2018

Midlife demographic and lifestyle characteristics and dementia in the Framingham heart study offspring cohort

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

MIDLIFE DEMOGRAPHIC AND LIFESTYLE CHARACTERISTICS AND DEMENTIA IN THE FRAMINGHAM HEART STUDY OFFSPRING COHORT

by

MATTHEW OGRODNIK

B.A., Simon Fraser University, 2007

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2018

Approved by

First Reader ______________________________
Janice Weinberg, Sc.D.
Professor, Department of Biostatistics
Director, MS in Clinical Investigation

Second Reader ______________________________
Rhoda Au, Ph.D.
Professor, Department of Anatomy & Neurobiology

Third Reader ______________________________
Helena Lau, B.S.N., M.P.H.
Instructor, Neurology

MIDLIFE DEMOGRAPHIC AND LIFESTYLE CHARACTERISTICS AND DEMENTIA IN THE FRAMINGHAM HEART STUDY OFFSPRING COHORT

MATTHEW OGRODNIK

ABSTRACT

Background

Dementia is the leading cause of dependence and disability in the elderly population worldwide. Effectively addressing the growing burden of dementia requires an understanding of the predictors of dementia in order to develop preventive strategies. Therefore, identifying potential associations between certain demographic and lifestyle characteristics and dementia may illuminate strategies for reducing the risk of dementia. This research analysis aims to highlight associations between demographic and lifestyle factors in midlife and dementia in later adulthood.

Methods

This is a secondary analysis of data that was collected as part of a longitudinal, prospective cohort study. Data from the Framingham Offspring cohort was analyzed using the Cox proportional hazards regression model to examine the associations between the demographic and lifestyle characteristics and the risk of developing dementia. The multivariate analysis controlled for medical history factors that may also impact dementia risk.

Results

There were 2462 dementia-free participants (aged $\geq$ 40 and $\leq$ 65 years) at baseline at the time of the 2nd exam cycle, during which all demographic, lifestyle, and medical

history factors were collected. During the follow-up period, 286 dementia events were observed (11% of participants). In univariate models, advanced age was significantly associated with an increased risk of dementia, while education level, alcohol use (vs. no use), and wine consumption demonstrated statistically significant protective effects against the development of dementia. After controlling for medical history in the multivariate model, older age remained a significant risk factor for dementia.

Conclusion

This study supports established research regarding the relationship between advancing age and increased risk of dementia, and this significant association remained constant when controlling for factors such as gender and medical history. Further, the associations observed between alcohol consumption, and specifically wine, and dementia risk support continued research on alcohol use and its relationship with dementia; while these protective effects did not remain statistically significant in the multivariate model, other studies have observed significant associations between alcohol and dementia risk in adjusted analyses. Additional research would be helpful to further examine if there are any potential protective effects of alcohol, and determine whether consumption is a worthwhile preventative strategy. Overall, identifying potential risk factors for dementia is an important focus of study, due to the aging worldwide population, and the corresponding increasing significance of this disease. This analysis adds to the literature regarding the associations between certain demographic and lifestyle characteristics and the risk of dementia.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AD	Alzheimer’s disease
APOE	Apolipoprotein E
BMI	Body Mass Index
CDR	Clinical Dementia Rating
CI	Confidence Interval
DR	Dementia Review
FHS	Framingham Heart Study
HR	Hazard Ratio
IRB	Institutional Review Board
MMSE	Mini Mental State Examination
NE	Neurology
NP	Neuropsychologist

INTRODUCTION

Dementia is a general term used to describe a chronic and/or progressive decline in cognitive ability. This decline is represented by a range of symptoms; there is no one established cause or manifestation.[1] The diagnostic criteria for all-cause dementia focus on cognitive or behavioral symptoms that interfere with one's ability to function during usual activities; and further, these symptoms must represent a decline as compared to previous levels of functioning, and cannot result from transient delirium or another psychiatric disorder.[2] In order to make a diagnosis of dementia, the impairment must manifest in at least two domains related to the following: acquiring and remembering new information, impaired reasoning, impaired visuospatial abilities, impaired language abilities, and changes in personality and/or behavior.[2]

The most commonly diagnosed types of dementia are Alzheimer's disease (AD) and vascular dementia; other types include Lewy Body dementia and frontotemporal dementia.[31]

AD constitutes 60-80% of diagnosed cases of dementia, and is characterized by progressive memory loss and other declines in cognitive abilities serious enough to interfere with daily living.[31] AD is presumed to be caused by proteins (beta amyloid and tau) accumulating in the brain and forming structures called 'plaques' and 'tangles,' respectively.[32] The plaques build up between the nerve cells of the brain due to an accumulation of beta-amyloid, while the neurofibrillary tangles form within the neurons, due to a breakdown in the tau protein.[36] These structures disrupt the connections between nerve cells, leading to the eventual death of these cells and the loss of brain tissue.[32]

Vascular dementia is tied to conditions (such as strokes) that block or reduce blood flow to the brain. This in turn deprives brain cells of oxygen and nutrients, resulting in cognitive decline.[33] Vascular dementia can manifest suddenly following an acute event, or can develop gradually due to worsening conditions in the brain over time.

Lewy Body dementia, estimated to be the third most common type of dementia,[34] occurs when protein deposits develop in nerve cells in the brain. These deposits progressively damage regions responsible for thinking, memory and motor control.[34] People with Lewy body dementia most commonly experience visual hallucinations, changes in alertness and attention, and symptoms similar to Parkinson's disease, such as tremors, rigidity, and slow movement.[35]

Frontotemporal dementia encompasses a group of rare disorders that affect the frontal and temporal lobes of the brain.[37] In this type of dementia, sections of these lobes of the brain shrink, resulting in extreme changes to behavior, problems with movement, and/or the loss of language abilities (such as aphasias). Frontotemporal dementia often begins at a younger age than AD, and is the most common form of dementia in individuals under the age of 60.[38]

Dementia is a disease of worldwide significance; the World Health Organization estimated that 47.5 million people worldwide were living with dementia in 2015.[3] This number is expected to double every twenty years, resulting in an estimated prevalence of 131.5 million by 2050.[4] Along with the difficulties experienced by those living with the disease, dementia places extremely high stressors on caregivers. Individuals caring for individuals with dementia are at an increased risk for stress, depression, and other health complications, and also show high rates of social isolation and financial hardship.[5] Research has shown that caring for a person with dementia is more stressful than caring for a person with a physical disability.[6] The economic impact of dementia is also substantial; in the United States alone, the health care costs are estimated at 818 billion USD per year at present, and are expected to increase at a higher rate than the overall prevalence; experts forecast that dementia costs will reach a trillion dollars in the United States by 2018.[4] As a result of these wide-ranging impacts, the medical field has devoted much time and resources to studying the causes and prevention of this disease.

