMD is progressive disease with less acute symptom onset when compared to nAMD and is a significant cause of moderate and severe loss of central vision in the elderly population (Lim et al., 2012; Ryan, 2013). The disease is diagnosed based on a

dilated fundus examination and diagnostic imaging including fundus photography, fundus autofluorescence, and optical coherence tomography (OCT). Dry AMD is characterized by the presence of drusen (yellowish deposits that develop within the macula) located under the retinal pigment epithelial layer that can be visualized during examination and documented based on fundus photography and OCT (Ryan, 2013). In dry AMD, thinning of the retinal pigment epithelial layer in the macula develops, along with other age-related changes to the adjacent retinal tissue layers. When severe, the late stage of dry AMD is associated with thinning and loss of function of the neural retinal located above the affected retinal pigment epithelial layer (Ryan, 2013). This collective phenotype in late stage dry AMD is termed geographic atrophy. The progressive degeneration of light-sensitive photoreceptor cells in geographic atrophy leads to severe visual loss in affected eyes. In addition, dry AMD can progress to the nAMD form of the disease (Holz, Strauss, Schmitz-Valckenberg, & van Lookeren Campagne, 2014). Dry AMD is the most common form of the disease, occurring in 85%-90% of AMD cases (Klein, Peto, Bird, & Vannewkirk, 2004). Currently, no approved therapy exists for non-neovascular AMD. The Age-Related Eye Disease Study (AREDS) has shown that taking lutein and zeaxanthine supplements (and eating those foods rich in these nutrients such as spinach and collard greens) is associated with a decreased risk of AMD and late stage AMD, which includes choroidal neovascularization and geographic atrophy (Age-Related Eye Disease Study 2 Research Group, 2013; SanGiovanni et al., 2008). The absence of

treatment options for dry AMD represents an area of urgent unmet medical need, and a major public health concern for the rapidly increasing elderly population.

Risk Factors for AMD

A number of population based cohort studies examined the relationship between AMD and a variety of possible risk factors. In 1992, the Age-Related Eye Disease Study (AREDS) Research Group enrolled participants with varying degrees of AMD severity in a study to understand the clinical course and prognosis of AMD. Since then, a number of epidemiological studies have provided insight into the complex interplay of genetic, environmental, metabolic, and demographic factors that have been shown to be associated with the development of AMD (E. Chew et al., 2014; Tomany et al., 2004). To illustrate these risk factors, data from the ten-year follow up of the AREDS cohort (E. Chew et al., 2014) as well as individual study data and pooled data from Tomany et al. (2004) that includes data from the 3 largest population based cohort studies (resulting in a pooled population of 9523 adults)- the Beaver Dam Eye Study (BDES, United States), the Blue Mountain Eye Study (Australia), and the Rotterdam Study (RS, Netherlands) will be used.

Age. Age is commonly accepted risk factor for AMD as the presentation of the disease is uncommon before the fifth decade of life (Ryan, 2013). In the longitudinally followed AREDS cohort, age was an identified factor that increased the risk of developing late stage AMD over each 5-year period in the 65-69, 70-74, ≥75 age groups by 33%, 53%, and 86%, respectively as compared to the 55-64 age group (E. Chew et al.,

2014). In the Blue Mountain Eye Study, age was strongly correlated with both late and early AMD ($p<0.0001$) (Joachim et al., 2015). Similar results were found in the BDES and RS studies (Klein et al., 2007; Smith et al., 2001).

Genetics. Studies on concordance rates of AMD between monozygotic (MZ) and dizygotic (DZ) twins have shown that rates are double in those twins that originate from the same ovum (18% and 6% for MZ pairs and DZ twin pairs, respectively) (Seddon, Cote, et al., 2005). Models predict that heritability may account for 46% to 71% of the variability with AMD (Seddon, Cote, et al., 2005). AMD has also been shown to have a strong association with a number of genetic mutations (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Jakobsdottir et al., 2005; Kanda et al., 2007; Klein, Myers, et al., 2013; Ratnapriya & Chew, 2013; Seddon et al., 2007; van Lookeren Campagne et al., 2014). AMD is most strongly associated with genes that code for CFH (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005) and the ARMS2/HTRA1 gene (Kanda et al., 2007; Seddon et al., 2007). The human genome project has greatly added to the understanding of this disease by allowing for the ability to perform genome wide association studies (GWAS). A number of GWAS studies have independently confirmed genetic variation at the same CFH (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005) and ARMS2/HTRA1 (Jakobsdottir et al., 2005; Rivera et al., 2005) coding regions. In a French cohort, those subjects with the high risk CFH polymorphism (OR, 6.21) and those subjects with the high-risk ARMS2/HTRA1 (OR, 11.7) polymorphisms were associated with significantly higher risks of developing nAMD (Zerbib et al., 2014).

Smoking. In the early 1990's researchers began to investigate the relationship between smoking and eye disease; in particular the association of smoking and AMD (Eye Disease Case-Control Study Group, 1992). In the pooled BDES, Blue Mountain Eye Study, and RS population, past smokers and current smokers were 5.52 and 6.19 times more likely to develop AMD compared to nonsmokers, respectively. In the AREDS cohort, current smokers had a 56% higher risk of advanced AMD versus nonsmokers (E. Chew et al., 2014).

Inflammation. There is evidence that both the wet and dry forms of AMD are associated with an inflammatory process (Ambati & Fowler, 2012; van Lookeren Campagne et al., 2014). Excessive activation of inflammatory and immune responses within the retina, coupled with the retinal pigment epithelial and photoreceptor degeneration, is thought to result in activation of cells that produce complement components, pro-inflammatory cytokines, and growth factors resulting in increased angiogenesis and vascular permeability (Ambati & Fowler, 2012). Patients with AMD have been shown to elevate systemic inflammatory biomarkers such as c-reactive protein (CRP), interleukin-6 (IL-6), and homocysteine (Seddon, George, Rosner, & Rifai, 2005). Surgically excised choroidal neovascularization tissue in patients with nAMD has been shown to contain a number of different types of inflammatory cells (Submacular Surgery Trials Research Group, 2005). Dry AMD has been associated with activation of the complement System (Reynolds et al., 2009; Whitmore et al., 2015). The complement pathway is part of the body's innate immune system that consists of a complex cascade of

serum proteins that interact to mount a defense against foreign pathogens. The complement cascade is activated via the classical (antibody-dependent), the alternative (antibody independent) and the lectin pathways. Local inflammation and activation of the complement cascade has been implicated in drusen formation, as the proteins of the complement pathway have been shown histologically to be a component of drusen (Wang et al., 2010). Furthermore, as stated previously, polymorphism in genes coding for complement or complement regulatory proteins have demonstrated increased risk in the development of AMD (Edwards et al., 2005; Haines et al., 2005; Klein, Myers, et al., 2013; Triebwasser et al., 2015).

Ethnicity. There are wide variations in the prevalence estimation of AMD and nAMD due to the heterogeneity of study populations and the use of different diagnostic criteria. However, there is a strong evidence suggesting that the prevalence of AMD, including nAMD, is much higher in the population of European ancestry than that in any other ethnicity (W. Wong et al., 2014). In the AREDS study there was a 183% higher risk of AMD in the Caucasian versus non-Caucasian populations (E. Chew et al., 2014). Among people of European ancestry, the annual incidence of late AMD is estimated to vary from 2.9 to 3.6 per 1,000 person-years (Buitendijk et al., 2013).

Sex. AMD is predominantly present in the female population (Klein et al., 2011). In the AREDS study there was a 23% higher risk of AMD in women vs. men (E. Chew et al., 2014). In the RS study, an increased number of years between menarche and

menopause were associated with GA, suggesting that female sex hormones may play a minor role in disease progression (Tomany et al., 2004).

Associated Disease. In a U.S. Medicare cohort, diagnosis of diabetic retinopathy (DR) significantly increased the risk of nAMD (Hahn, Acquah, Cousins, Lee, & Sloan, 2013). Compared with non-diabetics, those with proliferative retinopathy were at a considerably higher risk (115%) than those with non-proliferative (68%) DR. However, having diabetes alone was not associated with an increased risk of developing nAMD. Obesity has been weakly associated with a higher risk of developing nAMD (Zerbib et al., 2014; Q. Zhang et al., 2016).

Classification and Severity Scale of AMD

Classification and severity scales for AMD have been developed based on findings from clinical examination and diagnostic imaging using fundus photography, fluorescein angiography, and optical coherence tomography (OCT). These scales range from a categorization of no aging changes present in the retina to late AMD, which includes choroidal neovascularization and geographic atrophy (Ferris et al., 2013; Nivison-Smith, Milston, Madigan, & Kalloniatis, 2014). Nivison-Smith et al. (2014) provide a detailed description of the Age-Related Eye Disease Study (AREDS) classification scheme that identifies clinical signs and pigmentary changes within the macula associated with progression of early AMD to late AMD. These grading scales are often used in clinical trials and epidemiological studies where masked grading of images are used to characterize the presence and/or extent of disease (Nivison-Smith et al.,

2014). As this study will be using data from the masked grading of the 2005–2008 NHANES survey period, the classification proposed by Klein et al. (1991) and adopted for the NHANES Digital Grading Protocol (CDC, 2005) to define early and late AMD will be employed. This will be detailed further in Chapter 3 in the explanation of study methodology section. The NHANES Digital Grading Protocol defined "early" AMD as the presence of either soft drusen with a grid area of greater than a 500 μm circle and the presence of retinal pigment epithelial depigmentation or increased retinal pigment or by the presence of soft drusen within the center 125 μm circle with the presence of retinal pigment epithelial depigmentation or increased retinal pigment in absence of signs of late AMD. "Late" AMD was defined by the presence of any of late lesions, such as GA, subretinal hemorrhage or visible subretinal new vessels, PED/retinal detachment, subretinal fibrous scar or laser treatment scar, or self-reported history of photodynamic or anti–vascular endothelial growth factor treatment for exudative AMD (Klein et al., 2011).

AMD Epidemiology

Globally, 8.7% of all cases of blindness are attributed to AMD (W. Wong et al., 2014), a majority of which can be found in developed nations. The United Nations (UN) reports that population ageing is taking place in nearly all countries throughout the world resulting from decreasing mortality and declining fertility (United Nations, 2013). Similar trends are seen in the United States as the Census Bureau suggested that the number of Americans over 65 years of age will more than double to 87 million by the middle of this century (United States Census Bureau, 2015a). AMD prevalence in the United States is

estimated to double by 2050 from 2.07 to 5.44 million patients (NEI, 2016b). The global prevalence of early, late, and any AMD were shown in a meta-analysis of population-based studies to be to be 8.0%, 0.37%, and 8.7%, respectively (W. Wong et al., 2014). As seen in other multi-ethnic studies, the highest prevalence of AMD was found in the people of European ancestry at 0.50% followed by Asian and Hispanic ethnicities. The AMD prevalence rate is lowest among people of African ancestry at 0.28% (W. Wong et al., 2014).

Wong et al. (2014) estimated that by 2020, 11.26 million patients will be diagnosed with late AMD, and the current prevalence of 9.64 million will nearly double to 18.57 million within next 25 years. Due to global trends in population growth, maximum prevalence increase will be seen in Asia, followed by Europe. In Asia, the prevalence of late AMD is likely to increase from 4.59 million patients in 2014 to 9.92 million in 2040, whereas in Europe, the prevalence is projected to increase from 2.57 million to 3.69 million during the same time period (W. Wong et al., 2014).

There is some variation in the prevalence estimates of AMD and nAMD due to the heterogeneity of study populations and the use of different diagnostic criteria. Klein et al. (2011) reported that the overall prevalence of AMD in the 40 and older population of the United States based on the NHANES survey was 6.5%. Late AMD (choroidal neovascularization and geographic atrophy) was present in 0.8% of the population. The disease varies by ethnicity, and was shown to be present 7.3%, 2.4%, and 5.1% of non-Hispanic Whites, non-Hispanic Black, and Mexican Americans, respectively (Klein et al.,

2011). As the NHANES survey draws from predominantly Caucasian respondents, the prevalence numbers may not accurately represent other ethnic groups. In the Los Angeles Latinos Eye Study (LALES) the adjusted prevalence of AMD was 10.2% with late AMD present in 0.52% of the Latino population. The Multi-Ethnic Study of Atherosclerosis (MESA) aimed to study the incidence of AMD and associated risk factors in White, Black, Hispanic, and Chinese residents of the United States (Fisher et al., 2016). Subject retinal photography data was collected 8 years apart to look for signs of early and late AMD. The incidence of early and late AMD was 4.1% and 2.3%, respectively. Consistent with other studies of AMD, incidence of early and late AMD was highest in Whites (5.3% and 4.1%, respectively), followed by Chinese (4.5% and 2.2%, respectively), Hispanics (3.3% and 0.8%, respectively), and lowest in Blacks (1.6% and 0.4%, respectively) (Fisher et al., 2016).

SDB

SDB is defined by the American Academy of Sleep Medicine as a constellation of conditions that includes central sleep apnea (CSA), OSA, and sleep-related hypoventilation or hypoxemic syndromes (American Academy of Sleep Medicine, 2014). During SDB patients experience periods of apnea (breathing cessation) and hypopnea (periods of shallow breathing). The public health impact of SDB is significant, as the disease has been implicated as a risk factor for a number of chronic diseases including cardiovascular disease, obesity, diabetes, and depression (CDC, 2016b). Each of these diseases is associated with a significant morbidity and mortality profile and responsible

for much of the chronic disease burden in the United States (Bauer, Briss, Goodman, & Bowman, 2014). Long-term consequences of SDB include reduced quality of life (Batool-Anwar et al., 2016), cognitive impairment (Osorio et al., 2015), increased risk of motor vehicle accidents (Basoglu & Tasbakan, 2014); cerebrovascular (Arzt, Young, Finn, Skatrud, & Bradley, 2005), cardiovascular (Kendzerska, Gershon, Hawker, Leung, & Tomlinson, 2014), and metabolic disease (Kawada et al., 2015); and increased mortality (Kendzerska et al., 2014).

The gold standard for diagnosing and monitoring SDB and OSA is a polysomnography (PSG) examination, otherwise known as a "sleep study" (Epstein et al., 2009). During the sleep study, patients are monitored for events where there is cessation of breathing or shallow breathing as well as changes in brain activity, blood oxygen level, heart rate and eye/leg movements. This is most often done in a clinical setting over the course of one or more nights by highly trained staff. Home sleep monitoring devices are available, although reliability is poor compared to PSG and misclassification is possible (Aurora, Swartz, & Punjabi, 2015).

Current front-line treatment for moderate to severe OSA and SDB is the use of CPAP, a device that consists of an air pump connected to a hose/mask apparatus that is fitted to the face of the patient with SDB (Epstein et al., 2009). Air is forced through the hose/mask under positive pressure and forces open the upper airway, allowing for improved oxygenation in the lungs. CPAP has been shown to be highly effective in improving objective measures of SDB in a number of randomized clinical trials

(McMillan et al., 2014; T. Young et al., 1993). The effects of CPAP therapy are not limited to improving objective measures of SDB, but have been shown to improve cognitive functioning (Aaronson et al., 2016), glucose metabolism (Pamidi et al., 2015; Salord et al., 2016), cholesterol profile (McMillan et al., 2014), and cardiovascular outcomes (Marin, Carrizo, Vicente, & Agusti, 2005). Unfortunately, CPAP has been also found to be a notoriously non-compliant treatment modality (Weaver & Grunstein, 2008). Participants in clinical trials with low compliance do not attain the same results seen in those studies that utilize the device as prescribed. A number of recent trials have shown that real world initiation of CPAP therapy does not reduce oxidative stress (as measured by cardiovascular stress/inflammation biomarkers) or reduce long-term adverse cardiovascular outcomes (Paz et al., 2016; Peker et al., 2016). Once the data are adjusted for compliance to CPAP treatment, the reduction in inflammatory biomarkers from therapy becomes significant (Paz et al., 2016).

