Does a history of migraines increase the risk of late-life cognitive health outcomes?

by

Rebecca E. Morton

A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirement for the degree of

Master of Science

in

Health Studies and Gerontology

Waterloo, Ontario, Canada, 2011

Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners. I understand that my thesis may be made electronically available to the public.

Abstract

As the Canadian population ages, the burden on our community and health care systems of age-related conditions, such as dementia, is increasing and research in these areas is becoming more critical. Dementia is a major health concern for adults as they age. Although dementia is the most common neurological disease in older adults, headaches are the most common neurological disorder across all ages. Migraines are a common form of headache disorders that affect millions of people worldwide. Both neurological disorders—dementia and migraines—cause significant impairment for the individual and strain on their caregivers, as well as substantial economic impact on society. The relationship between migraines and late-life cognitive health outcomes has not yet been thoroughly explored.

Using data from the Manitoba Study of Health and Aging (MSHA), the relationship between migraines and various late-life cognitive health outcomes, including overall dementia, Alzheimer's disease (AD), vascular dementia (VaD) and cognitive impairment-no dementia (CIND), was examined. As migraines and cognitive impairments are often associated with various comorbid disorders, analyses also investigated the impact of possible associated intervening variables: hypertension, diabetes, stroke, myocardial infarction and other heart conditions. A secondary focus of this project was to examine whether the association between migraines and late-life cognitive health outcomes varied by sex and family history of dementia.

Migraines were a significant risk factor for both overall dementia and AD. However, the relationship between migraines and overall dementia appeared to be driven by the significant relationship between migraines and AD. Having a history of migraines was not significantly related to VaD. However, stroke was a statistically significant intervening

variable in the relationship between migraines and VaD, indicating that the vascular event, stroke, plays an important part in the migraine-VaD relationship. A history of migraines was not a significant risk factor for CIND.

Results could not be stratified by sex because of all participants with migraines, no men developed dementia and only one man developed CIND. Furthermore, despite a lack of significant results from models stratified by family history of dementia, the results are suggestive of possible genetic influences in the relationship between migraines and AD.

Overall, this study supports the conclusion that migraines are a significant risk factor for late-life cognitive health, specifically AD. In addition, this study highlights the possibility that vascular events, such as stroke, may play an important role in the relationship between migraines and VaD. Increased understanding of mid-life risk factors for late-life cognitive health outcomes has important implications for researchers and clinicians in the form of interventions, preventative treatments and medications. In addition, this study suggests that there is a need for further research regarding possible genetic influences in the relationship between migraines and AD. As it was unable to be fully addressed in this study, future studies should investigate gender differences among individuals with migraines developing late-life cognitive health outcomes. This research aims to help develop new strategies that could aid in the prevention of cognitive decline, improve quality of life, and increase the likelihood of healthy aging.

Acknowledgments

I would first like to thank my supervisor, Dr. Suzanne Tyas for her support and guidance throughout this process. The skills I have learned from working with her will help me in all of my future endeavours. Dr. Tyas has helped me to develop my analytical thinking and writing abilities, which I will forever be thankful for.

I would also like thank my committee members, Dr. John Mielke and Dr. George Heckman, for their invaluable advice and input throughout the development of my thesis.

A special thank-you to Audrey Blandford at the Manitoba Study for Health and Aging for taking the time to compile the dataset and answering any questions or queries during the data management process.

Finally, to my wonderful new husband, Chris, your support and encouragement has been fundamental to my success. Also, to my wonderful mom and brothers, thank you for always being there for me.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

3MS	Modified Mini-Mental State Exam
AD	Alzheimer's disease
ADL	Activities of daily living
APOE	Apolipoprotein E genotype
APOE-ε4	Apolipoprotein E genotype, □4 allele
APP	Amyloid precursor protein
Aβ	beta-amyloid
BMI	Body mass index
CDR	Clinical Dementia Rating scale
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence interval
CIND	Cognitive impairment-no dementia
CSD	Cortical spreading depression
CSHA	Canadian Study of Health and Aging
CVD	Cardiovascular disease
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition
GDS	Global Deterioration Scale
H-L GOF	Hosmer-Lemeshow goodness of fit
HRQoL	Health-related quality of life
IHS: ICHD-II	International Headache Society: International Classification of Headache Disorders 2nd Ed.
MA	Migraines with aura

MCI	Mild cognitive impairment
MMSE	Mini-Mental State Exam
MoA	Migraines without aura
MoCA	Montreal Cognitive Assessment
MSHA	Manitoba Study of Health and Aging
NIA-RI	National Institute for Aging - Ronald and Nancy Reagan Institute of Alzheimer's Disease
NINCDS-ADRDA	National Institute of Neurologic and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders
NINDS-AIREN	National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences
OR	Odds ratio
RR	Relative risk
VaD	Vascular dementia
WHO	World Health Organization

1. Introduction

As the Canadian population ages, the burden on our community and health care systems of age-related conditions, such as dementia, is increasing. According to a recent report by the Alzheimer Society, "Rising Tide: The Impact of Dementia on Canadian Society" (2010), approximately 500,000 people in Canada are currently suffering from dementia. The prevalence of dementia is expected to increase to approximately 1.1 million people by the year 2038 (Alzheimer Society, 2010). Trends such as this are causing increased awareness of the importance of research in this area.

Specifically, research regarding mid-life risk factors and their relationship with possible late-life cognitive health outcomes is becoming more of a focus. Various mid-life risk factors, such as smoking; lower levels of education; diabetes; and cardiovascular disease, including stroke, have been found to be related to the development of late life cognitive health outcomes (see reviews by Blennow, de Leon & Zetterberg, 2006; Kester & Scheltens, 2009; Patterson et al., 2007). It has become vital to determine how these mid-life risk factors can be treated or prevented to improve quality of life and increase the likelihood of healthy aging.

Although dementia is the most common neurological disease in older adults, headaches are the most common neurological disorder across all ages. Headache disorders are a serious neurological phenomenon that affect almost half of the global population of adults (Stovner et al., 2007). Migraines are the most debilitating form of headaches and affect 11% of the population: 20% of women and 8% of men (Diener & Beck, 2009; O'Bryant et al., 2006; Stovner et al., 2007). The relationship between migraines and

cognitive impairment has not been thoroughly examined. However, Tyas et al. (2001) found migraines to be a significant risk factor for Alzheimer's disease (AD).

The primary purpose of this thesis study is to determine if migraines are a risk factor for late-life cognitive health outcomes (overall dementia, AD, vascular dementia (VaD) and cognitive impairment-no dementia (CIND)). Analyses are based on data from the Manitoba Study of Health and Aging (MSHA), a longitudinal population-based cohort study, and extend the earlier work conducted by Tyas et al. (2001) using these data. Analyses also investigated the impact of possible intervening variables: hypertension, diabetes, stroke, and myocardial infarction. A secondary focus of this project was to examine whether the association between migraine and late-life cognitive health outcomes varied by sex or family history of dementia.

Identifying risk factors for cognitive health outcomes in late life is an important research area, given the current and expected increases in the proportion of older adults in the population. Identifying a mid-life risk factor for cognitive outcomes in latelife will allow earlier recognition of at-risk individuals. In addition, it will provide a rationale for the development of new preventative strategies and treatments targeting migraines and associated intervening variables. It is critical to continue to develop new strategies that will help prevent cognitive decline to improve quality of life and increase the likelihood of healthy aging.

2. Literature Review

2.1. Late-Life Cognitive Health Outcomes

2.1.1. Definition

2.1.1.1. Dementia

Dementia is a neurological syndrome that is characterized by a decline in cognitive function, of which a common symptom is memory loss. Various areas of the brain can be affected depending on the type and stage of dementia. As a result, cognitive symptoms can range from language dysfunction to visual perception issues and executive function problems (see review by Kester & Scheltens, 2009).The intensity of dementia symptoms can range from mild to severe and can be linked to the stages of dementia progression (see review by Burns & Iliffe, 2009).

The two most common types of dementia are AD and VaD, accounting respectively for 54% and 16% of all late-onset cases of dementia (see review by Kester & Scheltens, 2009). Two common causes of dementia that account for a large portion of the remaining 30% of cases are frontotemporal dementia and dementia with Lewy bodies (see reviews by Kester & Scheltens, 2009; Tedeschi et al., 2008). Mixed dementia, combining characteristics of both AD and VaD, also contributes to the number of dementia cases (see reviews by Kester & Scheltens, 2009; Tedeschi et al., 2008). Other subtypes of dementia include those resulting from alcoholism, depression, Huntington's disease, and Parkinson's disease (see review by Kester & Scheltens, 2009).

The early stages of dementia are often misinterpreted as being a part of normal aging (see review by Tyas & Gutmanis, 2008). This is because with aging there is a normal level of cognitive impairment or decline, such as occasional memory problems or forgetfulness (see

review by Peters, 2006). Between 25% and 75% of older adults report that their memory is worse than when they were younger (Chertkow et al., 2008). Occasional forgetfulness or normal memory function decline is not a form of dementia, as dementia involves impairment that is severe enough to cause difficulty with daily functioning.

2.1.1.2. Alzheimer's Disease

AD is an irreversible, progressive, neurodegenerative disease affecting older adults. Symptoms of AD have been categorized into three primary groups: cognitive dysfunction, psychiatric symptoms, and difficulty performing daily activities (see review by Burns & Iliffe, 2009). Cognitive dysfunction symptoms include memory loss, language problems and issues with executive function. For instance, problems with higher-level learning or intellectual coordination skills are common. Psychiatric symptoms include emotional and behavioural disturbances, such as depression, agitation, delusions or hallucinations (see review by Burns & Iliffe, 2009). Difficulties performing daily activities, such as driving, shopping, dressing or eating, are often noticed by family or friends of the individual with AD (see reviews by Burns & Iliffe, 2009; Cummings, 2004; Tedeschi et al., 2008). Such day-to-day activities are often described as either instrumental activities (e.g., driving or managing money) or basic activities (e.g., dressing or eating).

2.1.1.3. Vascular Dementia

Vascular cognitive impairment or vascular cognitive disorder are broad terms that are used to encompass a wide variety of vascular-based dementias or disorders, such as post-stroke dementia, multi-infarct dementia, CADASIL (cerebral autosomal dominant

arteriopathy with subcortical infarcts and leukencephalopathy) and VaD (see review by Jellinger, 2008). VaD is a form of dementia characterized by cognitive dysfunction due to vascular damage in the brain (see review by Kester & Scheltens, 2009). VaD has traditionally been associated with cardiovascular disease and associated risk factors, such as hypertension or hyperlipidemia (see reviews by Erkinjuntti & Gauthier, 2009; Viswanathan, Rocca & Tzourio, 2009). Severity of VaD is determined by the burden of vascular damage in the brain: individuals with more vascular lesions or infarcts in the brain will suffer from more severe dementia symptoms (see review by Jellinger, 2008). The overlap between AD and VaD is becoming more obvious as vascular risk factors, such as hypertension, diabetes or hypercholesterolemia, are more commonly diagnosed in patients with AD. Also, autopsy studies have noted the presence of vascular lesions coexisting with classic AD pathology (del Ser et al., 2005; Snowdon et al., 1997). The term "mixed dementia" has been used to refer to an overlap or combination of AD and vascular diseases of the brain, including cerebrovascular disease and vascular encephalopathy (see reviews by Jellinger & Attems, 2007; Kalaria, 2002). However, not all dementia definitions recognize mixed dementia as a separate form of dementia (see review by Jellinger & Attems, 2007).

2.1.1.4. Mild Cognitive Impairments

There are many terms used to describe forms of cognitive disorders milder than dementia. Some of these terms include CIND, mild cognitive impairment (MCI), mild dysfunction, pre-dementia, pre-Alzheimer's disease or borderline dementia (Tuokko & Frerichs, 2000). CIND and MCI have been the most popular terms and the most consistently defined. The most common criterion used to determine CIND or MCI is complaint of

memory loss that is not accompanied by any noticeable decline in day-to-day functioning or other non-memory cognitive dysfunction. These symptoms are not severe enough to meet criteria for a diagnosis of any type of dementia or other neurological explanation of the memory complaint. This is an important aspect of CIND or MCI (Chertkow et al., 2007; see reviews by Petersen et al., 2001; 2009). CIND and MCI are categorized based on their etiology. CIND can be divided into multiple subcategories: amnestic, vascular, medical/toxic, metabolic, psychiatric, neurologic, mixed, and not specified (Chertkow et al., 2007). MCI is typically divided into either amnestic, non-amnestic or multiple domain types (Nagai, Hoshide & Kario, 2010; Petersen et al., 2001). Many studies suggest that MCI or CIND is a precursor of AD (Tyas et al., 2007; see reviews by Burns & Iliffe, 2009; Tedeschi et al., 2008).

2.1.1.5. Diagnostic Criteria

Because of the variety of types or causes of dementia, there is also a wide range of diagnostic criteria used. Screening tools are used to distinguish between normal levels of cognitive decline related to aging and cognitive impairment due to disease or disorder. Screening tools are quick and inexpensive to administer and are most often used to identify individuals to target for a full neurological assessment, which is both lengthy and expensive. Common screening tools for cognitive impairment include the Mini-Mental State Exam (MMSE), the Modified Mini-Mental State Exam (3MS), as well as the Montreal Cognitive Assessment (MoCA) (Chertkow et al., 2007; Nasreddine et al., 2005).

Dementia is most commonly diagnosed clinically using the DSM-IV. Once this overall diagnosis has been made, clinicians and researchers use more specific diagnostic

criteria to determine the type of dementia. Both neuropsychological and pathologic diagnostic criteria have been developed to aid in the diagnosis of AD. There are three primary neuropsychological criteria that are currently utilized when making clinical diagnoses of AD: National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) (McKhann et al., 1984), DSM-IV (DSM-IV, 1994) and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Morris et al., 1989) criteria. The clinical definition most widely used in research is the NINCDS-ADRDA (McKhann et al., 1984; see reviews by Cummings, 2004; Cummings et al., 1998; Tedeschi et al., 2008). The NINCDS-ADRDA definition allows for classification of AD as definite, probable or possible (McKhann et al., 1984; see reviews by Cummings et al., 1998; Tedeschi et al., 2008). However, a clinical diagnosis of "definite AD" remains presumptive until confirmed by a post-mortem neuropathologic examination.

Various pathologic criteria have been developed to help diagnose AD. AD pathology is most definitively determined post-mortem, although new imaging techniques have begun to allow clinicians to identify plaques within the brain antemortem. The CERAD (Mirra et al., 1991) and the National Institute for Aging - Ronald and Nancy Reagan Institute of Alzheimer's Disease (NIA-RI) (NIA-Reagan, 1997) criteria are commonly used pathologic diagnostic criteria. The CERAD neuropathologic criterion uses the number of plaques to determine a neuropathologic diagnosis of no AD, possible AD, probable AD or definite AD (Mirra et al., 1991). The NIA-RI criteria combine the CERAD criteria with Braak staging (NIA-Reagan, 1997) and categorize the likelihood that dementia is due to AD as low, intermediate or high (NIA-Reagan, 1997). Braak staging is a quantification of the number and location of neurofibrillary tangles in the brain, which are divided into six stages (Braak

& Braak, 1991). Severity of AD neuropathology is most often assessed using Braak staging (Braak & Braak, 1991). (See Section 2.1.4.2 for a discussion of neurofibrillary tangles and other AD pathologies.)

VaD can be diagnosed using a variety of criteria including the DSM-IV (DSM-IV, 1994) and the National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (Roman et al., 1993) criteria. The NINDS-AIREN definition includes possible VaD, probable VaD and definite VaD (Roman et al., 1993). The criteria for probable VaD specifies that the individual must be suffering from cognitive decline that can be directly related to cerebrovascular disease, whereas the criteria for definite VaD also specifies that cerebrovascular disease must be confirmed by biopsy or autopsy and that AD neuropathology must not be present (Roman et al., 1993). A diagnosis of possible VaD is most often applied when some key features of the above definitions are missing (Roman et al., 1993). Clinical diagnoses are made using the DSM-IV and NINDS-AIREN, whereas neuropathologic diagnoses are generally based on brain imaging, which can be used to assess the level of vascular lesion burden on the brain (see review by Kester & Scheltens, 2009). The Hachinski Ischemic Score is used to determine the level of vascular burden on the brain; a higher score indicates that an individual is more likely to have vascular dementia due to the severity of vascular lesions (Hachinski et al., 1975).

There are no gold standard diagnostic criteria for mild cognitive impairment. A lower score on the Global Deterioration Scale (GDS) or Clinical Dementia Rating scale (CDR) or a normal range score on the MMSE or 3MS may indicate CIND/MCI (Chertkow et al., 2008; see review by Petersen et al., 2009). Specifically, a score of 0.5 on the CDR, and a

classification as stage 2 or 3 on the GDS will most often indicate MCI or CIND (Berg, 1988; Morris, 1993; Petersen et al., 1999; Reisberg et al, 1982; see review by Petersen et al., 2009). The MoCA is a cognitive screening tool that has high specificity and sensitivity for detecting MCI in individuals who have a normal score on the MMSE (Nasreddine et al., 2005). Often clinicians use a variety of cognitive tests, scales, or criteria in order to make a more complete diagnosis. Imaging can be used to assess MCI neuropathology before death (Solé-Padullés et al., 2007). In particular, the possible locations of lesions in the brains and overall brain atrophy as well as hippocampal atrophy can be identified through the use of brain imaging (Solé-Padullés et al., 2007; see review by Petersen et al., 2009).

2.1.2. Rates and Impact on the Population

2.1.2.1. Incidence and Prevalence of Dementia

Since dementia is a neurological syndrome that primarily affects older adults, the incidence of dementia is increasing globally as the population of older adults increases (Alzheimer Society, 2010; Alzheimer's Disease International, 2009; The Canadian Study of Health and Aging Working Group, 2000). According to a recent report by the Alzheimer Society, "Rising Tide: The Impact of Dementia on Canadian Society" (2010), the projected incidence of dementia in Canada will increase 2.5 times from 2008 to 2038. The prevalence of dementia across all ages in Canada is expected to more than double in 30 years: from approximately 500,000 people (1.5% of the population) in 2008 to 1.1 million people (2.8% of the population) by 2038 (Alzheimer Society, 2010). The World Alzheimer's Report (2009) estimates that approximately 35.6 million people globally will suffer from dementia

in 2010. The worldwide prevalence of dementia is estimated to double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050.

Age and gender differences have been observed in rates of dementia. In Canada, the prevalence of overall dementia has been shown to be higher in females than in males (Alzheimer Society, 2010). In the US, 14% of people over the age of 70 have dementia; 16% of those are women and 11% are men (Plassman et al., 2007; Alzheimer's Association, 2009). However, some studies have shown that age-specific incidence rates show no significant gender differences (Alzheimer's Association, 2009; Andersen et al., 1999; Fitzpatrick et al., 2004; Ruitenberg et al., 2001). Despite these inconsistent results in gender differences in the incidence vs. prevalence of dementia, the prevalence of dementia would be expected to be higher in women than in men because of women's greater life expectancy and the strong association between age and dementia (Alzheimer's Association, 2009; Ruitenberg et al., 2001; see review by Patterson et al., 2007). Prevalence of dementia in the population also increases by age groups: from 1% of individuals 60-65 years of age, to 10-35% of those over 85 years (see reviews by Kester & Scheltens, 2009; Prince, 2004; Tedeschi et al., 2008).

2.1.2.2. Incidence and Prevalence of Alzheimer's Disease

Alzheimer's disease is the most common form of dementia (see reviews by Kester & Scheltens, 2009; Tedeschi et al., 2008). More than 24 million people worldwide have AD; within Canada, approximately 300,000 people have AD (Alzheimer Society, 2010). Approximately 1% of older adults between the ages of 60 and 64 suffer from AD, increasing to 2% of adults between 65 and 69, 4% between 70 and 74, 8% between 75 and 79, 16%

between 80 and 85 and 40% of adults over 85 years (Cummings et al., 1998). These numbers are expected to rise as the population ages. Studies have shown that women are more likely than men to have AD; specifically, prevalence studies generally demonstrate higher risk in women than men (Alzheimer's Association, 2009; see review by Musicco, 2010). Some studies have speculated that these differences in rates may be due to the fact that women live longer than men (Hebert et al., 2001; Ruitenberg et al., 2001). Some studies have found no differences in age-specific incidence rates (Alzheimer's Association, 2009; Hebert et al., 2001; Heun & Kockler, 2002; Ruitenberg et al., 2001) although in the oldest old, incidence of AD may be higher in women than in men (Andersen et al., 1999; Ruitenberg et al. 2001).

2.1.2.3. Incidence and Prevalence of Vascular Dementia

Vascular dementia is the second most common form of dementia, accounting for 15-25% of prevalent dementia cases (see review by Jellinger, 2008). VaD is more common in men compared to women, demonstrated by prevalence rates among those under the age of 79 ranging from 2.2% in women to 16.3% in men (see reviews by Leys, Pasquier & Parentti, 1998). Ruitenberg et al. (2001) found that across all age groups, men were at a higher risk of developing VaD than were women. It has been speculated that this gender difference in VaD rates may be due to the protective effects of estrogens in women or the association between male gender and cardiovascular disease (Andersen et al., 1999). Mixed dementia, or overlap between AD and VaD, accounts for approximately 5-10% of all cases of dementia (see review by Jellinger & Attems, 2007). However, due to issues with under-diagnosis or misdiagnosis, the reported rates of incidence and prevalence for mixed dementia may be inaccurate.

2.1.2.4. Incidence and Prevalence of Mild Cognitive Impairments

It is difficult to determine the prevalence or incidence of MCI or CIND, as it may go undetected and therefore undiagnosed until it progresses to dementia. However, the prevalence of MCI has been estimated to be two to three times higher than that of AD and affect approximately 15% of the non-demented population (see reviews by Petersen et al., 2009; Tedeschi et al., 2008). It has been estimated that approximately 40-60% of people with MCI will eventually progress to meet criteria for AD; this varies by MCI subtype (see review by Tedeschi et al., 2008).

2.1.2.5. Impact of Cognitive Impairment

Dementia is a severe, debilitating disease that affects almost one-third of the older adult population, causing significant global economic impact. According to a recent report by the Alzheimer Society, "Rising Tide: The Impact of Dementia on Canadian Society" (2010), the economic burden of dementia as of 2008 is $10 billion annually; this is expected to rise to $97 billion by the year 2038. These estimates do not include unpaid services provided by caregivers, which have been estimated to be valued at $5 billion in 2008, increasing to $56 billion by the year 2038 (Alzheimer Society, 2010). Medical care costs for an AD patient are a significant concern, in addition to any loss of income due to absenteeism of either the AD patient or the caregiver.

Caregiver burden is becoming a growing concern, as families of dementia patients contend with the financial and emotional stresses associated with dementia. The emotional stress of caring for a spouse or parent who is unable to care for himself or herself is

psychologically exhausting, for both the individual with dementia as well as the caregiver (Black et al., 2009; see review by Burns & Iliffe, 2009). Often the level of disability necessitates acquiring additional medical help, such as home nurses or in the most severe cases, institutionalization (Rockwood, Stolee & McDowell, 1996).

According to the World Health Report (2001), AD and other dementias are ranked 13th as a cause of disability for all ages in both sexes and 9th for women alone. The Global Burden of Disease Report (World Alzheimer Report, 2009) estimates that dementia accounts for 4.1% of total disease burden (Disability-Adjusted Life Years) among people 60 years and older, 11.3% of years lived with disability and 0.9% of years of life lost. Dementia does not affect memory alone; it also has psychological and physical symptoms, which combine to cause disability. Psychological symptoms of dementia range from depression to behavioural changes to hallucinations (see review by Burns & Iliffe, 2009). Since motor function is affected by various forms of dementia, physical disability often occurs, such as balance problems resulting in falls (see review by Burns & Iliffe, 2009).

Estimated survival time from onset of dementia or dementia diagnosis ranges from 3-10 years (Wolfson et al., 2001; Xie et al., 2008; see review by Zanetti, Solerte & Cantoni, 2009). Dementia itself does not directly cause death, but the neurological systems that are affected can increase the risk of death. For example, problems with swallowing food are common in those suffering from AD, which can lead to food particles being inhaled into the lungs, possibly causing pneumonia and subsequent death (Ganguli et al., 2005). AD is currently the 6th leading cause of death in the US and the 8th leading cause of death in Canada in both sexes (Alzheimer's Association, 2009; Statistics Canada, 2010). In those over the age of 65, AD is the 5th leading cause of death in the US (see review by Lee & Chodosh, 2009).

In Canada, for those between the age of 75 and 84 years, AD is the 6th leading cause of death; in those over the age of 85, AD is the 5th leading cause of death (Statistics Canada, 2010). Deaths related to dementia are most often attributed to AD. However, the mortality rate of VaD may be higher than AD, because of the relationship between VaD and heart attack or stroke (see review by Leys, Pasquier & Parnetti, 1998). These vascular events are often fatal and are significantly associated with VaD (see review by Leys, Pasquier & Parnetti, 1998).

It is difficult to measure the impact of CIND or MCI on society, as many individuals are undiagnosed until further impaired. CIND and MCI may progress to dementia, with all its associated impacts on the individual, their family and society. However, even if these mild cognitive impairments do not become more severe, they may be a cause of concern for the affected individual. In addition, new treatments targeted at individuals with these impairments add to their economic impact.

2.1.3. Risk and Protective Factors

2.1.3.1. Overview of Risk and Protective Factors

A wide range of risk factors have been identified for dementia. The most definitive, non-modifiable risk factors for dementia are age, sex and genetics (see reviews by Blennow, de Leon & Zetterberg, 2006; Patterson et al., 2007). The most consistent risk factor for all forms of dementia is age (see reviews by Kester & Scheltens, 2009; Patterson et al., 2007). The risk for many diseases, including dementia, increases as people grow older. Hence, cardiovascular disease, including stroke, heart disease, myocardial infarction and various

other vascular events, becomes more common. Risk factors for dementia can be divided into environmental, behavioural, lifestyle and genetic factors, as well as diseases and disorders.

Risk factors for overall dementia are often difficult to determine, as the various factors that will convey the most risk for an individual are driven by the proportion of dementia subtypes within the population. For instance, in a population of individuals with dementia, if the majority of these individuals suffer from AD, then the risk factors identified can likely be attributed to AD.

2.1.3.2. Alzheimer's Disease

The majority of risk factor research has focused on AD, since it is the most common cause of dementia in most countries around the world. Sociodemographic risk factors for AD include age, female sex and lower educational status (Hebert et al., 2001; Ruitenberg et al., 2001; Tyas et al., 2001; see review by Patterson et al., 2007). A summary of AD risk factors is shown in Table 1.