Research on the development of dementia has focused heavily on underlying physical risk factors; for example, studies have demonstrated an association between the incidence of ischemic and/or hemorrhagic stroke and an increased risk of dementia,[7,8] as well as an association between low cardiac index and an increased relative risk of incident dementia and AD specifically.[9] Other researchers have identified susceptibility genes; these are genetic mutations that, when inherited, result in an increased lifetime dementia risk.[10, 11]

Medical history is not the only relevant factor, however; other studies have examined the association between certain lifestyle characteristics and the development of dementia and Alzheimer's disease. In a longitudinal study of Japanese-American men, individuals who did not smoke and were physically active had a decreased risk of developing vascular dementia; and further, higher BMI was significantly associated with a greater risk of all types of dementia. These findings are not consistent across all studies, however; there are differing hypotheses regarding the relationship between BMI and the development of dementia. Some scientists have theorized that certain hormones present in body fat, such as leptin and estrogen, have neuroprotective effects, and therefore a higher BMI in mid- and/or late-life may be associated with a lower risk of dementia.[13,14] Other researchers have observed an association between high BMI and an increased risk of dementia in longitudinal cohorts, and have hypothesized that these results are due in part to the chronic health issues that are often associated with obesity, such as cardiovascular disease, metabolic syndrome, and diabetes.[15,16] Research into the association between these health issues and the risk of dementia has suggested that high inflammation levels contribute to cognitive impairment, as high inflammation levels increase the risk of damage to the vascular system.[43] The damage to the blood vessels leads to conditions that affect the blood flow to the brain, resulting in microvascular effects and subclinical vascular disease.[44] Yet, even the observed associations between these health issues and the risk of dementia are not consistent. A longitudinal study conducted in Italy found that metabolic syndrome (defined in the study as a clustering of cardiovascular risk factors including abdominal obesity, hypertension, dyslipidemia, and hyperglycemia) was not associated with a risk of dementia; and in older adults, metabolic syndrome was actually associated with a lower risk of AD.[45] In an attempt to reconcile some of these differing results, researchers in 2011 conducted a meta-analysis of 15 different prospective studies that examined the association of BMI and risk of dementia.[17] This analysis found that underweight BMI, overweight BMI and obese BMI were all associated with increased risk of dementia, as compared to normal BMI; and further, that the risks were highest for underweight and obese BMI. These investigators did note that their results were limited by the study data; namely, the lack of consistent adjustments for health and demographic factors and other lifestyle choices such as diet, smoking, alcohol and physical activity. As these factors could influence the relationship between obesity and risk of dementia, it would be helpful to examine multiple factors in one cohort.

Participation in leisure activities has also been associated with a reduced risk of dementia; in one study, mental, physical, and social components of lifestyle activities all contributed to this reduced risk, especially when participants posted high scores in all or two of these domains.[18] Other scientists have examined possible links between personality traits and risk of dementia, such as a reduced risk of dementia in individuals with a combination of low neuroticism and high extraversion.[19] Researchers have also studied the relationship between sleep and the risk of dementia, and have again arrived at different results. A recent analysis using data from the Framingham Heart Study (FHS) found that individuals who reported sleeping more than nine hours per night had double the risk of developing dementia after 10 years as compared to individuals who slept for 9 hours or less.[20] The study imaging results also showed that the individuals who slept longer had comparatively smaller brain volumes.[20] In analyzing this association, these investigators posited that the differences in sleep times may indicate that excessive sleep is a symptom of dementia-related brain changes, rather than a cause.[20] Another research team examined the association between changes in sleep patterns over time and the risk of dementia. In a longitudinal study of Swedish adults aged 75 years and older, 28% of participants were diagnosed with all-cause dementia between the 6^{th} and 9^{th} year post-baseline. The researchers found that reduced sleep in this cohort (as compared to the amount of sleep reported at baseline) was associated with a 75% increased all-cause dementia risk, and that the risk for Alzheimer's disease was doubled.[21] These results remained after adjusting for all lifestyle and vascular factors, although not after adjusting for symptoms of depression. Again, however, the reduction in sleep from baseline may constitute a symptom, rather than a cause, of increasing cognitive impairment. Despite the different findings, both study teams concluded that identifying sleep problems early on may help to detect early signs of dementia.

Currently, despite substantial efforts, there is no effective treatment for the cure or prevention of certain subtypes of dementia, such as Alzheimer's disease and Lewy Body dementia.[22] There is a class of drugs called cholinesterase inhibitors that are used to provide short-term relief from the symptoms of Alzheimer's disease, as well as slow the progression (by increasing the chemical acetylcholine that aids in memory and learning), but these medications are unable to ultimately cure the disease.[61] In recent years, attention has shifted to trying to identify effective early intervention strategies, implemented at a stage when there is the time and potential to modify or slow disease progression.[22-24] Identifying lifestyle characteristics that are associated with dementia is appealing, as this creates the potential for modifying behaviors in order to reduce the probability of developing dementia. A similar approach has been followed successfully in the cardiovascular field in the Framingham Heart Study (FHS) in 1970s.[25-27] Researchers in other fields have also examined the effects of lifestyle changes on disease prevention;

studies have been conducted on the impact of behavioral modifications (such as weight loss, diet, and psychosocial stressors) in conditions as varied as gout, breast cancer, and polycystic ovary syndrome, for example.[38, 39, 40] The use of FHS lifestyle data to study the impact of preventative strategies for dementia have been more limited, however.

Purpose

While prior research has provided an important foundation for the investigation into how lifestyle factors are associated with the development of dementia and/or AD, further evidence is needed to better characterize and understand this relationship. An analysis of data from the Framingham Heart Study (FHS) Offspring Cohort will add valuable information to this area of cognitive and neurological research, as the research participants have provided data on an especially wide range of demographic and lifestyle characteristics. The FHS Offspring Cohort has been participating in this research study since 1971, and the comprehensive assessment of lifestyle factors during these exams, which have resulted in numerous discoveries regarding the implications for cardiovascular risk, provide a wealth of data for analyzing the associations between these factors and the development of dementia. Further, the 99% retention rate of participants regularly returning for scheduled examinations,[41] beyond demonstrating the dedication of the participants, provides a uniquely complete and valuable dataset for this analysis. In this study, we investigate how midlife demographic and lifestyle characteristics are associated with dementia risk. This analysis may lead to a clearer understanding of the effect of various lifestyle characteristics earlier in life on the development of dementia later in life, and inform effective preventative strategies in the future.

Primary Study Question

How are demographic and lifestyle characteristics (age, gender, BMI, education, sleep, activity level, coffee, tea, alcohol use, tobacco use, and obesity) associated with the development of dementia?

METHODS

Study Design

This is a secondary analysis of data that was collected as part of a longitudinal, prospective cohort study.

Participants

Initiated in 1948, the Framingham Heart Study is an ongoing, multi-generational longitudinal cohort study. The Original Cohort consisted of 5209 residents of Framingham, Massachusetts.[28] Beginning in 1971, a total of 5214 children of the Original Cohort and their spouses were enrolled into the Offspring Cohort. The participants in the Offspring Cohort have completed up to 9 examinations, which have taken place on average about every 4 years.[29]

At the second examination cycle (which took place from 1979 to 1983), the Offspring Cohort were screened for potential cognitive impairment, as described below under *Dementia Surveillance*. The demographic and lifestyle data used in this study were also collected at this second examination visit. In order to capture these data at midlife, the inclusion criteria for this analysis were dementia-free individuals in the FHS Offspring Cohort between 40 and 65 years of age at the time of the second examination.

Institutional Review Board (IRB) approval was obtained from the BU Medical Campus/Boston Medical Center IRB for the secondary analysis of this data. All participants provided written informed consent under the auspices of the main study to allow for future use of their data for this type of secondary analysis.

Demographic and Lifestyle Variables

The demographic characteristics and lifestyle factors were collected during the second examination using detailed self-report questionnaires, and a physical exam was conducted.