There are other treatment options for the patient with SDB including mandibular advancement devices (MAD) (oral appliances) that are worn in the mouth during sleep to attempt to mechanically open the upper airway by pushing the jaw forward (D. Young & Collop, 2014). Surgical interventions are available to patients with SDB, although they are highly invasive as compared to MAD or CPAP. Surgical intervention remains a second line treatment for moderate to severe OSA, even in light of the data illustrating that uvulopalatopharyngoplasty (UPPP) and maxillomandibular advancement (MMA) surgeries have shown statistically significant improvements in AHI (D. Young & Collop,

2014). A number of other strategies should be employed to combat SDB including diet/weight loss, increase in amount of exercise, and sleep posture regardless of CPAP/MAD/surgical approaches. Weight loss (Peppard, Young, Palta, Dempsey, & Skatrud, 2000) and increased exercise (Mendelson et al., 2016) have shown to improve objective measures of SDB. To date pharmacotherapy for SDB has not proven to be an effective treatment modality (Jordan, McSharry, & Malhotra, 2014).

Classification and Severity Scale of SDB

During the PSG examination, oxygen saturation of the blood is monitored. Shallow breathing causing reductions in blood oxygen saturation are termed hypopneas. Apnea is defined as a complete pause in breathing lasting at least 10 seconds during sleep (Epstein et al., 2009). By counting the number apneas and hypopneas in an hour of sleep, one can derive the apnea-hypopnea index (AHI), a categorical measure of OSA/SDB. The AHI is categorized in most of the currently published studies according to the following consensus cutoff points illustrated in Table 1 (Epstein et al., 2009).

Table 1

Apnea-Hypoapnea Index (AHI) Severity Categories for OSA

Category	AHI
Normal	0
Minimal OSA	> 0 to ≤ 5
Mild OSA	5 to ≤ 15
Moderate OSA	15 to ≤ 30
Severe OSA	≥ 30

Note: Adapted from *Epstein et al. (2009)*

Risk Factors Associated with SBD

Anatomy. OSA syndrome is defined as a condition where there are repeated episodes of complete or partial blockage of the upper airway during sleep (Jordan et al., 2014). There are a number of anatomical factors that lead to a restricted airway associated with OSA/SDB (Schwab et al., 2003). These include decreased size of the airway lumen, enlarged tonsils, craniofacial anatomy abnormalities (retrognathia for example), tongue volume, and body fat in the neck area surrounding the airway. These anatomical changes contribute to airway collapse during sleep. A number of upper airway muscles that are aroused during wakefulness and become relaxed during sleep have also been implicated as a causative factor (Mezzanotte, Tangel, & White, 1992). Inflammation of the upper airway due to environmental exposures such as smoking or chronic sinusitis can also play a role in SDB (Peppard et al., 2013; T. Young, Peppard, & Gottlieb, 2002).

Obesity. Obesity is a major risk factor for SDB, a significant public health concern as much of the United States population is considered overweight (Franklin, Sahlin, Stenlund, & Lindberg, 2013; Heinzer et al., 2015; Peppard et al., 2013). A number of studies have shown that weight loss, even in morbidly obese individuals undergoing gastric bypass surgery can improve symptoms of SDB (Barvaux, Aubert, & Rodenstein, 2000; Grunstein et al., 2007).

Age. SDB does not seem to be as prevalent in both young and elderly patients and has been shown to peak in the 45-64 year-old age group (Bixler et al., 1998). This

phenomenon of increasing prevalence of OSA with age and then a reduction in cases after age 60 was found in both men and women in the Wisconsin Sleep Cohort Study (T. Young et al., 1993). This phenomenon may be partially explained by unreliable results from the smaller sample of elderly participants represented in the study population. Many SDB studies choose working age populations as their sample, and therefore the elderly population is under sampled. These results were not found in a study of women in Sweden where participants were selected from the general population without bias for selecting certain age categories. In this study OSA was found in 24% (95% CI: 45–55%) of females aged 20–44 years, in 56% (95% CI: 47–65%) of females aged 45–54 years and in 75% (95% CI: 67–82%) of females aged 55–70 years (Franklin et al., 2013).

Gender. SDB is generally two times more prevalent in men than in women (Ip, Lam, et al., 2004; Kim et al., 2004; T. Young et al., 1993).

Smoking. Analysis of participants from the Wisconsin Sleep Cohort Study indicate that compared with those that have never smoked, current smokers had a significantly greater risk of moderate or worse SDB (OR, 4.44) (Wetter, Young, Bidwell, Badr, & Palta, 1994). In a study of 964 patients that were former and current smokers referred to an outpatient sleep clinic there was a statistically significant association with younger age of onset and severity of OSA (Varol, Anar, Tuzel, Guclu, & Ucar, 2015). Results to the contrary have been reported from a University Hospital sleep clinic study of over 3,000 men (Hoflstein, 2002). In the study logistic regression revealed that heavy smokers (>30 pack years) had approximately twice the risk of having AHI >50 compared

to nonsmokers, although the OR was <1.0 after adjusting for age, BMI, and gender (Hoflstein, 2002).

Alcohol. Alcohol use as a risk factor is inconclusive as it was studied as a variable in a number of epidemiological studies and an association was noted in some, but not found in others (Peppard, Austin, & Brown, 2007; Udwadia, Doshi, Lonkar, & Singh, 2004). In the Wisconsin Sleep Cohort study, men who consumed more alcohol had 25% greater odds of mild or worse SDB (OR = 1.25, 95% CI: 1.07-1.46, p = 0.006). For women, alcohol consumption was not significantly associated with increased risk of SDB (Peppard et al., 2007).

The Association of SDB and CVD

SDB is associated with a number of cardiovascular and cerebrovascular diseases (Arzt et al., 2005; Kendzerska et al., 2014; Marin et al., 2005; Redline et al., 2010) including hypertension (Nieto et al., 2000; O'Connor et al., 2009), and coronary heart disease (CHD) (Drager et al., 2010; Gottlieb et al., 2010; Hla et al., 2015). As AMD is a disease of the microvasculature it is important to understand the impact of SDB on the cardiovascular system. Drager et al. (2010) have illustrated that SDB may be present in >50% of subjects with hypertension. There is a strong scientific rationale as to why SDB may be related to hypertension as the vascular endothelium may be sensitive to the repeated decreased oxygen levels that occur in subjects with SDB (Ip, Tse, Lam, Tsang, & Lam, 2004). Theoretical mechanisms include SDB causing endothelial cell dysfunction and increased activation of the sympathetic nervous system, both of which have been

cited as underlying causality (Ip, Tse, et al., 2004). The same underlying disease process may be at play with AMD as the vascular endothelium in the eye is subject to the same stressors as the systemic circulation and associations with AMD and hypertension have been reported (Hyman, Schachat, He, & Leske, 2000).

Two population-based studies have provided important data on the impact of sleep apnea in the United States. The Sleep Heart Health Study (SHHS) is a prospective cohort study of the cardiovascular consequences of OSA (Quan et al., 1997). The Wisconsin Sleep Cohort is a stratified random sample from the year 1988 that includes state employees in Wisconsin between 30 and 60 years old (T. Young et al., 1993). In one of the seminal publications to investigate the association of SDB and hypertension, Nieto et al. (Nieto et al., 2000) performed a cross-sectional analysis of the SHHS. The primary exposure in this study was measured by AHI and the outcome of interest was hypertension (blood pressure >140/90) (Nieto et al., 2000). In this study prevalence of hypertension increased significantly with increasing SDB measures, although the authors point to the fact that at least some of the association was explained by body mass index (BMI). After adjusting for potential confounding variables, the OR for hypertension, comparing the highest category of AHI (AHI >30) with the lowest category (AHI<1.5), was 1.37 (95% confidence interval [CI, 1.03-1.83; P=.005)] (Nieto et al., 2000). O'Connor et al. (2009) reported on the association of hypertension with SDB (AHI<5) in the SHHS. In this study, the odds ratio (OR) for hypertension increased in relation to

increasing baseline AHI. Although the authors conclude that much of the relationship can be accounted for by baseline BMI (O'Connor et al., 2009).

Kenderska et al. (Kendzerska et al., 2014) performed a retrospective cohort study using a clinical database from major academic institution in Canada looking at the impact of SDB on a composite CVD outcome (myocardial infarction, stroke, congestive heart failure, revascularization procedures, or death from any cause). Cox regression models were used to analyze the association between baseline OSA and the composite outcome, while controlling for traditional risk variables. AHI was significantly associated with event-free survival in univariate analyses when treated as a continuous predictor in their model [HR= 1.49, 95% CI: 1.42–1.57; p<0.001] (Kendzerska et al., 2014). Even after controlling for a number of CVD risk factors (age, sex, smoking status, BMI, AHI) the association between AHI as a continuous variable and the composite outcome of remained statistically significant (HR= 1.12; 95% CI: 1.05–1.2, p<0.001).

Yeboah et al. (Yeboah et al., 2011) investigated the association between OSA and CVD in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. The sample for this study included 6814 men and women aged 45–84 years old from United States communities with diverse ethnic backgrounds. This provided a population that consisted of participants who were 38% White, 28% Black, 22% Hispanic, and 12% Chinese (Yeboah et al., 2011). The primary exposure in this study was AHI and the outcome of interest was CVD events (defined as CVD events that were adjudicated by a committee of physicians). When compared healthy participants, those with OSA were associated

with high CVD event rates in both univariate and multivariate models [hazard ratio (95%); 1.89(1.22–2.93), $p = 0.004$ and 1.91(1.20–3.04), $p = 0.007$, respectively] (Yeboah et al., 2011).

SDB and CVD

Marshall et al. (2014) studied 400 participants in Australia to investigate as to whether SDB increased the risk of stroke, all-cause mortality, CVD, and CHD. The primary exposure in this study was the respiratory disturbance index (RDI) and the outcome of interest was the prevalence of ischemic stroke (Marshall et al., 2014). OSA severity was quantified at a single night portable home PSG in 1990 and then participants were followed up in 2010. Moderate-severe OSA was statistically associated with all-cause mortality (HR = 4.2; 95% CI 1.9, 9.2) and stroke (3.7; 1.2, 11.8), but not associated with CVD (1.9; 0.75, 4.6) or CHD incidence (1.1; 0.24, 4.6) (Marshall et al., 2014). The authors comment that although the prevailing thought is that sleep apnea is thought to increase mortality through cardiovascular disease, the association was not statistically significant in this study (Marshall et al., 2014).

The SHHS study showed a significant positive association between stroke and AHI was in men (p=0.016) (Redline et al., 2010). Men in the highest AHI quartile (>19) had an adjusted hazard ratio of 2.86 (95% confidence interval, 1.1–7.4). In the mild to moderate range (AHI, 5–25), each one-unit increase in AHI in men was estimated to increase stroke risk by 6% (95% confidence interval, 2–10%). In women, stroke was not

significantly associated with AHI, but there was an increased risk observed when the AHI was > 25 (Redline et al., 2010).

Arzt et al. (Arzt et al., 2005) performed cross-sectional, longitudinal analyses on subjects from the Wisconsin Sleep Cohort. The primary exposure in this study was measured by AHI and the outcome of interest was stroke. In the study, participants with an AHI of ≥20 or greater had increased odds for stroke (OR=4.33; 95% confidence interval, 1.32– 14.24; p <0.02) compared with those without SDB (AHI <5) after adjustment for known confounding factors (Arzt et al., 2005).

The previous studies illustrated association between OSA and stroke, although their patient population represented middle-aged persons that may not be representative of the elderly population. To investigate whether OSA is associated with stroke in this population, Munoz et al. (2006) performed a prospective longitudinal study in elderly subjects from Spain. The primary exposure in this study was measured by AHI and the outcome of interest was stroke (Munoz et al., 2006). In subjects with severe OSA (defined as AHI > 30) at baseline had a statistically significant risk of stroke (hazard ratio= 2.52, 95% CI= 1.04 to 6.01, P= 0.04) (Munoz et al., 2006).

SDB and CHD

Hla et al. (2015) reported findings from the Wisconsin Sleep Cohort Study on the association of CHD and SDB. This study investigated 1,131 adults over the age of 30 who completed one or more overnight sleep studies, which were free of CHD baseline, and were not treated by CPAP. Participants were then followed longitudinally for 24

years. The primary exposure in this study was measured by AHI and the outcome of interest was CHD or heart failure (HF) (Hla et al., 2014). Participants with untreated severe SBD (AHI > 30) were 2.6 times more likely to have CHD or heart failure compared to those without SDB (Hla et al., 2015).

Gottlieb et al. (2010) reported an association of CHD with SDB in the SHHS. In their study, they investigated 1927 men and 2495 women >40 years of age and free of coronary heart disease and heart failure at the time of study entry (Gottlieb et al., 2010). Subjects were followed for a median of 8.7 years. The primary exposure in this study was measured by AHI and the outcome of interest was CHD (Gottlieb et al., 2010). OSA was shown to be a significant predictor of CHD only in men ≤70 years of age (adjusted hazard ratio 1.10 [95% confidence interval 1.00 to 1.21] per10-unit increase in apnea-hypopnea index [AHI]) but not in men >70 or in women of any age. In men age 40 to 70 years old, those participants that had AHI >30 were 68% more likely to develop CHD than those with AHI <5 (Gottlieb et al., 2010).

SDB Epidemiology

As with AMD, the estimated prevalence numbers for SDB have a broad range, likely based on the methodology and definitions for determining the presence of disease (Franklin et al., 2013; Heinzer et al., 2015; Peppard et al., 2013; T. Young et al., 1993). One of the highest prevalence estimates comes from Franklin et al. (2013) in a study of OSA in a Swedish population-based random sample of 10,000 women. The authors report that OSA (defined as AHI ≥5) occurs in 50% (95% CI 45–55%) of females aged

20–70 yrs. 20% of females have moderate (defined as AHI 15-<30) and 6% severe sleep apnea (defined as AHI ≥30). In those participants 55-70 years old or with a BMI ≥ 30 kg/m^2 severe sleep apnea was present in 14% (95% CI 8.1–21%) and 31% (95% CI 12–50%) of the population, respectively (Franklin et al., 2013). The higher estimates in this study may be due to the fact that home PSG was used to measure AHI and the measurement was not performed in a standardized clinical setting.

Heinzer et al. (2015) studied a population of 3043 participants in Lausanne, Switzerland. Participants were examined with PSG in a University Hospital setting and moderate to severe SDB was defined as AHI ≥15. The prevalence of moderate-to-severe SDB was 23.4% (95% CI: 20.9–26.0) in women and 49.7% (95% CI: 46.6–52.8) in men. There was a statistically significant difference across all categories of SDB based on those <60 versus ≥60 and men vs. women (Heinzer et al., 2015).