Table 1: Risk factors for dementia's major subtypes: Alzheimer's disease and vascular dementia

		AD	VaD
Demographic	Increased Age	✓	✓
	Sex	✓ (Female)	✓ (Male)
Genetic	APOE-ε4	✓	✓
	APP	✓	
	Presenilin-1 and 2	✓	
	Inflammatory genes	✓	
Behavioural and Lifestyle	Higher BMI	✓	✓
	Lower Level of Physical Activity	✓	✓
	Tobacco Use	✓	✓
	Alcohol Consumption	✓	✓
	Low Educational Level	✓	✓
	Poor Diet	✓	✓
	Low Occupational Status	✓	✓
	Rural Residence	✓	✓
Environmental	Pesticides/Fertilizers	✓	✓
	Defoliants/Fumigants	✓	
	Metals	✓	
	Vaccinations	✓	
Health Status and Comorbidity	Diabetes	✓	✓
	Depression	✓	✓
	Head Trauma	✓	
	Hyperthyroidism	✓	
	Higher Sex Hormone Levels	✓	
Vascular	Stroke	✓	✓
	Hypertension	✓	✓
	Atherosclerosis	✓	✓
	Hypercholesterolemia	✓	✓
	Coronary Heart Disease	✓	✓
	Congestive Heart Failure	✓	✓

* AD: Alzheimer's disease; VaD: vascular dementia; APOE (ε4): apolipoprotein E genotype, □4 allele; APP- amyloid precursor protein

2.1.3.2.1. Behavioural, Lifestyle and Environmental Factors

Certain lifestyle or behavioural factors have been found to increase the risk of developing AD (e.g., smoking, alcohol consumption, decreased physical activity, increased body mass index (BMI), and occupation) (Fitzpatrick et al., 2009; Laurin et al., 2001; Tyas et al., 2001; see reviews by Beydoun, Beydoun & Wang, 2008; Luchsinger & Mayeux, 2007; Patterson et al., 2007). Based on Canadian Study of Health and Aging (CSHA) data, Laurin et al. (2001) speculated that physical activity may act as a protective factor since it is related to lower BMI or weight and decreased risk for diabetes mellitus, hypertension, stroke and various vascular health outcomes. Some researchers have suggested that the association between AD and increased BMI may reflect underlying vascular diseases (Laurin et al., 2001; see review by Patterson et al., 2007). Smoking and alcohol consumption may be related to AD as they are often associated with cardiovascular disease and various vascular risk factors in an individual (Tyas et al., 2003; see review by Tyas, 2001).

2.1.3.2.2. Genetic Factors

There are two types of genetic factors: those that determine development of AD and those that increase the risk or susceptibility of developing AD (see review by Tyas & Gutmanis, 2008). Genetic factors that are considered to be deterministic are the cause of familial AD, whereas genetic factors that increase the risk of developing AD are often considered one of the causes of sporadic AD (see review by Tyas & Gutmanis, 2008). Familial AD is a rare autosomal dominant disorder that is the cause of early-onset AD (see reviews by Blennow, de Leon & Zetterberg, 2006; Tyas & Gutmanis, 2008). Familial AD is less common than sporadic AD and is caused by mutations of APP, presenilin-1 and

presenilin-2 (see reviews by Burns & Iliffe, 2009; Tyas & Gutmanis, 2008). These mutations are found on chromosomes 21, 14 and 1, respectively (see review by Burns & Iliffe, 2009). Individuals with APP and presenilin gene mutations will develop AD if they live long enough, and therefore these gene mutations are considered deterministic (see review by Tyas & Gutmanis, 2008).

Sporadic or late-onset AD is more common than familial AD and may be caused by various genetic or environmental risk factors (see reviews by Tyas & Gutmanis, 2008; Blennow, de Leon & Zetterberg, 2006). The apolipoprotein E (APOE-ε4) allele, located on chromosome 19, has been found to be associated with increased risk of developing AD and is often considered a primary cause of sporadic AD (Azad, Al Bugami & Loy-English, 2007; see reviews by Blennow, de Leon & Zetterberg, 2006; Patterson et al., 2007). APOE-ε4 leads to accelerated deposition of amyloid in the brain (see review by Cummings, 2004). A Swedish twin study estimated that between 60% and 80% of AD cases can be attributed to APOE (i.e., where an individual has at least one APOE-ε4 allele) (Gatz et al., 2005a; Pedersen et al., 2004). As the number of APOE-ε4 alleles increases, the risk of late-onset AD increases from 20% to 90%. The increase in number of APOE-ε4 alleles also affects age of onset, decreasing the mean age of onset from 84 to 68 years (see review by Blennow, de Leon & Zetterberg, 2006). APOE-ε4 status may have a deleterious effect on hippocampal pathology and memory performance that is greater in women than in men (Fleisher et al., 2005).

Inflammation plays an important role in dementia neuropathology and neurophysiology. Recent studies have found that specific inflammatory genes increase the risk of AD (see review by Salminen et al., 2009). The presence of a homozygous variant of

interlukin-1α-889 and interleukin-1β+3953 may indicate an increased risk for AD (Hedley et al., 2000; Nicoll et al., 2000; see review by Griffin & Mrak, 2002). Researchers have also found that the combination of APOE-ε4 and tumour necrosis factor-α identifies those with an increased risk of developing AD (McCusker et al., 2001; see review by McGeer & McGeer, 2001).

2.1.3.2.3. Health Status and Conditions

A variety of diseases, disorders and health conditions have been found to be related to, comorbid with, or risk factors for AD, including diabetes mellitus, epilepsy, Down's syndrome, hyperhomocysteinemia, hyperthyroidism, depression, sex hormone levels and head trauma. Specifically, the association between mid-life vascular risk factors and the development of dementia, including AD, in late life has been well documented (Alonso et al., 2009; Fillit et al., 2008; Hebert et al., 2000; Whitmer et al., 2005). Various vascular risk factors for AD have been identified, including hyperlipidemia, hypertension, atherosclerosis, stroke and coronary heart disease (Hebert et al., 2000; Tyas et al., 2001; see reviews by Duron & Hanon, 2008; Graves, 2004; Patterson et al., 2007; Tyas & Gutmanis, 2008).

2.1.3.2.3.1. Cardiovascular Disease

A variety of cardiovascular disease (CVD) outcomes and risk factors have been found to be related to dementia, including AD and VaD. Hypertension in mid-life has been shown to be a risk factor for cognitive decline and dementia (Freitag et al., 2006; Launer et al., 1995, 2000; Nagai, Hoshide & Kario, 2010; Skoog et al., 1996; Stewart et al., 2009). Studies have implicated both high and low systolic and diastolic blood pressure in the development of dementia (see reviews by Patterson et al., 2007; Qui, Winblad & Fratiglioni, 2005). The

association between mid-life high systolic blood pressure and late-life cognitive impairment has been observed for both AD and VaD (Freitag et al., 2006; Launer et al., 1995, 2000; Stewart et al., 2009).

In addition to vascular risk factors being associated with AD, vascular events, such as coronary artery disease, heart disease, atherosclerosis and heart failure, have also been shown to be risk factors for dementia, including AD (Qui, Winblad & Alessandra, 2006; Tyas et al., 2001; see reviews by Duron & Hanon, 2008; Graves, 2004; Patterson et al., 2007; Tyas & Gutmanis, 2008). Cerebrovascular disease, including the occurrences of symptomatic stroke or silent stroke, also increases the risk of developing AD (Honig et al., 2003; Ivan et al., 2004; Schneider et al., 2007; Snowdon et al., 1997; Troncoso et al., 2008; Vermeer et al., 2003a,b,c). Atherosclerosis has been found to increase the risk of developing dementia, including AD (Honig et al., 2005; Roher at al., 2010; see review by Duron & Hanon, 2008). However, this relationship may be mediated by CVD outcomes, such as stroke, coronary heart disease and congestive heart failure. Coronary heart disease and congestive heart failure have been found to be associated with cognitive decline and impairment (see review by Duron & Hanon, 2008).

2.1.3.2.3.2. Diabetes

Diabetics have an increased risk of cognitive dysfunction or dementia. Diabetes mellitus has been found to be a significant risk factor for AD (Arvanitakis, 2004; Kopf & Frölich, 2009; Luchsinger et al, 2001; Saczynski et al., 2008; see reviews by Launer, 2009; Patterson et al., 2007). Using data from the Religious Orders Study, Arvanitakis et al. (2004) found that those with diabetes had a 65% increased risk (hazards ratio=1.65, 95%

Confidence Interval (CI):1.10-2.47) of developing AD compared to those without diabetes. Diabetes may increase the risk of developing AD as it has been associated with the formation of beta-amyloid (Aβ) and inflammatory factors in the brain (see review by Craft, 2007). Diabetes mellitus often causes insulin resistance, which has been shown to be related to the formation of Aβ and various inflammatory factors in the brain (see review by Craft, 2007). This indicates that diabetes is indirectly associated with increased risk of AD (see review by Craft, 2007). However, diabetes is also closely associated with many vascular risk factors, which may also contribute to the relationship between diabetes and AD.

2.1.3.2.3.3. Depression

The presence of depressive symptoms has been shown to be related to or predictive of the development of dementia (Gatz et al., 2005b; Luchsinger et al., 2008; Ownby et al., 2006; see review by Patterson et al., 2007). However, results of studies on the relationship between AD and depression have sometimes been contradictory. Studies have shown that 20-30% of people with AD also have depressive symptoms (see review by Tsuno & Homma, 2009). It has been speculated that depressive symptoms may precede the onset of AD, coincide with AD development or possibly follow AD development. Using MSHA data, Gatz, et al. (2005b) found that depressive symptoms were predictive of AD and dementia development over five years, suggesting that depression is in fact a prodromal symptom of AD. These results are in contrast with results from a meta-analysis by Ownby et al. (2006), which considered depression more a risk factor than a prodrome for AD. Ownby et al. (2006) found that individuals with a history of depression were more likely to be diagnosed with AD later in life. They also examined whether the interval between diagnosis of depression and

subsequent diagnosis of AD was related to subsequent development and diagnosis of AD. Their results suggest that the interval was significant and positively related to an increased risk of developing AD. This finding suggests that depression is a risk factor for AD, rather than a prodrome of the disease (Ownby et al., 2006).

2.1.3.2.3.4. Epilepsy

People suffering from epilepsy have a two to five times increased risk of stroke, migraine and AD (Gaitatzis et al., 2004; Hermann et al., 2008; Tellez-Zenteno, Matijevic & Wiebe, 2005). The relationship between epilepsy and cognitive impairment may be due to the underlying neuropathology of epilepsy (see Section 2.2.3.2.), which either causes or exacerbates cognitive dysfunction (see review by Motamedi & Meador, 2003).

2.1.3.3. Vascular Dementia

Research has focused less on risk factors for VaD than for AD, resulting in fewer risk factors being identified. Sociodemographic risk factors for VaD include age, lower educational status, living in rural areas and male sex (Andersen et al., 1999; Ruitenberg et al., 2001). A summary of VaD risk factors, including behavioural, lifestyle and environmental risk factors, is shown in Table 1.

2.1.3.3.1. Behavioural, Lifestyle and Environmental Factors

Lifestyle or behavioural factors associated with increased risk of developing VaD are most often vascular risk factors such as smoking, alcohol consumption, increased BMI,

decreased physical activity and unhealthy diet (Hebert et al., 2000; see reviews by Leys & Pasquier, 1998; Patterson et al., 2007).

2.1.3.3.2. Genetic Factors

The majority of research pertaining to genetic factors for dementia has focused on AD and specifically inherited, familial AD. However, the presence of an APOE-ε4 allele, in addition to increasing the risk of developing AD, has also been observed to increase the risk of VaD as well as mixed dementia, according to data from the CSHA (Hebert et al., 2000). Researchers have speculated that this relationship is due to overlapping pathology of AD and VaD (Hebert et al., 2000). However, APOE-ε4 could be linked directly to VaD given APOE's role in brain metabolism and cholesterol transport (Hebert et al., 2000; see reviews by Martins et al., 2009; Morley & Banks, 2010)

2.1.3.3.3. Health Status and Conditions

A variety of diseases and disorders have been associated with VaD, such as diabetes mellitus and depression. Many vascular health conditions have been found to be associated with VaD, including hypertension, hyperlipidemia, atherosclerosis, stroke and coronary heart disease (Hebert et al., 2000; Lindsay, Hebert & Rockwood, 1997; see reviews by Patterson et al., 2007; Skoog, 1998).

2.1.3.3.3.1. Cardiovascular Disease

Although research has begun to demonstrate the relationship between CVD and AD, the relationship between CVD and VaD has been well documented (Alonso et al., 2009; Fillit et al., 2008; Morovic et al., 2009; Whitmer et al., 2005; see review by Patterson et al., 2007). Stroke, either symptomatic or silent, is commonly associated with VaD and is used as a diagnostic criterion (Hachinski et al., 1975; see reviews by Patterson et al., 2007). The occurrence of silent strokes increases dramatically as an individual ages: from 5% at 60 years of age, to 35% at 90 years of age (Price et al., 1997; Vermeer et al., 2002; 2003a). Although symptomatic strokes cause more physical damage to the brain than asymptomatic or silent strokes, these silent strokes (included in brain infarcts) are dangerous as they, by definition, have no outward symptoms to indicate that a stroke has occurred. Individuals who have had silent strokes may appear healthy otherwise, but are at an increased risk of developing dementia and will experience a steeper decline in cognitive function than older adults without silent strokes (Vermeer et al., 2003a,b).

As stated previously, hypertension is a risk factor for dementia, including VaD (Hebert et al., 2000; Lindsay, Hebert & Rockwood, 1997; Nagai, Hoshide & Kario, 2010). Cardiovascular diseases including coronary artery disease, heart disease, atherosclerosis and heart failure have also been found to be risk factors for VaD (Hebert et al., 2000; Lindsay, Hebert & Rockwood, 1997; Nagai, Hoshide & Kario, 2010; see reviews by Duron & Hanon, 2008; Patterson et al., 2007).

2.1.3.3.3.2. Diabetes

Diabetes mellitus has been found to be a significant risk factor for VaD (Hebert et al., 2000; MacKnight et al., 2002; Saczynski et al., 2008; see reviews by Launer, 2009; Patterson et al., 2007). Using CSHA data, Hebert et al. (2000) observed a significant odds ratio of 2.15 for diabetes in those diagnosed with VaD. Therefore, those with VaD were twice as likely to be diabetic. However, diabetes is closely associated with many vascular risk factors, such as increased BMI, which may mediate this relationship.

2.1.3.3.3.3. Depression

Having a history of depression has been shown to be associated with VaD (Hebert et al., 2000; Katzman et al., 1989). Using CSHA data, Hebert et al. (2000) found that depressive symptoms preceded the development of VaD, suggesting that depression may be a prodrome to VaD or a marker for cerebral damage.

2.1.4. Neuropathophysiology

2.1.4.1. Dementia

Dementia is a neurodegenerative disease that results in impairment of cognitive function. Dementia results from various disease processes within the brain, ranging from Parkinson's to alcohol abuse. As the two major subtypes of dementia are AD and VaD, their specific pathology and physiology will be focused on.

2.1.4.2. Alzheimer's Disease

Classic AD is characterized by three major hallmarks: senile plaques, neurofibrillary tangles and cholinergic deficiency (see reviews by Cummings, 2004; Cummings et al., 1998; Fisher, 2007). These are associated with neurodegeneration, atrophy and subsequent cognitive impairment.

Senile plaques are caused by the production and accumulation of beta-amyloid (Aβ) peptide (see review by Cummings, 2004). The Aβ peptide is made up of 40 to 42 amino acids and results from the cleavage of a larger amyloid precursor protein (APP). In a normal functioning brain, APP is critical to neural growth, survival and post neural injury repair (see reviews by Cummings, 2004; Querfurth & Laferla, 2010). In an AD brain, APP has been stimulated to be cleaved into small pieces (Aβ) through the successive action of two enzymes, β and γ secretase, respectively generating the N-terminus and C-terminus (see reviews by Cummings, 2004; Keller, 2006; Querfurth & Laferla, 2010). Aβ then accumulates to form various forms of plaques that are associated with AD neuropathology (see reviews by Cummings, 2004; Querfurth & Laferla, 2010). Senile plaques, which include diffuse plaques and classic neuritic plaques, are differentiated based on their appearance (see reviews by Cummings, 2004; Querfurth & Laferla, 2010).

Neurofibrillary tangles are proteinaceous structures made up of hyperphosphorylated tau protein (see reviews by Cummings, 1998; Keller, 2006; Querfurth & Laferla, 2010). Tau is a stabilizer protein, which aids in the internal support structure of neurons. Specifically, tau protein stabilizes microtubules within the cytoskeleton structure when phosphorylated (see review by Cummings et al., 1998). In an AD brain, however, tau becomes hyperphosphorylated and subsequently self-adheres or becomes "tangled" (see review by

Querfurth & Laferla, 2010). The distribution of tangles within the brain occurs in a systematic manner. This pattern correlates with early symptoms of memory impairment seen in AD patients and subsequent symptom progression (see review by Cummings et al., 1998). Both plaques and tangles disrupt normal neuronal and synaptic functioning, causing cell death and brain atrophy.

A major biochemical hallmark of Alzheimer's disease is cholinergic deficiency, including reduced choline uptake, reduced acetylcholine release and degeneration of cholinergic neurons (see review by Francis et al., 1999). The role of cholinergic neurotransmission in memory led to increased research into cholinergic deficiencies and their possible contribution to cognitive dysfunction and decline seen in AD individuals (see reviews by Francis et al., 1999; Querfurth & Laferla, 2010; Tyas & Gutmanis, 2008). These cholinergic deficiencies may affect aggregation of amyloid, leading to neuroinflammation (see reviews by Querfurth & Laferla, 2010; Salminen et al., 2009; Shen, 2004; Wenk, 2003). Aβ is neurotoxic to nicotinic acetylcholine receptors and impairs their signalling, in addition to reducing acetylcholine release from the presynaptic terminal (see reviews by Buckingham et al, 2009; Querfurth & Laferla, 2010). Since cholinergic deficits were the first neurotransmitter system impairment identified in relation to AD, many forms of AD treatments have been based on alleviating this deficiency (see review by Burns, 2009). Although the cholinergic system has been a focus of AD research, other neurotransmitter deficiencies have also been identified and are the basis of other treatment strategies, such as NMDA-receptor agonists (see reviews by Blennow, de Leon & Zetterberg, 2006; Tyas & Gutmanis, 2008). There are various other treatment strategies for AD, to address either symptoms (i.e., anti-convulsion or anxiety medication) or pathology (i.e., secretase

modulators, Aβ immunotherapy, anti-tau and anti-inflammatory medication) (see reviews by Blennow, de Leon & Zetterberg, 2006; Cummings, 2004).

2.1.4.3. Vascular Dementia

VaD is characterized by vascular injury in the brain. The terms multi-infarct encephalopathy and post-ischemic lesions describe overall neurovascular injury (see review by Jellinger, 2008). Vascular injury can be categorized as focal, multifocal or diffuse lesions. Lesions can then be further sub-categorized by size or location. For instance, lacunes are larger than micro-infarcts, while white matter lesions and hippocampal sclerosis describe specific locations of lesions in the brain. Lesions can also be distinguished based on whether they are related to large or small vessel disease (see review by Jellinger, 2008). The above types of vascular injury are the result of systemic, cardiac, local large or small vessel disease (see review by Jellinger, 2008). However, the type of lesion in the brain may not be as important as the volume of brain destroyed or the location or number of vascular lesions (see review by Jellinger 2008). Specifically, strategic locations of vascular injury, even when small in size, can cause more damage than larger lesions in 'unimportant' areas of the brain. Stroke and silent stroke are often the cause of vascular injury in the brain (Vermeer et al., 2003). Vascular events in the brain cause a cascade of events to occur, such as hypoxia, neuroinflammation and oxidative stress (see reviews by Jellinger, 2008; Querfurth & Laferla, 2010). These events can lead to further injury in the brain, such as neurodegeneration and atrophy.

2.1.4.4. Mixed Dementia

AD has many vascular components in addition to traditional AD pathology. Mixed dementia is diagnosed when a patient has evidence of AD plus cerebrovascular disease or vascular encephalopathy, which is identified based on neuroimaging or the occurrence of an ischemic event, such as stroke (see reviews by Jellinger, 2008; Kalaria, 2002). The overlap between neurodegenerative burden (i.e., pure AD) and vascular cerebral lesion burden (i.e., pure VaD) results in mixed dementia. It has been suggested that the overlap between AD and VaD neuropathology should be viewed as a continuum or spectrum of dementia (see review by Viswanathan, Rocca & Tzourio, 2009).

2.1.4.5. Mild Cognitive Impairments

The neuropathophysiology of CIND or MCI can be described as a mild version of dementia neuropathophysiology, such as that found in the very early stages of AD or VaD (Bennett et al., 2005; Markesbery et al., 2006). In those suffering from MCI or CIND, the burden of plaques and tangles or vascular lesions in the brain has not yet reached the critical threshold necessary for dementia (Markesbery et al., 2006; Schneider et al., 2009). In their study examining the various neuropathologies of those diagnosed with MCI, Bennett et al. (2005) found that nearly all persons had some level of AD pathology and 35% of people also had cerebral infarcts. It has also been suggested that neurofibrillary tangle density is important when determining the stage of MCI and whether it will progress to AD (Guillozet et al., 2003). Not all cases of MCI or CIND, however, will progress to a more severe form of cognitive impairment (Saito et al., 2007).

2.2. Migraines

2.2.1. Definition

2.2.1.1. Headache Disorders

The most common form of neurological disorder is a headache, which causes substantial disability in the population (Stovner et al., 2007; see review by O'Bryant et al., 2006). There are two broad groups of headache disorders: primary and secondary. Primary headache disorders are those where the headache is the primary problem. Conversely, secondary headache disorders are those that are caused by an underlying condition, such as a brain tumour or head injury (see review by Lipton, Hamelsky & Stewart, 2004). Migraines are one of the most common forms of primary headache disorders and are considered to be one of the most debilitating (see review by Lipton, Hamelsky & Stewart, 2004).

Migraines differ from other types of headaches in a number of ways, such as altered visual perception, phonophobia (sound sensitivity), photophobia (light sensitivity) and nausea (see review by Lipton, Hamelsky & Stewart, 2004). There are two distinct types of migraines defined by the International Headache Society (IHS) using the second edition of the International Classification of Headache Disorders (ICHD-II): migraines with aura (MA) and migraines without aura (MoA) (Silberstein et al., 2007; see reviews by Lipton & Bigal, 2005; Lipton, Hamelsky & Stewart, 2004).

2.2.1.2. Phases of a Migraine Attack

A migraine attack can be broken down into four phases: prodrome or premonitory, aura, pain or headache, and postdrome or resolution (see review by Lipton, Hamelsky & Stewart, 2004). Not all people who suffer from migraines experience each phase; the phases

experienced may vary for each migraine attack, as well as the accompanying symptoms. Prodromal symptoms usually occur hours or days before a migraine attack and can include altered mood, excessive sleepiness, cravings or stiff muscles (see reviews by Lipton, Hamelsky & Stewart, 2004; Silberstein, Lipton & Goadsby, 1998). Only about 40-60% of migraineurs suffer from prodromal symptoms. Aura is a neurological phenomenon that precedes or accompanies a migraine attack and can last from five minutes to an hour. Aura symptoms can be visual, motor or sensory: the most common form is visual aura. Visual aura may include a variety of positive features (e.g., seeing spots) and negative features (e.g., areas of visual loss) (see review by Lipton, Hamelsky & Stewart, 2004). Twenty to thirty percent of migraineurs suffer from MA. Individuals who suffer from MA often will also have MoA. The headache or pain phase usually follows aura. It is characterized by throbbing on one side of the head, which can range from moderate to severe intensity (see review by Lipton, Hamelsky & Stewart, 2004). The headache phase is often accompanied by photophobia, phonophobia, nausea and vomiting (see review by Lipton, Hamelsky & Stewart, 2004). During the resolution or postdromal phase, migraine pain and accompanying symptoms begin to subside. However, many migraineurs report suffering from long-term physical and psychological symptoms that can last for days or weeks (e.g., scalp tenderness or mood changes) (see review by Lipton, Hamelsky & Stewart, 2004).

2.2.1.3. Probable Migraine

Many people who report migraine-like features will fail to fully meet the criteria of the IHS: ICHD-II for either MA or MoA. This condition has become known as "probable migraine" and is considered a subtype of migraine headache disorders (Patel et al., 2004;

Silberstein et al., 2007; see reviews by Bigal, Lipton & Stewart, 2004; Lipton & Bigal, 2005). According to the IHS: ICHD-II, a probable migraine diagnosis is applicable when the individual meets all but one criterion for MA or MoA (Patel et al., 2004; Silberstein et al., 2007; see review by Bigal, Lipton & Stewart, 2004). Research suggests that the profile of a migraine changes over the course of an individual's life. This suggests that since the profile of a migraine varies over a lifetime, not all individuals suffering from probable migraine will progress to full migraine; although some may progress to a full migraine diagnosis, others will cease to experience migraines at all (see review by Bigal, Liberman & Lipton, 2006).

2.2.1.4. Diagnostic Criteria

Migraine diagnoses are based on an exclusion-inclusion standard. The IHS: ICHD-II diagnostic criteria are the gold standard of migraine diagnosis (IHS:ICHD, 1988; IHS:ICHD, 1997; 2004; Silberstein et al., 2007; see reviews by Lipton & Bigal, 2005; Lipton, Hamelsky & Stewart, 2004). Migraine diagnosis rates may be inaccurate because many individuals do not consult doctors or receive medical diagnoses for their migraine disorder (see review by Bigal, Lipton & Stewart, 2004). Lipton, Diamond et al. (2001) found that although migraine diagnoses have increased, approximately half of the population in the US suffering from migraines remains undiagnosed. Also, individuals who do not meet MA or MoA diagnostic criteria may meet the criteria for probable migraine (Patel et al., 2004; Silberstein et al., 2007; see review by Bigal, Lipton & Stewart, 2004). Migraine headache studies often use self-reported migraine history, rather than the IHS: ICHD criteria diagnoses. Research has shown that there is excellent agreement between questionnaire-based self-reported migraine and the IHS: ICHD-II criteria for migraine diagnoses (Schurks, Buring & Kurth, 2009). Even

when the questionnaire items have been modified from IHS: ICHD-II criteria questions, high sensitivity and specificity have been observed in validation studies among population samples (Schurks, Buring & Kurth, 2009; Lipton et al., 2001).

2.2.2. Rates and Impact on the Population

2.2.2.1. Incidence and Prevalence

Migraines affect approximately 11% of people experiencing a headache disorder (Stovner et al., 2007). It is estimated that 35 million people in the US suffer from severe migraine headaches (Diamond et al., 2007; see review by Bigal & Lipton, 2009). In Canada, it is estimated that four million people suffer from migraines (O'Brien, Goeree & Streiner, 1994; see review by Becker, Gladstone & Aube, 2007).

Both migraine incidence and prevalence vary by gender and age (see reviews by Bigal & Lipton, 2009; Diener & Beck, 2009; Lipton & Bigal, 2005a,b). Migraine rates vary by gender, affecting up to 20% of women and 8% of men globally (see review by Diener & Beck, 2009). Cumulative lifetime incidence of migraines has been found to be 43% in women and only 18% in men (Stewart et al., 2008). The incidence of MA is highest in females between the ages of 12 and 13, whereas incidence of MoA is highest in females between the ages of 14 and 17 (see reviews by Bigal & Lipton, 2009; Lipton & Bigal, 2005a,b). Incidence of both types of migraines peaks earlier for males: approximately 5 years of age for MA and 10 to 11 years of age for MoA (see reviews by Bigal & Lipton, 2009; Lipton & Bigal, 2005a,b). Prior to puberty, migraine prevalence is higher in boys than in girls, but as adolescence approaches, both incidence and prevalence increase more rapidly in girls than in boys (see reviews by Bigal & Lipton, 2009; Lipton & Bigal, 2005a,b). The

prevalence of migraines among women increases throughout childhood and early adulthood until approximately age 40, when it declines (see reviews by Bigal & Lipton, 2009; Lipton & Bigal, 2005a,b). The overall prevalence of migraine is higher in women than in men (see reviews by Bigal & Lipton, 2009; Lipton & Bigal, 2005a,b). For both men and women, overall migraine prevalence is highest from the ages of 25 to 55, which corresponds to the peak years of economic productivity (see reviews by Bigal & Lipton, 2009; Lipton & Bigal, 2005a,b). The gap between peak incidence in adolescence and peak prevalence in mid-life reflects the chronic nature of migraines (see review by Bigal & Lipton, 2009). Migraine prevalence does appear to decline in post-menopausal women. Some studies, however, have shown that a small number of women experience a worsening of symptoms or no change at all in their migraine status (MacGregor, 2009).

