The DissertationCommittee for Ola Soudah Certifies that this is the approved version of the following dissertation:

The Impact of Comorbidities on the Incidence of Cognitive Impairment and Dementia among Elderly Patients with Diabetes Mellitus

Committee:

Susan Weller, PhD, Supervisor

Yong-Fang Kuo, PhD, Co-Supervisor

Kyriakos Markides, PhD

Mukaila Raji, MD, MS, FACP

Jacqueline Angel, PhD

Dean, Graduate School of Biomedical Sciences

The Impact of Comorbidities on the Incidence of Cognitive Impairment and Dementia among Elderly Patients with Diabetes Mellitus

by

Ola Soudah, MS, CLS

Dissertation,

Presented to the Faculty of the Graduate School of

The University of Texas Medical Branch

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas Medical Branch

September, 2018

Dedication

To my husband and friend, Ahmed Yassin, Dad, Ali Soudah, and Mom , Amal Zwawi,

for their endless support and encouragement through my life journey.

Acknowledgements

I would like to thank my mentor, Dr. Weller, co-mentor, Dr. Kuo, my committee members and preventive medicine and community health department faculties and staff for their assistance and help.

The impact of comorbidities on the incidence of cognitive impairment and dementia among elderly patients with diabetes mellitus

Publication No._____

Ola Soudah, Ph.D

The University of Texas Medical Branch, 2018

Supervisor: Susan Weller

The rapid growth of older adult segment is striking not only in the United States but worldwide. One of the most serious and potentially high burdens on caregiver and economy are cognitive decline and Dementia.Diabetes and cognitive decline & dementia are strongly associated and prevalent among elderly. Better understanding of the mechanisms by which diabetes increase the risk of cognitive decline/dementia is crucial to improve management and prevention strategies in the future. In the light of mixed literature about the association of diabetes related diseases and factors, this dissertation will address that gap using a national representative sample, Health and retirement study, to examine (1) the impact of diabetes complications and co-existed diseases on the incidence of any-cognitive decline (Any-CI) / all-types dementia (All-D) among diabetic subjects compared to non-diabetic subjects, (2) the impact of hyperglycemia and diabetes complications and co-existed diseases on the incidence of Any-CI / All-D among diabetic subjects, while controlling for educational level, age, sex, ethnicity. Using Cox prpoprtional hazard modeling following subjects for 10 years, diabetes was associated with higher risk of both Any-CI and All-D. This association was independent of

microvascular or macrovascular complications, other chronic diseases, or geriatric conditions. Stroke was the single largest risk factor for Any-CI / All-D in the general population and the diabetic cohort compared to other macrovascular diseases. Micorvascular diseases weren't significantly associated with increased risk in both general and diabetic population. Hyperglycemia indicators (long duration, insulin use, and A1c ≥7%) were not associated with higher risk among diabetics. Other chronic diseases were not significantly associated with higher risk meanwhile geriatric conditions (like depressive symptoms, hearing loss and mobility) were associated with higher risk in general population only. There was a significant beneficial effect for lifestyle factors (physical activity, moderate drinking and no) on reducing the risk of developing both Any-CI / All-D in general population. Among diabetics, the negative impact of smoking was even higher. Further explorations of factors that may explain diabetes association with cognitive decline beyond clinical characteristics of the diseases are needed. The results suggest that Any-CI / All-D prevention strategies should focus on preventing diabetes in general population.

TABLE OF CONTENTS

List of Tables x

List of Figures xii

List of Abbreviations xiii

Chapter 1: Introduction 1

Chapter 2: Diabetes and Cognitive Impairment and Dementia 3

2.1 Cognition, cognitive impairment and dementia 3

2.2 Evaluation of cognitive impairment 5

2.3 Risk factors of cognitive impairment and dementia 6

2.4 Diabetes, glycemia and cognitive decline 9

2.5 Possible mechanisms for cognitive decline/dementia in patients with diabetes 11

2.5.1 Hyperglycemia 11

2.5.2 Vascular risk 16

2.5.3 Hypoglycemia 18

2.5.4 Other Risk Factors 19

2.6 Study significance and goal 20

Chapter 3: Diabetes, microvascular complications, macrovascular diseases and the incident Any-CI / All-D. 22

3.1 Introduction 22

3.2 Specific Aim 1 23

3.3 Methods 25

3.3.1 Dataset and Study population 25

3.3.2 Study sample 27

3.3.3 Key Measures 27

3.3.4 Covariates 33

3.3.5 Statistical analysis 34

3.4 Results 40

3.4.1 Analytic sample and Missing Data 40
3.4.2 Descriptive statistics 41
3.3.3 Diabetes and risk of incident Any-CI 44
3.3.4 Diabetes and risk of incident All-D 52
3.5 Chapter summary 60

Chapter 4: Hyperglycemia, microvascular complications, and macrovascular diseases and the risk of incident Any-CI / All-D among those with diabetes 62

4.1 Introduction 62
4.2 Specific Aim 2 63
4.3 Methods 65
4.3.1 Dataset and Study sample 65
4.3.2 Key Measures 65
4.3.3 Covariates 68
4.3.4 Statistical analysis 68
4.4 Results 72
4.4.1 Analytic sample and Missing Data 72
4.4.2 Descriptive statistics 73
4.4.3 Hyperglycemia, microvascular complications and incident Any-CI 77
4.4.4 Hyperglycemia, microvascular complications and incident All - D 89
4.5 Chapter Summary 100

Chapter 5: Discussion, Limitations, and conclusion 102

5.1 Discussion 102
5.2 Strengths 110
5.3 Limitations 110
5.4 Conclusion and future directions 112

References..113

Vita 136

List of Tables

Table 3.1: Baseline demographic characteristics for diabetic subjects compared to non-diabetics for Aim 1 study participants. 42

Table 3.2: Baseline clinical characteristics for diabetic subjects compared to non-diabetics for Aim 1 study participants. 43

Table 3.4: Aim1 Cox proportional hazard models for incident Any-CI. 47

Table 3.5: Aim 1 Estimated direct, indirect, total effect and proportion mediated by macrovascular diseases for diabetes and Any-CI relationship. 50

Table 3.6: Aim 1 Sensitivity analysis result comparison for incident Any-CI. 51

Table 3.7: Aim 1 Cox-proportional hazard models for incident All-D. 54

Table 3.8: Aim 1 Estimated direct, indirect, total effect and proportion mediated by macrovascular diseases for the diabetes and All-D relationship. 57

Table 3.9: Aim1 Sensitivity analysis result comparison for All-D model. 58

Table 4.1. Baseline demographic characteristics for Aim 2 study participants. 74

Table 4.2. Baseline clinical characteristics for Aim 2 study participants. 76

Table 4.3. Aim 2 Cox proportional hazard models for incident Any-CI. 82

Table 4.4: Aim 2 sensitivity analyses for incident Any-CI. 87

Table 4.5. Aim 2 Cox proportional hazard models for incident All-D. 93

Table 4.6. Aim 2 sensitivity analyses for incident All-D.....98

List of Figures

Figure 3.1. Flow chart from the complete, eligible Health and Retirement Study 2002 sample to study analytic sample (Aim 1).....41

Figure 3.2: Aim 1 Kaplan Meir survival curve for incident Any-CI. 45

Figure 3.3: Aim 1 Kaplan Meir survival curve for incident All-D. 52

Figure 4.1: Flow chart from the complete, eligible Health and Retirement Study 2003 diabetes sub-study to study analytic sample (Aim 2). 73

Figure 4.2. Aim 2 Kaplan Meir survival curve for incident Any-CI. 77

Figure 4.3. Aim 2 Kaplan Meir survival curve for incident All-D. 89

List of Abbreviations

Any-CI	Any-cognitive decline
All-D	All types dementia
A1c	Glycosylated hemoglobin
AD	Alzheimer's disease Abbreviation for Use in the Graduate College
MCI	Mild cognitive impairment
D	Dementia
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
CDT	Clock Drawing Test
SIS	Mini-Cog, Six-Item Screener
RR	Relative Risk
CI	Confidence Intervals
OD	Odds Ratio
HR	Hazard Ratio
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
NHANES	National Health and Nutrition Examination Survey
HRS	Health and Retirement Study
ARIC	Atherosclerosis Risk in Communities Study
LDL	Low density lipoprotein

BP	Blood pressure
ACCORD-MIND	Memory in Diabetes sub-study of the Action to Control Cardiovascular Risk in Diabetes trial
FINNISH	Finnish Diabetes Prevention Trial
DSST	Digit Symbol Substitution Test
TBV	Total brain volume
CRP	C-reactive protein
ADL	Activities of daily living
ADAMS	Aging, Demographics, and Memory Study
IADL	Instrumental activities of daily living
CIND	Cognitive impairment non-dementia
CES-D	Center for Epidemiologic Studies Depression Scale
KM	Kaplan- Meier method
CDE	Controlled direct effect
NDE	Natural direct effect
NIE	Natural indirect effect
TE	Total effect

Chapter 1: Introduction

The rapid growth of older adult segment is striking not only in the United States but worldwide. According to the U.S. census bureaus', 2030 will be a turning point in the U.S. population history. Older adults will account for 20% (about 61 million) of total population prompted by the aging of baby boomers[1]. This could be a good indicator for effective health care systems and public health where people tend to live longer than before. However, this comes with some penalties. Older adults tend to suffer more from multiple chronic diseases, frailty and disability, which come with a high burden on health care systems as well as society in general who provide the majority of care. Moreover, health care cost will increase by 25% by 2030 mainly because of the aging population. About 95% of health care costs go to treat chronic diseases in older Americans[2]. Getting older doesn't mean necessarily that a person will be ill and disabled. Older adults are a highly heterogeneous population where you may find some in their 70's with many chronic diseases and disabilities and others at the same age who are healthy and fully active[2]. This gives us hope that healthy aging is possible and age-related diseases and conditions can be prevented or delayed.