The Wisconsin Sleep Cohort Study estimated the prevalence of OSA in a random sample of 3,513 US employees in Wisconsin ages 30-60 years (T. Young et al., 1993). Participants were observed during an overnight PSG examination. The estimated prevalence of SDB (defined as AHI ≥5) was 9% for women and 24% for men. Peppard et al. (2013) investigated this same population during the periods of 1988–1994 and 2007–2010. The authors estimate moderate to severe SDB (AHI ≥15) are 10% (95% CI: 7-12) among 30–49-year-old men; 17% (95% CI: 15-21) among 50–70-year-old men; 3% (95% CI: 2, 4) among 30–49-year-old women; and 9% (95% CI: 7, 11) among 50–70 year-old women (Peppard et al., 2013). These results indicate that over the two decade study

period, there was between a substantial increase in SDB in the U.S. population (Peppard et al., 2013).

A number of epidemiological studies have been performed in populations that predominantly consist of ethnicities other than Caucasian. In a study of middle age Indian men, the prevalence of OSA was 19.5% (Udwadia et al., 2004). In a population-based sample from Korea, the prevalence of SDB was 27% and 16% in men and women, respectively (Kim et al., 2004). In a study of middle-aged Chinese men and women living in Hong Kong the prevalence of SDB was 8.8% and 3.7%, respectively (Ip et al., 2001; Ip, Lam, et al., 2004).

AMD and SDB

As humans age, there is evidence that the quality of sleep deteriorates (Bloom et al., 2009). Changes in circadian rhythms, the sleep–wake cycle, and decreased synthesis of melatonin may all contribute to this phenomenon (Bloom et al., 2009; Rosen et al., 2009). There is clear evidence that SDB is associated with the development of cardiovascular (Laaban et al., 2002; Lavie, Herer, & Hoffstein, 2000; Nieto et al., 2000; Peker, Hedner, Kraiczi, & Loth, 2000; Peppard, Young, Palta, & Skatrud, 2000; Shahar et al., 2001; Stone et al., 2016) and neurodegenerative diseases (Buratti et al., 2014; Osorio et al., 2015; Yaffe, Nettiksimmons, Yesavage, & Byers, 2015). Experimentally, it has been demonstrated that apnea leads to neuronal damage (apoptosis) in susceptible regions of the brain (Fung, Xi, Zhang, Sampogna, & Chase, 2012; J. H. Zhang, Fung, Xi, Sampogna, & Chase, 2009).

One common mechanism that has been proposed to describe this relationship between SBD and both cardiovascular and neurodegenerative diseases is vascular impairment (Buratti et al., 2014). Similarly, vascular impairment has been proposed as a possible mechanism for AMD pathogenesis (Boltz et al., 2010; Grunwald et al., 2005; Remsch et al., 2000). Based on the high-energy demand of human retina, nature has provided it with one of the greatest blood flow networks of any organ in the human body relative to its size (Ames et al., 1992; Blasiak et al., 2014; Boltz et al., 2010; Remsch et al., 2000; Sim & Fruttiger, 2013). This places the outer retina, which is avascular but highly metabolic, in a vulnerable state when there is insufficient energy and low oxygenation of the blood stream.

The eye allows researchers the ability to investigate microvascular changes in a non-invasive manner, therefore providing a window on the health of the systemic vasculature. Retinal arterioles are shown to be anatomically similar to cerebral and coronary arterioles, and systemic disease can often be diagnosed from ophthalmic examination or through the use of diagnostic techniques such as fundus photography, fluorescein angiography, and optical coherence tomography (OCT) (Klein, Klein, & Moss, 1997; T. Wong et al., 2001). In both the CHS and ARIC study cohorts, retinal microvascular abnormalities are strongly and independently associated with hypertension as evident by arteriolar narrowing (as measured by the arteriovenous ratio [AVR]) and arteriovenous nicking (Sharrett et al., 1999; T. Wong et al., 2002). Although there is a

significant relationship, it is unclear whether AVR and/or arteriovenous nicking are an appropriate measure of disease.

Microvascular changes have been shown to be associated with SDB in the Multi-Ethnic Study of Atherosclerosis (MESA) study (M. Chew et al., 2016). Women that were enrolled in the MESA study showed an association between SBD and narrower arterioles [regression coefficient (β)= -5.76; 95 % CI: -8.51, -3.02] after adjusting for cardio-metabolic risk factors. Although in men there was no association between SDB and arteriolar caliber, there was an association with incident CVD (M. Chew et al., 2016). The authors proposed that there may be a potential gender difference in the susceptibility to microvascular disease in association with SDB (M. Chew et al., 2016).

Boland et al. (2004) performed a sub study of the Sleep Heart Health Study (SHHS) that examined the relation between SDB (as measured by RDI) and retinal microvascular abnormalities. The SHHS is a prospective cohort design study consisting of subjects 40 years and older to investigate the association of SDB with cardiovascular disease (Quan et al., 1997). The authors found that the overall prevalence of retinopathy was slightly higher in people with higher RDI values, although after adjustment for age, body-mass index, hypertension, diabetes, and other factors, the association no longer held. The authors concluded that the weak association with SDB and early microvascular dysfunction should be investigated further.

Boltz et al. (2010) tested the hypothesis that lower retinal blood flow (inducing a hypoxic environment within the retina) may be associated with an increased risk of

developing choroidal neovascularization in an observational longitudinal study. Their research indicated that lower retinal blood flow had a statistically significant association with progression to choroidal neovascularization. This supports the hypothesis that the hypoxic environment created by SDB may also have an effect on the progression of AMD.

In addition to the retina allowing for insight into microvascular changes in the body, neurodegenerative changes in the eye have can also be examined, quantified, and imaged non-invasively in individuals with SDB (Huseyinoglu et al., 2014; Shiba et al., 2014; Xin, Wang, Zhang, Wang, & Peng, 2014). Huseyinoglu et al. (2014) investigated 101 subjects with OSA and 20 controls without OSA using OCT to look at impact on the retina nerve fiber layer (RNFL). The researchers performed PSG and ophthalmologic examination including visual field (VF) testing. Subjects were graded based on PSG score and placed into mild, moderate, and severe OSA categories. The researchers found that there was a significant reduction in RNFL thickness in the subjects with severe OSA compared with the other categorized groups. Shiba et al. (2014) corroborated these findings in a study of 124 consecutive subjects who underwent PSG and OCT to measure RNFL thickness, foveal thickness, and total macular volume. Their findings indicate that the RNFL thickness was correlated with higher AHI values (Shiba et al., 2014). PSG findings were not correlated with foveal thickness or total macular volume. These findings have been corroborated in other research studies illustrating that thinning of the retina and choroid occurs with increasing OSA severity (Xin et al., 2014). Similar to the

aforementioned retinal findings, multiple studies investigating the morphological changes in brains of subjects with OSA have shown that the volume of cortical gray matter is smaller in patients with OSA as compared to controls (Branger et al., 2016; Morrell et al., 2003; Torelli et al., 2011; Yaouhi et al., 2009).

Another important pathological finding that is shared by subjects with AMD or SDB is the accumulation of amyloid-beta (Aβ) in the retina (Mullins et al., 2000; Ohno-Matsui, 2011; Ratnayaka, Serpell, & Lotery, 2015) and brain, respectively (Branger et al., 2016; Sprecher et al., 2015). Retinal ganglion cells (RGC) and the retinal pigment epithelial layer have been identified as a source Aβ deposition within the retina as a component of drusen (Ohno-Matsui, 2011). Amyloid plaques in the brain have been shown to be a hallmark of Alzheimer's disease (Jack et al., 2013). Branger et al. (2016) have illustrated that Aβ accumulation in the brain, as assessed by structural MRI and florbetapir-PET scans, was associated with worse self-reported sleep quality. Sprecher et al. (2015) found similar results in participants enrolled in the Wisconsin Registry for Alzheimer's Prevention (WRAP). Results illustrated that participants with the perception of less adequate sleep, more sleep problems, and greater somnolence had a greater brain amyloid burden (Sprecher et al., 2015). In this study, Aβ was not associated with reported sleep amount, symptoms of SDB, trouble falling asleep, or the Epworth Sleepiness Scale (ESS) score (Sprecher et al., 2015). This phenomenon has been noted in other studies imaging Aβ deposition in the brain of those with symptoms of SDB (Spira et al., 2014).

As stated by Blasiak et al. (2014) “it is hard to determine whether any particular pathology is linked with the stress caused by a risk factor or if it is a consequence of the pathology or a combination of both”. Oxidative stress is defined as an imbalance with the production of reactive oxygen species (ROS) and antioxidant defenses against those free radicals (Betteridge, 2000). Cells have the ability to combat free radicals in most acute situations, although in chronic situations tissue damage can ensue that may be irreversible (Blasiak et al., 2014). The retina is constantly producing waste products from the reactions that transpire when light energy causes photochemical reactions with the photoreceptors. The retina has innate mechanisms of autophagy (intracellular mechanism of waste removal) to remove these waste products by the retinal pigment epithelial layer. Blasiak et al. (2014) proposes that any event that impairs blood flow to the retina or reduces retinal oxygenation (SDB, smoking, COPD for example) will induce hypoxia thus impairing the normal autophagy function within the retina, resulting in the build-up of waste products. This build-up of waste products in AMD (drusen for example) can cause a mechanical impairment of the transmission of signals from photoreceptors to the appropriate processing centers in the brain (Blasiak et al., 2014). Oxidative stress has been implicated as the cellular mechanism by which smoking is associated with AMD (Marazita, Dugour, Marquioni-Ramella, Figueroa, & Suburo, 2015). Marazita et al. (2015) demonstrated that exposure of human retinal pigment epithelial cells to a cigarette smoke concentrate enhanced ROS levels and caused DNA damage. In their experiment,

interleukin-6 (IL-6), IL-8, and VEGF levels were increased and CFH expression was downregulated (Marazita et al., 2015).

SDB and Treatment for AMD

SDB has also been shown to interfere with current anti-VEGF treatments for neovascular AMD. Barak et al. (2012) analyzed the functional and anatomical response to treating choroidal neovascularization with anti-VEGF therapy with Avastin® in patients before and after treatment of OSA. Untreated OSA in this study hampered the response to anti-VEGF therapy for the treatment of neovascular AMD. After CPAP therapy, the anatomical improvement provided by anti-VEGF treatment was evident, although functional vision improvement did not follow. Nesmith, Ihnen and Schaal (2014) looked at 103 patients with AMD compared to age-matched controls with regard to treatment response to anti-VEGF therapy. Symptoms associated with OSA were collected using the Berlin Questionnaire (BQ). The authors found that 30% of subjects with AMD that had a poor response to anti-VEGF therapy were at a significantly higher risk of OSA as assessed by the BQ ($p< 0.05$) (Nesmith et al., 2014).

SDB Associations with AMD

Recently, a number of studies have looked at whether sleep-associated variables are associated with AMD (Keenan et al., 2016; Khurana et al., 2016; Perez-Canales et al., 2016). Khurana et al. (2016) administered a prospectively designed sleep history questionnaire to 1,003 consecutive patients in a private retina practice. Participants were graded and placed into categories of no AMD, early AMD, nAMD, or geographic

atrophy using the modified Wisconsin Age-Related Maculopathy Grading System. Using multivariate analysis (controlling for age, gender, and smoking history), sleep hours were not associated with nAMD ($p = 0.97$) as compared to controls. Sleeping >8 hours was associated with GA ($p = 0.02$) when compared with patients without AMD (age-adjusted OR=7.09; 95% confidence interval, 1.59–31.6) (Khurana et al., 2016). The strength of this study is a large sample size as well as grading of retinal findings from fundus photographs. One of the weaknesses of the study is the questionable generalizability as all subjects were recruited from one clinic located in one geographic area.

Perez-Canales et al. (2016) performed a case control study that found a statistically significant association between sleep duration and AMD (for <6 hours, OR=3.29, 95% confidence interval 1.32–8.27; for 6–7 hours, OR= 2.25, 95% CI 0.80–6.32; and for >8 hours, OR=1.39, 95% CI 0.53–3.73) compared with the reference category of 7–8 hours. In addition, the highest utilization of sleep medication was being used in the population with AMD ($p < 0.001$). The results of the study remained statistically significant after adjustment for smoking status, history of depression, regular physical activity, BMI and hypertension (Perez-Canales et al., 2016). This trend towards a higher risk of nAMD in subjects with both short and long sleep duration when compared with those in the 7–8 hours group suggests a possible U-shaped relationship between sleep duration and nAMD (Perez-Canales et al., 2016). This study did not investigate the association of sleep duration and GA.

Keenan et al. (2016) linked English national hospital episode statistics (HES) for 248,408 patients with AMD that were admitted to English National Health Service (NHS) treatment facilities and also had OSA. Their results showed that OSA was positively associated with AMD (Keenan et al., 2016). The authors accounted for obesity as a potential confounder in the analysis, although it had little effect on the association. The strength of this study is that it includes a large number of participants from a major healthcare system, although as with many of the other studies AMD severity was not categorized.

Several studies have documented the association between SDB and other ophthalmological diseases, including nonischemic anterior optic neuropathy, chorioretinopathy, floppy eyelid syndrome, primary open-angle glaucoma, normal-tension glaucoma, and papilledema. There are several studies showing association between SDB and glaucomatous changes in the optic nerve characterized by optic nerve head changes (Casas et al., 2013), visual field defects, and RNFL thickness (Casas et al., 2013; Ferrandez et al., 2016; Lin et al., 2011) in light of the intraocular pressure (IOP) being normal.

Confounders

AMD and SDB share similar potential confounders that include age, gender, obesity, and past and current smoking status. Age is the most strongly associated risk factor for AMD and in concert with obesity is the most important risk factor for SDB. SDB has been shown to reach peak prevalence in the 45-64 year old age group (Bixler et

al., 1998), while AMD has been shown to increase in prevalence with increasing age (E. Chew et al., 2014; Tomany et al., 2004). Gender is a potential confounder in both diseases as with AMD there is a slightly higher prevalence in women (E. Chew et al., 2014; Tomany et al., 2004), whereas SDB is more prevalent in men (Heinzer et al., 2015; Peppard et al., 2013). There have been reports that menopausal status may influence the prevalence estimates of SDB and this same confounding has been suggested with AMD (Bixler et al., 2001; Tomany et al., 2004). Obesity is strongly associated with SDB, whereas the association with AMD is weak (Q. Zhang et al., 2016). In studies of SDB and AMD where obesity was taken into account as a confounder, the effect on the association was minimal (Keenan et al., 2016). Smoking is strongly associated with both AMD (E. Chew et al., 2014) and SDB (Varol et al., 2015). In both diseases, smoking is associated with earlier onset of disease and worse severity. Race/ethnicity is likely a stronger confounder for AMD than SDB as strong associations with AMD and participants of European ancestry have been reported (W. Wong et al., 2014). Smoking is shown to be strongly associated with AMD and studies have shown an association with SDB (Varol et al., 2015). Based on the shared confounders listed above it was important to control for these variables in the analyses that I discuss in more detail in Chapter 3.

Summary

In summary, the current research is inconclusive on the association between SDB and AMD and SDB and AMD severity. One of the main limitations to date has been the lack of a population-based research study to investigate the association between the two

diseases. In addition, there is no study to date that uses masked grading of retinal photographs to determine AMD severity and analyze these findings in light of a sleep questionnaire with multiple sleep related variables. Therefore, this study includes a large sample from the NHANES 2005–2008 survey period that includes fundus photography determined AMD status using masked graders and a validated grading protocol and a sleep questionnaire to capture self-reported variables for SDB. I will detail the methodology and analyses in Chapter 3.