In addition to age and gender differences in migraine prevalence and incidence, variation also occurs with race and geographic location (see review by Bigal & Lipton, 2009). The highest prevalence estimates have been found in North America. Within North America, Caucasian Americans experience the highest migraine prevalence, followed by African Americans, with the lowest prevalence seen in Asian Americans (Stewart et al., 1992, 1995, 1996; see review by Bigal & Lipton, 2009). Prevalence estimates are also low in Asia and Africa and continue to be low in North America for Asian and African-Americans. Researchers speculate that this implies a race-related genetic susceptibility for migraines (Stewart et al., 1996).

In addition to variation by race, migraine prevalence also varies by socioeconomic status. In the US, it has been shown that migraine prevalence is inversely related to household income (Lipton, Stewart et al., 2001; see reviews by Bigal & Lipton, 2009; Lipton

& Bigal, 2005a,b; Lipton et al., 2007), with low socioeconomic status, income or education related to an increased prevalence of migraines. This relationship is observed in adults and those without a family history or predisposition for migraines (Bigal et al., 2007). Bigal et al. (2007) noted that among adolescents with a family history of migraines, the relationship between household income and migraine prevalence was not significant. Bigal et al. (2007) speculated that this might be due to an increased biological predisposition: in those with a family history of migraines, a genetic predisposition may be more influential in causing migraines than environmental or socioeconomic factors.

2.2.2.2. Impact of Migraines

The burden of headache disorders on individuals and society is much greater than previously thought. The medical community is beginning to change its attitude towards headache disorders and specifically migraines, with the recognition that migraines are the cause of significant suffering, disability and impairments in quality of life (see review by Leonardi, 2005). This change in attitude may be in part due to the World Health Organization (WHO) acknowledging headache disorders as a high-priority public health issue as stated in the World Health Report 2001 (WHR, 2001). The WHO ranked migraine as the 19th cause of disability in both sexes and the 12th for women alone (Stovner et al., 2007; WHR, 2001; see review by Leonardi et al., 2005).

In the US, 25% of female migraine sufferers experience more than four severe migraine attacks per month and 35% experience one to four severe attacks per month (Lipton, Stewart et al., 2001; see reviews by Bigal & Lipton, 2009; Lipton & Bigal, 2005a,b; Lipton et al., 2003). These figures are similar in men. Migraine disorders are a complex

condition to manage, as an individual cannot always predict when a migraine attack will occur. This unpredictability can have adverse effects on an individual's psychological well-being. In particular, migraine sufferers report fear of their migraine condition disrupting their work and making them unable to care for themselves and others (see reviews by Bigal & Lipton, 2009; Lipton & Bigal 2005a,b; Lipton et al. 2003). Health-related quality of life (HRQoL) disability measures have been used to assess the impact of migraine on an individual. Many studies have shown that migraine reduces an individual's HRQoL not only during a migraine attack, but also prior to and following the attack (El Hasnaoui et al., 2003; see reviews by Bigal & Lipton, 2009; Lipton & Bigal, 2005a,b; Lipton et al., 2003, 2000). The issue of comorbid disorders is also a major concern for those suffering from migraines, as a comorbid disorder may cause added disability. Migraine sufferers are more likely to also suffer from vascular diseases or disorders (e.g., hypertension or diabetes) (Bigal et al., 2009; see reviews by Bigal et al., 2010; Scher et al., 2005). In addition, migraine medication is often expensive and may have side effects that cause further disability for the individual, such as insomnia (Bigal et al., 2007).

Migraines not only impact the individual in the form of disability, but also impact society. Direct costs of migraine can be quantified through the economic value of the disorder in relation to health care utilization (see reviews by Bigal & Lipton, 2009; Lipton & Bigal, 2005a,b; Lipton et al., 2003, 2000). Migraines increase the use of emergency departments and urgent care centers, in addition to prescription and over the counter medications. The indirect cost of migraine is primarily made up of loss of productivity due to absenteeism and reduced work performance while at work (Hu et al. 1999). Hu et al. (1999) estimated that productivity losses due to migraine cost US employers $13 billion per year.

2.2.2.4. Probable Migraine

Probable migraine shares a similar epidemiologic pattern with conventional migraines (Patel et al., 2004; Silberstein et al., 2007). However, prevalence estimates for probable migraine vary widely, ranging from 2.6% to 14.5% (Henry et al., 2002; Lipton, Stewart et al., 2001; Patel et al., 2004; Silberstein et al., 2007). These estimates vary due to under-diagnosis of probable migraine, as well as underestimates due to lack of self-report. Prevalence of probable migraine is slightly higher in women than in men (Henry et al., 2002; Lipton, Stewart et al., 2001; Patel et al., 2004; Silberstein et al., 2007). In both men and women, probable migraine prevalence peaks during mid-life, between the ages of 30 and 59 years (Patel et al., 2004; Silberstein et al., 2007). Race-specific differences have been observed for probable migraine as well as classic migraine (Silberstein et al., 2007). In contrast to migraine, probable migraine prevalence is higher in African-Americans than in Caucasian Americans (Silberstein et al., 2007). However, in an earlier study, probable migraine prevalence in different races mimicked estimates seen for migraine (Patel et al., 2004). Individuals suffering from probable migraine experience disability and loss of quality of life similar to those suffering from migraines (Patel et al., 2004; Silberstein et al., 2007).

2.2.3. Risk Factors, Triggers and Comorbidities

2.2.3.1. Definition of Risk Factors, Triggers and Comorbidities

It is important to distinguish between risk factors, triggers and comorbidities of migraine. A migraine risk factor increases the risk of an individual developing migraine, whereas a migraine trigger induces or precipitates a migraine attack in a migraine sufferer. Migraine comorbidity is the greater than coincidental association of separate diseases or

disorders with migraine, within the same individual. A summary of risk factors, triggers and comorbidities for headache disorders is shown in Table 2.

Table 2: Risk factors, triggers and comorbidities for headache disorders

	Migraine (MA[1]/MoA[2])	Probable Migraine
Risk Factors[3]	Family history of migraines Sex: Female Depression Epilepsy Low socioeconomic status	Family history of migraines Sex: Female
Triggers[4]	Dietary Environmental - Odours - Lights Behavioural - Activity level Physiological - Hormone cycles Psychological - Stress	
Comorbidities[5]	Psychiatric - Panic disorders - Anxiety - Depression - Bipolar disorder Neurological - Chronic pain disorders - Epilepsy - Tourette's syndrome Vascular - Raynaud's phenomenon - Diabetes - Hypertension - Hyperlipidemia - Family history of myocardial infarction - Congenital heart defects Other - Asthma - Allergies	

[1]MA- migraines with aura
[2]MoA- migraines without aura
[3]Risk factors increase the risk of an individual developing migraine
[4]Triggers induce or precipitate a migraine attack in a migraine sufferer
[5]Comorbidities are the greater than coincidental association of separate diseases or disorders with migraine, within the same individual

2.2.3.2. Risk Factors

Migraine risk factors are often difficult to identify, as they are occasionally mistaken for triggers. Migraine risk factors include female gender, family history of migraines, depression, epilepsy and low socioeconomic status (Bigal et al., 2007; Breslau et al., 2003; see reviews by Breslau & Rasmussen, 2001; Lipton, Hamelsky & Stewart, 2004).

Female gender is one of the most consistent risk factors for migraines, given that migraines affect up to 20% of women and only 8% of men globally (see review by Diener & Beck, 2009). The exact pathophysiological reason for this relationship between migraine incidence, prevalence and female gender is not known, although researchers have suggested that it is related to menstrual cycle hormones, specifically estrogen (MacGregor, 2009).

Given that family history of migraine is a risk factor for migraine, many researchers have speculated that there is a genetic component involved in migraine risk (see review by Breslau & Rasmussen, 2001). Certain rare forms of inherited migraine disorders have been linked to genetic factors: chromosomes 1 and 19 have specifically been identified (see review by Breslau & Rasmussen, 2001; Montagna, 2008). Despite some genes being implicated in inherited migraines, migraines are not inherited in a straightforward manner. Research suggests that although genetics play a part in inherited migraines, a multi-factorial inheritance pattern (multiple genes interacting with various environmental factors) is most likely (see review by Breslau & Rasmussen, 2001; Montagna, 2008). It is also possible that genetic factors may affect the association between migraines and cognitive health outcomes. Research on both migraines and AD has implicated chromosomes 1 and 19 (Azad, Al Bugami & Loy-English, 2007; see reviews by Blennow, de Leon & Zetterberg, 2006;

Breslau & Rasmussen, 2001; Burns & Iliffe, 2009; Patterson et al., 2007). This genetic relationship has not been thoroughly investigated (Lopera et al., 1997; Ringman et al., 2008).

Major depression has been shown to increase the risk of migraine, and migraine increases the risk for major depression (Breslau et al., 2003). Patel et al. (2004) found the overall prevalence of major depression to be 29.1% for migraine (MoA/MA), 19.5% for probable migraine and 23.1% for both migraine and probable migraine pooled together, compared to controls with only 10.3% prevalence of depression.

Epilepsy may be considered a risk factor for migraines, but also a comorbidity. Epilepsy can cause migraines; conversely, migraines can cause epileptic seizures (see reviews by Bigal et al., 2003; Diener, Kuper & Kurth, 2008). When a migraine headache precipitates an epileptic seizure, it is referred to as migralepsy (see review by Bigal et al., 2003). Alternatively, an epileptic seizure can trigger a migraine headache; this is often referred to as a post-seizure headache (see reviews by Bigal et al., 2003). The relationship between migraines and epilepsy is often mis- or under-diagnosed (see reviews by Bigal et al., 2003; Diener, Kuper & Kurth, 2008). Incidence of migraine is 2.4 times higher in people with epilepsy (see review by Diener, Kuper & Kurth, 2008). The relationship between migraines and epilepsy is due to the overlapping biological mechanisms in the brain (see reviews by Bigal et al., 2003; Diener, Kuper & Kurth, 2008). One such mechanism is cortical spreading depression, which is a wave of depolarization that propagates across the brain cortex, initiating excitation followed by depression of normal neuronal activity (Welch, Michael & Goadsby, 2003).

2.2.3.3. Triggers

Migraine triggers vary depending on the individual. They can be classified as endogenous or exogenous factors (see reviews by Breslau & Rasmussen, 2001; Lipton, Hamelsky & Stewart, 2004). Endogenous factors include those that originate within the migraine sufferer, such as hormone cycles (see reviews by Breslau & Rasmussen, 2001; Lipton, Hamelsky & Stewart, 2004). Exogenous factors are those that affect an individual from outside, for example, diet, activity level, foods or even certain smells (see reviews by Breslau & Rasmussen, 2001; Lipton, Hamelsky & Stewart, 2004). Triggers are often separated into subcategories, such as dietary, environmental, behavioural, physiological or psychological factors (see review by Lipton, Hamelsky & Stewart, 2004).

2.2.3.4. Comorbidities

Migraine comorbidities can cause confusion if they are not classified accurately, creating misleading research results and missed opportunities to treat or prevent the conditions involved (see review by Bigal & Lipton, 2009). Comorbidities of migraine are most often categorized as psychiatric, neurological, or vascular (see reviews by Bigal & Lipton, 2009; Scher, Bigal & Lipton, 2005). Migraine has been found to be comorbid with various psychiatric disorders, including panic disorders, anxiety, depression and bipolar disorder (see reviews by Bigal & Lipton, 2009; Scher, Bigal & Lipton, 2009). Neurological disorders that have been associated with migraine include epilepsy and Tourette's syndrome (see reviews by Bigal & Lipton, 2009; Scher, Bigal & Lipton, 2009). Other disorders that have been associated with migraines include Raynaud's phenomenon, congenital heart

defects, asthma, allergies and chronic pain disorders (see reviews by Bigal & Lipton, 2009; Scher, Bigal & Lipton, 2009).

The comorbid association between migraines and CVD has become a major research focus, as CVD is the leading cause of death in North America (WHO, 2002). Migraine sufferers have a higher prevalence of risk factors that are associated with CVD, such as diabetes, hypertension, hyperlipidemia and family history of myocardial infarction (Bigal et al., 2009; see reviews by Bigal et al., 2010; Scher et al., 2005). Migraine is associated with vascular events as well, such as myocardial infarction and stroke (Bigal et al., 2010; see reviews by Bigal et al., 2009; Scher, Bigal & Lipton, 2005). The association between migraine and stroke has been well documented, specifically MA and stroke. The relationship between migraine and CVD, including stroke, appears to be strongest in women (Kurth et al., 2009; see review by Kurth & Diener, 2006).

2.2.4. Neuropathophysiology

2.2.4.1. Neuropathophysiology of Triggers

The exact mechanism by which migraine triggers initiate migraine attacks is unknown. However, researchers have hypothesized that migraine sufferers are genetically predisposed to a hyper-excitable or under-inhibited cortex (Chakravarty, 2010; see review by Lambert & Zaqgami, 2008). The migraine trigger is thought to elicit a response in individuals with a low migraine threshold, which precipitates cortical discharges that give way to cortical spreading depression (CSD) (Chakravarty, 2010). Triggers are in essence a cortical phenomenon, as they can be viewed as sensations (Chakravarty, 2010). Triggers reach the cortex through sensory pathways (i.e., sight, smell, sound) or humorally through the blood stream (i.e., hormones, absorbed chemicals). Upon reaching the cortex, triggers may act by altering ionic flow across cell membranes, inducing CSD in an already hyper-excitable cortex (Chakravarty, 2010).

2.2.4.2. Acute Neuropathophysiology of Migraines

The major underlying biological mechanisms involved in migraine disorders include CSD, neural inflammation, and cranial vascular contraction and expansion. The same general pathophysiology occurs in both MA and MoA. Several areas and pathways within the brain are involved in the underlying mechanism of migraine headaches and vary based on the migraine phase.

The underlying mechanism of aura is CSD, which is a wave of depolarization that propagates across the brain cortex, initiating excitation followed by depression of normal neuronal activity (Welch, Michael & Goadsby, 2003). CSD is also associated with reduced

cerebral blood flow (Welch, Michael & Goadsby, 2003). CSD activates the trigemino-vascular system, which induces neurogenic inflammation due to the release of vasoactive peptides, specifically substance P and calcitonin gene-related peptide (see reviews by Buzzi & Moskowitz, 2005; Panconesi, Bartolozzi & Guidi, 2009). A transient increase in regional cerebral blood flow (vasodilation) is followed by a long-lasting considerable decrease in regional cerebral blood flow (vasoconstriction) (see review by Hamed, 2009). These events are sometimes referred to as spreading hypoperfusion.

A migraine moves from the aura phase to the headache or pain phase due to spreading depression causing stimulation of the trigeminal nucleus caudalis. The wave of cortical excitation and depression activates cortical-subcortical connections to nociceptive centers. Headache pain is due to the dilation of blood vessels caused by trigemino-vascular system activation, specifically stimulation of large cranial vessels and dura mater (see review by Hamed, 2009). This is in response to neural inflammation, which involves both vasodilation and plasma protein extravasation (i.e., leakage) that occurs in areas innervated by the trigemino-vascular system (see review by Buzzi & Moskowitz, 2005). Since CSD activates the trigemino-vascular system and causes a cascade of events leading to inflammation, this can become a persistent source of trigeminal stimulation and headache pain (Welch, Michael & Goadsby, 2003). The postdrome phase occurs when the headache pain and accompanying symptoms are subsiding due to decreasing inflammation in the brain (see review by Hamed, 2009).

2.2.4.3. Chronic Neuropathophysiology of Migraines

Repeated migraine attacks can cause long-term neurological damage, such as vascular injury and chronic inflammation (see reviews by Hamed, 2009; Panconesi, Bartolozzi & Guidi, 2009). Migraines cause changes in cranial vasculature: after the migraine attack has subsided, intracranial arteries have been seen to narrow. Various inflammatory markers have been observed in those suffering from chronic migraines. These markers include increased levels of C-reactive protein, interleukins (e.g. IL-1 and IL-6), tumour necrosis factor-alpha, and adhesion molecules (inter-cellular adhesion molecule and vascular cell adhesion molecules), which are markers for inflammation, oxidative stress, disturbed aggregability of the blood cells and thrombosis (see review by Hamed, 2009). Repeated vascular inflammation can thus result in endothelial injury of blood vessels, arteriopathy and thrombosis (see reviews by Hamed, 2009; Panconesi, Bartolozzi & Guidi, 2009). Vascular and ischemic injury has been shown to be associated with increased risk of stroke (Kurth et al., 2005; see review by Kurth & Diener, 2006). Hamed et al. (2010) concluded that endothelial injury, impaired endothelial vasoreactivity and increased carotid artery intima-media thickness occur with migraine. These vascular conditions are associated with various vascular risk factors and subsequently increase the risk of atherosclerosis (Hamed et al., 2010; 2009). These results suggest that migraines cause significant vascular injury and increase the risk of developing vascular diseases and conditions.

2.3. Migraines and Late-life Cognitive Health Outcomes

2.3.1. Migraines and Cognitive Impairment

Research regarding the relationship between migraines and cognitive function has produced conflicting results. Migraines have been shown to have deleterious effects on cognitive skills including attention, verbal ability, verbal and visual memory, and psychomotor ability (Calandre et al., 2002; D'Andrea et al., 1989; Hooker & Raskin, 1986; Le Pira et al., 2004, 2000; Mulder et al., 1999; Scherer, Bauer & Baum, 1997; Waldie et al., 2002; Zeitlin & Oddy, 1984). However, other studies have shown no differences in cognitive performance in those suffering from chronic migraines (Baars, Boxtel & Jolles, 2010; Bell et al., 1999; Burker, Hannay & Halsey, 1989; Gaist et al., 2005; Jelicic et al., 2000; Leijdekkers et al., 1990; Pearson et al., 2006). Variation in study results may be due to the variety of age groups studied, as well as the various cognitive performance tests utilized. Cognitive skills and performance tests used range from the Boston Scanning Test, which assesses conceptual abilities, to the California Verbal Learning Test, which assesses verbal memory and learning strategies. The age groups used in previous studies vary; few have looked at older adults. See Appendix A for a comparison of similarities and differences between the above studies.

Researchers have found an association between migraines and below average cognitive performance during mid-life (Le Pira et al., 2000; Waldie et al., 2007; Zetlin & Oddy, 1984; see review by Paemeleire, 2009). However, there is still controversy over the possible relationship between migraines and cognitive decline (Calandre et al., 2002; Kalaydjian et al., 2007; Pearson et al., 2005; see reviews by Paemeleire, 2009). Kalaydjian et al. (2007) observed that migraine sufferers' performance scores on cognitive tests were lower; however, their scores did not decline over time. They also noted that the effects of

migraine on cognitive tests were only seen in those over the age of 50 years (Kalaydjian et al., 2007).

2.3.2. Epidemiologic Studies of Migraines and Dementia

There have been very few epidemiological studies that have investigated the relationship between migraines and cognitive health outcomes. The majority of epidemiological studies focus on the relationship between migraines and cognitive performance (i.e., cognitive test scores), rather than a broader cognitive health outcome in late-life, such as dementia.

Only two studies have investigated the relationship between migraines and dementia, specifically AD. Using the MSHA dataset, Tyas et al. (2001) reported that migraines increased the risk of AD (Relative Risk (RR)=3.49, 95% CI:1.39-8.77); an even stronger effect was observed in women (RR=5.78, 95% CI:2.00-16.74). Tyas et al. (2001) adjusted for age, education and sex. However, these results disagree with a meta-analysis of eight case-control studies performed 10 years earlier (Breteler et al., 1991), although only four of the eight case-control studies contained data on migraines. Interestingly, one study included in the meta-analysis reported a non-significant higher risk for those with headaches; OR=1.60, 95% CI:0.48-5.61 (French et al., 1985). Breteler et al. (1991) found an inverse relationship between AD risk and migraines (RR=0.7, 95% CI:0.5-1.0). However, Breteler et al. (1991) saw an increased risk in men (RR=1.1, 95% CI:0.6-2.0) compared to women (RR=0.6, 95% CI:0.4-0.9). In contrast to Tyas et al. (2001), Breteler et al. (1991) only adjusted for age and sex. In addition, both studies examined interactions by gender.

A relationship between migraines and vascular dementia has been hypothesized because of the relationship between migraines and various vascular risk factors and health outcomes, such as stroke or heart attack. However, no epidemiologic study has been done to investigate this relationship (see review by Paemeleire, 2009).

2.3.3. Biological Mechanism Linking Migraines and Late-life Cognitive Health Outcomes

Migraines are a risk factor for various diseases and disorders, such as stroke and CVD (Scher et al., 2009; see review by Kurth et al., 2009). The reason for this may be the overlap of disease pathologies and underlying biological mechanisms. Many of the mechanisms involved in migraine neurophysiology, such as inflammation and reduced cerebral blood flow, are also underlying causes of dementia (Peers et al., 2009; see reviews by Hamed, 2009; McGeer, Rogers & McGeer, 2006; Panconesi, Bartolozzi & Guidi, 2009). Repeated exposure to these mechanisms, due to chronic migraine attacks, has been shown to cause permanent neurological damage (see review by Hamed, 2009). Levels of neurological damage may be related to the intensity, severity and frequency of migraine attacks; the varying levels of neurological damage may be similarly correlated with levels of dementia or cognitive decline (Calandre et al., 2002; see review by O'Bryant et al., 2006).

The overlap between the underlying biological mechanisms of both migraines and dementia suggests that having a history of migraines may increase the risk for negative cognitive health outcomes in late life. A hypothesized biological mechanism linking migraines and cognitive impairment is shown in Figure 1.

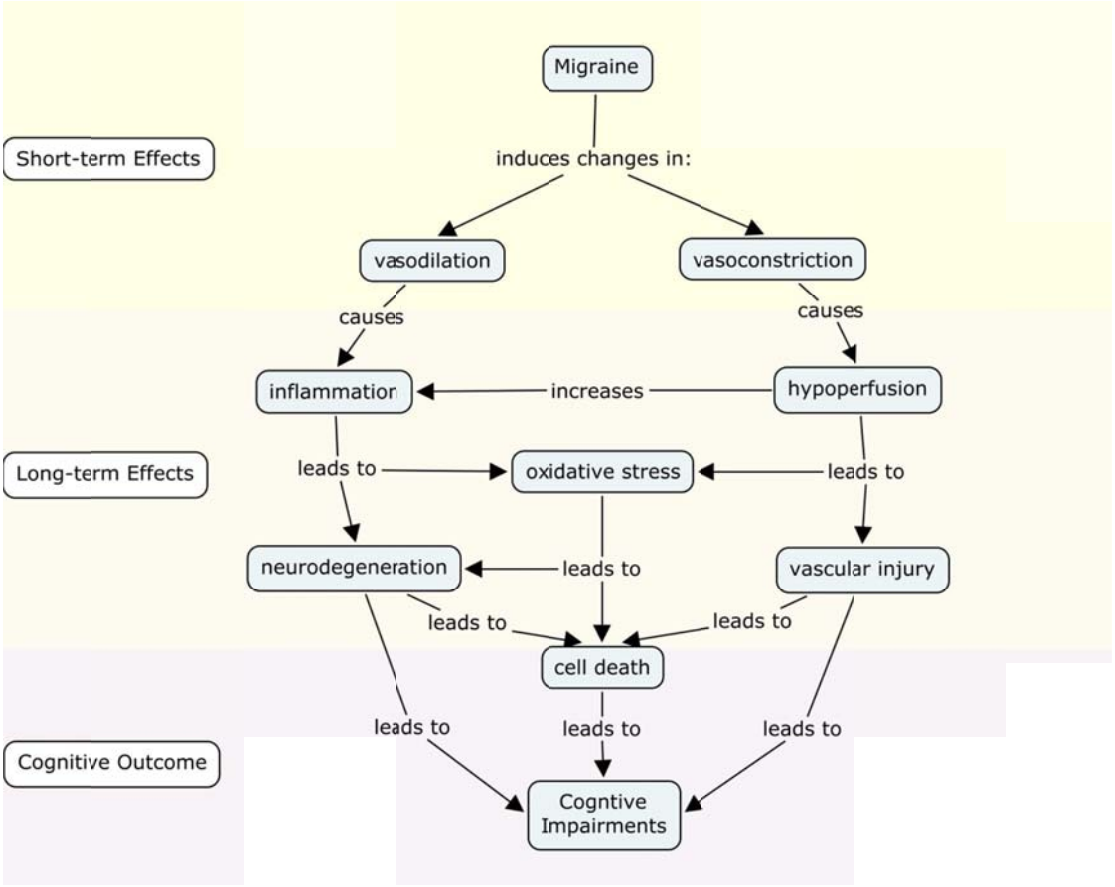

Figure 1: Hypothesized biological mechanism, illustrating both short and long-term effects, linking migraine pathophysiology to cognitive health outcomes

2.3.3.1 Description of Variable Types

To address the hypothesized biological mechanism linking migraine and cognitive impairment, variables were analyzed as confounding variables, intervening variables, or effect modifiers, based on evidence from the literature on each variable's relationship to the exposure and outcome.

Confounding variables are related to both the exposure and the outcome variables, but are not on the casual pathway between the exposure and outcome (see reviews by Kraemer et al, 2001; Last, 2001). Unless a confounding variable is addressed by adjusting in multivariate analyses or use of other strategies, its effects may distort the effects of the exposure under investigation on the outcome (see reviews by Kraemer et al, 2001; Last, 2001). An example of how confounding may apply to this thesis project can be seen when examining the effects of sex on the association between migraines and AD. Female sex increases the risk of migraines and AD and is not along the causal pathway between migraines and AD. Therefore, if the potential confounding effects of sex are not addressed, any relationship observed between migraines and AD may be incorrect and alternatively explained by the relationship between AD and sex. The possible confounding variables to be examined were age, sex, education, depression and epilepsy. These variables have been shown in the literature to be related to the exposure, migraines, and the outcome, late-life cognitive health.

Alternatively, intervening variables or mediators are variables that are related to the causal pathway between the exposure and outcome variables (see reviews by Kraemer et al, 2001; Baron & Kenny, 1986). An intervening variable can cause variation in how the exposure affects the outcome (see reviews by Kraemer et al, 2001; Baron & Kenny, 1986).

Intervening variables are statistically associated with the outcome variable (Last, 2001). Potential intervening variables to be examined were hypertension, diabetes, stroke, myocardial infarction and other heart conditions. These variables have been hypothesized to be related to the pathway connecting the exposure, migraines, and the outcome, late-life cognitive health outcomes.

In addition to confounding and intervening variables, this thesis project will also be addressing effect modifiers. An effect modifier modifies the effect of the exposure variable on the outcome (see reviews by Kraemer et al, 2001; Last, 2001). Effect modifiers are often observed as subgroups within which the relationship between the exposure and the outcome varies. The association between migraines and late-life cognitive health outcomes may vary by sex and family history of dementia, as supported by the literature. Sex and family history of dementia have been examined as effect modifiers as they may impact the relationship between the exposure, migraines, and the outcome, late-life cognitive health. Family history of dementia was used as a proxy for genetic predisposition to dementia. Refer to Figure 3 for the hypothesized relationship between MSHA variables.