Cognitive health is very important for older adults. One major concern for individuals and health care systems is how to maintain cognition intact with aging, as aging is associated with normal decline in certain cognitive abilities[3]. These changes are small and do not interfere with a person's daily activities. Some cognitive domains have a

subtle decline overtime like memory, reasoning, and processing speed while other domains are well preserved and may improve with age, like language[3]. Non-physiological cognitive decline ranges from mild cognitive decline without interference with daily life activities to a severe, pathological and disabling form called dementia. Alzheimer's disease (AD) is the most common type of dementia and is the fifth leading cause of death in the U.S, followed by diabetes[4]. Both AD and diabetes are highly prevalent in older adults and closely associated. The association between diabetes and cognitive decline has a broad negative impact on individual health, health care system, and social forces. Thus, a better understanding of the relationship between diabetes and cognitive decline is crucial to improve management and prevention strategies in the future.

Chapter 2: Diabetes and Cognitive Impairment and Dementia

2.1 Cognition, cognitive impairment and dementia

Cognition is the ability to understand and process information; thinking and other related processes[5]. Cognitive abilities might be categorized into two major categories; crystallized and fluid intelligence. Crystallized intelligence includes a person's ability to accumulate knowledge, information, and skills which remain stable or improve by age[3,6]. Fluid intelligence is the ability to learn new knowledge, solve problems and reason about things that weren't learned before. It includes many domains; memory, attention, processing speed, and executive function[3]. Fluid intelligence normally declines over time mainly in the aspects of processing speed and memory[6]. Normal cognitive aging shouldn't interfere with an individual's ability to perform daily tasks. When cognition declines faster than normal cognitive aging, it is considered to be pathological[5]. This cognitive decline ranges from mild cognitive impairment (MCI) that doesn't impact individual's ability to perform daily activities to a more severe decline, dementia (D), characterized by loss of independence[5]. MCI is considered to be an intermediate state between normal cognitive decline and dementia. MCI involves cognitive deficit in one or more domain(s) without interfering with daily life activities[7]. If the deficit includes memory impairment, it is known as amnestic MCI, and non-amnestic MCI if it doesn't[8]. MCI is very common in elderly above 65, with a prevalence ranging between 16% and 20%[9,10]. Individuals with MCI have a higher risk of developing dementia than people with normal cognition[7,11], but not everyone with MCI will progress to dementia[12]. Within 2 to 5 years, persons with MCI are more likely to develop dementia; about 14.9% of older adults above 65 with MCI will develop dementia within 2 years[8]. Cognitive decline that includes memory deficit was known to be a strong predictor for developing dementia[13].

However, a MCI diagnosis is not stable; some individuals with MCI improve over time, within 1-3 years, to even normal and about 11% of MCI subjects revert to normal within 3 years of diagnosis[14,15]. The conversion rate was reported to range from 14% to 56%[8]. This phenomenon may reflect study differences in MCI definitions or a possible treatable causes of MCI[16]. However, even those who regained normal cognitive status continued to have a higher risk of developing dementia in the future[16,17].

On the other hand, dementia is the severe form of cognitive decline that involves decline in two or more cognitive domains, enough to interfere with daily activities[18].Dementia symptoms vary based on disease etiology; loss of judgment, disorientation, inability to understand and communicate effectively, but the most common and first noticed one is memory loss[19]. Among Medicare beneficiaries during 2011-2013 enrollments with age ≥ 68 years, about 14.4% (about 3.1 million from 21.6 million) had a claim for a service and/or treatment for dementia[20]. Another national study reported that dementia trend is decreasing in the last 25 years among those 65 and older from 11.6% in 2000 to 8.8% in 2012[21]. The most prevalent type of dementia in older adults is Alzheimer's disease (AD) which represents 60% to 80% of dementia cases. This is followed by vascular dementia which accounts for ~20 – 25% of the cases[22]. AD is a neurodegenerative disease characterized by deposition of amyloid plaques, formation of tangles and progressive loss of neurons. Meanwhile, vascular dementia occurs due to recurrent strokes secondary to recurrent large vessel occlusions and/or minor symptomatic or subclinical small vessel occlusions[23]. Mixed pathology of dementia, plaques and cerebrovascular disease, is also common. Nearly, 5.5 million Americans had AD in 2013[19]. This number is expected to increase to 13.8 million due to population growth and the aging of "baby boom generation" regardless of the prevalence decrease

noted above[19]. This means that in spite of the fact that dementia rates are decreasing, the absolute number of people with dementia is increasing, and so dementia remains a huge challenge in many different ways. The cost of long term care for demented patients and their medical expenses exceeded those of patients with heart diseases or cancer, with an approximate cost of $157 – 215 billion each year[2]. This is besides the heavy burden on family members who provide most of the supervision and personal care for people with dementia[19].

2.2 EVALUATION OF COGNITIVE IMPAIRMENT

In clinical practice, diagnosis of MCI and dementia is a multi-step process. Even with the advancement of neuroimaging technologies, MCI and dementia diagnoses are not direct and heavily rely on patient's history, cognitive assessment batteries, and physical examination. Frequently, the first one to complain about decline in cognitive ability is not the patient himself but rather one of the family members[22]. Reported memory loss by a family member was found to be a more significant predictor of future development of dementia compared with self-reported complaint[24]. Usually, multiple assessments overtime are needed before confirming MCI or dementia diagnoses. There are many cognitive scales to assess cognition in both clinical setting and general population. A commonly used cognitive screening tool in the US is The Mini-Mental State Examination (MMSE) scale. MMSE evaluates multiple cognitive abilities including orientation to time and place, registration, attention and calculation, recall, language and praxis[25]. More sensitive and reliable tests are used, such as The Montreal Cognitive Assessment (MoCA) test, which is designed to detect subtle cognitive impairment in older adults, Clock Drawing Test (CDT), Mini-Cog, Six-Item Screener (SIS), etc[25]. There

are different more comprehensive tests evaluating multiple cognitive areas, like word recall which is a key test for memory, called neuropsychological batteries[25]. Epidemiologic studies used cognitive scales and batteries to assess and screen for cognitive decline outside clinical setting to promote early diagnosis and interventions in order to postpone further decline.

2.3 RISK FACTORS OF COGNITIVE IMPAIRMENT AND DEMENTIA

Cognitive impairment and dementia have a complex etiology that involves many factors. Generally, dementia is not curable but can be modified, delayed or even prevented[26]. Many risk factors have been identified to increase the individual's risk of MCI and dementia. The greatest risk factor for cognitive decline overall is aging itself. After age 65, cognitive decline risks exponentially increase[8]. Although aging is irreversible, the Lancet Commissions report argued that good management for risk factors of cognitive decline accounted for 35% risk reduction of dementia prevalence in developed countries[26].These risk factors included lower education level, decreased social engagement, vascular risk factors, hearing loss, depressive syndromes, low physical activity and smoking[26]. A major critique for the Lancet report was that education level and hearing loss accounted for most of decline in cognition level in their cohort[26].

Higher education level is associated with higher cognitive reserve; which enables people to preserve their cognitive function despite the vascular and AD neuropathology and consequently slows dementia development. People with lower education level had a higher risk of dementia compared to those with higher education, relative risk (RR) = 1.59 (95% CI 1.26-2.01)[26]. Decrease in dementia rate observed in the last decades might

be due to increase in education level even though there is a higher prevalence of cardiovascular risk factors[21,27]. Vascular risk factors like midlife hypertension, high cholesterol, high body mass index (BMI), and diabetes are associated with higher risk for development of cognitive decline and dementia[28]. Improvements in the management of vascular risk factors like hypertension, stroke, and other heart diseases couldn't explain completely the reduction in dementia prevalence noted above[29].

There is a strong association between hearing loss and cognitive decline. In a recent meta-analysis of 15,521 individuals, hearing impairment was found to be associated with increased risk of MCI and dementia; RR of 1.3 (95% CI 1.12-1.51) for MCI and 2.39 (95% CI 1.58-3.61) for dementia[30]. Hearing impairment is very common; occurring in 32% of individuals above 55 years old[26]. The new emerging risk associated with hearing loss is not well understood; how hearing loss increases the risk of MCI and dementia[30]. It is suggested that it could be related to the decreased cognitive reserve in individuals with hearing loss as they are less engaged in social life and cognitive stimulating activities. Others suggested that hearing impairment could be an early symptom (prodromal symptom) of AD[26].

Similarly, depressive symptoms were suggested to be a risk factor and/or prodromal symptoms of dementia. Studies showed strong association between depressive symptoms and dementia incidence[31]. However, a cohort study with very long follow up period, 28 years, reported that incidence of depression only in the last 10 years of the study, preceding dementia diagnosis, was significantly associated with the risk of developing dementia. Depression for 11 years of follow up had a Hazard Ratio (HR) of 1.72 (95% CI 1.21-2.44) whereas depression over 28 years of follow up had a HR of 1.21

(95% CI 0.95-1.54) [32]. Higher level of physical activity was found to reduce cognitive decline risk and AD as well; high level of exercise had a HR of 0.62 (95% CI 0.54-0.7) in a meta-analysis of 15 cohort studies which followed 33,816 individuals[33]. Smoking was found to increase the risk of cognitive decline and dementia; RR=1.79 (95% CI 1.43-2.23)[34]. This could be due to the contribution of smoking in increasing the risk of cardiovascular disease. It is suggested that clustering of risk factors have the highest impact on dementia incidence[24,27,33]. No clinical trial to our knowledge examined the impact of multi-dimensional intervention to reduce the risk of dementia.

Multiple chronic medical conditions is one of the characteristic features of aging; about 55-98% of older adults above 60 have more than one chronic disease[35]. The direct sum of 17 comorbid diseases (hyperlipidemia, hypertension, depression, diabetes, arthritis, cancer, cardiac arrhythmias, asthma, coronary artery disease, substance abuse disorders (drugs and alcohol), Chronic Obstructive Pulmonary Disease (COPD), osteoporosis, chronic kidney disease, stroke, congestive heart failure, schizophrenia, and hepatitis) was reported to be associated with an increased risk of MCI and dementia; the hazard ratio for MCI/dementia for those with more than one chronic condition was 1.38 (CI: 1.05–1.82)[36]. It was higher in persons with ≥4 conditions, HR: 1.61, (CI: 1.21–2.13), compared to persons with only one condition and those with 2-3 chronic conditions[36]. Some diseases like arthritis[37] and COPD[38,39] are also associated with a higher risk for MCI and dementia, independent of other risk factors. It is not well explored how these medical conditions and risk factors all together will behave when they are included in one model and how they will impact the individual's risk of cognitive decline.