Chapter 3: Research Method

Introduction

The purpose of this quantitative cross-sectional study was to evaluate the association between SDB and AMD in noninstitutionalized U.S. adults from 2005-2008 and to serve as proof of concept to promote future research on causality. In Chapter 3, I present the study design and describe the study population, criteria for sample selection, definition of variables, data collection methodology, and instrumentation and materials. I also cover the NHANES 2005–2008 dataset and data analysis, the ethical protection of participants; and the Institutional Review Board () review and approval.

Research Design and Rationale

To address the research questions related to the purpose of this research, I investigated whether respondents with SDB (independent variable) had an increased prevalence of AMD (dependent variable) using nationally representative data, both with and without controlling for confounders. Cross-sectional study designs have been commonly used to study associations between dependent and independent variables using population-based surveys such as NHANES (Creswell, 2014). There were no time or resource constraints for this study.

Research Hypotheses

The research questions and associated hypotheses that will guide this study are as follows:

Research Question 1: Is there an association between self-reported SDB and fundus photography identified AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI?

$H_0$1: There is no association between self-reported SDB and fundus photography identified AMD among adults 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

$H_1$1: There is an association between self-reported SDB and fundus photography identified AMD among adult 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

Research Question 2: Is there an association between self-reported SDB and fundus photography identified neovascular AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI?

$H_0$2: There is no association between self-reported SDB and fundus photography identified neovascular AMD among adults 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

$H_1$2: There is an association between self-reported SDB and fundus photography identified neovascular AMD among adult 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

Research Question 3: Is there an association between self-reported SDB and fundus photography identified geographic atrophy among adults 40 years and older who

participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI?

$H_0$3: There is no association between self-reported SDB and fundus photography identified geographic atrophy among adults 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

$H_1$3: There is an association between self-reported SDB and fundus photography identified geographic atrophy among adult 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

Methodology

Population

This study comprises adults 40 years and older that participated in the NHANES survey during the sampling timeframes of 2005-2006 and 2007-2008. The NHANES survey period of 2005–2008 is unique in that these two sampling frames include digital fundus photographs captured at a mobile examination center (MEC). Participants included in this study provided responses to the Sleep Disordered Questionnaire (SLQ) and had digital fundus photographs acquired as a part of NHANES. The population is comprised of noninstitutionalized individuals from the 50 states and the District of Columbia. The NHANES dataset does not include active duty military members by design (Zipf et al., 2013).

Sampling and Sampling Procedures

The NHANES survey uses a multistage probability sampling design to select a sample representative of the civilian noninstitutionalized household population of the United States (Zipf et al., 2013). Sample selection, collection, and cleaning procedures for NHANES has been previously published (Zipf et al., 2013).

An a priori power analysis was conducted to determine an adequate sample size using G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009). Assumptions in determining minimum sample size included a two-tailed alpha of 0.05 and a power of 90% to detect a weak association indicated by an OR of 1.2 (Monson, 1990). Monson (1990) indicates that an OR below 1.2 indicates no association. Therefore an OR of 1.2 was used to estimate the minimum sample size needed; which was 1984 participants. According to Klein et al. (2011), 5553 participants that were ≥40 years of age in the 2005–2008 NHANES dataset had at least 1 eye that could be evaluated for AMD. As nAMD and geographic atrophy (late AMD) are only present in a small portion of the population, the entire sample of participants that were ≥40 years of age, had at least 1 eye that could be evaluated for AMD, and completed the sleep disorder questionnaire will be included in the analyses.

Procedures for Recruitment, Participation, and Data Collection

The NHANES Survey is a national survey conducted by the National Center for Health Statistics and consists of a representative sample of the noninstitutionalized and civilian population of the United States. The first National Health Examination Survey

(NHES-1) was performed in 1959 (Zipf et al., 2013). During the years 1959-1970 the survey was performed periodically. As of 1999, the data has been continuously collected during concurrent sampling timeframes. The goals of this continuous survey is to provide prevalence data on selected diseases and risk factors for the U.S. population, to monitor trends in selected diseases, behaviors, and environmental exposures, to explore emerging public health needs, and to maintain a national probability sample of baseline information on health and nutritional status in the United States (Zipf et al., 2013). The NHANES is a unique survey as it not only contains participants' self-reported health information from survey instruments, but also information from physical examinations and laboratory tests (Zipf et al., 2013). The participant interviews are conducted in the home, while the physical examinations are performed at a MEC. The combination of self-reported health information, physical examinations, and laboratory tests allows for analyses to be performed that would otherwise not be possible, or as accurate, with self-reported information alone (Zipf et al., 2013). Datasets from the NHANES survey are publically available and can be downloaded from the CDC website (http://www.cdc.gov/nchs/nhanes/).

The MEC was used to collect retinal fundus images to assess the prevalence of vision loss and retinal diseases, such as AMD. Digital fundus photography was performed to obtain two 45° digital retinal images for each eye of NHANES participants involved in this ancillary study using the Canon CR6 non-mydriatic camera with a Canon 10D camera back (6.3 megapixels per image) (CDC, 2005). Masked grading of digital

fundus photos eliminates recall bias that would otherwise be present from participant self-report, although this does not completely rule out the potential for misclassification bias that will be discussed further in this chapter. As this study investigated AMD as an ordinal variable, the grading of fundus photos will allow for the diagnosis of early signs of AMD that often do not cause visual disturbance in the patient and may not be communicated in survey findings alone.

Operationalization of Variables

The dependent variables for this study depend upon the research questions asked and included AMD status (categorical-none, early, and late AMD), nAMD, and geographic atrophy as defined by masked fundus photo grading. The independent variables included demographic variables (age, gender, race, BMI), diabetes status, smoking status (past or current smoker) and SDB variables (sleep apnea, sleep apnea symptoms of snoring and snorting/stop breathing, insomnia, short sleep duration, and any sleep disorder diagnosed by a physician or other health professional).

Dependent variables (AMD, geographic atrophy, and choroidal neovascularization). The following AMD Variables are defined from masked grading of fundus photos as specified in the NHANES Digital Grading protocol and illustrated in Table 2 (CDC, 2005). Definitions for No AMD, Early AMD, and Late AMD are defined in the NHANES Digital Grading Protocol and this approach has been used in other NHANES research (Klein et al., 2011). No AMD is defined as gradable images without evidence of lesions associated with AMD. Early AMD was defined by the presence of

either soft indistinct drusen or the presence of retinal pigment epithelial depigmentation or increased retinal pigment, together with any type of drusen, or by the presence of soft drusen with an area of 500 μm or larger in absence of signs of late AMD. Late AMD was defined by the presence of any of the following: geographic atrophy or retinal pigment epithelial layer detachment, subretinal hemorrhage or visible subretinal new vessels, subretinal fibrous scar or laser treatment scar, or self-reported history of photodynamic or anti–vascular endothelial growth factor treatment for exudative AMD. I present these definitions in Table 2.

Table 2

AMD Variables: NHANES 2005-2008

Data variable	Variable category	Definition	Variable recode
OPDUARM	No AMD	Gradable images with no evidence of lesions associated with AMD.	0
	Early AMD	Defined as either soft drusen present with a grid area of greater than a 500μm circle and a pigmentary abnormality present (increased pigment or depigmentation in the grid) or soft drusen present in the center circle and a pigmentary abnormality is present (increased pigment or depigmentation in the grid). No evidence of late AMD as defined below will be present.	1
	Late AMD	Defined as the presence of any late lesions, such as GA, PED/RD detachments, subretinal hemorrhage, subretinal fibrous scar, subretinal new vessels, or laser treatment and/or /photodynamic therapy for AMD.	2
OPDUGA		Geographic Atrophy	Absent = 0 Present = 1
OPDUEXU		Exudative AMD	Absent = 0 Present = 1

Independent variables (SDB variables). SDB variables were based on participant self-report and came from the NHANES 2005–2008 sleep disorders questionnaire (SLQ). Previously published NHANES research has used this dataset and categorized the SDB variables in a similar fashion to what was done for this study (Chen et al., 2014; Seicean, Neuhauser, Strohl, & Redline, 2011). SDB variables were placed in

the following high-level categories: sleep apnea, SDB symptoms, insomnia, and insomnia symptoms. Sleep apnea was defined based on answering in the affirmative to following question: “Have you ever been told by a doctor or other health professional that you have a sleep disorder: sleep apnea?” SDB symptoms were captured from questions on duration of sleep, habitual snoring, and snorting/stop breathing. Sleep duration was dichotomized to ≥6 hours vs. <6 hours. Habitual snoring was asked using the question: (1) “In the past 12 months, how often did you snore while you were sleeping?”. Snorting/Stop Breathing was collected using the question: “In the past 12 months, how often did you snort, gasp, or stop breathing while you were asleep?”. Participants who responded with “frequently (five or more nights per week)” were considered as having “habitual snoring” and “snorting/stop breathing,” respectively. Those participants that responded with “never,” “rarely (1-2 nights/week),” or “occasionally (3-4 nights/week)” were considered as having no snoring or snorting/stop breathing, respectively. Insomnia was defined based on answering yes to the following: “Have you ever been told by a doctor or other health professional that you have a sleep disorder (Insomnia)?” Insomnia symptoms were based on the answers to the following questions: “Do you have trouble falling asleep” (sleep latency) and “Do you wake up during the night and had trouble getting back to sleep” (nocturnal awakenings). A response to each insomnia symptom question was categorized as follows: negligible (2-4 times per month or less), mild to moderate (5-15 times per month), and severe (>15 times/month). These variables are presented in Table 3.

Table 3

SDB Variables: NHANES 2005-2008

Data set code	Question	Response(s)	Study code
Sleep Apnea			Sleep Apnea
SLQ.060	Have you ever been told by a doctor or other health professional that you have a sleep disorder?	Yes	
SLQ.070	AND What was the sleep disorder?	AND Sleep Apnea	
Sleep Disturbed Breathing Symptoms			
SLQ.010	How much sleep do you usually get at night on weekdays or workdays?	≥6 hours <6 hours	Sleep Duration
SLQ.030	In the past 12 months, how often did you snore while you were sleeping?	Habitual Snoring (Frequently, ≥5 nights/week) No Smoking (Never; Rarely, 1-2 nights/week; Occasionally, 3-4 nights/week)	Snoring
SLQ.040	In the past 12 months, how often did you snort, gasp, or stop breathing while you were asleep?	Snorting/Stop Breathing (Frequently, ≥5 nights/week) No Snorting/Stop Breathing (Never; Rarely, 1-2 nights/week; Occasionally, 3-4 nights/week)	Snort/Stop Breathing
SLQ.120	In the past month, how often did you feel excessively or overly sleepy during the day?	Severe (Almost always, 16-30 times a month) Mild to Moderate (Often, 5-15 times a month) Negligible (Sometimes, 2-4 times a month; Rarely, 1 times a month; Never)	Hypersomnolence
Insomnia			Diagnosed Insomnia

Continued

Data set code	Question	Response(s)	Study code
SLQ.060	Have you ever been told by a doctor or other health professional that you have a sleep disorder?	Yes	
SLQ.070	AND What was the disorder?	AND Insomnia	
Insomnia Symptoms			
SLQ.080	In the past month, how often did you have trouble falling asleep?	Severe (Almost always, 16-30 times a month) Mild to Moderate (Often, 5-15 times a month) Negligible (Sometimes, 2-4 times a month; Rarely, 1 times a month; Never)	Sleep Latency
SLQ.080	In the past month, how often do you wake up during the night and have trouble getting back to sleep?	Severe (Almost always, 16-30 times a month) Mild to Moderate (Often, 5-15 times a month) Negligible (Sometimes, 2-4 times a month; Rarely, 1 times a month; Never)	Nocturnal Awakenings

Sociodemographic and lifestyle characteristics. I present individual demographic data based on participant self-report in Table 4. These include age, gender, and race.

Table 4

Demographic Variables: NHANES 2005-2008

Variable name	Description	Level of measurement	Study code	Variable recode
RIAGENDER	Gender	Binominal	Gender	Male = 1 Female = 2
RIDAGEYR	Age in years of the participant at the time of screening.	Nominal	Age	40-59 ≥ 60
RIDRETH1	Recode of reported race and ethnicity information.	Nominal	Ethnicity	Mexican American = 1 Other Hispanic = 2 Non-Hispanic White = 3 Black = 4 Other race = 5
BMXBMI	Calculated BMI (kg/m^2)	Nominal	BMI	Normal = 0-24.9 Overweight= 25.0-29.9 Obese = ≥30
DIQ.010	Other than during pregnancy, have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes?	Binominal	Diabetes	Yes=1 No=2

Smoking history variables. Smoking status was based on participant self-report, and was divided into three categories, “current smoker”, “past smoker”, and nonsmoker. These variables are presented in Table 5. Current smokers were categorized as all individuals who responded positively to smoking at least 100 cigarettes in a lifetime and

smoking cigarettes every day or some days. Past smokers were categorized as those who had smoked at least 100 cigarettes and who replied that they no longer smoked cigarettes. A nonsmoker was categorized as any individual who had smoked fewer than 100 cigarettes in their lifetime.

Table 5

Smoking Variables: NHANES 2005-2008

Data set code	Question	Response	Study code
Current smoker			Current smoker
SMQ.020	Have you smoked at least 100 cigarettes in your entire life?	Yes	
SMQ.040	AND Do you now smoke cigarettes?	AND Every day OR Some days	
Past smoker			Past smoker
SMQ.020	Have you smoked at least 100 cigarettes in your entire life?	Yes	
SMQ.040	AND Do you now smoke cigarettes?	AND Not at all	
Nonsmoker			Nonsmoker
SMQ.020	Have you smoked at least 100 cigarettes in your entire life?	No	

Data Analysis Plan

Analyses was performed using SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Mac, Version 23.0. Armonk, NY: IBM Corp). Datasets from the 2005-2006 and 2007-2008 survey periods were merged to produce an analysis dataset.

Variables were recoded, as needed, based on the specifications previously described in the section on operationalization of variables.

The research questions and associated hypotheses that guided this study are as follows:

Research Question 1: Is there an association between self-reported SDB and fundus photography identified AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI?

$H_0$1: There is no association between self-reported SDB and fundus photography identified AMD among adults 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

$H_1$1: There is an association between self-reported SDB and fundus photography identified AMD among adult 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

Research Question 2: Is there an association between self-reported SDB and fundus photography identified neovascular AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI?

$H_0$2: There is no association between self-reported SDB and fundus photography identified neovascular AMD among adults 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

$H_1$2: There is an association between self-reported SDB and fundus photography identified neovascular AMD among adult 40 years and older who participated in the NHANES 2005 to 2008 survey before and before and after controlling for age, smoking, and BMI.

Research Question 3: Is there an association between self-reported SDB and fundus photography identified geographic atrophy among adults 40 years and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI?

$H_0$3: There is no association between self-reported SDB and fundus photography identified geographic atrophy among adults 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

$H_1$3: There is an association between self-reported SDB and fundus photography identified geographic atrophy among adult 40 years and older who participated in the NHANES 2005 to 2008 survey before and after controlling for age, smoking, and BMI.