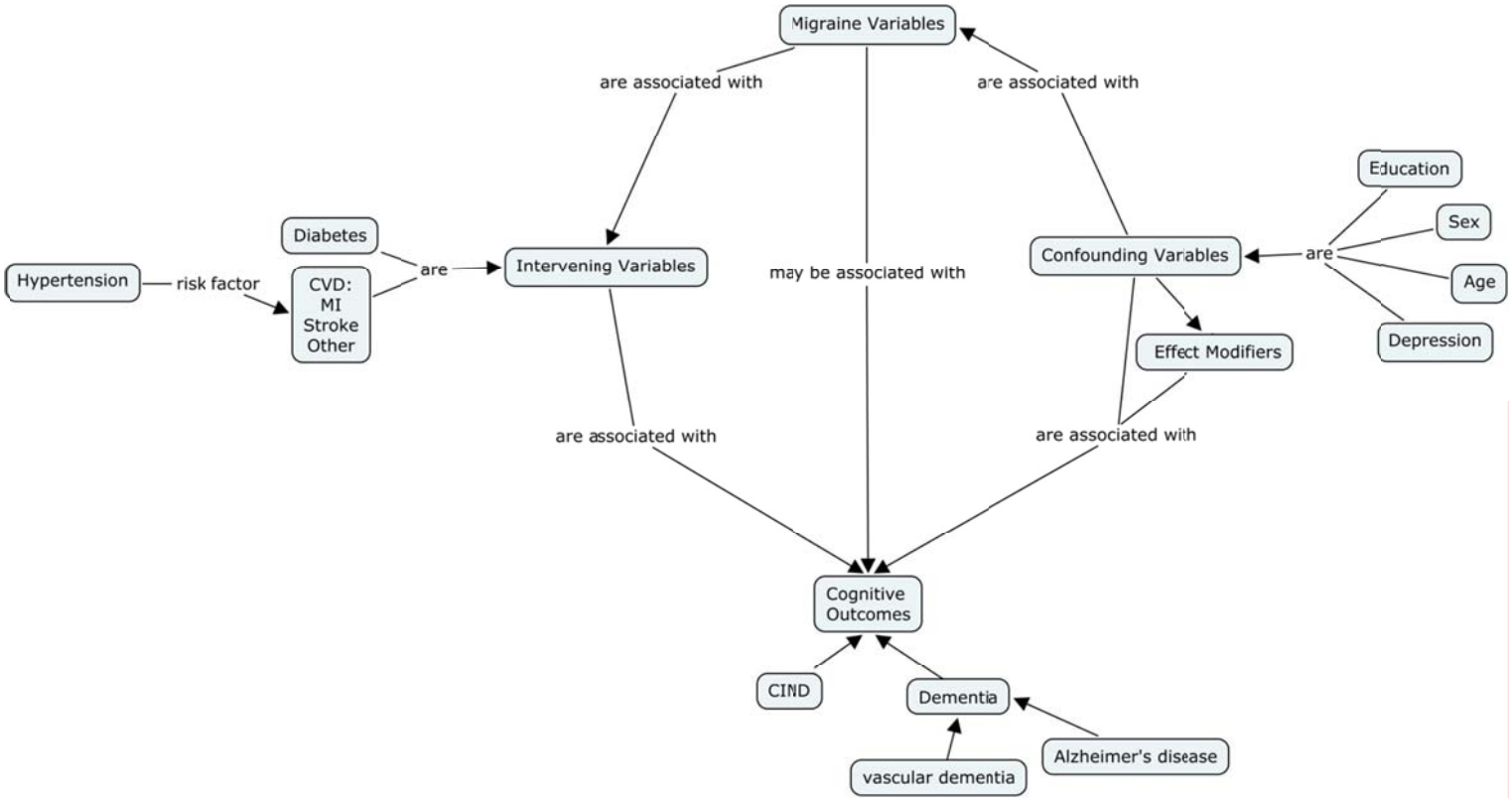

Figure 2: Hypothesized relationship between Manitoba Study of Health and Aging variables.

Exposure variables:
- History of migraine
- Duration of migraine disorder

Cognitive outcomes:
- CIND (cognitive impairment-no dementia)
- Overall dementia
- Alzheimer's disease
- Vascular dementia

Intervening variables:
- Hypertension
- Diabetes
- CVD (cardiovascular disease)
  - Myocardial Infarction
  - Stroke
  - Other heart condition

Confounding variables:
- Education
- Age
- Sex
- Depression

2.4. Summary

Dementia is a major health concern for adults. Migraines are a common form of headache disorders that affect millions of people worldwide. Dementia and migraines are both neurological disorders that cause significant economic impact and psychological strain on society.

Repeated exposure to migraine attacks causes permanent long-term neurovascular damage. Migraines are risk factors for various diseases and disorders, such as hypertension and stroke. These disorders are in turn significant risk factors for cognitive impairment and dementia. The association between migraines and cognitive health outcomes is biologically plausible given the overlap in underlying neuropathophysiology. There is evidence, despite conflicting results, that migraines may be related to cognitive impairment. It has been observed in one study that migraines are a risk factor for AD (Tyas et al., 2001). Migraines sufferers have a higher prevalence of vascular risk factors, suggesting that migraines may be a risk factor for VaD. It is clear that the possible relationship between migraines and late-life cognitive health outcomes requires further research and examination.

3. Study Rationale

3.1. Gaps in Research

Both migraines and dementia are common neurological disorders and represent a global health concern, indicating the importance of continued research of these disorders. However, the association between migraines and late-life cognitive health outcomes has not been thoroughly explored. A relationship between migraines and AD has been observed (Tyas et al., 2001), but has yet to be fully examined. Despite evidence that chronic exposure to migraine neuropathophysiology can cause permanent neurovascular damage, the link between neurological damage caused by migraines in mid-life and late-life cognitive function has not been fully explored.

Modification of the association between migraines and dementia by gender is possible given the observed gender differences in rates of migraines and dementia. In addition, migraines and epilepsy are linked by overlapping biological mechanisms, which has prompted debate over the relationship between epilepsy and dementia (Bigal et al., 2003; Hermann et al., 2008; Tellez-Zenteno et al., 2005). It is also possible that genetic factors may affect the association between migraines and cognitive health outcomes. As there are many unanswered questions regarding migraines and late-life cognitive health outcomes, this research area requires further investigation.

3.2. Research Objective

Using the MSHA dataset, Tyas et al. (2001) investigated various risk factors for AD. The results indicated that migraines were one of many significant risk factors for AD. However, there has yet to be a study investigating possible associations between a history of

migraines and risk for multiple late-life cognitive health outcomes. Since the study by Tyas et al. (2001) was not focused on migraines, possible intervening variables such as stroke, heart attack or diabetes were not investigated.

Data from the MSHA will be used to investigate relationships between migraines and risk for late-life cognitive health outcomes (dementia, AD, VaD, CIND) taking into consideration the possible associated intervening variables. A secondary focus of this study is to examine whether the association between migraine and these cognitive health outcomes varies by sex, epilepsy, and family history of dementia.

3.3. Research Questions

Does a history of migraines increase the risk of overall dementia, AD, VaD or CIND?

a) Do these associations persist after adjusting for potential confounders (age, sex, education, and depression)?
b) Do these associations persist after adjusting for potential intervening variables (hypertension, diabetes, stroke, and myocardial infarction)?
c) Do these associations vary within subgroups (sex and family history of dementia)?

4. Methods

4.1. Literature Search

The goal of this literature search was to systematically review the available literature relevant to migraines and cognitive impairment. Using various databases, including Medline, PsycINFO and Scopus, peer-reviewed articles were identified.

The key search database utilized was Medline; the interface used for these searches was PubMed. Using the MeSH terms “dementia” and “migraine disorders,” 93 articles were identified in Medline, including 58 review articles. In order to include articles not specifically discussing dementia, the MeSH terms “migraine disorders” and “cognition disorders” were used. This search yielded 80 articles, including 23 review articles. All articles that focused on the relationship between migraines and cognitive impairment, dysfunction, or decline were identified using these searches. As this core search was designed to be exhaustive and systematic, all articles were reviewed.

To locate relevant articles for migraine background information, broad searches were conducted in Medline to identify key review articles and original articles. To identify key articles regarding migraine epidemiology and specifically risk factors, the following MeSH terms were used: “migraine disorders”, “risk factors”, “depression”, “epilepsy”, “hypertension”, “hypercholesterolemia”, “cardiovascular disease”, “cerebrovascular disease”, “alcohol drinking” and “smoking”. This broad search yielded 3273 articles, including 667 review articles. To identify key articles regarding migraines and neuropathophysiology, the following MeSH terms were used: “migraine disorders”, “inflammation”, “pathology” and “physiology”. This search yielded 163 articles, including

50 review articles. The above searches were broad searches to give overall background information on migraine disorders.

To locate relevant articles for dementia background information, broad searches were conducted in Medline to identify key review articles and original articles. To identify key articles regarding dementia epidemiology, including AD, VaD and specifically dementia risk factors, the following MeSH terms were used: “dementia”, “Alzheimer disease”, “dementia, vascular”, “risk factors”, “depression”, “epilepsy”, “cardiovascular disease”, “cerebrovascular disease” and “diabetes mellitus”. This all-inclusive search yielded 12425 articles, including 2514 review articles. To identify key articles regarding MCI or CIND, MeSH terms were used in combination with non-MeSH terms ‘mild cognitive impairment’ and ‘cognitive impairment no dementia’, as MCI and CIND do not have MeSH terms. The MeSH terms included “risk factors” and “epidemiology”. This search yielded 337 articles, including 61 review articles. To identify key articles regarding dementia neuropathophysiology, the following MeSH terms were used: “dementia”, “inflammation”, “pathology”, “physiology”, “cardiovascular disease” and “cerebrovascular disease”, “receptors, cholinergic” and “receptors, neurotransmitter”. This search yielded 5315 articles, including 1219 review articles. To identify key articles regarding dementia and disability, the following MeSH terms were used: “dementia”, “caregivers”, “morbidity” and “mortality”. The non-MeSH term “caregiver burden” was also used. This search yielded 6214 articles, including 779 review articles. The above searches were broad searches to give overall background information on dementia and cognitive impairments.

To ensure that all relevant articles were identified, PsycINFO and Scopus were utilized in addition to PubMed. The searches performed in these databases confirmed that all relevant articles had been identified.

All searches were limited to English language articles and most were limited to more recent articles, within the last 10-15 years. Results from the above searches were manually examined for relevance; priority was given to the most recent articles or reviews, as well as key reviews in each research area. In addition to using article databases to identify relevant articles, article reference lists provided many important articles. Relevant articles were also identified by performing citation searches.

4.2. Data Source: Manitoba Study of Health and Aging

4.2.1. Study Population

The Canadian Study of Health and Aging (CSHA) is a population-based, longitudinal study of aging and dementia in Canada. Participants were adults 65 years of age and older and included both community and institutional residents.

The Manitoba Study of Health and Aging (MSHA) is a parallel study to the CSHA, using similar methods for data collection and diagnoses. The MSHA expanded the CSHA samples in Manitoba. Unlike the CSHA, the MSHA included rural farming communities, villages, towns and small cities. The community sample of the MSHA was derived by random sampling from the provincial health plan list. Those excluded were members of the military, RCMP, First Nations living on reserves, or residents of a remote, sparsely populated region of the province. The study population was stratified by health region and age group (65-74, 75-84, >85 years) and the two oldest age groups were over-sampled to ensure

sufficient numbers of older participants. At baseline (1991/92), 2890 people were contacted to be interviewed; 1751 people agreed and were able to participate. Reasons for non-participation included refusal (n=443), ineligibility (n=480), inability to be contacted (n=162) or inability to complete screening (n=54). This resulted in 1751 participants that were part of the study sample. At both time points the Modified Mini-Mental State Exam (3MS) was used to screen for cognitive impairment. A score of less than 78 on the 3MS identified a participant as potentially cognitively impaired. These participants were invited for an in-depth clinical examination. At the baseline interview in 1991/92, 1355 participants screened not cognitively impaired and comprised the incidence cohort. The Risk Factor Questionnaire was left with participants to be sent in by mail: 1039 (76.7%) returned their questionnaires. A summary of the MSHA study population and derivation of the analytic sample can be seen in Figure 3.

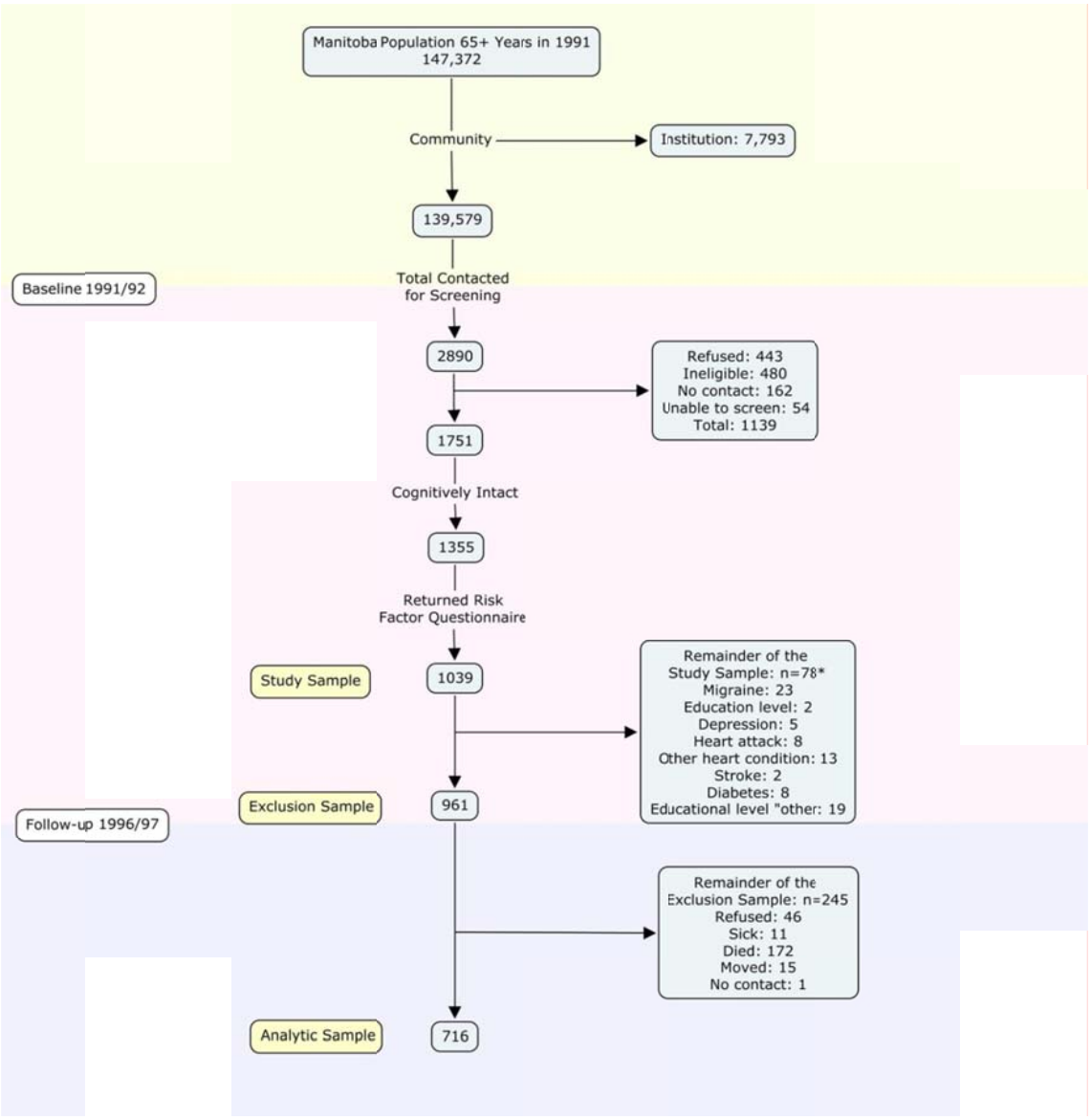

Figure 3: Manitoba Study of Health and Aging study population and derivation of the analytic sample

*Missing data on variables were often accounted for by other variables; see Section 4.3.1. for details on the reduction of the sample from n=1039 to n=961.

4.2.2. Data Collection

The primary purpose of the MSHA was to investigate aging and dementia in Manitoba. The focus of the MSHA study at baseline (MSHA-1) was to estimate the prevalence of and risk factors for dementia. Also examined were caregiver burden issues, as well as patterns of service use for older adults suffering from dementia and their caregivers (MSHA Research Group, 1995). The MSHA-2 objectives were to estimate incidence of dementia in Manitoba, identify risk factors for dementia and to compare cognitive status between MSHA-1 and MSHA-2. The study also continued to focus on caregiver and quality of life issues, such as estimating dependence in activities of daily living (ADLs), identifying factors that predicted development of frailty and ADL dependence, and examining factors associated with institutionalization and community-based service utilization by caregivers and community-residing older adults (MSHA-2 Research Group, 1998). At both time points in the study, data were collected on a variety of topics using many techniques, including interviews, self-reported questionnaires and clinical and psychological examinations. The self-report Risk Factor Questionnaire covered important aspects of participants' health, lifestyle and environment that could be risk factors for cognitive impairment. The screening interview portion of both the MSHA-1 and MSHA-2 covered key topics including sociodemographic characteristics, life satisfaction, psychological well-being, depression, health status indicators, chronic illness and ADLs. A screening test for cognitive impairment (Modified Mini-Mental State Exam (3MS)) was included and used to determine participation in the full clinical evaluation. Following a full clinical evaluation, consensus meetings were conducted with all members of the clinical team to determine a final clinical diagnosis.

Using established diagnostic criteria, cognitive status was divided into four categories: cognitively intact, possible cognitive impairment, cognitive impairment-no dementia and dementia. If a participant scored less than 78 on the 3MS they were considered potentially cognitively impaired and were invited to participate in a clinical assessment. This assessment then determined if they were cognitively impaired; if so, the type of cognitive impairment was identified. The dementia categories included AD, VaD, other specific dementia and unclassifiable dementia. Unclassifiable dementia included those who could not be diagnosed with another specific type of dementia (n=3; 2.1%). Overall dementia was diagnosed using the DSM-IV criteria (Hebert et al, 2000; DSM-IV, 1994). The diagnostic categories of probable AD and possible AD were assigned according to the NINCDS-ADRDA criteria (McKhann et al., 1984, Tyas et al., 2001). VaD was diagnosed using the DSM-III criteria at time 1 and NINDS-AIREN criteria at time 2 (Hebert et al, 2000; Roman et al., 1993). Diagnoses of CIND were based on the exclusion of dementia, despite the presence of impairment identified through clinical examination and neuropsychological tests (Graham et al., 1997).

4.3. Current Thesis Project

4.3.1. Sample Population

The analyses for the thesis project are based on the incidence cohort of 1039 individuals who screened cognitively intact at the time 1 interview of the MSHA. The study used data from individuals who completed the MSHA-Risk Factor Questionnaire, were cognitively intact at time 1 (n=1039) and had all relevant information available at time 2

(n=716). See Figure 3 for a summary of the MSHA study population and derivation of the analytic sample.

All variables were assessed for missing data. Specifically, 23 individuals had missing data on the exposure variable, history of migraines. The variable educational level had 19 individuals with missing or incomplete data (see Appendix B for further details). Twenty-three individuals had missing data on the variable depression. Twenty-five individuals had missing data on myocardial infarction, whereas 37 individuals had missing data on "other heart condition". Twenty individuals had missing data on stroke and diabetes. Finally, 26 individuals had missing data on hypertension.

Due to the hierarchical method of sample reduction, missing data for variables were often accounted for in previous reduction steps, as missing data for each variable were not mutually exclusive. Missing data on key MSHA-1 variables reduced the analytic sample for this study from 1039 to 961, as follows. Missing data on migraine history reduced the sample size from 1039 to 1016. Missing data on the educational level further reduced the sample to 997. Missing data on depression reduced the sample to 992. Exclusion of participants missing data on myocardial infarction reduced the sample from 992 to 984. Missing data for the variable "other heart condition" further reduced the sample from 984 to 971. Missing data on stroke reduced the sample from 971 to 969 and diabetes further reduced the sample from 969 to 961. The missing hypertension data were accounted for in previous steps.

Excluding those unable to complete the screening interview at MSHA-2 (moved n=15; refused n=31; sick n=8; died n=165) reduced the sample size to 742. The final analytic sample was determined by restricting to those with complete data on their cognitive status at MSHA-2: this included those who screened above the cut-point and thus were not required to

undergo clinical assessment as well as those who screened below the cut-point and were referred to and completed the clinical assessment (n=716). Twenty-six participants were missing cognitive outcome data, as they did not complete the MSHA-2 Clinical Examination (no contact n=1; refused n=15; sick n=3; died n=7).

In the final analytic sample, among participants suffering from migraines (n=74), duration of migraine disorder was available on a subset of the sample (n=36). Analyses have been done on this subset where sample sizes permit.

4.3.2. Variable Selection

The study primarily used variables from the MSHA-1 Risk Factor Questionnaire. However, a small number of variables from the MSHA-1 and the MSHA-2 Screening Interviews were also utilized. The exposure variables (history of migraines and duration of migraine disorder) are from the MSHA-1 Risk Factor Questionnaire. The migraine variables were used to explore the possible association with cognitive outcomes, using the final diagnosis from the MSHA-2 Screening Interviews and clinical examinations. Cognitive status (i.e., final diagnosis) at MSHA-1 was used to identify a cognitively intact sample at baseline and to determine cognitive outcomes at MSHA-2. The specific cognitive outcomes used as the outcome variables include overall dementia, AD, VaD and CIND.

The variables from the MSHA-1 Screening Interview included the possible confounders age, sex, and education. The variables from the MSHA-1 Risk Factor Questionnaire included potential intervening variables (hypertension, diabetes, stroke, myocardial infarction and other heart conditions), family history of dementia, depression and epilepsy. The variable ‘stroke’ represents those who have suffered from a clinical stroke and

therefore does not include silent or undiagnosed strokes. Epilepsy was unable to be examined as a confounding variable as only one study participant in the analytic sample suffered from this disorder. For a full list of variables and sources see Appendix C.

4.4. Data Access Request Protocol

To gain access to the MSHA dataset, a formal request was sent to the MSHA Research Centre at the University of Manitoba's Centre on Aging. The request included a brief background of the proposed research project, proposed data analysis strategy, estimated timeline for completion and a table of all variables of interest. Data access approval was granted on November 24th, 2010. A copy of the approved data access request is provided in Appendix D.

4.5. Ethics Approval

The MSHA and MSHA-2 received ethics approval from the Faculty Committee on the Use of Human Subjects in Research at the University of Manitoba. This thesis study received ethics approval on November 8th, 2010 from the University of Waterloo Office of Research Ethics. A copy of the University of Waterloo ethics approval is provided in Appendix E.

5. Data Analysis

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). General statistical methods and specific analyses are outlined in the following sections.

5.1. Descriptive Analyses

Univariate and bivariate analyses have been conducted to provide an overall sample description. These descriptive analyses have been conducted for all variables, including the general sample characteristics, intervening and confounding variables, as well as exposure variables and outcomes. The characteristics of the full and analytic samples have been compared to assess nonresponse bias. The association between exposure variables and various outcomes has been examined as outlined in the analytic plan (see Table 3). For bivariate analyses, Pearson chi-square values have been used to measure the associations between categorical variables, with Fisher's exact tests used as necessary. The strength of the associations has been assessed using odds ratios (OR) and 95% confidence intervals (CI). T-tests with unequal variance assumption have been used to measure the associations between continuous and dichotomous categorical variables.

Table 3: Analytic plan for migraine history and dementia including statistical method used and variables included in each model

Dementia:* Unadjusted	Statistical method:	Logistic regression
	Outcome variable:	Dementia
	Exposure variable:	Migraine history (Y/N)
	Confounding variables:	---
	Intervening variables:	---
Dementia: Confounding Variables	Statistical method:	Logistic regression
	Outcome variable:	Dementia
	Exposure variable:	Migraine history (Y/N)
	Confounding variables:	Age, sex, education, epilepsy[1] and depression
	Intervening variables:	---
Dementia: Confounding and Intervening Variables	Statistical method:	Logistic regression
	Outcome variable:	Dementia
	Exposure variable:	Migraine history (Y/N)
	Confounding variables:	Age, sex, education, epilepsy[1] and depression
	Intervening variables:	Hypertension, diabetes, stroke, myocardial infarction and other heart condition
Dementia: Final	Statistical method:	Logistic regression
	Outcome variable:	Dementia
	Exposure variable:	Migraine history (Y/N)
	Confounding variables:	Significant variables
	Intervening variables:	Significant variables

*reflects the set of models to assess the association between migraines and overall dementia. This set of models has been repeated for each remaining outcome: Alzheimer's disease, vascular dementia and cognitive impairment-no dementia; as well as repeated for all outcomes for the other measure of migraine exposure (duration).

[1]Epilepsy was unable to be used as a confounding variable as only one participant suffered from this disorder

5.2. Multivariate Modeling

In order to meet the stated research objective, a set of research questions were developed. The plan of analysis for each question is described in Table 3 and Table 4 below for the exposure variable "history of migraines." The analytic strategies shown below have also been used for the secondary exposure variable, duration of migraine disorder. The variables involved are listed for each analytic strategy. The model name indicates the outcome variables that are being referred to (dementia, AD, VaD, CIND). The model name also indicates which subquestion of each research question is being addressed (i.e., which variables are included).

The influence of exposure, confounding and intervening variables on the outcomes of interest was assessed using multiple logistic regression procedures. Although backward elimination was the preferred method of variable selection for the logistic regression models (Tyas, Koval & Pederson, 2000), sample sizes were insufficient to support backward elimination and thus stepwise selection methods for variable selection were used. The significance (α) levels used for the stepwise selection regression models were 0.15 for main effects and 0.05 for interactions. Significance was defined as a p-value less than 0.05. Results with p-values less than 0.10, but greater or equal to 0.05 were considered marginally significant. The logistic regression models were adjusted for the potential confounding variables age, sex, education, and depression. All variables were assessed for first-order interactions with the exposure variable history of migraines in the dementia and AD models: no significant interactions were observed. In addition, given the *a priori* hypothesized effect modification by sex and family history of dementia, the association between migraines and cognitive health outcomes within subgroups based on sex or family history of dementia were

investigated regardless of the significance of the relevant interaction terms. Hosmer-Lemeshow goodness of fit (H-L GOF) tests were performed on each model. Models were rejected if they had a p-value of <.05 for the H-L GOF. Additional model diagnostics to assess model fit, including assessment of influential outliers and tests of collinearity, were performed on all final models. Assessment of influential outliers was achieved by analysing DFBETA, C and CBAR results from SAS outputs for residual diagnostics. If participants had DFBETA, C or CBAR values exceeding the cut-point of +/-1.96, which corresponds to a significance level of 0.05, they would be deleted and the model re-run. Collinearity between variables was also assessed using SAS. The standard recommended by Kleinbaum et al. (1988) indicates the presence of multicollinearity between variables when two or more variance proportions greater than 0.90 are associated with condition indices greater than 30. For a more in-depth description of the multivariate modeling techniques that were used, see Tyas, Koval & Pederson (2000).

Table 4: Analytic plan for migraine history and dementia including statistical method used and variables included in each stratified model

Dementia Stratified: Unadjusted[1]	Statistical method:	Logistic regression
	Outcome variable:	Dementia
	Exposure variable:	Migraine history (Y/N)
	Confounding variables:	---
	Intervening variables:	---
	Effect modifiers:	Sex, and family history of dementia[1]
Dementia Stratified: Confounding Variables	Statistical method:	Logistic regression
	Outcome variable:	Dementia
	Exposure variable:	Migraine history (Y/N)
	Confounding variables:	Age, sex, education, epilepsy[2] and depression
	Intervening variables:	---
	Effect modifiers:	Sex, and family history of dementia[3]
Dementia Stratified: Confounding and Intervening Variables	Statistical method:	Logistic regression
	Outcome variable:	Dementia
	Exposure variable:	Migraine history (Y/N)
	Confounding variables:	Age, sex, education, epilepsy[2] and depression
	Intervening variables:	Hypertension, diabetes, stroke, myocardial infarction and other heart condition
	Effect modifiers:	Sex, and family history of dementia[3]

[1]Due to sample sizes stratification by family history of dementia was only possible when performed on the unadjusted dementia model. Stratification by sex was not able to be performed for any model.
[2]Epilepsy was unable to be used as a confounding variable as only one participant suffered from this disorder
[3]No other variables were found to have significant interactions with migraine history.

