Dementia and Mild Cognitive Impairment:

Epidemiologic Research of Risk Factors

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DEDICATION

For my mother, Erica Hardiman George, who has always been my strongest, most persistent supporter, and my grandmother, Gwendolyn Cox Hardiman, who dreamed of being a data scientist and rejected the notion that there are things Black women cannot do.

ABSTRACT

Dementia and mild cognitive impairment (MCI) are often caused by progressive and irreversible pathologic brain changes. Alzheimer's disease, cerebrovascular disease, and Lewy body-related diseases are the most common causes with many individuals having mixed etiologies. Characterizing risk factors for dementia and MCI is complex due to overlapping etiologies, long latency periods, and the influence of cognitive reserve. While major risk factors including advanced age, hypertension, and the *ApoE4* allele have been identified, further investigation of early- and mid-life risk factors is needed. Using data from the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study, we examined prospectively risk factors for dementia and MCI.

In the first manuscript, we assessed the association between life course socioeconomic status (LC-SES) and dementia and MCI. Low individual-level LC-SES was associated with an increased risk of dementia. Low individual-level economic factors of LC-SES (e.g. income, home ownership) were associated with increased risk of dementia independent of educational attainment. However, neighborhood-level LC-SES was not associated with risk of dementia or MCI.

The second manuscript assessed the association between thyroid dysfunction (measured via autoimmune thyroid disease (AITD) and thyroid hormone levels) and risk of dementia and MCI. We found no association between AITD and dementia and MCI. Subclinical hypothyroidism was associated with a lower risk of dementia while overt hyperthyroidism, particularly with very elevated serum FT4 hormone levels, was associated with an increased risk of dementia compared to euthyroid participants.

The third manuscript examined the association between lifetime history of migraine symptoms and risk of dementia and MCI. Despite published evidence of brain abnormalities in migraineurs, which might lead to cognitive impairment, we found no association between migraine and dementia and MCI.

This dissertation extends our understanding of risk factors for cognitive impairment underscoring the importance of early- and mid-life exposures on late-life risk of dementia and MCI.

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1.1. Introduction

Cognitive function is typically characterized by five domains: learning and memory, language, visuo-spatial, executive, and psychomotor.[1,2] These domains roughly correspond to their cerebral location and are identified and assessed using a mental status exam or neuropsychological testing.[1,2] Mild cognitive impairment (MCI) generally involves deficiency of one domain whereas dementia involves impairment in two or more domains.[1,2] MCI is a symptomatic pre-dementia state of clinical importance because of the increased risk of progressing to dementia (a decline in cognitive ability severe enough to compromise daily functioning).[1,3] MCI and dementia can lead to a loss of independence and functioning that puts incredible strain on individuals, their families, caretakers, and healthcare systems.[4,5]

Neurocognitive decline reflects a continuum of changes in cognitive function that can range from normal aging to pathologic decline (a change in cognition that exceeds the decline expected due to aging alone) caused by neurocognitive disease.[6,7] Risk of neurocognitive decline (normal and pathologic) increases with age, especially among those over age 65.[6,8] Neurocognitive decline and disease leading to MCI and dementia have become an ever-increasing public health burden in the United States as life expectancies rise and the older adult population at risk grows. However, there are still gaps in the knowledge of these devastating outcomes. Using rigorous epidemiologic methods to identify risk factors for MCI and dementia is important for identifying areas

to target for prevention of neurocognitive decline and disease to stop irreversible cognitive changes.[6]

1.2. Natural History of Alzheimer's Disease and Related Dementias

Pathological changes to the brain in those with MCI and dementia are heterogeneous and caused by a variety of conditions.[9] Etiology of neurocognitive disease is often identified as part of testing for MCI and dementia. For a definitive diagnosis, a brain autopsy or biopsy is necessary; however, brain imaging and assessment of symptoms are sufficient for diagnosis in many cases.[10] The etiologic diagnoses for the majority of dementia and MCI cases include Alzheimer's disease (44-70%) or cerebrovascular disease (15-37%), with other causes such as Lewy body disease and Parkinson's disease (PD) being less common (5-17%).[10-12] Approximately 56% of individuals with dementia and MCI have mixed etiology with mixed AD-cerebrovascular disease etiologies being the most common.[10,11]

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a neurodegenerative disease with histopathological features of amyloid plaques containing β-amyloid protein (Aβ) and aggregation of tau protein in neurofibrillary tangles.[12,13] These abnormalities are primarily found in the hippocampus, temporal cortex, and nucleus basalis of Meynert in the brain.[12-14] Formation of plaques containing Aβ is thought to be central to the pathogenesis of AD.[15,16] Aβ is derived from the cleavage of amyloid precursor protein (APP) by a complex group of enzymes that include presenilin 1 (PS1 related to the *PSEN1* gene) and presenilin 2 (PS2 related to the *PSEN2* gene).[15] While the neuronal function of APP is unknown, Aβ is a normal product of APP metabolism.[15] Mutations in genes associated

with early-onset AD (including *APP*, *PSEN1*, and *PSEN2* genes) are all associated with an over production of Aβ supporting the integral role of amyloid plaques with Aβ in the pathogenesis of disease.[15]

Tau is a microtubule-associated-protein (MAP) found in the axons of mature neurons and whose function is to promote the assembly of tubulin into microtubules and stabilize their structure.[17,18] Under the right pathological conditions, tau binding to microtubules is disrupted leading to an increase in the levels of unbound tau and hyper-phosphorylation of tau.[17,18] Unbound tau is more likely to become misfolded creating early deposits called "pre-tangles."[17] A structural transition occurs leading to aggregation that is more organized and the development of hyper-phosphorylated neurofibrillary tangles.[17,18] While the mechanisms of tau aggregation are not fully understood, levels of total-tau (T-tau) and phosphorylated tau (P-tau) are increased in the brains of individuals with AD making it an important component of the disease.[15]

While Aβ and tau are neuropathological and neurochemical hallmarks of AD, a number of cognitive, metabolic, structural, and molecular abnormalities have been observed years, even decades, before symptom onset.[15] Levels of $A\beta_{42}$ in cerebral spinal fluid (CSF) and Aβ deposition seen in brain imaging are above normal levels 20 years before symptom onset, followed by elevated tau levels measured in CSF 15 years before onset.[15] Structural changes associated with synaptic loss such as hippocampal atrophy are seen 10 years before onset and cognitive changes measured by Clinical Dementia Rating-Sum of Boxes (CDR-SB) as well as impaired glucose metabolism subsequently occur about 5 years before symptom onset.[15]

Clinically, AD starts as a progressive decline in cognitive function. Early on, this cognitive impairment predominantly affects complex daily living activities and causes short-term memory loss.[19,20] Often, individuals mistakenly attribute these deficits to normal aging or stress and may not seek care or meet the diagnostic criteria for AD for several years.[15,19,20] Episodic memory, the ability to consciously remember a particular episode in one's life, and semantic memory, the ability to store conceptual and factual knowledge not related to a specific memory, are memory domains most severely impacted by AD.[21] As the disease progresses, memory deficits worsen and may be accompanied by behavioral and psychological symptoms including emotional disturbances like depression, anxiety, apathy, and elated mood, delusions, disturbances in motor function, changes to circadian rhythm, and changes in appetite and eating.[22] In the severest stages of disease, patients can no longer care for themselves, are unable to communicate verbally, and are often bed ridden. After AD diagnosis, the mean survival is 5.9 years (standard deviation ± 3.7 years), with the most common immediate causes of death including cardiovascular disease (CVD), respiratory or blood infections, and cancer.[23,24]

Cerebrovascular Disease (CeVD)

Cerebrovascular disease (CeVD) is characterized by a spectrum of conditions that involve cognitive impairment and evidence of stroke (cerebrovascular accident – CVA) or vascular brain injury.[12] Vascular dementia (VaD) is a term that refers to individuals who develop dementia due to a vascular lesion, regardless of the pathogenesis.[25] Vascular cognitive impairment (VCI) has been proposed as a term that better describes the range in

cognitive deficits related to cerebrovascular disease with VaD being the most severe manifestation.[25]

CeVD is caused by a heterogeneous group of conditions that can be divided into ischemic (80%) and hemorrhagic (20%) events.[26,27] Hemorrhagic strokes are caused by spontaneous hemorrhage associated with hypertension, congenital and other atrial aneurysms, and arteriovenous malformations.[28] Hypertension is the major risk factors for hemorrhagic stroke.[26,28] Ischemic events are often associated with atherosclerosis and embolic disease and fall into three major categories, atherothrombotic occlusion, embolic occlusion, and small vessel occlusion.[26,28] Atherosclerosis causes narrowing of blood vessels (with significant hemodynamic changes at 70% or more occlusion) due to atherosclerotic plaques and can lead to erosion of the endothelium.[28] Embolic disease is generally caused by cardiac abnormalities such as atrial fibrillation or valvular disease that lead to occlusion with clot material or atheromatous (macrophage cells, lipids, calcium, etc.).[28] Transient ischemic attacks (TIAs) are brief, reversible events caused by temporary occlusion of a vessel.[26] Ten to 40% of patients who experience a TIA will go on to develop an ischemic stroke.[26] Risk factors for ischemic events include age, hypertension, diabetes, and history of ischemic heart disease.[26,28]

From neuroimaging, damage caused by CeVD can be identified including evidence of large infarcts, lacunar infarcts, and white matter lesions (WMLs).[29,30] Large infarcts are associated with VaD and can be caused by a single large vessel infarct that causes extensive damage or multiple large vessel infarcts.[29] These infarcts are more likely to be found in the left hemisphere of the brain, but can be bilateral.[29] Cognitive impairment usually becomes evident within three months of the large infarction and

persist indefinitely.[29] Lacunar (small) infarcts are caused by small vessel occlusions or partial vessel occlusion in the deep cerebral white matter, basal ganglia, or pons, and 1-2 are commonly found via neuroimaging in older adults without cognitive impairment.[29,31] More than two lacunes are usually necessary for VCI diagnosis and often occur concurrently with WMLs.[29] WMLs are usually found in periventricular regions and can extend deep into white matter.[29] To cause VCI, WMLs must be extensive and confluent.[29] A combination of risk factors, vascular disease, and brain damage are the hallmarks of CeVD and VCI.[30]

Parkinson's Disease (PD) and Lewy Body Disease (LB disease)

Parkinson's disease (PD) and Lewy body disease can also impair cognition. Lewy bodies (LBs) are aggregated protein deposits of insoluble α-synuclein that can be found in the cortical and subcortical regions of the brain in LB-related dementias which include PD and LB disease.[12] However, LBs are not strongly correlated with severity of LB-related dementia.[32,33] The abundance of Lewy neurites (LNs) and neuritic degeneration in the hippocampus and periamygdaloid cortex are strongly associated with cognitive impairment by disruption of the limbic loop (controlling emotion, memory, and motivation).[33,34] While PD and LB disease share neuritic pathology based on abnormal aggregation of LBs, they are considered separate disorders despite debate about how to characterize their relationship.[32]

PD is characterized by movement disorder at least 1 year prior to cognitive decline, while LB disease is characterized by cognitive impairment up to 2 years prior or in conjunction with movement disorder.[12,33] There are three core features of LB-related disease: 1) fluctuating cognition with variations in attention and alertness, 2) recurrent

visual hallucinations, and 3) spontaneous features of Parkinsonism.[32,33,35] If only one core feature is present, there are three suggestive features including: 1) REM sleep behavior disorder, 2) neuroleptic sensitivity, and 3) low dopamine transporter uptake in the basal ganglia evident in neuroimaging.[33] Unlike AD and CeVD, cognitive impairment is not necessarily the primary early clinical feature of PD or LB disease.[35] Many clinical features of PD and LB disease overlap making the temporal relationship between cognitive impairment and movement disorder (Parkinsonism) the differentiating factor (**Table 1.1**).[32,33,35]

Table 1. 1. Clinical and diagnostic features of Lewy Body disease dementia and Parkinson's disease with dementia, adapted from Jellinger, 2018[33]

Major Clinical Features	**Lewy Body Dementia**	**Parkinson's Disease Dementia**
Chronology	Dementia precedes by ≤ 2 years prior to onset of Parkinsonism	Parkinsonism precedes dementia by ≥ 1 year
Cognitive impairment	Deficits in attention, executive function, and visuospatial ability	Impairment of more than one memory domain (executive function, episodic memory, etc.)
	Memory impairment less prominent at onset, but increasing (fast rate of decline)	
Fluctuating cognition	Marked variation in alertness and attention	If present, similar to LB disease
Hallucinations	Recurrent, most often visual	Particularly present after drug therapy (Levodopa) and in some drug naïve patients
Motor Parkinsonism	Usually absent before dementia occurs, tremor rare or absent	Variable akinesia, rigidity, tremor frequent
REM sleep behavior disorder (RBD)	May precede onset for many years or develop after onset	Similar to LB disease
Associated non-motor clinical features	Daytime sleepiness, episodes of unresponsiveness, neuroleptic sensitivity, orthostatic	Mood and personality changes similar to LB disease

	hypotension, urine incontinence, constipation, falls, syncopes, hyposmia, depression, apathy, anxiety	with neuroleptic sensitivity less frequent

1.3. Cognitive Reserve

Cognitive reserve is based on the observation that brain pathology and damage are not directly related to cognitive function.[36,37] Cognitive reserve is considered an effect modifier on the relationship between brain pathology and clinical outcomes (MCI and dementia). Mature adults with higher cognitive abilities are hypothesized to tolerate more brain pathology before cognition is noticeably impacted compared to those with lower cognitive abilities.[36,37] Neuroimaging and autopsy studies for AD, CeVD, PD, and LB disease have found that those with high measures of cognitive reserve had higher levels of cognitive function with more pathological evidence of disease compared to those with lower measures of cognitive reserve.[38-42]

There are several hypotheses used to explain cognitive reserve and describe how it develops. One of the more widely accepted theories includes concepts of passive and active reserve. Passive reserve, also referred to as brain reserve, describes brain structures (such as size and neuronal count) that make the brain more efficient as evidenced by enhanced memory retrieval and problem solving.[36-38] Active reserve, also referred to as cognitive reserve, is defined as neuronal compensation, which allows the brain to utilize alternate networks to compensate for pathology.[36-38] Education, complex occupation, and sustained intellectual engagement are thought to be factors in determining levels of active reserve.[36-38]

There is no standard measure of cognitive reserve despite its important to our understanding of the development of MCI and dementia. Measures of active reserve, including education and socioeconomic status (SES), are widely used proxies, because of their association with environmental exposures related to cognitive advantage.[36]

Education

Education is the most commonly used surrogate measure of cognitive reserve.[38,43] The hypothesized relationship between education and dementia through cognitive reserve theory is supported by autopsy studies that have found no association between brain pathology at autopsy and years of education; this suggests that while education may not protect against developing neurocognitive disease, among those who do develop disease, their risk of MCI and dementia is lower.[44,45] However, education as a surrogate measure for cognitive reserve remains complicated and our understanding is incomplete.

How education is measured reflects the cultural context of the population being studied. Studies in developing regions may include participants with no education, whereas in developed nations, even the lowest categories of educational attainment include some years of education. A meta-analysis of papers examining education and dementia found that the association between education and dementia did not depend on categorical cut points for educational attainment.[43] The relationship between education and dementia is more complex than increased education linearly reducing risk of dementia. To address this complexity, some researchers have opted to use SES (which includes measures of education) as a proxy for cognitive reserve.[46,47]

Socioeconomic Status (SES)

SES, also referred to as socioeconomic position (SEP), is defined as "social and economic factors that influence which positions individuals or groups will hold within the structure of a society."[48] Education, wealth, income, occupation, and housing characteristics (renter/owner) are common measures of SES and can be assessed at the individual- and neighborhood/area- level. In measuring SES, there are three main components: education, employment, and money.[49] In particular, education is an integral part of SES because higher levels of education are generally associated with greater upward mobility, leading to higher levels of other SES factors (more wealth, higher income, complex occupation, more likely to own home, etc.) as well as social and behavioral advantages.[49,50]

The connection between SES and health has long been established with some researchers describing SES as a 'fundamental' determinant of health.[49] Low SES, specifically, has been identified as a risk factor for many chronic diseases including diabetes, cancer, CVD, and dementia.[51-55] Further, the relationship between low SES on risk factors and health behaviors on chronic disease risk are seen as early as childhood and adolescence.[56] Contributions of SES to cognitive reserve are not fully understood, but these sociodemographic factors represent a complex accumulation of lifetime exposures that must be considered with examining MCI and dementia outcomes later in life.

1.4. Diagnosis and Treatment

Diagnosis of MCI and dementia involves neuropsychological testing, assessment of medical, neurological, and psychiatric history, a medical exam, neurological and psychiatric exam, laboratory tests, and brain imaging, usually with magnetic resonance

imaging (MRI).[57] The most common tests used for the neuropsychological testing are the Mini Mental State Exam (MMSE) and the Clock Drawing Test (CDT).[58] Cognitive tests are meant to be quick and easy, have an acceptable positive likelihood ratio (diagnostic accuracy), and be repeatable over time to track cognitive change.[57,58] Medical, neurological, and psychiatric history, a medical exam, and laboratory tests, are used to distinguish between pathologic decline and normal aging as well as identify potentially reversible causes of cognitive impairment including depression, side effects of medication, thyroid dysfunction, and B12/folate deficiency.[59] Finally, neuroimaging is used to help determine etiology of disease; though, as mentioned previously, definitive etiologic diagnosis for MCI and dementia can only be determined after death with a brain autopsy or biopsy.[59]

Identifying disease etiology in patients with MCI and dementia is important for predicting the course of disease and deciding on secondary and tertiary prevention strategies. For AD, PD, and LB disease, there are no effective treatments to stop or reverse cognitive decline, only tertiary prevention interventions that may temporarily slow disease progression as well as treatments to help with symptoms, particularly related to behavior and mood.[60,61] For CeVD, cognitive impairment caused by CeVD events cannot be reversed with treatment, however, there are effective secondary and tertiary prevention interventions.[62,63] Common treatments include antihypertensive medications, statins for hyperlipidemia, antiplatelet therapy such as aspirin, carotid endarterectomy, smoking cessation, and anticoagulant therapy such as warfarin.[62]

Overall, there are no effective treatments for MCI and dementia, and development of treatments is complicated by the major overlap in brain pathologies.[64]

CHAPTER 2. EPIDEMIOLOGY AND PUBLIC HEALTH IMPACT OF COGNITIVE IMPAIRMENT

2.1. Incidence and Prevalence

MCI has an estimated prevalence of 16-20% in those ages 50 and older and increases markedly with age.[59,65] MCI is associated with an increased risk of incident dementia and total mortality.[59,65] Of those with MCI, 12-20% will progress to dementia annually, 40-70% will not progress to dementia even after 10 years, and 15-20% will experience improved cognition within 2 years (though this group remains at elevated risk for future cognitive decline).[59] The incidence of MCI ranges widely from 5.1 to 168.0 cases per 1000 person years among those ages 50 and older.[65] Of note, the term MCI does not have a standard definition, so incidence and prevalence estimates can fluctuate substantially between studies depending on the diagnostic criteria for MCI that was used.[66]

An estimated 5.3 million Americans are living with dementia and 5.1 million of those are over the age of 65.[67] The prevalence of dementia is estimated to be 13% in those ages 65 and older and increases exponentially with age, doubling every 5 years after age 65.[67-69] The incidence of dementia is estimated to be approximately 33.3 cases per 1000 person years in those 65 and older.[69-71] As with prevalence, incidence of dementia increases with age, though, by ages 85-90, the rise in incidence rate begins to decelerate and may even plateau.[69]

In addition, there are important differences in the epidemiology of MCI and dementia sub-types. AD has a prevalence of 10-30% and a mean annual incidence of 10-30 cases per 1000 people among those ages 65 and older.[15] The prevalence of CeVD is

3% in the U.S. adult population; however, 11% of those between ages 55-64 have asymptomatic cerebral ischemic abnormalities on neuroimaging, rising to 43% among those ages 85 and older.[72] The incidence of stroke doubles each decade after age 55 with those 65-74 having an annual incidence of 6.7-9.7 incident strokes per 1000 people.[72] PD has an estimated prevalence of 1-5% and older and an annual incidence of 0.13 cases per 1000 people among those ages 65 older.[73,74] The estimated prevalence of LB disease among those 50 years and older is 0.4% with an annual incidence of 0.04 cases per 1000 person years.[75,76] Overall, AD is by far the most common cause of MCI and dementia among older adults followed by CeVD, PD, and LB disease.

2.2. Disparities

There are notable variations in the prevalence and incidence of MCI and dementia among subpopulations in the United States that will likely have major public health implications as demographics of the country shift over time. The U.S. population is getting older and more diverse, which, with no other change, will lead to an increased number of individuals at elevated risk of dementia as well as a heightened need for culturally appropriate dementia assessment and management tools.[77] By 2030, 20% of the population is projected to be 65 or older, a 6% increase from 2012.[78] The racial diversity of the older adult population is also increasing with the proportion of non-Hispanic whites projected to decrease by 18% (from 79% to 61%) by 2050.[77,78] Racial disparities have become an important area of research in MCI and dementia because of these expected changes to the population. Additionally, there are geographic, sex, and birth cohort disparities in neurocognitive disease that should be considered.

Racial Disparities

There is increasing interest and research in identifying and characterizing racial disparities in dementia due the projected population trends. A 2010 report estimated that African Americans and Hispanics had 2 and 1.5 times the risk of all-type dementia, respectively, compared to non-Hispanic whites.[67] Valid comparison of incidence and prevalence of MCI and dementia across race groups is challenging because few studies have been able to use standardized diagnostic criteria to assess MCI and dementia within a diverse, multi-racial population.[67] A recent study of inequalities in dementia incidence attempted to address this problem using data from older adults (≥ 65 years old) receiving medical care through Kaiser Permanente Northern California.[79] African Americans had the highest incidence and hazard of dementia followed by American Indians/Alaskan Natives, Latinos, Pacific Islanders, and whites with Asian Americans as the references group (**Table 2.1**).[79] Further, there are many bi-racial studies, most often comparing African Americans and whites or Hispanics and whites, which have shown racial disparities in MCI and dementia.[80-83]

Table 2. 1. Incidence rates (95% CI) and hazard ratios (95% CI) of dementia by race, 2000-2013, adapted from Mayeda, 2016[79]

Race/Ethnicity	Age-adjusted Incidence Rate per 1000 person years (95% CI)	Hazard Ratio (95% CI)
African American	26.60 (25.83, 27.37)	1.65 (1.58, 1.72)
American Indian/Alaskan Native	22.18 (20.85, 23.52)	1.32 (1.24, 1.41)
Latino	19.59	1.24

	(18.97, 20.20)	(1.19, 1.29)
Pacific Islander	19.63 (14.51, 24.75)	1.23 (0.95, 1.58)
White	19.35 (19.16, 19.54)	1.22 (1.18, 1.26)
Asian American	15.24 (14.73, 15.74)	1.00 (ref)

Despite evidence suggesting prevalence and incidence of dementia varies between ethno-racial groups, there is no consensus on racial disparities in MCI and dementia for several reasons.[84] There is concern that cognitive tests used to identify cognitive decline and dementia may lack convergent validity between race groups, cultural biases may interfere with self-report and informant-report of cognitive function, and socioeconomic differences (such as education and income) often, in part, the result of racism, make comparison between race groups challenging.[80,84] Further, there may be delays in diagnosis and treatment for cognitively impaired individuals from minority populations leading to more severe symptoms at diagnosis.[80,84] These cultural factors likely influence the disparities in MCI and dementia that have been observed, but further research is needed to determine the extent of these biases.

Sex Disparities

Sex disparities have been observed in MCI and dementia, but their cause is believed to vary by subtype. AD prevalence is significantly higher in women than men, with almost two-thirds of individuals living with AD in the U.S. being women.[85] However, studies of incident disease show that risk of AD is not significantly higher in women compared to men, suggesting the difference in prevalence is explained by the fact

that women live longer on average.[85,86] Based on the current literature, there is no sex disparity in AD, only sex differences in life expectancy and thus lifetime at risk of AD.[85]

CeVD and stroke incidence is higher in men than women until age 85 after which women have a higher incidence.[87] Incident stroke in women occurs, on average, 5 years later than men, women have a greater lifetime risk due to a longer life expectancy, and women are more likely to experience stroke related disability and cognitive impairment, possibly due experiencing stroke at an older age when pre-stroke independence and abilities were already compromised.[88-90] The delayed onset of CeVD has been hypothesized to be caused by cardio protective estrogen; however, this view has been disputed in clinical trials.[91] Sex differences in CeVD are likely caused by a combination of longer life expectancy in women, modifiable vascular risk factors, and genetics.[91]

Unlike AD and CeVD, sex disparities in dementia with LBs (including PD and LB disease) have not been extensively studied and are not well established, likely due to the relative rarity of these diseases. Evidence from autopsy indicates men have a higher prevalence of dementia with LBs compared to women.[92] This sex disparity is especially evident among those with pure LB pathology compared to those with mixed pathologies (LB disease + AD).[92] Researchers have hypothesized that the disparity is related to a neuro-protective role of estrogen, but is likely related to a complex mix of biological and environmental factors.[92-94]

Geographic Disparities

In addition to possible racial and sex disparities, there are geographic disparities in MCI and dementia across the United States. The "Stroke Belt" is a well-established phenomenon where stroke morbidity and mortality is highest in the 8-state region of the

Southeastern part of the country.[95,96] Vascular risk factors are believed to explain half of the disparity, but there remains regional drivers that are not fully understood.[95] The geographic pattern of stroke incidence and mortality as well as the overlap between vascular risk factors, cerebrovascular disease, and dementia, have prompted further investigation of the relationship between geography and dementia incidence and mortality. Studies have shown that not only do individuals who spent their early years in the "Stroke Belt" have an elevated risk of stroke later in life regardless of where they reside, but also that states with high stroke mortality tend to have elevated Alzheimer's disease mortality.[97-99] Going further, individuals born in the "Stroke Belt" have a greater risk of incident dementia as well as dementia mortality regardless of residence late in life or at death.[100,101] The geographic disparity in dementia suggests that there are robust early life and childhood geographic risk factors for MCI and dementia that require further investigation.

Birth Cohort Disparities

Epidemiologic study of older adult populations has shown that changes in educational attainment and improved modifiable vascular risk factors have led to reduced risk of MCI and dementia among younger birth cohorts compared to older cohorts. Glymour, et al., 2008 examined changes to compulsory schooling laws (mandatory enrollment age and years of compulsory schooling) in the United States as a natural experiment to understand the association between education and cognitive impairment between birth cohorts (birth year <1914, 1914-1921, 1922-1930, 1931-1941, and 1942-1947).[102] The study found that birth cohorts affected by changes in compulsory schooling laws had higher educational attainment and performed better on cognitive tests later in

life (≥ age 50) compared to earlier birth cohorts that completed school before the law changes.[102] In addition, CVD mortality peaked in the United States in the late 1960s and has since declined, due, in part, to improved vascular risk factors and treatment including reduced smoking and the development of statins and antihypertensive medications.[103] Some studies have observed a decline in dementia incidence and prevalence between the 1970s and 2010s and have attributed these changes to a combination of increased education and improved risk factors.[104,105] However, these trends have not been consistent between study cohorts and require further longitudinal examination (especially in light of the rapidly aging population).

2.3. Economic Burden

The cost of dementia care in the United States was estimated to be $215 billion in 2010, and with the aging population and increased life expectancy, these costs are expected to more than double by 2040.[106] While Medicare provides nearly universal healthcare for Americans over age 65, the population most at risk for MCI and dementia, Medicare does not cover all dementia-related expenses such as homecare services, homecare equipment, and non-rehabilitative nursing home care.[107] Average out of pocket spending during the last five years of life for dementia patients was estimated to be $61,522 versus $28,818 for cancer patients and $35,294 for heart disease patients.[107] The high costs associated with MCI and dementia primarily come from the formal and informal care patients need as the disease progresses and they lose their ability to carry out activities of daily living and instrumental activities of daily living.[107]

The majority of dementia patients (70-81%) live in the community and rely on caregivers to help with daily activities.[108] Caregiving is considered “informal” work, and

caregivers are most likely to be a female family member of the MCI or dementia patient such as a spouse, sibling, or adult child.[109,110] The estimated monetary value of caregiving in 2010 was $27,789 in addition to $13,188 in forgone wages.[106] Caregiving is associated with a number of negative outcomes including family dysfunction, depression, financial stress, and reduced quality of life.[110] Because patients with MCI and dementia often live for several years with increasing disability, the impact of neurocognitive disease on families and communities can be tremendous. Research into prevention and treatment of MCI and dementia is essential not only for those who will be at risk of disease, but also their families who will be deeply impacted.

CHAPTER 3. RISK FACTORS

3.1. Introduction

MCI and dementia are caused by a complex mix of demographic, genetic, behavioral, and vascular risk factors. This chapter will describe these major risk factors for MCI and dementia as well as possible mechanisms by which they influence disease risk. Unless otherwise specified, estimates of dementia incidence and prevalence as well as the epidemiology of risk factors will refer to U.S. or European studies. While there are noted geographic disparities throughout the world, methodological issues and limited data prevent wider generalization.[111] Socioeconomic status will be described in detail in Chapter 5 followed by novel risk factors of thyroid function and migraine described in Chapters 6 and 7, respectively.