To answer these research questions, I first conducted a chi-square test for association to determine any differences in the distribution of AMD across sociodemographic, lifestyle, and sleep characteristics. Cumulative odds OLR with proportional odds (ordinal dependent variable= no AMD, early AMD, late AMD) regression and binomial logistic regression modeling (dependent variable=no choroidal neovascularization, choroidal neovascularization present; no geographic atrophy, geographic atrophy present) were fit to understand the association between AMD and

sleep parameters with adjustment for sociodemographic and lifestyle factors. Survey specific sampling design variables and sampling weights were incorporated in the analyses to account for the complex multistage sampling design of NHANES. The two main objectives of this OLR were as follows: (a) to determine which of the independent variables (if any) have a statistically significant effect on AMD; and (b) determine how well the OLR model predicts AMD. An OLR analysis was performed that only included SDB variables (sleep apnea, sleep apnea symptoms of snoring and snorting/stop breathing, insomnia, short sleep duration, and any sleep disorder diagnosed by a physician or other health professional). The second model was adjusted for demographic variables identified as confounders (age, BMI) and smoking status (past or current smoker) and tested with a multivariable regression analysis. Binomial logistic regression models were created to test the association with nAMD and geographic atrophy with SDB, respectively. These binomial logistic regression models were adjusted for the same independent variables as with the cumulative odds OLR with proportional odds analyses listed above. In accordance with the number of analyses conducted, adjustment of the significance level by the method of Sequential Sidak was incorporated. Data analyses were performed using SPSS software using the Cross Tabs, Complex Samples OLR, and Complex Samples Logistic Regression procedures (IBM Corp. Released 2013. IBM SPSS Statistics for Mac, Version 23.0. Armonk, NY: IBM Corp). ORs and 95% confidence intervals (95% CIs) were calculated for all models.

Threats to Validity

The current study used data from the 2005–2008 NHANES sampling periods to evaluate the association between AMD and SDB. The NHANES survey captures data from a single point in time (cross-sectional) and therefore provided little to no basis for assumptions about causality. Due to this limitation of the design, the study was only interpreted in terms of illustrating an association between AMD and SDB.

NHANES participants are only sampled from the United States, so generalizability to other populations may not be accurate (external validity). In addition, the NHANES survey does not include individuals who were institutionalized (e.g., nursing home residents, incarcerated individuals, long term care facility residents) at the time of the survey. Based on this study's requirements for interpreted retinal fundus photographs, I was unable to include a substantial number of participants who did not have photographs taken, or for whom the photos taken were considered ungradable. Participants that had no ability to perceive light, severe visual impairment in both eyes, or an infection in at least one eye were excluded from fundus photography (CDC, 2005). Lastly, due to the sampling timeframes and the limited years available in this analysis, certain ethnic subgroups may be underestimated. NHANES provides ethnicity as a recoded data variable with the categories of Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other. As there is no granularity with regards to the ethnicity/race in the Other categories, it was not possible to assess the association with populations other than the recoded variable provided by NHANES. This may have

had little impact on the analyses as AMD has a relatively high prevalence in the non-Hispanic White population while it is relatively rare in Blacks and Latinos (Klein et al., 2011). The entire available sample that met my inclusion criteria was analyzed regardless of ethnicity.

Ethical Considerations

As this study used secondary data from persons who participated in the NHANES survey, measures were employed to ensure participant protection prior to and during data collection (Zipf et al., 2013). This study used de-identified data and there was and will be no effort to contact those NHANES participants who are included in the study. In this study, I used all available data that met the pre-specified inclusion criteria of ≥40 years of age, had at least one eye that could be evaluated for AMD, and completed the sleep disorder questionnaire.

The NHANES survey data is publicly available; it has been previously reviewed by the NCHS Research Ethics Review Board [ERB] (CDC, 2016a). All subjects were administered and provided informed consent prior to participation in NHANES. The Walden University Institutional Review Board (IRB) provided a review and was responsible for oversight for the analyses of this secondary data set (IRB approval number 11-15-16-0260551). The anonymized data sets were downloaded from the publically available NHANES website and stored on my local workstation with appropriate back-up software in place. I will maintain the data for the latter of 3 years

after the publication of this dissertation and/or the publication of the results in a peer-reviewed journal.

Summary

In Chapter 3, I provided the methodology to perform this quantitative, cross-sectional study based on a life course approach to chronic disease. The primary objective of this project was to identify if there is an association with AMD and SDB for noninstitutionalized U.S. adults over the age of 40 from the NHANES sampling periods 2005-2008. The association was investigated in the context of demographic variables, smoking variables, and SDB variables. The results of the current study may provide patients, caregivers, and healthcare providers essential information for the prevention and treatment of AMD.

Results, including the demographics of the sample and the findings gleaned from my use of ordinal and binomial logistic regression are presented in Chapter 4.

Chapter 4: Results

Introduction

The purpose of this quantitative cross-sectional study was to evaluate the association between SDB and AMD in noninstitutionalized U.S. adults from 2005-2008 and to serve as proof of concept to promote future research on causality. To achieve this purpose, I tested the hypotheses using secondary data from the 2005–2008 NHANES survey sampling frames. A multistage probability sampling design was used by NHANES to select a sample representative of the civilian, noninstitutionalized household population of the United States that has been previously published in the peer reviewed literature (Zipf et al., 2013).

In Chapter 4, I present the demographics of the study sample, bivariate relationships between the dependent and independent variables, an evaluation of potential confounders to that relationship, and the odds ratios determined through my use of ordinal and binary logistic regression. The first hypothesis, testing the association between SDB and AMD was assessed by performing a preliminary chi-square test for association to determine any differences in the distribution of AMD across sociodemographic, lifestyle, and sleep characteristics. Each SDB variable was then incorporated into a complex samples OLR model with and without adjustment for covariates. I used a multivariate model to incorporate the statistically significant SDB and covariate variables to estimate the strength, significance, and direction of the primary relationships. The second and third hypothesis testing the association between SDB and

choroidal neovascularization and SDB and geographic atrophy, respectively, had to be collapsed due to the rare prevalence of these two subpopulations in the study sample. This resulted in a single research question addressing the association of SDB with late AMD (choroidal neovascularization and geographic atrophy). Therefore, RQ 2 is as follows: Is there an association between self-reported SDB and fundus photography identified late AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey before and after controlling for age, smoking, and BMI? This research question was analyzed using the complex samples binary logistic regression model and included the covariates age, BMI, and smoking status identified in in the assessment of the first research question.

Data Collection

The source of secondary data for this study was the NHANES 2005–2008 survey. The NHANES is an appropriate data collection tool as it utilizes sampling techniques to survey a representative of the civilian noninstitutionalized household population of the United States during each sampling timeframe (Zipf et al., 2013). The sampling design for the 2005–2008 survey years has been previously described in detail in the peer-reviewed literature (National Center for Health Statistics [U.S.], 2012, 2013). In summary, a multistage sample design was used in NHANES 2005-2008. The first stage of the sample design consisted of selecting the primary sampling units (PSU) from all U.S. counties, using the 2000 U.S. Census Bureau data. The second sampling stage divided each PSU into blocks or groups of blocks containing household clusters.

NHANES oversampled specific populations that could be underrepresented with basic survey methodology and are of particular public health interest. In the 2005-2006 sampling timeframe, Mexican-American, Black, low-income White, and other persons (at or below 130% of federal poverty level); adolescents aged 12–19; and non-Hispanic White and other adults aged 70 and over were oversampled (National Center for Health Statistics [U.S.], 2013). In the 2007-2008 sampling timeframe Hispanic, non-Hispanic Black, low-income non-Hispanic White, and other persons (at or below 130% of federal poverty level); and non-Hispanic White and other adults aged 80 and over were oversampled (National Center for Health Statistics [U.S.], 2013).

Results

Descriptive Characteristics

The NHANES survey is a national survey that collects data from approximately 5,000 participants within the U.S. population each year such that the data will enable extrapolation to the U.S. population (CDC, 2011). A total of 10,348 participants were included in the 2005-2006 NHANES survey; 9,950 and 398 participants were administered interviews and examinations or interviews alone, respectively (CDC, 2009a). Data from these participants was collected from November 1, 2005 to October 31, 2006. A total of 10,149 participants were included in the 2007-2008 NHANES survey; 9,762 and 387 participants were administered interviews and examinations or interviews alone, respectively (CDC, 2009b). Data from these participants was collected from November 1, 2007 to October 31, 2008. The sample for these analyses was limited

to those survey participants that had data for both the dependent (AMD) and independent variables (SDB). Only those survey participants that were 40 years and older were eligible to have ophthalmology examinations, therefore by definition the sample only included individuals above this age cut-off. The available cases for analyses are detailed in Figure 4.

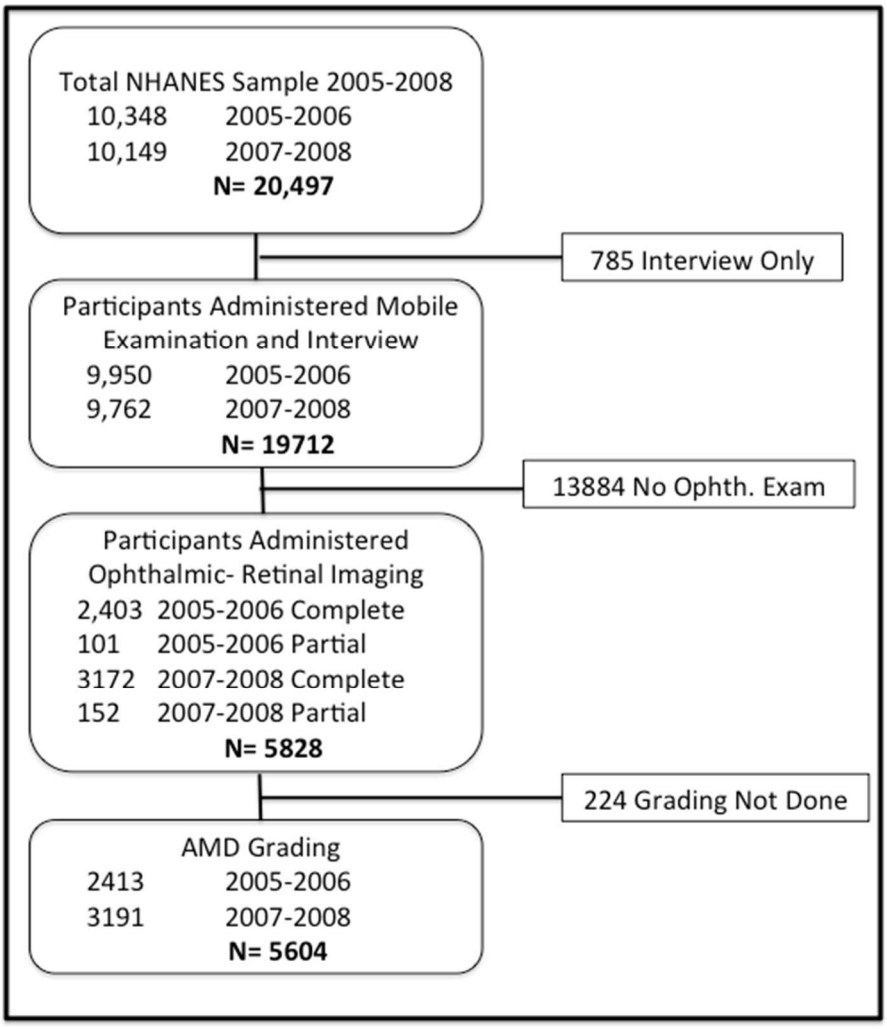

Figure 4. Participant flowchart detailing the number of cases available for analysis.

In Table 6, I report the frequencies and percentages of the sociodemographic characteristics of the unweighted NHANES sample (*n* = 20,497), the unweighted study sample (n=5,604) and the weighted study sample (*n* = 227,456,895). During the survey periods 2005-2006 and 2007-2008, 20,497 participants were interviewed and/or examined in NHANES. Only those participants ≥ 40 had the option of participating in the ophthalmology-retinal imaging examination and therefore the available sample size for this study was 5,604 participants (Figure 4). As AMD presents rarely before the age of 40 years, this inherent age cut-off due to the NHANES examination methodology did not adversely alter the study sample. The weighted sample demographics are provided in Table 6 to allow estimates of the parameters that would have been obtained were the entire U.S. population surveyed (CDC, 2009b).

Table 6

Sociodemographic characteristics of NHANES Sample, Study Sample, and Weighted Study Sample

Characteristic	NHANES Sample[1,2] N=7,081 n (%)	Study Sample[1] N=5604 n (%)	Weighted Study Sample N=227,456,895 (%)
Age			
40-59	3357 (47.4)	2829 (50.5)	64.4
≥ 60	3724 (52.6)	2775 (49.5)	35.6
Gender			
Women	3575 (50.5)	2793 (49.8)	52.6
Men	3506 (49.5)	2811 (50.2)	47.4
Race/Ethnicity[3]			
Non-Hispanic White	3688 (52.1)	3017 (53.8)	77.1
Non-Hispanic Black	1514 (21.4)	1139 (20.3)	9.6
Other Hispanic	518 (7.3)	864 (15.4)	7.6
Mexican American	1103 (15.6)	40 (7.2)	4.7
Other race	258 (3.6)	183 (3.3)	NA[2]
Smoking status[4]			
Nonsmoker	3433 (48.5)	2648 (47.3)	48.5
Past smoker	2248 (31.8)	1812 (32.3)	30.9
Current smoker	1391 (19.7)	1142 (20.4)	20.6
Diabetes status			
No	5744 (81.2)	4643 (83.0)	87.4
Yes	1329 (18.8)	954 (17.0)	12.6
BMI			
Normal	1724 (26.3)	1410 (25.7)	27.5
Overweight	2328 (35.5)	1973 (35.9)	35.3
Obese	2505 (38.2)	2109 (38.4)	37.2

[1]Unweighted

[2]NHANES sample of those participants >40 years of age

[3]Weighted estimates not provided for "other race" category that includes multiple ethnic groups.

[4]Nonsmoker was defined as a respondent who had not smoked at least 100 cigarettes in their life; a past smoker was defined as a respondent who had smoked at least 100 cigarettes in their life although do not now smoke cigarettes, current smoker

defined as survey respondents who have smoked at least 100 cigarettes in their life and now smoke cigarettes.

The sample included slightly more men (51.2%) than women. The sample also include more Non-Hispanic Whites (51.2%) than the combined other races/ethnicities. Half of the sample responded that they were nonsmokers, while 17% reported having received a diagnosis of diabetes. Of note, a higher percentage of the sample was identified as obese rather than overweight or normal based on the CDC definitions using BMI.

As I was unable to use the entire sample for NHANES 2005–2008 due to the need for the AMD grading, I used the chi-square Goodness of Fit test to compare my sample to the NHANES sample over the age of 40. The results of this analysis are presented in Table 7.

Table 7

Goodness of Fit Results from Comparison of NHANES and this Study's Sample

Characteristic	Chi-square	*p* value
Age	0.64	0.42
Gender	0.04	0.84
Race/ethnicity	17.01	0.002
Diabetes	0.26	0.61
BMI	0.21	0.90

These results suggest that the sample I used was not significantly different from the original sample in all sociodemographic variables except race/ethnicity. As the weighting is based on the entire NHANES sample, I had to use caution in my

interpretation of race/ethnicity. The impact of this is minimal in later analyses as only age, smoking status, and BMI were included in my models as potential confounders.