The variables were defined as follows: Age at the time of the exam ranged from 40 years to 65 years of age. Gender was defined as male or female. Body Mass Index (BMI) was calculated using height (cm) and weight (kg). Education level was calculated using years of education, and analyzed as a continuous variable. Smoking status was classified as current smoker (yes/no). Sleep was calculated based upon self-reported hours per day, and was analyzed both continuously and categorically, as hours of sleep per day, as well as defined by < 7 hours a day or ≥ 7 hours a day, according to the recommended daily sleep duration for adults 40 to 65 years of age[46]. Activity level was divided into four categories at the time of the FHS exam: sedentary, slight, moderate, and heavy. The participants self-reported the number of hours per day for each activity level. Obesity was calculated as No, Maybe, and Yes (as determined by the opinion of the FHS examiner). The answer of Maybe was included when a definitive determination could not be made based upon the available information. Maybe and Yes for obesity were analyzed as separate categories. Coffee and tea consumption were calculated as cups per day. Alcohol use was divided into three categories: beer, wine, and cocktails. For each category, participants provided the number of servings per week. Alcohol use was also categorized as drinkers or non-drinkers in the analysis; non-drinkers reported zero alcohol consumption, while drinkers reported ≥1 serving per week of any of the three categories of alcohol.

Medical History Variables:

While there is no established agreement in the published literature on the association between cardiovascular risk factors and all-cause dementia, or cancer and dementia, for example, there are known relationships between these factors and certain subtypes, such as the relationship between vascular dementia and stroke. Due to the heterogeneity of the subtypes within all-cause dementia, and the potential for interplay between dementia diseases processes and other medical history, the following medical history risk factors of participants at the time of the 2nd cycle examination were included in the analysis as control variables. History of stroke and cancer, as well as current diagnosis of diabetes were calculated as No, Maybe, and Yes, based upon self-report and review of medical records at the time of the exam. If the examiner could not make a definitive determination, Maybe was used, based upon the evidence available at the time, as the determination was made on examiner opinion. Maybe and Yes for diabetes were analyzed separately. The categories Yes and Maybe for stroke and cancer were merged to allow for sufficient statistical power in the analysis, due to the low number of events in this population. Hypertension was measured as Normal, Definite, or Borderline. Dyslipidemia was measured as total cholesterol mg/dl and analyzed continuously.

Outcome Measure

The outcome measure was the diagnosis of dementia, as defined below. In brief, participants were screened for dementia continuously during the study, as well as after death, if they died in 1989 or later. For participants who were never diagnosed with dementia, date of death (if participant was deceased) or date of last exam were used for censoring in the analysis.

Dementia Surveillance:

At the second Offspring examination, all participants were initially screened for possible cognitive impairment using a subjective memory question.[29] The initial cognitive screen used for serial tracking was the Mini-Mental State Examination (MMSE). In the Offspring Cohort, this screening has been administered at each examination since 1991. Any of the following participant scores results in an MMSE flag (the highest possible score is 30 points):

- an absolute score of <23 for all persons;
- a score <24 for persons with a high school education;
- a score <26 for college-educated persons;
- a decline of 3 points since the participant's previous exam, or;
- a decline of 5 points from their personal best score.

These cut-off points are based on normative data and previous work conducted by the New Haven Epidemiologic Catchment Area Program.[30]

Participants may also be flagged if they, or a family member or physician, expresses concern about their thinking either spontaneously or during an FHS study visit.

After being flagged, when possible, participants are administered a full neuropsychological test battery. At the end of this battery, an FHS neuropsychologist (NP) administering the neuropsychological evaluation assigns an examiner impression dementia NP severity ranging from 0 = not demented, to 0.25 = very slight concern that cognitive performance is below expected level but person does not have mild cognitive impairment or dementia, 0.5 = mild cognitive impairment, 1 = mildly demented, 1.5 = at least mildly demented, possibly more, 2 = moderately demented, 2.5 = at least moderately demented, possibly more, and 3 = severely demented, or 5 = non progressive impairment. Participants with values between 0.5 and 3 are considered to have been flagged by NP, and those with values of 0, 0.25 are considered to not need further follow-up.

Participants flagged by this testing are then referred to an FHS neurologist who performs a neurological exam that includes a Clinical Dementia Rating (CDR) assessment. The cognitive test performance of participants assigned a dementia NP severity of 0.25 are discussed with a second senior neuropsychologist to decide if the person needs additional assessment by a neurologist. The neurologist's impression of dementia severity is recorded as 0 = none, 1 = mild, 2 = moderate, and 3 = severe, corresponding to overall CDR scores of 1, 2 and 3. Values ≥ 1 are considered to constitute a Neurology (NE) flag which results in the person's records being taken to dementia review (DR).

Participants are brought to DR and reviewed by a panel consisting of at least one neurologist and one neuropsychologist, and this review may occur at multiple points during their individual cognitive tracking: when they are first suspected to have dementia, when the severity of their dementia changes, after death, and, if they have elected to be a brain donor, for a final time after a clinical-pathological conference at which the ante-mortem clinical and post-mortem pathological diagnoses are reviewed in tandem.

Participants who are alive are evaluated at DR if they have been: 1) flagged by NE and have either never had a full DR, or their NE severity is greater than the severity recorded at a previous DR; or 2) flagged by NP and have not yet had a FHS neurology assessment or DR, and either live outside New England or live in New England but had the NP evaluation at least 1 year earlier and had NP severity >1. If participants decline the FHS neuropsychologist or neurologist assessments, they may still be flagged for review at DR based only on their medical record and, if available, a family interview.

A separate review panel of FHS physicians performs a full post-mortem medical review of all deceased Framingham participants to establish date and cause of death, and to review medical records for cardiovascular events. Since 1989, this review has also looked for any mention of cognitive impairment in the records; this is considered to be a flag at death review. Participants who have died are evaluated for post mortem DR if they: 1) had an ante-mortem DR; 2) died after 1989 and were flagged prior to death by MMSE, NP, NE, or were flagged at post mortem medical review; 3) died before 1989 and were flagged prior to death by MMSE, NP or NE; or 4) died before 1989 but after exam 14 (when the first cognitive battery was administered), with no flag.

For cases that were detected before 2001, a repeat review was completed after 2001 so that up-to-date diagnostic criteria could be applied.[29] In this analysis, participants were included if they did not have a diagnosis of dementia, based upon the above criteria, at the time of their 2nd examination visit.

Statistical Analysis

Descriptive statistics were used to define the characteristics of the study sample. The Cox proportional hazards regression model was used to examine the associations between the explanatory variables (the above-defined demographic and lifestyle characteristics) and the risk of developing dementia. The Cox proportional hazards model allows for the calculation of dementia probability based upon the differing lengths of follow-up for each individual participant in this study (based upon diagnosis of dementia, date of death, or date of last exam). Censoring is used in statistical analysis when the time to the outcome event (in this case, diagnosis of dementia) is not available for all study participants.[62] In this study, the majority of participants were by censored by using the date of death (if they have died) or date of last visit. This is necessary because data on the time to dementia diagnosis for these participants was not available, because they either did not develop dementia prior to death or they have yet not developed dementia. The time to event or censorship was calculated in days in this analysis. The univariate analysis was unadjusted, and each explanatory variable was examined individually in the univariate model. Hazard ratios (HRs) and 95% confidence intervals (95% CIs for HR) were calculated for the association between the demographic and lifestyle characteristics and the development of dementia, and p-values were calculated to determine statistical significance. While statistical significance in the univariate model was pre-defined by a p-value < 0.05, the significance required for inclusion in the multivariate model was less stringent. If an explanatory variable met a pre-defined level of statistical significance (p-value ≤ 0.20) in the univariate analysis, it was included in the second multivariate model.