3.2. Demographic

Age

Age is the strongest risk factor for MCI and dementia, and among those ages 80 and older, it is the only consistent statistically significant predictor of cognitive impairment.[69] "Late-onset" is sometimes used to describe dementia (especially AD) that is diagnosed at or after age 65 while "early-onset" describes dementia diagnosed before age 65. Late-onset dementia is far more common than early-onset, though, cognitive and structural changes are measureable well before symptomatic onset of disease regardless of age at diagnosis.[15] Between ages 65 and 90, the risk of dementia increases exponentially and almost doubles every 5 years (**Table 3.1**).[67-69] However, few studies have examined dementia and MCI in those ages 90 and older. There is some debate whether MCI and dementia incidence continues to rise after age 90 and how

quickly.[70,112,113] However, prevalence of dementia in this group is estimated to be 28-44%.[114]

Table 3. 1. Age-stratified incidence rates (95% CI) of dementia per 1000 person years in the United States, adapted from Jorm,1998[115]

Age Group, years	Estimated Incidence per 1000 person years	(95% CI)
65-69	2.4	(1.9, 3.0)
70-74	5.0	(4.3, 5.7)
74-79	10.5	(9.4, 11.6)
80-84	17.7	(16.1, 19.4)
85-89	27.5	(23.7, 32.0)

Early-onset (also known as young-onset) dementia represents less than 10% of AD cases, has an incidence of 0.67-0.98 cases per 1000 people, and is most likely to occur between the ages 45 and 64.[116,117] As with late-onset dementia, the most common etiologic causes are AD and CeVD, followed by frontotemporal dementia.[116] Patients with early-onset MCI and dementia are more likely to be misdiagnosed compared to late-onset cases, likely due to their age rather than differing manifestations of disease.[116]

Sex

Female sex is strongly associated with risk for MCI and dementia as well as a source of disparities.[118] As mentioned previously, higher risk of AD and CeVD in women is largely related to the longer life expectancy, while higher risk of dementia with LBs in men may be due neuroprotective estrogen.[96,118] Contributing to the sex disparities evident in MCI and dementia are disparities in modifiable risk factors.

Men are more likely to smoke, have CVD (specifically coronary artery disease), and experience a brain injury with loss of consciousness, while women are more likely to be obese, all factors that increase risk of MCI and dementia.[118] In addition, there is mounting evidence that diabetes and hypertension disproportionately affect women's risk of cognitive impairment compared to men's risk despite similar prevalences.[119] Coronary heart disease (CHD) is a major risk factor for MCI and dementia that is more prevalent in men; however, the female risk advantage is negated in women with diabetes.[119-121] Further, women with diabetes are estimated to have a 19% increased risk of MCI and dementia compared to men with diabetes.[122] Prevalence of hypertension, a particularly important risk factor of stroke and CeVD, is higher in men compared to women in middle age, but as age increases, prevalence rises to 75% among women 75 years and older compared to only 65% among men of a similar age.[123]

Thus, sex alone may not be a risk factor for dementia, but men and women differ in risk factor prevalences, particularly age that must be addressed in research. Midlife vascular risk factors are associated with the development of later life MCI and dementia, and are modifiable in men and women.[124]

Race and Ethnicity

As mentioned in Chapter 2, there are disparities in MCI and dementia incidence and prevalence by race; specifically, higher rates in African Americans, American Indians/Alaskan Natives, and Hispanics followed by whites, and lower rates in Asian Americans.[79,125] However, there is no consensus on racial disparities due to convergent validity of cognitive tests, cultural biases that interfere with self and informant-report of cognitive function, and socioeconomic differences.[80,84,125] Moreover, there are disparities

in modifiable vascular risk factors for MCI and dementia that may, in part, be driving potential racial disparities.

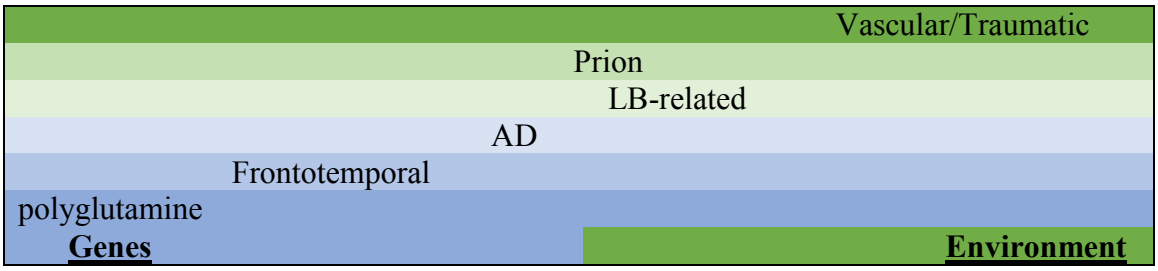
A meta-analysis found that African Americans and Hispanics had higher prevalence of hypertension, diabetes, obesity, hypercholesteremia, smoking, and physical inactivity compared to whites.[126] In contrast, Asian Americans had a lower prevalence of hypertension, diabetes, smoking, obesity, and physical inactivity compared to whites.[127] These risk factor levels mirror the differences in incidence and prevalence of MCI and dementia by race. There is also a strong relationship between race and socioeconomic status (typically measured by income and education), as well as heterogeneity within racial and ethnic groups, that further complicate documenting the independent relationship between race and MCI and dementia.[128,129] As with sex disparities, studies generally adjust for modifiable risk factors in addition to race and SES. However, the complexity of the relationship between SES, race, and cognitive impairment may require advanced statistical methods to fully adjust for potential confounders.

3.3. Genetic

Genetic variations play an important role in the development of most age-related dementias. Neurodegenerative disease etiologies can be thought of as falling along a spectrum of genetic and environmental influence (**Figure 3.1**).[130] As discussed in Chapter 1, AD and LB-related dementias are caused by misfolding and aggregation of proteins, known as proteinopathy. Dementias caused by proteinopathy can be hereditary and caused by dominant-acting disease gene mutations or non-hereditary (also known as sporadic) and involve a number of genetic and environmental factors.[130] The genetic

factors associated specifically with AD and LB-related disease most often play a role in the development of proteinopathy.[130]

Figure 3. 1. Spectrum of influence by genes versus environment on various dementias, adapted from Paulson and Igo, 2011[130]



Alzheimer's Disease and Apolipoprotein E (ApoE)

The majority of AD, especially late-onset cases, are sporadic, while early-onset AD is more likely to be hereditary.[130] Early-onset familial AD is caused by autosomal-dominant single-gene mutations on chromosomes 21, 14, and 1.[117,130] Amyloid precursor protein gene (*APP*) found on chromosome 21 encodes amyloid precursor protein (APP), a neuronal membrane protein from which Aβ is released.[117,130] Any one of 32 mutations in *APP* can cause the formation of abnormal APP from which Aβ is derived.[130-132] This abnormality in APP leads to the over production of a less soluble, more toxic form of Aβ called $A\beta_{42}$ (relative to $A\beta_{40}$).[130,132] One of 179 single gene mutations on the presenilin 1 gene (*PSEN1*) on chromosome 14 or one of 14 mutations on the presenilin 2 gene (*PSEN2*) on chromosome 1 create proteins called presenilins (PS1 and PS2) that are important in the γ-secretase complex.[130,132] The enzymes produced by *PSEN1* and *PSEN2* are responsible for creating complex enzymes that cleave APP into Aβ.[130,132] Mutations

in these enzymes result in the over production of $A\beta_{42}$ relative to $A\beta_{40}$, the same consequence of *APP* mutations.[130,132] These gene mutations are responsible for less than 2% of all AD cases and of them, *PSEN1* mutations are the most common.[132]

In 50-70% of sporadic (late and some early-onset) AD cases, genetic factors play a significant role, though sporadic AD is not considered a genetic disorder.[130,132] The most important genetic risk factor, contributing to approximately half of the genetic risk, is the apolipoprotein E (*ApoE*) gene found on chromosome 19.[130,132] This gene is responsible for making a protein called apolipoprotein E, which combines lipids to form lipoproteins.[133] Lipoproteins are responsible for packaging and carrying cholesterol and other fats through the bloodstream, which makes *ApoE* a significant factor in maintaining healthy cholesterol levels.[131,133] Elevated cholesterol (hypercholesteremia) is associated with elevated risk of CVD and is strongly related to AD pathogenesis.[131,133] *ApoE* mediates the delivery of cholesterol to the brain, an essential component for axonal growth, synaptic formation, and remolding.[131] These events are vital to learning, memory, and neuronal repair.[131] *ApoE* is also believed to influence Aβ metabolism by causing deposition of Aβ to form senile plaques and cause cerebral amyloid angiopathy, two hallmarks of amyloid pathology in AD brains.[131]

ApoE has three common polymorphic alleles, ε4 (*ApoE4*), ε3 (*ApoE3*), and ε2 (*ApoE2*), which vary at two amino acids.[130,132] *ApoE4* is present in 10-20% of the American population and increases risk of AD, *ApoE2* is the rarest allele and believed to have a protective effect, and *ApoE3* is the most common allele and is believed to play a neutral role.[132] The prevalence of *ApoE* alleles as well as the risk of AD varies by race/ethnic group (**Table 3.2**).[134,135] An individual with two *ApoE4* alleles will have the

highest risk of AD followed by those with one allele.[117] Individuals with no *ApoE4* alleles have the lowest risk of AD.[117] It is important to note that *ApoE4* is a genetic risk factor, not a disease causing mutation, meaning that *ApoE4* cannot cause AD nor does it need to be present for AD to develop, unlike the mutations in *APP*, *PSEN1*, and *PSEN2* implicated in familial early-onset AD.[130] There is evidence of an *ApoE* gene-environment interaction with increased lifetime cognitive activity reducing the Aβ burden in the brains of *ApoE4* carriers compared to *ApoE4* carriers with less lifetime cognitive activity.[136] Genome-wide association studies have identified additional genetic risk factors for AD including *CLU*, *PICALM*, *CR1*, *NIN1*, *ABCA7 MS4A* cluster, *CD2AP*, *CD33*, and *EPHA1* genes, but none are as significant as *ApoE* with increased disease odds ratios of 1.1-1.2 compared to 3.0-4.0 for *ApoE4*.[130]

Table 3. 2. Odds ratios (95% CI) of developing AD by *ApoE* allele and race, adapted from Farrer, 1997[134] and prevalence (% ± standard deviation) by *ApoE* allele, adapted from Singh, 2006[135]

***ApoE* alleles**	**Whites**	**African Americans**	**Hispanics**	**Japanese**	***ApoE* allele**	**Prevalence in North America**
ε2/ε2	0.9 (0.3, 2.8)	2.4 (0.3, 22.7)	2.6 (0.2, 33.3)	1.1 (0.1, 17.2)	**ε2**	0.05 ± 0.04
ε2/ε3	0.6 (0.5, 0.9)	0.6 (0.4, 1.7)	0.6 (0.3, 1.3)	0.9 (0.4, 2.5)		
ε3/ε3	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	**ε3**	0.82 ± 0.06
ε2/ε4	1.2 (0.8, 2.0)	1.8 (0.4, 8.1)	3.2 (0.9, 11.6)	2.4 (0.4, 15.4)		
ε3/ε4	2.7 (2.2, 3.2)	1.1 (0.7, 1.8)	2.2 (1.3, 3.4)	5.6 (3.9, 8.0)	**ε4**	0.13 ± 0.06

ε4/ε4	12.5 (8.8, 17.7)	5.7 (2.3, 14.1)	2.2 (0.7, 6.7)	33.1 (13.6, 80.5)		

Lewy Body-related Diseases

As with AD, LB-related diseases (LB disease and PD) are most often sporadic. However, research has identified a strong genetic component including several genes associated with the development of LB-related diseases. A mutation found in the α-synuclein gene (*SNCA*) was the first evidence of a genetic basis for LB-related diseases, implicated in both PD and LB disease.[137,138] Pathogenic mutations in *SNCA* are rare, but the gene is thought to cause α-synuclein aggregation, a pathogenic event in early LB dementias.[137-139] Not all mutations in SNCA are fully penetrant, which is likely why there can be heterogeneity between members of the same family in terms of age at onset, phenotype, and pathology.[138] Another gene identified in LB-related disease is *LRRK2*; 1% of sporadic and 4-5% of familial PD is associated with the (relatively) common mutation p.G2019S, while rarer disease-associated variants are implicated in LB disease.[137,139,140] The wide clinical-pathological variability associated with *LRRK2* suggests there are strong genetic modifiers yet to be identified.[137] Finally, disease-associated mutations in the *GBA* gene are the third major genetic factor commonly implicated in LB-related diseases.[139] *GBA* mutations are believed to reduce the activity of the enzyme β-glucocerebrosidase leading to impaired degradation of α-synuclein and, thus, the aggregation commonly seen in LB-related disease.[138]

Of note, while PD and LB disease are related and share genetic risk factors (as do AD and LB disease), there is no known genetic overlap between PD and AD.[138] *PSEN1*,

PSEN2, and *APP* mutations typically associated with AD are also believed to play a role in LB disease.[138] The mechanism is not totally understood, however some researchers believe this association may be due to misdiagnosis of LB disease in AD patients or evidence of mixed AD-LB disease pathologies, both of which can only be confirmed with autopsy data.[139] In addition, *ApoE4* increases risk of both AD and LB disease and may be stronger risk factor for mixed AD-LB pathology than for AD pathology alone.[139,141]

Cerebrovascular Disease

CeVD is caused by a combination of vascular, environmental, and genetic components. The genetic factors in CeVD are most often multifactorial and result from the interaction of many genes each with a relatively small affect.[142] While monogenic diseases and susceptibility for CeVD are rare, some have been identified.[142,143] Cerebral autosomal dominant ateriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare, but well-characterized autosomal dominant small vessel disease that occurs in 2-4 per 100,000 adults. CADASIL is caused by a mutation in the *NOTCH3* gene that is known for causing infarcts and increasing risk of ischemic stroke with onset as early as the mid-20s through 30s.[142,143] Additional rare CeVD-causing genetic mutations include, Fabry disease (an X-link recessive lysosomal storage disorder), mitochondrial encephalomyopathy lactic acidosis and stroke episodes (MELAS) (a disorder that is caused by mutations in mtDNA and known to cause stroke), and Myoma disease (MYMY) (a progressive, occlusive cerebrovascular ateriopathy).[142]

While monogenic diseases do not explain most CeVD related dementia, nor is CeVD considered a genetic disease, genetics of lipid disorders have been identified as potentially playing a role in the assessment of CeVD risk, especially ischemic stroke.[142]

A systematic review of 42 studies (n = 29,965) found that, compared to *ApoE3*, *ApoE4* was associated with increased prevalence of cerebral micro-bleeds, (especially in the lobar region of the brain), *ApoE2* was associated with increased frequency of brain infarcts, and both *ApoE4* and *ApoE2* were associated with an increased risk of white matter hyperintensities.[144] The underlying mechanism of *ApoE*'s association with CeVD is not fully understood, and it is unclear how *ApoE* variants influence lipid metabolism in the brain or whether they are related to neuro-inflammation, unlike AD where *ApoE*'s role is thought to be through Aβ metabolism.[144] In addition to *ApoE*, familial hypercholesterolemia (FH), characterized by elevated blood cholesterol, tendinous xanthoma, and premature vascular disease (especially CHD), has been shown to increase risk of stroke in a Finnish study of more severe forms of FH, but few studies have looked at specific FH gene mutations (such as *LDLR*, *ApoB*, and *PCSK*9) and CeVD.

While there are clear genetic components to certain CeVDs, the relationship between genetics and cerebral events is not as strong as with other dementia etiologies. Further, pathophysiologic mechanisms are not well understood, in part, because of the blood brain barrier.[145] There is limited understanding of the complex relationship between microvascular dysfunction and degeneration, neurovascular disintegration, defective blood brain barrier, and vascular risk factors.[145]

3.4. Vascular

Hypertension

Despite advancements in prevention and treatment of hypertension, it remains one of the most important risk factors for stroke and dementia (mainly through CeVD and AD etiology).[146] The brain is particularly susceptible to damage caused by hypertension.[146]

Blood pressure is involved in the conduit and cushioning functions of the large arteries.[147] These functions are responsible for delivering blood throughout the body (conduit function) and transforming a pulsatile flow at the heart level to a steady-state flow at the peripheral level (cushioning function).[147] As individuals age, large artery stiffening increases systolic blood pressure (SBP) and pulsatility, damaging microcirculation in the brain, heart, retina, and kidneys.[148] The brain relies on adequate supply of oxygen and glucose, and microvascular damage caused by hypertension can cause profound alterations to the regulatory mechanisms that ensure this supply.[146,149] This dysfunction is associated with lacunar infarcts, white matter damage, microinfarcts, and micro- and macro-bleeds, all hallmarks of CeVD and stroke.[146,149] In clinical trials, a 10 mm Hg reduction in systolic blood pressure is associated with a 30% reduction in risk of stroke; this linear association continues down to a systolic blood pressure of 115 mm Hg and diastolic blood pressure of 75 mm Hg.[150] Further, there is increasing evidence that hypertension-induced brain lesions associated with CeVD have a synergistic or additive effect on AD pathology.[146] Nevertheless, a meta-analysis found that there was no consistent statistically significant association between AD and hypertension when measuring hypertension in mid- or late-life.[151]

Unlike CeVD and AD, data on hypertension and LB-related diseases is sparse. A meta-analysis of seven studies found that history of hypertension significantly increased risk of PD with a pooled relative risk of 1.80 (95% CI: 1.07, 3.04).[152] However, three cohort studies used Taiwan National Health Insurance data and there was substantial publication bias.[152] To our knowledge, no studies have assessed the association between LB disease and hypertension.

Obesity

The mechanisms by which obesity may increase risk of dementia are believed to be via the vascular and behavioral risk factors associated with obesity such as sedentary lifestyle, poor diet, hypertension, and obesity as well as white adipose tissue (WAT).[153] WAT is endocrine tissue that secretes cell-signaling molecules called adipokines, which refer to cytokines, acute phase reactants, growth factors, and other inflammatory mediators.[153] There are hundreds of adipokines and the relationship between these molecules and dementia has been largely unexplored despite epidemiologic evidence supporting an association between adiposity and dementia.[153]

High midlife body mass index (BMI) defined as overweight (> 25-30 kg/m^2) or obese (> 30 kg/m^2) as well as high central adiposity (≥ 25cm) were each associated with double the risk of CeVD, AD, and total dementia in later life compared to those with a normal BMI (18.5-25 kg/m^2) or normal central adiposity (< 25 cm).[154-157] The relationship between obesity and PD or LB disease has not been studied as extensively, however, the evidence suggests there is a weak or no association with obesity.[158,159] Further, BMI over the life course generally follows a trajectory of increasing weight with age until reaching an inflection point between mid- and late life after which BMI decreases.[153] This decrease later in life is associated with brain atrophy, white matter changes, and disturbances of the blood brain barrier suggesting midlife obesity may be more important for risk of cognitive decline compared to late-life obesity.[153]

Diabetes Mellitus

Diabetes is an established risk factor for ischemic stroke and small vessel disease as well as associated with several vascular risk factors for dementia including obesity,

hypertension, and hypercholesteremia.[160] There is a well-established relationship between type 1 and type 2 diabetes mellitus and modest changes in cognition.[161] For type 1 diabetes, this includes slowing of mental speed and reduced mental flexibility, and for type 2 diabetes, there may be changes in learning and memory, mental flexibility, and mental speed.[162,163] A meta-analysis of 14 longitudinal studies found that diabetes was associated with almost double the risk of total dementia, AD, and CeVD.[161] Few epidemiologic studies have assessed the relationship between diabetes and LB-related diseases, but a Finnish study found that risk of PD was almost two-fold higher in those with diabetes, compared to those without, mirroring study results for total dementia, AD, and CeVD.[164]

There are four main mechanisms by which diabetes is believed to be associated with cognitive impairment, chronic glucose toxicity, chronic hypoglycemia, impaired insulin sensitivity, and inflammation.[160] Glucose toxicity is caused by hyperglycemia-induced tissue damage, particularly in the retina, kidneys, and brain causing oxidative stress related to vascular damage and neurodegenerative brain disorders.[160,165] Hypoglycemia, particularly recurrent, severe episodes, can cause permanent neurologic damage and increase platelet aggregation and fibrinogen formation.[160,166] Changes in insulin sensitivity can have profound effects on cerebral carbohydrate metabolism, due to the large concentrations of insulin receptors in the brain, and lead to energy deficits associated with neurodegenerative diseases.[167] Finally, chronic inflammation, which is believed to be involved in type 2 diabetes, is also thought to play a role in cognitive impairment, though study of this relationship has been limited and relies on the measure of non-specific inflammatory biomarkers such as C-reactive protein and interleukin-6.[160]

Hypercholesteremia

The relation between blood levels of cholesterol and dementia is complicated by the blood brain barrier. While 23% of the body's cholesterol is found in the central nervous system, all brain cholesterol is made locally and cut off from the blood supply of the rest of the body.[168] Even so, cholesterol metabolism is believed to play an important role in neurodegenerative diseases, particularly with the discovery of *ApoE4* as a genetic risk factor for AD.[168] Cholesterol is known to influence the activity of enzymes involved in the metabolism of amyloid precursor protein and Aβ deposition.[169] Animal and in-vitro studies have shown that increased dietary cholesterol accelerates Aβ deposition in the brain, though the mechanism is not fully understood.[169] Further, cholesterol is also believed to play a role in tau production and production of neurofibrillary tangles.[169] Epidemiologic studies have found that hypercholesteremia in midlife increases the risk of late-life AD; though, no relationship has been found between late-life hypercholesteremia and risk of AD, suggesting the association may be age-dependent.[170,171]

In PD and LB disease, cholesterol oxidation has been hypothesized as a factor in α-synuclein aggregation, a pathological hallmark of LBs.[168,172] Chronic inflammation is believed to cause cholesterol oxidation leading to α-synuclein overexpression.[172] However, the temporal relationship between the components in this proposed progression has not been established.[172] A case-control study of brain samples from cases with LB-related diseases (n=15) and controls without LB-related brain pathology (n=18) found that concentrations of oxidative cholesterol metabolites were significantly elevated in cases.[172]

The relationship between blood cholesterol levels and cerebrovascular disease is equally complex with epidemiologic studies suggesting high total cholesterol is associated with ischemic stroke, while low total cholesterol is associated with hemorrhagic stroke.[173] Hypercholesteremia is an important risk factor for coronary heart disease, and the strongest association between lipids and ischemic stroke is within the large artery atherothrombotic stoke subtype. However, there is no association between hypercholesteremia and embolic stroke.[173] Low total cholesterol may play a role in hemorrhagic stroke due to the importance of cholesterol in the architecture and integrity of the endothelium of small vessels.[173] Low cholesterol levels may impair endothelial repair causing "leakage" or obstruction of the vessels putting individuals at elevated risk of a hemorrhagic event.[173]

3.5. Behavioral

Cigarette Smoking

Cigarette smoking is the leading preventable cause of a number of chronic diseases including CVD, and prevalence in the United States is estimated to be 20%.[174] Smoking affects CVD risk via the pharmacological effects of nicotine including sympathetic stimulation and coronary vasoconstriction, inhaled carbon monoxide decreasing oxygen availability in the blood, smoke causing increased thrombotic factors including platelet activation, and inflammatory effects of toxic chemicals in cigarette smoke.[174] These same mechanisms are the foundation of the relationship between cigarette smoking and CeVD events, including both ischemic and hemorrhagic stroke.[175] Current cigarette smokers have a 3-4-fold increased risk of stroke compared to never smokers, and those exposed to secondhand smoke have a 1.5-2-fold higher risk of stroke

compared to those not exposed to secondhand smoke.[175] Further, smokers had a 1.38-fold (95% CI: 1.18, 1.45) higher risk of VaD compared to never smokers based on a meta-analysis of five longitudinal studies.[176]

The relationship between other dementias (AD, and LB-related disease) and smoking is inconsistent and less well understood.[176] A meta-analysis found that current smokers had 1.3-fold (95% CI: 1.2, 1.4) increased risk of all-cause dementia compared to never smokers, and that there was no statically significantly difference in dementia risk between former smokers and never smokers.[176] However, the same meta-analysis found only a marginally significant association between current smoking and AD with a relative risk of 1.1 (95% CI: 1.0, 1.3).[176] Further, a study of smoking and LB-pathology upon autopsy found no significant difference in LB pathology between those who had smoked 0-5 pack years versus those who smoked >5-50 pack years, while participants who smoked >50 pack years had a relative risk of 0.4 (95% CI: 0.2, 0.9) compared to those who smoked >5-50 pack years.[177]

The inconsistent association between smoking and dementia, particularly AD and LB-related disease, is likely related to bias. Increased attrition seen in study participants that smoke as well as survival of some smokers given the known lethality of smoking, suggests that there may be beneficial characteristics (e.g. genetic risk factors, access to care, etc.) of smokers who survive long enough to be at risk for/develop dementia as well as chose to participate in epidemiologic studies.[178,179] This selection bias pushes results towards (and sometimes beyond) the null.[178] However, smoking is such a strong risk factor for disease (including CeVD and other dementia risk factors) that it is still an important behavioral risk factor for dementia and must be included in analysis.

Alcohol Consumption

Alcohol consumption at any age has an acute neurotoxic effect on the brain, which can lead to symptoms of cognitive impairment, blackout, and hangover that are reversible with alcohol withdrawal.[180] Researchers believe the repeated neurotoxic effect of drinking, particularly heavy drinking and abuse, can cause alcohol-related brain damage/injury, a form of cognitive impairment that is clinically different from AD, VaD, and LB-related diseases and characterized by ventricular enlargement and diffuse atrophy primarily affecting the prefrontal regions.[180,181] Alcohol-related brain damage/injury is often overlooked as a comorbid factor in dementia diagnosis.[182] One review estimated 9-22% of dementia patients abused alcohol and among alcohol abusers, 10-24% had dementia.[182] However, the neuropathological link between alcohol-related brain damage/injury and dementia is not clear.[182] Further, consumption patterns, type of alcohol, genetics, and a number of other clinical factors complicate the relationship and understanding of alcohol-related brain damage/injury.[180,181,183]

A meta-analysis of 15 longitudinal studies (n=14,646) found that light to moderate alcohol consumption was associated with a 25-28% reduction in risk of AD, VaD, and all-type dementia compared to non-drinkers, while risk of dementia in heavy drinkers versus non-drinkers did not significantly differ.[184] Further, a case-control study found no association between risk of LB-related disease and alcohol consumption.[185] However, there are several caveats to these results. Heavy drinkers were less likely to live to old age, likely because heavy drinking is associated with elevated risk of cardiovascular disease, cancer, liver disease, and other chronic conditions that significantly increase mortality.[184] The protective effect seen among light to moderate

drinkers may be a reflection of those individuals possessing other beneficial characteristics similar to what we see among smokers (e.g. genetics, access to care, etc.) as well as inadequate control for confounders.[186] Emerging research using Mendelian randomization, pooled cohort studies, and multivariable adjusted meta-analysis has shown no protective effect of drinking on total mortality, cardiovascular disease, or AD, further suggesting the protective effect of alcohol on dementia may be due to bias.[186-189]

Diet

The role of diet in prevention of chronic disease, particularly CVD, is primarily through maintaining a balanced, healthy food regimen and preventing vascular risk factors such as obesity, hypertension, and hypercholesteremia.[190,191] The Mediterranean diet and Dietary Approaches to Stop Hypertension (DASH) diet have been studied and promoted as diets specifically for CVD prevention. The Mediterranean diet has been the most extensively studied and is associated with reduced risk of a number of chronic and age-related conditions including stroke, type 2 diabetes, CVD, and total mortality.[191-196] Traditionally, this diet is characterized by high intake of fruits, vegetables, cereals, and legumes, olive oil as the main source of fat, low consumption of red meat and processed meat, and moderate alcohol consumption (particularly wine).[191] A meta-analysis of 11 prospective cohort and cross-sectional studies and one randomized controlled trial showed that higher adherence to the Mediterranean diet was associated with reduced risk of AD and lower rates of cognitive decline.[191]

The DASH diet was inspired by the Mediterranean diet and developed to prevent hypertension. This diet is characterized by an emphasis on consumption of fruits, vegetables, and low-fat dairy while restricting consumption of sodium, commercial

sweets, and saturated fat.[197] A small clinical trial of 124 overweight (BMI: 25-40 kg/m^2) men and women found that participants randomized to the DASH diet had better psychomotor speed after 4 months compared to usual diet controls.[198] A cohort study from the Rush Memory and Aging Project found that increased adherence to the DASH diet was associated with significantly slower rate of cognitive decline on global cognitive test scores over an average follow-up of 4.1 years.[199]

While the Mediterranean and DASH diets have shown inverse associations with cognitive decline and dementia, neither were developed to increase the types of foods identified to be neuroprotective for dementia.[197] Individual nutrients including vitamin E, B vitamins, folic acid, and n-3 fatty acids have been identified as potentially reducing risk of dementia.[197] Observational and clinical studies have shown increased intake of n-3 polyunsaturated fatty acids measured via food frequency questionnaires were associated with reduced risk of incident AD.[200] Observational studies also supported increased consumption of vitamin E, B, and folic acid to reduce dementia risk, but results from intervention studies did not find a protective effect.[200] Nevertheless, these nutrients have been identified as possible targets for a diet to prevent cognitive decline and dementia.

The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet was developed to address this gap by emphasizing plant-based foods, especially green leafy vegetables and berries, and limiting animal and high saturated fat foods.[197] Two cohort studies conducted in the Rush Memory and Aging Project cohort found that the MIND diet was associated with significantly slower cognitive decline on global cognitive scores over 4.7 years of follow-up and 35-53% reduction in risk of AD among those with the middle and highest tertiles of MIND adherence compared to those in the

lowest.[201,202] As with the Mediterranean and DASH diets, there is a consistent statistically significant association between diet and dementia.