2.4 DIABETES, GLYCEMIA AND COGNITIVE DECLINE

Diabetes is very prevalent disease in both young and older adults. It also is associated with a wide range of severe complications; such as retinopathy, nephropathy, diabetic foot, neuropathies, and coronary and carotid artery diseases[40]. Based on the national representative sample, NHANES study, approximately 25.2 % (12 million) of older adult, 65 years and above, in the U.S. are diabetic[41,42]. Diabetes and cognitive decline & dementia are strongly associated. One of the earliest observations on the association of diabetes and dementia was that both diseases often co-exist; about 46% of clinically diagnosed AD patients had diabetes and 24% had impaired fasting glucose[43]. Diabetes may double the risk of all types of dementia including AD and vascular dementia[44,45]. This suggested a possible role of diabetes or diabetes related factors in the pathology of cognitive decline and dementia. The severe impact of both diseases on individual's health, health care systems, and society[19,46,47], along with the high prevalence of diabetes in general population raise the interest in understanding how diabetes impacts cognition and how it may cause cognitive decline.

The Rotterdam Study was one of the first studies that proposed diabetes as a risk factor for dementia[48]. It reported that diabetic patients had 1.9 higher risk of dementia compared to non-diabetics, and those on insulin treatment had an even higher risk (HR= 4.3, 95% CI: 1.7-10.5)[44,48]. Since then, many studies reported similar findings. A recent large meta-analysis confirmed the risk of cognitive decline associated with diabetes; pooling the relative risk from 19 longitudinal studies, with total sample of 6,184 individuals with diabetes and 38,350 without diabetes, showed that there was 1.51 times greater risk for all–cause of dementia (RR=1.51, 95% CI: 1.31–1.74), 1.46 times greater risk for AD (RR=1.46, 95% CI: 1.20–1.77), 2.48 times greater risk for vascular dementia

(RR=2.48, 95% CI: 2.08–2.96) and 1.21 greater risk for MCI (RR=1.21, 95% CI: 1.02–1.45) in patients with diabetes compared with non-diabetics[49].This meta-analysis included only high quality studies. However, there was a significant heterogeneity among them.

Diabetic patients usually perform worse in cognitive function tests and experience a more accelerated cognitive decline compared to non-diabetics[50-52]. In one study, both diabetes and pre-diabetes were found to speed up the transition from MCI to dementia by 3.18 years; HR was 2.87 (95% CI: 1.30–6.34) for diabetes and 4.96 (95% CI: 2.27–10.84) for pre-diabetes[53]. Moreover, Long disease duration, uncontrolled diabetes and being on insulin treatment all showed to be associated with even higher risk of cognitive decline[54,55].The Whitehall II cohort study in Britain showed that only well-established diabetes disease with long duration was associated with a more rapid cognitive decline over 10 years[56]. Compared with nondiabetic subjects, those with diabetes had a 45% faster drop in memory, a 29% faster drop in reasoning, and a 24% faster drop in global cognition[56]. Those with impaired glucose regulation, prediabetes, or newly diagnosed diabetes did not show any significant difference[56]. In contrast, prediabetes was shown to be associated with some degree of cognitive decline and increased the risk of developing dementia[57]. Other studies examined the relationship between diabetes status and cognition among older adults in the health and retirement study (HRS) reached to the same conclusion; baseline diabetics showed worse average memory scores and higher average dementia compared to non-diabetic (odds ratio (OR) 1.35, 95% CI: 1.05–1.69)[55]. Diabetes had a 10% faster rate of memory decline over 10 years[58]. However, the study found no association between diabetes duration or incident diabetes with cognitive decline or dementia[59]. Preventing diabetes by targeting lifestyle factors among those with

prediabetes didn't benefit cognitive after 9 years of follow up[60]. This could be explained by early termination of this study after interim analysis (after 4 years) that show a beneficial difference of lifestyle intervention in preventing or delaying diabetes onset in intervention arm and the switch of control group into intervention arm[61]. Wether this association between diabetes and cognitive decline is causal or not is still debated in the scientific society.

2.5 POSSIBLE MECHANISMS FOR COGNITIVE DECLINE/DEMENTIA IN PATIENTS WITH DIABETES

The exact mechanism/s by which diabetes may result in a cognitive decline or dementia is unclear. It may be a multifactorial process that reflects the complexity of diabetes disease. The possible mechanisms can be summarized into four major categories: (1) chronic hyperglycemia (2) vascular diseases pathway[23,62], (3) hypoglycemia[63] and (4) other shared risk factors, such as obesity, hypertension, smoking and socioeconomic factors that may confound the relationship between diabetes and dementia[23].

2.5.1 Hyperglycemia

Chronic hyperglycemia, or elevated blood glucose level, can result in a cognitive decline or dementia[64]. The Atherosclerosis Risk in Communities (ARIC) Study, which included 13,351 adults aged 48-67 years with over 20 years of follow up, reported that high glycosylated hemoglobin A1c (A1c) level at baseline was found to have the most significant association with cognitive decline[54]. The greatest decline in cognitive function over 20 years was found in the group with baseline A1c level ≥7.0 % compared to

persons with A1c <7 % (adjusted difference in global cognitive Z score= -0.16)[54]. Even prediabetes with A1c between 5.7-6.4% was significantly associated with higher cognitive decline than those without diabetes (A1c<5.7%) (adjusted difference in global cognition Z score= -0.07)[54]. In a national representative sample (HRS study), diabetes accelerated memory loss by 8% compared to non-diabetics (β=-0.037, CI: -0.06 to -0.01)[58]. One percent increase in baseline A1c level was associated with 0.05 unit decrease in memory score per decade; about 10% decrease[58]. In 58 elderly in Germany, higher A1c was associated with higher risk of incident all-cause dementia and AD[65]. When A1c level was treated as a continuous variable, one percent increase in A1c value was associated with 29% increase in all-cause dementia (All-D) and AD incidence (OR= 1.29, CI: 1.01-1.64 and 1.29, CI: 1.01-1.66, respectively) after adjusting for baseline cognitive score and vascular risk[65]. A1c higher than 7% was associated with 4.14 (CI: 1.5-11.4) higher risk of incident all-cause of dementia and 3.59 (CI: 1.14-11.2) for incident AD[65]. Even after accounting for A1c level variability over time, 1% increase in A1c level was associated with 1.73 points decrease in MMSE score (P-value = 0.0002, 95% CI: −2.07 to −0.66) among 101 community-dwelling non-diabetic elderly (≥ 75 years of age)[66]. Moreover, A1c level ≥ 5.9% showed to be associated with increased risk of MCI incidence (RR: 2.28, 95% CI: 1.59-3.91) among elderly(≥ 60 years)[67]. Thus, chronic hyperglycemia is associated with increased risk of cognitive decline and dementia for elderly[66] and young adult[54,68]. Higher A1c level (> 7%) is reported to accelerate the conversion of mild cognitive decline into dementia; HR 1.29 (CI: 1.105–1.573)[69]. Diabetic patients with baseline A1c level below 7% did not show an increased risk of dementia incidence over 6 years[65,70].

Clinical trials examining diabetes treatment effect on diabetes-related outcomes rarely used cognitive function as an endpoint. Second analysis of clinical trials suggested that improvement in glycemic control (keeping A1c level within normal range <5.7%) may delay this decline and even improve cognitive performance[71-73]. Diabetes Education and Telemedicine Study (IDEATel) was conducted on 2,169 persons with diabetes above 54 years of age[71]. The primary endpoint of the trial was to measure the impact of telemedicine intervention on diabetes control measures (glycosylated hemoglobin A1C (A1c), blood pressure (BP), and low density lipoprotein (LDL)) and compare that with the usual clinical care[71]. The baseline population had long standing diabetes, duration was more than 10 years in both arms, and the majority of patients with severe comorbid diseases were excluded. The secondary endpoint of the study was to look at the relationship between diabetes control measures and global cognitive decline. The study showed that maintaining A1c level ≤ 7% (or ≤ 8% for participants with reduced life expectancy and/or severe hypoglycemic attacks) was associated with slower global cognitive decline over 5 years. This association was mainly mediated by controlling A1c, and not by controlling BP or LDL[71].

The Memory in Diabetes (MIND) sub-study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, (ACCORD-MIND), assessed this assumption also. The baseline evaluation revealed that 1% increase of A1C value was associated with a significantly lower score on four different cognitive tests; 1.75-point lower DSST score, a 0.20-point lower MMSE score, a 0.11-point lower memory score, and a worse score (i.e., 0.75 s more) on the Stroop Test[74]. A follow-up study after the trial termination (ACCORDION-MIND) found no beneficial long-term effects of intensive treatment of hyperglycemia, blood pressure or lipid levels on cognitive function after

4 years of intervention termination[75]. This could be explained by loss of separation between intensive arm (where A1C is designed to be ≤6%) and standard arm (where A1C is designed to be between 7 - 7.9 %) in the trial. After 80 months, both arms had A1c level of ≈ 8.2%[75]. The trial results should be interpreted with caution; baseline study sample already had a high risk of cardiovascular diseases and A1c level above 7.5%, and it was early terminated because of the increased mortality in the intensive glycemic control group[76,77].

A secondary analysis of the Finnish Diabetes Prevention Trial (lifestyle intervention study on middle-aged, overweight persons with impaired glucose tolerance but no diabetes diagnosis at baseline, n=522) reported no statistical difference in the rate of cognitive decline between participants who developed diabetes and those who did not[78]. Among participants with diabetes, long duration and high glycemia were associated with worse cognitive performance[72]. After 9 years follow up, better glycemic control among diabetics predicted better cognitive performance[72]. The difference between the two trials (ACCORD-MIND study versus the FINNISH prevention study) could be due to the vast difference in their baseline populations. The ACCORD-MIND study population consisted of patients with long-standing diabetes, >10 years, with high risk for cardiovascular disease, while FINNISH prevention study included overweight subjects with impaired glucose tolerance but no diabetes at baseline only (prediabetes)[72,75].