Table 8 summarizes the SDB variables for the unweighted NHANES sample (n=7,081), the unweighted study sample (n=5,604) and the weighted study sample (n=227,456,895).

Table 8

SDB characteristics of NHANES Sample, Study Sample, and Weighted Study Sample

Characteristic	NHANES Sample[1,2] N=7,081 n (%)	Study Sample[1] N=5604 n (%)	Weighted Study Sample N=227,456,895 (%)
Any diagnosed sleep disorder[3]			
No	6431 (90.8)	5088 (90.8)	95.3
Yes	650 (9.2)	516 (9.2)	4.7
Diagnosed sleep apnea			
No	6656 (94.7)	5260 (94.5)	97.4
Yes	373 (5.3)	305 (5.5)	2.6
Snoring			
No	3869 (62.6)	3048 (61.7)	70.0
Habitual	2315 (37.4)	1891 (38.3)	30.0
Snorting/stop breathing			
No	5913 (93.1)	4705 (93.2)	97.1
Yes	435 (6.9)	343 (6.8)	2.9
Diagnosed insomnia			
No	6905 (98.2)	5468 (98.3)	99.6
Yes	124 (1.8)	97 (1.7)	0.4
Prolonged sleep latency[4]			
Negligible	5825 (82.3)	4624 (82.5)	83.1
Mild to moderate	658 (9.3)	512 (9.1)	8.0
Severe	591 (8.3)	466 (8.3)	8.9
Nocturnal awakenings[4]			
Negligible	5513 (78.0)	4351 (77.7)	75.9
Mild to moderate	918 (13.0)	753 (13.4)	15.0
Severe	640 (9.1)	499 (8.9)	9.1
Hypersomnolence[4]			
Negligible	5870 (83.1)	4675 (83.5)	82.3
Mild to moderate	754(10.7)	599 (10.7)	11.1
Severe	442 (6.3)	324 (5.8)	6.6
Sleep duration			
≥6 hours	5916 (83.5)	4706 (84.0)	89.4
< 6 hours	1165 (16.5)	898 (16.0)	10.6

[1]Unweighted

[2]NHANES sample of those participants >40 years of age

[3]Sleep Disorders categorized as sleep apnea, insomnia, restless leg syndrome, other

[4]Prolonged Sleep Latency, Nocturnal Awakenings, and Hypersomnolence defined as Severe (Almost Always 16-30 times a month); Mild to Moderate (Often 5-15 times a month); Negligible (Sometimes 2-4 times a month; Rarely 1 time a month; Never).

Nine percent of participants self-reported that they had been diagnosed with a sleep disorder; 6% and 2% were diagnosed with sleep apnea and insomnia, respectively. In contrast 38% of participants self-reported snoring more than 5 or more nights per week and 18% reported receiving less than 6 hours of sleep on average.

There were more participants providing responses to the sleep questionnaire than participated in the mobile examination center data collection of retinal fundus photos. Therefore, the sample size of the study sample is limited by the availability of data from the masked grading of fundus photos. Figure 5 illustrates the AMD demographics (worse eye) based on grading performed using the modified Wisconsin Age-Related Maculopathy Grading System. Overall the prevalence of any AMD in the study sample was 7.9% with 6.9% categorized as early AMD and 1.0% as late AMD. Of the participants with late AMD, 0.6% and 0.4% were graded as having geographic atrophy and choroidal neovascularization, respectively.

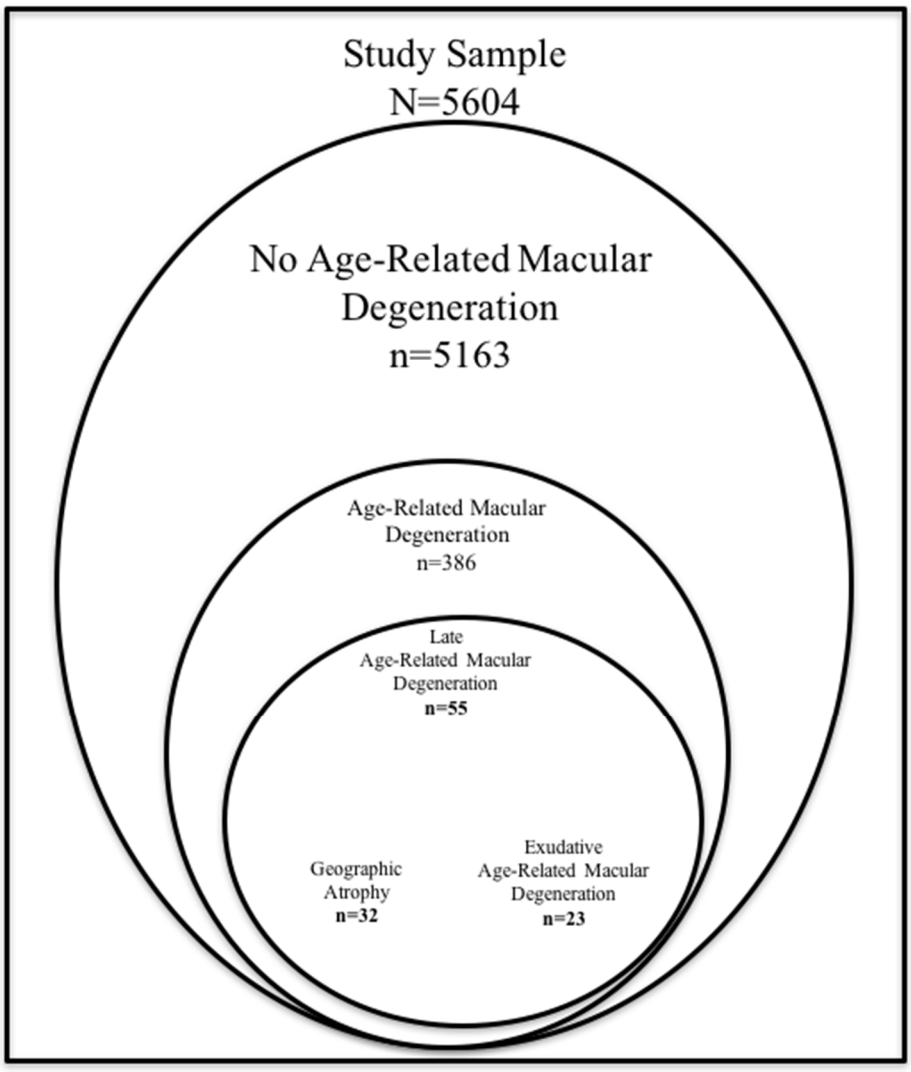

Figure 5. AMD demographics (worse eye) in 5604 participants in the NHANES 2005–2008 survey.

Research Question 1: Chi-Square Analyses

In the first research question, I asked whether there is an association between self-reported SDB and fundus photography identified AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey. A preliminary chi-square test for

association was conducted between the presence or absence of AMD and sociodemographic characteristics of the study sample. The results of these analyses are presented in Table 9.

Table 9

Chi-square Test of Association between AMD and Sociodemographic Characteristics

Characteristic	No AMD n=5163 n (%)	Any AMD n=441 n (%)	*p* Value[1]
Age			<.001
40-59	2753 (53.3)	76 (17.2)	
≥ 60	2410 (46.7)	365 (82.8)	
Gender			.439
Women	2581 (50.0)	212 (48.1)	
Men	2582 (50.0)	229 (51.9)	
Race/Ethnicity			<.001
Non-Hispanic White	2703 (52.4)	314 (71.2)	
Non-Hispanic Black	1103 (21.4)	36 (8.2)	
Other Hispanic	376 (15.7)	25 (12.0)	
Mexican American	811(3.3)	53 (2.9)	
Other race	170 (7.3)	13 (5.7)	
Smoking status[2]			<.001
Nonsmoker	2451 (47.5)	197 (44.7)	
Past smoker	1634 (31.7)	178 (40.3)	
Current smoker	1076 (20.8)	66 (15.0)	
Diabetes status			.791
No	4280 (83.0)	363 (82.5)	
Yes	877 (17.0)	77 (17.5)	
BMI[3]			.021
Normal	1290 (25.5)	120 (27.8)	
Overweight	1800 (35.6)	173 (40.0)	
Obese	1970 (38.9)	139 (32.2)	

[1] χ^2 test for association was conducted, $p < .05$

[2]Nonsmoker defined as survey respondents that have not smoked at least 100 cigarettes in their life, past smoker defined as survey respondents that have smoked at least 100

cigarettes in their life although do not now smoke cigarettes, current smoker defined as survey respondents that have smoked at least 100 cigarettes in their life although and now smoke cigarettes.
[3]BMI categories as defined by CDC

All expected cell frequencies were greater than five. There was a statistically significant association between AMD and age, $\chi 2$ ($df = 1$) = 211.68, $p < .001$; race/Ethnicity, $\chi 2$ ($df = 4$) = 66.86, $p < .001$; smoking status, $\chi 2$ ($df = 2$) = 17.09, $p < .001$; and BMI, $\chi 2$ ($df = 2$) = 7.76, $p = .021$. There was no association between AMD and gender or diabetes status. Thus, those variables were not included as potential confounders in the remaining analyses.

A chi-square test for association was conducted between AMD and SDB characteristics of the study sample. The results are presented in Table 10.

Table 10

Chi-square Test of Association between AMD and SDB Characteristics

Characteristic	No AMD n=5163 n (%)	Any AMD n=441 n (%)	*p* Value[1]
Any diagnosed sleep disorder			.004
No	4671 (90.5)	417 (94.6)	
Yes	492 (9.5)	24 (5.4)	
Diagnosed sleep apnea			.015
No	4833 (94.3)	427 (97.0)	
Yes	292 (5.7)	13 (3.0)	
Snoring			.144
No	2804 (61.4)	244 (65.2)	
Habitual	1761 (38.6)	130 (34.8)	
Snorting/stop breathing			.022
No	4324 (93.0)	382 (96.0)	
Yes	327 (7.0)	16 (4.0)	
Diagnosed insomnia			.311
No	5033 (98.2)	435 (98.9)	
Yes	92 (1.8)	5 (1.1)	
Prolonged sleep latency[2]			.172
Negligible	4254 (82.4)	370 (83.9)	
Mild to moderate	482 (9.3)	30 (6.8)	
Severe	425 (8.2)	41 (9.3)	
Nocturnal awakenings[2]			.503
Negligible	4014 (77.8)	337 (76.4)	
Mild to moderate	695 (13.5)	58 (13.2)	
Severe	453 (8.8)	46 (10.4)	
Hypersomnolence[2]			.230
Negligible	4318 (83.7)	357 (81.1)	
Mild to moderate	549 (10.6)	50 (11.4)	
Severe	291 (5.6)	33 (7.5)	
Sleep duration			.087
≥6 hours	4323 (83.7)	383 (86.8)	
< 6 hours	840 (16.3)	58 (13.2)	

[1] χ^2 test for association was conducted, $p < .05$

[2]Prolonged Sleep Latency, Nocturnal Awakenings, and Hypersomnolence defined as Severe (Almost Always 16-30 times a month); Mild to Moderate (Often 5-15 times a month); Negligible (Sometimes 2-4 times a month; Rarely 1 time a month; Never)

All expected cell frequencies were greater than five. There was a statistically significant association between AMD and self-reported diagnosis of any sleep disorder, χ^2 (1) = 8.119, p=.004; self-reported diagnosis of sleep apnea, χ^2 (1) = 5.89, p=.015; and self-reported snorting/gasping/stop breathing χ^2 (1) = 5.25, p=.022. There were no associations between AMD and snoring, insomnia, prolonged sleep latency, nocturnal awakenings, hypersomnolence, or sleep duration.

Research Question 1: Complex Samples OLR. To address the hypotheses associated with these research questions, I included the variable for the 3-level AMD severity (dependent variable) and the nine SDB (independent variables) included separately in the models and then adjusted for covariates. As NHANES uses a complex, multistage, probability sampling design (including oversampling) to select participants, I elected to use the Complex Samples OLR procedure in SPSS for analyses. Weighting variables were applied to assure that the output is representative of the U.S. civilian noninstitutionalized 2000 Census population (CDC, 2009a, 2009b). The dependent variable was the categorical AMD severity scale (no AMD, early AMD, and late AMD) determined from the grading of fundus photos. Independent variables were tested for multicollinearity in SPSS using the linear procedure. All tolerance values were greater than 0.1 (the lowest value was 0.639) and Variance Inflation Factor (VIF) values were less than 10 (the highest value was 1.565), indicating that the assumption related to multicollinearity was met. The results of the OLR models for the association of AMD and SDB characteristics are presented in Table 11.

Table 11

Ordinal Logistic Regression Models: Association of SDB and AMD

Outcome variable	Unadjusted OR (95% CI)	*p* Value[1]	Adjusted[2] OR (95% CI)	*p* Value[1]
Any diagnosed sleep disorder	2.2 (1.2-3.9)	.009	2.0 (1.2-3.6)	.015
Diagnosed sleep apnea	2.6 (1.4-5.1)	.005	2.6 (1.3-4.9)	.006
Snoring	1.5 (1.1-2.0)	.018	1.3 (1.0-1.8)	.070
Snorting/stop breathing	2.8 (1.3-6.0)	.010	2.4 (1.1-5.1)	.024
Diagnosed insomnia	3.1 (1.1-9.0)	.029	2.3 (0.9-6.4)	.095
Prolonged sleep latency				
Mild to moderate vs. Negligible	1.3 (0.8-1.9)	.454	1.1 (0.7-1.7)	.430
Severe vs. Negligible	0.9 (0.5-1.5)	.454	0.8 (0.5-1.3)	.430
Nocturnal awakenings				
Mild to moderate vs. Negligible	1.0 (0.6-1.5)	.186	0.9 (0.6-1.4)	.693
Severe vs. Negligible	0.9 (0.6-1.4)	.186	0.8 (0.6-1.1)	.693
Hypersomnolence				
Mild to moderate vs. Negligible	1.0 (0.6-1.7)	.752	1.0 (0.5-1.6)	.444
Severe vs. Negligible	0.8 (0.4-1.5)	.752	0.7 (0.3-1.3)	.444
Sleep duration	1.3 (0.8-2.1)	.232	1.2 (0.8-1.8)	.493

[1] Complex Samples Ordinal Logistic Regression was conducted, $p < .05$
[2]The SDB variables were adjusted for age, BMI, and smoking status.

Models are presented unadjusted as well as adjusted for age, BMI, and smoking status. Though race/ethnicity was significantly associated with AMD in the chi-square analysis as presented in Table 9, this association was negated with the addition of the SDB variables; thus, this variable was not included as a potential confounder in the

multivariate analysis. Participants with AMD were associated with self-reported diagnosis of any sleep disorder (OR, 2.2; 95% CI, 1.2-3.9), self-reported diagnosis of sleep apnea (OR, 2.6; 95% CI, 1.4-5.1), and self-reported snorting/stop breathing (OR, 2.8; 95% CI, 1.3-6.0). Association between AMD and snoring (OR, 1.5; 95% CI, 1.1-2.0) and between AMD and Insomnia (OR, 3.1; 95% CI, 1.1-9.0) were significant in unadjusted models, although once I controlled for the covariates, did not exhibit a significant association. Prolonged sleep latency, nocturnal awakenings, hypersomnolence, and sleep duration were not associated with AMD.