The first multivariate analysis adjusted for age and gender alone; while gender was not significantly associated with dementia in the univariate model, age and gender are common covariates and prior research has suggested that women are at a higher risk of dementia (although this may be due to their longer lifespan). The second multivariate analysis adjusted for age, gender and the medical history risk factor control variables (stroke, diabetes, hypertension, cancer, and dyslipidemia). The analysis was conducted using R software i386 3.4.2 and RStudio Version 1.1.383.

RESULTS

There were 2462 dementia-free participants (aged ≥ 40 and ≤ 65 years) at baseline at the time of the 2nd exam cycle. The mean age of the participants at the time of the baseline exam was 49.9 years, and the gender distribution was nearly equal with females constituting 50.4% of the population. During the follow-up period, 286 dementia events were recorded in this study population (11% of participants).

See Table 1 for the descriptive statistical analysis of this cohort.

Table 1 Descriptive Statistics

	Total			
	Number	Proportion (%)	Mean	Median
Age at baseline, years	2462		49.94	50
Gender				
Female	1241	50.4		
Education, years			13.59	13
BMI, Kg/m^2			25.48	26.04
Sleep, hours			7.34	7
Recommended Sleep				
≥ 7 hours/night	1991	81		
≤ 7 hours/night	468	19		
Coffee, servings/week			2.84	2
Tea, servings/week			0.66	0
Alcohol User				
Yes	1851	75.2		
Beer, servings/week			3.09	0
Wine, servings/week			1.89	0
Cocktails, servings/week			3.12	1
Obesity				
Yes	594	24.1		
Maybe	94	3.8		
	Total			

	Number	Proportion (%)	Mean	Median
Activity Level				
Sedentary, hours/day			5.91	5
Slight, hours/day			7.62	8
Moderate, hours/day			2.53	2
Heavy, hours/day			0.61	0
History of Stroke				
Yes	11	0.4		
History of Cancer				
Yes	62	2.5		
Hypertension				
Yes	162	6.6		
Borderline	607	24.6		
Diabetes				
Yes	49	1.9		
Maybe	15	0.6		
Dyslipidemia, total mg/dl			212.8	210

Univariate Models:

As expected, older age was strongly associated with a higher risk of dementia, representing the most statistically significant relationship in this model (HR = 1.2, p = < .001). Education level was also significantly associated with dementia risk; each year of additional schooling resulted in a decreased risk of dementia (HR=0.9, p = < 0.001). Alcohol use was significantly associated with decreased risks of dementia compared to non-use (HR = 0.7, p = 0.013), and consumption of wine in particular demonstrated a protective effect from dementia in this model (HR = 0.95, p = 0.034). While not statistically significant, other lifestyle factors met the pre-defined threshold for inclusion in the second multivariate model, based upon a p-value ≤ 0.20. Higher BMI and obesity (Yes) demonstrated some association with an increased risk of dementia (HR =0.99, p

0.15; HR = 1.3, p = 0.066), while receiving the recommended duration of sleep per night (≥7 hours) demonstrated some minor protective effects from the risks of dementia (HR = 0.79, p = 0.16). Gender and other lifestyle factors (total hours of sleep per day, coffee and tea consumption, tobacco use, beer and cocktail consumption, obesity (Maybe) and (Maybe + No combined), and hours of activity per day) were not significantly related to dementia risk.

See Table 2 for the full results of the univariate analysis.

Table 2 Univariate Models

Variable		**HR**	**(95% CI for HR)**	**p-value**
Age	Years	1.2	(1.2 - 1.2)	< 0.001^
Gender	Female	1.1	(0.85 - 1.5)	0.42
Education	Years	0.9	(0.86 - 0.95)	< 0.001^*
BMI	Kg/m^2	0.99	(0.99 - 1.1)	0.15*
Sleep	Hours/Night	0.94	(0.83 - 1.1)	0.39
Recommended Sleep	≥ 7 Hours/Night	0.79	(.57 - 1.1)	0.16*
Coffee	Cups/Day	0.99	(0.94 - 1)	0.71
Tea	Cups/Day	0.93	(0.82 - 1)	0.22
Alcohol User	Yes	0.7	(0.52 - 0.93)	0.013^*
Beer	Servings/Week	1	(0.98 - 1)	0.79
Wine	Servings/Week	0.95	(0.91 - 1)	0.034^*
Cocktails	Servings/Week	0.99	(0.96 - 1)	0.36
Tobacco use	Yes	0.86	(0.64 – 1.2)	0.31
Obesity	Yes	1.3	(0.98 - 1.8)	0.066*
Obesity	Maybe	1	(0.53 -2)	0.9
<u>Activity Level</u>				
Sedentary	Hours/Day	1	(0.95 -1)	0.85
Slight	Hours/Day	1	(0.96 -1)	0.84
Moderate	Hours/Day	1	(0.96 - 1.1)	0.44
Heavy	Hours/Day	0.96	(0.85 - 1.1)	0.49

^statistical significance
*included in multivariate model

Multivariate Model 1:

In the first multivariate analysis, age and gender were included in the model. Advanced age remained a statistically significant risk for dementia (HR = 1.19, p = ≤ 0.001), while gender demonstrated no association with the risk of developing dementia.

Table 3 Multivariate Model 1

Variable		**HR**	**(95% CI for HR)**	**p-value**
Age	Years	1.19	(1.16 - 1.22)	< 0.001
Gender	Female	1	(0.76 - 1.31)	0.996

Multivariate Model 2:

In the second multivariate analysis, the lifestyle factors which showed a statistically significant association with dementia risk in the univariate analysis were included in the model (age, education level, alcohol use, and wine consumption) along with those factors which trended significance, meeting the pre-defined threshold for inclusion (BMI, obesity (Yes), and recommended sleep duration (Y/N).

The medical history variables were also included in this model, in order to account for their potential effects on the development of dementia. These included hypertension (Yes and Borderline), diabetes (Yes and Maybe), history of stroke, history of cancer, and dyslipidemia.

After controlling for the relevant medical history, advanced age (per year of age) remained the only factor demonstrating a statistically significant association with dementia risk (HR = 1.18, p = < 0.001). In regards to medical history, participants with a history of cancer were more than twice as likely to develop dementia (HR = 2.11, p = 0.007). A documented diagnosis of Maybe for diabetes was also associated with a higher risk for dementia (HR = 3.68, p = 0.005). Interestingly, a Yes diagnosis of diabetes did not demonstrate a significant association. Also of note, history of stroke showed no statistically significant relationship with the development of dementia.

See Table 4 for the full results of the second multivariate model analysis.