5.2.1. Recoding

Age and educational level were recoded to avoid small cell sizes. Age was recoded from a continuous variable into three categories: 65-74 years of age, 75-84 years of age and 85 years of age or older. Educational level was originally classified into 12 categories: No formal school; Some primary school; Finished primary school; Some high school; Completed high school; Some college; Completed college; Some university; Bachelor's degree; Master's degree; PhD; and Other. These categories were recoded to four categories: Did not complete primary school; Completed primary school; Completed high school; and Completed college/university (Bachelor's degree; Master's degree; PhD). In order to assess the appropriateness of the recoded educational level, the original educational level with 12 categories was compared to the recoded educational level with 4 categories. Although the 4-level classification of education differed significantly between the exclusion sample and the remainder sample, as well as the analytic sample and the remainder of the exclusion sample, this pattern did not differ from that of the original 12-level classification (see Appendix B).

5.2.2. Age of Onset

This thesis project explored age of onset of migraine disorder as a possible exposure variable using the length of time that participants suffered from migraines and their age when they reported the duration of their migraines. Migraine duration data, however, were only reported by a subset (n=36) of those with a history of migraines (n=74). Migraine duration ranged from 0.5 to 70 years among those who had a history of migraines. Of the thirty-six individuals included in the analytic sample with migraine duration data, the mean migraine duration was 28.6 years (SD=20.2). It might be assumed that the older the individual, the

longer they would have suffered from migraines. However, a dose-dependent relationship was not observed between age and migraine duration: a negative correlation (correlation coefficient=-0.14, p=0.42) was observed between migraine duration and age. In addition, many of those experiencing the longest duration of migraine disorder were in the youngest two age groups (65-74 years and 75-84 years). Only one participant with migraine duration data was in the oldest age group (85+ years) and reported experiencing migraines for only 10 years. These results raised concerns in interpretation and, in addition to the limited sample size, precluded use of age at migraine onset in further analyses.

6. Results

6.1. Sample Description

The characteristics of the analytic sample (n=716) are presented in Table 5. The study sample characteristics (n=1039) can be found in Appendix F. The derivation of the analytic sample from the study sample is described in Section 4.3.1 (Figure 2).

The sample excluding all missing data on exposure, intervening and confounding variables (n=961 – exclusion sample) was compared to the remainder of the study sample (n=1039 - n=961, i.e., n=78) to assess response bias and the representativeness of the sample. Response bias comparison results for the exclusion sample (n=961) compared to the remainder of the study sample (n=78) are shown in Appendix G: Table 1. All outcomes and confounding and intervening variables, except educational level, did not differ significantly between the exclusion sample and the remainder of the study sample. Educational level differed significantly between the exclusion sample and the remainder of the study sample. This was due to the exclusion of the educational level "Other" from the exclusion sample (see Appendix B: Coding of Education: Removal of "Other" Category from the Educational Level Variable).

The final analytic sample (n=716) was compared to the remainder of the exclusion sample (n=961 - n=716, i.e., n=245) to assess response bias and the representativeness of the sample. Response bias assessment of the analytic sample (n=716) compared to the remainder of the exclusion sample (n=245) is presented in Appendix G: Table 2. When comparing the analytic sample to the remainder of the exclusion sample, dementia, AD, and CIND were found to differ significantly between the two samples. The above late-life cognitive health outcomes were more common in the analytic sample. Within the analytic sample, 7.1% were

diagnosed with dementia, 4.8% were diagnosed with AD, and 5.2% were diagnosed with CIND. Within the remainder of the exclusion sample, there were no cases of CIND or any type of dementia.

Among the confounding and intervening variables, age, education in years and level, as well as myocardial infarction and stroke were found to differ significantly between the two samples. The average age of participants in the analytic sample was 75.9 (SD=6.1) years compared to an average of 78.5 (SD=7.4) years for those in the remainder of the exclusion sample. Within the analytic sample, 42.2% were 65 to 74 years of age compared to 33.9% of the remainder of the exclusion sample. Of participants in the analytic sample, 48.3% were between the ages of 75 and 84 years compared to 40.8% of the remainder of the exclusion sample. Finally, 9.5% of the analytic sample was over the age of 85 compared to 25.3% of the remainder of the exclusion sample. Participants in the analytic sample achieved an average of 10.4 (SD=3.1) years of education, compared to 9.7 (SD=3.2) years in the remainder of the exclusion sample. Educational level differed significantly between the two samples. Those who completed the final cognitive assessment were more likely to have completed college or university, compared to those who did not make it to the final cognitive assessment.

Within the analytic sample, 5.2% of participants suffered from a stroke compared to 9.8% of participants in the remainder of the exclusion sample. A greater number of participants reported myocardial infarction: 7.8% within the analytic sample and 15.1% in the remainder of the exclusion sample.

Table 5: Baseline characteristics and cognitive health outcomes for participants in the Manitoba Study of Health and Aging, 1991-1996: Analytic sample (n=716)

Participant Characteristics*	Baseline (%)	Follow-up (%)
Exposures		
Migraine history	10.3	
Migraine duration ($\bar{x}$(SD))	28.6 (20.2)	
Outcomes		
Dementia	0	7.5
Alzheimer's disease	0	5.1
Vascular dementia	0	1.9
Cognitive impairment-no dementia	0	5.6
Confounding Variables		
Age ($\bar{x}$(SD))	75.9 (6.1)	
Age group:		
65-74 years	42.2	
75-84 years	48.3	
85+ years	9.5	
Sex:		
Male	38.1	
Female	61.9	
Education**:		
Number of years ($\bar{x}$(SD))	10.4 (3.1)	
Level		
Did not complete primary school	8.5	
Completed primary school	48.0	
Completed high school	26.5	
Completed college/university	16.9	
Depression	9.5	
Epilepsy	0.1	
Family history of dementia	10.3	
Intervening Variables		
Hypertension	32.8	
Diabetes	6.6	
Stroke	5.2	
Myocardial infarction	7.8	
Other heart condition	17.5	

* Exposure, confounding and intervening variables were measured at baseline; outcomes were measured at follow-up five years later.

**Both measures of education were examined in univariate and bivariate analyses to determine which measure to use in the multivariate analyses.

6.2. Bivariate Results

Bivariate analyses were performed between cognitive outcomes and all other variables within the analytic sample (n=716). Results are summarized in Table 6, with odds ratios presented in Table 7.

Within the analytic sample, 13.9% of participants diagnosed with dementia also had migraines; this relationship between dementia and migraines is marginally significant. Of participants diagnosed with AD, 11.4% also had migraines; this relationship between AD and migraines is statistically significant. The relationship between CIND and migraine duration was also marginally significant, with 5.3% suffering from CIND. In addition, the odds of developing overall dementia or AD were significantly increased in those with a history of migraines. Migraine sufferers had 2.23 times greater odds of developing overall dementia and 2.81 times greater odds of developing AD. For additional bivariate odds ratio results, see Table 8.

The mean age of the participants varied with different cognitive outcomes: 81.5 years for participants diagnosed with dementia (SD=5.3) and AD (SD=5.6), 81.7 (SD=5.5) years for those with VaD, 80.3 (SD=7.3) years for those with CIND, and 75.1 (SD=5.7) years for those who were cognitively intact. Each cognitive outcome (AD, VaD, CIND) was significantly associated with age (categorized into groups: 65-74 years, 75-84 years and 85 years of age or older). For the participants diagnosed with dementia, AD, and CIND, the relationship between each cognitive outcome and age was statistically significant, whereas the relationship between VaD and age was marginally significant.

The relationship of dementia, AD, VaD, and CIND with years of education was statistically significant. For participants with dementia, an average of 9.0 (SD=3.5) years of

education was attained: 8.8 years for those with AD (SD=3.4) and VaD (SD=2.8), and 8.7 (SD=2.7) years for those with CIND. The mean number of years of education attained for those who were cognitively intact was 10.6 (SD=3.0) years. Among those diagnosed with dementia, AD and CIND, the relationship between each cognitive outcome (dementia, AD, CIND) and educational level was found to be statistically significant. In contrast, educational level was not significantly associated with VaD.

Various health conditions, including depression, stroke and other heart conditions, were also found to be significantly associated with dementia, including both VaD and CIND. None of these health conditions were significantly associated with AD. Depression was found to be significantly associated with CIND. Among the participants diagnosed with CIND, 21.6% also had depression, whereas only 8.6% of participants without CIND were also diagnosed with depression. The relationship between dementia and stroke was statistically significant. Among participants diagnosed with dementia, 13.7% had also had a stroke, compared to only 4.3% in those without dementia. In addition, VaD was significantly associated with stroke, as well as other heart conditions. Of the participants diagnosed with VaD, 33.3% had also had a stroke and 41.7% also had another heart condition, compared to 4.3% and 16.6% respectively in those without VaD.

Bivariate analyses were also performed between the exposure variables, history of migraines and duration of migraine disorder, and all variables within the analytic sample (n=716). All statistically significant results are discussed in this section; all migraine bivariate results are presented in Appendix H.

For participants suffering from migraines, 17.6% were male and 82.4% female. For the migraine sufferers, 20.3% also have experienced depression. Those with a history of

migraines were 2.83 times more likely to suffer from depression. In addition, 10.8% also reported having had a stroke and 14.9% reported diabetes. Those with a history of migraines were 2.94 times more likely to suffer from diabetes and 2.56 times more likely to have a stroke. Age was marginally significantly associated with migraine (see Appendix H: Table 1 for more results).

Unadjusted models for each outcome were performed for the exposure variable, duration of migraine disorder. However, the results were not statistically significant (see Appendix H: Table 2). In addition, there is the potential for confounding in the duration of migraine disorder models, as we were unable to adjust the models; interactions were also unable to be assessed. A positive correlation or protective effect was observed between duration of migraine disorder and age, indicating that older individuals were more likely to have a shorter duration of migraine disorder. However, this relationship was not statistically significant. See Appendix H: Table 3 for more results.

Table 6: Bivariate analyses of the association of cognitive health outcomes with exposure, confounding and intervening variables in the Manitoba Study of Health and Aging (n=716)

	Dementia	**AD[1]**	**VaD[2]**	**CIND[3]**
Exposure Variables	(%)	(%)	(%)	(%)
History of migraines	13.9†	11.4*	3.1	3.1
Duration of migraine disorder ($\bar{x}$(SD))	29.1 (24.1)	26.0 (24.8)	48.0[4]	5.3† (6.7)
Confounding Variables				
Age ($\bar{x}$(SD))	81.5*** (5.3)	81.5*** (5.6)	81.7*** (5.5)	80.3*** (7.3)
Age group				
65-74 years	11.8	11.8	16.7	27.0
75-84 years	56.9	55.9	50.0	37.8
85+ years	31.4***	32.4***	33.3**	35.1***
Sex				
Male	33.3	32.4	33.3	37.8
Female	66.7	67.7	66.7	62.2
Education				
Number of years ($\bar{x}$(SD))	9.0** (3.5)	8.8** (3.4)	8.8* (2.8)	8.7** (2.7)
Level				
Did not complete primary school	19.6	23.5	16.7	21.6
Completed primary school	45.1	44.1	58.3	56.8
Completed high school	21.6	14.7	25.0	18.9
Completed college/university	13.7*	17.7**	0	2.7**
Depression	11.8	8.8	25.0	21.6*
Family history of dementia	6.8	7.1	8.3	12.9
Intervening Variables				
Hypertension	41.2	35.3	50.0	40.5
Diabetes	9.8	11.8	0	5.4
Stroke	13.7**	5.9	33.3***	8.1
Myocardial infarction	9.8	8.8	8.3	2.7
Other heart condition	23.5	17.7	41.7†	24.3

Marginally Significant:† $0.05 \leq p < 0.10$
Significant:* p□0.05; ** p□0.01; *** p□0.0001
[1]AD- Alzheimer's disease; [2]VaD- vascular dementia; [3]CIND- cognitive impairment-no dementia
[4]Unable to calculate standard deviation due to sample size; n=1

Table 7: Crude odds ratios for each late-life cognitive health outcome by exposure, confounding and intervening variables in the Manitoba Study of Health and Aging (n=716)

	Dementia		AD[1]		VaD[2]		CIND[3]	
Exposure Variables								
History of migraines	2.23	(1.06-4.66)	2.81	(1.22-6.47)	1.83	(0.39-8.52)	0.48	(0.11-2.04)
Confounding Variables								
Sex	0.80	(0.44-1.46)	0.76	(0.37-1.59)	0.80	(0.24-2.68)	0.99	(0.50-1.95)
Depression	1.42	(0.58-3.47)	1.03	(0.30-3.48)	3.54	(0.93-13.48)	2.85	(1.25-6.50)
Family history of dementia	0.63	(0.19-2.08)	0.66	(0.15-2.84)	0.78	(0.10-6.13)	1.30	(0.44-3.85)
Intervening Variables								
Hypertension	1.51	(0.84-2.70)	1.18	(0.57-2.42)	2.16	(0.69-6.77)	1.42	(0.72-2.80)
Diabetes	1.60	(0.6-4.24)	1.96	(0.66-5.84)	--*		0.81	(0.19-3.46)
Stroke	3.54	(1.46-8.59)	1.39	(0.32-6.11)	11.13	(3.15-39.26)	1.67	(0.49-5.73)
Myocardial infarction	1.26	(0.48-3.31)	1.12	(0.33-3.79)	1.05	(0.13-8.31)	0.32	(0.04-2.34)
Other heart condition	1.55	(0.79-3.06)	1.08	(0.44-2.67)	3.60	(1.12-11.56)	1.56	(0.72-3.39)

*Unable to calculate odds ratio as no participants suffered from both vascular dementia and diabetes

[1]AD- Alzheimer's disease; [2]VaD- vascular dementia; [3]CIND- cognitive impairment-no dementia

6.3. Association of Dementia with Migraine History

6.3.1. Unadjusted Dementia Model

In the unadjusted analyses of history of migraine by dementia, the odds of dementia were 2.23 (95% CI: 1.06-4.66) times higher in those with a history of migraines than in those without a history of migraines (Table 8).

6.3.2. Dementia Model with Confounding Variables

The dementia model with confounding variables allowed confounding variables that met the required level of significance to enter the model. The odds of dementia were 3.28 (95% CI: 1.41-7.21) times higher in those with a history of migraines than in those without a history of migraines, in the presence of the significant confounders age and education. The odds of dementia in those with a history of migraines increased when confounding variables were added to the model (OR=3.28) compared to the unadjusted dementia model (OR=2.23). Increasing age was significantly related to the odds of developing dementia. Higher educational level decreased the odds of developing dementia. For more detailed results on all variables examined, see Table 8.

6.3.3. Dementia Model with Confounding and Intervening Variables

The odds of dementia were 2.97 (95% CI: 1.25-6.61) times higher in those with a history of migraines than in those without a history of migraines, in the presence of significant confounding and intervening variables. The odds of dementia in those with a history of migraines decreased when significant confounding (age, educational level) and intervening (stroke) variables were added to the model, compared to the dementia model

with confounding variables only (OR=3.28). In spite of stroke meeting the criteria to enter the model, it was not an independent statistically significant predictor of dementia. However, the presence of stroke affected the strength of the association between migraines and dementia. Both age and educational level were significant predictors of dementia. Increasing age was significantly related to increased odds of developing dementia. Higher educational level decreased the odds of developing dementia. For more detailed results for all variables examined, see Table 8.

All dementia models met statistical specifications for model fit and had no influential outliers or multicollinearity issues.

6.3.4. Dementia Model Stratified by Family History of Dementia

Due to small sample sizes, stratification by family history of dementia was limited to a dementia model without adjustment for covariates. When stratified by family history of dementia, migraines were not a statistically significant predictor for the development of dementia in those with (OR=3.64; 95% CI: 0.29-45.60) or without a family history of dementia (OR=1.43; 95% CI: 0.58-3.57). The interaction term, migraine by family history of dementia, was also not statistically significant.

Stratification of each model by sex was not possible as no male participants suffered from migraines as well as dementia and only one male participant suffered from migraines as well as CIND.

Table 8: Association of migraine history with dementia in the Manitoba Study of Health and Aging (n=716)

	Dementia		
	Unadjusted	Adjusted for confounding variables	Adjusted for confounding and intervening variables
		OR (95% CI)	
Exposure			
Migraine history	2.23 (1.06-4.66)	3.28 (1.41-7.21)	2.97 (1.25-6.61)
Confounding Variables			
Age group:			
65-74 years	[1]	1.0	1.0
75-84 years		4.36 (1.89-11.90)	4.21 (1.82-11.58)
85+ years		21.94 (8.24-66.06)	20.60 (7.73-62.06)
Sex (male)		[2] -	-
Educational level:			
Did not complete primary school		1.0	1.0
Completed primary school		0.41 (0.18-1.01)	0.41 (0.17-1.01)
Completed high school		0.32 (0.12-0.87)	0.32 (0.12-0.86)
Completed college/university		0.30 (0.10-0.88)	0.32 (0.10-0.94)
Depression			-
Intervening Variables			
Hypertension			-
Diabetes			-
Stroke			2.52 (0.90-6.42)
Heart attack			-
Other heart condition			-

[1] Crossed out cells indicate variables that were not eligible to be included in that model.
[2] A dash (-) in a cell indicates variables that did not meet the required level of significance to enter that model.

6.4. Association of Alzheimer's Disease with Migraine History

6.4.1. Unadjusted Alzheimer's Disease Model

In the unadjusted analyses of history of migraine by AD the odds of AD were 2.81 (95% CI: 1.22-6.47) times higher in those with a history of migraines than in those without a history of migraines (Table 9).

6.4.2. Alzheimer's Disease Model with Confounding Variables

The AD model with confounding variables allowed confounding variables that met the required level of significance to enter the model. The odds of AD were 4.22 (95% CI: 1.59-10.42) times higher in those with a history of migraines than in those without a history of migraines, in the presence of age and educational level. The odds of AD in those with a history of migraines increased when confounding variables were added to the model (OR=4.22) compared to the unadjusted AD model (OR=2.81). Increasing age was significantly related to increased odds of developing AD. Higher educational level decreased the odds of developing AD. For more detailed results on all variables examined, see Table 9.

6.4.3. Alzheimer's Disease Model with Confounding and Intervening Variables

The odds of AD were 4.22 (95% CI: 1.59-10.42) times higher in those with a history of migraines than in those without a history of migraines, in the presence of significant confounding and intervening variables. The odds of AD in those with a history of migraines did not change when confounding and intervening variables were added to the model, compared to the AD model with confounding variables only because there were no significant intervening variables. Despite allowing for the inclusion of all potential

confounding as well as intervening variables, only the confounders age and educational level met the required level of significance to enter the model. For more detailed results on all variables examined, see Table 9.

All AD models met statistical specifications for model fit and had no influential outliers or multicollinearity issues.

Table 9: Association of migraine history with Alzheimer's disease in the Manitoba Study of Health and Aging (n=716)

	Alzheimer's disease		
	Unadjusted	Adjusted for confounding variables	Adjusted for confounding and intervening variables
		OR (95% CI)	
Exposure			
Migraine history	2.81 (1.22-6.47)	4.22 (1.59-10.42)	4.22 (1.59-10.42)
Confounding Variables			
Age group:			
65-74 years	[1]	1.0	1.0
75-84 years		4.16 (1.51-14.67)	4.16 (1.51-14.67)
85+ years		23.03 (7.12-90.12)	23.03 (7.12-90.12)
Sex (male)		[2] -	-
Educational level:			
Did not complete primary school		1.0	1.0
Completed primary school		0.35 (0.14-0.99)	0.35 (0.14-0.99)
Completed high school		0.18 (0.05-0.61)	0.18 (0.05-0.61)
Completed college/university		0.32 (0.09-1.05)	0.32 (0.09-1.11)
Depression			-
Intervening Variables			
Hypertension			-
Diabetes			-
Stroke			-
Heart attack			-
Other heart condition			-

[1] Crossed out cells indicate variables that were not included in that model.
[2] A dash (-) in a cell indicates variables that did meet the required level of significance to enter that model.

6.5. Association of Vascular Dementia with Migraine History

6.5.1. Unadjusted Vascular Dementia Model

In the unadjusted analyses of history of migraine by VaD the odds of VaD were 1.83 (95% CI: 0.39-8.52) times higher in those with a history of migraines than in those without a history of migraines (Table 10). However, this result was not statistically significant. Due to small sample sizes, interactions could not be assessed in the VaD models.

6.5.2. Vascular Dementia Model with Confounding Variables

The VaD model with confounding variables allowed confounding variables that met the required level of significance to enter the model. The odds of VaD were 2.21 (95% CI: 0.32-9.77) times higher in those with a history of migraines than in those without a history of migraines, in the presence of significant confounders age and depression. The association of migraine history with VaD was not statistically significant. Depression met criteria to be entered into the model, but was not an independent significant predictor of VaD. However, the odds of VaD in those with a history of migraines increased in the adjusted model (OR=2.21) compared to the unadjusted VaD model (OR=1.83). Increasing age was significantly related to the odds of developing VaD. For more detailed results on all variables examined, see Table 10.

6.5.3. Vascular Dementia Model with Confounding and Intervening Variables

The odds of VaD were 1.52 (95% CI: 0.20-7.23) times higher in those with a history of migraines than in those without a history of migraines, in the presence of significant confounding and intervening variables. However, this result was not statistically significant.

Despite allowing all potential confounding as well as intervening variables to be included in the model, only age, depression and stroke met the required level of significance to enter the model. When the intervening variables were included in the model the odds ratio between migraines and VaD dropped from 2.21 to 1.52. Increasing age was significantly related to increased odds of developing VaD. Additionally, those who suffered from stroke were significantly more likely to develop VaD. For more detailed results on all variables examined, see Table 10.

All VaD models met statistical specifications for model fit and had no influential outliers or multicollinearity issues.

Table 10: Association of migraine history with vascular dementia in the Manitoba Study of Health and Aging (n=716)

	Vascular dementia		
	Unadjusted	Adjusted for confounding variables	Adjusted for confounding and intervening variables
		OR (95% CI)	
Exposure			
Migraine history	1.83 (0.39-8.52)	2.21 (0.32-9.77)	1.52 (0.20-7.23)
Confounding Variables			
Age group:			
65-74 years	[1]	1.0	1.0
75-84 years		3.04 (0.69-21.0)	2.87 (0.64-20.09)
85+ years		17.38 (3.16-133.44)	14.28 (2.46-112.64)
Sex (male)		[2] -	-
Educational level:			
Did not complete primary school		-	-
Completed primary school		-	-
Completed high school		-	-
Completed college/university		-	-
Depression		3.51 (0.73-13.03)	2.95 (0.57-11.61)
Intervening Variables			
Hypertension			-
Diabetes			-
Stroke			7.90 (1.82-29.71)
Heart attack			-
Other heart condition			-

[1] Crossed out cells indicate variables that were not included in that model.
[2] A dash (-) in a cell indicates variables that did meet the required level of significance to enter that model.

6.6. Association of CIND with Migraine History

6.6.1. Unadjusted CIND Model

In the unadjusted bivariate analyses of history of migraine by CIND the odds of CIND were 0.52 (95% CI: 0.12-2.22) times higher in those with a history of migraines than in those without a history of migraines (Table 11). However, this result was not statistically significant. Due to small sample sizes, interactions could not be assessed in the CIND models.

6.6.2. CIND Model with Confounding Variables

The CIND model with confounding variables allowed confounding variables that met the required level of significance to enter the model. The odds of CIND were 0.70 (95% CI: 0.11-2.57) times higher in those with a history of migraines than in those without a history of migraines, in the presence of age, educational level and depression. When the confounding variables were included in the model, the association between migraines and CIND weakened (crude OR=0.52 vs. adjusted OR=0.70). However, the association between migraine history and CIND was not statistically significant. Increasing age was significantly related to increased odds of developing CIND. Higher educational level decreased the odds of developing CIND. In addition, those who reported depression were significantly more likely to develop CIND. For more detailed results on all variables examined, see Table 11.

6.6.3. CIND Model with Confounding and Intervening Variables

The CIND model with confounding and intervening variables allowed confounding and intervening variables that met the required level of significance to enter the model. The

odds of CIND were 0.70 (95% CI: 0.11-2.57) times higher in those with a history of migraines than in those without a history of migraines, in the presence of age, educational level and depression. The association between migraine history and CIND was not statistically significant and did not differ from the model including only potential confounders, because there were no significant intervening variables. For more detailed results on all variables examined, see Table 11.

All CIND models met statistical specifications for model fit and had no influential outliers or multicollinearity issues.

Table 11: Association of migraine history with cognitive impairment-no dementia (CIND) in the Manitoba Study of Health and Aging (n=716)

	Cognitive impairment-no dementia		
	Unadjusted	Adjusted for confounding variables	Adjusted for confounding and intervening variables
		OR (95% CI)	
Exposure			
Migraine history	0.52 (0.12-2.22)	0.70 (0.11-2.57)	0.70 (0.11-2.57)
Confounding Variables			
Age group:			
65-74 years	[1]	1.0	1.0
75-84 years		1.28 (0.55-3.07)	1.28 (0.55-3.07)
85+ years		10.01 (3.92-26.50)	10.01 (3.92-26.50)
Sex (male)		[2]-	-
Educational level:			
Did not complete primary school		1.0	1.0
Completed primary school		0.47 (0.19-1.26)	0.47 (0.19-1.26)
Completed high school		0.27 (0.08-0.84)	0.27 (0.08-0.84)
Completed college/university		0.06 (0.003-0.37)	0.06 (0.003-0.37)
Depression		3.52 (1.36-8.45)	3.52 (1.36-8.45)
Intervening Variables			
Hypertension			-
Diabetes			-
Stroke			-
Heart attack			-
Other heart condition			-

[1] Crossed out cells indicate variables that were not included in that model.
[2] A dash (-) in a cell indicates variables that did meet the required level of significance to enter that model.

7. Discussion

Healthy aging, including cognitive health, has become a significant focus for researchers as the Canadian population ages. An important part of understanding late-life cognitive health is understanding late-life cognitive impairments and their mid-life risk factors. The possible relationship between migraines and late-life cognitive health outcomes was highlighted by the literature review, which also identified gaps in the research. This thesis project developed hypotheses based on results and gaps in the research (Breteler et al., 1991; Tyas et al. 2001). The primary hypothesis driven by the literature is the possibility that migraines are a mid-life risk factor for developing late-life cognitive impairment. In addition, the possible intervening relationship of vascular risk factors on the relationship between migraines and late-life cognitive health outcomes, as well as modification by sex and family history of dementia, were also questions directed by the literature review.

7.1. Overall Findings

The incidence rates of overall dementia and AD found in this study, 7.5% and 5.1% respectively, are similar to what have been presented in the literature (Alzheimer's Association, 2009; Alzheimer Society, 2010). The incidence of VaD observed in this study, 1.9%, is also similar to what has been seen in the literature (see review by Jellinger, 2008). The incidence of CIND observed in this study was 5.6%. As this result represents incident cases of CIND, it is lower than prevalence rates previously reported in the literature (see reviews by Petersen et al., 2009; Tedeschi et al., 2008). However, incidence rates are known to vary widely depending on the diagnostic criteria used (see reviews by Chertkow et al., 2008).

This thesis project has indicated that migraines are a significant risk factor for both overall dementia and AD. However, the relationship between migraines and overall dementia appears to be mostly driven by the significant relationship between migraines and AD. Despite not observing a significant relationship between a history of migraines and VaD, stroke was found to be a significant intervening variable in the pathway between migraines and VaD. A non-significant relationship was observed between migraines and CIND, with depression as an independently significant variable along this pathway.