Physical Activity

Several controlled trials, primarily with aerobic exercise interventions such as walking or biking, have shown physical activity improves cognitive function or hippocampal volume after relatively short follow-up (4 weeks to 1 year).[203] A meta-analysis of 37 prospective cohort studies found that the highest levels of physical activity were associated with slower cognitive decline compared to the lowest levels of physical activity (RR: 0.65; 95% CI: 0.55, 0.76) as well as reduction in dementia risk (RR: 0.86; 95% CI: 0.76, 0.97).[204] The evidence consistently points to habitual physical activity as a potential protective factor against cognitive impairment. Ideal physical activity for improvement or maintenance of cognitive function has been identified as aerobic exercise lasting at least 20-30 minutes per session with sustained increase in heart rate and need for oxygen that, over time, leads to improved cardiovascular fitness (measured by peak oxygen consumption per unit time).[205]

Loss of muscle strength and mass (sarcopenia) are common, natural parts of the aging process that limits independence in older adults.[206] These processes are accelerated by lack of physical activity putting individuals at greater risk of immune system dysfunction, metabolic disease, musculoskeletal disorders, falls, cancer, and neurological disorders.[206] Little is known about the mechanisms that may facilitate any protective effects of physical activity on the brain. One hypothesis suggests that age-related reduction in levels of growth factors such as brain-derived neurotrophic factor (BDNF) correlate with decline in hippocampal volume and elevated memory deficits. Evidence

suggests aerobic exercise in older adults can increase BDNF levels, increase the size of the anterior hippocampus, improve spatial memory, and increase plasticity of brain networks (frontal executive, fronto-parietal, primary motor cortex, and primary auditory cortex).[206-209] This response to exercise is thought to be mediated by insulin-like growth factor (IGF-1) because blood levels and brain uptake of IGF-1 are elevated with exercise, and it is the first biochemical pathway shown to influence brain aging.[206,210,211]

3.6. Summary

Demographic, genetic, vascular, and behavioral risk factors implicated in dementia heavily overlap to those implicated in CVD and vary in strengths of their associations (**Table 3.3**). A recent study assessing the association between the American Heart Association's Life's Simple 7 metrics of smoking, physical activity measures, diet measure, BMI, total cholesterol, blood pressure, and fasting plasma glucose found that risk of dementia decreased by approximately 10% with each metric at recommended or ideal levels [hazard ratio (95% CI): 0.90 (0.84, 0.97) per additional metric].[212] An optimal Life's Simple 7 score was also associated with slower rate of global cognitive decline.[212] In fact, over half the burden of AD (the most common cause of dementia) has been attributed to modifiable risk factors including diabetes, hypertension, obesity, physical inactivity, depression, smoking, and low educational attainment.[213] In the U.S., these risk factors have a combined population attributable risk of 52.7% (95% CI: 25.9%, 72.8%) reduced to 30.6% (95% CI: 14.5%, 45.3%) when adjusted for lack of independence between risk factors.[213] The CAIDE Dementia Risk Score was developed using data from the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) Study in Finland and identified age, sex, education, systolic blood pressure, BMI, total cholesterol, physical

activity, and *ApoE4* carrier status as significant predictors (AUC: 0.78 and 95% CI: 0.72, 0.84) of 20-year risk of cognitive impairment and decline.[214] Because there is no known treatment for dementia, identifying modifiable risk factors for individual intervention, such as treatment for hypertension and hypercholesterolemia, is important. Further, educational public health interventions could be used to encourage physical activity and Mediterranean-like diets, while policy and environmental public health interventions could be used to reduce structural discrimination that leads to systemic disadvantage for minorities and those with low SES. In sum, MCI and dementia prevention will have to focus on primordial and primary prevention strategies.

Table 3. 3. Summary of risk factors for MCI and dementia and clinical trial evidence, direction of risk, and strength of association

Risk Factor	Clinical Trial Evidence Supporting Improved Cognition through Intervention	Strength of Association
Advanced Age	-	Strong
***ApoE4* carrier**	-	
Hypertension[a]	SHEP[215], Syst-Eur[216], PROGRESS[217], SCOPE[218]	
African American or Hispanic	-	
Obesity	None	Moderate
Physical Inactivity[b]	FABS[219], FINGER[220], Train the Brain[221], DAPA[222]	
Diet (Mediterranean, DASH, or MIND reduce risk)[c]	FINGER[220], PREDIMED[223], Wardle, et al.[224]	
Diabetes	None	
Hypercholesteremia[d]	ADCS[225], LEADe[226], ADCLT[227]	
Female Sex	-	Weak
Tobacco Smoking	None	

Moderate Alcohol Consumption (reduces risk)	None	

[a] Antihypertensive medication given to patients with hypertension
[b] Physical activity intervention included aerobic exercise or a combination of aerobic and anaerobic exercise
[c] FINGER Trial: Diet intervention based on Finnish Nutrition Recommendations; PREDIMED Trial: Diet intervention based on a Mediterranean diet; Wardle, et al.: Diet intervention based on a low-fat diet arm and a Mediterranean diet arm
[d] Trial interventions with statins was conducted on those with mild to moderate Alzheimer's disease and normal blood cholesterol levels

CHAPTER 4. STUDY DESIGN: ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY COHORT

4.1. Overview

Funded by the National Heart, Lung, and Blood Institute (NHLBI), the Atherosclerosis Risk in Communities (ARIC) study cohort was developed as a prospective epidemiologic investigation of the etiology and natural history of atherosclerosis in four U.S. communities.[228] Since it began in 1987, the study has expanded to include research of the heart, kidneys, and brain in addition to cardiovascular risk factors, medical care, and disease by race, gender, location, and time.[229] The focus of this dissertation is dementia and MCI using neurocognitive data from the ARIC Neurocognitive Study (ARIC-NCS). ARIC-NCS is an ancillary study that was integrated into regular ARIC clinic examinations as a way to determine the prevalence of cognitive impairments and their association with mid-life vascular risk factors as well as track cognitive change and identify genetic markers and cerebral imaging features of dementia and MCI.

4.2. Study Design and Population

ARIC is a multi-center prospective cohort study that enrolled 15,792 participants between 1987 and 1989.[229] The study has completed six visits, visit 1 (1987-89), visit 2 (1990-92), visit 3 (1993-95), visit 4 (1996-98), visit 5 (2011-13), visit 6 (2016-17), with visit 7 ongoing (2018-19).[229] Predominantly white (73%) and African American (27%) participants ages 45-64 were enrolled using probability sampling from defined populations in Forsyth County, North Carolina, Jackson, Mississippi, the northwestern suburbs of Minneapolis, Minnesota, and Washington County, Maryland.[228] Only African

American participants were recruited from Jackson, while the participants from Minneapolis and Washington County were overwhelmingly white.[228] Forsyth County included both whites and African Americans.[228]

After IRB approval and informed consent, participants were invited to attend the seven clinic visits, and various ancillary studies, from 1987 through the present (**Figure 4.1 and Table 4.1**). These visits typically lasted 3-6 hours and included comprehensive physical examinations, interviews on social, demographic, and medical histories, and imaging. Of note, if a participant could not attend a clinic visit, they were not censored, but had the opportunity to participate in subsequent exams.[230] To encourage continued attendance and gather data between visits, annual or semi-annual follow-up calls have been conducted since ARIC began.[229]

Figure 4. 1. ARIC visits and follow-up calls from 1987-present, adapted from the ARIC website[229]

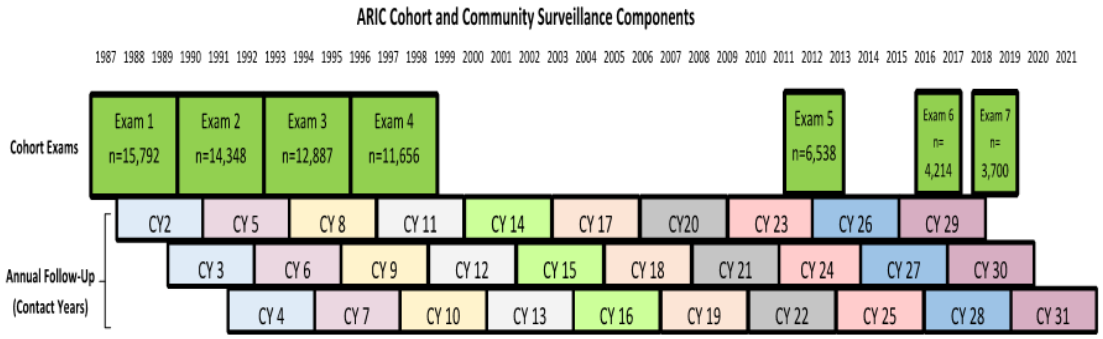


Table 4. 1. Summary of ARIC-NCS clinic exams and components from 1987-present[229]

ARIC & Neurocognitive (NCS) Design Overview							
Exam	**ARIC Initial Contract Visits**				**ARIC-NCS Visits**		
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4 ***	**Visit 5***	**Visit 6**	**Visit 7***
Calendar year	1987-1989	1990-1992	1993-1995	1996-1998	2011-2013	2016-2017	2018-2019
Follow-up, y	0	3	6	9	25	30	32
Age range, y	45-64	48-67	51-70	54-73	71-90	75-94	77-97
Cohort Size							
Alive, n	15,792	15,305	14,821	14,351	10,152	8,403	6,895
Surveillance (CHD, Dementia), n				12,928	9420	7353	6206
Seen in clinic, n	15,792	14,348	12,887	11,656	6,538	4,003	~3,450
Vascular Risk Factors and Markers							
Completed	X	X	X	X	X	X	X
Imaging							
Systemic	Carotid IMT	Carotid IMT	Carotid IMT	Carotid IMT	Echo, PWV	PWV	Echo, [Ocular CT, CAC]
Brain MRI			1,929		1,950+	~1,000	
Brain PET (amyloid)					346	~315	
Cognitive Function							
Core tests		X	X	X	X	X	X
Full battery (1 hour)					X	X	X
Informant interviews					X	X	X

4.3. Neurocognitive Study (NCS)

During visit 2 (1990-92), a 3-instrument cognitive battery was introduced to assess cognitive function.[231] The Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST), and Word Fluency Test (WFT) were administered in a quiet room in a standardized order by trained interviewers (**Table 4.2**).[231,232] To ensure

consistent administration, interviewer performance was monitored by taping and reviewing a sample of testing sessions as well as confirming no systematic differences in mean test scores administered by different interviewers.[231] These three tests were administered at visits 2, 4, 5, 6, and 7; however, at visit 5, the ARIC-NCS battery was expanded to include the Logical Memory Test, Incidental Learning Test, Animal Naming Test, Boston Naming Test, Trail Making Test, Digit Span Backwards Test, Smell Test, and Mini-Mental State Exam (MMSE) (**Table 4.2**) using standardized protocols.[232] For comparison, test scores (with the exception of the MMSE) were converted to z-scores by subtracting the test mean from each participant's individual score and dividing by the test standard deviation.[229] For longitudinal comparisons, z-scores were standardized to visit 2 for the original 3-instrument battery (DWRT, DSST, WFT) or visit 5 for the newly added cognitive tests.[229]

Table 4. 2. Description of cognitive tests administered as part of ARIC-NCS, 1990-2017[229,231,232]

Cognitive Test	Visits Administered	Cognitive Domain	Overview of Test
Delayed Word Recall	2, 4, 5, 6, and 7	Memory	Participants are presented with 10 nouns and asked to use them in a sentence. After a 5-minute delay, participants were given 60 seconds to recall the 10 words.
Digit Symbol Substitution	2, 4, 5, 6, and 7	Sustained Attention and Processing Speed	This test was adapted from the Wechsler Adult Intelligence Scale-revised (WAIS-R). Participants were asked to translate numbers to symbols using a key.
Word Fluency	2, 4, 5, 6, and 7	Language and Verbal Fluency	Participants are asked to generate as many words (no proper nouns) as

			they can beginning with the letters F, A, and S. They are given 60 seconds for each word.
Logical Memory	5, 6, and 7	Memory	Participants are read two short stories and asked to recall the details after each reading. A filled delay of 20-minutes occurs, after which, participants are asked to recall the details of the two stories.
Incidental Learning	5, 6, and 7	Memory	After completion of the DSST, participants are asked to remember the symbols and corresponding digit-symbol pairs. (Participants are not asked to memorize the digit-symbol pairs for DSST)
Animal Naming	5, 6, and 7	Language and Verbal Fluency	Participants are asked to name as many animals as they can in 60 seconds.
Boston Naming	5, 6, and 7	Language and Verbal Fluency	Participants are shown 30 line drawings, on at a time, and given 20 seconds to name the object in each drawing.
Trail Making	5, 6, and 7	Sustained Attention and Processing Speed	This test has two parts, A and B. In part A, participants are given numbered dots "1-25" dispersed around a page and must draw lines connecting the numbers sequentially. In part B, participants are given numbers "1-13" and letters "A-L" and asked to draw lines connecting the number and letters sequentially, but alternating with a number then letter.
Digit Span Backwards	5, 6, and 7	Sustained Attention and Processing Speed	The interviewer reads a series of numbers increasing in length from 2-7 digits each. Participants are asked to repeat each number series backwards.
Smell Test	5, 6, and 7	Sensory and Motor Function	Participants are presented with 12 odorous pens and asked to identify the smell in a multiple-choice format.

Mini-Mental State Exam	5, 6, and 7	All 5 domains	The MMSE was developed to be a fast, standardized screening instrument for a number of cognitive impairments.

After the cognitive battery, participants meeting the following criteria were invited to participate in the second stage of the ARIC-NCS exam: 1) low score on the MMSE (defined as an MMSE score of <21 for whites or <19 for African Americans) or 2) a low cognitive test z-score (defined as falling at or below the worst 20th percentile of change or below the worst 10th percentile of score on at least one test). In addition, a small proportion (approximately 10%) of cognitively "normal" participants were randomly chosen to participate in the second stage as a comparative sample. Informants were used to provide information on the behaviors and functional ability if an ARIC participant was suspected of being cognitively impaired. This portion of the exam also included physical and neurological examinations where participants were given the Unified Parkinson's Rating Scale (used to assess motor and non-motor symptoms of PD), the Clinical Dementia Rating (CDR) subject (as well as CDR informant if an informant was present), and the Hachinski Ischemic Scale (a questionnaire used to diagnose VaD).[233,234] In addition, retinal photographs were taken, a neuropsychiatry inventory was taken, neurological and dementia history were collected, and participants were asked about their neurological family history. Finally, stage two attendees were asked to provide informed consent to participate in the final stage of the ARIC-NCS exam, which included cerebral magnetic resonance imaging (MRI) from which primary and secondary etiology was identified. Of note, at visits 6 and 7, participants suspected of being

cognitively impaired underwent a second stage of testing, but, unlike visit 5, this portion of the exam did not included the Unified Parkinson's Rating Scale, Hachinski Ischemic Scale, nor was etiology of suspected dementia cases identified.

Dementia and MCI Classifications and Adjudication

Based on the data collected through ARIC-NCS, annual/semi-annual follow-up calls, and surveillance of hospital discharge codes and state and national death records, MCI and dementia cases were identified based on the quality of data available (**Table 4.3 and Table 4.4**). The first level, involved adjudicated cases identified during ARIC-NCS at visits 5 (2011-13) or 6 (2016-17) and included the longitudinal cognitive assessments from visits 2, 4, 5, and 6.[83] A standardized definition for dementia and MCI was used for level 1 classification to generate computer algorithmic diagnoses; a panel of physicians and neuropsychologists then reviewed each case of suspected cognitive impairment as well as a random sample of cognitively normal participants.[83]

Level 2 dementia and MCI included cases identified in level 1 as well as participants who did not attend ARIC-NCS and were identified through the modified telephone interview for cognitive status (TICSm), informant telephone interview using a modified version of the Clinical Dementia Rating (CDR: Informant), and a random sample used to correct for missed cases.[83] Telephone screening began in 2011 and primarily identified cases during visits 5 and 6 among participants who could not attend the ARIC-NCS visit or a home visit.[83] Finally, level 3 included levels 1 and 2 as well as participants identified through surveillance for hospitalization discharge codes (ICD-9 or ICD-10) or death certificate codes related to dementia. These cases were primarily identified prior to visit 5.[83] Overall, MCI cases could only be identified among

participants who attended ARIC-NCS visits (starting at visit 5), whereas dementia cases were identified throughout the ARIC follow-up using various methods.

Due to the varying levels of MCI and dementia cases, separate analyses were run using two definitions of dementia and MCI outcomes. The first definition included incident dementia cases from visits 1 through 5 or 6 (level 3 criteria). The second definition only included adjudicated dementia and MCI cases (level 1 criteria), which were identified at ARIC visits 5 and 6 and included information on etiology (AD, CeVD, LBD or unknown) determined from participants' brain MRIs at visit 5).

Table 4. 3. Summary of dementia and MCI cases identified in ARIC, 1987-2016

	Level 1	**Level 2 (includes Level 1)**	**Level 3 (includes Level 1 and 2)**
Death or Hospital Code (prior to Visit 5)			756
Visit 5 MCI	1366		
Visit 5 Dementia	341	1014	1566
Visit 6 MCI	759		
Visit 6 Dementia	585	1778	2702

Table 4. 4. Summary of etiology of adjudicated dementia and MCI cases (Level 1) at ARIC Visit 5, 2011-13

Etiology	Dementia (%)	MCI (%)
Pure AD	72 (22.3)	425 (37.0)
AD with CeVD	78 (24.2)	299 (26.0)
AD with LBD	33 (10.2)	100 (8.7)
AD with other	14 (4.3)	82 (7.1)
Total Primary AD	**197 (61.0)**	**906 (78.8)**
Pure CeVD	8 (2.5)	14 (1.2)
CeVD with AD	63 (19.5)	110 (9.6)
CeVD with LBD	10 (3.1)	9 (0.8)
CeVD with other	0 (0.0)	2 (0.2)
Total Primary CeVD	**81 (25.1)**	**135 (11.8)**
Other	19 (5.9)	69 (6.0)
Unknown	26 (8.1)	40 (3.5)
Total	**323**	**1150**

CHAPTER 5. MANUSCRIPT 1: LIFE COURSE SOCIOECONOMIC STATUS AND RISK OF DEMENTIA AND MCI

5.1. Overview

Introduction

The biological and behavioral risk factors of Alzheimer's disease and related dementias may be influenced by life course socioeconomic status (LC-SES). Using the Atherosclerosis Risk in Communities Study (ARIC), we assessed the associations of individual- and neighborhood-level SES across the lifespan with risk of incident dementia.

Methods

ARIC is a prospective cohort study of white and African American adults initiated in 1987-89. Individual- and neighborhood-level SES at various life epochs was assessed via a telephone questionnaire in 2001-02 and summarized as a LC-SES score. Dementia diagnosis through 2013 was ascertained using cognitive examinations, telephone interviews and hospital and death certificate codes. Cox regression was used to examine the relation of individual LC-SES and neighborhood LC-SES with incident dementia in race-specific models.

Results

The 12,599 participants included in the analysis were 75% white and 25% African American with a mean age of 54 ± 5.7 years. A total 1,707 cases of incident dementia occurred over a median follow-up of 24 years. After adjustment, each standard deviation (SD) greater individual LC-SES score was associated with a 14% (HR (95% CI): 0.86 (0.81, 0.92)) lower risk of dementia in whites and a 21% (HR (95% CI): 0.79 (0.71,

0.87)) lower risk in African Americans. When education was taken out of the individual LC-SES score, an SD greater individual LC-SES score was associated with a 10% (HR (95% CI): 0.90 (0.84, 0.97)) lower dementia risk in whites and 15% (HR (95% CI): 0.85 (0.76, 0.96)) lower risk in African Americans. Neighborhood LC-SES was not associated with dementia for either group.

Conclusion

Individual LC-SES is an important risk factor for incident dementia in whites and blacks, whereas cumulative neighborhood LC-SES is not. Future research is needed to identify critical periods over the life course where SES factors have the greatest effect on dementia risk and further examination of neighborhood-level SES using a LC-SES model is needed.

5.2. Background

There is increasing evidence that chronic diseases in older adults are caused by a complex accumulation and interaction of lifetime exposures.[235] Socioeconomic status (SES), also referred to as socioeconomic position, reflects the "social and economic factors that influence which positions individuals or groups will hold within the structure of a society."[48] SES collected across the life course can be used to quantify the accumulation of risk factors over the progression of life epochs.[236,237] Life epochs can be measured at the individual- and neighborhood-levels and generally include childhood, young adulthood, active professional life, and older adulthood (**Table 5.1**). Life course SES (LC-SES) models hypothesize that life epochs do not occur independently of one another, but events occurring during these periods can accumulate and interact leading to increased risk of chronic disease over a lifetime.[236,237]

Table 5. 1. Examples of SES measures at different life epochs.[236,237]

Life Epoch	Example SES Measures
Childhood	Birthweight, Parent's education, Parent's occupation, Household income, Household conditions, Overcrowding
Young Adulthood	Education
Active Professional Life	Occupation, Household income, Employment status, Wealth, Partner's SES, Household conditions
Retirement/Older adulthood	Household income, Wealth/deprivation, Household conditions

SES is an especially crucial component in the development of dementia due to the importance of cognitive reserve.[36] The concept of cognitive reserve reflects the observation that cognitive function does not always correspond to observable brain pathology.[36] While there is no standard measure of cognitive reserve, measures of SES and education are widely used proxies, because they signify beneficial environmental exposures.[36] Further, Alzheimer's disease and related dementias have biological and behavioral risk factors whose associations may be confounded or modified by SES.[238] For instance, confounding of associations between mid-life vascular risk factors and incident dementia by SES may not be eliminated by adjustment for mid- or late-life SES alone.[124,239,240] We are interested in characterizing the association between LC-SES and dementia at the individual and neighborhood levels, assessing separately the potential effects of economic versus educational dimensions of SES.

A number of studies have found a significant inverse association between individual-level SES and cognitive decline and dementia (**Table A.1**).[55,102,129,241-252] However, the methods used to measure SES have varied widely among studies, and many relied on SES measured only during middle age or later adulthood. Taking a life course approach to understanding dementia is important in order to better classify risk factors that may have cumulative effects on disease risk but are masked (partially or fully) by examining one life epoch only.[237,239] Among studies that have assessed LC-SES and cognitive function, very few have measured both individual and neighborhood-level SES. Neighborhood SES adds context to individual SES and may independently influence dementia risk through physical and social characteristics of neighborhoods that contribute to disparities and influence individual behaviors and stress levels.[253]

Using the African American and white participants of the ARIC-NCS cohort, we hypothesized that higher LC-SES was inversely associated with risk of incident dementia, with both higher individual- and neighborhood-level LC-SES independently contributing to lower dementia risk. We also hypothesized economic measures of LC-SES would be associated with lower risk of dementia independent of education. In addition to evaluating LC-SES, we report associations of SES at three life epochs (i.e. childhood, young adulthood, middle/older adulthood) with incident dementia risk.

5.3. Methods

The ARIC-NCS cohort was used to prospectively examine the association between cumulative LC-SES (childhood through older adulthood) and dementia outcomes from visit 1 (1987-89) through visit 5 (2011-13). In addition, participants were followed continuously for hospitalizations and mortality. For our analysis, incident dementia was ascertained from visit 1 (1987-89) through visit 5 (2011-13). Participants were excluded if they were not white or African American or African Americans from Maryland or Minnesota (n=93), they did not participate in the LC-SES ancillary study (2001-2002) (n=2,626), they developed dementia before the questionnaire was administered (n=141), or they were missing baseline covariates (n=323). After exclusions, 12,599 participants were included in the analysis.

Individual- and neighborhood-level LC-SES data were obtained using questionnaires administered over the phone in 2001-02. Questions evaluated SES factors including education, occupation, occupational role, home ownership, income, and wealth over three life epochs: childhood (approximately age 10 – SES pertained to parental SES), young adulthood (approximately age 30), and middle/older adulthood (ages 45-64

when participants entered the ARIC study) (**Table 5.2**). Cumulative individual-level LC-SES scores were created by summarizing SES variables related to the three epochs following an approach developed by Carson, et al. 2007.[254] For individual LC-SES, variables related to each epoch had a range of possible values between 0 (lowest SES) and 5 (highest SES).[254] These epoch scores were summed to get a cumulative individual LC-SES score ranging between 0 and 15.[254] We also assessed cumulative individual LC-SES without education by removing individual level educational attainment from the score (keeping in parental education). We then adjusted for educational attainment separately in the models to determine whether economic factors of SES were associated with dementia independent of individual educational attainment.

Neighborhood-level LC-SES variables were identified in a factor analysis from available census data covering the three life epochs and representing several decades.[254] Z-scores were calculated by subtracting individual neighborhood SES variable measures (derived from census tract data at each epoch) from the group mean and dividing by the standard deviation. Because of the potential impact of segregation on SES and different racial distributions across the four ARIC field centers, race-specific z-scores were obtained for each census variable and summed to develop a summary *z* score for cumulative neighborhood LC-SES where a higher *z* score indicated higher SES.[254] We created race-specific, distribution-based tertiles of the cumulative neighborhood-level LC-SES score for analysis.

Table 5. 2. Individual and neighborhood life course socioeconomic factors and scoring adapted from Carson AP, 2007[254]

Individual LC-SES		**Life Epoch**	**Neighborhood LC-SES**	
Variable	**Score**		**Variable**	**Z-Score[a]**
Parental Education	<8th grade = 0	**Childhood (age 10)**	Adult Education	Proportion with H.S. or College degree
	8th grade = 1			
	>8th grade = 2			
Parental Occupation	Manual = 0		Adult Occupational Role	Proportion with managerial roles
	Non-manual = 1			
Parental Occupational Role	Non-managerial = 0		Dwellings Occupied by Owner	Proportion of homes occupied by owner
	Managerial = 1			
Parental Home Ownership	Rent or other = 0		Log Median Home Value	Median value of homes
	Own home = 1			
Education	<High school = 0	**Young Adulthood (age 30 years)**	Adult Education	Proportion with H.S. or College degree
	High school = 1			
	>High school = 2			
Occupation	Manual = 0		Adult Occupational Role	Proportion with managerial roles
	Non-manual = 1			
Occupational Role	Non-managerial = 0		Log Median Income	Median family income
	Managerial = 1			
Home Ownership	Rent or other = 0		Dwellings Occupied by Owner	Proportion of homes occupied by owner
	Own home = 1			
			Log Median Home Value	Median value of homes
Income	<$25,000 = 0	**Middle/Older Adulthood (age 45-64 years)**	Adult Education	Proportion with H.S. or College degree
	$25-34,999 = 1			
	≥$35,000 = 2			
Occupation	Manual = 0		Adult Occupational Role	Proportion with managerial roles
	Non-manual = 1			

Occupational Role	Non-managerial = 0		Log Median Income	Median family income
	Managerial = 1			
Home Ownership	Rent or other = 0		Dwellings Occupied by Owner	Proportion of homes occupied by owner
	Own home = 1			
			Median Home Value	Median value of homes
			Households with Passive Income	Proportion with income besides wages/salary

[a]Values for z-scores derived from census tract data representing the location a participant reported living during each epoch

Covariate information was collected at baseline (visit 1; 1987-1989) and included age, sex, *ApoE4*, body mass index (BMI), tobacco smoking status, hypertension, diabetes, alcohol drinking status, HDL cholesterol, and total cholesterol. BMI was calculated from measured weight and height (kg/m^2). Hypertension was defined as having a systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 90 mm Hg, or self-report of antihypertensive medication use. Diabetes was defined as non-fasting serum glucose $\geq$ 200 mg/dL, fasting glucose $\geq$ 126 mg/dL, self-report of diabetes diagnosis from a physician, or report of taking medication for diabetes or high blood sugar.

Dementia and MCI cases were identified from ARIC-NCS clinic examinations conducted at visit 5, surveillance of hospital and death certificate codes, and annual and semi-annual telephone-based cognitive assessments. Methods are described in detail in Chapter 4. Our primary analysis included all incident dementia cases available in ARIC between visits 1 and 5. This included cases identified using surveillance of hospital and death records, informant interviews for deceased participants suspected to have had

dementia, annual and semi-annual telephone follow-up calls with the administration of the modified telephone interview for cognitive status (TICSm) to participants who were alive and did not attend visits 5, and adjudicated dementia identified in ARIC-NCS. We conducted a secondary analysis using only adjudicated dementia and MCI cases identified in ARIC-NCS at visit 5. Dementia surveillance is believed to be relatively complete, but because analyses of MCI required attendance at visit 5, there was likely informative censoring of participants over the follow-up period.[83] To account for this potential selection bias, we used inverse probability of attrition weights (IPAW) in our analyses of adjudicated cases.[83,255]

Statistical Analysis

Individual- and neighborhood-level LC-SES measures were ascertained retrospectively causing several variables to have missing data. The amount of missing data for individual LC-SES variables was around 14%. For neighborhood LC-SES, the amount of missing data was approximately 25% and primarily due to changes in census questions over several decades. To address this issue, we used multiple imputation by chained equations (MICE)[256] to impute individual- and neighborhood- level LC-SES scores. We created 10 sets of imputations to obtain a series of data points taking into account within- and between-variance of each imputation. We then used the average of the multiple imputed values for analysis.

We described prevalences and means of baseline covariates and individual LC-SES. Incidence rates of dementia between visits 1 (1987-89) and 5 (2011-13) stratified by life epoch (childhood, young adulthood, and middle/older adulthood) and race-specific, distribution-based individual LC-SES tertiles were estimated using Poisson regression.

Cox regression was used to assess the association between cumulative LC-SES and risk of dementia. We modeled LC-SES in three ways: i) cumulative individual-level LC-SES score, ii) cumulative individual-level LC-SES score after removing education and adjusting for education separately in the model, and iii) cumulative neighborhood LC-SES score with adjustment for cumulative individual LC-SES score separately in the model. To account for clustering of individual-level SES within neighborhood, we also ran a Cox regression with a random effect for neighborhood-level LC-SES. This design effect was of small magnitude and did not visibly affect individual LC-SES estimates so is not presented.