A recent meta-analysis of clinical trials reported that intensive glycemic control, lowering A1c to the normal level, didn't improve cognitive performance compared to standard treatment for diabetes[79]. Five trials were included in this meta-analysis with a total of 24,297 patients; 12,165 participants in the intensive treatment group and 12,132

in the standard treatment group. The pooled mean difference between intensively treated group and standard care group was 0.02 (95% CI: -0.03 to 0.08)[79]. Most of studies had long diabetes duration at baseline ranging between 5.4 to 10.8 years, the only one study included diabetes detected by screening (ADDITION). Four trials reported similar cognitive decline rate in intensive treatment group and standard treatment group except for IDEATel trial which reported slower rate of cognitive decline in intensive treatment group[79]. As mentioned earlier, IDEATel trial included only elderly persons with well controlled diabetes and excluded those with severe complications and comorbid diseases which questions study generalizability[71,79]. All trials had a follow up duration less than 10 years, which may not be enough to significantly show the difference of cognitive decline between the two arms[71].

Other meta-analyses examined the effect of intensive glycemic control (A1c <7%) on different cognitive domains and reported some benefit in patients with type 2 diabetes in terms of processing speed and executive function but worse performance in the memory and attention domains, while patients with type 1 diabetes had no benefits from intensive glycemic control[80]. Collectively, these trails reported that neither lifestyle intervention (diet and physical activity)[81] nor medical treatment[75] reported reduction in cognitive decline among diabetic patients detected during screening[82]. This contradicted the last report on MCI and dementia prevention mentioned earlier, where treatment of diabetes may account for 3.2% population attributable risk reduction in cognitive decline prevalence[26]. This study was considered overoptimistic in the light of the mixed literature results[83]. Collectively, preventing the development of diabetes may contribute to decreasing the risk of dementia development in future. However, once diabetes disease is diagnosed, preventing cognitive decline becomes harder and more complex. Thus any

intervention to prevent cognitive decline among diabetics should be done in the very early stage of the disease or during the prediabetes period.

2.5.2Vascular risk

As mentioned before, vascular dementia occurs due to recurrent strokes secondary to recurrent large vessel occlusions and/or minor symptomatic or subclinical small vessel occlusions[23]. Diabetes association with vascular dementia was higher compared to other types of dementia[84]. It is evident that vascular diseases (mainly stroke) are the underlying causes of vascular dementia[85]. Macrovascular diseases increase the risk of cognitive decline in both diabetic and non-diabetic subjects[86,87]. Diabetes disease contributes to atherosclerotic changes; in both large vessels (macrovascular), like stroke, and small vessels (microvascular), like retinopathy[88]. The rate of cardiovascular diseases was higher rate among diabetic subjects compared to non-diabetics and it is the major cause of death in diabetes[89]. Diabetes and prediabetes are known risk factors for stroke[90]. Targeting vascular risk factors among diabetics was suggested to reduce cognitive decline and dementia. However, treatment of hypertension and hyperlipidemia didn't succeed in preventing cognitive decline in patients with diabetes[75,91]. As mentioned earlier, in ACCORDION-MIND study, there was no significant difference in 80 month mean change from baseline in Digit Symbol Substitution Test (DSST) and total brain volume (TBV) scores between the glycaemic intervention groups, or the BP and lipid interventions[75]. Also, in a nationwide retrospective cohort study, dementia risk was higher in diabteics than in the non-diabetics (adjusted hazard ratio (HR) = 1.47, 95% confidence interval (CI) = 1.30-1.67, $p < 0.001$). In diabetics, the presence of both hypertension and hyperlipidemia did not significantly increase the risk of dementia

compared with the risk of dementia in those without hypertension and hyperlipidemia ($p = 0.529$), or those with hypertension alone ($p = 0.341$) or hyperlipidemia alone ($p = 0.189$)[91]. In non-diabetics, hypertension and hyperlipidemia treatment didn't prevent cognitive decline beyond stroke diagnosis; it preserved cognition in stroke patients by preventing recurrent stroke events[92,93].

On the other hand, microvascular complications of diabetes were reported to be associated with higher risk of cognitive decline in diabetic patients. For example, Retinopathy or retinal microvascular abnormalities are linked to cognitive decline and dementia in people with and without diabetes[94-96]. Severe diabetic retinopathy had a 1.42 higher risk of incident dementia compared to diabetic patients without retinopathy (HR =1.42: 95% CI 1.27-1.58)[97]. Retinal microvascular abnormalities were suggested to act as biomarker for dementia[95] and a proxy for diabetes related cognitive decline since those with retinopathy subgroup had a higher risk for future cognitive decline[96]. Also, nephropathy or kidney diseases in diabetic[98,99] and non-diabetic[100] patients are associated with higher risk of cognitive decline similar to retinopathy. Increased levels of cystatin C, a biomarker of kidney function, was associated with increased risk of cognitive impairment in patients with type 2 diabetes, with an Odds Ratio (OR) of 1.42 (95% CI 1.25-4.24) after additional adjustment for all other variables[98]. In diabetic people with A1C >7.5%, cognitive impairment was associated with nephropathy as measured by albumin/creatinine ratio, a measure of microvascular endothelial disease, and cystatin C in adjusted models[99]. Lower estimated Glomerular Filtration Rate (eGFR) values at baseline, after adjustment for diabetes among other vascular risk factors and diseases, were associated with a more rapid rate of cognitive decline (estimate 0.0008, SE <0.001, $p = 0.017$). Patients with impaired kidney function (eGFR< 60 mL/min/1.73 m(2)) at

baseline had even a more rapid rate of cognitive decline (estimate -0.028, SE <0.009, p = 0.003)[100]. Elevated A1C is associated with increased risk of microvascular disease in diabetics, and intensive blood-glucose control substantially decreases the risk of microvascular complications in patients with type 2 diabetes[40]. It was also reported that having diabetes with other chronic conditions, like kidney disease, increased the risk of dementia incidence compared to non-diabetic cohort with or without the same chronic condition[101]. Diabetes was reported to be associated with microvasculr lesion of the brain which in turn resulted in cognitive decline[102].

In summary, the persistent association between diabetes and cognitive decline even after adjusting for macrovascular diseases suggests that diabetes could be initially associated with cognitive decline through microvascular process.

2.5.3 Hypoglycemia

Another possible mechanism for cognitive decline/dementia in patients with diabetes is severe hypoglycemic events. Poor cognitive performance and accelerated cognitive decline were reported to be higher in those who experienced severe hypoglycemic events[63]. Even one hypoglycemic event was associated with higher risk of dementia (HR=1.27; 95%CI 1.06-1.51). This risk increased as the number of events increased (HR for 2 or more events=1.5; 95%CI 1.03-1.54)[103]. This relationship is shown to be bidirectional; cognitive impairment is associated with poor disease control which in turn may lead to hypoglycemic episodes[104,105]. It could be that hypoglycemic events and chronic hyperglycemia have a U-shape relationship with cognition, similar to the relationship between HbA1C and mortality[106].

2.5.4 Other Risk Factors

Chronic inflammation is another proposed mechanism for both diabetes disease and cognitive decline. Serum inflammatory markers, like CRP, are related cognitive decline and risk of diabetes as well[23,107]. Chronic diseases with inflammatory pathology that are prevalent in elderly as diabetes are also reported to be associated with increased risk of cognitive decline (like arthritis[37,108] and COPD[38,39]). Majority of elderly, about 84.6%, with diabetes are known to have at least one other chronic disease at the time of diabetes diagnosis and about 25% of them will develop at least one comorbid disease in the first year afterwards[109]. One study in Taiwan examined the impact of comorbidity on dementia incidence among diabetic subjects[101]. Diabetic patients with chronic conditions have an elevated risk of dementia; the HR rose from 1.41 in those without any chronic condition to 2.49 in those with more than 4 conditions (hypertension, hyperlipidemia, stroke, coronary artery and/or kidney disease) in a dose-response pattern with condition count[101].

The only studies that we found on possible interaction between diabetes and co-existing chronic diseases were on depression. The presence of depressive symptoms was found to be associated with greater decline in cognitive function in older American Mexicans who had diabetes[38]. There is a significantly increased risk of cognitive decline for those having both diabetes and depression compared to those having one disease only[110]. Those with both diseases had a hazard for developing dementia of 2.17 (95% CI 2.1-2.24) vs 1.83 (95% CI 1.8-1.87) and 1.2 (95% CI 1.17-1.23) for those having one disease, depression or diabetes, respectively[110]. This could be explained by shared underlying pathology and/or shared risk factors between diabetes and other chronic diseases including dementia. For example, obesity, hypertension, smoking and

socioeconomic factors are all reported to be associated with reduced cognitive performance and act as confounders for dementia and diabetes as well[23,92,107].

2.6 STUDY SIGNIFICANCE AND GOAL

Most of studies that examined the relationship between diabetes and cognitive decline didn't address the problem of diabetes disease complexity resulting from the complications of the disease and other diseases that co-exist with it. Macrovascular and microvascular complications have not been considered separately from other co-existing diseases. For example, retinopathy and arthritis were shown to be associated with cognitive decline and dementia but they rarely get included in diabetes dementia relationship studies[37,94]. Moreover, it is difficult to know how diabetes contributes to cognitive decline, through microvascular or macrovascular pathway or through an inflammatory pathway. The interaction between diabetes and other co-existed diseases is not well explored; whether it has an additive or multiplicative effect that would accelerate the cognitive decline or not. No study, to our knowledge, has examined these effects by their possible mechanisms or with possible interactions between complications and other conditions. We don't know how all these variables that may coexist with diabetes will behave if they are included in one model and it is unclear which variable accounts more for cognitive decline. In addition, few studies explored the impact of complications as well as comorbid diseases in national representative sample on the incidence of cognitive decline and dementia in diabetic and non-diabetic subjects and within diabetic population. To address this, this study will evaluate the impact of diabetes complications (microvascular and macrovascular diseases), other co-existed diseases (like arthritis, COPD, and cancer), geriatric conditions (like depressive symptoms, activities of daily

living (ADL), hearing loss and vision loss) and lifestyle factors (like exercise, smoking and drinking) on the incidence of any cognitive impairment and all-cause dementia among elderly with diabetes. Also, how glycemic control, and physical activity may moderate this relationship. The specific aims will be: (1) to examine the impact of diabetescomplications and co-existed diseases on the incidence of any-cognitive decline (Any-CI) / all-cause dementia (All-D) among diabetic subjects compared to non-diabetic subjects, while controlling for educational level, age, sex, ethnicity (2) to examine the impact of diabetes complications and co-existed diseases on the incidence of any-cognitive decline (Any-CI) /all-cause dementia (All-D)across different A1c levels among diabetic subjects, while controlling for educational level, age, sex, ethnicity.