Although the relationship between migraines and overall dementia appears to be primarily driven by the significant relationship between migraines and AD, the association between migraines, VaD and stroke also plays a role. Despite stroke not being an independent statistically significant predictor of dementia, it did meet the criteria to enter the model. This is most likely due to the strong association between stroke and VaD, as no vascular risk factors were found to be significantly related to AD.

Despite the vascular mechanisms involved in migraine biology, migraines were not a significant risk factor for VaD. Stroke was a significant risk factor for VaD, which has been previously demonstrated in the literature (Hachinski et al., 1975; see reviews by Patterson et al., 2007). Furthermore, migraines are a significant risk factor for stroke (Bigal et al., 2010; see reviews by Bigal et al., 2009; Scher, Bigal & Lipton, 2005). This is supported by the significant bivariate association between migraines and stroke in this thesis. When the intervening variables (including stroke) were included in the VaD model, the strength of the association between migraines and VaD decreased and stroke remained a significant predictor. The lack of a significant relationship between VaD and migraines may be driven by the lack of a direct biological mechanism connecting migraines to VaD. This is supported

by the observation that migraines were not a significant risk factor for VaD before or after the addition of stroke as an intervening variable. However, this type of relationship may indicate that the association between migraines and VaD is affected by presence of stroke as an intervening variable. The literature and results suggest that any relationship between migraines and VaD is dependent on the occurrence of stroke. These results demonstrate an area of research to be investigated further in the future.

Results from this thesis project suggest that migraines are a significant risk factor for the development of AD. This result supports what has been previously reported by Tyas et al. (2001) in the same data set. However, this thesis project's results are not supported by Breteler et al. (1991), who found an inverse relationship between AD risk and migraines (RR=0.7, 95% CI:0.5-1.0). However, one study included in that meta-analysis reported a non-significant higher risk of AD for those with headaches (French et al., 1985). In addition, the studies included in the meta-analysis by Breteler et al. (1991) utilized a case-control study design, compared to the longitudinal study design of the MSHA used by Tyas et al. (2001) as well as this study. A longitudinal study design is more appropriate when attempting to assess a temporal sequence between migraines and late-life cognitive health outcomes. Furthermore, the studies included in the Breteler et al. (1991) meta-analysis did not always differentiate between severe headaches or migraines. Moreover, headaches or migraines were not the primary risk factor being investigated, but rather just one of many health and environmental risk factors being examined by the studies. These differences suggest that different samples may yield different results depending on study design, and the criteria and definitions used for diagnoses, especially in an emerging field of research, as standards still have yet to be established. For example, diagnostic criteria or definitions used

for headaches, migraines or cognitive impairments may play an important role in determining if there is a significant relationship between migraines and AD. The significant relationship, observed in this study, between migraines and AD may be the result of various biological mechanisms. Previous studies have observed relationships between vascular risk factors and AD (Alonso et al., 2009; Fillit et al., 2008; Hebert et al., 2000; Whitmer et al., 2005), as well as vascular risk factors and migraines (Bigal et al., 2009; see reviews by Bigal et al., 2010; Scher et al., 2005). Despite these results in the literature, it appears that the relationship between migraines and AD cannot be explained in this study by vascular dysfunction in the brain, as there was no significant association between vascular variables and the relationship between migraines and AD.

A possible alternative explanation for the relationship between migraines and AD may be the specific location of damage in the brain due to migraine neuropathophysiology. A variety of cognitive domains can be affected by cognitive impairment; the domains affected are specific to dementia type. The different cognitive domains affected by migraine neuropathophysiology may indicate specific relationships to dementia types. It is difficult to determine the cognitive domains affected by migraines, as migraine research often tests a wide variety of cognitive domains and yields a similar wide variety of results (See Table 3). However, the relationship between migraines and specific cognitive domains may indicate future research directions that should be pursued, as it has not been thoroughly investigated.

The relationship between migraines and AD also may be due to a genetic relationship. Individuals with familial AD due to presenilin-1 mutations are more likely to suffer from migraines or recurrent headaches (Lopera et al., 1997; Ringman et al., 2008). Research on both migraines and AD has implicated chromosomes 1 and 19 (Azad, Al

Bugami & Loy-English, 2007; see reviews by Blennow, de Leon & Zetterberg, 2006; Breslau & Rasmussen, 2001; Burns & Iliffe, 2009; Patterson et al., 2007). This possible genetic relationship may explain the association between migraines and AD. The results of stratification by family history of dementia might support a possible genetic relationship between migraines and AD that warrants future research using APOE data. Those suffering from migraines with a family history of dementia were more likely to develop AD, compared to those without a family history of dementia. Despite this result not being statistically significant, it is interesting as we used family history of dementia as a proxy for APOE, since the MSHA does not have genetic information for participants. This possible genetic relationship has not been fully investigated and may be a fruitful avenue future research.

In addition to stratifying by family history of dementia, stratification by sex was attempted. However, this thesis project was unable to stratify by sex because no male participants suffered from migraines as well as dementia, and only one male participant suffered from migraines as well as CIND. This is an intriguing descriptive result, as of the participants with migraines, only female participants developed dementia. The literature has demonstrated that women are more likely to suffer from migraines (see reviews by Bigal & Lipton, 2009; Lipton & Bigal, 2005 a, b) and are at an increased risk of developing AD (Alzheimer's Association, 2009; see review by Musicco, 2010). This unanswered question regarding the possible increased risk for women should be addressed in future research.

A protective relationship was observed between migraines and CIND; however this relationship was not statistically significant. CIND is often considered an early stage of AD and those who suffered from migraines were more likely to develop AD. It has been estimated that approximately 40-60% of people with MCI will eventually progress to meet

criteria for AD (see review by Tedeschi et al., 2008). If those suffering from CIND were mostly young older adults (i.e. 65-70 years of age), this might indicate that the participants still had time to progress to AD as they aged. However, the mean age of those with CIND was 80.3 years, ranging from 69 years old to 98 years old. This suggests that many of those suffering from CIND in this sample will not progress to AD, as these participants are already among some of the oldest old. A closer look at individuals with CIND in this sample informs us that the majority of participants with CIND have a specific sub-type of CIND or a specific cause of CIND that is not likely to progress to AD. For example, seven participants were diagnosed with CIND due to depression; six participants with CIND were diagnosed with an age-associated sub-type of CIND. These descriptive results suggest that the non-significant protective relationship observed between migraines and CIND may only be generalizable to those suffering from sub-types of CIND that will not progress to AD. Depression was a significant risk factor for CIND, and the strength of association between migraines and CIND did not change with the inclusion of depression. This is most likely due to the seven participants diagnosed with CIND caused by depression. Alternatively, this relationship may also be related to the occurrence of depressive symptoms early in those who develop dementia or some type of cognitive impairment (Gatz et al., 2005 b; Luchsinger et al., 2008; Ownby et al., 2006; see review by Patterson et al., 2007). In addition, depression has been shown to be a risk factor for and comorbid with migraines, which may also explain the above relationship (Breslau et al., 2003; Patel et al. 2004). Further research is required to clarify the observed relationships between migraine, CIND and depression.

7.2. Limitations

It is important for the results of this study to be interpreted in the context of its various limitations. There are a variety of limitations that should be noted with regard to the available data and various analytic methods that have been used. The following sections address several key limitations that should be taken into account when interpreting the results of this study.

7.2.1. Sample

The study used data from individuals who completed the MSHA-Risk Factor Questionnaire, were cognitively intact at MSHA-1 (n=1039) and had all relevant information available at MSHA-2 (n=716). After a detailed examination of study sample characteristics, participants who were included in the final analytic sample (n=716) were found to be younger and healthier than those who were excluded due to missing values on key variables. Thus, the results of this study are most appropriately generalized to a younger and healthier older adult population. This introduces a potential selection bias in this study and may affect the generalizability of the results. However, this potential bias is unavoidable, due to the sample restrictions that were made. Younger and healthier older adults were more likely to be able to complete the various interviews involved in the MSHA study leading to a largely younger, healthier sample. Additionally, as the sample was restricted to those without missing data, participants who did not answer certain questions may have different traits and characteristics than those who did answer. These participants' characteristics were not able to be represented by this sample due to this selection issue.

7.2.2. MSHA Data

The analyses of this project were based on secondary data that had been previously collected by the MSHA. Analyses conducted using secondary data may have some limitations such as reliance on the quality of previously collected data, which was not collected with the intended use of the specific research questions of this study.

Migraine data were self-reported and did not include medical records with migraine diagnoses based on standardized migraine criteria (i.e., IHS: ICHD-II). Fortunately, self-reported migraine has been shown to have excellent agreement with the IHS: ICHD-II criteria for migraine diagnoses (Schurks, Buring & Kurth, 2009). In addition, the MSHA questions on migraines did not distinguish between migraines with and without aura. The type of migraine however, does not appear to be a vital characteristic of migraine exposure, since both types cause similar long-term neurological damage (see review by Hamed, 2009). The health questions regarding migraines do not include some characteristics of migraine disorders, such as use of migraine medications, number of migraine attacks in a month, and severity or intensity of migraine attacks. However, the survey questions pertaining to migraines include the most essential features, such as whether the survey participant experienced migraines, as well as limited data on duration of the migraine disorder.

Another limitation of the MSHA data is the lack of clinical and genetic information. Thorough clinical information, such as blood pressure and cholesterol level, would help support many aspects of the study (i.e., intervening variables). Clinical diagnoses of CVD and related disorders may be more reliable than self-reports of these health issues. Clinical examinations, including ascertaining blood pressure levels or obtaining blood samples for

pathology tests would also provide useful medical information. Such in-depth clinical examinations, however, are not feasible for all participants of large epidemiologic studies.

Genetic information, specifically APOE status, would also have been useful in determining participants at increased risk of developing dementia. "Family history of dementia: Alzheimer's disease and senile dementia," was used as a proxy for genetic risk of all types. Although the "family history of dementia" variable is not as specific as APOE, it could be a useful variable to help identify groups at risk from APOE and other genetic factors. However, the variable family history of dementia is not an ideal proxy for APOE status. This variable does not identify which participants have genes that increase the risk of developing dementia or AD, since many cases are due to environmental rather than genetic factors. In addition, APOE status does not necessarily determine whether an individual will develop dementia or AD.

Although the MSHA utilized thorough clinical diagnostic criteria to identify cognitively impaired participants, the MSHA lacked neuropathological data. However, a neuropathologic diagnosis cannot be made without an autopsy and thus is rare for large population-based studies. Another possible limitation due to diagnostic criteria is the wide range of definitions and standards. Depending on the criteria used, risk factors as well as incidence and prevalence may vary in different studies. However, the diagnostic criteria used by the MSHA for assessment and diagnosis of cognitive impairment were standard at the time of data collection and remain well-accepted criteria.

A common issue in older adult populations is polypharmacy, i.e. the use of too many medications or the prescription of multiple medications. Polypharmacy may influence the health conditions that older adults self-report, as well as cause additional health problems.

This issue may cause problems with unadjusted confounding. Many vascular risk factors for dementia, such as the intervening variables in this thesis, have common medications prescribed to help control the condition or disorder. Due to this unadjusted confounding, any effect that the intervening variables may have on the relationship between migraines and dementia may not be seen. For instance, if a participant is taking antihypertensive medication, the effect of hypertension on the relationship between migraines and dementia may not be seen. Unfortunately, the MSHA only has data on medication use for a subset of the sample and thus it was not possible to adjust for medications.

7.2.3. Data Analyses

The relatively small sample sizes in certain analyses contributed to the inability to develop final models for migraine duration and to stratify models by sex and family history of dementia. There is the potential for confounding in the duration of migraine disorder models, as the sample size was insufficient to adjust for potential confounding variables. There is also the potential for confounding in the unadjusted dementia model stratified by family history of dementia. Since no male participants suffered from migraines as well as dementia and only one male participant suffered from migraines as well as CIND, stratification of each model by sex was not possible.

7.2.4. General Issues

Various challenges are inherent to late-life cognitive impairment research. Such challenges include the timing between risk factors and disease development and the variety of cognitive impairment definitions. Various risk factors for late-life cognitive impairment

occur during early or mid-life, such as occupational exposures or low educational level. For example, the peak prevalence of migraines occurs during mid-life, whereas the peak prevalence of dementia is in late-life. The gap between peak prevalence of several decades in these neurological disorders may make it difficult to establish a direct causal connection.

Another challenge when studying cognitive impairment is the wide variety of definitions used to diagnose and categorize the many types of cognitive impairments. The field of research will often determine the accepted definition to use, either based on clinical or pathologic criteria. The MSHA used a clinical definition to diagnose cognitive impairment in its participants. Therefore, the results from this thesis are most readily generalizable to populations diagnosed clinically and other studies using clinical diagnostic criteria.

7.3. Strengths

Despite the various limitations discussed, there are many important strengths related to the thesis project. The MSHA is a large, population-based, longitudinal survey examining aging and dementia. A longitudinal study design with two screening time points allows for the investigation of predictors of incident cases of the cognitive outcomes, rather than prevalent cases. This is important as incidence measures the risk of developing a cognitive outcome, compared to prevalence, which measures the total number of people with a cognitive outcome in a population. Another important strength of the MSHA is that the study population includes both rural and urban populations. Analyzing data from a population-based study with such a large, diverse sample size, such as the MSHA, allows for greater generalizability of the results.

The MSHA has a standardized diagnostic protocol to determine the final cognitive outcome of the survey participants. This allows confidence in the assessment of various cognitive outcomes (overall dementia, AD, VaD, and CIND) as our end points. Furthermore, the MSHA data set questionnaire included a wide range of questions on health history, which allowed this thesis project to examine multiple confounding and intervening variables. These strengths allowed a comprehensive examination of the relationship between migraines and late-life cognitive health outcomes.

7.4. Implications and Future Research Directions

Further research is required to understand the possible relationships between migraines and late-life cognition. Identifying risk factors for cognitive health outcomes in late-life is an important research area, given the current and expected increases in the proportion of older adults in the population.

The possible relationship between cognitive domains affected by migraine long-term neurological damage and subsequent development of a late-life cognitive outcomes should be investigated further. Cognitive domains affected by migraines may indicate the type of cognitive impairment that an individual is at risk of developing in late life. This area has yet to be investigated.

This research project has attempted to provide further insight into various effect modifiers on cognitive health outcomes. However, this project was unable to address the effect that sex has on the relationship between migraines and late-life cognitive health outcomes. Future studies utilizing a larger sample of those with a history of migraines, both men and women, would allow researchers to address this question. Additionally, this thesis

project was only able to stratify by family history of dementia in an unadjusted dementia model. Despite the lack of significant results, further studies using APOE and genes identified in certain types of migraines may help us to better understand the relationship between migraines and AD. The possible genetic relationship between migraines and AD should be investigated further, as some studies have observed that those with AD gene mutations are more likely to suffer from migraines or recurrent headaches. Furthermore, research on both migraines and AD has implicated chromosomes 1 and 19. This possible genetic relationship between these two disorders has not been fully investigated.

It is critical to identify at-risk groups as early as possible in order to attempt to prevent cognitive decline and improve overall health. Identifying a mid-life risk factor for cognitive outcomes in late life will allow earlier recognition of at-risk individuals and allow for migraine or vascular-related interventions. Additionally, migraines may represent a modifiable risk factor for AD, as interventions such as migraine medications or reduction of vascular risk factors may decrease the risk of developing AD. Future studies should explore the relationship between various migraine medications and possible reductions in the risk of late-life cognitive health outcomes. Vascular risk factors, such as hypertension, hypercholesterolemia and diabetes, should also be examined in relation to migraine medication and late-life cognitive health outcomes, as many migraine medications target vascular issues. Addressing both migraine and any related vascular risk factors would allow for more targeted treatment and subsequent reduced risk of late-life cognitive health outcomes.

The relationship between migraines, stroke, and VaD should be investigated further. Since migraines are a significant risk factor for stroke and stroke is a significant risk factor

for VaD, there may be some unidentified aspect of this relationship that was unable to be addressed by this thesis project. Furthermore, the relationship between migraines and CIND raised more questions than it answered regarding a potential protective relationship, as well as the role depression may play. Future studies involving a larger population of those diagnosed with CIND, with a variety of subtypes, could answer some of these questions and clarify the association between migraines and CIND.

Migraines cause a cascade of pathophysiologic events in the brain. In order to understand more fully how migraines affect cognitive health, studies involving animal models can be performed to determine the possible biological mechanisms that may link migraines and late-life cognitive health outcomes. This would allow more targeted pharmaceutical interventions and treatments to be manufactured and tested.

The association between migraines and late-life cognitive health outcomes may vary by subgroups. This area of research has yet to be fully investigated. This project has identified that stroke may play an important part in the migraine-VaD relationship. A potential association with depression, migraines and CIND has also been observed. Those with a history of migraines as well as stroke or depression may represent subgroups at increased risk of developing late-life cognitive health outcomes. It is possible that there may be other subgroups of high-risk individuals that have yet to be identified.

Identifying the association of migraines with late-life cognitive health outcomes and the role of intervening variables in this association has important implications for researchers and clinicians in the form of non-pharmaceutical interventions, preventative treatments and medications. It is critical to continue to develop new strategies that will help prevent cognitive decline to improve quality of life and increase the likelihood of healthy aging.

References

Alonso, A., Jacobs, D. R., Jr., Menotti, A., Nissinen, A., Dontas, A., Kafatos, A., et al. (2009). Cardiovascular risk factors and dementia mortality: 40 years of follow-up in the seven countries study. *Journal of the Neurological Sciences, 280*(1-2), 79-83.

Alzheimer Society of Canada. (2010). *Rising tide: The impact of dementia on Canadian society*. Canada: Alzheimer Society of Canada.

Alzheimer's Society of Canada. (2005). *Alzheimer's disease statistics.* Retrieved 10/04, 2009, from http://www.alzheimer.ca/english/disease/stats-intro.htm

Alzheimer's Association. (2009). 2009 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 5*(3), 234-270.

Alzheimer's Disease International. (2009). *World Alzheimer's Report*. London: Scientific Group, Institute of Psychiatry, King's College.

Andersen, K., Launer, L. J., Dewey, M. E., Letenneur, L., Ott, A., Copeland, J. R., et al. (1999). Gender differences in the incidence of AD and vascular dementia: The EURODEM studies. EURODEM Incidence Research Group. *Neurology, 53*(9), 1992-1997.

Arvanitakis, Z., Wilson, R. S., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2004). Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Archives of Neurology, 61*(5), 661-666.

Azad, N. A., Al Bugami, M., & Loy-English, I. (2007). Gender differences in dementia risk factors. *Gender Medicine, 4*(2), 120-129.

Baars, M. A. E., van Boxtel, M. P. J., & Jolles, J. (2010). Migraine does not affect cognitive decline: Results from the Maastricht aging study. *Headache, 50*(2), 176-184.

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51*(6), 1173-1182.

Becker, W. J., Gladstone, J. P., & Aube, M. (2007). Migraine prevalence, diagnosis, and disability. *The Canadian Journal of Neurological Sciences, 34*(4), S3-9.

Bell, B. D., Primeau, M., Sweet, J. J., & Lofland, K. R. (1999). Neuropsychological functioning in migraine headache, nonheadache chronic pain, and mild traumatic brain injury patients. *Archives of Clinical Neuropsychology, 14*(4), 389-399.

Bennett, D. A., Schneider, J. A., Bienias, J. L., Evans, D. A., & Wilson, R. S. (2005). Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology, 64*(5), 834-841.

Berg, L. (1988). Clinical Dementia Rating (CDR). *Psychopharmacology Bulletin, 24*(4), 637-639.

Beydoun, M. A., Beydoun, H. A., & Wang, Y. (2008). Obesity and central obesity as risk factors for incident dementia and its subtypes: A systematic review and meta-analysis. *Obesity Reviews, 9*(3), 204-218.

Bigal, M. E., Kurth, T., Santanello, N., Buse, D., Golden, W., Robbins, M., et al. (2010). Migraine and cardiovascular disease: A population-based study. *Neurology, 74*(8), 628-635.

Bigal, M. E., Kurth, T., Hu, H., Santanello, N., & Lipton, R. B. (2009). Migraine and cardiovascular disease: Possible mechanisms of interaction. *Neurology, 72*(21), 1864-1871.

Bigal, M. E., Liberman, J. N., & Lipton, R. B. (2006). Age-dependent prevalence and clinical features of migraine. *Neurology, 67*(2), 246-251.

Bigal, M. E., & Lipton, R. B. (2009). The epidemiology, burden, and comorbidities of migraine. *Neurologic Clinics, 27*(2), 321-334.

Bigal, M. E., Lipton, R. B., & Stewart, W. F. (2004). The epidemiology and impact of migraine. *Current Neurology and Neuroscience Reports, 4*(2), 98-104.

Bigal, M. E., Lipton, R. B., Winner, P., Reed, M. L., Diamond, S., Stewart, W. F., et al. (2007). Migraine in adolescents: Association with socioeconomic status and family history. *Neurology, 69*(1), 16-25.

Bigal, M. E., Lipton, R. B., Cohen, J., & Silberstein, S. D. (2003). Epilepsy and migraine. *Epilepsy & Behavior, 4 Suppl 2*, S13-24.

Black, S. E., Gauthier, S., Dalziel, W., Keren, R., Correia, J., Hew, H., et al. (2010). Canadian Alzheimer's disease caregiver survey: Baby-boomer caregivers and burden of care. *International Journal of Geriatric Psychiatry, 25*(8), 807-813.

Blennow, K., de Leon, M. J., & Zetterberg, H. (2006). Alzheimer's disease. *The Lancet, 368*(9533), 387-403.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica, 82*(4), 239-259.

Breslau, N., Lipton, R. B., Stewart, W. F., Schultz, L. R., & Welch, K. M. (2003). Comorbidity of migraine and depression: Investigating potential etiology and prognosis. *Neurology, 60*(8), 1308-1312.

Breslau, N., & Rasmussen, B. K. (2001). The impact of migraine: Epidemiology, risk factors, and co-morbidities. *Neurology, 56*(6 Suppl 1), S4-12.

Breteler, M. M., van Duijn, C. M., Chandra, V., Fratiglioni, L., Graves, A. B., Heyman, A., et al. (1991). Medical history and the risk of Alzheimer's disease: A collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *International Journal of Epidemiology, 20*(Suppl 2), S36-42.

Buckingham, S. D., Jones, A. K., Brown, L. A., & Sattelle, D. B. (2009). Nicotinic acetylcholine receptor signalling: Roles in Alzheimer's disease and amyloid neuroprotection. *Pharmacological Reviews, 61*(1), 39-61.

Burker, E., Hannay, H. J., & Halsey, J. H. (1989). Neuropsychological functioning and personality characteristics of migrainous and nonmigrainous female college students. *Neuropsychology, 3*(2), 61-73.

Burns, A. (2009). Alzheimer's disease: On the verges of treatment and prevention. *Lancet Neurology, 8*(1), 4-5.

Burns, A., & Iliffe, S. (2009). Alzheimer's disease. *BMJ (Clinical Research Ed.), 338*, b158.

Buzzi, M. G., & Moskowitz, M. A. (2005). The pathophysiology of migraine: Year 2005. *The Journal of Headache and Pain, 6*(3), 105-111.

Calandre, E. P., Bembibre, J., Arnedo, M. L., & Becerra, D. (2002). Cognitive disturbances and regional cerebral blood flow abnormalities in migraine patients: Their relationship with the clinical manifestations of the illness. *Cephalalgia, 22*(4), 291-302.

Chakravarty, A. (2010). How triggers trigger acute migraine attacks: A hypothesis. *Medical Hypotheses, 74*(4), 750-753.

Chertkow, H., Massoud, F., Nasreddine, Z., Belleville, S., Joanette, Y., Bocti, C., et al. (2008). Diagnosis and treatment of dementia: 3. mild cognitive impairment and cognitive impairment without dementia. *Canadian Medical Association Journal, 178*(10), 1273-1285.

Craft, S. (2007). Insulin resistance and Alzheimer's disease pathogenesis: Potential mechanisms and implications for treatment. *Current Alzheimer Research, 4*(2), 147-152.

Cummings, J. L. (2004). Alzheimer's disease. *The New England Journal of Medicine, 351*(1), 56-67.

Cummings, J. L., Vinters, H. V., Cole, G. M., & Khachaturian, Z. S. (1998). Alzheimer's disease: Etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology, 51*(1 Suppl 1), S2-17; discussion S65-7.

D'Andrea, G., Nertempi, P., Ferro Milone, F., Joseph, R., & Cananzi, A. R. (1989). Personality and memory in childhood migraine. *Cephalalgia, 9*(1), 25-28.

Del Ser, T., Hachinski, V., Merskey, H., & Munoz, D. G. (2005). Alzheimer's disease with and without cerebral infarcts. *Journal of the Neurological Sciences, 231*(1-2), 3-11.

Diagnostic and statistical manual of mental disorders, 4th ed. DSM-IV (1994). In American Psychiatric Association (4th Ed.). Washington, D.C.: American Psychiatric Association.

Diamond, S., Bigal, M. E., Silberstein, S., Loder, E., Reed, M., & Lipton, R. B. (2007). Patterns of diagnosis and acute and preventive treatment for migraine in the United States: Results from the American migraine prevalence and prevention study. *Headache, 47*(3), 355-363.

Diener, H. C., & Beck, C. A. (2009). Migraine and risk of cardiovascular disease in women: Learning about relative and absolute risk. *Neurology, 73*(8), 576-577.

Diener, H. C., Kuper, M., & Kurth, T. (2008). Migraine-associated risks and comorbidity. *Journal of Neurology, 255*(9), 1290-1301.

Duron, E., & Hanon, O. (2008). Vascular risk factors, cognitive decline, and dementia. *Vascular Health and Risk Management, 4*(2), 363-381.

El Hasnaoui, A., Vray, M., Richard, A., Nachit-Ouinekh, F., Boureau, F., & MIGSEV Group. (2003). Assessing the severity of migraine: Development of the MIGSEV scale. *Headache, 43*(6), 628-635.

Erkinjuntti, T., & Gauthier, S. (2009). The concept of vascular cognitive impairment. *Frontiers of Neurology and Neuroscience, 24*, 79-85.

Fillit, H., Nash, D. T., Rundek, T., & Zuckerman, A. (2008). Cardiovascular risk factors and dementia. *American Journal of Geriatric Pharmacotherapy, 6*(2), 100-118.

Fisher, A. (2007). M1 muscarinic agonists target major hallmarks of Alzheimer's disease--an update. *Current Alzheimer Research, 4*(5), 577-580.

Fitzpatrick, A. L., Kuller, L. H., Ives, D. G., Lopez, O. L., Jagust, W., Breitner, J. C., et al. (2004). Incidence and prevalence of dementia in the cardiovascular health study. *Journal of the American Geriatrics Society, 52*(2), 195-204.

Fleisher, A., Grundman, M., Jack, C. R., Jr, Petersen, R. C., Taylor, C., Kim, H. T., et al. (2005). Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. *Archives of Neurology, 62*(6), 953-957.

Francis, P. T., Palmer, A. M., Snape, M., & Wilcock, G. K. (1999). The cholinergic hypothesis of Alzheimer's disease: A review of progress. *Journal of Neurology, Neurosurgery, and Psychiatry, 66*(2), 137-147.

Freitag, M. H., Peila, R., Masaki, K., Petrovitch, H., Ross, G. W., White, L. R., et al. (2006). Midlife pulse pressure and incidence of dementia: The Honolulu-Asia Aging Study. *Stroke, 37*(1), 33-37.

French, L. R., Schuman, L. M., Mortimer, J. A., Hutton, J. T., Boatman, R. A., & Christians, B. (1985). A case-control study of dementia of the Alzheimer type. *American Journal of Epidemiology, 121*(3), 414-421.