Two models were tested for each of the Cox analyses. Model 1 was adjusted for age, sex, and *ApoE4* status. Model 2 was adjusted for model 1 covariates plus baseline BMI, hypertension, diabetes, HDL cholesterol, total cholesterol, alcohol drinking status, and tobacco smoking status. We used a restricted cubic spline model to investigate the continuous non-linear relation between cumulative individual-level LC-SES and hazard of dementia with knots specified at the 5^{th}, 50^{th}, and 95^{th} percentiles. To test the proportional hazards assumption, we included an interaction term between each LC-SES measure and log follow-up time, and the assumption was met. The analysis was re-run without applying MICE procedures to impute missing LC-SES data and results were similar.

As a secondary analysis, we used relative risk regression with a Poisson distribution, log link, and inverse probability of attrition weights (IPAW) to assess the association between LC-SES modeled three ways and risk of adjudicated dementia and MCI at visit 5. However, adjudicated dementia and MCI cases could only be identified in

participants that attended visit 5. These participants were generally healthier, had higher SES, and were more likely to be white than participants that refused to attend or died prior to this exam likely biasing the analyses.[230] Because of these issues with bias, results of our adjudicated analyses are presented in **Tables A.2 and A.3** of the Appendix and results presented here only discuss risk of incident dementia.

All statistical analysis were conducted using SAS 9.4 (SAS Inc., Cary, NC).

5.4. Results

Among the 12,599 participants included in the analysis, 9,675 (75%) were white and 3,248 (25%) were African American with a mean age of 54 ± 6 years at baseline (1987-89). African Americans at baseline were more likely than whites to carry the *APOE ε4* allele, have not attained high school completion, have a family income of less than $25,000, smoke tobacco, be non-drinkers, have a higher BMI and HDL cholesterol, and have prevalent hypertension and diabetes (**Table 5.3**). African Americans also had a lower cumulative individual-level LC-SES score than did whites (**Table 5.3**).

A total 1,707 cases of incident dementia occurred (1,170 cases in whites and 537 cases in African Americans) over a median follow-up of 24.3 years. In both African Americans and whites after adjustment for age, sex, and *ApoE4* status, being in the lowest race-specific tertile of individual LC-SES at each life epoch (childhood, young adulthood, and middle/older adulthood) was associated with the highest incidence of dementia, followed by the middle SES tertile, and then the highest SES tertile (**Figure 5.1**). In both races, these differences in the incidence rates of dementia by individual SES tertile were statistically significant for young and middle/older adulthood, but not for childhood. Among whites, low young adulthood SES was associated with a 36% [RR

(95% CI): 1.36 (1.18, 1.56)] greater dementia risk compared to high young adult SES. Low middle/older adulthood SES was associated with a 49% [RR (95% CI): 1.49 (1.25, 1.76)] greater dementia risk compared to high SES. Among African Americans, low young adulthood SES was associated with a 41% [RR (95% CI): 1.41 (1.16, 1.71)] greater and low middle/older adulthood SES was associated with a 53% [RR (95% CI): 1.53 (1.23, 1.90)] greater dementia risk compared to high SES tertiles for each epoch respectively. There was also a statistically significant interaction between SES tertile and race for each life epoch, indicating a stronger association between low SES and dementia in African Americans compared to whites.

We also assessed the race-specific associations between dementia and cumulative individual LC-SES score as a continuous variable calculating HRs per increment of the pooled standard deviation (**Table 5.4**). Among whites, after model 1 adjustments, a standard deviation greater cumulative individual LC-SES score was associated with a 17% lower risk of dementia [HR (95% CI): 0.83 (0.77, 0.88)]. The association was slightly attenuated after additional model 2 adjustments [HR (95% CI): 0.86 (0.81, 0.92)]. Among African Americans, a standard deviation greater cumulative individual LC-SES score was associated with a 23% lower risk of dementia [HR (95% CI): 0.77 (0.70, 0.85)] after model 1 adjustments and HR (95% CI): 0.79 (0.71, 0.87) in model 2.

We then assessed the association between cumulative individual LC-SES score independent of individual educational attainment. Education was removed from the cumulative individual LC-SES score calculation (keeping parental education in the score) and adjusted for separately in the models (**Table 5.4**). For whites, a standard deviation greater individual LC-SES score without education was associated with a 12% lower risk

of dementia [HR (95% CI): 0.88 (0.82, 0.95)] that weakened slightly with model 2 adjustments [HR (95% CI): 0.90 (0.84, 0.97)]. In African Americans, a standard deviation increment of cumulative individual LC-SES score without education was associated with a 14% lower risk of dementia [HR (95% CI): 0.86 (0.77, 0.98)] after model 1 adjustment and HR (95% CI): 0.85 (0.76, 0.96) in model 2.

Using restricted cubic splines to assess the non-linear association between cumulative individual LC-SES score and risk of dementia, we found that in both whites and African Americans, the association between LC-SES score (with and without education) and risk of dementia was linear (**Figure 5.2**).

Finally, we examined the relationship between neighborhood-level cumulative LC-SES score in whites and African Americans (**Table 5.5**). After adjustments, including adjustment for cumulative individual-level LC-SES score, there were no statistically significant, independent associations between cumulative neighborhood-level LC-SES score and dementia after multivariable adjustment (Model 2 HR (95% CI): 1.00 (0.96, 1.04) in whites and 1.06 (1.00, 1.13) in African Americans).

5.5. Discussion

This prospective cohort study of community-dwelling African American and white adults followed for 24 years had three main findings. Higher individual-level LC-SES was associated in both whites and African Americans with moderately lower incidence of dementia; these associations were statistically significant for young adulthood and middle/older adulthood SES, and the pattern was similar for childhood SES though not statistically significant. After removing education from the individual-level LC-SES score and adjusting for educational attainment separately, a higher

individual LC-SES score was associated with lower risk of dementia, suggesting that measures of economic status (income, home ownership, and wealth) may be associated with incident dementia independent of education. Finally, in both whites and African Americans, there was no association between cumulative neighborhood-level LC-SES score and incident dementia independent of individual-level LC-SES score.

The results of this analysis suggest that low cumulative individual-level LC-SES is an important risk factor for dementia. While SES can change over the life course, an inverse association was seen with incident dementia at each life epoch. These findings corroborate previous studies of LC-SES in relation to cognitive decline or dementia, which found that, across the life course, markers of high SES were associated with lower risk of cognitive impairment in older adulthood.[55,102,129,244,249,251,257]

We also found that cumulative individual-level LC-SES was inversely associated with dementia independent of individual-level education. While education is an important indicator of SES and likely a proxy for cognitive reserve, our findings suggest that other (primarily economic) SES factors also contribute to the association between LC-SES and dementia. These results mirror what other studies of LC-SES have found: a statistically significant, albeit weaker than for education, association between economic factors and cognitive impairment independent of education.[55,244,251] In studies that used economic SES measures from middle or older adulthood only, results have been more mixed with some studies finding an association, [246,247,258] but most finding no association.[242,243,245,248] Efforts to reduce risk of dementia at the population level must address economic inequalities that are foundational to proximal causes of differences in dementia risk such as education.[259]

Finally, the lack of association between cumulative neighborhood-level LC-SES and dementia indicates that individual level factors may be more important than neighborhood factors in the causation of dementia. These findings corroborate Canadian and British cohort studies that found no association between neighborhood-level SES and risk of dementia, [246,258] but differ from a Korean study that found that higher neighborhood SES was associated with higher cognitive test scores.[252] However, all three of these studies assessed neighborhood-level factors in mid- or late-life. To our knowledge, ours is the only study of cumulative neighborhood-level LC-SES and dementia, making this a novel finding. Further examination of the relation between neighborhood SES and dementia is needed, particularly neighborhood-level LC-SES. In addition, there is evidence that neighborhood-level environmental factors related to SES, such as lead exposure and air pollution, increase dementia risk.[260-262]

Our study has several strengths including a large sample size and number of dementia cases, a long follow-up period, and the ability to incorporate SES over the entire life course. By not having to rely on mid- or late-life SES measures, we could account for SES over the entire latency period of dementia, which is believed to span multiple decades.[15] The LC-SES approach allowed for adjustment for the cumulative effect of SES, without making assumptions about relative importance of individual epochs. In addition, no studies have previously examined the relation between neighborhood level LC-SES and dementia or how neighborhood and individual LC-SES interact.

Despite our study's strengths, there are limitations to our analyses. Firstly, in the ascertainment of dementia cases, selection bias related to censoring and death over

follow-up may have occurred and distorted hazard ratio estimates. To reduce selection bias, the ARIC study used a variety of strategies to completely identify dementia cases among participants that did not attend every ARIC visit, including annual follow-up calls with telephone interviews for cognitive status and surveillance of hospitals and death certificate codes. Secondly, cognitive tests used to identify cognitive decline and dementia may lack convergent validity between race groups due to cultural biases and socioeconomic differences.[80,84] Race-specific analysis were conducted to minimize race-related differences in validity of cognitive testing that may be related to SES and cultural background. Further, by using race-specific analyses, we avoided issues of comparison and differences in attainable LC-SES over the lifetimes of whites and African Americans that would be inhibited by segregation and discrimination. However, there may still be issues of generalizability due to lack of geographic variability in ARIC, given that African Americans were from Mississippi and North Carolina while white participants were from Minnesota, Maryland, and North Carolina.

A third limitation was that individual and neighborhood LC-SES data relied on participants' knowledge and ability to remember, at mid-life, the conditions they experienced during childhood and early adulthood. While memory may not be precise, in measuring SES, the significance is in identifying where in the hierarchy of social position an individual fell relative to others like them. This means that precise measurement was not as important as relative knowledge of one's circumstances, which were not likely forgotten. A fourth limitation was that missing data, particularly within neighborhood-level LC-SES variables, required MICE methods, but a sensitivity analysis without the imputed values yielded similar results.

Our longitudinal analysis indicates that incident dementia is inversely associated with individual-level LC-SES whereas neighborhood-level LC-SES is not associated. Future research is needed to identify critical periods over the life course where SES factors have the greatest effect on dementia risk and might warrant targeted intervention that aims to enable social and economic opportunities. In addition, further examination of neighborhood-level SES factors using a LC-SES model is needed.

5.6. Tables and Figures

Table 5. 3. Baseline characteristics stratified by race, ARIC, 1987-89

Risk Factors	White	African American
	n = 9,570	**n = 3,029**
Age, mean	53.9 ± 5.6	52.9 ± 5.7
Men, %	45.6	35.7
***ApoE4* carriers, %**	26.3	39.0
Basic Education[a], %	15.4	38.0
Family Income < $25,000[b], %	14.4	53.5
Current Tobacco Smoker, %	21.8	26.2
Current Alcohol Drinker, %	65.7	31.2
BMI, kg/m^2	26.9 ± 4.8	29.8 ± 6.1
Hypertension[c], %	25.3	52.6
Diabetes[d], %	7.5	15.6
Total Cholesterol, mg/dL	214.2 ± 40.3	214.8 ± 44.7
HDL Cholesterol, mg/dL	51.1 ± 16.8	55.4 ± 17.1
Cumulative Individual LC-SES score[e], units	10.2 ± 2.5	7.5 ± 2.7

Mean ± Standard Deviation

[a]Based on self-report of some high school education or less at visit 1

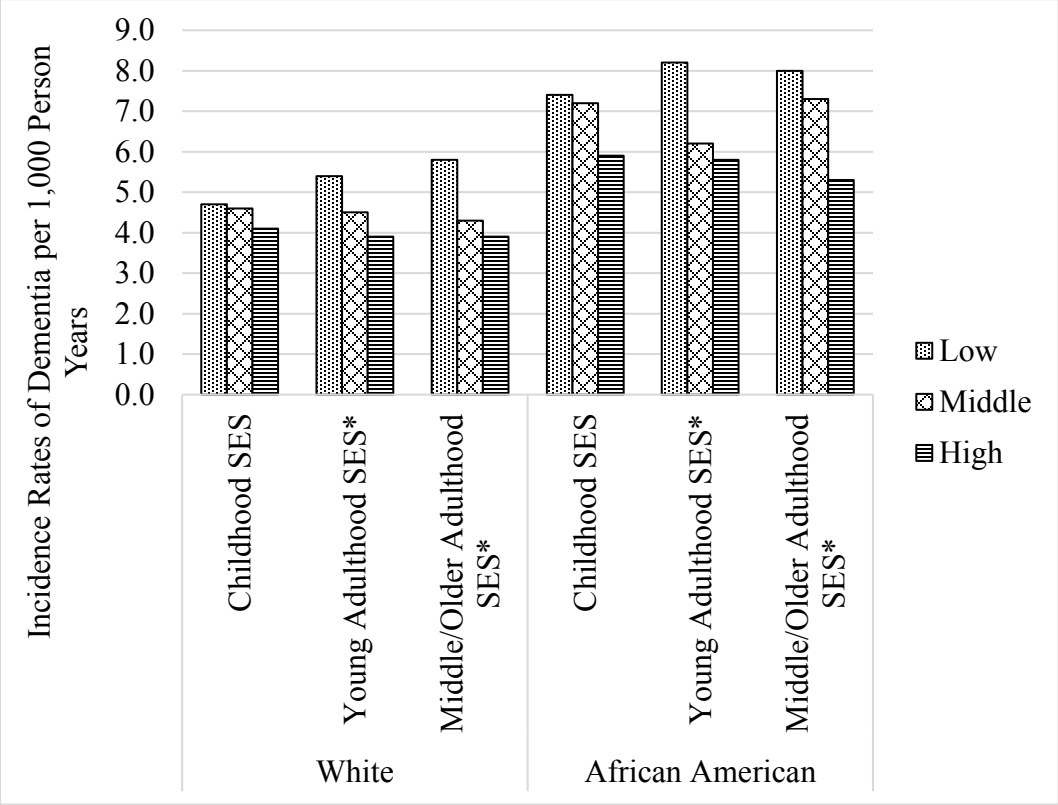
[b]Based on self-report of income at visit 1

[c]Defined as diastolic blood pressure ≥ 90 mm Hg, systolic blood pressure ≥ 140 mm Hg, or use of hypertensive medication

[d]Defined as non-fasting blood glucose ≥ 200 mg/dL, fasting blood glucose ≥ 126 mg/dL, self-report of diabetes, or reporting taking medication for diabetes or high blood sugar

[e]SES score based on sum of scores from three life epochs, childhood (age 10), young adulthood (age 30), and middle/older adulthood (ARIC baseline age 45-64)

Figure 5. 1. Incidence rates of dementia stratified by life epoch and race-specific individual SES tertiles (low, middle, and high), ARIC 1987-2013



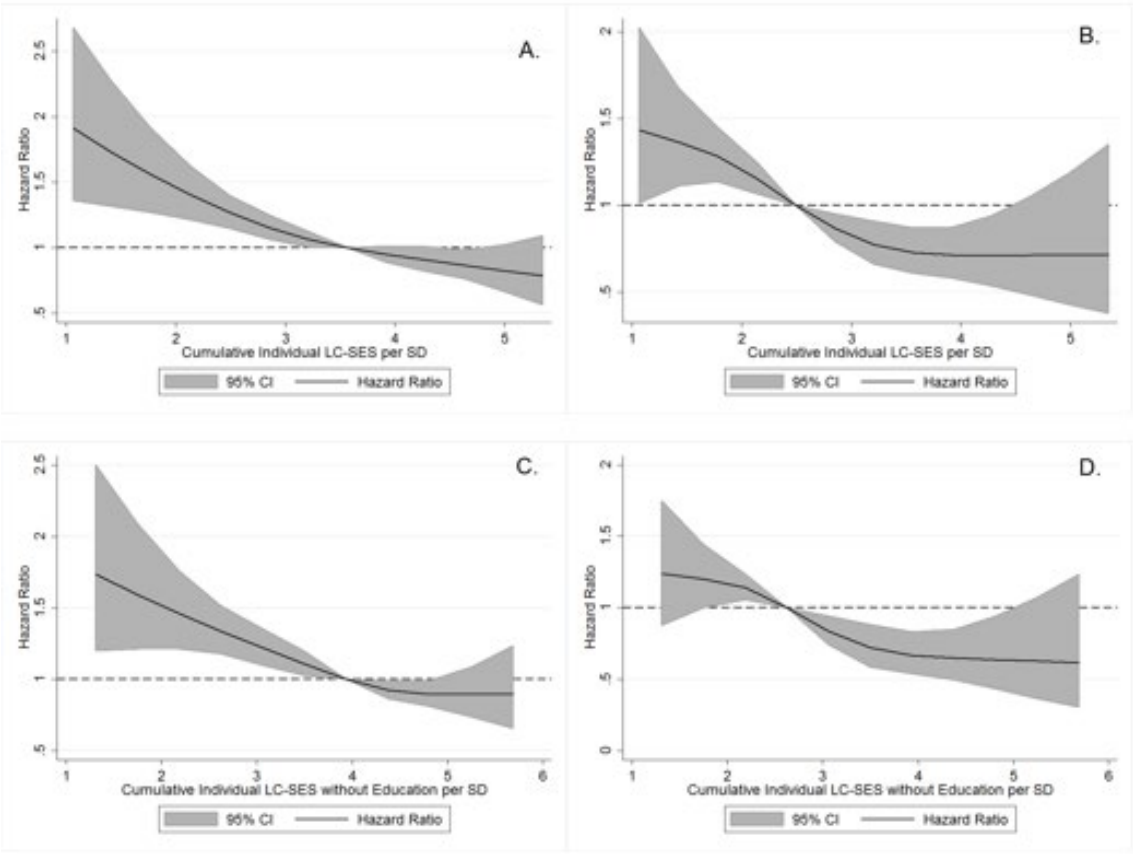
Adjusted for age, sex, and *ApoE4* status
*Statistically significant (p-value < 0.05) difference across life epoch SES tertiles
Childhood: age 10
Young adulthood: age 30
Middle/Older adulthood: ages 45-64

Table 5. 4. Hazard ratios (95% CI) of dementia per pooled standard deviation increment of cumulative individual LC-SES and cumulative individual LC-SES with education removed, ARIC 1987-2013

Cumulative Individual Life Course SES†			
		White	**African American**
		n total = 9,570	**n total = 3,029**
		n events = 1,170	**n events = 537**
Model 1 HR		0.83* (0.77, 0.88)	0.77* (0.70, 0.85)
Model 2 HR		0.86* (0.81, 0.92)	0.79* (0.71, 0.87)
Cumulative Individual Life Course SES with Education Adjusted Separately‡			
		White	**African American**
		n total = 9,674	**n total = 3,248**
		n events = 1,180	**n events = 572**
Model 1 HR	**LC-SES**	0.88* (0.82, 0.95)	0.86* (0.77, 0.98)
	Education		
	Some High School or Less	1 (Ref)	1 (Ref)
	High School Graduate	0.75 (0.64, 0.87)	0.74 (0.59, 0.92)
	Some College or More	0.74 (0.62, 0.88)	0.68 (0.52, 0.87)
Model 2 HR	**LC-SES**	0.90* (0.84, 0.97)	0.85* (0.76, 0.96)
	Education		
	Some High School or Less	1 (Ref)	1 (Ref)
	High School Graduate	0.80 (0.68, 0.93)	0.76 (0.61, 0.95)
	Some College or More	0.81 (0.68, 0.96)	0.74 (0.57, 0.96)

*Statistically significant (p-value < 0.05)
†Pooled standard deviation = 2.80
‡Pooled standard deviation = 2.29
Model 1: adjusted for age, sex, and *ApoE4* status
Model 2: adjusted for Model 1 + BMI, hypertension, diabetes, HDL cholesterol, total cholesterol, alcohol drinking status, tobacco smoking status

Figure 5. 2. Race-specific age, sex, and *ApoE4* status adjusted hazard ratio (95% CI) of incident dementia in relation to cumulative individual LC-SES with and without education, ARIC 1987-2013



A. Association between cumulative individual LC-SES and dementia in whites; **B.** Association between cumulative individual LC-SES and dementia in African Americans; **C.** Association between cumulative individual LC-SES without education and dementia in whites; **D.** Association between cumulative individual LC-SES without education and dementia in African Americans

*Analyzed using restricted cubic splines with knots at the 5th, 50th, and 95th percentiles of the individual LC-SES distribution.

Table 5. 5. Hazard ratios (95% CI) of dementia per standard deviation† increment of cumulative neighborhood LC-SES, ARIC 1987-2013

	White	**African American**
	n total = 9,570	**n total = 3,029**
	n events = 1,170	**n events = 537**
Model 1 HR	0.99 (0.95, 1.03)	1.05 (0.99, 1.12)
Model 2 HR	1.00 (0.96, 1.04)	1.06 (1.00, 1.13)

Abbreviation: HR: Hazard ratio; CI: Confidence interval
†Standard deviation = 1 for whites and African Americans
Model 1: adjusted for age, sex, *ApoE4* status, and cumulative individual LC-SES
Model 2: adjusted for Model 1 + BMI, hypertension, diabetes, HDL cholesterol, Total cholesterol, alcohol drinking status, tobacco smoking status

CHAPTER 6. MANUSCRIPT 2: ASSOCIATION OF ABNORMAL THYROID FUNCTION WITH DEMENTIA AND MCI

6.1. Overview

Background

Abnormal thyroid hormone levels (high or low) and autoimmunity from autoimmune thyroid disease (AITD) may increase dementia risk.

Methods

We examined the associations of thyroid dysfunction or possible AITD in 1990-92 with dementia through 2017 in the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study. Thyroid dysfunction (subclinical and overt hypo- or hyperthyroidism and euthyroidism) was categorized from serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) cut-points and AITD from anti-TPO antibody positivity. Dementia was identified primarily based on cognitive test performance, neuropsychological examinations, and clinician review of suspected cases. Additional cases of dementia were ascertained through telephone interviews or relevant hospital and death certificate codes. Cox regression with multivariable adjustment was used for analysis.

Results

After exclusions for missing data, 12,481 participants were included in the analysis (mean index exam age 57 ± 5.7 (44% male, 25% black), and 2,235 incident dementia cases were identified. AITD was not associated with dementia. Subclinical hypothyroidism was associated with a lower risk of dementia [HR (95% CI): 0.74 (0.60, 0.92] while overt hyperthyroidism was associated a higher risk of dementia [HR (95%

CI): 1.40 (1.02, 1.92)] compared to euthyroid participants. Participants with serum FT4 concentrations above the 95th percentile were at an increased risk of dementia compared to those in the middle 90% of FT4 [HR (95% CI): 1.23 (1.02, 1.48)].

Conclusions

Subclinical hypothyroidism was associated with reduced risk of dementia, whereas overt hyperthyroidism, particularly very elevated FT4, was associated with increased risk of dementia. The association between subclinical hypothyroidism and reduced risk of dementia cannot be explained, but may have been an artifact due to chance. By extrapolation, effective treatment of overt hyperthyroidism may modestly reduce dementia risk in older adults.

6.2. Background

The thyroid gland regulates metabolism in adults as part of the endocrine system.[263] Triiodothyronine (T3) and thyroxine (T4) represent "thyroid hormones" and are responsible for regulating cellular energy use affecting almost every organ in the body.[264,265] T3 and T4 are produced from dietary iodine absorbed through the small intestine and circulated to the thyroid where the iodine is concentrated, oxidized, and incorporated into thyroglobulin (Tg).[266] This process occurs in thyroid epithelial cells that form spherical structures called thyroid follicles.[264] Thyroid hormone is found in three states, stored as droplets within thyroid follicles, bound to carrier proteins circulating in the blood, or circulating freely (biologically active) as free T3 (FT3) and free T4 (FT4).[263] T4 comprises 90% of thyroid hormone, though T3 is more biologically active.[267]

A negative feedback loop regulates thyroid hormone activity. Thyrotropin-releasing hormone (TRH) produced in the hypothalamus stimulates the anterior pituitary gland to release thyroid-stimulating hormone (TSH).[267] TSH, in turn, stimulates release of FT3 and FT4 from the thyroid increasing levels of biologically active thyroid hormone.[267] This change in hormone levels increases metabolism of almost all body tissues which can result in increased body temperature, strengthened heartbeat, accelerated pulse, increased digestion of macronutrients, and activation of the nervous system.[263,267] The loop closes when biologically active T3 and T4 act back on the hypothalamus inhibiting further TRH release and shutting off the system.[267,268]

Thyroid dysfunction is quite common, especially among older adults, and can have serious clinical implications.[269] Thyroid function is generally classified as

euthyroidism (normal thyroid function), hypothyroidism (underactive thyroid), and hyperthyroidism or thyrotoxicosis (overactive thyroid). Elevated TSH and subnormal FT4 levels characterize overt hypothyroidism, while elevated TSH with normal FT4 characterize subclinical hypothyroidism.[270] Common symptoms if hypothyroidism include dry skin, hair loss, cold sensitivity, fatigue, muscle cramps, and bradycardia.[270] Subnormal TSH and elevated FT4 levels characterize overt hyperthyroidism, while subnormal TSH with normal FT4 characterize subclinical hyperthyroidism.[271] Hyperthyroidism symptoms include weight loss, osteoporosis, atrial fibrillation, muscle weakness, tremor and neuropsychiatric symptoms.[271] See **Table 6.1** for prevalence of thyroid disorders in the U.S.

Table 6. 1. Prevalence of thyroid dysfunction in those ages ≥12: NHANES III (1988-1994).[272]

Thyroid Disorder	Estimated Prevalence
Overt Hypothyroidism	0.3%
Subclinical Hypothyroidism	4.3%
Total Hypothyroidism	**4.6%**
Overt Hyperthyroidism	0.5%
Subclinical Hyperthyroidism	0.7%
Total Hyperthyroidism	**1.2%**
Total Disorder	**5.8%**

Thyroid dysfunction is more prevalent in women compared to men and among whites than African Americans.[272] Further, average TSH levels and prevalence of anti-

thyroid antibodies, indicators of autoimmune thyroid disorder, are higher in women compared to men (a disparity that increases with age) and higher among whites than African Americans.[272] While thyroid dysfunction is common, most cases are subclinical.

In iodine-replete countries like the U.S., autoimmune thyroid disease (AITD) is the most common cause of thyroid dysfunction with an estimated prevalence of 5%.[273] AITD is caused by an immune attack on the thyroid and results in infiltration of the thyroid tissue by lymphocytes.[273] A combination of genetic susceptibility and environmental factors, including radiation, smoking, infection, stress, and drugs, can trigger the autoimmune response.[273,274] The two main clinical presentations of AITD are Grave's disease (GD), which presents clinically as hyperthyroidism, and Hashimoto's thyroiditis (HT), which presents clinically as hypothyroidism.[273] All forms of AITD are associated with the presence of serum thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies, though the presence of antibodies does not necessitate disease.[275,276] Anti-TPO antibodies are more common and a stronger indicator of thyroid disease than anti-Tg antibodies.[276] Anti-TPO antibodies are prevalent in 90-95% of AITD patients and an estimated 17% of women and 9% of men without known AITD.[275,276]

Thyroid dysfunction can cause a range of mood and cognitive disturbances, especially in severe cases. Hypothyroidism is associated with increased rates of anxiety and depression as well as mild to moderate deficits in memory and executive function.[277] Hyperthyroidism can also cause anxiety and depression as well as irritability, agitation, and deficits in concentration and executive function.[277] Increased screening and better treatment has reduced the rate of thyroid-related cognitive symptoms by reducing the incidence of severe disorder and reversing cognitive symptoms with effective

treatment.[277] Despite these advancements, there is still interest in the relationship between thyroid disorder and dementia due to the thyroid's well-established influence on brain development and function including neuronal maturation and myelination.[278,279]

There are two mechanisms by which thyroid disorders may be associated with dementia: action of abnormal thyroid hormone concentrations (high TSH causing low FT4 or high FT4 causing low TSH) on the brain causing impairment[280] or autoimmunity causing AITD and encephalopathy leading to permanent brain damage.[281] While some studies have found a relation between elevated TSH levels and increased rates of dementia or cognitive decline, the literature regarding other thyroid hormones (necessary for diagnosing dysfunction) and AITD (measured via anti-TPO positivity) is mixed, limited by modest sample sizes (n<3,000), and focused on primarily older participants (ages 65 and older at baseline) (**Table A.4**).[278,282-289] Using data from ARIC-NCS, we tested the hypothesis that AITD (anti-TPO antibodies) and abnormal thyroid hormone (TSH and FT4) levels are associated with increased incidence of dementia over 20 years of follow-up.

6.3. Methods

We analyzed the association between thyroid dysfunction and dementia and MCI in ARIC-NCS using a prospective cohort study design with baseline at visit 2 (1990-92) through visit 6 (2016-17). Participants were excluded from follow-up if they were non-white or African Americans from MD or MN (n = 103), did not attend visit 2 (n = 1,432), had missing serum TSH, FT4, or anti-TPO antibody measures (n = 1,769), or had prevalent dementia at visit 2 (n = 4) for a final analytic sample of 12,481 participants.

Thyroid function was assessed using serum samples stored at -70˚C since collection at visit 2 that were thawed and tested at Advanced Research Diagnostics Laboratory (University of Minnesota) between 2011 and 2013. Assays from Roche Diagnostics were used on an Elecsys 2010 Analyzer using a sandwich immunoassay method for TSH and competition immunoassay methods for FT4 and ant-TPO antibodies.[290] Interassay coefficients of variation were ≤ 10%.[290] Anti-TPO antibody positivity was defined as >34 kIU/L, based on assay manufacturer guidelines.[291] Five clinical categories (subclinical hypothyroidism, subclinical hyperthyroidism, overt hypothyroidism, overt hyperthyroidism, and euthyroidism) were used to define thyroid dysfunction based on ARIC-derived cut points associated with thyroid-related genes and genetic risk score (**Table 6.2**).[272,291] We also examined categorical variables based on the lowest 5%, middle 90%, and highest 5% of TSH and FT4 levels as well as continuously.