Table 4 Multivariate Model 2

Variable		**HR**	**(95% CI for HR)**	**p-value**
Age	Years	1.18	(1.15 - 1.21)	< 0.001*
Gender	Female	0.9	(0.67 - 1.20)	0.468
Education	Years	0.96	(0.91 - 1.02)	0.173
BMI	Kg/m^2	0.99	(0.96 - 1.05)	0.979
Recommended Sleep	≥ 7 Hrs/Night	0.93	(0.66 - 1.298)	0.657
Alcohol Use	Yes	0.89	(0.64 - 1.23)	0.471
Wine	Servings/Week	0.97	(0.92 - 1.02)	0.177
Obesity	Yes	1.02	(0.68 - 1.53)	0.931
<u>Medical History</u>				
Stroke	Yes	1.36	(0.54 - 3.38)	0.512
Cancer	Yes	2.11	(1.22 - 3.64)	0.007*
Hypertension (Yes)	Yes	1.03	(0.59 - 1.78)	0.927
Hypertension (Borderline)	Borderline	1.03	(0.75 - 1.41)	0.868
Diabetes (Yes)	Yes	0.43	(0.11 - 1.74)	0.236
Diabetes (Maybe)	Maybe	3.68	(1.48 - 9.12)	0.005*
Dyslipidemia	Total cholesterol mg/dl	1	(0.997- 1.005)	0.572

*statistically significant

DISCUSSION

The likelihood of developing dementia in each individual participant was analyzed based on the presence and/or level of the demographic and lifestyle characteristics, as well as the medical history of the participant.

In all of the models, age was strongly associated with an increased risk of dementia, as would be expected from prior research and from the knowledge of the disease processes behind certain types of dementia.[31-37] Conversely, gender did not account for any differences in dementia risk, in any of the statistical models. This finding is similar to some previous research,[48] but there is no widespread agreement in the literature; other studies have suggested that women do have an elevated risk of developing dementia, especially AD, perhaps due mostly to the fact that they live longer than men.[46-47] The findings from this study support this theory that a higher prevalence in women is likely due to their longer average lifespan, which provides more opportunity to develop dementia. While the risk of dementia was not significantly higher in women in the univariate model, there was a very small association; this association completely disappeared, however, when controlled for by age in the multivariate model.

The statistically significant protective effects of alcohol use seen in the univariate analyses are consistent with prior research findings examining light to moderate consumption.[50-51, 53-54, 60] Wine consumption was specifically linked with significantly decreased risk of dementia in the univariate analysis, and demonstrated a mild protective association with dementia in the multivariate analysis. These findings agree with previous studies[51, 54], including a similar Swedish population-based study examining midlife alcohol consumption.[52] A meta-analysis performed on 143 prior studies on the association between alcohol use and dementia demonstrated that moderate drinkers were 23 percent less likely to develop cognitive impairment or AD and other forms of dementia, and that wine demonstrated the most beneficial effects.[54] A number of potential factors have been hypothesized to be behind these findings; for example, that individuals who are more social are also more likely to be alcohol consumers (or vice versa), and that the resulting social support networks and interpersonal interactions later in life help protect against the onset of dementia. Other researchers have posited that it is due to the known cardiovascular effects of certain types of alcohol, and/or that the cellular stresses induced by alcohol increases the cells' ability to cope with more major stressors in advanced age that could otherwise cause dementia.[54] The results of this analysis cannot definitively support any of these hypothesized reasons behind the protective association between alcohol use and dementia, however, as the significant links disappeared when adjusted for in the multivariate model. Instead, it is possible that confounding was responsible for the significant association between dementia risk and alcohol use seen in the univariate model. Alcohol use has been shown to be associated with years of education, for example; highly educated individuals are more likely to drink alcohol.[65] It may be that the lower risk of dementia in alcohol users seen in the univariate model was wholly or partly due to the higher education level of these participants, as more years of education was also associated with lower risks of dementia. Similarly, previous research has also shown that American individuals with a higher socioeconomic status are more likely to drink alcohol.[65] Higher socioeconomic status is also associated with lower risks of dementia, and therefore this may be another factor that confounded the relationship between alcohol use and dementia risk. Older age was significantly associated with dementia in all models; it is possible that younger individuals were more likely to be alcohol users. If this was true, this would have led to the protective effects of alcohol use seen in the univariate model, and would explain why this association disappeared in the multivariate analysis. While the protective effects of alcohol shown in the univariate model are consistent with previous research, this observed relationship may have been caused solely by the interplay of other factors.

Education level also demonstrated significant protective effects against dementia in the univariate model. Other than the link between advanced age and increased risk of dementia, this protective effect of education level also represents the closest association with dementia risk in the multivariate analysis. The mechanism behind this association is not entirely clear. In prior studies, poor scores on the cognitive screening tests have been considered as a potential cause behind observed links between low education and cognitive decline,[55] but in the Framingham Heart Study, participants were flagged for dementia review based upon on a decline in cognitive ability; the thorough dementia review panel helps ensure that dementia diagnoses are not based upon low cognitive ability at baseline. The neuropsychological instruments administered to the FHS participants are also very sensitive; and thus, while the highly educated may look better on the surface, the researchers were able to determine whether the participants had declined significantly as compared to their original baseline. Higher education level may be associated with decreased risk of dementia due to corresponding higher socioeconomic status, which could result in healthier diet, more free time for exercise, and increased access to health care. These socioeconomic differences provide a more intuitive explanation for the protective effects of education level, as compared to any neuroprotective processes created purely as a result of more years of schooling.

In the multivariate analysis, the lack of a significant association between an increased risk of dementia and a history of stroke and/or a definitive diagnosis of diabetes was surprising, as the vascular damage caused by these conditions contributes to the development of certain types of dementia.[7-8,33] This may have resulted from the use of all-cause dementia as the outcome of interest. While vascular dementia is known to be caused by vascular issues such as stroke and diabetes, other types of dementia, such as Lewy Body dementia and Parkinson's disease dementia are not related to stroke, and therefore this result would not be unexpected. Further, a noted previously, diabetes was classified as No, Yes, and Maybe, based upon examiner opinion, and the classification of Maybe did demonstrate a strong significant association with an increased risk of dementia in the multivariate analysis. It is possible that diabetes pathology was beginning in these participants in midlife, and the resulting disease progression over time played a role in their increased risk of dementia development.

A history of cancer diagnosis was also significantly related to an increased risk of dementia in the multivariate analysis. This may be due to changes in mental health after the illness and/or as a result of the negative consequences of cancer treatment on overall health; certain chemotherapy medications, for example, have neurotoxic effects.[56] Other researchers have posited that the relationship between cancer and dementia is due to similar exposures and risk factors, such as smoking, diabetes and obesity (although these factors were not associated with dementia risk in this study), or shared genetic pathways. It is important to note, however, that there is a discrepancy between the results of this study and a prior study using FHS data.[57] In the previous study, cancer survivors had a lower risk of AD than those without cancer, and patients with AD had a lower risk of cancer. This previous analysis, therefore, suggested an inverse association between dementia risk and cancer incidence.[57] The previous study examined all types of cancer, however, rather than a general diagnosis of cancer, as was analyzed in this study, and also included data from both the FHS Original and Offspring cohorts.

The major strength of this study is the longitudinal nature of the follow-up for the outcome of interest, as the cohort underwent over 30 years of rigorous dementia surveillance. The 99% retention rate of participants regularly returning for scheduled examinations[41] provides a uniquely complete and valuable dataset for this analysis. It should be noted, however, that there are several limitations in this study.