Gaist, D., Pedersen, L., Madsen, C., Tsiropoulos, I., Bak, S., Sindrup, S., et al. (2005). Long-term effects of migraine on cognitive function: A population-based study of Danish twins. *Neurology, 64*(4), 600-607.

Gaitatzis, A., Carroll, K., Majeed, A., & W Sander, J. (2004). The epidemiology of the comorbidity of epilepsy in the general population. *Epilepsia, 45*(12), 1613-1622.

Ganguli, M., Dodge, H. H., Shen, C., Pandav, R. S., & DeKosky, S. T. (2005). Alzheimer disease and mortality: A 15-year epidemiological study. *Archives of Neurology, 62*(5), 779-784.

Gatz, M., Fratiglioni, L., Johansson, B., Berg, S., Mortimer, J. A., Reynolds, C. A., et al. (2005). Complete ascertainment of dementia in the Swedish twin registry: The HARMONY study. *Neurobiology of Aging, 26*(4), 439-447.

Gatz, J. L., Tyas, S. L., St John, P., & Montgomery, P. (2005). Do depressive symptoms predict Alzheimer's disease and dementia? *The Journals of Gerontology, 60*(6), 744-747.

Graham, J. E., Rockwood, K., Beattie, B. L., Eastwood, R., Gauthier, S., Tuokko, H., et al. (1997). Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet, 349*(9068), 1793-1796.

Graves, A. (2004). Alzheimer's disease and vascular dementia. *Neuroepidemiology: From principles to practice*. (Ch. 5: pp. 102-130)New York: Oxford University Press, Inc.

Griffin, W. S., & Mrak, R. E. (2002). Interleukin-1 in the genesis and progression of and risk for development of neuronal degeneration in Alzheimer's disease. *Journal of Leukocyte Biology, 72*(2), 233-238.

Guillozet, A. L., Weintraub, S., Mash, D. C., & Mesulam, M. M. (2003). Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Archives of Neurology, 60*(5), 729-736.

Hachinski, V. C., Iliff, L. D., Zilhka, E., Du Boulay, G. H., McAllister, V. L., Marshall, J., et al. (1975). Cerebral blood flow in dementia. *Archives of Neurology, 32*(9), 632-637.

Hamed, S. A., Hamed, E. A., Ezz Eldin, A. M., & Mahmoud, N. M. (2010). Vascular risk factors, endothelial function, and carotid thickness in patients with migraine: Relationship to atherosclerosis. *Journal of Stroke and Cerebrovascular Diseases, 19*(2), 92-103.

Hamed, S. A. (2009). The vascular risk associations with migraine: Relation to migraine susceptibility and progression. *Atherosclerosis, 205*(1), 15-22.

Headache Classification Committee of the International Headache Society. (1988). Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia, 8*(Suppl 7), 1-96.

Headache Classification Subcommittee of the International Headache Society. (2004). The international classification of headache disorders 2nd ed. *Cephalalgia, 24*(Suppl 1), 1-160.

Hebert, R., Lindsay, J., Verreault, R., Rockwood, K., Hill, G., & Dubois, M. F. (2000). Vascular dementia: Incidence and risk factors in the Canadian Study of Health and Aging. *Stroke; a Journal of Cerebral Circulation, 31*(7), 1487-1493.

Hedley, R., Hallmayer, J., Groth, D. M., Brooks, W. S., Gandy, S. E., & Martins, R. N. (2002). Association of interleukin-1 polymorphisms with Alzheimer's disease in Australia. *Annals of Neurology, 51*(6), 795-797.

Henry, P., Auray, J. P., Gaudin, A. F., Dartigues, J. F., Duru, G., Lanteri-Minet, M., et al. (2002). Prevalence and clinical characteristics of migraine in France. *Neurology, 59*(2), 232-237.

Hermann, B. P., Jones, J. E., Sheth, R., Koehn, M., Becker, T., Fine, J., et al. (2008). Growing up with epilepsy: A two-year investigation of cognitive development in children with new onset epilepsy. *Epilepsia, 49*(11), 1847-1858.

Heun, R., & Kockler, M. (2002). Gender differences in the cognitive impairment in Alzheimer's disease. *Archives of Women's Mental Health, 4*(4), 129-137.

Honig, L. S., Tang, M. X., Albert, S., Costa, R., Luchsinger, J., Manly, J., et al. (2003). Stroke and the risk of Alzheimer disease. *Archives of Neurology, 60*(12), 1707-1712.

Hooker, W. D., & Raskin, N. H. (1986). Neuropsychologic alterations in classic and common migraine. *Archives of Neurology, 43*(7), 709-712.

Hu, X. H., Markson, L. E., Lipton, R. B., Stewart, W. F., & Berger, M. L. (1999). Burden of migraine in the United States: Disability and economic costs. *Archives of Internal Medicine, 159*(8), 813-818.

ICD-10 Guide for Headaches. Guide to the classification, diagnosis and assessment of headaches in accordance with the tenth revision of the international classification of diseases and related health problems and its application to neurology. (1997). *Cephalalgia, 17*(Supp 19), 1-91.

Ivan, C. S., Seshadri, S., Beiser, A., Au, R., Kase, C. S., Kelly-Hayes, M., et al. (2004). Dementia after stroke: The Framingham Study. *Stroke, 35*(6), 1264-1268.

Jelicic, M., van Boxtel, M. P., Houx, P. J., & Jolles, J. (2000). Does migraine headache affect cognitive function in the elderly? Report from the Maastricht Aging Study (MAAS). *Headache, 40*(9), 715-719.

Jellinger, K. A. (2008). The pathology of "vascular dementia": A critical update. *Journal of Alzheimer's Disease, 14*(1), 107-123.

Jellinger, K. A., & Attems, J. (2007). Neuropathological evaluation of mixed dementia. *Journal of the Neurological Sciences, 257*(1-2), 80-87.

Kalaria, R. (2002). Similarities between Alzheimer's disease and vascular dementia. *Journal of the Neurological Sciences, 203-204*, 29-34.

Kalaydjian, A., Zandi, P. P., Swartz, K. L., Eaton, W. W., & Lyketsos, C. (2007). How migraines impact cognitive function: Findings from the Baltimore ECA. *Neurology, 68*(17), 1417-1424.

Katzman, R., Aronson, M., Fuld, P., & Kawas, C. (1989). Development of dementing illnesses in an 80-year-old volunteer cohort. *Annals of Neurology, 25*(4), 317-324.

Keller, J. N. (2006). Age-related neuropathology, cognitive decline, and Alzheimer's disease. *Ageing Research Reviews, 5*(1), 1-13.

Kester, M. I., & Scheltens, P. (2009). Dementia: The bare essentials. *Practical Neurology, 9*(4), 241-251.

Kleinbaum D, Kupper, Muller P. (1988). *Applied regression analysis and other multivariable methods* (2nd ed.). Boston: PWS-Kent.

Kopf, D., & Frolich, L. (2009). Risk of incident Alzheimer's disease in diabetic patients: A systematic review of prospective trials. *Journal of Alzheimer's Disease, 16*(4), 677-685.

Kurth, T., Schurks, M., Logroscino, G., & Buring, J. E. (2009). Migraine frequency and risk of cardiovascular disease in women. *Neurology, 73*(8), 581-588.

Kraemer, H. C., Stice, E., Kazdin, A., Offord, D., & Kupfer, D. (2001). How do risk factors work together? mediators, moderators, and independent, overlapping, and proxy risk factors. *The American Journal of Psychiatry, 158*(6), 848-856.

Lambert, G. A., & Zagami, A. S. (2009). The mode of action of migraine triggers: A hypothesis. *Headache, 49*(2), 253-275.

Last, J. M. (2001). *A dictionary of epidemiology* (4th ed.). United States: Oxford University Press.

Launer, L. J. (2009). Diabetes: Vascular or neurodegenerative: An epidemiologic perspective. *Stroke, 40*(3 Suppl), S53-5.

Launer, L. J., Masaki, K., Petrovitch, H., Foley, D., & Havlik, R. J. (1995). The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *The Journal of the American Medical Association, 274*(23), 1846-1851.

Launer, L. J., Ross, G. W., Petrovitch, H., Masaki, K., Foley, D., White, L. R., et al. (2000). Midlife blood pressure and dementia: The Honolulu-Asia Aging Study. *Neurobiology of Aging, 21*(1), 49-55.

Laurin, D., Verreault, R., Lindsay, J., MacPherson, K., & Rockwood, K. (2001). Physical activity and risk of cognitive impairment and dementia in elderly persons. *Archives of Neurology, 58*(3), 498-504.

Le Pira, F., Lanaia, F., Zappala, G., Morana, R., Panetta, M. R., Reggio, E., et al. (2004). Relationship between clinical variables and cognitive performances in migraineurs with and without aura. *Functional Neurology, 19*(2), 101-105.

Le Pira, F., Zappala, G., Giuffrida, S., Lo Bartolo, M. L., Reggio, E., Morana, R., et al. (2000). Memory disturbances in migraine with and without aura: A strategy problem? *Cephalalgia, 20*(5), 475-478.

Lee, M., & Chodosh, J. (2009). Dementia and life expectancy: What do we know? *Journal of the American Medical Directors Association, 10*(7), 466-471.

Leijdekkers, M. L., Passchier, J., Goudswaard, P., Menges, L. J., & Orlebeke, J. F. (1990). Migraine patients cognitively impaired? *Headache, 30*(6), 352-358.

Leonardi, M., Steiner, T. J., Scher, A. T., & Lipton, R. B. (2005). The global burden of migraine: Measuring disability in headache disorders with WHO's classification of functioning, disability and health (ICF). *The Journal of Headache and Pain, 6*(6), 429-440.

Leys, D., & Pasquier, F. (1998). Subcortical vascular dementia: Epidemiology and risk factors. *Archives of Gerontology and Geriatrics,* (Suppl6), 281-294.

Leys, D., Pasquier, F., & Parnetti, L. (1998). Epidemiology of vascular dementia. *Haemostasis, 28*(3-4), 134-150.

Lindsay, J., Hebert, R., & Rockwood, K. (1997). The Canadian Study of Health and Aging: Risk factors for vascular dementia. *Stroke, 28*(3), 526-530.

Lipton, R.B., Hamelsky, S.W., Stewart, W.F. (2004). Migraine and tension-type headache. *Neuroepidemiology: From principles to practice* (Ch. 13: pp. 319-334). New York: Oxford University Press, Inc.

Lipton, R. B., & Bigal, M. E. (2005). The epidemiology of migraine. *The American Journal of Medicine, 118*(Suppl 1), 3S-10S.

Lipton, R. B., & Bigal, M. E. (2005). Migraine: Epidemiology, impact, and risk factors for progression. *Headache, 45*(Suppl 1), S3-S13.

Lipton, R. B., Bigal, M. E., Diamond, M., Freitag, F., Reed, M. L., Stewart, W. F., et al. (2007). Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology, 68*(5), 343-349.

Lipton, R. B., Diamond, S., Reed, M., Diamond, M. L., & Stewart, W. F. (2001). Migraine diagnosis and treatment: Results from the American Migraine Study II. *Headache, 41*(7), 638-645.

Lipton, R. B., Hamelsky, S. W., Kolodner, K. B., Steiner, T. J., & Stewart, W. F. (2000). Migraine, quality of life, and depression: A population-based case-control study. *Neurology, 55*(5), 629-635.

Lipton, R. B., Scher, A. I., Steiner, T. J., Bigal, M. E., Kolodner, K., Liberman, J. N., et al. (2003). Patterns of health care utilization for migraine in England and in the United States. *Neurology, 60*(3), 441-448.

Lipton, R. B., Stewart, W. F., Diamond, S., Diamond, M. L., & Reed, M. (2001). Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache, 41*(7), 646-657.

Lopera, F., Ardilla, A., Martinez, A., Madrigal, L., Arango-Viana, J. C., Lemere, C. A., et al. (1997). Clinical features of early-onset Alzheimer disease in a large kindred with an E280A presenilin-1 mutation. *JAMA : The Journal of the American Medical Association, 277*(10), 793-799.

Lopez, O. L. (2007). Risk factors and epidemiology of vascular dementia. *Brain and Cognition, 63*, 191-196.

Luchsinger, J. A., Honig, L. S., Tang, M. X., & Devanand, D. P. (2008). Depressive symptoms, vascular risk factors, and Alzheimer's disease. *International Journal of Geriatric Psychiatry, 23*(9), 922-928.

Luchsinger, J. A., & Mayeux, R. (2007). Adiposity and Alzheimer's disease. *Current Alzheimer Research, 4*(2), 127-134.

Luchsinger, J. A., Tang, M. X., Stern, Y., Shea, S., & Mayeux, R. (2001). Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *American Journal of Epidemiology, 154*(7), 635-641.

MacGregor, E. A. (2009). Migraine headache in perimenopausal and menopausal women. *Current Pain and Headache Reports, 13*(5), 399-403.

MacKnight, C., Rockwood, K., Awalt, E., & McDowell, I. (2002). Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian Study of Health and Aging. *Dementia and Geriatric Cognitive Disorders, 14*(2), 77-83.

Markesbery, W. R., Schmitt, F. A., Kryscio, R. J., Davis, D. G., Smith, C. D., & Wekstein, D. R. (2006). Neuropathologic substrate of mild cognitive impairment. *Archives of Neurology, 63*(1), 38-46.

Martins, I. J., Berger, T., Sharman, M. J., Verdile, G., Fuller, S. J., & Martins, R. N. (2009). Cholesterol metabolism and transport in the pathogenesis of Alzheimer's disease. *Journal of Neurochemistry, 111*(6), 1275-1308.

McCusker, S. M., Curran, M. D., Dynan, K. B., McCullagh, C. D., Urquhart, D. D., Middleton, D., et al. (2001). Association between polymorphism in regulatory region of gene encoding tumour necrosis factor alpha and risk of Alzheimer's disease and vascular dementia: A case-control study. *Lancet, 357*(9254), 436-439.

McGeer, P. L., Rogers, J., & McGeer, E. G. (2006). Inflammation, anti-inflammatory agents and Alzheimer disease: The last 12 years. *Journal of Alzheimer's Disease, 9*(3), Supplement, pp. 271-276.

McGeer, P. L., & McGeer, E. G. (2001). Polymorphisms in inflammatory genes and the risk of Alzheimer disease. *Archives of Neurology, 58*(11), 1790-1792.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology, 34*(7), 939-944.

Mirra, S. S., Heyman, A., McKeel, D., Sumi, S. M., Crain, B. J., Brownlee, L. M., et al. (1991). The consortium to establish a registry for Alzheimer's disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology, 41*(4), 479-486.

Montagna, P. (2008). Migraine genetics. *Expert Review of Neurotherapeutics, 8*(9), 1321-1330.

Morley, J. E., & Banks, W. A. (2010). Lipids and cognition. *Journal of Alzheimer's Disease: JAD, 20*(3), 737-747.

Morovic, S., Jurasic, M. J., Martinic Popovic, I., Seric, V., Lisak, M., & Demarin, V. (2009). Vascular characteristics of patients with dementia. *Journal of the Neurological Sciences, 283*(1-2), 41-43.

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology, 43*(11), 2412-2414.

Motamedi, G., & Meador, K. (2003). Epilepsy and cognition. *Epilepsy & Behavior*, 4 (Suppl 2), S25-38.

Mulder, E. J., Linssen, W. H., Passchier, J., Orlebeke, J. F., & de Geus, E. J. (1999). Interictal and postictal cognitive changes in migraine. *Cephalalgia, 19*(6), 557-65; discussion 541.

Musicco, M. (2010). Gender differences in the occurrence of Alzheimer's disease. *Functional Neurology, 25*(2), 89-92.

Nagai, M., Hoshide, S., & Kario, K. (2010). Hypertension and dementia. *American Journal of Hypertension, 23*(2), 116-124.

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699.

National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. (1997). Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. *Neurobiology of Aging, 18*(4 Suppl), S1-2.

Nicoll, J. A., Mrak, R. E., Graham, D. I., Stewart, J., Wilcock, G., MacGowan, S., et al. (2000). Association of interleukin-1 gene polymorphisms with Alzheimer's disease. *Annals of Neurology, 47*(3), 365-368.

Nilsson, L. (2003). Memory function in normal aging. *Acta Neurologica Scandinavica, 107*(Suppl179), 7-13.

O'Brien, B., Goeree, R., & Streiner, D. (1994). Prevalence of migraine headache in Canada: A population-based survey. *International Journal of Epidemiology, 23*(5), 1020-1026.

O'Bryant, S. E., Marcus, D. A., Rains, J. C., & Penzien, D. B. (2006). The neuropsychology of recurrent headache. *Headache, 46*(9), 1364-1376.

Ownby, R. L., Crocco, E., Acevedo, A., John, V., & Loewenstein, D. (2006). Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. *Archives of General Psychiatry, 63*(5), 530-538.

Paemeleire, K. (2009). Brain lesions and cerebral functional impairment in migraine patients. *Journal of the Neurological Sciences, 283*(1-2), 134-136.

Panconesi, A., Bartolozzi, M. L., & Guidi, L. (2009). Migraine pain: Reflections against vasodilatation. *The Journal of Headache and Pain, 10*(5), 317-325.

Patel, N. V., Bigal, M. E., Kolodner, K. B., Leotta, C., Lafata, J. E., & Lipton, R. B. (2004). Prevalence and impact of migraine and probable migraine in a health plan. *Neurology, 63*(8), 1432-1438.

Patterson, C., Feightner, J., Garcia, A., & MacKnight, C. (2007). General risk factors for dementia: A systematic evidence review. *Alzheimer's & Dementia, 3*(4), 341-347.

Pearson, A. J., Chronicle, E. P., Maylor, E. A., & Bruce, L. A. (2006). Cognitive function is not impaired in people with a long history of migraine: A blinded study. *Cephalalgia, 26*(1), 74-80.

Pedersen, N. L., Gatz, M., Berg, S., & Johansson, B. (2004). How heritable is Alzheimer's disease late in life? Findings from Swedish twins. *Annals of Neurology, 55*(2), 180-185.

Peers, C., Dallas, M. L., Boycott, H. E., Scragg, J. L., Pearson, H. A., & Boyle, J. P. (2009). Hypoxia and neurodegeneration. *Annals of the New York Academy of Sciences, 1177*, 169-177.

Peters, R. (2006). Ageing and the brain. *Postgraduate Medical Journal, 82*(964), 84-88.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology, 56*(3), 303-308.

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., et al. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology, 58*(12), 1985-1992.

Petersen, R. C., Roberts, R. O., Knopman, D. S., Boeve, B. F., Geda, Y. E., Ivnik, R. J., et al. (2009). Mild cognitive impairment: Ten years later. *Archives of Neurology, 66*(12), 1447-1455.

Plassman, B. L., Langa, K. M., Fisher, G. G., Heeringa, S. G., Weir, D. R., Ofstedal, M. B., et al. (2007). Prevalence of dementia in the United States: The aging, demographics, and memory study. *Neuroepidemiology, 29*(1-2), 125-132.

Price, T. R., Manolio, T. A., Kronmal, R. A., Kittner, S. J., Yue, N. C., Robbins, J., et al. (1997). Silent brain infarction on magnetic resonance imaging and neurological abnormalities in

community-dwelling older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Stroke, 28*(6), 1158-1164.

Prince, M. (2004). Epidemiology of dementia. *Psychiatry, 3*(12), 11-13.

Purnell, C., Gao, S., Callahan, C. M., & Hendrie, H. C. (2009). Cardiovascular risk factors and incident Alzheimer disease: A systematic review of the literature. *Alzheimer Disease and Associated Disorders, 23*(1), 1-10.

Qiu, C., Winblad, B., & Fratiglioni, L. (2005). The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurology, 4*(8), 487-499.

Qiu, C., Winblad, B., & Marengoni, A. (2006). Heart failure and risk of dementia and Alzheimer disease: A population-based cohort study. *Archives of Internal Medicine, 166*(9), 1003-1008.

Querfurth, H. W., & LaFerla, F. M. (2010). Alzheimer's disease. *The New England Journal of Medicine, 362*(4), 329-344.

Reisberg, B., Ferris, S. H., de Leon, M. J., & Crook, T. (1982). The Global Deterioration Scale for assessment of primary degenerative dementia. *The American Journal of Psychiatry, 139*(9), 1136-1139.

Ringman, J. M., Romano, J. D., Medina, L. D., Rodriguez-Agudelo, Y., Schaffer, B., Varpetian, A., et al. (2008). Increased prevalence of significant recurrent headache in preclinical familial Alzheimer's disease mutation carriers. *Dementia and Geriatric Cognitive Disorders, 25*(4), 380-384.

Rockwood, K., Stolee, P., & McDowell, I. (1996). Factors associated with institutionalization of older people in Canada: Testing a multi-factorial definition of frailty. *Journal of the American Geriatrics Society, 44*(5), 578-582.

Román, G. C., Tatemichi, T. K., Erkinjuntti, T., & Cummings, J. L. (1993). Vascular dementia: Diagnostic criteria for research studies: Report of the NINDS-AIREN International Workshop. *Neurology, 43*(2), 250-260.

Ruitenberg, A., Ott, A., van Swieten, J. C., Hofman, A., & Breteler, M. M. (2001). Incidence of dementia: Does gender make a difference? *Neurobiology of Aging, 22*(4), 575-580.

Saczynski, J. S., Jonsdottir, M. K., Garcia, M. E., Jonsson, P. V., Peila, R., Eiriksdottir, G., et al. (2008). Cognitive impairment: An increasingly important complication of type 2 diabetes: The age, gene/environment susceptibility--Reykjavik Study. *American Journal of Epidemiology, 168*(10), 1132-1139.

Salminen, A., Ojala, J., Kauppinen, A., Kaarniranta, K., & Suuronen, T. (2009). Inflammation in Alzheimer's disease: Amyloid-beta oligomers trigger innate immunity defence via pattern recognition receptors. *Progress in Neurobiology, 87*(3), 181-194.

Scher, A. I., Bigal, M. E., & Lipton, R. B. (2005). Comorbidity of migraine. *Current Opinion in Neurology, 18*(3), 305-310.

Scher, A. I., Terwindt, G. M., Picavet, H. S., Verschuren, W. M., Ferrari, M. D., & Launer, L. J. (2005). Cardiovascular risk factors and migraine: The GEM Population-based Study. *Neurology, 64*(4), 614-620.

Scherer, P., Bauer, H., & Baum, K. (1997). Alternate finger tapping test in patients with migraine. *Acta Neurologica Scandinavica, 96*(6), 392-396.

Schneider, J. A., Boyle, P. A., Arvanitakis, Z., Bienias, J. L., & Bennett, D. A. (2007). Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. *Annals of Neurology, 62*(1), 59-66.

Schurks, M., Buring, J. E., & Kurth, T. (2009). Agreement of self-reported migraine with ICHD-II criteria in the Women's Health Study. *Cephalalgia, 29*(10), 1086-1090.

Shen, Z. X. (2004). Brain cholinesterases: II. The molecular and cellular basis of Alzheimer's disease. *Medical Hypotheses, 63*(2), 308-321.

Silberstein, S. D., Lipton, R. B., & Goadsby, P. J. (1998). *Headache in clinical practice*. Oxford, UK: Isis Medical Media.

Silberstein, S., Loder, E., Diamond, S., Reed, M. L., Bigal, M. E., Lipton, R. B., et al. (2007). Probable migraine in the United States: Results of the American migraine prevalence and prevention (AMPP) study. *Cephalalgia, 27*(3), 220-234.

Skoog, I., Lernfelt, B., Landahl, S., Palmertz, B., Andreasson, L. A., Nilsson, L., et al. (1996). 15-year longitudinal study of blood pressure and dementia. *Lancet, 347*(9009), 1141-1145.

Snowdon, D. A., Greiner, L. H., Mortimer, J. A., Riley, K. P., Greiner, P. A., & Markesbery, W. R. (1997). Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA: The Journal of the American Medical Association, 277*(10), 813-817.

Solé-Padullés, C., Bartrés-Faz, D., Junqué, C., Vendrell, P., Rami, L., Clemente, I. C., et al. (2009). Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging, 30*(7), 1114-1124.

Statistics Canada. (2010). *Causes of death.* Retrieved from http://cansim2.statcan.gc.ca/cgi-win/cnsmcgi.pgm?Lang=E&ResultTemplate=/Stu-Etu/Stu-Etu3&ChunkSize=25&AS_Theme=2979&ChunkStart=1&AS_Date=.&AS_Ser=.&AS_Auth=.&AS_Srch=&AS_SORT=0&AS_UNIV=3&Version=2&AS_Mode=2

Statistics Canada. (2010). *Leading causes of death in Canada.* Retrieved fromhttp://cansim2.statcan.gc.ca/cgi-win/cnsmcgi.pgm?Lang=E&ResultTemplate=/Stu-Etu/Stu-Etu3&ChunkSize=25&AS_Theme=2979&ChunkStart=1&AS_Date=.&AS_Ser=.&AS_Auth=.&AS_Srch=&AS_SORT=0&AS_UNIV=3&Version=2&AS_Mode=2

Stewart, R., Xue, Q. L., Masaki, K., Petrovitch, H., Ross, G. W., White, L. R., et al. (2009). Change in blood pressure and incident dementia: A 32-year prospective study. *Hypertension, 54*(2), 233-240.

Stewart, W. F., Wood, C., Reed, M. L., Roy, J., Lipton, R. B., & AMPP Advisory Group. (2008). Cumulative lifetime migraine incidence in women and men. *Cephalalgia, 28*(11), 1170-1178.

Stewart, W. F., Lipton, R. B., Celentano, D. D., & Reed, M. L. (1992). Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA: The Journal of the American Medical Association, 267*(1), 64-69.

Stewart, W. F., Lipton, R. B., & Liberman, J. (1996). Variation in migraine prevalence by race. *Neurology, 47*(1), 52-59.

Stewart, W. F., Simon, D., Shechter, A., & Lipton, R. B. (1995). Population variation in migraine prevalence: A meta-analysis. *Journal of Clinical Epidemiology, 48*(2), 269-280.

Stovner, L., Hagen, K., Jensen, R., Katsarava, Z., Lipton, R., Scher, A., et al. (2007). The global burden of headache: A documentation of headache prevalence and disability worldwide. *Cephalalgia: An International Journal of Headache, 27*(3), 193-210.

Tedeschi, G., Cirillo, M., Tessitore, A., & Cirillo, S. (2008). Alzheimer's disease and other dementing conditions. *Neurological Sciences, 29*(Suppl 3), 301-307.

Tellez-Zenteno, J. F., Matijevic, S., & Wiebe, S. (2005). Somatic comorbidity of epilepsy in the general population in Canada. *Epilepsia, 46*(12), 1955-1962.

Troncoso, J. C., Zonderman, A. B., Resnick, S. M., Crain, B., Pletnikova, O., & O'Brien, R. J. (2008). Effect of infarcts on dementia in the Baltimore Longitudinal Study of Aging. *Annals of Neurology, 64*(2), 168-176.

Tsuno, N., & Homma, A. (2009). What is the association between depression and Alzheimer's disease? *Expert Review of Neurotherapeutics, 9*(11), 1667-1676.

The Canadian Study of Health and Aging Working Group. (2000). The incidence of dementia in Canada. *Neurology, 55*, 66-73.

Tuokko, H., & Frerichs, R. J. (2000). Cognitive impairment with no dementia (CIND): Longitudinal studies, the findings, and the issues. *Clinical Neuropsychologist, 14*(4), 504-525.

Tyas, S. L. (2001). Alcohol use and the risk of developing Alzheimer's disease. *Alcohol Research & Health: The Journal of the National Institute on Alcohol Abuse and Alcoholism, 25*(4), 299-306.