Covariates included age, sex, race-center (MS-blacks, NC-whites, NC-blacks, MN-whites, and MD-whites), *ApoE4*, income, and education from visit 1 (1987-89). At visit 2 baseline (1990-92), BMI, tobacco smoking status, hypertension, diabetes, alcohol drinking status, HDL cholesterol, total cholesterol, prevalent cardiovascular disease (CVD), and thyroid medication use were measured. BMI was calculated from measured weight and height. Hypertension was defined as having a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or self-report of antihypertensive medication use. Diabetes was defined as non-fasting serum glucose ≥ 200 mg/dL, fasting glucose ≥ 126 mg/dL, self-report of diabetes diagnosis from a physician, or report of taking medication for diabetes or high blood sugar. Prevalent CVD was defined as having prevalent stroke, coronary heart disease, myocardial infarction (MI), or atrial fibrillation

(AF) at visit 2 ascertained via hospital surveillance, self-report, or detected at an ARIC clinic visit (MI and AF), with clinical events other than AF adjudicated by a panel of experts.[292-295] Participants were asked to bring medication containers for any medication taken in the past four weeks prior to each clinic visit, from which thyroid medication use was determined at baseline and throughout follow-up.

Dementia and MCI cases were identified from ARIC-NCS clinic examinations conducted at visits 5 and 6, surveillance of hospital and death certificate codes, and annual and semi-annual telephone-based cognitive assessments. Methods are described in detail in Chapter 4. Our primary analysis included all incident dementia cases available in ARIC between visits 2 and 6. This included cases identified using surveillance of hospital and death records, informant interviews for deceased participants suspected to have had dementia, annual and semi-annual telephone follow-up calls with the administration of the modified telephone interview for cognitive status (TICSm) to participants who were alive and did not attend visits 5 or 6, and adjudicated dementia identified in ARIC-NCS. We conducted a secondary analysis using only adjudicated dementia and MCI cases identified in ARIC-NCS at visits 5 and 6. In this analysis, we also used brain MRI data at visit 5, classifying dementia and MCI cases as being CeVD-related if primary or secondary CeVD etiology was identified in imaging. Dementia surveillance is believed to be relatively complete, but because analyses of MCI required attendance at visits 5 or 6, there was likely informative censoring of participants over the follow-up period.[83] To account for this potential selection bias, we used inverse probability of attrition weights (IPAW) in our analyses of adjudicated cases.[83,255]

Statistical Analysis

We described means and prevalences of baseline covariates, thyroid hormone levels, and AITD status stratified by clinical categories of thyroid dysfunction. To characterize the association between abnormal thyroid function and dementia, we used Cox regression to assess the hazard of incident dementia between visits 2 and 6 as our primary analysis. We modeled thyroid function in several ways: i) anti-TPO antibody status (positive/negative); ii) clinical categories of thyroid dysfunction with euthyroidism as the reference; iii) categorical TSH and FT4 hormone levels (i.e. 3 categories, comparing participants whose hormone levels fell within the middle 90% (reference), lowest 5%, and highest 5%); and iv) per standard deviation difference in TSH or FT4 level.

For each analysis, three models were tested. Model 1 adjusted for age, sex, center-race, *ApoE4*, income, and education. Model 2 adjusted for model 1 covariates as well as BMI, smoking status, hypertension, diabetes, prevalent CHD, drinking status, HDL cholesterol, and total cholesterol. Model 3 adjusted for model 2 covariates in addition to prevalent CVD and baseline thyroid medication use.

Sensitivity analyses were conducted to assess whether taking thyroid medication throughout follow-up (versus at baseline) was associated with risk of dementia; however, medication use was not associated with dementia and results did not change. We verified that the proportional hazards assumption was met by testing the interaction between each measure of abnormal thyroid function by log follow-up time. We also used a restricted cubic spline model to investigate the continuous non-linear relationship between thyroid hormone levels and dementia with knots specified at the 10^{th}, 50^{th}, and 90^{th} percentiles.

Hormone levels were truncated at the 1st and 99th centiles to minimize the influence of extreme values.

As a secondary analysis, we used relative risk regression with a Poisson distribution, log link, and IPAW to assess the association between thyroid dysfunction and risk of adjudicated dementia and MCI at visits 5 and 6. However, results were null likely due to survival bias.[296] Adjudicated dementia and MCI cases could only be identified in participants that attended visits 5 or 6, and these participants were generally healthier, had higher SES, and were more likely to be white than participants that refused to attend or died prior to ARIC-NCS exams.[230] Because of issues with bias, results of our adjudicated analyses are presented in **Tables A.5-A.8** of the appendix.

All statistical analyses were conducted using SAS 9.4 (SAS Inc., Cary, NC).

6.4. Results

Of the 15,792 ARIC participants, 12,481 were included in the analysis after exclusions. The mean age of participants was 57 ± 5.7 at visit 2. Among these, 13.3% were anti-TPO positive, 2.3% had overt hypothyroidism, 4.7% subclinical hypothyroidism, 3.4% overt hyperthyroidism, 1.9% subclinical hyperthyroidism, 87.8% were euthyroid, and 7% were taking thyroid medication. Overall, participants with hypo- or hyperthyroidism had higher prevalences of risk factors for dementia compared to those with euthyroidism (**Table 6.2**). Participants with hypo- or hyperthyroidism were more likely to be women. Participants with hypothyroidism were less likely to be African American while participants with hyperthyroidism were more likely to be African American compared to those with euthyroidism. Those with hypothyroidism were less likely to be current tobacco smokers, less likely to have diabetes, and had higher mean

total cholesterol concentrations compared to participants in euthyroid or hyperthyroid categories. Participants with hyperthyroidism had higher HDL cholesterol and more prevalent CVD than those who were euthyroid or hypothyroid. Thyroid medication use was most common among participants with overt dysfunction.

A total of 2,235 dementia events occurred over a median follow-up of 21.9 (maximum 27.7) years. Participants identified as anti-TPO antibody positive, a marker of AITD, did not have a statistically significant increased hazard of dementia compared to participants who were anti-TPO antibody negative even after multivariable adjustment [HR (95% CI): 0.90 (0.80, 1.03)] (**Table 6.3**). No association was found between overt hypothyroidism and dementia, compared to euthyroidism (**Table 6.4**). Subclinical hypothyroidism was associated with a 26% reduced hazard of dementia after full adjustment for covariates compared to participants with euthyroidism [HR (95% CI): 0.74 (0.60, 0.92]. Overt hyperthyroidism was associated with a 40% increased hazard of dementia compared to participants with euthyroidism [HR (95% CI): 1.40 (1.02, 1.92)], while subclinical hyperthyroidism was not statistically significantly associated.

We also examined the association between categorical serum TSH and FT4 levels and dementia (**Table 6.5**). There was no association between continuous TSH level and dementia after multivariable adjustment including adjustment for serum FT4 levels. There was also no association between having TSH levels in the lowest 5% or highest 5% of categorical distribution and hazard of dementia compared to those in the middle 90% of TSH levels. A one standard deviation greater FT4 concentration was associated with a 5% greater hazard of dementia after multivariable adjustment including adjustment for TSH [HR (95% CI): 1.05 (1.01, 1.09)]. Correspondingly, compared to participants in the

middle 90% of FT4 level, having serum FT4 in the highest 5% of the categorical distribution was associated with a 23% increased hazard of dementia after full adjustment [HR (95% CI): 1.23 (1.02, 1.48)]. In contrast, participants in the lowest 5% of FT4 level were not at increased hazard of dementia. Using a restricted cubic spline model, we found levels of FT4 ≥ 1.1 ng/dL were positively, linearly associated with risk of dementia (**Figure 6.1**). In an ad hoc analysis, we tested a TSH*FT4 interaction term. The interaction term was not statistically significant.

6.5. Discussion

In this prospective cohort study of community-dwelling adults who were followed for 22 years from middle-age to older adulthood, subclinical hypothyroidism was associated with a reduced risk of dementia and overt hyperthyroidism with an increased risk of dementia, compared to euthyroid participants. We also found that neither continuous TSH nor categorical TSH were associated with increased risk of dementia. However, a standard deviation increase in FT4 was associated with an increased risk of dementia and those in the highest 5% of categorical FT4 were at increased risk.

Our findings suggest that overt hyperthyroidism and elevated FT4 (the hormone used to diagnose hyperthyroidism) are associated with increased risk of dementia. These results are consistent with previous studies that found an association between elevated serum FT4 levels and dementia risk.[282,283,286,287] We did not find an association between overt hypothyroidism and dementia nor TSH and dementia. This was inconsistent with the literature [278,283,288,289], which found a significant association between serum TSH (the hormone used to define hypothyroidism) and dementia. In addition, we found that subclinical hypothyroidism was associated with a reduced risk of dementia, an

association that we cannot explain. However, these results for clinical hypothyroidism may be related to lack of power. Despite ARIC's large sample size, the vast majority of participants fell within the euthyroid category reducing the precision of our effect estimates.

Strengths of this analysis include the long follow-up period, large sample size, as well as comprehensive ascertainment of dementia cases; however, some limitations warrant consideration. In our assessment of AITD, we only had one measure of autoimmunity, anti-TPO antibody levels. Yet, anti-TPO autoantibodies are found in over 90% of patients with AITD and likely allowed us to capture the most AITD cases.[297] Another limitation is the change in thyroid hormone levels with aging that may have led to misclassification of subclinical hypothyroidism. As shown in our data and reported by others,[285] in healthy adults ages 60 and older, average TSH levels rise with advancing age while FT4 concentrations remain fairly stable.[298] Subclinical hypothyroidism is characterized by elevated TSH with FT4 in the normal range. Older ARIC participants may have had age-related changes in TSH levels that caused them to be misclassified as having euthyroidism when they had subclinical hypothyroidism. We were also only able to use one measure of thyroid hormone levels and could not adjust for age-related changes. However, these changes were likely modest and misclassification would have pushed effect estimates towards the null. Thus, misclassification does not likely explain the paradoxical inverse association between subclinical hypothyroidism and dementia, in the face of no association between overt hypothyroidism and dementia. In addition, our measure of AITD status should not be affected by age-related misclassification, and our analysis of thyroid hormone levels still allowed us to determine whether thyroid hormone

levels affect risk of incident dementia regardless of the cause of thyroid hormone dysfunction.

Participants may have developed thyroid dysfunction over the follow-up period, and we tried to address this by adjusting for thyroid medication use at baseline as well as over follow-up. In these analyses, medication use was not associated with dementia and results did not change. Finally, while the ascertainment of dementia was extensive and included several different methods including adjudicated cases at clinic visits, surveillance of hospital and death certificate codes, and telephone interviews for cognitive status, there is still potential for either selection bias due to attrition or misclassification of cases. However, dementia cases were ascertained throughout the entire ARIC-NCS follow-up period, and our results do corroborate previous findings in the literature.

Our analysis suggests that subclinical hypothyroidism may be associated with reduced risk of dementia, though the biological pathway is unclear and this potential association warrants further investigation. Additionally, our results show that overt hyperthyroidism may be a risk factor for dementia. By extrapolation from these observational data, it may be that effective treatment and management of thyroid hormone levels in overt hyperthyroidism could modestly reduce the risk of incident dementia.

6.6. Tables and Figures

Table 6. 2. Baseline characteristics stratified by clinical categories of thyroid dysfunction, ARIC 1990-92

	Hypothyroidism		Eu-thyroidism (n = 10,956)	Hyperthyroidism	
Risk Factors	**Overt** (n = 281)	**Subclinical** (n = 581)		**Subclinical** (n = 429)	**Overt** (n = 234)
	TSH > 5.1 mIU/L; FT4 < 0.85 ng/dL	**TSH > 5.1 mIU/L; FT4 = 0.85 - 1.4 ng/dL**	**TSH = 0.56 - 5.1 mIU/L; FT4 = 0.85 - 1.4 ng/dL**	**TSH < 0.56 mIU/L; FT4 = 0.85 - 1.4 ng/dL**	**TSH < 0.56 mIU/L; FT4 > 1.4 ng/dL**
Age, years	58.4 ± 5.4	58.4 ± 5.7	56.8 ± 5.7	56.5 ± 5.8	57.1 ± 5.8
Men, %	22.8	33.4	45.9	33.6	19.7
African American, %	12.8	11.0	25.1	41.5	23.1
***ApoE4* carriers, %**	29.2	29.6	29.9	27.3	28.2
Basic Education[a], %	23.1	16.8	21.5	29.2	16.2
Family Income < $16,000[b], %	24.2	21.3	25.2	34.3	22.2
Current Alcohol Drinker, %	48.8	58.7	57.1	49.2	56.0
Current Tobacco Smoker, %	13.9	12.9	22.3	29.6	25.2
BMI, kg/m^2	28.9 ± 5.7	27.7 ± 5.5	28.0 ± 5.4	27.6 ± 5.4	27.4 ± 5.4
Hypertension[c], %	34.1	30.9	35.8	40.0	32.6
Diabetes[d], %	7.5	10.3	11.3	15.9	12.8
HDL Cholesterol, mg/dL	49.4 ± 16.6	49.7 ± 16.3	49.4 ± 16.8	52.8 ± 17.9	52.1 ± 15.7
Total Cholesterol, mg/dL	229.2 ± 48.9	214.3 ± 41.2	209.7 ± 39.2	208.1 ± 38.0	199.5 ± 35.2

Prevalent CVD[e], %	8.5	8.1	8.8	11.0	9.8
Thyroid Medication Use[f], %	40.9	28.6	2.8	27.5	71.4
TSH, mIU/L	26.3 ± 32.7	8.0 ± 4.4	2.0 ± 1.0	0.3 ± 0.2	0.1 ± 0.2
FT4, ng/dL	0.7 ± 0.2	1.0 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.8 ± 0.6
Anti-TPO positive (> 34 IU/L), %	79.4	51.1	9.3	13.8	27.4

SD: Standard deviation

[a] Based on self-report of some high school education or less at visit 1 (1987-89)

[b] Based on self-report of income at visit 1 (1987-89)

[c] Defined as diastolic blood pressure $\geq$ 90 mm Hg, systolic blood pressure $\geq$ 140 mm Hg, or use of hypertensive medication

[d] Defined as non-fasting blood glucose $\geq$ 200 mg/dL, fasting blood glucose $\geq$ 126 mg/dL, self-report of diabetes, or reporting taking medication for diabetes or high blood sugar

[e] Defined as prevalent stroke, coronary heart disease, myocardial infarction, or atrial fibrillation at visit 2

[f] Participants who reported thyroid medication use at baseline

Table 6. 3. Hazard ratios (95% CI) of dementia by anti-TPO positivity status, ARIC 1990-2017

	Anti-TPO Negative ≤ 34 IU/L	**Anti-TPO Positive >34 IU/L**
	n total = 10,821	n total = 1,660
	n events = 1,932	n events = 303
Model 1 HR	1 (ref)	0.92 (0.82, 1.04)
Model 2 HR	1 (ref)	0.93 (0.82, 1.05)
Model 3 HR	1 (ref)	0.90 (0.80, 1.03)

Abbreviation: HR: Hazard ratio; CI: Confidence interval
Model 1: age, sex, race-center, *ApoE4*, income, and education
Model 2: Model 1 + BMI, smoking status, hypertension, diabetes, drinking status, HDL cholesterol, and total cholesterol
Model 3: Model 2 + CVD and baseline thyroid medication

Table 6. 4. Hazard ratios (95% CI) of dementia by clinical categories of thyroid dysfunction, ARIC 1990-2017

	Hypothyroidism		**Eu-thyroidism**	**Hyperthyroidism**	
	Overt	**Subclinical**		**Subclinical**	**Overt**
	TSH > 5.1 mIU/L; FT4 < 0.85 ng/dL	**TSH > 5.1 mIU/L; FT4 = 0.85 - 1.4 ng/dL**	**TSH = 0.56 - 5.1 mIU/L; FT4 = 0.85 - 1.4 ng/dL**	**TSH < 0.56 mIU/L; FT4 = 0.85 - 1.4 ng/dL**	**TSH < 0.56 mIU/L; FT4 > 1.4 ng/dL**
	n total = 281	n total = 581	n total = 10,956	n total = 429	n total = 234
	n events = 60	n events = 98	n events = 1,952	n events = 74	n events = 51
Model 1 HR	1.03 (0.80, 1.33)	0.78* (0.64, 0.96)	1 (Ref)	1.07 (0.85, 1.35)	1.51* (1.14, 1.99)
Model 2 HR	1.01 (0.78, 1.31)	0.76* (0.61, 0.93)	1 (Ref)	1.03 (0.81, 1.31)	1.49* (1.12, 1.98)
Model 3 HR	0.96 (0.73, 1.26)	0.74* (0.60, 0.92)	1 (Ref)	1.01 (0.79, 1.29)	1.40* (1.02, 1.92)

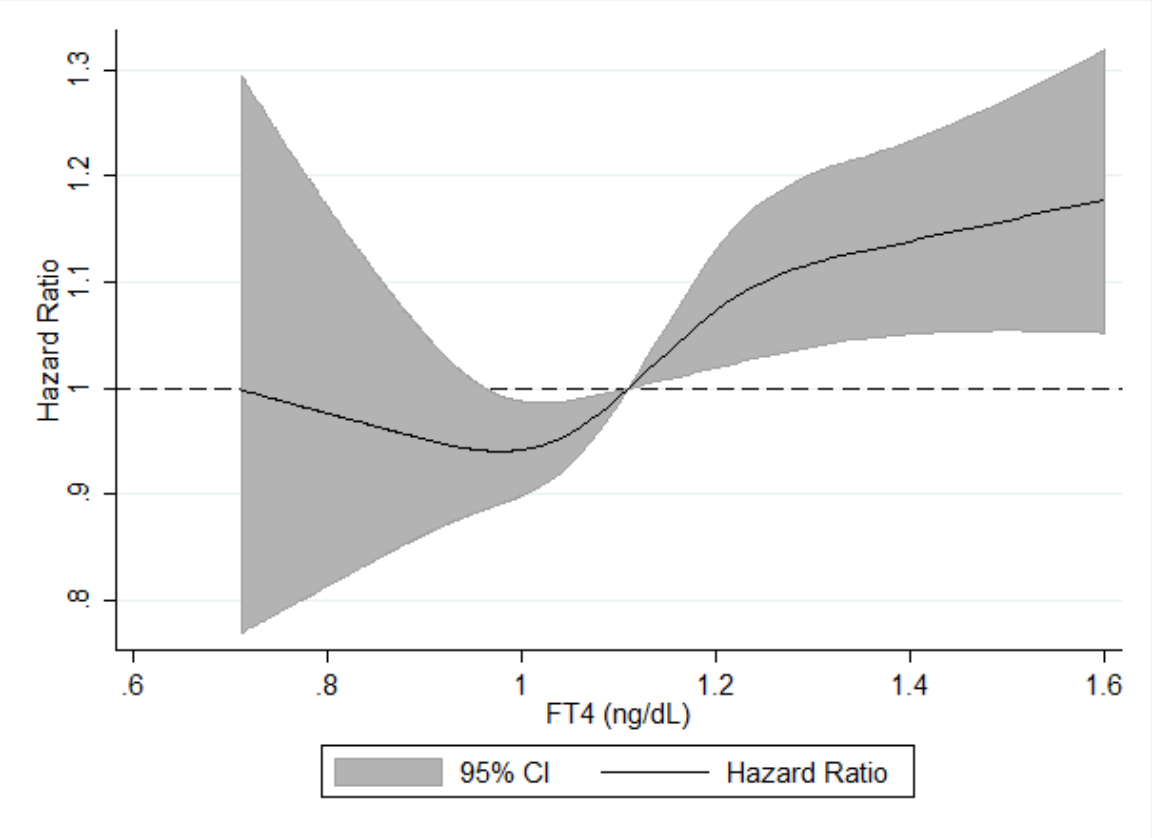
Abbreviation: HR: Hazard ratio; CI: Confidence interval
*P-value < 0.05
Model 1: age, sex, race-center, *ApoE4*, income, and education
Model 2: Model 1 + BMI, smoking status, hypertension, diabetes, drinking status, HDL cholesterol, and total cholesterol.
Model 3: Model 2 + CVD and baseline thyroid medication

Table 6. 5. Hazard ratios (95% CI) of dementia by categorical distribution of thyroid hormone level, ARIC 1990-2017

Thyroid Stimulating Hormone				
	Lowest 5% ≤ 0.54 mIU/L	**Middle 90% 0.55 – 5.97 mIU/L**	**Highest 5% ≥ 5.98 mIU/L**	**TSH per 6.35 mIU/L**
	n total = 626	n total =11,226	n total = 629	n total = 12,481
	n events = 116	n events = 1,998	n events = 121	n events = 2,235
Model 1 HR	1.24* (1.03, 1.50)	1 (ref)	0.93 (0.77, 1.12)	1.03 (0.98, 1.07)
Model 2 HR	1.13 (0.92, 1.39)	1 (ref)	0.94 (0.77, 1.14)	1.03 (0.98, 1.07)
Model 3 HR	1.09 (0.87, 1.36)	1 (ref)	0.90 (0.73, 1.11)	1.02 (0.97, 1.07)
Free T4				
	Lowest 5% ≤ 0.89 ng/dL	**Middle 90% 0.90 – 1.35 ng/dL**	**Highest 5% ≥ 1.36 ng/dL**	**FT4 per SD (0.19 ng/dL)**
	n = 628	n = 11,170	n = 683	n = 12,481
	n events = 123	n events = 1,981	n events = 131	n events = 2,235
Model 1 HR	0.96 (0.79, 1.18)	1 (ref)	1.30* (1.08, 1.55)	1.06* (1.02, 1.09)
Model 2 HR	0.96 (0.78, 1.17)	1 (ref)	1.26* (1.05, 1.51)	1.05* (1.01, 1.09)
Model 3 HR	0.95 (0.77, 1.16)	1 (ref)	1.23* (1.02, 1.48)	1.05* (1.01, 1.09)

Abbreviation: HR: Hazard ratio; CI: Confidence interval
*P-value < 0.05
Model 1: age, sex, race-center, *ApoE4*, income, education, and TSH or FT4
Model 2: Model 1 + BMI, smoking status, hypertension, diabetes, drinking status, HDL cholesterol, and total cholesterol.
Model 3: Model 2 + prevalent CVD and baseline thyroid medication use

Figure 6. 1. Age, sex race-center, *ApoE4*, income, education, and TSH adjusted hazard ratio (95% CI) of incident dementia in relation to serum FT4*, ARIC, 1990-2017



*Analyzed using restricted cubic splines with knots at the 5th (0.90 ng/dL), 50th (1.11 ng/dL), and 95th (1.35 ng/dL) percentiles of the FT4 distribution. FT4 hormone levels were truncated at the 1st (0.71 ng/dL) and 99th (1.61 ng/dL) centiles to minimize the influence of extreme values.

CHAPTER 7. MANUSCRIPT 3: MIGRAINES AND RISK OF DEMENTIA AND MCI

7.1 Overview

Background

Migraine headache is a common neurological disorder that is associated with white matter hyperintensities. White matter disease is associated with cognitive decline in the general population, but the relation has not been studied in the context of migraine. Our aim was to use the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study (1993-2017) to determine whether migraine is associated with incident dementia and mild cognitive impairment (MCI), particularly of cerebrovascular disease etiology, and whether this association varies by sex.

Methods

Lifetime history of migraine and severe non-migraine headache symptoms were ascertained via questionnaire. Adjudicated cases of dementia and MCI were identified using cognitive tests, neuropsychological examinations, and clinician review of suspected cases. Cerebrovascular disease etiology was identified in brain imaging. Total dementia cases were identified using adjudicated dementia cases, annual and semi-annual telephone interviews for cognitive status, and surveillance of hospital and death certificate codes. Relative risk regression with inverse probability of attrition weighting was used to assess the risk of adjudicated dementia and MCI, and Cox regression was used to assess hazard of total dementia.

Results

Analysis included 12,501 white and African American participants ages 51-70, of whom 1,398 reported migraine and 1,244 reported severe non-migraine headache symptoms at baseline. There was no association between history of migraine or severe non-migraine headache symptoms and incidence of adjudicated dementia and MCI [Migraine RR (95% CI): 1.00 (0.89, 1.14)] nor total dementia [Migraine HR (95% CI): 1.04 (0.91, 1.20)]. The lack of association did not differ by sex nor were migraine or severe non-migraine headache symptoms associated with incident cerebrovascular disease-related dementia and MCI.

Conclusion

Despite reported evidence of brain abnormalities in migraineurs associated with cognitive changes in older adult populations, there was no association between history of migraine symptoms and incident dementia and MCI in this prospective cohort followed for 25 years.

7.2. Background

Migraine headache is a complex neurological disorder characterized by throbbing, severe, and typically unilateral pain in the head.[299] Among Americans ages 12 and older, prevalence is about 6.5% in men and 18.2% in women and has remained stable over time.[300,301] Migraine prevalence peaks between the ages of 30 and 39 for both men and women before falling to reach its lowest prevalence in those 60 and older.[302] For both sexes, prevalence is significantly higher in whites than African Americans and among those with low versus high income.[302] It is a heritable disorder with relatives of migraineurs at three times the risk compared to those without relatives with migraines.[303]

Approximately 64% of migraines are without aura, 18% with aura, and some individuals experience both.[299] Migraine is associated with autonomic, sensory, affective, and cognitive symptoms including nausea, vomiting, sensitivity to light, sound, and movement, depression and irritability, attention deficit, and transient amnesia.[299,304] This constellation of early migraine symptoms, also known as prodromes, can vary substantially between individuals.

Prodromes can precede migraine headache by several hours and are explained by two main hypotheses.[304] The first theorizes that hypothalamic neurons respond to changes in brain homeostasis by activating meningeal nociceptors that alter the balance of parasympathetic and sympathetic activity in the meninges toward predominance of parasympathetic activity.[304] The second theory proposes that hypothalamic and brainstem neurons that respond to brain homeostasis lower the threshold for transmission of nociceptive trigeminovascular signals from the thalamus to the cortex.[304] This can alter the amount of brain activity required to manage emotional and physiological stress,

making migraineurs more susceptible to external and internal stressors.[304] Both theories identify neuronal hyper-excitability as well as alterations to the brain structure and function, resultant from the repetitive state of headache, as essential features of migraine progression.[304-306]

There is an important distinction between migraine with and without aura, and evidence suggests the two subtypes of migraine may be separate disorders.[306] Aura is characterized by fully reversible neurologic dysfunction related to visual, sensory, speech/language, motor, brainstem, or retinal symptoms that proceed or accompany headache.[307] Onset is usually gradual with a duration of 5-60 minutes, and visual aura is the most commonly reported with prevalence estimates as high as 99%.[307] Aura is distinct from prodromes and caused by cortical spreading depression (CSD).[307] Evidence suggests that CSD involves a wave of hyper-excitation followed by suppression of cortical neurons and glia.[304,306] This process is associated with disruption of ionic flow and leads to an increase and subsequent decrease of cerebral blood flow.[307] As with prodromes, it is unknown what triggers CSD associated with aura.[307]

The mechanisms of the headache stage of migraine are better characterized than prodromes and aura. The initial "vascular hypothesis" proposed that migraines were a vasospastic disorder that started with meningeal blood vessel constriction followed by dilation, activating the surrounding trigeminal sensory nerves and causing pain.[308,309] However, vasodilation alone does not fully explain prodromes that can accompany headache, and current hypotheses focus primarily on neural activation with vascular changes as a secondary factor.[308] It is hypothesized that migraine headache is caused by activation of the trigeminovascular system via dilation of meningeal blood vessels that

mechanically activate surrounding trigeminal sensory nerve fibers.[306,310] Activation of these fibers triggers release of the vasoactive neurotransmitter calcitonin gene-related peptide (CGRP).[306,310] Signals spread via CGRP to the pain matrix of the brain, the thalamus, followed by the brainstem and spinal cord regions causing headache.[306,310] As migraine progresses, areas of the brain that receive pain impulses may become sensitized, leading to perpetuation of CGRP release, worsening of pain, and increased sensitivity to stimuli.[306,310,311] Concentration of CGRP is elevated in migraine patients, and the neurotransmitter has been a target for intervention using selective CGRP receptor antagonists.[310,311]

While current hypotheses deemphasize the importance of vasodilation in migraine, there is still a clear vascular component, which has led researchers to test the connection between migraine, stroke, and cognitive decline. Several studies have found an association between migraine and ischemic stroke with a pooled relative risk of 1.7 (95% CI: 1.3, 2.4); this association was significant in women [RR (95% CI): 2.1 (1.1, 3.8)], but not in men [RR (95% CI): 1.4 (0.9, 2.1)].[312] An ARIC study found a history of migraine symptoms was cross-sectionally associated with cerebral white matter hyperintensities.[313] In addition, a recent review concluded that history of migraine was associated with increased odds of white matter abnormalities, subclinical infarct-like lesions, and volumetric changes in the brain.[314] Stroke, white matter hyperintensities, silent infarcts, and volumetric changes are associated with increased risk of cognitive impairment, suggesting migraine may be a risk factor for cognitive decline and dementia.[315]

Accumulating evidence indicates that many cases of dementia have mixed pathologies, with a combination of AD and CeVD being the most common.[316,317] It is plausible that migraine could contribute not only to CeVD-specific dementia cases, but also more broadly to risk of dementia and mild cognitive impairment (MCI), a clinically significant pre-dementia state.[315,318] Few longitudinal studies have looked at migraine and risk of developing dementia and MCI (**Table A.9**).[319-322] Of the studies that have assessed this relationship, results have been mixed and most sample sizes have been small. Further, to our knowledge, no studies in U.S. community-based cohorts have assessed this association.