It is possible that the identified associations may not be fully generalizable to other populations, due to the demographic breakdown of the Framingham Heart Study. FHS is comprised largely of whites of European descent, and individuals with Italian, Irish and English ancestry make up the majority of the cohort.[58] About 85% of the Original Cohort was born in the U.S. or Canada, and 35% reported ethnic origins in the British Isles; another 19% are of Italian ethnicity, 32% are of other Western European ancestry, 5% Canadian and 6% Eastern European. Less than 4% of the cohort are of non-European origins or of unknown ethnicity.[58] These demographics affect the generalizability of the data because prior researchers have observed differences between ethnic groups in regards to rates of dementia. In the United States, the majority of research has found higher rates of dementia in Hispanics and non-Hispanic blacks, as compared to non-Hispanic whites,[63] for example, and a lower incidence of dementia in Asian-Americans as compared to all other groups.[64] There are a number of possible reasons for these differences in dementia rates across ethnic groups. In some cases, the rates could be artificially high; differences in culture and language may impact the results of cognitive testing, for example. Health-related factors may also play a role; differences in genetic makeup may result in increased risk, whether due to genes that have been identified as related to dementia risk (such as APOE), or genetic factors that influence other medical issues that are associated with dementia (such as diabetes or Parkinson's Disease). And further, these medical issues do not need to be caused by genetics to differ among ethnic groups; medical risk factors such as stroke and diabetes could differ between ethnicities for socioeconomic or environmental factors, rather than genetics. The homogenous nature of the FHS study population therefore needs to be considered when generalizing these results to other races and ethnic backgrounds, as they are not represented in this research.

Second, family history and/or genetics, which represent additional risk factors of dementia, were not measured in this study. The APOE genotype, for example, has been identified as significantly related to the development of dementia and AD.[59] These factors were not included in the analysis due to the limitation of the data collected via the questionnaires and review of the medical records. These variables were not assessed during the 2nd cycle Offspring examination; and therefore, we were unable to determine their association with the development of dementia or control for their presence, as we only used data collected during this visit. The inclusion of these additional factors in future research may serve to further illuminate the nature of the association between various demographic and lifestyle characteristics and dementia risk.

Third, the analyses in this study focused on overall dementia incidence; this study did not examine the results by each individual dementia subtype. Due to different disease processes and underlying pathologies, it is possible that specific risk factors may be different for AD and vascular dementia, for example, or among the other previously-described types of dementia. In this study, the aim was to identify demographic and lifestyle characteristics that are associated with the risk of dementia, in order to highlight modifiable behaviors that the average individual could change to reduce their probability of developing dementia. As such, we used all-cause dementia as the outcome of interest; from a purely practical standpoint, individuals would aim to modify behaviors and other lifestyle characteristic in the hope of preventing any type of dementia, and not just one specific subtype. Examining potential differences between the relationships of demographic and lifestyle characteristics and individual dementia subtypes will be an important next step, however, for future research in this domain.

Fourth, the demographic and lifestyle characteristics that were included in this study were measured at one time-point in this analysis (Examination 2), rather than longitudinally. It is possible that some of these characteristics may have changed during the 30-year follow-up period. Also, lifestyle factors are usually measured as timedependent covariates, but were analyzed as fixed in this analysis. The lifestyle variables were measured in this manner intentionally, however; evaluating these characteristics in midlife, years prior to the onset of dementia, facilitated the analysis of potentially contributing long-term factors, as compared to examining characteristics that may only be present in later years. And further, preclinical AD, for example, may be present years before any noticeable or evaluable symptoms manifest;[59] midlife measurement of these demographic and lifestyle factors may therefore provide a more accurate baseline for the analysis and of their associations with AD risk.

In conclusion, this secondary analysis of data that was collected as part of a longitudinal, prospective cohort study supports prior research regarding the relationship between advancing age and increased risk of dementia. This significant association remained constant when controlling for factors such as gender and medical history. In regards to the demographic and lifestyle characteristics, the majority of the variables studied did not demonstrate any meaningful relationship with dementia risk. The results of the univariate analyses did, however, identify three factors that showed some protective effects; education level, alcohol use, and wine consumption. While these associations were significant in the univariate analysis, the results were not conclusive, as none of these relationships remained significant when controlled for in the multivariate analysis. While the associations demonstrated in the univariate analysis may therefore have been solely caused by confounding, it may be worthwhile to continue studying moderate consumption of alcohol, specifically wine, and its relationship with dementia, as other studies have returned significant protective effects in adjusted analyses;

continued research in this area would be helpful to further examine the potential protective effects of alcohol, and determine whether consumption could be used as an appropriate preventative strategy, or whether this observed association is only due to the interplay of confounding factors. Overall, identifying potential risk factors for dementia is an important focus of study, due to the aging worldwide population and the increasing significance of this disease. On an individual level, dementia causes debilitating adverse effects for both the sufferer and the caregiver(s), and identification of preventative strategies could help mitigate the projected rise in incidence. This analysis adds to the growing literature regarding the associations between certain demographic and lifestyle characteristics and the risk of dementia.

Future research in this area should continue to focus on studying the association between lifestyle characteristics and dementia risk, as identifying modifiable behaviors would provide practical utility for patients and physicians. Future analyses could examine potential links between midlife factors and specific dementia subtypes; as Alzheimer's disease represents such a sizable proportion of diagnosed dementia cases, it would be worthwhile to identify modifiable behaviors that are linked with the buildup of plaques and neurofibrillary tangles, for example. Other research could examine lifestyle factors over time. In this study, the lifestyle factors were fixed as they were only measured at one time point; future analyses could incorporate longitudinal measurements throughout midlife, in order to examine the effects of certain characteristics remaining constant or changing in different participants, and the subsequent impact on the probability of developing dementia. Researchers should also continue to look beyond the scope of the relationship between demographics and lifestyle characteristics and dementia. It will be important for investigators to identify biological markers that indicate the presence of dementia, as currently the only validated way to confirm the diagnosis is via documented cognitive decline.[66] Researchers have identified some promising biomarkers in Alzheimer's disease and Lewy Body dementia, such as the presence of certain proteins in blood and cerebrospinal fluid, and changes within the brain that are detectable by neuroimaging, but more studies are needed to validate these methods.[66,67] Validated biomarkers would help with the drug development process; the identification of physical biomarkers may help scientists understand the physical processes underlying these diseases, and the effects of investigational medications could be measured by changes to the biomarkers. And further, if clinicians were able to rely on validated biomarkers to make diagnoses, this would enable earlier detection of the disease, and thus treatment and lifestyle changes could be started at a less advanced stage. Finally, investigators should continue to study the genetic factors behind dementia. Identifying and isolating the genes that cause or contribute to the development of dementia would help scientists understand the cellular mechanisms behind dementia-related neurological changes and assist in both screening and drug development. The progression and improvement of different gene-editing technologies offers exciting potential for the treatment of dementia, but genetic pathways linked to the different subtypes need to be identified in order to test this type of treatment in future clinical trials. These future directions for dementia research are crucial to determining methods to detect, diagnose, and treat this disease.

REFERENCES

1 What Is Dementia? (n.d.). Alzheimer’s Association. Retrieved March 16, 2016 from: http://www.alz.org/what-is-dementia.asp.

2 McKhann, GM, et al. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011 May; 7(3):263–269.doi: http://dx.doi.org/10.1016/j.jalz.2011.03.005.