Chapter 3: Diabetes, microvascular complications, macrovascular diseases and the incident Any-CI / All-D.

3.1 INTRODUCTION

The purpose of this chapter is to examine the impact of diabetes, microvascular complications, macrovascular diseases, co-existed diseases, geriatric conditions, and life style factors on the incidence of any-cognitive decline (Any-CI) / all-cause dementia (All-D) among diabetic subjects compared to non-diabetic subjects. It is expected that patients with diabetes will have a higher risk of cognitive impairment and dementia compared to non-diabetic individuals. Macrovascular diseases are known to be a partial mediator for this association[111]. Cardiovascular and cerebrovascular diseases share common risk factors with Alzheimer's disease and vascular dementia and can also independently result in cognitive decline by multiple different mechanisms. Microvascular complications; renal disease, retinopathy or neuropathy, are also linked to cognitive decline[94,112]. One of the ways to look at this relationship is that microvascular complications like retinal vascular changes could represent markers for the changes in the cerebral microvasculature which results in cognitive decline in the elderly due to ischemic effects[94]. Chronic hyperglycemia and microvascular disease contribute to cognitive dysfunction in both type 1 and type 2 diabetes[112]. The Edinburgh type 2 diabetes study[113]showed that general cognitive ability in elderly people aged 60–75 years with type 2 diabetes was significantly lower in people with moderate-to-severe diabetic retinopathy (mean −0·44, 95% CI −0·73 to −0·16) than in those without retinopathy (0·05, −0·03 to 0·12; p=0·003). Other co-existed chronic diseases like arthritis, depression and lung diseases impact on cognition among diabetic patients beyond disease complications are not fully studied. Diabetic patients with comorbidities, including

hypertension, hyperlipidemia, stroke, coronary artery and/or kidney disease, had a higher hazard ratio for dementia compared with diabetics without such comorbidities[101]. However, such comorbidities are considered in a way or another, as vascular complications for diabetes itself rather than completely independent diseases. Depression was shown to increase the cognition decline risk when it co-existed with diabetes[110,114]. Arthritis[37] and lung diseases[115] are associated with cognitive decline, but this association among diabetic patients has been rarely studied. The main goal of this study is to evaluate the interactive effect of chronic diseases on cognition among elderly diabetic patients compared to non-diabetics.

3.2 Specific Aim 1

To examine the impact of diabetes disease complications, co-existed diseases and geriatric conditions on the incidence of any-cognitive decline (Any-CI) / all-cause dementia (All-D) among diabetic subjects compared to non-diabetic subjects in a national representative sample prospectively followed for ten years.

Representative Hypotheses

- Diabetes with microvascular complications (kidney disease) will independently increase the risk of incident Any-CI / All-D after adjusting for demographic characteristics (educational level, age, sex, ethnicity, income, and BMI) compared to non-diabetic subjects.
- The presence of macrovascular diseases (hypertension, heart diseases, and stroke) may mediate the association between diabetes and cognitive function.

- Other chronic diseases (arthritis, lung diseases, and cancer) may increase the risk of incident Any-CI / All-D.
- Geriatric conditions (depressive symptoms, difficulty performing ADLs, hearing loss, and vision loss) may be associated with higher risk of incident Any-CI / All-D.
- Examine the possible moderating effects of health behaviors (exercise, smoking and alcohol drinking) on the association between diabetes with microvascular complications, macrovascular diseases, co-morbidities and cognitive decline.

3.3 METHODS

3.3.1 Dataset and Study population

Health and Retirement Study (HRS) was established in 1992 to provide a nationally representative longitudinal data on aging. The survey included more than 37,000 individuals over age 50 in 23,000 households in the USA[116]. The initial survey cohort (born 1931-1941) was recruited in 1992; it is referred to as the HRS cohort. The following year, another study was established in order to capture those 70 years old and above (born 1890–1923), the Asset and Health Dynamics Among the Oldest Old (AHEAD). Both studies were combined, and two additional cohorts, the Children of the Depression (CODA; born 1924-1930) and the War Babies (WB; born 1942-1947), were added in 1998 in order to make a representative sample for US population over age 50. Since then, HRS is refreshing the sample every six year with new birth cohort. Wave 7 (2004) included The Early Baby Boomers cohort (EBB; born 1948-1953) and wave 10 (2010) included The Mid Baby Boomers cohort (MBB, born 1954-1959) with supplemental oversample of Blacks, Hispanics and residents of the state of Florida. The Late Baby Boomers (LBB, born 1960-1964) were included in wave 13 (2016). Institutionalized individuals (prisons, jails, nursing homes, long-term or dependent care facilities) were excluded from the study population but those moved to nursing homes after baseline retained and were interviewed[117].

The HRS sample is a multi-stage probabilistic sample that included geographic stratification, clustering and oversampling of minorities. Sampling weights account for complex study design and differential non-response in each wave. A primary respondent is randomly selected and interviewed along with their spouses or partners regardless of age. A proxy interview, usually with a family member within the household, was used

for those unwilling or unable to do an interview themselves. In each wave, approximately 9% of interviews were with a proxy respondent, 18% for those who are 80 and older. Proxy interviews are essential to reduce bias due to non-response or severe impairment especially in cognition[118]. HRS questionnaire covered many topics related to aging: income and wealth, work and retirement, family connections, health, cognition, and healthcare services usage. The survey was conducted by telephone or face-to-face. (For more information, see http://hrsonline.isr.umich.edu).

In order to make the HRS data more accessible to researchers, the RAND Center for the Study of Aging, with funding and support from the National Institute on Aging (NIA) and the Social Security Administration (SSA), created the RAND HRS data files[119]. The RAND Enhanced Fat Files contain most of the original HRS variables with household data merged to the Respondent level. It is a user-friendly version of a subset of the HRS variables. It contains cleaned and processed variables with consistent and intuitive naming conventions, model-based imputations and imputation flags, and spousal counterparts of most individual-level variables. The RAND HRS Data is distributed as a single file which includes 12 waves of the HRS. All the RAND data products are available to download from the HRS website (http://hrsonline.isr.umich.edu/data /index.html). For more information about the RAND HRS data products, please visit the RAND Center for the Study of Aging website at (http://www.rand.org/labor/aging).

For this study, most of Aim 1 variables were extracted from RAND Enhanced Fat Files (v.P). Variables not included in the fat file, proxy cognitive measures and geriatric conditions, were retrieved from wave specific RAND/HRS core file[120]. Sampling weights were not used since the scope of this study is to understand the mechanisms by which

diabetes, related chronic diseases and cognition are associated. Future work may account for sampling weight to promote more generalizable conclusions.

3.3.2 Study sample

Baseline sample is based on 2002 wave HRS cohort followed through 2012 wave. It included 18,165 subjects with 88.4% response rate. Response rate ranged from 2002 to 2012 waves between 87.1 – 89.1%[116]. Proxy interviews were about 11.2% of 2002 wave interviews, 2,036 subjects. Proxy interviews ranged from 2002-2012 was from 5.57-11.2%[116]. This study included those 51 years old and above. Exclusions included: subjects living in nursing home, baseline proxy interviews, missing baseline cognition or diabetes status, or missing follow up interview or cognition status. Since our study goal is to study incidence of Any-CI/ All-dementia, 4,328 subjects with cognitive impairment at baseline were excluded too. The total final analytic sample size was 11,825 subjects (Figure 3.1).

3.3.3 Key Measures

Outcome: Cognitive impairment and Dementia

Cognitive function in HRS was assessed at every wave from 1992 to 2016. A wide range of measures and tests were used to comprehensively evaluate cognitive function of respondents and certain measures were used for proxy interviews. The telephone interview for cognitive status (TICS) was developed to be administered in large scale in HRS study. It is similar to MMSE but doesn't need a face to face interaction between patient and examiner. TICS and MMSE were highly correlated; Pearson

coefficient was 0.94[121]. Test re-test reliability for TICS is also high (r = 0.965) with high intra-class correlation coefficient (r = 0.99). TICS has a good sensitivity (94%) and specificity (100%) for cognitive impairment of Alzheimer's disease patients; it significantly discriminates between demented subjects and those with normal cognition[121]. Crimmins et al.[122] described an approach developed by Langa and Weir (2009)[123] to define cognitive impairment and dementia using HRS data that produces the same population distribution of Aging, Demographics, and Memory Study (ADAMS) with few tests of full HRS battery. This approach dropped object naming test to assess language, and recall of the date and president and vice president to assess orientation from the full HRS cognitive battery in order to include participants less than 65 years. It included: (1) the 10-word immediate recall test for short-term memory (scored 0–10); (2) the delayed recall test for long-term memory (scored 0–10); (3) the serial 7's subtraction test to assess working memory (scored 0–5); and (4) counting backwards from 20 to assess attention and processing speed (scored 0–2). Participants were allowed 5 trials for the serial 7's task, and the backward counting was scored as correct/incorrect. Thus, the total cognitive functioning score could range from 0 to 27. Scores were categorized as the following; from 0 to 6 were classified as having dementia (D), 7–11 as having cognitive impairment without dementia (CIND), and 12–27 as having no cognitive impairment[122].

At 2002 baseline sample, proxy interviews and those with cognitive score less than 12 were excluded. However, proxy cognitive function in the follow up interviews (from 2004 wave to 2012 wave) was included in the outcome measure. This approach reduced bias in the results of cognitive function assessment since subjects with severe cognitive impairment are more likely to not respond[122,124]. Proxy cognitive function was measured by: a direct question about respondent memory rate with responses ranging

from excellent to poor (Scored 0–4), and assessment of limitations in five instrumental activities of daily living (IADLs); managing money, taking medication, preparing hot meals, using phones, and doing groceries (Scored 0–5). Also, the survey interviewer was asked to make a judgment about the survey participant's cognitive ability. The interviewer's rating on respondent difficulty to complete the interview because of cognitive limitation was also included (scored 0–2 indicating, none, some, and prevents completion). Here, scoring followed Crimmins et al.[122] and the total score from both proxies and informants information was classified as; high scores as demented (6–11), medium scores (3–5) as CIND, and <3 as normal cognition[122]. Combining both self and proxy respondent cognitive status with this categorization method correctly classifies 74% of cognitive decline and dementia subjects into groups as ADAMS study diagnosed groups[122].