Our first aim was to evaluate the association between migraine status based on self-reported headache symptoms with risk of dementia and MCI. We hypothesized that ARIC participants who reported historical symptoms of migraine would be at increased risk of dementia and MCI. We also hypothesized that participants who were classified as having a history of migraine with aura would be at increased risk of dementia compared to those who experienced migraine without aura, severe headache, or no headache. Our second aim was to evaluate the association between self-reported history of migraine symptoms with risk of dementia and MCI with cerebrovascular disease etiology and non-CeVD-related etiology, separately. We hypothesized that the association between migraine and dementia would be stronger in those with dementia and MCI with a CeVD etiology compared to non-CeVD etiology. Our third aim was to determine whether there was effect modification on the association between migraine and dementia and MCI by sex. We hypothesized that the association between migraine and dementia would be

stronger in women compared to men based previous study findings and the higher prevalence of migraines in women than men.

7.3. Methods

We analyzed the association between migraine and dementia and MCI in ARIC-NCS using a prospective cohort study design with a baseline at visit 3 (1993-95) through visit 6 (2016-17). Participants were excluded if they did not attend visit 3 (n = 2,886), were missing migraine status based on self-reported headache symptoms (n = 57), had prevalent stroke (n = 245), prevalent dementia (identified via ICD codes) (n = 6), or were non-white or African American or were African American from Maryland or Minnesota (n = 103) for a final analytic sample of 12,495 participants.

Migraine status was assessed at visit 3 via questionnaire of self-reported headache symptoms adapted from the International Headache Society diagnostic criteria. Migraine was defined as: 1) headache lasting 4 or more hours, 2) headache with throbbing, pounding, or pulsating pain, or that was unilateral, 3) symptoms of nausea, vomiting, or sensitivity to light or sound, and 4) one or more years with history of headaches.[313] Those who reported headache lasting four or more hours, but did not meet all the other criteria for migraine were defined as suffering from severe non-migraine headache, and participants who denied having a headache lasting 4 or more hours were classified as having no headache.[318] Participants meeting the definition of migraine were defined as having aura if they reported the occurrence of visual aura (e.g. spots, jagged lines, etc.).[318]

Covariates included age, sex, race-center (MS-blacks, NC-whites, NC-blacks, MN-whites, and MD-whites), *ApoE4*, income, and education from visit 1 and BMI,

smoking status, hypertension, diabetes, prevalent CHD, drinking status, HDL cholesterol, and total cholesterol from visit 3. BMI was calculated from weight and height measurements taken at the visit. Hypertension was defined as having a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or self-report of antihypertensive medication use. Diabetes was defined as non-fasting glucose ≥ 200 mg/dL, fasting blood glucose ≥ 126 mg/dL, self-report of diabetes diagnosis from a physician, or report of taking medication for diabetes or high blood sugar.

Dementia and MCI cases were identified from ARIC-NCS clinic examinations conducted at visits 5 and 6, surveillance of hospital and death certificate codes, and annual and semi-annual telephone-based cognitive assessments. Methods are described in detail in Chapter 4. Separate analyses were run using two criteria for dementia and MCI cases. The first definition included all incident dementia cases available in ARIC between visits 3 and 6. This included cases identified using surveillance of hospital and death records, annual and semi-annual modified telephone interviews for cognitive status (TICSm), and adjudicated dementia identified in ARIC-NCS. The second definition included only adjudicated dementia and MCI cases identified in ARIC-NCS at visits 5 and 6. Further, from brain MRI data at visit 5, adjudicated dementia and MCI cases were classified as being CeVD-related if primary or secondary CeVD etiology was identified. Dementia surveillance is believed to be relatively complete, but because analysis of MCI required attendance at visits 5 or 6, there was likely informative censoring of participants over the follow-up period.[83] To account for this potential selection bias, we used inverse probability of attrition weights (IPAW) in our analyses of adjudicated cases.[83,255]

Statistical Analysis

Poisson regression was used to estimate incidence of dementia stratified by headache subtype (migraine, severe non-migraine headache, no headache) and sex. We then evaluated the association between self-reported history of migraine symptoms with risk of dementia and MCI (Aim 1). Cox regression was used to calculate hazard ratios of dementia stratified by headache subtype between visits 3 and 6 with no headache as the reference. Relative risk regression with a Poisson distribution and log link was used to assess the association between migraine and adjudicated dementia or MCI using IPAW to account for informative censoring caused by death or failure to attend visits 5 or 6 (methods described in detail elsewhere).[255] The association of migraine with aura and dementia or MCI was assessed by repeating the Cox regression and relative risk regression models using an added "migraine with aura" headache subtype.

To address aim 2, we evaluated the association between self-reported history of migraine symptoms with risk of dementia and MCI with primary or secondary CeVD etiology compared to dementia cases without CeVD etiology. Etiologic data are available for dementia and MCI cases only at visit 5, so analysis was restricted to individuals seen at visit 5. Relative risk regression with IPAW was used to assess the association between migraine and CeVD-related and non-CeVD-related dementia and MCI in separate models.

Finally, to determine whether there is effect modification on the association between migraine and dementia and MCI by sex (Aim 3), a sex by migraine multiplicative interaction term was tested in the models. Cox regression and relative risk

regression were used to assess hazard and risk of dementia and MCI, respectively. For both analyses, sex-specific models are presented.

A hazard ratio of approximately 1.4 and a relative risk ratio of 1.6 or greater would have been needed to detect an effect with 80% power and a type I error rate of 0.5.

7.4 Results

After exclusions, analysis included an analytic sample of 12,495 participants with a mean age of 60 and median follow-up time of 21 years. Participants who reported experiencing migraine symptoms were more likely to be younger, white, female, and had higher HDL and total cholesterol than those who reported no headache symptoms or severe non-migraine headache symptoms (**Table 7.1**). In addition, migraineurs were less likely to have hypertension, diabetes, or be a current alcohol drinker. There was no statistically significant difference in the overall incidence of dementia between those who experienced migraine symptoms compared to those who experienced severe non-migraine headaches or no headaches between visits 3 and 6 (**Figure 7.1**).

Those who experienced migraine symptoms at baseline had neither a significantly increased hazard of incident dementia [HR (95% CI): 1.04 (0.91, 1.20)] nor a significantly increased risk of adjudicated dementia or MCI [RR (95% CI): 1.00 (0.89, 1.14)], compared to those with no headache (**Table 7.2**). There was no significant association between migraine with aura and incident dementia or with adjudicated dementia or MCI. There also was no association for severe non-migraine headache compared to no headache, and relationships remained insignificant even after full adjustment for risk factors.

As shown in **Table 7.3**, history of migraine or severe non-migraine headache symptoms was not significantly associated with increased risk of adjudicated dementia and MCI with or without cerebrovascular disease etiology even after full adjustment. Finally, the sex*migraine status interaction term was not statistically significant in any model, indicating that the associations between migraine status and risk of dementia and MCI were similarly null for men and women (**Table 7.4**).

7.5. Discussion

Using a large population-based prospective study, we found no association between history of migraine symptoms and risk of dementia or MCI. This lack of association was found in cerebrovascular and non-cerebrovascular etiologies and in both men and women. While migraine is associated with cerebrovascular lesions, migraine-related lesions are reported to be stable over time and may not contribute to dementia pathophysiology later in life.[313] This analysis is an important contribution to the literature because few studies have assessed the association between migraine and dementia and MCI in a large, American cohort with over 25 years of follow-up.

There are several limitations to our analysis. Despite the size of our cohort, power was somewhat limited. A hazard ratio of approximately 1.4 and a relative risk ratio of 1.6 would have been needed to detect an effect with an alpha of 0.05 and 80% power. In addition, there was potential selection bias due to attrition and misclassification of the dementia and MCI cases that were not examined directly. However, IPAW was used to correct for selection bias in analysis of adjudicated dementia and MCI cases, and ARIC used a variety of strategies to prevent attrition and identify possible dementia cases

among participants who did not attend all clinic visits including surveillance of hospital and death records as well as follow-up telephone interviews.

Another limitation was potential misclassification of migraine status due to reliance on report of headache symptoms over participants' lifetimes measured via self-report when participants ranged in age from 51-70.[302] Two population-based studies using questionnaires adapted from the International Headache Society diagnostic criteria, from which the ARIC questionnaire was derived, confirmed the validity and reliability of using abbreviated diagnostic criteria to accurately identify migraineurs estimating Cohen's kappa coefficients ranging from 0.43-0.68.[323,324] Further, the symptoms associated with migraine, including unilateral, severe pain, prodromes, and aura, would not likely be forgotten and should be easily distinguishable from a severe non-migraine headache in most cases. By asking participants about their migraine history after prevalence peaked in young adulthood and middle age, it is less likely cases were missed. Misclassification of migraine status would have tended to mask any associations with dementia. Because migraine in ARIC is associated with increased stroke risk, [325] as in other studies, [312,326,327] the validity of the ARIC migraine classification is likely adequate. Finally, we were unable to account for age of onset or duration of migraines.

In summary, we found no association between history of migraine headache and incident dementia or MCI in ARIC. While there is evidence that migraine is associated with brain alterations that have been linked to cognitive changes, these alterations may not be clinically meaningful or they may resemble white matter hyperintensities associated with vascular disease, but have a different underlying pathophysiologic

process.[313-315] Additional research with a larger sample size and more extensive migraine history is warranted.

7.6 Tables and Figures

Table 7. 1. Baseline participant characteristics stratified by migraine status, ARIC, 1993-1995

Characteristic	No Headache	Severe Non-migraine Headache	Migraine
	n total = 9,855	**n total = 1,243**	**n total = 1,397**
Age, years	60.4 ± 5.7	58.7 ± 5.5	58.3 ± 5.5
African American, %	24.7	15.3	14.5
Male, %	48.2	36.0	22.1
***ApoE4* carriers, %**	29.3	27.0	29.3
Basic Education[a], %	20.8	15.5	18.5
Family Income < $16,000[b], %	23.9	19.2	23.4
Current Alcohol Drinker, %	52.5	53.9	49.5
Current Tobacco Smoker, %	18.0	16.4	16.7
BMI, kg/m^2	28.6 ± 5.6	27.9 ± 5.3	28.4 ± 5.9
Hypertension[c], %	41.7	36.1	35.9
Diabetes[d], %	15.9	12.4	11.6
HDL Cholesterol, mg/dL	51.7 ± 18.2	53.9 ± 18.4	55.1 ± 18.3
Total Cholesterol, mg/dL	207.0 ± 37.4	207.0 ± 37.9	211.6 ± 39.3

Mean ± Standard Deviation

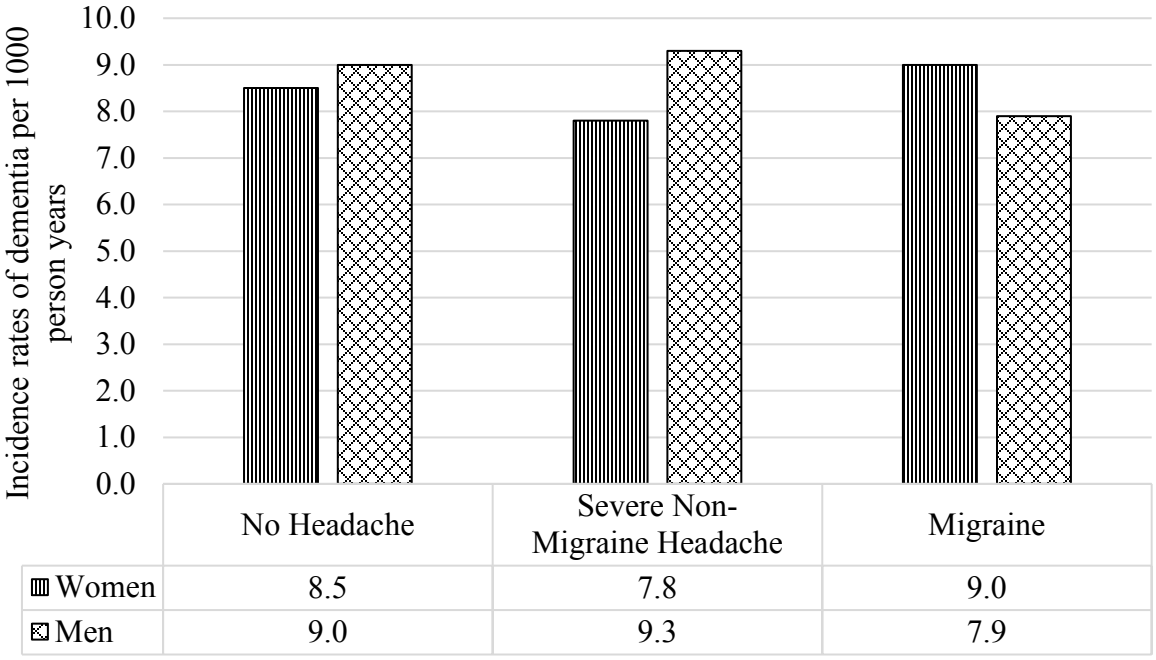
[a] Based on self-report of some high school education or less at visit 1

[b] Based on self-report of income at visit 1 (1987-89)

[c] Defined as diastolic blood pressure ≥ 90 mm Hg, systolic blood pressure ≥ 140 mm Hg, or use of hypertensive medication

[d] Defined as non-fasting blood glucose ≥ 200 mg/dL, fasting blood glucose ≥ 126 mg/dL, self-report of diabetes, or reporting taking medication for diabetes or high blood sugar

Figure 7. 1. Incidence rates of dementia adjusted for age and stratified by baseline headache subtype and sex, ARIC, 1993-2017



	No Headache	Severe Non-Migraine Headache	Migraine
Women	8.5	7.8	9.0
Men	9.0	9.3	7.9

Table 7. 2. Hazard ratios (95% CI) and relative risks (95% CI) of dementia and MCI in relation to baseline headache status, ARIC 1993-2017

Dementia only				
	No Headache	**Severe Non-Migraine Headache**	**Migraine**	
	n total = 9,855	**n total = 1,243**	**n total = 1,397**	
	n events = 1,821	**n events = 196**	**n events = 233**	
Model 1 HR	1 (Ref)	1.00 (0.86, 1.16)	1.02 (0.89, 1.17)	
Model 2 HR	1 (Ref)	1.00 (0.87, 1.17)	1.04 (0.91, 1.20)	
	No Headache	**Severe Non-Migraine Headache**	**Migraine without Aura**	**Migraine with Aura**
	n total = 9,855	**n total = 1,243**	**n total = 992**	**n total = 405**
	n events = 1,821	**n events = 196**	**n events = 165**	**n events = 68**
Model 1 HR	1 (Ref)	1.00 (0.86, 1.16)	0.99 (0.84, 1.16)	1.11 (0.87, 1.42)
Model 2 HR	1 (Ref)	1.00 (0.87, 1.17)	1.01 (0.86, 1.19)	1.12 (0.88, 1.43)
MCI and Dementia at visits 5 and 6				
	No Headache	**Severe Non-Migraine Headache**	**Migraine**	
	n total = 8,517	**n total = 1,104**	**n total = 1,242**	
	n events = 1,760	**n events = 236**	**n events = 261**	
Model 1 RR	1 (Ref)	0.96 (0.83, 1.10)	0.99 (0.87, 1.12)	
Model 2 RR	1 (Ref)	0.96 (0.83, 1.11)	1.00 (0.89, 1.14)	
	No Headache	**Severe Non-Migraine Headache**	**Migraine without Aura**	**Migraine with Aura**
	n total = 8,517	**n total = 1,104**	**n total = 879**	**n total = 363**
	n events = 1,760	**n events = 236**	**n events = 191**	**n events = 70**
Model 1 RR	1	0.96	0.97	1.03

	(Ref)	(0.83, 1.11)	(0.84, 1.13)	(0.82, 1.29)
Model 2 RR	1 (Ref)	0.96 (0.83, 1.11)	0.98 (0.85, 1.13)	1.06 (0.85, 1.34)

Abbreviations: HR: Hazard ratio; RR: Risk ratio; CI: Confidence interval
Model 1: age, sex, race-center, *ApoE4*, income, and education
Model 2: Model 1 + BMI, smoking status, hypertension, diabetes, prevalent CHD, drinking status, HDL cholesterol, and total cholesterol.

Table 7. 3. Relative risks (95% CI) of dementia and MCI at visits 5 and 6 by etiology in relation to baseline headache status, ARIC 1993-2017

Cerebrovascular Disease Etiology			
	No Headache	**Severe Non-Migraine Headache**	**Migraine**
	n total = 7,383	**n total = 953**	**n total = 1,068**
	n events = 441	**n events = 40**	**n events = 57**
Model 1 RR	1 (Ref)	1.34 (0.95, 1.88)	1.05 (0.79, 1.41)
Model 2 RR	1 (Ref)	1.36 (0.97, 1.91)	1.09 (0.82, 1.46)
Non-Cerebrovascular Disease Etiology			
	No Headache	**Severe Non-Migraine Headache**	**Migraine**
	n total = 8,076	**n total = 1,064**	**n total = 1,185**
	n events = 1,134	**n events = 151**	**n events = 174**
Model 1 RR	1 (Ref)	1.05 (0.88, 1.24)	0.94 (0.79, 1.13)
Model 2 RR	1 (Ref))	1.06 (0.90, 1.25)	0.97 (0.81, 1.16)

Abbreviations: RR: Risk ratio; CI: Confidence interval
* Statistically significant (p-value < 0.05)
Model 1: age, sex, race-center, *ApoE4*, income, and education
Model 2: Model 1 + BMI, smoking status, hypertension, diabetes, prevalent CHD, drinking status, HDL cholesterol, and total cholesterol.

Table 7. 4. Hazard ratios (95% CI) and relative risks (95% CI) of dementia and MCI in relation to baseline headache status and sex, ARIC 1993-2017

Sex-specific Dementia only						
	Women (n = 6,988)			**Men** (n = 5,507)		
	No Headache	**Severe Non-Migraine Headache**	**Migraine**	**No Headache**	**Severe Non-Migraine Headache**	**Migraine**
	n total = 5,105	**n total = 795**	**n total = 1,088**	**n total = 4,750**	**n total = 375**	**n total = 309**
	n events = 1,012	**n events = 123**	**n events = 190**	**n events = 809**	**n events = 73**	**n events = 43**
Model 1 HR	1 (Ref)	0.96 (0.80, 1.16)	1.09 (0.93, 1.28)	1 (Ref)	1.09 (0.85, 1.38)	0.82 (0.60, 1.11)
Model 2 HR	1 (Ref)	0.97 (0.80, 1.17)	1.13 (0.96, 1.32)	1 (Ref)	1.09 (0.85, 1.39)	0.79 (0.58, 1.08)
Sex-specific MCI and Dementia at visits 5 and 6						
	Women (n = 6,020)			**Men** (n = 4,843)		
	No Headache	**Severe Non-Migraine Headache**	**Migraine**	**No Headache**	**Severe Non-Migraine Headache**	**Migraine**
	n total = 4,350	**n total = 706**	**n total = 964**	**n total = 4,167**	**n total = 398**	**n total = 278**
	n events = 900	**n events = 145**	**n events = 193**	**n events = 860**	**n events = 91**	**n events = 68**
Model 1 RR	1 (Ref)	0.99 (0.83, 1.17)	0.99 (0.85, 1.15)	1 (Ref)	0.88 (0.69, 1.12)	0.90 (0.71, 1.13)
Model 2 RR	1 (Ref)	0.99 (0.84, 1.17)	1.00 (0.86, 1.16)	1 (Ref)	0.88 (0.69, 1.12)	0.90 (0.72, 1.13)

Abbreviations: HR: Hazard ratio; RR: Risk ratio; CI: Confidence interval
Model 1: age, race-center, *ApoE4*, income, and education
Model 2: Model 1 + BMI, smoking status, hypertension, diabetes, prevalent CHD, drinking status, HDL cholesterol, and total cholesterol.

CHAPTER 8. CONCLUSIONS

The public health burden of dementia and MCI is increasing as the population ages. The objective of this dissertation was to describe the etiology and epidemiology of dementia and MCI, characterize major demographic, genetic, vascular, and behavioral risk factors, and examine three novel risk factors in early- and mid-life that may influence late-life risk. Using the ARIC study cohort, we assessed life-course SES, thyroid dysfunction, and lifetime history of migraine symptoms as three novel risk factors for dementia and MCI using a prospective cohort study design and epidemiologic methods.

In manuscript 1, we examined the association between LC-SES at the individual- and neighborhood-levels and risk of dementia and MCI using a LC-SES summary score. SES has been studied in relation to cognitive impairment extensively, in part, due to the relation between SES and cognitive reserve. However, few studies have assessed this association using SES over the life-course, from childhood through middle/older adulthood, and at the individual and neighborhood level. After stratifying by life epoch (childhood, young adulthood, and middle/older adulthood) and SES tertile (low, middle, high), we found that incidence of dementia was significantly lower among those in the highest SES tertile vs. the lowest during young adulthood and middle/older adulthood. This association was similar, but not statistically significant during childhood. Additionally, a standard deviation (SD) increase in individual-level LC-SES score was associated with moderately lower incidence of dementia in both whites [HR (95% CI): 0.86 (0.81, 0.92)] and African Americans [HR (95% CI): 0.79 (0.71, 0.87)]. When education was taken out of the individual LC-SES score and adjusted for separately, a SD increase in individual LC-SES score was still associated with lower dementia risk in

whites [HR (95% CI): 0.90 (0.84, 0.97)] and African Americans [HR (95% CI): 0.85 (0.76, 0.96)] though associations were attenuated. We found no association between cumulative neighborhood-level LC-SES and incident dementia independent of individual-level LC-SES. Results were similar in our analysis of adjudicated dementia and MCI.

In manuscript 2, we assessed the association between mid-life thyroid dysfunction and dementia and MCI. We found no association between autoimmune thyroid disease as measured via anti-TPO antibodies and risk of dementia. Subclinical hypothyroidism was associated with a reduced risk of dementia [HR (95% CI): 0.74 (0.60, 0.92] and overt hyperthyroidism with an increased risk of dementia [HR (95% CI): 1.40 (1.02, 1.92)] compared to euthyroid participants. Neither continuous nor categorical TSH levels were associated with increased risk of dementia. However, a SD increase in FT4 was associated with an increased risk of dementia, and those in the highest 5% of categorical FT4 were at increased risk of incident dementia. Our findings suggest that subclinical hypothyroidism is associated with reduced risk of dementia though the biological pathway is unclear and warrants further investigation. In addition, overt hyperthyroidism may be a risk factor for dementia, particularly at very high levels of FT4. We analyzed the association between thyroid dysfunction and adjudicated dementia and MCI and found no associations.

Finally, in manuscript 3, we assessed the association between lifetime history of migraine symptoms and risk of dementia and MCI. Brain abnormalities associated with cognitive impairment in older adults, including white matter hyperintensities and volumetric changes, have been identified in migraineurs. History of migraine is also

associated with increased risk of ischemic stroke. However, we found no association between lifetime history of migraine symptoms or severe-non migraine headache and risk of dementia and MCI. There was no association between migraine and dementia and MCI with cerebrovascular etiology nor an interaction between migraine and sex. While migraineurs have increased odds of brain alterations linked to cognitive impairment, these changes may not be clinically meaningful despite resembling vascular pathology.

Dementia and MCI are complex conditions that represent several different etiologies and phenotypes. Outside of disease-causing gene mutations, the cause of dementia and MCI cannot be isolated to a single risk factor. This dissertation has focused on identifying novel early- and mid-life risk factors for dementia and MCI. Our findings suggest that life course socioeconomic factors have a moderate influence on late-life dementia risk and that both economic and educational aspects of SES contribute to that risk. Further, thyroid dysfunction, particularly overt hyperthyroidism may moderately increase risk of dementia. Lifetime history of migraine symptoms were not associated with dementia or MCI, though migraine has been previously associated with brain abnormalities detected by brain imaging.

Future research should continue to examine risk factors for dementia and MCI, particularly in large, diverse cohorts. In addition, results from observational studies of risk factors should be used to develop primary prevention studies that can attempt to prevent dementia and MCI outcomes through risk factor modification.

REFERENCES

1. Knopman DS, Petersen RC. Mild cognitive impairment and mild dementia: a clinical perspective. *Mayo Clin Proc.* 2014;89(10):1452-1459.
2. Katz MJ, Lipton RB, Hall CB, et al. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. *Alzheimer Dis Assoc Disord.* 2012;26(4):335-343.
3. Snowden MB, Steinman LE, Bryant LL, et al. Dementia and co-occurring chronic conditions: a systematic literature review to identify what is known and where are the gaps in the evidence? *Int J Geriatr Psychiatry.* 2017;32(4):357-371.
4. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. *Lancet.* 2006;367(9518):1262-1270.
5. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology.* 2007;29(1-2):125-132.
6. Plassman BL, Williams JW, Jr., Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med.* 2010;153(3):182-193.
7. Salthouse T. Consequences of age-related cognitive declines. *Annu Rev Psychol.* 2012;63:201-226.
8. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med.* 2013;29(4):737-752.
9. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med.* 2014;275(3):214-228.
10. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology.* 2007;69(24):2197-2204.
11. Goodman RA, Lochner KA, Thambisetty M, Wingo TS, Posner SF, Ling SM. Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011-2013. *Alzheimers Dement.* 2017;13(1):28-37.
12. Bonifacio G, Zamboni G. Brain imaging in dementia. *Postgrad Med J.* 2016;92(1088):333-340.
13. Goedert M, Klug A, Crowther RA. Tau protein, the paired helical filament and Alzheimer's disease. *J Alzheimers Dis.* 2006;9(3 Suppl):195-207.
14. Teipel SJ, Flatz WH, Heinsen H, et al. Measurement of basal forebrain atrophy in Alzheimer's disease using MRI. *Brain.* 2005;128(Pt 11):2626-2644.
15. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. *Nat Rev Dis Primers.* 2015;1:15056.
16. Golde TE, Eckman CB, Younkin SG. Biochemical detection of Abeta isoforms: implications for pathogenesis, diagnosis, and treatment of Alzheimer's disease. *Biochim Biophys Acta.* 2000;1502(1):172-187.
17. Ballatore C, Lee VM, Trojanowski JQ. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nat Rev Neurosci.* 2007;8(9):663-672.

18. Iqbal K, Liu F, Gong CX, Grundke-Iqbal I. Tau in Alzheimer disease and related tauopathies. *Curr Alzheimer Res.* 2010;7(8):656-664.
19. Wilson RS, Segawa E, Boyle PA, Anagnos SE, Hizel LP, Bennett DA. The natural history of cognitive decline in Alzheimer's disease. *Psychol Aging.* 2012;27(4):1008-1017.
20. Khyade VB, Khyade SV, Jagtap SG. Alzheimer's Disease: Overview. *International Academic Institute for Science and Technology.* 2016;3(12):23-38.
21. Gold CA, Budson AE. Memory loss in Alzheimer's disease: implications for development of therapeutics. *Expert Rev Neurother.* 2008;8(12):1879-1891.
22. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. *Front Neurol.* 2012;3:73.
23. Kukull WA, Brenner DE, Speck CE, et al. Causes of death associated with Alzheimer disease: variation by level of cognitive impairment before death. *J Am Geriatr Soc.* 1994;42(7):723-726.
24. Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST. Alzheimer disease and mortality: a 15-year epidemiological study. *Arch Neurol.* 2005;62(5):779-784.
25. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke.* 2011;42(9):2672-2713.
26. Good DC. *Cerebrovascular Disease.* Third ed. Boston: Butterworths; 1990.
27. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. *Cerebrovasc Dis.* 2009;27(5):493-501.
28. Cohen J, Fadul C, Jenkyn L, Ward T. Chapter 27 - Cerebrovascular Disorders. *Disorders of the Nervous System* 2008.
29. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord.* 2014;28(3):206-218.
30. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. *Lancet Neurol.* 2003;2(2):89-98.
31. Wardlaw JM. What causes lacunar stroke? *J Neurol Neurosurg Psychiatry.* 2005;76(5):617-619.
32. McKeith I. Dementia with Lewy bodies. *Dialogues Clin Neurosci.* 2004;6(3):333-341.
33. Jellinger KA. Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. *J Neural Transm (Vienna).* 2018;125(4):615-650.
34. Swenson R. Chapter 9 - Limbic System. *Review of Clinical and Function Neuroscience* 2006.
35. Mrak RE, Griffin WS. Dementia with Lewy bodies: Definition, diagnosis, and pathogenic relationship to Alzheimer's disease. *Neuropsychiatr Dis Treat.* 2007;3(5):619-625.
36. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc.* 2002;8(3):448-460.
37. Whalley LJ, Deary IJ, Appleton CL, Starr JM. Cognitive reserve and the neurobiology of cognitive aging. *Ageing Res Rev.* 2004;3(4):369-382.
38. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol.* 2012;11(11):1006-1012.