3 Dementia: Fact sheet. April 2016. World Health Organization. Retrieved February 1, 2017, from: http://www.who.int/mediacentre/factsheets/fs362/en/.

4 Prince M, Wimo AGM, Ali GC, Wu YT, Prina M. World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends. London: alzheimer ’s Disease International; 2015.

5 Brodaty H, Donkin M. Family caregivers of people with dementia. *Dialogues in Clinical Neuroscience*. 2009 Jun; 11(2): 217–228.

6 Ory MG., Hoffman R., Yee JL., et al. Prevalence and impact of caregiving: a detailed comparison between dementia and nondementia caregivers. *Gerontologist.* 1999; 39:177–185.

7 Desmond, DW, et al. Incidence of dementia after ischemic stroke: results of a longitudinal study. *Stroke*. 2002. 33: 2254-2262.doi: 10.1161/01.STR.0000028235.91778.95.

8 Garcia, PY, et al. Cognitive Impairment and Dementia After Intracerebral Hemorrhage: A Cross-sectional Study of a Hospital-based Series. *Journal of Stroke and Cerebrovascular Diseases.* 2013 January. 22(1): 80-86. doi:10.1016/j.jstrokecerebrovasdis.2011.06.013.

9 Jefferson, AL, et al. Low Cardiac Index Is Associated With Incident Dementia and Alzheimer Disease: The Framingham Heart Study. *Circulation*. 2015. 131: 1333-1339. doi: 10.1161/CIRCULATIONAHA.114.012438.

10 Seshadri, S, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *Journal of the American Medical Association*. 2010 May. 303(18): 1832-40. DOI: 10.1001/jama.2010.574.

11 Loy, CT, et al. Genetics of dementia. *The Lancet*. 2014. 383(9919): 828-840. DOI: 10.1016/S0140-6736(13)60630-3.

12 Gelber, RP, et al. Lifestyle and the risk of dementia in Japanese-american men. *Journal of the American Geriatrics Society*. 2012 Jan; 60(1):118-23. doi: 10.1111/j.1532-5415.2011.03768.x.

13 Atti AR, Palmer K, Volpato S, Winblad B, De Ronchi D, Fratiglioni L. Late-life body mass index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. *Journal of the American Geriatrics Society.* 2008; 56: 111–116.

14 Bagger YZ, Tanko LB, Alexandersen P, Qin G, Christiansen C. The implications of body fat mass and fat distribution for cognitive function in elderly women. *Obesity Research.* 2004; 9: 1519–1526.

15 Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, Vendemiale G, Baldereschi M, Crepaldi G, Di Carlo A, Galluzzo L, Gandin C, Inzitari D, Maggi S, Capurso A, Panza F. Metabolic syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Ageing. *Journal of Neurology, Neurosurgery, and Psychiatry.* 2010; 81: 433–440.

16 Bagi Z. Mechanisms of coronary microvascular adaptation to obesity. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology.* 2009; 297: R556–R567.

17 Anstey, K. J., Cherbuin, N., Budge, M. and Young, J. (2011), Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obesity Reviews*, 12: e426–e437. doi:10.1111/j.1467-789X.2010.00825.x

18 Karp, A, et al. Mental, Physical and Social Components in Leisure Activities Equally Contribute to Decrease Dementia Risk. *Dementia and Geriatric Cognitive Disorders*. 2006 November. 21: 65-73. doi: 10.1159/000089919.

19 Wang, HX, et. al. Personality and lifestyle in relation to dementia incidence. *Neurology*. 2009 January. 72(3): 253-259. doi: 10.1212/01.wnl.0000339485.39246.87.

20 BUSM Research. Prolonged Sleep May Predict Dementia Risk. Retrieved February 3, 2017 from: https://www.bumc.bu.edu/busm/2017/02/23/prolonged-sleep-may-predict-dementia-risk/.

21 Hahn, EA, Wang, H, Andel, R, Fratiglioni, L. A Change in Sleep Pattern May Predict Alzheimer Disease. *The American Journal of Geriatric Psychiatry*, November 2014, Vol.22(11), pp.1262-1271.

22 Exalto LG, Biessels GJ, Karter AJ, Huang ES, Katon WJ, Minkoff JR, et al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort

study. *Lancet Diabetes and Endocrinology*. 2013 Nov; 1(3):183–90.

23 Carrillo MC, Brashear HR, Logovinsky V, Ryan JM, Feldman HH, Siemers ER, et al. Can we prevent Alzheimer's disease? Secondary "prevention" trials in Alzheimer's disease. Alzheimers *Alzheimer's & Dementia*. 2013 Mar; 9(2):123–131.e1.

24 The European Dementia Prevention Initiative - PIIS1474442213700309.pdf [Internet]. [Cited 2016Jun17].Available from:
http://www.thelancet.com/pdfs/journals/laneur/PIIS1474442213700309.pdf

25 D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke: A Journal of Cerebral Circulation*. 1994 Jan;25(1):40

26 Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke: A Journal of Cerebral Circulation*. 1991 Mar; 22(3):312–8.

27. FHS. Risk Functions | Framingham Heart Study [Internet]. 2016 [cited 2016 Jun 17]. Available from: https://www.framinghamheartstudy.org/risk-functions/index.php

28. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham Study. *American Journal of Public Health and the Nation's Health*. 1951 Mar;41(3):279–81.

29 Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. *New England Journal of Medicine*. 2016 Feb 11;374(6):523–32.

30 Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. *Journal of the American Medical Association*. 1993 May 12; 269(18):2386-91.

31 What is Alzheimer's? (n.d.). Alzheimer's Association. Retrieved July 17, 2017 from: http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp.

32 Alzheimer's disease. (n.d.). Alzheimer's Society. Retrieved July 17, 2017 from: https://www.alzheimers.org.uk/info/20007/types_of_dementia/2/alzheimers_disease.

33 Alzheimer's and Dementia: Vascular Dementia. (n.d.). Alzheimer's Association. Retrieved July 17, 2017 from: http://www.alz.org/dementia/vascular-dementia-symptoms.asp.

34 Alzheimer's and Dementia: Dementia with Lewy Bodies. (n.d.). Alzheimer's Association. Retrieved July 17, 2017 from: http://www.alz.org/dementia/dementia-

with-lewy-bodies-symptoms.asp.

35 Lewy Body Dementia. July 29 2017. Mayo Clinic. Retrieved August 1, 2017 from: http://www.mayoclinic.org/diseases-conditions/lewy-body-dementia/home/ovc-20200344.

36 MacGill M. Alzheimer's Disease: Causes, Symptoms and Treatments. April 29 2016. Retrieved July 17, 2017 from http://www.medicalnewstoday.com/articles/159442.php.

37 Frontotemporal Dementia. October 29 2016. Mayo Clinic. Retrieved July 19, 2017 from: http://www.mayoclinic.org/diseases-conditions/frontotemporal-dementia/home/ovc-20260614.

38 Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. *Arthritis Research & Therapy*. 2006 Apr 12: 8(Suppl 1):S2. https://doi.org/10.1186/ar1907.

39. Rock CL, Demark-Wahnefried W. Can Lifestyle Modification Increase Survival in Women Diagnosed with Breast Cancer? *The Journal of Nutrition*. 2002 Nov 1: Vol 132(11): 3504S-3509S.