For this study, we followed Crimmins et al.[122] definition of cognitive impairment and dementia. Although proxy interviews were excluded at baseline, they were included in follow up. Both self-respondent cognitive measure and proxy measure will be categorized, as shown previously, and thenwill be combined to have a total measure for cognition. So, someone with a total cognitive score less than 12 or with a proxy cognitive score greater than 2 was coded as cognitively impaired. Self-respondents cognitive measure were obtained from RAND file (v.P)[119]. The advantage of using RAND file is the use of imputation for missing data in one or more of cognitive tests inorder to get a more complete data set[125]. The need for imputation stems from the fact that a respondent will less likely answer a cognitive test question because they do not know the answer or afraid to answer incorrectly. This could be related to their level of education, cognitive functioning or perceived level of cognitive functioning[125]. As a result, the data are not

missing at random which may bias late estimates. Prior wave cognitive scores and a combination of relevant demographic, health, and economic variables were used to perform the imputations using a regression-based procedure[125]. Imputation used to replace missing values due to refusals (RF), and any not applicable (NA) response. Don't Know (DK) responses, proxy interviews or non-participants in a given wave were not imputed. Also, those who never did any self-core interview were excluded from imputation[125]. RAND file (v.P) didn't include proxy measure used by Crimmins et al.[122]; only original HRS wave data were used to get proxy measures on cognition[120].

Independent variables

Diabetes exposure

Self-reported diabetes diagnosis at baseline was identified with the question "have you ever had, or has a doctor ever told you that you have, diabetes or high blood sugar?". Diabetes duration is not available for 2002 wave, but was retrieved from 2003 diabetes wave. Duration was calculated as the following equation; Baseline interview year – Age at diagnosis (from 2003 file) and categorized as no diabetes, diabetes ≤ 10 years, diabetes >10 years, and unknown for missing values (N=565). Diabetes treatment was assessed with two questions about diabetes oral medicine and insulin. It was combined to one single measure; re-coded as no-diabetes, diabetes with oral diabetes medication only, and insulin medication (with and without oral medication).

Indicators of Macrovascular diseases

Self-reported macrovascular diseases at baseline (2002 wave) were assessed with the question "Has a doctor ever told you that you had …?". This included hypertension, stroke and heart diseases (Myocardial infarction, angina, congestive heart failure and

other heart problems). Hypertension medications were extracted from the following question: “In order to lower your blood pressure, are you now taking any medication?”. Positive response to hypertension medication question with negative response to self-reported hypertension diagnosis question was recoded as having hypertension.

Indicators of Microvascular diseases

The presence of microvascular complications, renal disease, neuropathy symptoms, and eye disease wasn’t fully addressed in baseline 2002 wave. The only variable available was kidney problems due to diabetes; “Has your diabetes caused you to have trouble with your kidneys or protein in your urine?”. This question has been asked for subjects with positive answer on diabetes diagnosis question. Thus it was re-coded to no diabetes, diabetes with no kidney problems, and diabetes with kidney problem.

Other co-existing chronic diseases

The presence of other chronic diseases like arthritis, lung disease/emphysema, and cancer (not skin cancer) were assessed with “Has a doctor ever told you that you had …. ?” question (yes/no).

Geriatrics conditions

Four variables covered common geriatric problems: hearing, vision, depression, and mobility. Baseline hearing loss and vision loss were retrieved from the original HRS file since RAND file didn’t include them. The following questions were used for: hearing loss; “Is your hearing excellent, very good, good, fair, or poor (using a hearing aid as usual)?”, and vision loss; “Is your eyesight excellent, very good, good, fair, or poor (using glasses or corrective lenses as usual)?”. Those with excellent, very good and good

answer were considered as negative response and coded as 0 and those with fair and poor answers were considered as positive response and coded as 1. Depressive symptoms and Activities of Daily Living (ADLs) summary scores were retrieved from RAND file (v.P). Difficulties in performing the following ADLs were looked at: bathing, dressing, eating, getting in/out of bed and walking across a room. Score of 1 or more was categorized as having difficulties (yes). Depressive symptoms were assessed using the short version of the Center for Epidemiologic Studies Depression Scale (CES-D). This scale is a sum of 5 negative indicators minus 2 positive indicators. The negative indicators measure whether the respondent experienced the following sentiments all or most of the time: depression, everything is an effort, sleep is restless, felt alone, felt sad, and could not get going. The positive indicators measure whether the respondent felt happy and enjoyed life, all or most of the time. Score ranges from 0 – 8 and was categorized as no depression(< 4) or depression (≥ 4)[126].

Health behaviors and lifestyle factors

Three variables assessed lifestyle: physical exercise, smoking, and drinking. Physical activity was retrieved from original HRS 2002 core file, the rest of variables were taken from RAND file. Baseline physical activity was measured by the following question: “On average over the last 12 months have you participated in vigorous physical activity or exercise three times a week or more? By vigorous physical activity, we mean things like sports, heavy housework, or a job that involves physical labor” (yes/no). Baseline smoking was extracted from two questions; “Have you ever smoked cigarettes?” (yes/no), for those with yes answer “Do you smoke cigarettes now?” (yes/no). Smoking was categorized into (never, former and current smoker). To measure alcohol drinking, self-reported number of days per week and number of drinks per day were used to

calculate number of drinks per day; "In the last three months, on average, how many days per week have you had any alcohol to drink? (For example, beer, wine, or any drink containing liquor)", and "In the last three months, on the days you drink, about how many drinks do you have?" respectively. The number of drinks per day were calculated as following: the number of drinks consumed on days the participant drinks multiplied by the number of days per week the participant reported drinking and the result is divided by seven[127]. About 70.78% of the sample had 0 drinks per day; the number of drinks per day was categorized as 0, 1-2, and 3 and more drinks per day.

3.3.4 Covariates

Self-reported age, sex, race/ethnicity, marital status, education, and BMI were included as covariates in all models. The HRS participants who identified themselves or were identified by their proxy respondent as "Hispanic" were considered Hispanic regardless of their race. Thus, for this report, "Whites" include only non-Hispanic Whites, and "African-Americans" include only non-Hispanic African-Americans. Based on that, race/ethnicity categories were non-Hispanic White, non-Hispanic Black, Hispanic, and non-Hispanic others. Marital status was categorized as "married or partnered" and "not married or not partnered". Education was categorized as ("high school and less", "some college" and "college and greater"). The HRS study included many measures of income and financial status of respondents. The RAND v.P file contained summary measures of income and assets. Total household income (sum of all household income; respondent and spouse only) was used as socioeconomic status measure and coded approximately in thirds ($0 to $19,999; $20,000 to $39,999, $40,000 or greater)[37,128]. Body Mass Index (BMI) (kg/m2) was dichotomized using standard

cutoffs of not obese <30 kg/m2, obese ≥30 kg/m2, and "unknown" for missing values was used as a separate category (N=190)[129].

3.3.5 Statistical analysis

Censoring

The study began in 2002 and ended in 2012 and included 6 waves. Interview beginning date (2002) was used to calculate time to event; incident Any-CI or All-D. The incident date for Any-CI/All-D was calculated as halfway point between the interview date at which Any-CI/All-D was first reported and the previous wave; survival time calculation. Those with changing cognitive status, who scored low and were categorized as cognitively impaired in one wave then got normal score and normal cognitive status in another wave, were not accounted in the analysis since they still have higher risk for developing cognitive decline or dementia compared to normal subjects[16,17]. Participants who didn't get the event were censored at their last interview date, death or at the end of the study period, 10 years, whichever time point was first.

Bivariate analysis

Descriptive statistics were created for each variable used in the analysis. For categorical variables, counts and percentages were reported, while for continuous (age) variables, means and standard deviations were reported. Bivariate relationships were compared between diabetic and non-diabetic individuals for all individual predictors, covariates and outcome variables using chi-square and ANOVA. The unadjusted survival curve for the incidence of Any-CI / All-D was examined by Kaplan- Meier method (KM) for the entire sample. Groups in KM were compared using log rank test.

Multivariable analysis: Cox proportional hazard

The incident of Any-CI and All-D were evaluated separately. Seven-model set was run that added progressively more variables as shown below:

- Model 1: Demographic variables (Age, sex, race, education, marital status, income, and BMI), diabetes, and the incident Any-CI/All-D outcome.
- Model 2: Demographic variables, diabetes with microvascular complication (kidney problems), and the incident Any-CI/All-D outcome.
- Model 3: Model 2 + macrovascular diseases (hypertension, hypertension medication, heart diseases, and stroke).
- Model 4: Model 3 + other chronic diseases (arthritis, lung diseases, and cancer).
- Model 5: Model 4 + geriatric problems (depressive symptoms, ability to perform ADLs, hearing difficulty, and vision loss).
- Model 6: Model 5 + lifestyle factors (physical activity, alcohol drinking, and smoking status).
- Model 7: Moderation effect (interaction terms) of other chronic diseases, geriatric conditions, and life style factors with diabetes on the incidence of Any-CI/All-D.

Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) of incident Any-CI and All-D. Tied events were handled using Exact method for all models. Results were reported as hazard ratio (HR) and their 95% confidence intervals (95% CI). Model assumptions and diagnostics were checked for all models used in the analysis. Model diagnostics were assessed using Schoenfled residual, interaction term for

each variable with time and log-minus-log plot to evaluate the proportionality assumption (Martingale residual assumption check took very long computing time and that's why it was substituted by Schoenfled residual). For Any-CI models, Age (as continuous variable), race, and education violated the proportional assumption of cox model. Age was categorized into 4 groups (<65, 65-74.99, 75-84.99, ≥85 years old) which remedied the model for this covariate. Race and education were included in STRATA statement in proc PHREG in SAS to overcome the assumption violation. However, this method will not produce hazard ratios for these two variables; race and education effect on cognitive decline is not the main interest for our study. About 37 outliers were identified using Deviance residual; models estimates were evaluated with and without outliers. The effect of outliers didn't severely impact the model estimates, they kept in the analysis. The overall model fit was evaluated using Cox-Snell residual plot; no major problem with all models (See Appendix A.1). Non- informative censoring was evaluated using competing risk model where death was considered as a competing event. As it was explained earlier, AD and diabetes increase the risk of death which can't be ignored in our analysis. Those who died before having the event may produce biased estimates for our analysis.