39. Pinter D, Enzinger C, Fazekas F. Cerebral small vessel disease, cognitive reserve and cognitive dysfunction. *J Neurol.* 2015;262(11):2411-2419.
40. Nunnari D, Bramanti P, Marino S. Cognitive reserve in stroke and traumatic brain injury patients. *Neurol Sci.* 2014;35(10):1513-1518.
41. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology.* 2006;66(12):1837-1844.
42. Hindle JV, Martyr A, Clare L. Cognitive reserve in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord.* 2014;20(1):1-7.
43. Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. *Alzheimer Dis Assoc Disord.* 2011;25(4):289-304.
44. Munoz DG, Ganapathy GR, Eliasziw M, Hachinski V. Educational attainment and socioeconomic status of patients with autopsy-confirmed Alzheimer disease. *Arch Neurol.* 2000;57(1):85-89.
45. Members ECC, Brayne C, Ince PG, et al. Education, the brain and dementia: neuroprotection or compensation? *Brain.* 2010;133(Pt 8):2210-2216.
46. Xu W, Tan L, Wang HF, et al. Education and Risk of Dementia: Dose-Response Meta-Analysis of Prospective Cohort Studies. *Mol Neurobiol.* 2016;53(5):3113-3123.
47. Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC Public Health.* 2014;14:643.
48. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annu Rev Public Health.* 1997;18:341-378.
49. Glymour MM, Avendano M, Kawachi I. *Socioeconomic Status and Health.* Second ed. New York: Oxford; 2014.
50. Jones RN, Manly J, Glymour MM, Rentz DM, Jefferson AL, Stern Y. Conceptual and measurement challenges in research on cognitive reserve. *J Int Neuropsychol Soc.* 2011;17(4):593-601.
51. Tucker-Seeley RD, Li Y, Sorensen G, Subramanian SV. Lifecourse socioeconomic circumstances and multimorbidity among older adults. *BMC Public Health.* 2011;11:313.
52. Maty SC, Lynch JW, Raghunathan TE, Kaplan GA. Childhood socioeconomic position, gender, adult body mass index, and incidence of type 2 diabetes mellitus over 34 years in the Alameda County Study. *Am J Public Health.* 2008;98(8):1486-1494.
53. Smith GD, Hart C, Blane D, Hole D. Adverse socioeconomic conditions in childhood and cause specific adult mortality: prospective observational study. *BMJ.* 1998;316(7145):1631-1635.
54. Lawlor DA, Ronalds G, Macintyre S, Clark H, Leon DA. Family socioeconomic position at birth and future cardiovascular disease risk: findings from the Aberdeen Children of the 1950s cohort study. *Am J Public Health.* 2006;96(7):1271-1277.
55. Marden JR, Tchetgen Tchetgen EJ, Kawachi I, Glymour MM. Contribution of Socioeconomic Status at 3 Life-Course Periods to Late-Life Memory Function and

Decline: Early and Late Predictors of Dementia Risk. *Am J Epidemiol.* 2017;186(7):805-814.
56. Lowry R, Kann L, Collins JL, Kolbe LJ. The effect of socioeconomic status on chronic disease risk behaviors among US adolescents. *JAMA.* 1996;276(10):792-797.
57. Tsolaki M. Clinical workout for the early detection of cognitive decline and dementia. *Eur J Clin Nutr.* 2014;68(11):1186-1191.
58. Velayudhan L, Ryu SH, Raczek M, et al. Review of brief cognitive tests for patients with suspected dementia. *Int Psychogeriatr.* 2014;26(8):1247-1262.
59. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. *JAMA.* 2014;312(23):2551-2561.
60. Scarpini E, Scheltens P, Feldman H. Treatment of Alzheimer's disease: current status and new perspectives. *Lancet Neurol.* 2003;2(9):539-547.
61. McKeith I. Dementia with Lewy bodies. *Handb Clin Neurol.* 2007;84:531-548.
62. Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. *JAMA.* 2002;288(11):1388-1395.
63. O'Brien JT, Thomas A. Vascular dementia. *Lancet.* 2015;386(10004):1698-1706.
64. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet.* 2011;377(9770):1019-1031.
65. Roberts R, Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med.* 2013;29(4):753-772.
66. Stephan BC, Matthews FE, McKeith IG, et al. Early cognitive change in the general population: how do different definitions work? *J Am Geriatr Soc.* 2007;55(10):1534-1540.
67. Alzheimer's A. 2010 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2010;6(2):158-194.
68. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* 2013;9(1):63-75 e62.
69. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. *Clin Geriatr Med.* 2014;30(3):421-442.
70. Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch Gen Psychiatry.* 1998;55(9):809-815.
71. Plassman BL, Langa KM, McCammon RJ, et al. Incidence of dementia and cognitive impairment, not dementia in the United States. *Ann Neurol.* 2011;70(3):418-426.
72. Ovbiagele B, Nguyen-Huynh MN. Stroke epidemiology: advancing our understanding of disease mechanism and therapy. *Neurotherapeutics.* 2011;8(3):319-329.
73. Kowal SL, Dall TM, Chakrabarti R, Storm MV, Jain A. The current and projected economic burden of Parkinson's disease in the United States. *Mov Disord.* 2013;28(3):311-318.
74. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *Am J Epidemiol.* 2003;157(11):1015-1022.

75. Vann Jones SA, O'Brien JT. The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. *Psychol Med.* 2014;44(4):673-683.
76. Savica R, Grossardt BR, Bower JH, Boeve BF, Ahlskog JE, Rocca WA. Incidence of dementia with Lewy bodies and Parkinson disease dementia. *JAMA Neurol.* 2013;70(11):1396-1402.
77. Yeo G. How will the U.S. healthcare system meet the challenge of the ethnogeriatric imperative? *J Am Geriatr Soc.* 2009;57(7):1278-1285.
78. Ortman JM, Velkoff VA, Hogan H. *An Aging Nation: The Older Population in the United States.* United States Census Bureau;2014.
79. Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimers Dement.* 2016;12(3):216-224.
80. Froehlich TE, Bogardus ST, Jr., Inouye SK. Dementia and race: are there differences between African Americans and Caucasians? *J Am Geriatr Soc.* 2001;49(4):477-484.
81. Manly J, Mayeux R. *Chapter 4 Ethnic Differences in Dementia and Alzheimer's Disease.* Washington, D.C.: The National Academies Press; 2004.
82. Tang MX, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. *Neurology.* 2001;56(1):49-56.
83. Knopman DS, Gottesman RF, Sharrett AR, et al. Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Alzheimers Dement (Amst).* 2016;2:1-11.
84. Chin AL, Negash S, Hamilton R. Diversity and disparity in dementia: the impact of ethnoracial differences in Alzheimer disease. *Alzheimer Dis Assoc Disord.* 2011;25(3):187-195.
85. Alzheimer's A. 2013 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2013;9(2):208-245.
86. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clin Epidemiol.* 2014;6:37-48.
87. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics--2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2007;115(5):e69-171.
88. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke.* 2009;40(4):1032-1037.
89. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol.* 2008;7(10):915-926.
90. Turtzo LC, McCullough LD. Sex differences in stroke. *Cerebrovasc Dis.* 2008;26(5):462-474.
91. Lam CS, Little WC. Sex and cardiovascular risk: are women advantaged or men disadvantaged? *Circulation.* 2012;126(8):913-915.

92. Nelson PT, Schmitt FA, Jicha GA, et al. Association between male gender and cortical Lewy body pathology in large autopsy series. *J Neurol.* 2010;257(11):1875-1881.
93. Shulman LM, Bhat V. Gender disparities in Parkinson's disease. *Expert Rev Neurother.* 2006;6(3):407-416.
94. Manly JJ, Merchant CA, Jacobs DM, et al. Endogenous estrogen levels and Alzheimer's disease among postmenopausal women. *Neurology.* 2000;54(4):833-837.
95. Karp DN, Wolff CS, Wiebe DJ, Branas CC, Carr BG, Mullen MT. Reassessing the Stroke Belt: Using Small Area Spatial Statistics to Identify Clusters of High Stroke Mortality in the United States. *Stroke.* 2016;47(7):1939-1942.
96. Mensah GA, Mokdad AH, Ford ES, Greenlund KJ, Croft JB. State of disparities in cardiovascular health in the United States. *Circulation.* 2005;111(10):1233-1241.
97. Glymour MM, Kosheleva A, Boden-Albala B. Birth and adult residence in the Stroke Belt independently predict stroke mortality. *Neurology.* 2009;73(22):1858-1865.
98. Glymour MM, Avendano M, Berkman LF. Is the 'stroke belt' worn from childhood?: risk of first stroke and state of residence in childhood and adulthood. *Stroke.* 2007;38(9):2415-2421.
99. Steenland K, MacNeil J, Vega I, Levey A. Recent trends in Alzheimer disease mortality in the United States, 1999 to 2004. *Alzheimer Dis Assoc Disord.* 2009;23(2):165-170.
100. Gilsanz P, Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Association Between Birth in a High Stroke Mortality State, Race, and Risk of Dementia. *JAMA Neurol.* 2017;74(9):1056-1062.
101. Glymour MM, Kosheleva A, Wadley VG, Weiss C, Manly JJ. Geographic distribution of dementia mortality: elevated mortality rates for black and white Americans by place of birth. *Alzheimer Dis Assoc Disord.* 2011;25(3):196-202.
102. Glymour MM, Kawachi I, Jencks CS, Berkman LF. Does childhood schooling affect old age memory or mental status? Using state schooling laws as natural experiments. *J Epidemiol Community Health.* 2008;62(6):532-537.
103. Mensah GA, Wei GS, Sorlie PD, et al. Decline in Cardiovascular Mortality: Possible Causes and Implications. *Circ Res.* 2017;120(2):366-380.
104. Wu YT, Fratiglioni L, Matthews FE, et al. Dementia in western Europe: epidemiological evidence and implications for policy making. *Lancet Neurol.* 2016;15(1):116-124.
105. Langa KM, Larson EB, Crimmins EM, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. *JAMA Intern Med.* 2017;177(1):51-58.
106. Hurd MD, Martorell P, Langa KM. Monetary costs of dementia in the United States. *N Engl J Med.* 2013;369(5):489-490.
107. Kelley AS, McGarry K, Gorges R, Skinner JS. The burden of health care costs for patients with dementia in the last 5 years of life. *Ann Intern Med.* 2015;163(10):729-736.
108. Brodaty H, Donkin M. Family caregivers of people with dementia. *Dialogues Clin Neurosci.* 2009;11(2):217-228.

109. Lin PJ, Neumann PJ. The economics of mild cognitive impairment. *Alzheimers Dement.* 2013;9(1):58-62.
110. Etters L, Goodall D, Harrison BE. Caregiver burden among dementia patient caregivers: a review of the literature. *J Am Acad Nurse Pract.* 2008;20(8):423-428.
111. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet.* 2005;366(9503):2112-2117.
112. Miech RA, Breitner JC, Zandi PP, Khachaturian AS, Anthony JC, Mayer L. Incidence of AD may decline in the early 90s for men, later for women: The Cache County study. *Neurology.* 2002;58(2):209-218.
113. Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH. Dementia incidence continues to increase with age in the oldest old: the 90+ study. *Ann Neurol.* 2010;67(1):114-121.
114. Gardner RC, Valcour V, Yaffe K. Dementia in the oldest old: a multi-factorial and growing public health issue. *Alzheimers Res Ther.* 2013;5(4):27.
115. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology.* 1998;51(3):728-733.
116. Kuruppu DK, Matthews BR. Young-onset dementia. *Semin Neurol.* 2013;33(4):365-385.
117. Aging NIo. Alzheimer's Disease Genetics Fact Sheet. *Causes of Alzheimer's Disease* 2015; https://www.nia.nih.gov/health/alzheimers-disease-genetics-fact-sheet. Accessed August 28, 2018.
118. Podcasy JL, Epperson CN. Considering sex and gender in Alzheimer disease and other dementias. *Dialogues Clin Neurosci.* 2016;18(4):437-446.
119. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis.* 2015;241(1):211-218.
120. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ.* 2006;332(7533):73-78.
121. George KM, Selvin E, Pankow JS, Windham BG, Folsom AR. Sex Differences in the Association of Diabetes With Cardiovascular Disease Outcomes Among African-American and White Participants in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol.* 2018;187(3):403-410.
122. Chatterjee S, Peters SA, Woodward M, et al. Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia. *Diabetes Care.* 2016;39(2):300-307.
123. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation.* 2012;125(1):e2-e220.
124. Knopman DS, Gottesman RF, Sharrett AR, et al. Midlife vascular risk factors and midlife cognitive status in relation to prevalence of mild cognitive impairment and dementia in later life: The Atherosclerosis Risk in Communities Study. *Alzheimers Dement.* 2018.

125. Harwood DG, Ownby RL. Ethnicity and dementia. *Curr Psychiatry Rep.* 2000;2(1):40-45.
126. Kurian AK, Cardarelli KM. Racial and ethnic differences in cardiovascular disease risk factors: a systematic review. *Ethn Dis.* 2007;17(1):143-152.
127. Ye J, Rust G, Baltrus P, Daniels E. Cardiovascular risk factors among Asian Americans: results from a National Health Survey. *Ann Epidemiol.* 2009;19(10):718-723.
128. Braveman PA, Cubbin C, Egerter S, Williams DR, Pamuk E. Socioeconomic disparities in health in the United States: what the patterns tell us. *Am J Public Health.* 2010;100 Suppl 1:S186-196.
129. Haan MN, Zeki Al-Hazzouri A, Aiello AE. Life-span socioeconomic trajectory, nativity, and cognitive aging in Mexican Americans: the Sacramento Area Latino Study on Aging. *J Gerontol B Psychol Sci Soc Sci.* 2011;66 Suppl 1:i102-110.
130. Paulson HL, Igo I. Genetics of dementia. *Semin Neurol.* 2011;31(5):449-460.
131. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol.* 2013;9(2):106-118.
132. O'Brien RJ, Wong PC. Amyloid precursor protein processing and Alzheimer's disease. *Annu Rev Neurosci.* 2011;34:185-204.
133. Reference GH. APOE Gene. 2018; https://ghr.nlm.nih.gov/gene/APOE.
134. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA.* 1997;278(16):1349-1356.
135. Singh PP, Singh M, Mastana SS. APOE distribution in world populations with new data from India and the UK. *Ann Hum Biol.* 2006;33(3):279-308.
136. Wirth M, Villeneuve S, La Joie R, Marks SM, Jagust WJ. Gene-environment interactions: lifetime cognitive activity, APOE genotype, and beta-amyloid burden. *J Neurosci.* 2014;34(25):8612-8617.
137. Bonifati V. Recent advances in the genetics of dementia with lewy bodies. *Curr Neurol Neurosci Rep.* 2008;8(3):187-189.
138. Orme T, Guerreiro R, Bras J. The Genetics of Dementia with Lewy Bodies: Current Understanding and Future Directions. *Curr Neurol Neurosci Rep.* 2018;18(10):67.
139. Vergouw LJM, van Steenoven I, van de Berg WDJ, et al. An update on the genetics of dementia with Lewy bodies. *Parkinsonism Relat Disord.* 2017;43:1-8.
140. Ross OA, Toft M, Whittle AJ, et al. Lrrk2 and Lewy body disease. *Ann Neurol.* 2006;59(2):388-393.
141. Tsuang D, Leverenz JB, Lopez OL, et al. APOE epsilon4 increases risk for dementia in pure synucleinopathies. *JAMA Neurol.* 2013;70(2):223-228.
142. Della-Morte D, Pacifici F, Rundek T. Genetic susceptibility to cerebrovascular disease. *Curr Opin Lipidol.* 2016;27(2):187-195.
143. Alberts MJ. Genetics of cerebrovascular disease. *Stroke.* 2004;35(2):342-344.
144. Schilling S, DeStefano AL, Sachdev PS, et al. APOE genotype and MRI markers of cerebrovascular disease: systematic review and meta-analysis. *Neurology.* 2013;81(3):292-300.

145. Zlokovic BV. Cerebrovascular effects of apolipoprotein E: implications for Alzheimer disease. *JAMA Neurol.* 2013;70(4):440-444.
146. Faraco G, Iadecola C. Hypertension: a harbinger of stroke and dementia. *Hypertension.* 2013;62(5):810-817.
147. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation.* 2003;107(22):2864-2869.
148. Scuteri A, Nilsson PM, Tzourio C, Redon J, Laurent S. Microvascular brain damage with aging and hypertension: pathophysiological consideration and clinical implications. *J Hypertens.* 2011;29(8):1469-1477.
149. Iadecola C, Yaffe K, Biller J, et al. Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association. *Hypertension.* 2016;68(6):e67-e94.
150. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. *Stroke.* 2004;35(4):1024.
151. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. *Epidemiology.* 2011;22(5):646-659.
152. Hou L, Li Q, Jiang L, et al. Hypertension and Diagnosis of Parkinson's Disease: A Meta-Analysis of Cohort Studies. *Front Neurol.* 2018;9:162.
153. Kiliaan AJ, Arnoldussen IA, Gustafson DR. Adipokines: a link between obesity and dementia? *Lancet Neurol.* 2014;13(9):913-923.
154. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes Rev.* 2011;12(5):e426-437.
155. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology.* 2008;71(14):1057-1064.
156. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol.* 2005;62(10):1556-1560.
157. Gustafson DR, Backman K, Waern M, et al. Adiposity indicators and dementia over 32 years in Sweden. *Neurology.* 2009;73(19):1559-1566.
158. Chen J, Guan Z, Wang L, Song G, Ma B, Wang Y. Meta-analysis: overweight, obesity, and Parkinson's disease. *Int J Endocrinol.* 2014;2014:203930.
159. Chan PC, Wei CY, Hung GU, Chiu PY. Reduced vascular risk factors in Parkinson's disease dementia and dementia with Lewy bodies compared to Alzheimer's disease. *Brain Behav.* 2018;8(3):e00916.
160. Ninomiya T. Diabetes mellitus and dementia. *Curr Diab Rep.* 2014;14(5):487.
161. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol.* 2006;5(1):64-74.
162. Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP. The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care.* 2005;28(3):726-735.

163. Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *J Clin Exp Neuropsychol.* 2004;26(8):1044-1080.
164. Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. *Diabetes Care.* 2007;30(4):842-847.
165. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes.* 2005;54(6):1615-1625.
166. Wright RJ, Frier BM. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? *Diabetes Metab Res Rev.* 2008;24(5):353-363.
167. Park CR. Cognitive effects of insulin in the central nervous system. *Neurosci Biobehav Rev.* 2001;25(4):311-323.
168. Martin MG, Pfrieger F, Dotti CG. Cholesterol in brain disease: sometimes determinant and frequently implicated. *EMBO Rep.* 2014;15(10):1036-1052.
169. Shobab LA, Hsiung GY, Feldman HH. Cholesterol in Alzheimer's disease. *Lancet Neurol.* 2005;4(12):841-852.
170. van Vliet P. Cholesterol and late-life cognitive decline. *J Alzheimers Dis.* 2012;30 Suppl 2:S147-162.
171. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. *Am J Geriatr Psychiatry.* 2008;16(5):343-354.
172. Bosco DA, Fowler DM, Zhang Q, et al. Elevated levels of oxidized cholesterol metabolites in Lewy body disease brains accelerate alpha-synuclein fibrilization. *Nat Chem Biol.* 2006;2(5):249-253.
173. Yaghi S, Elkind MS. Lipids and Cerebrovascular Disease: Research and Practice. *Stroke.* 2015;46(11):3322-3328.
174. Luepker RV. *Smoking and Passive Smoking.* New York: demosMEDICAL; 2015.
175. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. *Expert Rev Cardiovasc Ther.* 2010;8(7):917-932.
176. Zhong G, Wang Y, Zhang Y, Guo JJ, Zhao Y. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. *PLoS One.* 2015;10(3):e0118333.
177. Tsuang D, Larson EB, Li G, et al. Association between lifetime cigarette smoking and lewy body accumulation. *Brain Pathol.* 2010;20(2):412-418.
178. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology.* 2012;23(1):119-128.
179. Hernan MA, Alonso A, Logroscino G. Cigarette smoking and dementia: potential selection bias in the elderly. *Epidemiology.* 2008;19(3):448-450.
180. Kim JW, Lee DY, Lee BC, et al. Alcohol and cognition in the elderly: a review. *Psychiatry Investig.* 2012;9(1):8-16.
181. Sachdeva A, Chandra M, Choudhary M, Dayal P, Anand KS. Alcohol-Related Dementia and Neurocognitive Impairment: A Review Study. *Int J High Risk Behav Addict.* 2016;5(3):e27976.
182. Ritchie K, Villebrun D. Epidemiology of alcohol-related dementia. *Handb Clin Neurol.* 2008;89:845-850.

183. Campbell CA, Hahn RA, Elder R, et al. The effectiveness of limiting alcohol outlet density as a means of reducing excessive alcohol consumption and alcohol-related harms. *Am J Prev Med.* 2009;37(6):556-569.
184. Anstey KJ, Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. *Am J Geriatr Psychiatry.* 2009;17(7):542-555.
185. Boot BP, Orr CF, Ahlskog JE, et al. Risk factors for dementia with Lewy bodies: a case-control study. *Neurology.* 2013;81(9):833-840.
186. Collaborators GA. Alcohol Use and Burden for 195 Countries and Territories, 1990-2016: A Systematic Analysis for the Global Burden of Disease Study 2016. *The Lancet.* 2018;S0140-6736.
187. Holmes MV, Dale CE, Zuccolo L, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ.* 2014;349:g4164.
188. Stockwell T, Zhao J, Panwar S, Roemer A, Naimi T, Chikritzhs T. Do "Moderate" Drinkers Have Reduced Mortality Risk? A Systematic Review and Meta-Analysis of Alcohol Consumption and All-Cause Mortality. *J Stud Alcohol Drugs.* 2016;77(2):185-198.
189. Larsson SC, Traylor M, Malik R, et al. Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *BMJ.* 2017;359:j5375.
190. Eapen DJ, Bhatia NK, Patel A, Cassimatis D, Sperling L. *Primary Prevention of Cardiovascular Disease Guidelines.* New York: demosMedical; 2015.
191. Lourida I, Soni M, Thompson-Coon J, et al. Mediterranean diet, cognitive function, and dementia: a systematic review. *Epidemiology.* 2013;24(4):479-489.
192. Martinez-Gonzalez MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, et al. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. *BMJ.* 2008;336(7657):1348-1351.
193. Mitrou PN, Kipnis V, Thiebaut AC, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. *Arch Intern Med.* 2007;167(22):2461-2468.
194. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr.* 2010;92(5):1189-1196.
195. Gardener H, Wright CB, Gu Y, et al. Mediterranean-style diet and risk of ischemic stroke, myocardial infarction, and vascular death: the Northern Manhattan Study. *Am J Clin Nutr.* 2011;94(6):1458-1464.
196. Estruch R, Ros E, Salas-Salvado J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med.* 2018;378(25):e34.
197. Morris MC. Nutrition and risk of dementia: overview and methodological issues. *Ann N Y Acad Sci.* 2016;1367(1):31-37.
198. Smith PJ, Blumenthal JA, Babyak MA, et al. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. *Hypertension.* 2010;55(6):1331-1338.

199. Tangney CC, Li H, Wang Y, et al. Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons. *Neurology.* 2014;83(16):1410-1416.
200. Otaegui-Arrazola A, Amiano P, Elbusto A, Urdaneta E, Martinez-Lage P. Diet, cognition, and Alzheimer's disease: food for thought. *Eur J Nutr.* 2014;53(1):1-23.
201. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. *Alzheimers Dement.* 2015;11(9):1015-1022.
202. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement.* 2015;11(9):1007-1014.
203. Denkinger MD, Nikolaus T, Denkinger C, Lukas A. Physical activity for the prevention of cognitive decline: current evidence from observational and controlled studies. *Z Gerontol Geriatr.* 2012;45(1):11-16.
204. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. *BMC Public Health.* 2014;14:510.
205. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc.* 2011;86(9):876-884.
206. Foster PP, Rosenblatt KP, Kuljis RO. Exercise-induced cognitive plasticity, implications for mild cognitive impairment and Alzheimer's disease. *Front Neurol.* 2011;2:28.
207. Erickson KI, Prakash RS, Voss MW, et al. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. *J Neurosci.* 2010;30(15):5368-5375.
208. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A.* 2011;108(7):3017-3022.
209. Voss MW, Prakash RS, Erickson KI, et al. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci.* 2010;2.
210. Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J Neurosci.* 2001;21(5):1628-1634.
211. Kenyon CJ. The genetics of ageing. *Nature.* 2010;464(7288):504-512.
212. Samieri C, Perier MC, Gaye B, et al. Association of Cardiovascular Health Level in Older Age With Cognitive Decline and Incident Dementia. *JAMA.* 2018;320(7):657-664.
213. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol.* 2014;13(8):788-794.
214. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol.* 2006;5(9):735-741.

215. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA.* 1991;265(24):3255-3264.
216. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet.* 1998;352(9137):1347-1351.
217. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med.* 2003;163(9):1069-1075.
218. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens.* 2003;21(5):875-886.
219. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA.* 2008;300(9):1027-1037.
220. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet.* 2015;385(9984):2255-2263.
221. Train the Brain C. Randomized trial on the effects of a combined physical/cognitive training in aged MCI subjects: the Train the Brain study. *Sci Rep.* 2017;7:39471.
222. Lamb SE, Sheehan B, Atherton N, et al. Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. *BMJ.* 2018;361:k1675.
223. Martinez-Lapiscina EH, Clavero P, Toledo E, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. *J Neurol Neurosurg Psychiatry.* 2013;84(12):1318-1325.
224. Wardle J, Rogers P, Judd P, et al. Randomized trial of the effects of cholesterol-lowering dietary treatment on psychological function. *Am J Med.* 2000;108(7):547-553.
225. Sano M, Bell KL, Galasko D, et al. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. *Neurology.* 2011;77(6):556-563.
226. Feldman HH, Doody RS, Kivipelto M, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology.* 2010;74(12):956-964.
227. Sparks DL, Connor DJ, Sabbagh MN, Petersen RB, Lopez J, Browne P. Circulating cholesterol levels, apolipoprotein E genotype and dementia severity influence the benefit of atorvastatin treatment in Alzheimer's disease: results of the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial. *Acta Neurol Scand Suppl.* 2006;185:3-7.

228. Investigators TA. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol.* 1989;129(4):687-702.
229. Study ARIC. Atherosclerosis Risk in Communities Study Description. 2018, 2018.
230. George KM, Folsom AR, Kucharska-Newton A, Mosley TH, Heiss G. Factors Related to Differences in Retention among African American and White Participants in the Atherosclerosis Risk in Communities Study (ARIC) Prospective Cohort: 1987-2013. *Ethn Dis.* 2017;27(1):31-38.
231. Cerhan JR, Folsom AR, Mortimer JA, et al. Correlates of cognitive function in middle-aged adults. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Gerontology.* 1998;44(2):95-105.
232. Rawlings AM, Bandeen-Roche K, Gross AL, et al. Factor structure of the ARIC-NCS Neuropsychological Battery: An evaluation of invariance across vascular factors and demographic characteristics. *Psychol Assess.* 2016;28(12):1674-1683.
233. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord.* 2008;23(15):2129-2170.
234. Hachinski V, Oveisgharan S, Romney AK, Shankle WR. Optimizing the Hachinski Ischemic Scale. *Arch Neurol.* 2012;69(2):169-175.
235. Lynch J, Smith GD. A life course approach to chronic disease epidemiology. *Annu Rev Public Health.* 2005;26:1-35.
236. Galobardes B, Shaw M, Lawlor DA, Smith GD, Lynch J. *Methods in Social Epidemiology.* San Francisco, CA: Jossey-Bass; 2006.
237. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. *J Epidemiol Community Health.* 2003;57(10):778-783.
238. Whalley LJ, Dick FD, McNeill G. A life-course approach to the aetiology of late-onset dementias. *Lancet Neurol.* 2006;5(1):87-96.
239. Pollitt RA, Rose KM, Kaufman JS. Evaluating the evidence for models of life course socioeconomic factors and cardiovascular outcomes: a systematic review. *BMC Public Health.* 2005;5:7.
240. Gottesman RF, Albert MS, Alonso A, et al. Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. *JAMA Neurol.* 2017;74(10):1246-1254.
241. Wu YT, Prina AM, Brayne C. The association between community environment and cognitive function: a systematic review. *Soc Psychiatry Psychiatr Epidemiol.* 2015;50(3):351-362.
242. Rusmaully J, Dugravot A, Moatti JP, et al. Contribution of cognitive performance and cognitive decline to associations between socioeconomic factors and dementia: A cohort study. *PLoS Med.* 2017;14(6):e1002334.
243. Staff RT, Chapko D, Hogan MJ, Whalley LJ. Life course socioeconomic status and the decline in information processing speed in late life. *Soc Sci Med.* 2016;151:130-138.