40 Norman RJ, Davies MJ, Lord J, Moran LJ. The role of lifestyle modification in polycystic ovary syndrome. *Trends in Endocrinology and Metabolism*. 2002 Aug: Vol 13(6): 251-257. https://doi.org/10.1016/S1043-2760(02)00612-4.

41 Tsao CW, Ramachandran VS. Cohort Profile: The Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology. *International Journal of Epidemiology*. 2015 Dec; 44(6): 1800-1813.

42 NATIONAL SLEEP FOUNDATION RECOMMENDS NEW SLEEP TIMES. February 2 2015. National Sleep Foundation. Retrieved July 7, 2017 from https://sleepfoundation.org/press-release/national-sleep-foundation-recommends-new-sleep-times

43 Yaffe K, Kanaya A, Linquist K. The Metabolic Syndrome, Inflammation, and Risk of Cognitive Decline. *Journal of the American Medical Association.* 2004; 292(18):2237-2242. doi:10.1001/jama.292.18.2237

44 Prince MJ Vascular risk factors and atherosclerosis as risk factors for cognitive decline and dementia. *Journal of Psychosomatic Research.* 1995; 39525- 530.

45 Forti P, Pisacane N; Rietti E; Lucicesare A; Olivelli V; Mariani E; Mecocci P; Ravaglia G. Metabolic Syndrome and Risk of Dementia in Older Adults. *Journal of the American Geriatrics Society*. 2010 March: Vol. 58(3), pp.487-492.

46 Brayne C, Best N, Muir M, Richards SJ, Gill C. Five-year incidence and prediction of dementia and cognitive decline in a population sample of women aged 70-79 at baseline. *International Journal of Geriatric Psychiatry*. 1997. 12: pp. 1107-1118.

47 Hebert LE, Scherr PA, McCann JJ, Beckett LA, Evans DA. Is the risk of developing Alzheimer's disease greater for women than for men? *American Journal of Epidemiology*. 2001. 153: pp. 132-136.

48 Paykel ES1, Brayne C, Huppert FA, Gill C, Barkley C, Gehlhaar E, Beardsall L, Girling DM, Pollitt P, O'Connor D. Incidence of dementia in a population older than 75 years in the United Kingdom. *Archives of General Psychiatry*. 1994 Apr; 51(4):325-32.

49 Chêne G, Beiser A, Au R, Preis SR, Wolf PA, Dufouil C, Seshadri S. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimer's & Dementia*. 2015 Mar; 11(3) 310-320.

50 McMillen M. Alcohol May Help Prevent Dementia. WebMD. Retrieved September 20, 2017 from: https://www.webmd.com/alzheimers/news/20110302/alcohol-may-help-prevent-dementia.

51 Panza F; Frisardi V ; Seripa D; Logroscino G; Santamato A; Imbimbo, BP; Scafato, Emanuele ; Pilotto, Alberto ; Solfrizzi, Vincenzo. Alcohol consumption in mild cognitive impairment and dementia: harmful or neuroprotective? *International Journal of Geriatric Psychiatry*. 2012 Dec; Vol. 27(12): 1218-1238.

52 Handing, EP, Andel, R, Kadlecova, P, Gatz, M, Pedersen, NL. Midlife Alcohol Consumption and Risk of Dementia Over 43 Years of Follow-Up: A Population-Based Study From the Swedish Twin Registry. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*. 2015; Vol. 70(10): 1248-1254.

53 Letenneur L. Risk of dementia and alcohol and wine consumption: a review of recent results. *Biological Research*. 2004; 37(2):189-93.

54 Moderate drinking may protect against Alzheimer's and cognitive impairment, study suggests. Loyola University Health System. August 19, 2011. Retrieved on September 20, 2017 from: https://www.sciencedaily.com/releases/2011/08/110816112134.htm.

55 Education level and dementia: A review of the scientific literature on this subject. G. Neroni-Mercati, M. Mele, E. Giannandrea and S. Bonaiuto. *Neurobiology of Aging*, 1992; Vol.13: S119-S119.

56 Ganguli M. Cancer and Dementia: It's Complicated. *Alzheimer Disease & Associated Disorders*. 2015 Apr-June; 29(2): 177–182.

57 Driver JA, Beiser A, Au R, Kreger BE, Splansky GL, Kurth T. Inverse association between cancer and Alzheimer's disease: results from the Framingham Heart Study. *BMJ*. 2012; 344:1442.

58 Govindaraju D.R., Cupples L.A., Kannel W.B., O'Donnell C.J., Atwood L.D., D'Agostino R.B., Fox C.S., Larson M., Levy D., Murabito J., et al. Genetics of the Framingham Heart Study Population. *Advances in Genetics*. 2008; 62:33–65. doi: 10.1016/S0065-2660(08)00602-0.

59 Prince, M, Lovestone S, Cervilla J, Joels S, Powell J, Russ, C, and Mann A. The association between APOE and dementia does not seem to be mediated by vascular factors. *Neurology.* 2000 Jan; 54(2): 397.

59 What is preclinical Alzheimer's disease? Alzheimer's Association. October 27, 2016. Retrieved on September 22, 2017 from: http://www.alzheimersblog.org/2016/10/27/preclinical-alzheimers-disease/

60 Mukamal M, Kuller LH, Fitzpatrick AL. Prospective Study of Alcohol Consumption and Risk of Dementia in Older Adults. *Journal of the American Medical Association.* 2003;289(11):1405-1413. doi:10.1001/jama.289.11.1405.

61 Medications for Memory Loss. (n.d.). Alzheimer's Association. Retrieved on November 1, 2017 from: https://www.alz.org/alzheimers_disease_standard_prescriptions.asp.

62 Prinja S, Gupta N, Verma R. Censoring in Clinical Trials: Review of Survival Analysis Techniques. *Indian Journal of Community Medicine*. 2010 Apr; 35(2): 217–221. doi: 10.4103/0970-0218.66859.

63 National Research Council (US) Panel on Race, Ethnicity, and Health in Later Life. Anderson NB, Bulatao RA, Cohen B, editors. Critical Perspectives on Racial and Ethnic Differences in Health in Late Life. Washington (DC): National Academies Press (US); 2004. 4, Ethnic Differences in Dementia and Alzheimer's Disease. Available from: https://www.ncbi.nlm.nih.gov/books/NBK25535/.

64 Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimers & Dementia*. 2016 Mar; 12(3): 216–224.

65 Jones JM. Drinking Highest Among Educated, Upper-Income Americans. Gallup News. July 27, 2015. Retrieved on November 18, 2017 from:

http://news.gallup.com/poll/184358/drinking-highest-among-educated-upper-income-americans.aspx.

66 Alzheimer's and Dementia Testing for Earlier Diagnosis._(n.d.). Alzheimer's Association Research Center. Retrieved on November 19, 2017 from: https://www.alz.org/research/science/earlier_alzheimers_diagnosis.asp.

67 Lewy Body Dementias and Biomarkers. (n.d.). Lewy Body Dementia Association. Retrieved on November 19, 2017 from: https://www.lbda.org/node/555.

68 Ganguli M. Cancer and Dementia: It's Complicated. *Alzheimer Disease and Associated Disorders*. 2015 Apr-Jun; 29(2): 177–182. doi: 10.1097/WAD.0000000000000086.

39

CURRICULUM VITAE

[redacted]

[redacted]

[redacted]

[redacted]