Moderation analysis

The interaction of diabetes with other chronic diseases, geriatric conditions, and lifestyle factors were evaluated in the full model (model 4) as individual term then were introduced all in one model. The hypothesis of no excess hazard due to interaction was considered significant at P-value <0.05. Only significant interaction was reported.

Mediation analysis

Diabetes is associated with higher risk of cognitive decline through increased risk of macrovascular diseases[88]. Macrovascular diseases; hypertension, stroke, and heart diseases, are risk factors of cognitive decline and vascular dementia[87]. Therefore, it is important to know how much macrovascular diseases account for cognitive decline. The potential mediating role of macrovascular diseases on the relationship between diabetes and cognitive decline was examined using a method developed by Vanderweele and Valeri[130-132], see e-appendix(http://links.lww.com/EDE/A877) for more details[130]. This method estimates the causal effect under the counterfactual framework for time to event data and allows for effect decomposition even in the presence of exposure–mediatorinteraction. In contrast to traditional mediation analysis methods, counterfactual framework allows for nonlinearities and account for possible interactive relationship between the mediator and the outcome[133,134]. The main goal of mediation analysis is to estimate the direct effect for an exposure X on certain outcome Y and how much Y would change by X, controlling for any mediator M effect. Unfortunately, controlling for M as a constant (M=m), not allowing it to change, is impractical in reality. In the counterfactual model, mediators were allowed to vary and the exposure effect on the outcome were compared when the exposure X=1 to those X=0 but ignore all mediator values except those in which M achieves the value $M = m$[134]. This permits the assessment of a more natural type of direct and indirect effects, which is applicable for both linear and nonlinear models[133]. Under this model, the causal effect was decomposed into[132,135]:

1) Controlled direct effect (CDE); which compares how much the outcome would change in average when exposure changes from x=0 to x=1

controlling for mediator at fixed level M=m(CDE(m) = E − E (Y (0, m))). On other words, CDE is the direct effect of X on Y, unmediated by M.

2) Natural direct effect (NDE); compares how much the outcome would change in average when exposure is set at level x=1 compared to x=0 keeping the mediator level at the level where its exposure is absent x=0, (NDE = E [Y (1, M (0))] − E [Y (0, M (0))]). If there is no interaction between X and M, then CDE = NDE since M is the same (within subject) in both X situations.
3) Natural indirect effect (NIE); expresses how much the outcome would change in average if the exposure level is set on level x=1 and the mediator changes from the level it would be when the exposure x=0 to the level it would become when exposure is x=1 (NIE = E [Y (1, M (1))] − E [Y (1, M (0))]) (NIE = E [Y (1, M (1))] − E [Y (1, M (0))]).
4) Total effect (TE); is the overall change of the outcome on average for exposure change from x=0 to x=1 (TE = NDE + NIE = E [Y (1, M (0))] − E [Y (0, M (0))] + E [Y (1, M (1))] − E [Y (1, M (0))] = E [Y (1, M (1))] − E [Y (0, M (0))]).

For this study, the hazard ratio scale of cox-proportional hazard models was used to estimate the causal effect, however, this model requires a rare outcome at the end of follow up[132]. The mediation analysis using this method would be valid if there no un-measured confounder that may impact the exposure – outcome, mediator – outcome and exposure – mediator relationship. Also, none of the mediator–outcome confounders should be affected by the exposure[132]. Automated macro software for mediation for survival data for SAS 9.3 is available for download at the authors' websites

(https://www.hsph.harvard.edu/tyler-vanderweele/tools-and-tutorials). In order to perform mediation analysis for macrovascular disease, all macrovascular diseases (hypertension, heart diseases, and stroke) were re-categorized in one variable 0/1. The interaction terms between diabetes and macrovascular variable was not significant, thus, mediation analysis didn't include any interaction term.

Sensitivity analysis

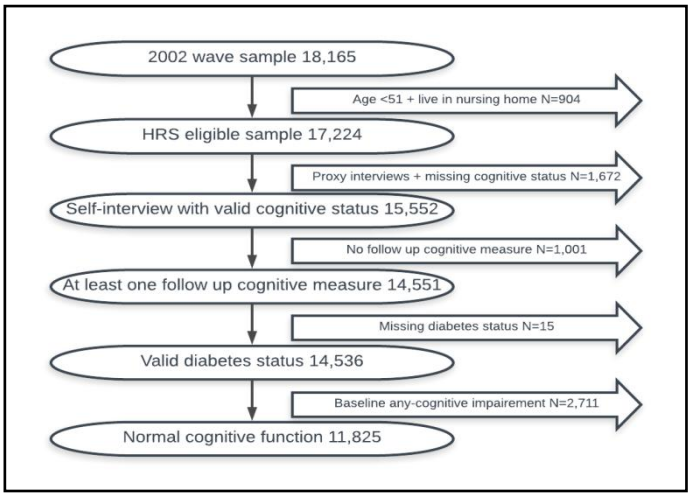
The idea of sensitivity analysis is to evaluate the degree to which the study final result is robust; doesn't change very much over different types of analysis. Several sensitivity analyses were conducted: first, competing risk model was used to account for death during study follow up which may impede the observation of cognitive decline using Fine and Gray's extension of cox-regression model[136]. Second, the impact of interval censoring on study time to event definition was examined for the full model using proc Icphreg option in SAS 9.4. However, this model doesn't have strata statement that will account for model assumption violation for race and education. Finally, the study sample was restricted to those 65 and above.

3.4RESULTS

3.4.1 Analytic sample and Missing Data

The 2002 HRS has a total of 18,165 completed interviews, 2036 by proxy. For the scope of this aim, the sample was limited to those individuals who are HRS age-eligible, over 50 years, and not institutionalized. Nursing home residents, proxy interviews and those with missing key variable of cognition or diabetes status were excluded from the sample. This brings the initial analytic sample to a total of 14,536 individuals (Figure 3.1). Since our study goal is to measure cognitive decline incidence, all individuals with abnormal baseline cognitive score were excluded, reducing the sample to 11,825 subjects (65.1% of the original sample). The percentage of missing in covariate, marital status, education and total household income, variables less than 1% was re-coded as "negative response". Those with more than 1% missing (diabetes duration- 565 missing out of 1,722, and BMI- 190 missing out of 11,635) were re-coded as different category called "un-known".

Figure 3.1. Flow chart from the complete, eligible Health and Retirement Study 2002 sample to study analytic sample (Aim 1).



3.4.2 Descriptive statistics

The total sample used for aim 1 analysis was 11,825 subjects with an average age at baseline of 66.78 years old (Table 3.1). However the majority of the sample was between 51 and 65 years old (about 44.74% less than 65). More than 50 % of the sample was female, Non-Hispanic White, married or partnered, finished high school or less, and non-obese (Table 3.1). Approximately 48.25% of the sample falls under ≥ $40,000 bracket of total house hold income.

Table 3.1: Baseline demographic characteristics for diabetic subjects compared to non-diabetics for Aim 1 study participants.

	No diabetes		**Diabetes**		**Total**	
	% (N=10,103)		**% (N=1,722)**		**% (N=11,825)**	
Age (yrs ; mean(std))	66.81(8.77)		67.25(8.23)		66.87	(8.79)
Age categories**						
< 65	45.27	(4,574)	41.58	(716)	44.74	(5,290)
65-74.99	34.53	(3,489)	38.27	(659)	35.08	(4,148)
75-84.99	16.92	(1,709)	17.94	(309)	17.07	(2,018)
≥ 85	3.28	(331)	2.21	(38)	3.12	(369)
Female**	62.51	(6,315)	54.82	(944)	61.39	(7,259)
Race**						
Non-Hispanic White	84.07	(8,494)	70.85	(1,220)	82.15	(9,714)
Non-Hispanic Black	8.97	(906)	17.60	(303)	10.22	(1,209)
Hispanic	5.40	(546)	9.41	(162)	5.99	(708)
Others	1.55	(157)	2.15	(37)	1.64	(194)
Married/Partnered	69.28	(6,999)	67.42	(1,161)	69.07	(8,160)
Education**						
≤ High school	53.68	(5,423)	62.31	(1,073)	54.93	(6,496)
Some college	23.14	(2,338)	20.44	(352)	22.75	(2,690)
≥ College	23.18	(2,342)	17.25	(297)	22.32	(2,639)
Annual Household Income**						
< $20,000	21.62	(2,184)	30.72	(529)	22.94	(2,713)
$20,000-39,999	28.38	(2,867)	31.36	(540)	28.81	(3,407)
≥ $40,000	50.00	(5,052)	37.92	(653)	48.25	(5,705)
BMI (kg/m2)****						
Normal <30	75.46	(7,624)	51.80	(892)	72.02	(8,516)
Obese ≥30	22.94	(2,318)	46.52	(801)	26.38	(3,119)
Unknown	1.59	(161)	1.68	(29)	1.61	(190)

** P-value <0.0001. * P-value <0.01.

Only 14.56% of the sample reported to have diabetes while hypertension and arthritis were the most prevalent chronic diseases in the sample; percentages were 49.59 and 54.58% respectively (Table 3.2). Heart diseases and stroke were present in less than 20% of the sample, 19.59% and 5.3% respectively. Geriatric conditions, depressive symptoms, difficulties with ADL, hearing loss, and vision loss were significantly higher among diabetic subjects. Vision loss among diabetics could be majorly a complication of the disease; however, it can't be confirmed in this sample. Amazingly, subjects of this

sample did relatively well in terms of lifestyle factors (physical activity, smoking and drinking alcohol); where the majority didn't smoke (85.45%), did not drink alcohol (66.26%) and (45%) reported to exercise. The majority of those with diabetes (64.58%) were on oral medications only and 20.38% were using insulin treatment.

About 8.48% of diabetics already had kidney problems. Diabetic subjects with kidney problems were more likely to have long disease duration; 60.22% (N=56) had 10 years and above disease duration while 39.78% (N=37) only had less than 10 years disease duration. Diabetics with no kidney problems were more likely to have shorter disease duration; 53.1% (N=565) had < 10 years disease duration while 46.9 (N=494) had ≥ 10 years disease duration (P-value 0.01). These figures could be underestimating the real situation due to missing data on disease duration for 32.81% (N=365 of 1,722) of diabetic subjects, specially that in KM analysis those with missing information on disease duration behaved like those with 10 years and above disease duration (there was no statistical difference between these two group (P-value 0.4)).