A multivariate model was built with independent variables and covariates that were statistically significant with a p value of < 0.1 based on any of the OLR analyses of the unadjusted/adjusted models illustrated in Table 11. Independent variables included in the model were diagnosed sleep apnea, snoring, snorting/stop breathing, and diagnosed insomnia. Although the p value for any diagnosed sleep disorder met the threshold for inclusion, this variable was inclusive of the variables for sleep apnea and insomnia (also included choices of restless leg syndrome and other) and did not present as having as strong of an association as diagnosed sleep apnea alone. Insomnia was statistically significant in the unadjusted model and was therefore included. Covariates that were included in the multivariate model were age, smoking, and BMI. The results of the multivariate model are presented in Table 12.

Table 12

Multivariate Model for Association of SDB and AMD

Outcome variable	OR (95% CI)	*p* Value[1]
Diagnosed sleep apnea	2.2 (1.1-4.5)	.03
Snoring	1.1 (0.8-1.5)	.45
Snorting/stop breathing	2.4 (1.3-4.5)	.007
Diagnosed insomnia	1.8 (0.6-5.2)	.30
Age	5.3 (3.5-8.0)	<.001
Smoking	1.1 (0.8-1.3)	.31
BMI	0.9 (0.8-1.1)	.28

[1] Based on complex samples ordinal logistic regression.

In the multivariate model, I found significant associations between diagnosed sleep apnea, snorting/stop breathing, and age; and AMD. Thus, I was able to reject the null hypothesis associated with RQ 1.

Cox & Snell R^2, Nagelkerke R^2, and McFadden R^2 tests were performed for all models to compare the relative strength of each model. These are presented in Table 13.

Table 13.

Cox & Snell R^2, Nagelkerke R^2, and McFadden R^2 Values, by Model

Outcome Variable	Cox & Snell R^2	Nagelkerke R^2	McFadden R^2
Any diagnosed sleep disorder	.042	.101	.080
Diagnosed Sleep Apnea	.043	.103	.082
Snoring	.040	.099	.079
Snorting/Gasping/Stop breathing	.040	.098	.078
Multivariate Model[1]	.045	.109	.087

[1] Reported for those variables exhibiting a statistically significant (p<.1) association with AMD severity in Complex Samples Ordinal Logistic Regression models (variables included in the equation were diagnosed sleep apnea, diagnosed insomnia, snoring, snorting/gasping/stop breathing, snoring, age, smoking, and BMI).

Whether I referenced the Cox & Snell R^2, Nagelkerke R^2, or McFadden R^2 methods the pseudo R^2 for any diagnosed sleep disorder alone ranges from 4.2% to 10.1%. The pseudo R^2 based on the self-reported diagnosis of sleep apnea model ranges from 4.3% to 10.3%. The pseudo R^2 based on the snoring model ranges from 4.0% to 7.9%. The pseudo R^2 based on the self-reported snorting/gasping model ranges from 4.0% to 9.8%. The pseudo R^2 based on the multivariate model ranges from 4.5% to 10.9%. This suggests that the multivariate model is the strongest one, though none can be considered predictive.

The assumption of proportional odds was tested in SPSS by performing separate binomial logistic regressions on cumulative dichotomous dependent variables. NHANES provides a collapse of Early AMD and Late AMD to form the Any AMD variable as well as the collapse of the No AMD and Early AMD to form the Late AMD variable. Table 14 summarizes the odds ratios and 95% CI for each independent variable for the two logistic regression analyses.

Table 14

Proportional Odds Testing: Separate Binomial Logistic Regression Models

Outcome variable	No AMD vs. Any AMD OR (95% CI)[1]	No Late AMD vs. Late AMD OR (95% CI)[1]
Diagnosed sleep apnea	2.2 (1.1-4.5)	NA[2]
Snoring	1.1 (0.8-1.5)	NA[2]
Snorting/stop breathing	2.4 (1.3-4.4)	NA[2]
Diagnosed insomnia	1.8 (0.7-5.0)	NA[2]
Smoking	1.0 (0.6-1.7)	NA[2]
Age	5.5 (3.8-7.9)	NA[2]
BMI	1.2 (0.9-1.6)	NA[2]

[1] Complex Samples Logistic Regression
[2] A quasi-complete separation was detected in the data; therefore the results should be interpreted with caution.

The number of participants in the late AMD category was small and a complete separation occurred when performing the logistic regression. Therefore, the results should be interpreted with caution, as the assumption of proportional odds was not met.

Research Question 2 and 3: Complex Samples Logistic Regression

Research questions 2 and 3 were performed to investigate the association of SDB variables with choroidal neovascularization and geographic atrophy, respectively. Based on the complete separation that occurred when assessing proportional odds for RQ 1 and performing logistic regression using Late AMD as the dependent variable, I decided to collapse the choroidal neovascularization and geographic atrophy variables for analysis. Combining these variables modified RQ 2 and 3 into the following single research question:

Research Question 2: Is there an association between self-reported SDB and fundus photography identified late AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey after controlling for age, smoking, and BMI?

$H_0$2: There is no association between self-reported SDB and fundus photography identified late AMD among adults 40 years and older who participated in the NHANES 2005 to 2008 survey after controlling for age, smoking, and BMI.

$H_1$2: There is an association between self-reported SDB and fundus photography

identified late AMD among adult 40 years and older who participated in the NHANES 2005 to 2008 survey after controlling for age, smoking, and BMI.

Late AMD was a variable provided in the NHANES dataset and therefore no recoding of variables was necessary. The variable for Late AMD (dependent variable) and the omnibus variable for Any Diagnosed Sleep Disorder (independent variable) were used to assure model saturation and to address the hypothesis associated with this question. The results of the Complex Samples Logistic Regression are presented in Table 15.

Table 15

Multivariate Model of the Association of Late AMD and Any Diagnosed Sleep Disorder

Outcome Variable	OR (95% CI)	*p* Value[1]
Any Diagnosed Sleep Disorder	0.8 (0.2-4.2)	.74
Age	130.8 (16.6-1030.8)	<.001
Smoking	0.9 (0.6-1.3)	.66
BMI	0.6 (0.4-1.0)	.04

[1] Complex Samples Logistic Regression $p < .05$

In this model, there was no association of late AMD to any diagnosed sleep disorder. Thus, I was unable to reject the null hypothesis.

Summary

The first hypothesis tested whether there was an association between self-reported SDB and fundus photography identified AMD among adults 40 years and older who participated in the 2005–2008 NHANES survey. Diagnosed sleep apnea, self-reported snorting/stop breathing, snoring, and diagnosed insomnia were all identified as risk

factors for AMD based on OLR analyses. A multivariate model that included the variables sleep apnea, self-reported snorting/stop breathing, snoring, diagnosed insomnia, age, and BMI provided the best model fit. However, the results should be interpreted with caution, as the assumption of proportional odds was not met. The second and third hypotheses of an association between self-reported SDB and choroidal neovascularization or geographic atrophy, respectively had to be collapsed based on the small sample size of these late AMD subpopulations. Therefore, the second hypothesis that was tested was the association of any diagnosed sleep disorder with late AMD. There was no association between any diagnosed sleep disorder and late AMD based on binary logistic regression.

I provide a detailed interpretation of the results in Chapter 5 and a comparison of these results to evidence available with regards to the association between SDB and AMD in the current literature. The limitations and strengths of the study will be evaluated. Lastly, recommendations for additional research as well as the potential impact that these research findings may have on social change and public health will be discussed.

Chapter 5: Discussion

Introduction

By the year 2050, the estimated number of people with AMD in the United States is expected to more than double, from 2.07 million to 5.44 million (National Eye Institute, 2016a). Although there has been much progress over the last decade in understanding the etiology of AMD, an understanding of the factors associated with the development and/or progression of AMD is still missing.

In this study, quantitative data from the 2005–2008 NHANES survey were used to explore the association between SDB and AMD. SDB has been shown to interfere with current anti-VEGF treatments for neovascular AMD. Barak et al. (2012) reported that OSA hampered the response to anti-VEGF therapy for the treatment of neovascular AMD. Khurana et al. (2016) demonstrated that sleeping more than 8 hours a day was associated with geographic atrophy. These results were also corroborated by research from Perez-Canales et al. (2016), who found a statistically significant association between sleep duration and AMD. In addition, Keenan et al. (2016) reported that OSA was positively associated with AMD. To date, there have been no published studies of population-based research on the association between various SDB measures and AMD.

In Chapter 5, I interpret my findings in relation to those of previous studies and the life course theory. I discuss the limitations of this research and suggest future research that is needed to address those limitations. Finally, I discuss the significance of this research in terms of its significance and potential to contribute to positive social change.

Interpretation of Findings

According to the findings of this study, SDB is associated with AMD. The association of a number of SDB variables with AMD remained statistically significant even after controlling for the sociodemographic characteristics of age, smoking status, and BMI. This is the first known? study on the association of numerous SDB characteristics with AMD in a nationally representative population of the United States.

Study Sample and Sociodemographic Characteristics

This study evaluated potential sociodemographic characteristics that could be relevant to investigating the association between SDB and AMD using a nationally representative sample. The NHANES sample from 2005–2008 was oversampled for certain race/ethnicity groups, namely Mexican Americans and Hispanics. The analysis I performed indicated that there is a statistically significant difference in race/ethnicity between the NHANES sample and the study sample. This is likely explained by the fact that fewer Mexican Americans had their retinal photos obtained because only 22% of the population was over the age of 40. To account for this oversampling, all analyses were performed using the weighting factors provided by NHANES.

Preliminary chi-square analysis was performed to understand the association between AMD and the predefined sociodemographic characteristics (see Table 9). Age, race/ethnicity, smoking status, and BMI illustrated a statistically significant relationship with AMD. This was not unexpected because risk factors for AMD have been previously reported in the peer-reviewed literature: increasing age (E. Chew et al., 2014; Tomany et

al., 2004), non-Hispanic White race/ethnicity (T. Wong et al., 2002), past/current smoking status (E. Chew et al., 2014), and elevated BMI (Q. Zhang et al., 2016). There was a clear difference in the age categorizations of the population of participants without AMD as compared to those with AMD. In the group of participants without AMD, 47% of participants were >60 years of age, while in the group of participants with AMD 83% were >60 years of age. The population of non-Hispanic White in the AMD population was 71% compared to 53% in the population without AMD. Conversely, there were fewer non-Hispanic Black participants (8%) in the population with AMD as compared to those without AMD (21%). These racial/ethnic differences are consistent with previous reports from NHANES as well as other epidemiological studies, though with the addition to the model of the SDB variables, the observed association was negated (Klein et al., 2011; Klein, Clegg, et al., 1999; Klein, Klein, et al., 1999; Klein et al., 2006). The number of current smokers in the population with AMD was 15%, while 21% of participants with no signs of AMD reported currently smoking. The number of current smokers in the 40-59-year-old category was 27%, while there were only 13% current smokers in the ≥ 60-year-old category. These findings are consistent with current CDC data showing that fewer people aged ≥65 are current smokers (Jamal et al., 2015). The number of participants reporting as a past smoker in the ≥ 60-year-old category was 42%, outweighing the 23% in the 40-59-year-old category responding as past smokers. In these analyses, past smokers were defined as anyone who smoked over 100 cigarettes in their lifetime. This definition allows for a significant amount of potential variation within the

group as it pertains to the overall exposure (packs of cigarettes smoked, years of smoking, etc.) to the harmful effects of smoking.

There was no apparent association with gender or diabetes status in the study sample. Those sociodemographic characteristics that illustrated a statistically significant association ($p < 0.1$) with AMD were included in adjusted models for all SDB characteristics as well as multivariate models.

As the study sample consisted of all available participants in an attempt to be able to study the smaller late AMD population, it was important to investigate whether the study sample was representative of the NHANES sample. A chi-square Goodness of Fit was performed to assess whether the study sample was similar to the overall NHANES sample as it pertained to these characteristics. Only gender and smoking status were found to reflect the NHANES sample. The other characteristics were statistically significant illustrating a dissimilar distribution in both populations. As age and BMI are included in the multivariate analysis and weighting is based on the original sample, I must use caution when interpreting the association of these variables to AMD.

Association of SDB with AMD

Preliminary chi-square analysis was performed to investigate the association of a number of SDB characteristics with AMD (Table 10). There was a statistically significant association with AMD in participants that self-reported a doctors' diagnosis of any sleep disorder or sleep apnea. In addition, there was a statistically significant association with AMD in those participants reporting snorting, gasping, or cessation of breathing. There

were no associations between AMD and snoring, insomnia, prolonged sleep latency, nocturnal awakenings, hypersomnolence or sleep duration. Regardless of association, SDB variables were included in both adjusted and unadjusted OLR models.

Any sleep disorder. SDB variables were analyzed using Complex Samples OLR models (Table 10). Those participants with any self-reported diagnosed sleep disorder (sleep apnea, insomnia, restless leg syndrome, or other) were two times (OR, 2.2; 95% CI, 1.2-3.9) more likely to have AMD than those without a diagnosed sleep disorder. This is the first report of an association with an open-ended query for any diagnosed sleep disorders from a population based sample. The association remained statistically significant even after adjustment for covariates (age, smoking status, and BMI). As the understanding and identification of sleep disorders has evolved and improved over the last decade, it is possible that the number of participants with diagnosed sleep disorders is low during the 2005–2008 survey periods as compared to more recent sampling frames. The HypnoLaus study that collected data from 2009-2013 reported SDB prevalence to be as high as 49% and 23% of men and women in Switzerland, respectively (Heinzer et al., 2015). It has been postulated that this higher prevalence is due to the improved sensitivity of SDB recording techniques and to a newer definition of respiratory events (particularly the hypopnea definition) (Heinzer, 2016).

Sleep apnea. Sleep apnea has been previously reported to be associated with AMD in a large national health service cohort in the United Kingdom (Keenan et al., 2016). The current study based on the U.S. population corroborates these findings with

those with a diagnosis of sleep apnea 2.6 times (OR, 2.6; 95% CI, 1.4-5.1) more likely to develop AMD as compared to those participants without diagnosed sleep apnea. The odds of having AMD in participants with sleep apnea remained unchanged even after adjustment for sociodemographic variables. Fraser et al. (2013) performed a prospective fundus photographic study of patients undergoing PSG in a community sleep center. Retinal vascular changes were much more common in patients with sleep apnea, even after controlling for history of diagnosed hypertension (Fraser et al., 2013). AHI>40 conferred a doubling of the odds of retinal vascular changes as compared to those with AHI<5, even after controlling for confounding variables. Research by Nesmith et al. (2014) provided some insight into an underlying mechanism whereby sleep apnea is shown to exert pathological changes on the underlying retinal vasculature. In their study, the researchers investigated patients that were refractory (defined as persistent subretinal fluid after 3 consecutive injections) to treatment with anti-VEGF medications, the current standard of care for neovascular AMD. VEGF blocking agents have been shown to exert their effects on the retina by reducing vascular permeability and improving retinal edema and subretinal fluid (CATT Research Group, 2011). The result that more patients with OSA in this study were found to have refractory subretinal fluid indicated that sleep apnea modifies retinal vascular permeability despite anti-VEGF therapy. This same phenomenon was noted by Barak et al. (2012) who also noted that the fluid accumulation could be reversed once CPAP therapy for sleep apnea was initiated.