244. Dekhtyar S, Wang HX, Scott K, Goodman A, Koupil I, Herlitz A. A Life-Course Study of Cognitive Reserve in Dementia--From Childhood to Old Age. *Am J Geriatr Psychiatry.* 2015;23(9):885-896.
245. Yaffe K, Falvey C, Harris TB, et al. Effect of socioeconomic disparities on incidence of dementia among biracial older adults: prospective study. *BMJ.* 2013;347:f7051.
246. Fischer C, Yeung E, Hansen T, et al. Impact of socioeconomic status on the prevalence of dementia in an inner city memory disorders clinic. *Int Psychogeriatr.* 2009;21(6):1096-1104.
247. Marengoni A, Fratiglioni L, Bandinelli S, Ferrucci L. Socioeconomic status during lifetime and cognitive impairment no-dementia in late life: the population-based aging in the Chianti Area (InCHIANTI) Study. *J Alzheimers Dis.* 2011;24(3):559-568.
248. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimaki M, Batty GD. Socioeconomic status as a risk factor for dementia death: individual participant meta-analysis of 86 508 men and women from the UK. *Br J Psychiatry.* 2013;203(1):10-17.
249. Melrose RJ, Brewster P, Marquine MJ, et al. Early life development in a multiethnic sample and the relation to late life cognition. *J Gerontol B Psychol Sci Soc Sci.* 2015;70(4):519-531.
250. Everson-Rose SA, Mendes de Leon CF, Bienias JL, Wilson RS, Evans DA. Early life conditions and cognitive functioning in later life. *Am J Epidemiol.* 2003;158(11):1083-1089.
251. Turrell G, Lynch JW, Kaplan GA, et al. Socioeconomic position across the lifecourse and cognitive function in late middle age. *J Gerontol B Psychol Sci Soc Sci.* 2002;57(1):S43-51.
252. Kim GH, Lee HA, Park H, et al. Effect of Individual and District-level Socioeconomic Disparities on Cognitive Decline in Community-dwelling Elderly in Seoul. *J Korean Med Sci.* 2017;32(9):1508-1515.
253. Diez Roux AV, Mair C. Neighborhoods and health. *Ann N Y Acad Sci.* 2010;1186:125-145.
254. Carson AP, Rose KM, Catellier DJ, et al. Cumulative socioeconomic status across the life course and subclinical atherosclerosis. *Ann Epidemiol.* 2007;17(4):296-303.
255. Rawlings AM, Sharrett AR, Schneider AL, et al. Diabetes in midlife and cognitive change over 20 years: a cohort study. *Ann Intern Med.* 2014;161(11):785-793.
256. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res.* 2011;20(1):40-49.
257. Karlamangla AS, Miller-Martinez D, Aneshensel CS, Seeman TE, Wight RG, Chodosh J. Trajectories of cognitive function in late life in the United States: demographic and socioeconomic predictors. *Am J Epidemiol.* 2009;170(3):331-342.
258. Cadar D, Lassale C, Davies H, Llewellyn DJ, Batty GD, Steptoe A. Individual and Area-Based Socioeconomic Factors Associated With Dementia Incidence in

England: Evidence From a 12-Year Follow-up in the English Longitudinal Study of Ageing. *JAMA Psychiatry.* 2018;75(7):723-732.
259. Galea S, Vaughan R. Socioeconomic Status, Principles, and Pragmatism: A Public Health of Consequence, June 2019. *Am J Public Health.* 2019;109(6):842-843.
260. Reuben A. Childhood Lead Exposure and Adult Neurodegenerative Disease. *J Alzheimers Dis.* 2018;64(1):17-42.
261. Fuller-Thomson E, Jopling SA. Exposure to lead in petrol and increased incidence of dementia. *Lancet.* 2017;389(10087):2371.
262. Kilian J, Kitazawa M. The emerging risk of exposure to air pollution on cognitive decline and Alzheimer's disease - Evidence from epidemiological and animal studies. *Biomed J.* 2018;41(3):141-162.
263. How does the thyroid gland work? 2010; https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072572/. Accessed April 12, 2018.
264. Santisteban P. *Werner & Ingbar's The Thyroid A Fundamental and Clinical Text.* Tenth ed. Philadelphia: Lippincott Williams & Wilkins; 2013.
265. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. *Physiol Rev.* 2014;94(2):355-382.
266. Rousset B, Dupuy C, Miot F, Dumount J. *Endotext.* South Dartmouth, MA: Endotext [Internet]; 2000.
267. Hiller-Sturmhofel S, Bartke A. The endocrine system: an overview. *Alcohol Health Res World.* 1998;22(3):153-164.
268. Stathatos N. Thyroid physiology. *Med Clin North Am.* 2012;96(2):165-173.
269. Visser WE, Visser TJ, Peeters RP. Thyroid disorders in older adults. *Endocrinol Metab Clin North Am.* 2013;42(2):287-303.
270. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid.* 2012;22(12):1200-1235.
271. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid.* 2016;26(10):1343-1421.
272. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab.* 2002;87(2):489-499.
273. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. *Autoimmun Rev.* 2015;14(2):174-180.
274. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. *N Engl J Med.* 2003;348(26):2646-2655.
275. McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity. *Endocrine.* 2012;42(2):252-265.
276. Frohlich E, Wahl R. Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. *Front Immunol.* 2017;8:521.

277. Samuels MH. Thyroid disease and cognition. *Endocrinol Metab Clin North Am.* 2014;43(2):529-543.
278. Beydoun MA, Beydoun HA, Rostant OS, et al. Thyroid hormones are associated with longitudinal cognitive change in an urban adult population. *Neurobiol Aging.* 2015;36(11):3056-3066.
279. Smith JW, Evans AT, Costall B, Smythe JW. Thyroid hormones, brain function and cognition: a brief review. *Neurosci Biobehav Rev.* 2002;26(1):45-60.
280. Brent GA. Mechanisms of thyroid hormone action. *J Clin Invest.* 2012;122(9):3035-3043.
281. Flanagan EP, Caselli RJ. Autoimmune encephalopathy. *Semin Neurol.* 2011;31(2):144-157.
282. de Jong FJ, Masaki K, Chen H, et al. Thyroid function, the risk of dementia and neuropathologic changes: the Honolulu-Asia aging study. *Neurobiol Aging.* 2009;30(4):600-606.
283. Chaker L, Wolters FJ, Bos D, et al. Thyroid function and the risk of dementia: The Rotterdam Study. *Neurology.* 2016;87(16):1688-1695.
284. Napthali K, Boyle M, Tran H, et al. Thyroid antibodies, autoimmunity and cognitive decline: is there a population-based link? *Dement Geriatr Cogn Dis Extra.* 2014;4(2):140-146.
285. Pasqualetti G, Pagano G, Rengo G, Ferrara N, Monzani F. Subclinical Hypothyroidism and Cognitive Impairment: Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab.* 2015;100(11):4240-4248.
286. Yeap BB, Alfonso H, Chubb SA, et al. Higher free thyroxine levels predict increased incidence of dementia in older men: the Health in Men Study. *J Clin Endocrinol Metab.* 2012;97(12):E2230-2237.
287. Volpato S, Guralnik JM, Fried LP, Remaley AT, Cappola AR, Launer LJ. Serum thyroxine level and cognitive decline in euthyroid older women. *Neurology.* 2002;58(7):1055-1061.
288. Moon JH, Park YJ, Kim TH, et al. Lower-but-normal serum TSH level is associated with the development or progression of cognitive impairment in elderly: Korean Longitudinal Study on Health and Aging (KLoSHA). *J Clin Endocrinol Metab.* 2014;99(2):424-432.
289. Tan ZS, Beiser A, Vasan RS, et al. Thyroid function and the risk of Alzheimer disease: the Framingham Study. *Arch Intern Med.* 2008;168(14):1514-1520.
290. Martin SS, Daya N, Lutsey PL, et al. Thyroid Function, Cardiovascular Risk Factors, and Incident Atherosclerotic Cardiovascular Disease: The Atherosclerosis Risk in Communities (ARIC) Study. *J Clin Endocrinol Metab.* 2017;102(9):3306-3315.
291. Schultheiss UT, Teumer A, Medici M, et al. A genetic risk score for thyroid peroxidase antibodies associates with clinical thyroid disease in community-based populations. *J Clin Endocrinol Metab.* 2015;100(5):E799-807.
292. Goff DC, Jr., Howard G, Wang CH, et al. Trends in severity of hospitalized myocardial infarction: the atherosclerosis risk in communities (ARIC) study, 1987-1994. *Am Heart J.* 2000;139(5):874-880.

293. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol.* 1996;49(2):223-233.
294. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J.* 2009;158(1):111-117.
295. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke.* 1999;30(4):736-743.
296. Mayeda ER, Filshtein TJ, Tripodis Y, Glymour MM, Gross AL. Does selective survival before study enrolment attenuate estimated effects of education on rate of cognitive decline in older adults? A simulation approach for quantifying survival bias in life course epidemiology. *Int J Epidemiol.* 2018;47(5):1507-1517.
297. Iddah MA, Macharia BN. Autoimmune thyroid disorders. *ISRN Endocrinol.* 2013;2013:509764.
298. Bensenor IM, Olmos RD, Lotufo PA. Hypothyroidism in the elderly: diagnosis and management. *Clin Interv Aging.* 2012;7:97-111.
299. Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. *N Engl J Med.* 2002;346(4):257-270.
300. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA.* 1992;267(1):64-69.
301. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache.* 2001;41(7):646-657.
302. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology.* 2007;68(5):343-349.
303. Cutrer FM, Smith JH. Human studies in the pathophysiology of migraine: genetics and functional neuroimaging. *Headache.* 2013;53(2):401-412.
304. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. *J Neurosci.* 2015;35(17):6619-6629.
305. Sprenger T, Borsook D. Migraine changes the brain: neuroimaging makes its mark. *Curr Opin Neurol.* 2012;25(3):252-262.
306. Ferrari MD, Klever RR, Terwindt GM, Ayata C, van den Maagdenberg AM. Migraine pathophysiology: lessons from mouse models and human genetics. *Lancet Neurol.* 2015;14(1):65-80.
307. DeLange JM, Cutrer FM. Our evolving understanding of migraine with aura. *Curr Pain Headache Rep.* 2014;18(10):453.
308. Silberstein SD. Migraine pathophysiology and its clinical implications. *Cephalalgia.* 2004;24 Suppl 2:2-7.
309. Graham JR, Wolff HG. Mechanism of Migraine Headache and Action of Ergotamine Tartrate. *American Medical Association Archives of Neurology and Psychiatry.* 1938;39(4):737-763.
310. Durham PL. Calcitonin gene-related peptide (CGRP) and migraine. *Headache.* 2006;46 Suppl 1:S3-8.

311. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol.* 2018;17(2):174-182.
312. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ.* 2009;339:b3914.
313. Hamedani AG, Rose KM, Peterlin BL, et al. Migraine and white matter hyperintensities: the ARIC MRI study. *Neurology.* 2013;81(15):1308-1313.
314. Bashir A, Lipton RB, Ashina S, Ashina M. Migraine and structural changes in the brain: a systematic review and meta-analysis. *Neurology.* 2013;81(14):1260-1268.
315. Paemeleire K. Brain lesions and cerebral functional impairment in migraine patients. *J Neurol Sci.* 2009;283(1-2):134-136.
316. Kapasi A, Schneider JA. Vascular contributions to cognitive impairment, clinical Alzheimer's disease, and dementia in older persons. *Biochim Biophys Acta.* 2016;1862(5):878-886.
317. Liu W, Wong A, Law AC, Mok VC. Cerebrovascular disease, amyloid plaques, and dementia. *Stroke.* 2015;46(5):1402-1407.
318. Rist PM, Kurth T. Migraine and cognitive decline: a topical review. *Headache.* 2013;53(4):589-598.
319. Kalaydjian A, Zandi PP, Swartz KL, Eaton WW, Lyketsos C. How migraines impact cognitive function: findings from the Baltimore ECA. *Neurology.* 2007;68(17):1417-1424.
320. Rist PM, Kang JH, Buring JE, Glymour MM, Grodstein F, Kurth T. Migraine and cognitive decline among women: prospective cohort study. *BMJ.* 2012;345:e5027.
321. Rist PM, Dufouil C, Glymour MM, Tzourio C, Kurth T. Migraine and cognitive decline in the population-based EVA study. *Cephalalgia.* 2011;31(12):1291-1300.
322. Hagen K, Stordal E, Linde M, Steiner TJ, Zwart JA, Stovner LJ. Headache as a risk factor for dementia: a prospective population-based study. *Cephalalgia.* 2014;34(5):327-335.
323. Hagen K, Zwart JA, Vatten L, Stovner LJ, Bovim G. Head-HUNT: validity and reliability of a headache questionnaire in a large population-based study in Norway. *Cephalalgia.* 2000;20(4):244-251.
324. Lipton RB, Dodick D, Sadovsky R, et al. A self-administered screener for migraine in primary care: The ID Migraine validation study. *Neurology.* 2003;61(3):375-382.
325. Stang PE, Carson AP, Rose KM, et al. Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. *Neurology.* 2005;64(9):1573-1577.
326. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ.* 2005;330(7482):63.
327. Bousser MG, Welch KM. Relation between migraine and stroke. *Lancet Neurol.* 2005;4(9):533-542.

APPENDIX

Life Course SES (Chapter 5)

Table A. 1. Literature review of the association between socioeconomic status and cognitive impairment

Citation	Study Design	Population	Exposure	Follow-up Time	Outcome(s)	Results
Wu, 2015[241]	Systematic-Review (n studies = 15)	Participants from US, UK, The Netherlands, China, and Singapore	Community-Level SES (poverty, homeownership, education, etc.)	n/a	MMSE, 3MSE, TICS, cognitive function tests	11 studies found significant associations between community-level SES and cognitive function
Rusmaully, 2017[242]	Prospective Cohort (n = 7,499)	Whitehall II Study (age: 45-69)	Individual-Level SES (education and occupation)	18.0 years	Global cognitive function test, dementia	SES was not associated with cognitive decline or dementia
Staff, 2016[243]	Prospective Cohort (n = 478)	Aberdeen Birth Cohort (age: 63-78)	Individual-Level SES (education, parent and participant occupation)	15.0 years	Cognitive function test (Digit Symbol Substitution)	SES is not associated with decline in cognitive test score
Dekhtyar, 2015[244]	Prospective Cohort (n = 7,574)	Uppsala Birth Cohort Multigenerational Study (age: 41-55)	Life Course Cognitive Reserve (education, school grades, occupational complexity)	21.0 years	Dementia	Higher graders in school and high occupational complexity were associated with reduced risk of dementia

Yaffe, 2013[245]	Prospective Cohort (n = 2,457)	Health, Aging, and Body Composition Study (age: 70-79)	Individual- Level SES (family income, financial inadequacy, education, literacy)	12.0 years	Dementia	SES was not associated with risk of dementia by race (Black/White), but SES may account for increased risk of dementia in Blacks
Glymour, 2008[102]	Prospective Cohort (n = 11,427 and 5% of US Census 1980 sample)	Health and Retirement Study and US Census 1980 (age: 66-33)	Compulsory schooling law-induced change in educational attainment (as instrumental variable)	3.9 years	MMSE, Cognitive function tests (Delayed Word Recall), TICS	Education is statistically significantly associated with memory and mental status due to the causal effect of education
Fischer, 2009[246]	Case-Control (n = 217)	Patients from Toronto's St. Michael's Hospital Memory Disorders Clinic (age: 21-91)	Individual and Neighborhood-Level SES (annual income and neighborhood income quartiles)	4.0 years	Dementia	Low annual income was significantly associated with dementia while low neighborhood income was not associated
Marengoni, 2011[247]	Prospective Cohort (n = 1,012)	Aging in the Chianti Area: InCHIANTI Study (age: 65+)	Individual- Level SES (education, occupation, job stress, financial condition)	3.0 years	MMSE, Activities of Daily Living questionnaire	Low education, manual occupation, and high job physical demands were significantly associated with incident cognitive impairment without dementia
Russ, 2013[248]	Meta-Analysis (n = 86,508; n studies = 11)	Cross-sectional studies from Health	Individual-Level SES (occupation, education)	n/a	Dementia-Related Death	No association between social class and dementia, but an

		Survey of England (age: 35-107)				association between low education and dementia in women
Melrose, 2015[249]	Prospective Cohort (n = 333)	UC Davis Aging Diversity Cohort (age: 60+)	Childhood Individual-Level SES (morphometric data, parents' education, father's occupation, siblings, etc.)	4.0 years	Cognitive function tests (Spanish and English Neuropsychological Assessment Scales)	Low SES was associated with greater decline in SENAS score
Marden, 2017[55]	Prospective Cohort (n = 10,781)	Health and Retirement Study (HRS) (age: 50+)	Individual-Level Life Course SES (childhood, early adult, late-life)	14.0 years	Cognitive function tests (Delayed word recall and Informant Questionnaire for Cognitive Decline)	Stable high SES was associated with best memory function and slowest cognitive decline over 10 years
Everson-Rose, 2003[250]	Prospective Cohort (n = 4,398)	Chicago Health and Aging Project (ages: 65+)	Individual-Level Childhood SES (parent occupation, parent education, family financial status, etc.)		MMSE and Cognitive function tests (Symbol Digit Modalities Test)	Childhood SES was not statistically significantly associated with cognitive change
Turrell, 2002[251]	Cross-sectional (n = 486)	Kuopio Ischemic Heart Disease Risk Factor Study	Life Course Individual-Level SES (education,	n/a	Cognitive function tests (Trail Making,	Lower SES associated with worse performance on cognitive tests;

		(ages: 58-64)	income, socioeconomic trajectory)		Selective Reminding, Verbal Fluency, Visual Reproduction, and MMSE)	Upward mobility reduced risk of decline whereas downward mobility did not increase risk of decline
Kim, 2017[252]	Retrospective Cohort (n = 136,217)	Seoul Dementia Management Project (SDMP) (ages: 60-90)	Individual and Neighborhood-Level SES (medical aid, education, income)	3.0 years	Cognitive impairment (defined by MMSE score)	Low SES at the individual and neighborhood levels, low education, and history of stroke were independent risk factors for cognitive impairment
Haan, 2011[129]	Prospective Cohort (n = 1,789)	Sacramento Area Latino Study on Aging (SALSA) (ages: 60-101)	Life Course Individual-Level SES (child and adulthood)	9.0 years	3MSE and Spanish English Verbal Learning Test (SEVLT)	Participants with advantages life course SES trajectories were less likely to have cognitive decline; association stronger in first and second generation Mexican families

Abbreviations: MMSE: Mini-mental State Exam; 3MSE: modified Mini-mental State Examination; TICS: Telephone Interview for Cognitive Status

Table A. 2. Relative risks (95% CI) of adjudicated dementia and MCI per pooled standard deviation increment in cumulative individual LC-SES and cumulative individual LC-SES with education removed, ARIC 1987-2013

Cumulative Individual Life Course SES†			
		White	**African American**
		n total = 8,588	**n total = 2,617**
		n events = 1,257	**n events = 389**
Model 1 RR		0.98 (0.92, 1.04)	0.94 (0.85, 1.04)
Model 2 RR		0.97 (0.91, 1.03)	0.91 (0.82, 1.02)
Cumulative Individual Life Course SES With Education Adjusted Separately ‡			
		White	**African American**
		n total = 8,588	**n total = 2,617**
		n events = 1,257	**n events = 389**
Model 1 RR	**LC-SES**	0.90* (0.84, 0.96)	0.88* (0.78, 1.00)
	Education		
	Some High School or Less	1 (Ref)	1 (Ref)
	High School Graduate	1.32* (1.11, 1.57)	1.03 (0.82, 1.29)
	Some College or More	1.40* (1.15, 1.69)	1.14 (0.88, 1.47)
Model 2 RR	**LC-SES**	0.90* (0.84, 0.96)	0.87* (0.76, 0.99)
	Education		
	Some High School or Less	1 (Ref)	1 (Ref)

	High School Graduate	1.31* (1.09, 1.56)	0.98 (0.78, 1.24)
	Some College or More	1.39* (1.14, 1.68)	1.09 (0.84, 1.41)

*Statistically significant (p-value < 0.05)
†Pooled standard deviation = 2.79
‡Pooled standard deviation = 2.29
Model 1: adjusted for age, sex, and *ApoE4* status
Model 2: adjusted for Model 1 + BMI, hypertension, diabetes, HDL cholesterol, total cholesterol, alcohol drinking status, tobacco smoking status

Table A. 3. Relative risks (95% CI) of dementia and MCI per standard deviation† increment of cumulative neighborhood LC-SES, ARIC 1987-2013

	White	**African American**
	n total = 8,588	**n total = 2,617**
	n events = 1,257	**n events = 389**
Model 1 RR	0.97 (0.94, 1.01)	0.99 (0.93, 1.05)
Model 2 RR	0.97 (0.94, 1.01)	0.98 (0.92, 1.05)

Abbreviation: HR: Hazard ratio; CI: Confidence interval

†Standard deviation = 1 for whites and African Americans

Model 1: adjusted for age, sex, *ApoE4* status, and cumulative individual LC-SES

Model 2: adjusted for Model 1 + BMI, hypertension, diabetes, HDL cholesterol, Total cholesterol, alcohol drinking status, tobacco smoking status

Thyroid Dysfunction (Chapter 6)

Table A. 4. Literature review of the association between thyroid function and cognitive impairment

Citation	Study Design	Population	Exposure	Mean Follow-up	Outcome	Results
Beydoun, 2015[278]	Prospective Cohort (n = 2,630)	Whites and Blacks in Baltimore, MD (age: 30-64)	TSH, T4, FT4, T3	4.6 years	Cognitive Test Scores	Higher TSH associated with faster cognitive decline
de Jong, 2009[282]	Prospective Cohort (n = 665)	Japanese-American men (age: 71-93)	FT4, T4	4.7 years	Incident Dementia and brain autopsy in sub-sample (n = 143)	Greater T4 and FT4 (per SD) associated with 20% and 30% higher hazard of dementia; greater T4 associated with higher number of plaques and tangles
Chaker, 2016[283]	Prospective Cohort (n = 9,446)	Rotterdam Study (mean age: 65)	TSH, FT4, TPO	8.0 years	Incident Dementia and MRI	Higher TSH, FT4 associated with increased hazard of dementia, while TPO positivity had decreased hazard. Thyroid function not associated with vascular brain abnormalities.

Napthali, 2014[284]	Cross-sectional (n = 3,253)	Australians in Hunter Community Study (age: 55-84)	TPO	n/a	Cognitive Test Scores	No association between TPO positivity and cognitive test score
Pasqualetti, 2015[285]	Meta-Analysis (n = 13 studies)	N/A	Subclinical Hypothyroidism	n/a	Incident Dementia and Cognitive Test Scores	Subclinical Hypothyroidism was not associated with cognitive decline and dementia
Yeap, 2012[286]	Prospective Cohort (n = 3,401)	Australian Men (age: 70-89)	FT4, TSH	5.9 years	Dementia-related ICD codes	Higher levels of FT4 was associated with dementia diagnosis, but TSH was not associated.
Volpato, 2002[287]	Prospective Cohort (n = 628)	Women's Health and Aging Study (age: ≤65)	T4, TSH	3.0 years	Cognitive Test Scores	Higher levels of T4 were associated with greater cognitive decline, but no association with TSH.
Moon, 2014[288]	Prospective Cohort (n = 313)	Korean Longitudinal Study on Health and Aging (KLoSHA) (age: ≤65)	T4, TSH	5.0 years	Dementia and MCI	Low TSH levels were associated with incident dementia and MCI, but T4 was not associated

Tan, 2008[289]	Prospective Cohort (n = 1,864)	The Framingham Study (mean age: 71)	TSH	12.7 years	Dementia	Lowest and Highest TSH levels associated with dementia in women (not men).

Abbreviations: SD: standard deviation

Table A. 5. Relative risks (95% CI) of adjudicated dementia and MCI by anti-TPO positivity status, ARIC 1990-2017

	Anti-TPO Negative ≤ 34 IU/L	**Anti-TPO Positive >34 IU/L**
	n total = 9,379	n total = 1,441
	n events = 1,817	n events = 280
Model 1 RR	1 (ref)	1.02 (0.85, 1.22)
Model 2 RR	1 (ref)	1.00 (0.84, 1.19)
Model 3 RR	1 (ref)	1.02 (0.85, 1.21)

Abbreviation: RR: Relative risk; CI: Confidence interval
Model 1: age, sex, race-center, *ApoE4*, income, and education
Model 2: Model 1 + BMI, smoking status, hypertension, diabetes, drinking status, HDL cholesterol, and total cholesterol
Model 3: Model 2 + CVD and baseline thyroid medication

Table A. 6. Relative risks (95% CI) of adjudicated dementia and MCI by anti-TPO positivity status and etiology, ARIC 1990-2013

	Primary or Secondary Cerebrovascular Etiology		**Other Etiologies**	
	Anti-TPO Negative ≤ 34 IU/L	**Anti-TPO Positive >34 IU/L**	**Anti-TPO Negative ≤ 34 IU/L**	**Anti-TPO Positive >34 IU/L**
	n total = 8,213	n total = 1,268	n total = 8,929	n total = 1,371
	n events = 450	n events = 70	n events = 1,166	n events = 173
Model 1 RR	1 (ref)	0.95 (0.71, 1.28)	1 (ref)	0.88 (0.73, 1.05)
Model 2 RR	1 (ref)	0.93 (0.69, 1.24)	1 (ref)	0.88 (0.73, 1.04)
Model 3 RR	1 (ref)	0.93 (0.69, 1.27)	1 (ref)	0.87 (0.73, 1.04)

Abbreviation: RR: Relative risk; CI: Confidence interval

Model 1: age, sex, race-center, *ApoE4*, income, and education

Model 2: Model 1 + BMI, smoking status, hypertension, diabetes, drinking status, HDL cholesterol, and total cholesterol.

Model 3: Model 2 + CVD and baseline thyroid medication

Table A. 7. Relative risks (95% CI) of adjudicated dementia and MCI by clinical categories of thyroid dysfunction, ARIC 1990-2017

	Hypothyroidism		**Eu-thyroidism**	**Hyperthyroidism**	
	Overt	**Subclinical**		**Overt**	**Subclinical**
	TSH > 5.1 mIU/L; FT4 < 0.85 ng/dL	**TSH > 5.1 mIU/L; FT4 = 0.85 - 1.4 ng/dL**	**TSH = 0.56 - 5.1 mIU/L; FT4 = 0.85 - 1.4 ng/dL**	**TSH < 0.56 mIU/L; FT4 = 0.85 - 1.4 ng/dL**	**TSH < 0.56 mIU/L; FT4 > 1.4 ng/dL**
	n total = 233	n total = 508	n total = 9,518	n total = 369	n total = 192
	n events = 43	n events = 85	n events = 1,873	n events = 62	n events = 34
Model 1 RR	1.36 (0.70, 2.62)	1.04 (0.72, 1.50)	1 (Ref)	1.04 (0.67, 1.62)	1.19 (0.90, 1.56)
Model 2 RR	1.24 (0.66, 2.34)	0.98 (0.68, 1.40)	1 (Ref)	1.02 (0.66, 1.58)	1.14 (0.87, 1.49)
Model 3 RR	1.25 (0.65, 2.38)	0.97 (0.68, 1.39)	1 (Ref)	1.04 (0.67, 1.63)	1.13 (0.85, 1.49)

Abbreviation: RR: Relative Risk; CI: Confidence interval

*P-value < 0.05

Model 1: age, sex, race-center, *ApoE4*, income, and education

Model 2: Model 1 + BMI, smoking status, hypertension, diabetes, drinking status, HDL cholesterol, and total cholesterol.

Model 3: Model 2 + CVD and baseline thyroid medication

Table A. 8. Relative risks (95% CI) of adjudicated dementia and MCI by categorical distribution of thyroid hormone level, ARIC 1990-2017 (Aim 2)

Thyroid Stimulating Hormone				
	Lowest 5% **≤ 0.55 mIU/L**	**Middle 90%** **0.56 – 5.97 mIU/L**	**Highest 5%** **≥ 5.97 mIU/L**	**TSH per 6.40 mIU/L**
	n total = 541	n total = 9,738	n total = 541	n total = 10,820
	n events = 90	n events = 1,910	n events = 97	n events = 2,097
Model 1 RR	0.88 (0.56, 1.38)	1 (ref)	1.01 (0.70, 1.45)	0.98 (0.94, 1.03)
Model 2 RR	0.89 (0.57, 1.37)	1 (ref)	1.01 (0.71, 1.43)	0.98 (0.94, 1.03)
Model 3 RR	0.89 (0.57, 1.37)	1 (ref)	0.99 (0.68, 1.45)	0.98 (0.94, 1.03)
Free T4				
	Lowest 5% **≤ 0.89 ng/dL**	**Middle 90%** **0.90 – 1.35 ng/dL**	**Highest 5%** **≥ 1.36 ng/dL**	**FT4 per 0.18 ng/dL**
	n total = 544	n total = 9,697	n total = 579	n total = 10,820
	n events = 101	n events = 1,896	n events = 100	n events = 2,097
Model 1 RR	1.42 (0.94, 2.15)	1 (ref)	1.28* (1.03, 1.59)	0.96 (0.90, 1.02)
Model 2 RR	1.33 (0.89, 1.99)	1 (ref)	1.24* (1.00, 1.54)	0.97 (0.92, 1.04)
Model 3 RR	1.33 (0.89, 1.97)	1 (ref)	1.24 (0.99, 1.54)	0.98 (0.92, 1.04)

Abbreviation: RR: Relative risk; CI: Confidence interval

*P-value < 0.05

Model 1: age, sex, race-center, *ApoE4*, income, education, and TSH or FT4

Model 2: Model 1 + BMI, smoking status, hypertension, diabetes, drinking status, HDL cholesterol, and total cholesterol.

Model 3: Model 2 + prevalent CVD and baseline thyroid medication use

Migraine (Chapter 7)

Table A. 9. Literature review of the association between migraine and cognitive impairment

Citation	Study Design	Population	Exposure(s)	Follow-up Time	Outcome(s)	Results
Kalaydjian, 2007[319]	Prospective Cohort (n = 1448)	Baltimore ECA study participants (mean age = 52)	Self-report of migraine symptoms	12.0 years	MMSE and Rey Verbal Learning Test	Those with migraine had significantly less decline in MMSE and verbal memory over follow-up
Rist, 2012[320]	Prospective Cohort (n = 6349)	Women's Health Study (mean age = 65)	Self-report of migraine headaches	3.4 years	TICS and cognitive tests	Women with migraine did not have greater cognitive decline compared to women without migraine
Rist, 2011[321]	Prospective Cohort (n = 1170)	EVA Study (mean age = 69)	Self-report of migraine symptoms	4.0-5.0 years	MMSE and cognitive tests	There was no difference in cognitive decline between those with and without history of migraine
Hagen, 2014[322]	Prospective Cohort (n = 51,859)	The HUNT Study (Norway) (age = 50-95)	Self-report of migraine symptoms	13.0 years	Dementia registry from hospital records	Experience of headache was associated with

						2.3 (95% CI: 1.4, 3.8) and 2.0 (95% CI: 1.1, 3.5) increased hazard of VaD and mixed VaD and AD, respectively

Abbreviations: MMSE: Mini-Mental State Exam; TICS: Telephone Interview for Cognitive Status