Tyas, S.L., Gutmanis, I. (2008). Alzheimer's disease. (2nded.). *Managerial epidemiology: Concepts and cases* (Ch. 17:pp. 441-472). Chicago, IL: Health Administration Press.

Tyas, S. L., Koval, J. J., & Pederson, L. L. (2000). Does an interaction between smoking and drinking influence the risk of Alzheimer's disease? Results from three Canadian data sets. *Statistics in Medicine, 19*(11-12), 1685-1696.

Tyas, S. L., Manfreda, J., Strain, L. A., & Montgomery, P. R. (2001). Risk factors for Alzheimer's disease: A population-based, longitudinal study in Manitoba, Canada. *International Journal of Epidemiology, 30*(3), 590-597.

Tyas, S. L., Salazar, J. C., Snowdon, D. A., Desrosiers, M. F., Riley, K. P., Mendiondo, M. S., et al. (2007). Transitions to mild cognitive impairments, dementia, and death: Findings from The Nun Study. *American Journal of Epidemiology, 165*(11), 1231-1238.

Tyas, S. L., White, L. R., Petrovitch, H., Webster Ross, G., Foley, D. J., Heimovitz, H. K., et al. (2003). Mid-life smoking and late-life dementia: The Honolulu-Asia Aging Study. *Neurobiology of Aging, 24*(4), 589-596.

Vermeer, S. E., Den Heijer, T., Koudstaal, P. J., Oudkerk, M., Hofman, A., Breteler, M. M., et al. (2003). Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke, 34*(2), 392-396.

Vermeer, S. E., Hollander, M., van Dijk, E. J., Hofman, A., Koudstaal, P. J., Breteler, M. M., et al. (2003). Silent brain infarcts and white matter lesions increase stroke risk in the general population: The Rotterdam Scan Study. *Stroke, 34*(5), 1126-1129.

Vermeer, S. E., Koudstaal, P. J., Oudkerk, M., Hofman, A., & Breteler, M. M. (2002). Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke, 33*(1), 21-25.

Vermeer, S. E., Prins, N. D., den Heijer, T., Hofman, A., Koudstaal, P. J., & Breteler, M. M. (2003). Silent brain infarcts and the risk of dementia and cognitive decline. *New England Journal of Medicine, 348*(13), 1215-1222.

Viswanathan, A., Rocca, W. A., & Tzourio, C. (2009). Vascular risk factors and dementia: How to move forward? *Neurology, 72*(4), 368-374.

Waldie, K. E., Hausmann, M., Milne, B. J., & Poulton, R. (2002). Migraine and cognitive function: A life-course study. *Neurology, 59*(6), 904-908.

Welch, K. M., Cutrer, F. M., & Goadsby, P. J. (2003). Migraine pathogenesis: Neural and vascular mechanisms. *Neurology, 60*(7, Suppl 2), S9-S14.

Wenk, G. L. (2003). Neuropathologic changes in Alzheimer's disease. *Journal of Clinical Psychiatry, 64*(Suppl 9), 7-10.

Whitmer, R. A., Sidney, S., Selby, J., Johnston, S. C., & Yaffe, K. (2005). Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology, 64*(2), 277-281.

Wolfson, C., Wolfson, D. B., Asgharian, M., M'Lan, C. E., Østbye, T., Rockwood, K., et al. (2001). A re-evaluation of the duration of survival after the onset of dementia. *New England Journal of Medicine, 344*(15), 1111-1116.

World Health Organization. (2001). *The World Health Report 2001 - Mental Health: New Understanding, New Hope*. Geneva, Switzerland.

World Health Organization. (2002). *World Health Organization Fact Sheet: The top ten causes of death*. Geneva, Switzerland.

Xie, J., Brayne, C., Matthews, F. E., & Medical Research Council Cognitive Function and Ageing Study Collaborators. (2008). Survival times in people with dementia: Analysis from population based cohort study with 14 year follow-up. *BMJ (Clinical Research Ed.), 336*(7638), 258-262.

Zanetti, O., Solerte, S. B., & Cantoni, F. (2009). Life expectancy in Alzheimer's disease (AD). *Archives of Gerontology and Geriatrics, 49*(Suppl 1), 237-243.

Zeitlin, C., & Oddy, M. (1984). Cognitive impairment in patients with severe migraine. *The British Journal of Clinical Psychology, 23*(Pt 1), 27-35.

Appendices

Appendix A: Epidemiologic Studies Assessing Cognitive Impairment or Cognitive Performance in Migraine Sufferers

Reference	Temporality	Sample	Migraine Definition	Cognitive Domains Tested	Results	Evidence for association between migraines and neuropsycho-logical or cognitive impairment?
Alzheimer's Disease						
Tyas et al. 2001	Longitudinal population-based	75 migraineurs (65 years of age and older); Manitoba Study of Health and Aging	Chronic health condition question	Memory	Migraines increased the risk of AD (Relative Risk (RR)=3.49, 95% CI:1.39-8.77); an even stronger effect was observed in women (RR=5.78, 95% CI:2.00-16.74)	YES
Breteler et al., 1991	Cross-sectional	169 migraineurs (50 years of age and older)	Chronic health condition question	Memory	Inverse relationship between AD risk and migraines (RR=0.7, 95% CI:0.5-1.0). Increased risk in men (RR=1.1, 95% CI:0.6-2.0) compared to women (RR=0.6, 95% CI:0.4-0.9)	NO

Reference	Temporality	Sample	Migraine Definition	Cognitive Domains Tested	Results	Evidence for association between migraines and neuropsycho-logical or cognitive impairment?
Cognitive Performance						
Zeitlin & Oddy, 1984	Cross-sectional	19 migraineurs (20-50 years)	Criteria by Crisp et al. 1977	Reaction time, visual attention, sustained/divided attention, working memory, verbal intelligence	Migraineurs performed poorly on a series of memory and information processing tests.	YES
Hooker & Raskin, 1986	Cross-sectional	31 migraineurs (with and without aura mean age 41.1-41.9 years)	Ad Hoc Committee on Classification of Headache	Sensory ability, spatial and working memory, motor functions, verbal ability, visual processing, cognitive ability	Migraineurs (with and without aura) had greater impairment on neuropsycho-logical composite score and delayed memory. Migraineurs with aura performed more poorly on measures of sustained attention, information processing and psychomotor speed.	YES

Reference	Temporality	Sample	Migraine Definition	Cognitive Domains Tested	Results	Evidence for association between migraines and neuropsycho-logical or cognitive impairment?
Burker, Hannay & Halsey, 1989	Cross-sectional	47 migraineurs (with and without aura-female only, mean age 19.2-19.5 years)	Adrasik and Burke's Criteria for Diagnosing Headache	Psychomotor ability, auditory ability, recall, visuospatial abilities, memory (working), attention, planning (executive functions)	No difference between migraineurs and controls.	NO
D'Andrea et al., 1989	Cross-sectional	20 migraineurs (children, 7-11 years)	Ad Hoc Committee on Classification of Headache	Cognitive ability, visuospatial abilities, memory (short-term, working, logical, episodic), attention, planning (executive functions)	Observed decreased short and long-term memory function.	YES
Leijdekkers et al., 1990	Cross-sectional	37 migraineurs (with and without aura, female only, mean age 38.4 years)	Headache Classification Committee of the International Headache Society Criteria	Spatial perception, visual abstract processing, problem solving, cognitive function	No difference between migraineurs and controls.	NO

Reference	Temporality	Sample	Migraine Definition	Cognitive Domains Tested	Results	Evidence for association between migraines and neuropsycho-logical or cognitive impairment?
Scherer, Bauer & Baum, 1997	Cross-sectional	25 migraineurs (12-61 years)	Headache Classification Committee of the International Headache Society Criteria	Psychomotor function/ability	Migraineurs <40 years had significant delays in time to complete runs of alternate finger tapping.	YES
Bell et al., 1999	Cross-sectional	20 migraineurs (with and without aura, mean age 40.2 years)	Headache Classification Committee of the International Headache Society Criteria	Recall/recognition, memory (logical, working), visual attention reaction time, spatial perception, visual abstract processing, problem solving, semantic fluency, sustained/divided attention	No difference between migraineurs and controls.	NO
Mulder et al., 1999	Cross-sectional	30 migraineurs (with and without aura, mean age 24.3-24.9 years)	Headache Classification Committee of the International Headache Society Criteria	Cognitive ability, learning and memory, psychomotor ability	Those with migraine with aura were slower on tests of selective attention.	YES

Reference	Temporality	Sample	Migraine Definition	Cognitive Domains Tested	Results	Evidence for association between migraines and neuropsycho-logical or cognitive impairment?
Le Pira et al., 2000	Cross-sectional	30 migraineurs (with and without aura, mean age 32.2 years)	Headache Classification Committee of the International Headache Society Criteria	Visuospatial abilities, memory (working, short-term, visual short-term), attention, planning (executive functions), recall/recognition	Migraineurs performed more poorly on immediate and delayed visual memory	YES
Jelicic et al., 2000	Longitudinal population-based	99 migraineurs (25-80 years); Maastricht Aging Study	Chronic health condition question	Cognitive function, verbal ability, recall/recognition	No difference between migraineurs and controls; also no difference in those over ≥64 years.	NO
Waldie et al., 2002	Longitudinal birth cohort study	114 migraineurs (3-26 years); Dunedin Multi-disciplinary Health and Development Study	Headache Classification Committee of the International Headache Society Criteria	Receptive vocabulary, verbal ability, recognition, psychomotor function, cognitive ability	Intelligence and verbal comprehension was lower in those with migraines.	YES

Reference	Temporality	Sample	Migraine Definition	Cognitive Domains Tested	Results	Evidence for association between migraines and neuropsycho-logical or cognitive impairment?
Calandre et al., 2002	Cross-sectional	60 migraineurs (15-68 years)	Headache Classification Committee of the International Headache Society Criteria	Cognitive ability, reaction time, visual attention, visuospatial abilities, memory (short-term, working, logical), attention, planning, (executive functions)	Migraineurs had delayed reaction time; attention and memory were also impaired. Brain perfusion abnormalities found in 43%.	YES
Le Pira et al., 2004	Cross-sectional	45 migraineurs (with and without aura-mean age 32.95 & 33.54 years)	Headache Classification Committee of the International Headache Society Criteria	Visuospatial abilities, memory (working, short-term, visual short-term), attention, planning (executive functions) recall/recognition	Headache pain was associated with poor immediate and delayed visual memory.	YES
Gaist et al., 2005	Population based	536 migraineurs (with and without aura-age groups: <50, 50-59, 60+); Danish Twin Registry	Headache Classification Committee of the International Headache Society Criteria	Short term memory, recall, cognitive function	No difference between migraineurs and controls.	NO

Reference	Temporality	Sample	Migraine Definition	Cognitive Domains Tested	Results	Evidence for association between migraines and neuropsycho-logical or cognitive impairment?
Pearson et al., 2006	Cross-sectional	74 migraineurs (51-84 years)	Headache Classification Committee of the International Headache Society criteria	Problem solving, visuospatial abilities, processing speed, verbal ability	Average scores on cognitive tests did not differ between migraineurs and controls.	NO
Kalaydjian et al., 2007	Cross-sectional	204 migraineurs (mean age 47.5 years); Baltimore Epidemiologic Catchment Area Study	Headache Classification Committee of the International Headache Society Criteria	Memory	Migraineurs scored lower on tests of immediate and delayed memory.	YES
Baars, Boxtel & Jolles, 2010	Longitudinal population-based	99 migraineurs (25-80 years); Maastricht Aging Study	Chronic health condition question	Memory, recall/recognition, reaction time, cognitive function	Migraine headaches were found to have no effects on any cognitive measure.	NO

Appendix B: Coding of Education: Removal of "Other" Category from the Educational Level Variable

Seventeen participants from the study sample (n=1039) were included in the "other" category of the educational level variable. This category had no additional description. To further understand the "other" category, bivariate analyses were performed between educational level and years of education. Participants in the "other" category achieved between 9 and 22 years of education. Since the range of years of education attained in the "other" category was so wide, we were unable to include those individuals in one of the alternate educational level categories.

Assessment of education level by migraine and cognitive outcomes, indicated that only one participant from the "other" category reported a history of migraines and none of the participants in the "other" category were diagnosed with a late-life cognitive health outcome.

Comparing the selection bias results when including the "other" category to the results excluding the "other" category demonstrated that the samples did not differ significantly. When comparing potential selection bias of the n=978 vs. n=1039 to the n=961 vs. n=1039, the prevalence of VaD did not differ significantly, converting from marginally significant (p-value=0.053) to non-significant (p-value=0.18). The prevalence of CIND also did not change significantly, shifting from marginally significant (p-value=0.094) to non-significant (p-value=0.42). Other heart condition prevalence went from non-significant (p-value=0.19) to marginally significant (p-value=0.06).

When comparing the potential selection bias of the n=727 vs. n=978 to the n=716 vs. n=716, the prevalence of VaD converted from significant (p-value: 0.044) to marginally significant (p-value: 0.09).

Appendix C: MSHA and MSHA-2 Variables for the Study

Variable Description	**MSHA Dataset: Variable Source**			
	MSHA-1 (scr.)	**MSHA-1 (risk factor)**	**MSHA-2 (scr.) v.1, v.2**	**Role**
Date of Screening Interview	T1_Day, T1_Month, T1_year		T2_Day, T2_Month, T2_Year	Descriptor
T1 Status Variables	CONDIAG			Descriptor
T2 Screening Status			SCRSTAT2	Descriptor
MSHA-2 Screening Interview Version			SCRVER, VERSION	Descriptor
Provincial Subject Identification	PROVID		PROVID	Descriptor
Sex	SEX			Confounding Variable/ Effect Modifier
Years of Education Completed	EDUYEAR			Confounding Variable
Level of Education	EDULEVEL			Confounding Variable
Age at Screening Interview	AGET1			Confounding Variable
Depression		DEPRESSN, DEPYR		Confounding Variable
Epilepsy		EPILEPSY, EPIYR		Confounding Variable/ Effect Modifier
Migraine		MIGRAINE, MIGYR		Exposure
Alzheimer's disease (Family History)		ALZ1, ALZ2, ALZ3		Effect Modifier- proxy for genetic risk
Senile Dementia (Family History)		SEN1, SEN2, SEN3		Effect Modifier- proxy for genetic risk
Heart Attack		ATTACK, ATYR		Intervening Variable
Other Heart condition		OHEART, HEYR		Intervening Variable
Stroke		PRSTROKE, STRYR		Intervening Variable
High Blood Pressure		PROXHBP, HBPYR		Intervening Variable
Diabetes		PROXDIAB, DIAYR		Intervening Variable
Clinical Diagnoses	FINALDX1		FINALDX2	Cognitive Outcome

Appendix D: Data Access Approval

UNIVERSITY OF MANITOBA | Centre on Aging

338 Isbister Building
Winnipeg, Manitoba
Canada R3T 2N2
Telephone (204) 474-8754
Fax (204) 474-7576
aging@umanitoba.ca

June 1, 2010

Dr. Suzanne Tyas and Ms. Rebecca Hader
Department of Health Studies and Gerontology
University of Waterloo
200 University Avenue West
Waterloo, ON N2L 3G1

Dear Dr. Tyas and Ms. Hader:

I am pleased to notify you that your request for access to the Manitoba Study of Health and Aging (MSHA-1 and MSHA-2) data, as outlined in your proposal of May 21, 2010 has been approved. Release of the data is subject to receipt of ethics approval from the University of Waterloo.

As you know, the following are conditions associated with access to these data:

1. You will include the following acknowledgement(s) in your published work/presentations based on these data:

MSHA-1: *The Manitoba Study of Health and Aging (MSHA-1) was funded primarily by Manitoba Health, with additional funding provided through the Canadian Study of Health and Aging by the Seniors Independence Research Program of the National Health Research and Development Program of Health Canada (Project No. 6606-3954-MC[S]).*

MSHA-2: *The Manitoba Study of Health and Aging (MSHA-2) was funded primarily by Manitoba Health's Healthy Communities Development Fund with additional funding provided through the Canadian Study of Health and Aging by the Seniors Independence Research Program of the National Health Research and Development Program of Health Canada (Project No. 6606-3954-MC[S]).*

...2/

2. The following disclaimer must be included in your published work/presentations:

> *The results and conclusions are those of the author and no official endorsement by the Centre on Aging or Manitoba Health is intended or should be inferred.*

3. Individuals will provide the Centre on Aging with a final copy of their published work/ presentations. All data files will be returned to the Centre on Aging upon completion of the research.

Best wishes with your research. Please do not hesitate to contact me or Audrey Blandford if you have any questions or require further information.

Sincerely,

Laurel A. Strain, PhD
MSHA Principal Investigator

Cc: A. Blandford

Appendix E: University of Waterloo Ethics Approval

UNIVERSITY OF WATERLOO
OFFICE OF RESEARCH ETHICS

Feedback on Ethics Review of Application to Conduct Research with Humans

All research involving human participants at the University of Waterloo must be carried out in compliance with the Office of Research Ethics Guidelines for Research with Human Participants and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

ORE File #: 16798

Project Title: Does a history of migraines increase the risk of late-life cognitive health outcomes?

Faculty Supervisor: Suzanne Tyas **Department/School:** Health Studies & Gerontology
Student Investigator: Rebecca Hader **Department/School:** Health Studies & Gerontology

---

The above research application has undergone ethics review through the Office of Research Ethics and received the following ethics review category:

☑ **Ethics Clearance.** The application is considered acceptable on ethical grounds and complies with ORE Guidelines for Research with Human Participants and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. No revisions are required.

CONDITIONS ASSOCIATED WITH ETHICS CLEARANCE:
1. Ethics clearance is valid for four years from the date ethics clearance is granted.
2. Projects must be conducted in accordance with the description in the application for which full ethics clearance is granted. All subsequent modifications to the protocol must receive prior ethics clearance through the Office of Research Ethics.
3. An annual progress report (ORE Form 105) must be submitted for ethics review for each year of an ongoing project.
4. Any events, procedures, or unanticipated problems that adversely affect participants must be reported to the ORE using ORE Form 106.

☐ The application is considered acceptable on ethical grounds and complies with ORE Guidelines for Research with Human Participants and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. * **Minor/editorial revisions are required** as outlined in a transmitted email. Revised materials must be provided for the ORE file.

☐ Acceptance of the application on ethical grounds is **conditional on revisions and/or additional information.** The following revisions and/or additional information must be provided for ethics review and are requested within **10 days**. A study may not begin until it receives ethics clearance.

- ☐ Information Letter was not provided and is required for ethics review.
- ☐ Information Letter provided is incomplete and requires revisions outlined in the email message.
- ☐ Information Letter and Consent Form were not provided and are required for ethics review.
- ☐ Information Letter and Consent Form provided are incomplete and require revisions outlined in the email message.
- ☐ Copy of interview/survey questions was not provided and is required for ethics review.
- ☐ Other revisions/information are required as outlined in the email message.

☐ Due to the level and/or number of questions and concerns raised during the ethics review process the application is considered not acceptable on ethical grounds at this time . Comments are summarized in the attached ethics review feedback. A new application is required.

11/8/2010
Date

Susan E. Sykes, Ph.D., C.Psych.
Director, Office of Research Ethics

OR
Susanne Santi, M. Math
Senior Manager, Research Ethics

OR
Julie Joza, B.Sc.
Manager, Research Ethics

Appendix F: Baseline Characteristics and Cognitive Health Outcomes for Participants in the Manitoba Study of Health and Aging, 1991-1996: Study Sample (n=1039)

Participant Characteristics*	Baseline (%)	Follow-up (%)
Exposures		
Migraine history (n=1016)	10.4	
Migraine duration (n=47) ($\bar{x}$(SD))	26.7 (20.4)	
Outcomes (n=1029)		
Dementia	-	77.7
Alzheimer's disease	-	25.0
Vascular dementia	-	11.8
Cognitive impairment-no dementia	-	37.5
Confounding Variables		
Age (n=1039) ($\bar{x}$(SD))	76.5 (6.6)	
Age group (n=1039):		
65-74 years	40.2	
75-84 years	46.2	
85+ years	13.6	
Sex (n=1039):		
Male	38.8	
Female	61.2	
Education**:		
Number of years (n=1035) ($\bar{x}$(SD))	10.2 (3.3)	
Level (n=1037):		
Did not complete primary school	10.3	
Completed primary school	47.8	
Completed high school	25.1	
Completed college/university	15.1	
Other	1.6	
Depression (n=1016)	9.7	
Epilepsy (n=1019)	0.1	
Family history of dementia (n=1039)	8.6	
Intervening Variables		
Hypertension (n=1013)	32.9	
Diabetes (n=1019)	7.1	
Stroke (n=1019)	6.8	
Myocardial infarction (n=1014)	10.1	
Other heart condition (n=1002)	19.1	

* Exposure, confounding and intervening variables were measured at baseline; outcomes were measured at follow-up five years later.

**Both measures of education have been examined in univariate and bivariate analyses to determine which measure to use in the multivariate analyses.

Appendix G: Response Bias Comparison for All Samples

Table 1: Response bias comparison: exclusion sample (n=961) vs. the remainder of the study sample (n=78)

	Exclusion Sample n=961	Study Sample n=78	
Exposures	(%)	(%)	p-value
Migraine history	10.1	16.4	0.21
Migraine duration	27.2 (20.3)	2.0	0.22
Outcomes			
Dementia	5.3	6.4	0.88
Alzheimer's disease	3.5	2.6	0.90
Vascular dementia	1.3	3.9	0.18
Cognitive impairment-no dementia	3.9	6.4	0.42
Confounding Variables			
Age ($\bar{x}$(SD))	76.5 (6.54)	76.3 (6.85)	0.72
Age Group:			
65-74 years	40.1	42.3	0.89
75-84 years	46.4	43.6	
85+ years	13.5	14.1	
Sex:			
Male	38.3	44.9	0.30
Female	61.7	55.1	
Education:			
Number of years ($\bar{x}$(SD))	10.2 (3.12)	10.8 (4.65)	0.12
Level			
Did not complete primary school	10.0	14.5	<.0001
Completed primary school	48.7	36.8	
Completed high school	25.7	17.1	
Completed college/university	15.6	9.2	
Other	0	22.4	
Depression	9.2	20.0	0.02
Epilepsy	0.1	0.0	1.0
Family History of Dementia	10.2	4.5	0.19
Intervening Variables			
Hypertension	32.9	32.7	1.0
Diabetes	7.2	5.2	0.75
Stroke	6.4	13.8	0.06
Myocardial Infarction	9.7	17.0	0.14
Other Heart Condition	18.5	31.7	0.06

Table 2: Response bias comparison: analytic sample (n=716) vs. the remainder of the exclusion sample (n=245)

	Exclusion Sample n=716	Study Sample n=245	
Exposures	(%)	(%)	p-value
Migraine History	10.3	9.4	0.76
Migraine Duration ($\bar{x}$(SD))	28.6 (20.2)	22.2 (20.9)	0.38
Outcomes			
Dementia	7.1	0	<.0001
Alzheimer's disease	4.8	0	0.001
Vascular dementia	1.7	0	0.09
Cognitive impairment-no dementia	5.2	0	<.001
Confounding Variables			
Age ($\bar{x}$(SD))	75.9 (6.1)	78.5 (7.41)	<.0001
Age Group:			
65-74 years	42.2	33.9	<.0001
75-84 years	48.3	40.8	
85+ years	9.5	25.3	
Sex:			
Male	38.1	38.8	0.92
Female	61.9	61.2	
Education:			
Number of years ($\bar{x}$(SD))	10.4 (3.1)	9.7 (3.23)	0.02
Level			
Did not complete primary school	8.5	14.3	0.02
Completed primary school	48.0	50.6	
Completed high school	26.5	23.3	
Completed college/university	16.9	11.8	
Depression	9.5	8.2	0.62
Epilepsy	0.1	0.0	1.0
Family History of Dementia	10.3	9.8	0.93
Intervening Variables			
Hypertension	32.8	33.1	1.0
Diabetes	6.6	9.0	0.26
Stroke	5.2	9.8	0.02
Myocardial Infarction	7.8	15.1	0.001
Other Heart Condition	17.5	21.6	0.17

Appendix H: Bivariate Results for Migraine History (n=74) and Migraine Duration (n=36)

Table 1: Bivariate results for migraine history and confounding and intervening variables (n=74)

Migraine history					
	YES (%)	NO (%)	p-value	Odds Ratios	
Sex:					
Male	17.6	40.5	<.001	0.31	(0.17-0.58)
Female	82.4	59.5			
Age group:					
65-74 years	48.7	41.4	0.09		
75-84 years	48.7	48.3			
85+ years	2.7	10.3			
Educational Level:					
Did not complete primary school	6.8	8.7	0.25		
Completed primary school	39.2	49.1			
Completed high school	35.1	25.6			
Completed college/university	18.9	16.7			
Hypertension	39.2	32.1	0.27	1.36	(0.8-2.24)
Diabetes	14.9	5.6	0.005	2.94	(1.43-6.06)
Stroke	10.8	4.5	0.04	2.56	(1.13-5.83)
Myocardial infarction	10.8	7.5	0.43	1.5	(0.68-3.31)
Other heart condition	16.2	17.6	0.89	0.91	(0.47-1.74)
Depression	20.3	8.3	0.002	2.83	(1.5-5.32)
Family history of dementia	11.6	10.2	0.88	1.16	(0.53-2.54)
	($\bar{x}$(SD))	($\bar{x}$(SD))	p-value		
Age (n=716)	75.1 (5.3)	76.0 (6.2)	0.22		
Education years (n=712)	10.5 (3.1)	10.3 (3.1)	0.65		

Table 2: Unadjusted models for the exposure variable duration of migraine disorder by each cognitive health outcome

	Dementia	**AD[1]**	**VaD[2]**	**CIND[3]**
Exposure				
Duration of Migraine Disorder (years)	1.0 (0.96-1.04)	0.99 (0.94-1.04)	1.06 (0.93-1.21)	0.81 (0.61-1.08)

[1]AD- Alzheimer's disease; [2]VaD- vascular dementia; [3]CIND- cognitive impairment-no dementia

Table 3: Bivariate results for migraine duration and confounding and intervening variables (n=36)

Migraine duration			
	($\bar{x}$(SD))		p-values
Dementia	29.1 (24.1)		0.9
Alzheimer's disease	26.0 (24.8)		0.65
Vascular dementia	48.0 (-*)		0.37
Cognitive impairment-no dementia	5.3 (6.7)		0.08
Age group:			
65-74 years	29.8 (21.2)		0.73
75+ years	27.4 (19.6)		
Educational Level:			
Did not complete primary school (n=3)	13.3 (5.8)		0.49
Completed primary school (n=12)	32.9 (18.4)		
Completed high school (n=14)	29.9 (22.2)		
Completed college/university (n=7)	25.4 (22.4)		
	YES ($\bar{x}$(SD))	NO ($\bar{x}$(SD))	p-values
Hypertension	28.1 (21.0)	28.9 (20.1)	0.91
Diabetes	18.0 (9.1)	30.3 (21.0)	0.21
Stroke	31.7 (16.1)	28.3 (20.7)	0.79
Myocardial infarction	27.5 (10.4)	28.8 (21.2)	0.91
Other heart condition	39.3 (30.0)	27.3 (18.8)	0.27
Depression	20.3 (17.1)	31.0 (20.6)	0.19
Family history of dementia	49.0 (1.4)	29.6 (20.1)	0.20
	Male	Female	
Sex	26.9 (10.3)	28.8 (21.2)	0.86
	($\bar{x}$(SD))	Correlation coefficient	p-values
Migraine duration	28.3 (20.4)		
Age	74.2 (5.8)	-0.14	0.42
Education (years)	10.6 (3.3)	0.16	0.37

*Unable to calculate standard deviation due to sample size; n=1