One potential theory to explain the underlying etiology of this phenomenon is the presence of circulating inflammatory proteins. Zychowski et al. (2016) incubated human endothelial cells with serum from patients with sleep apnea and healthy controls. In patients with sleep apnea, the cell cultures resulted in greater serum inflammatory potential, thereby driving endothelial activation/dysfunction (Zychowski et al., 2016). Importantly, collecting serum from the same sleep apnea patients after initiation of CPAP therapy resulted in a reduction in endothelial cell inflammatory potential and activation/dysfunction. Sleep apnea is a chronic disease that goes undiagnosed in much of the affected population, sometimes for decades. Chronically exposing the vulnerable retina vasculature to recurrent hypoxia, resulting in persistent circulating inflammatory proteins, may explain the underlying cause for the association evident in this study.

Insomnia and Sleep Duration. This study is the first to look directly at the association of diagnosed insomnia with AMD. In the study sample, those with diagnosed insomnia were three times (OR, 3.1; 95% CI, 1.1-9.0) as likely to have AMD as those without a diagnosis of insomnia. When adjusted for sociodemographic characteristics, diagnosed insomnia no longer had a statistically significant association with AMD. Interestingly, insomnia has been associated with neurodegenerative disorders such as Alzheimer's and Parkinson's disease and the deposition of Aβ (Keene & Joiner, 2015). With Aβ deposition noted as a drusen component, I must consider the possibility that similar mechanisms could be at play with AMD pathogenesis promoted by SDB.

In this study, sleep duration did not demonstrate a statistically significant association with AMD. In the literature, AMD was shown to be associated with sleep duration, although the reports in the literature have been specific to geographic atrophy and choroidal neovascularization, and not early AMD (Khurana et al., 2016; Perez-Canales et al., 2016). The findings from the current study may be consistent with the literature reported associations with late AMD, although the OLR modelling was not designed to answer this question. In addition, there were a very small number of participants with late AMD in the study sample. I will discuss this lack of participants in the study sample with fundus photograph identified late AMD in more detail as it pertains to RQ 2.

Snorting/Gasping/Stop Breathing and Snoring. Snorting/Gasping/Stopping breathing during sleep is representative of a decrease in oxygen saturation that stimulates arousal and can be quantified using AHI scores. AHI values have been associated with a reduction in RNFL thickness (Huseyinoglu et al., 2014; Shiba et al., 2014). Snorting/Gasping/Stopping Breathing in this study was statistically significant for an association with AMD, illustrating a three (OR, 2.8; 95% CI, 1.3-6.0) times greater odds of having AMD. This continued to be statistically significant even after adjusting for covariates. Snoring was also significantly associated with AMD, introducing a 1.5 times (OR, 1.5; 95% CI, 1.1-2.0) greater likelihood of AMD. Snoring did not remain statistically significant after adjusting for covariates.

Prolonged Sleep Latency, Nocturnal Awakenings and Hypersomnolence. Prolonged sleep latency, nocturnal awakenings, and hypersomnolence, were not associated with AMD. The responses to these survey questions may be subject to significant recall bias as the answers may not be as easy to remember as compared to answering whether there was a previous doctor's diagnosis of sleep disorders such as sleep apnea or insomnia. Therefore, it is hard to interpret whether the lack of association is accurate, or if the instrument was not sensitive enough to detect the association.

Sociodemographic Characteristics

Age. As expected, increased age was highly statistically associated with AMD in all models. In the current study, using multivariate OLR modelling, age ≥60 conferred more than five times the likelihood of developing AMD as compared to those in the 45-59-year-old category. The increased odds associated with increasing age were consistent and statistically significant across all adjusted models and in multivariate modelling. Even with the advent of anti-VEGF therapy, AMD is a leading cause of permanent blindness in adults aged 60 and older in the United States, and present in more than 14% of White Americans over the age of 80 (NEI, 2016a).

Smoking. Smoking has been consistently shown in the literature to be the most strongly associated modifiable risk factor for AMD (E. Chew et al., 2014; Evans, Fletcher, & Wormald, 2005). In this study, smoking was strongly associated AMD when assessed using the chi-square test of association ($p < .001$). When smoking was

incorporated into multivariate models, the OR was 1.1 indicating a non-statistically significant contribution to the prediction of AMD.

BMI. BMI has previously been shown to be mildly associated with AMD (Q. Zhang et al., 2016) and significantly associated with SDB (Heinzer et al., 2015). In this study, BMI was associated with AMD when assessed using the chi-square test of association ($p < .02$). When BMI was incorporated into the multivariate models this statistically significant association with AMD was negated.

Multivariate Modelling. Multivariate modelling was performed on independent variables and covariates that demonstrated a statistically significant association ($P<0.1$) with chi-square tests of association and/or OLR. A model was built that included diagnosed sleep apnea, diagnosed insomnia, snoring, snorting/gasping/stop breathing, and snoring as independent variables. Age, smoking status, and BMI were included as covariates. The multivariate model provided the best model fit compared to all other univariate models.

Association of SDB with Late AMD

Keenan et al. (2016) demonstrated an association between AMD and sleep apnea in a record linkage study from the United Kingdom. Based on this data, and the findings from Fraser et al. (2013) that illustrated increased prevalence of vascular changes with sleep apnea, I hypothesized that sleep apnea may be associated with choroidal neovascularization. Additionally, Khurana et al. (2016) have shown an association with

sleep duration and geographic atrophy, so it is plausible that a diagnosed sleep disorder may have an association with atrophic changes in the retina.

The prevalence of AMD in the study sample was 6.9%, consistent with estimates from the same survey periods previously reported by Klein et al (2011). Late AMD was present in only 1.0% of the sample; therefore, adjustments were made to the original analysis plan which divided choroidal neovascularization and geographic atrophy into separate research questions. As the presence of late AMD disease was so rare in the study sample, I collapsed the choroidal neovascularization and geographic atrophy categories to form a single late AMD variable for analyses. Similarly, the omnibus variable for any diagnosed sleep disorder (NHANES questionnaire choices included sleep apnea, insomnia, restless leg syndrome, and other) was used in the analysis to assure model saturation. The model included the covariates of age, smoking status, and BMI as used in the OLR analyses. There was no association found with any diagnosed sleep disorder and AMD. Based on a post-hoc power calculation, it would take approximately 1039 participants to detect a moderate OR of 1.5. Therefore, it is likely that the available number of participants in the study sample with late AMD (n=55) was not robust enough to provide the power to detect an association.

Overall Findings

In using the life course theory of chronic disease as the framework for this quantitative cross-sectional study, I was able to find significant associations between a number of SDB variables and AMD. Although the OLR analyses did not meet the

assumption of proportional odds due to the small number of participants with late AMD, the ORs from the OLR were almost identical when performing separate binomial logistic regression for any AMD. These findings provide confidence that the interpretation of association is valid and that it is primarily driven by the participants with early AMD in this sample. The application of the life course theory of chronic disease in this study posited that SDB would have a temporal relationship with presentation of early AMD in exposed participants. As previously stated, there is a temporal relationship between the age of peak presentation of SDB and the age at which signs associated with early AMD are evident (Bixler et al., 1998; Bourne et al., 2014). The findings of the current study implicated SDB as a factor along the life course of the AMD patient and represent another modifiable risk factor that could be addressed with public health intervention.

There are several strengths of the current study. First, the dependent variable for AMD was assessed using independent grading of retinal photographs. This allowed for a highly objective measure to assess AMD classification and eliminated participant recall biases that would be present if this data was collected from a questionnaire. Second, the study participants are a nationally representative sample of the U.S. civilian non-institutionalized population from the NHANES 2005–2008 survey. The sample has a nearly equal distribution of men and women and has been over-sampled to allow for an assessment of association in under-represented racial/ethnic groups. The multi-stage sampling scheme employed by NHANEs may reduce the referral biases that have been noted in studies using sleep-clinic based populations (Seicean et al., 2011). Lastly, a

robust set of statistical analyses was performed by applying chi-square, OLR, and multivariate logistic regression analyses to examine the associations between AMD and SDB.

Limitations of the Study

There are several limitations to this study. The NHANES survey is a cross-sectional survey by design, and therefore the data was collected at one single point in time. Due to this limitation, longitudinal trends in health behavior cannot be examined. This study is correlational in nature, and as such, care must be taken when interpreting the results. Although statistically significant associations were identified between AMD, SDB-related variables, and other covariates; causality cannot be assessed.

Although one of the strengths of this study is that the AMD variable was assessed by independent photography graders using a standardized protocol and definitions for findings, the SDB variables were all questionnaire derived. Recall bias may have led to misclassification of participants that could have impacted my results. The gold standards for defining SDB are an airway evaluation with an accompanying polysomnographic (overnight sleep study) assessment. This would have been a more objective measure of SDB as compared to questionnaire data, although this is not part of the examinations offered for NHANES, likely due to its inherently high cost.

The NHANES survey is a useful tool to assess the health of the U.S. population. One of the limitations of the survey is that data collection is limited to civilian, non-institutionalized U.S. citizens (CDC, 2011). Therefore, the results of this study cannot be

generalized to the non-civilian or institutionalized populations of the United States or abroad. With AMD primarily affecting the elderly, the institutionalized population may be an important population to consider in future attempts to understand the true magnitude of the association between SDB and AMD.

There were a number of limitations based on the composition of the study sample. First and foremost, the small number of participants with late AMD required a modification of the analysis plan. Additionally, not all participants participated in the MEC acquisition of fundus photos. Although the sample that had fundus photography performed was similar in sociodemographic characteristics to the sample that did not have photos taken, the exclusion of those without this exam reduced the available sample size and therefore my power to detect significant differences. Some of the reasons for not having photos taken included participants having no light perception, severe visual impairment in both eyes, or an infection in at least one eye (CDC, 2005). Those participants with no light perception or severe visual impairment in both eyes may have actually had AMD, and likely late AMD, and therefore may have reduced the available number of cases with disease in the data set.

In the 2005–2008 sampling timeframes, there were a number of ethnic and age groups oversampled in NHANES (National Center for Health Statistics [U.S.], 2013). Although this may have allowed for better estimation of association in these groups, it is possible that this oversampling could have had unseen adverse consequences with regard to the results of the non-Hispanic White group that has the highest prevalence of AMD in

the U.S. population. The NHANES survey may not contain a representative sample of some ethnic groups as the data collected included Non-Hispanic Whites, Non-Hispanic Blacks, Mexican-Americans, other Hispanic, and all other groups are lumped into the "Other Race" category (Johnson et al., 2013). Therefore, certain ethnic groups such as Asian-Americans are not represented in the dataset and the association with SDB and AMD is unable to be assessed. While weighting is available to adjust for the sampling scheme, it is based on the full and not the reduced sample I was able to use for this sample.

Lastly, the assumption of proportional odds was not met when performing OLR analyses. Separate binomial logistic regressions were performed using cumulative dichotomous dependent variables to test this assumption. It was clear that the number of participants in the "Late AMD" category was too small to support the assumption of proportional odds and therefore the ordinal nature of the dependent variable was lost. By collapsing the AMD category into "Any AMD" the ORs for the association of SDB variables and AMD were able to be calculated meeting all assumptions of this analysis. In interpreting the results of this study, I recognized that the resultant ORs were driven primarily by participants with early AMD and not late AMD.

Recommendations

Although the study indicated that there is a statistically significant association between SDB and AMD, I was unable to investigate causality. Future research should be performed to define the causal link between SDB and AMD. The collection of

longitudinal data starting with an early diagnosis of SDB by polysomnography in individuals under the age of 50 followed by regularly scheduled retinal examination and/or diagnostic imaging would further enhance the body of research available on SDB and AMD.

The understanding of this association would be further enhanced by diagnosis of SDB by more objective sleep quality measures such as polysomnography instead of participants responding to a questionnaire. Young et al. (1997) have shown that as many as 82% of men and 92% of women with SDB are undiagnosed and therefore a study with a large cohort screened by polysomnography could provide more accurate classification of SDB as compared to the current study. When coupled with independently graded retinal photography, this screening could provide a powerful, albeit costly, dataset for answering this important research question.

I was unable to investigate the association between SDB and choroidal neovascularization or geographic atrophy. Future research should be directed at understanding the association in those participants who develop late AMD. Among the group of subjects that present with choroidal neovascularization with SDB the data suggests a higher incidence of retinal vascular abnormalities; this warrants further evaluation in an enriched population.

This study used data from the most recent NHANES survey periods where retinal photography was incorporated. In contrast, the sleep questionnaire has been administered a number of times from 2005-2014. Future research could include retinal photography as

a part of examination data in conjunction with the sleep questionnaire to allow this study to be replicated. In addition, current NHANES questionnaires include non-Hispanic Asian as an ethnic/race category, therefore the association between SDB and AMD could be investigated in the Asian population.

Implications

The findings from this study have the potential to have a profound and positive impact on social change. AMD prevalence is expected to double in the next three decades (NEI, 2016b). It is estimated that the global cost of visual impairment due to AMD is $343 billion, including $255 billion in direct health care costs (BrightFocus Foundation, 2016). The ability to prevent AMD represents a significant opportunity for saving healthcare costs in the United States and other industrialized countries. Currently, there are no therapies proven to prevent AMD, only to treat AMD symptoms once diagnosed. Potential modifiable risk factors that have shown some promise in reducing AMD incidence include diet and smoking. SDB represents a third modifiable risk factor that if diagnosed and treated could have an impact on new cases of AMD. Public health programs that develop SDB screening guidelines and subsequently promote treatment compliance could have a major impact on AMD and a number of other potential complications of SDB.

At the individual patient level, SDB diagnosis rates as well as CPAP treatment compliance are notoriously poor. Public health practitioners may choose to use the fear of blindness as a motivating factor to get patients to get screened for SDB as well as to

promote continued adherence to CPAP therapy. Improving screening of SDB patients and adherence to SDB therapy of specific individuals and at-risk populations will aid the public health community in meeting the objectives for Healthy People 2020, specifically to reduce vision impairment due to AMD (Office of Disease Prevention and Health Promotion, 2016).

Currently, sleep medicine practitioners and retina specialists do not co-manage patients. The current guideline for OSA states that disease management should be as a chronic condition, using a multidisciplinary approach (Epstein et al., 2009). However, there is no mention of ophthalmology and/or eye health in the OSA guidance. This study, in addition to those aforementioned in the literature review, creates a growing body of evidence that SDB is associated with AMD and can have a negative impact on treatment outcomes for patients with AMD. The current Preferred Practice Patterns for AMD published by the American Academy of Ophthalmology (AAO) mentions a number of risk factors for AMD although SDB was not listed as one of them (AAO, 2015). Increasing healthcare practitioners' understanding of the association of SDB and AMD may encourage their incorporation of screening and preventative measures into delivery of care guidelines.

Conclusions

Based on my extensive literature review, I believe this was the first research study to investigate the association between SDB and AMD in a civilian, non-institutionalized population of the United States. The results from this cross-sectional study suggest that

AMD is associated with diagnosed sleep disorders including sleep apnea and insomnia, as well as sleep apnea symptoms (snorting/gasping/stop breathing and snoring). Furthermore, these associations were independent of sociodemographic and lifestyle factors. AMD can be added to the growing list of chronic diseases that have been linked to SDB such as cardiovascular disease and Alzheimer's disease.

Future research should aim to look at the association of SDB with late AMD (choroidal neovascularization and geographic atrophy). Study designs should employ the most objective measures available for assessing SDB (polysomnography) and AMD (multimodal retinal diagnostic imaging). Additionally, research is needed to determine causal relationships that will help direct interventional and preventative public health programs.

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Appendix A

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RE: Academic Permissions Request Form

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