Table 3.2: Baseline clinical characteristics for diabetic subjects compared to non-diabeticsfor Aim 1 study participants.

	No diabetes % (N=10,103)		**Diabetes % (N=1,722)**		**Total % (N=11,825)**	
Kidney problems due to diabetes	N.A	N.A	8.48	(146)		
Hypertension**	45.43	(4,590)	73.81	(1,271)	49.59	(5,861)
Heart Problems**	17.51	(1,768)	31.36	(540)	19.53	(2,308)
Stroke**	4.69	(474)	8.89	(153)	5.30	(627)
Arthritis*	53.34	(5,389)	61.44	(1,058)	54.58	(6,447)
Lung diseases*	6.48	(655)	8.19	(141)	6.73	(796)
Cancer*	12.28	(1,241)	14.17	(244)	12.57	(1,485)
Depressive Symptoms**	12.02	(1,214)	16.32	(281)	12.64	(1,495)
ADL (any difficulties +1)**	9.29	(939)	19.69	(339)	10.81	(1,278)
Hearing Loss**	15.91	(1,607)	20.73	(357)	16.61	(1,964)
Vision Loss**	14.12	(1,427)	25.09	(432)	15.78	(1,859)
Physical Activity (Active)**	46.64	(4,712)	35.25	(607)	45.00	(5,319)

Alcohol drinking (drinks per day)**						
None	63.98	(6,464)	79.62	(1,371)	66.26	(7,835)
1-2 drinks	32.70	(3,304)	18.52	(319)	30.64	(3,623)
≥ 3 drinks	3.32	(335)	1.86	(32)	3.10	(367)
Smoking Status**						
Never	42.49	(4,293)	39.50	(681)	41.06	(4,794)
Current	13.97	(1,411)	10.86	(187)	13.51	(1,598)
Former	43.54	(4,399)	49.59	(854)	44.42	(5,253)
Any cognitive decline**	36.55	(3,693)	47.97	(826)	38.22	(4,519)
Dementia **	9.19	(928)	13.7	(236)	9.84	(1,164)

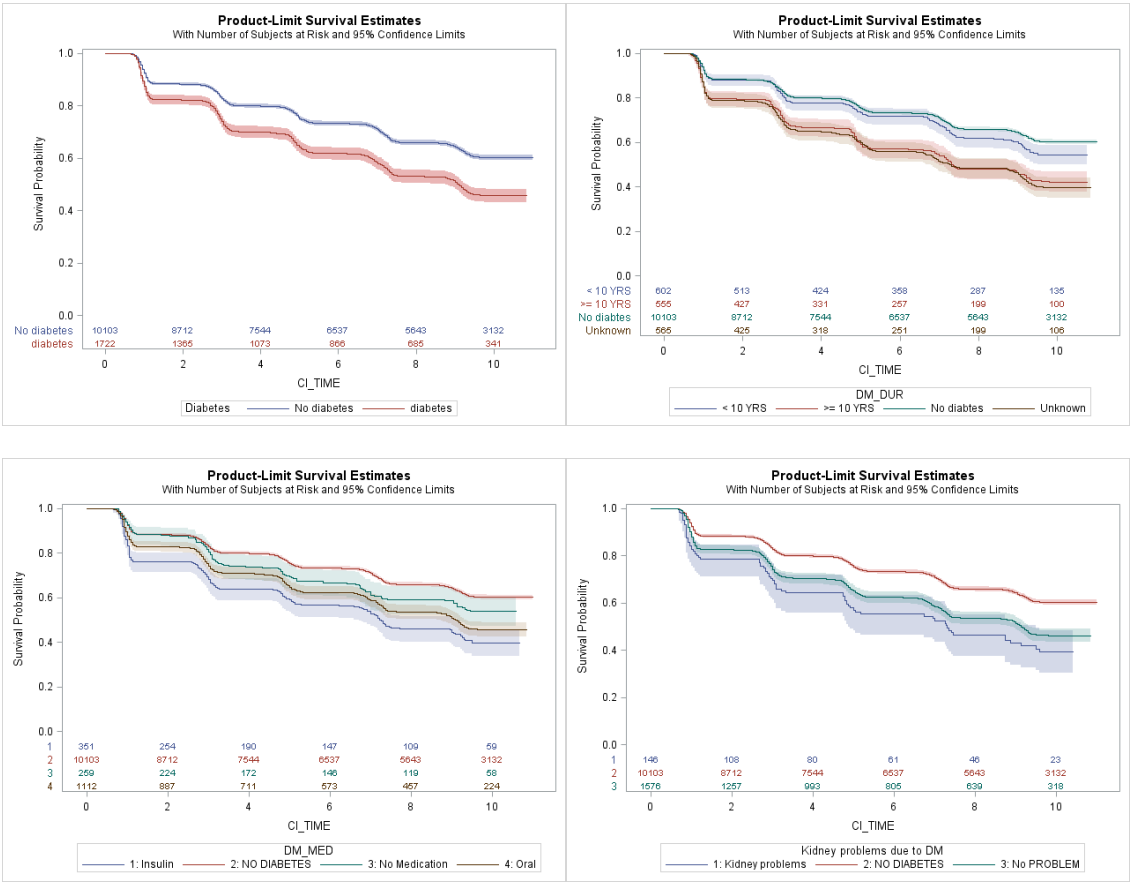
** P-value <0.0001. * P-value <0.01.

3.3.3Diabetes and risk of incident Any-CI

Kaplan-Meir analysis

In Kaplan-Meir analysis, those with diabetes had significantly lower survival rate (which means higher rate of Any-CI) compared to non-diabetics (Logrank P-value <0.0001). This is similar for those with longer duration, insulin medication and kidney problems (Figure 2). The first two waves had the highest rate of incident Any-CI as the curve had a steep decline over time. This could attributed to the oldest old age group (age ≥ 85 years old) in the sample. Although these variables were significant, only diabetes with kidney problems were included in Cox-regression models as other variables (disease duration and medication) had the same control group (non-diabetics).

Figure 3.2: Aim 1 Kaplan Meir survival curve for incident Any-CI.



Multivariable Cox proportion hazard for incident Any-CI

Over a median of 8.87 years of follow up (interquartile range, 3.42 - 10.0), Any-CI developed in 4,519 of the 11,825 respondents (38.22%) at the end of follow up. Rate of cognitive impairment was higher among those reporting diabetes. Based on KM analysis, among 1,722 Diabetic subjects, about 826 developed cognitive impairment (47.97%). Meanwhile, among 10,103 non-diabetic subjects, 3,693 developed Any-CI (36.55%). Association between diabetes, microvascular, and macrovascular complications and the development of any cognitive decline is shown in Table 3.4 (all

models in Appendix A). The strongest risk factor was aging itself. Being female and having high income were negatively associated with Any-CI development risk. Diabetes was associated with 31% higher risk of incident Any-CI compared to non-diabetics (Model 1) after adjustment for demographics variables. Diabetic subjects with kidney problems had higher risk for Any-CI compared to non-diabetics. This significant association was persistent in all models (from model 2 through 6). The level of association attenuated through models with a HR ranging from 1.72 in demographics model (model 2) to 1.39 in the full model (model 6). However, having kidney problems due to diabetes was not significant when it was compared to those with diabetes only (without kidney problems) in the full model; HR= 1.17 (95% CI 0.92-1.48). For macrovascular diseases, heart diseases were significantly associated with higher risk of developing Any-CI in all models except for model 6 where it lost its significance after the adjustment of lifestyle factors. Hypertension and stroke remained significantly associated with higher risk throughout all the models, in model 6 HR=1.09 (95% CI: 1.02-1.16) and 1.3 (95% CI: 1.16-1.46), respectively. None of the coexisting chronic diseases (arthritis, lung diseases and cancer) were significantly associated with Any-CI. Arthritis was significant in model 4, HR=1.09 (95% CI 1.02-1.16), but it lost its significance once geriatric conditions were introduced to the model; mainly due to ADL adjustment. All geriatric conditions were significantly associated with higher risk of Any-CI. Exercising was negatively associated with Any-CI (HR=0.93; 95% CI: 0.87-0.99). Drinking 1-2 drinks of alcohol per day had also a lower HR compared to those who didn't drink (HR=0.83; 95% CI: 0.77-0.9). Smoking increased the risk of incident Any-CI compared to subjects who never smoked, HR was greater for current smokers, 1.26 (95% CI 1.15-1.39), compared to former smokers, 1.1 (95% CI: 1.03-1.17).

Table 3.4: Aim1 Cox proportional hazard models for incident Any-CI.

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Age categories												
< 65	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
65-74.99	1.77	1.64 - 1.91	1.77**	1.65-1.91	1.75**	1.62-1.88	1.74**	1.62-1.87	1.77**	1.64-1.91	1.8**	1.67-1.94
75-84.99	3.85	3.5-4.18	3.87	3.56-4.2	3.7	3.4-4.02	3.7	3.4-4.03	3.74	3.44-4.08	3.86	3.54-4.21
≥ 85	6.2	5.38 - 7.13	6.23	5.41-7.17	5.85	5.08-6.75	5.85	5.07-6.75	5.46	4.73-6.32	5.7	4.92-6.6
Female	0.83	0.78 - 0.88	0.83**	0.78-0.88	0.84**	0.79-0.9	0.83**	0.78-0.89	0.84**	0.78-0.89	0.83**	0.77-0.89
Married/Partnered	1.01	0.94 - 1.08	1	0.94-1.08	1	0.93-1.08	1	0.93-1.08	1.02	0.94-1.09	1.02	0.95-1.1
Annual Household Income												
< $20,000	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
$20,000-39,999	0.77	0.71 - 0.83	0.77**	0.71-0.83	0.78**	0.72-0.84	0.78**	0.72-0.84	0.80**	0.74-0.86	0.81**	0.75-0.88
≥ $40,000	0.59	0.54 - 0.65	0.59	0.55-0.65	0.61	0.56-0.66	0.61	0.56-0.67	0.64	0.59-0.7	0.66	0.6-0.72
BMI (kg/m2)**												
Normal <30	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Obese ≥30	0.98	0.91 - 1.05	0.98	0.91-1.5	0.96	0.89-1.03	0.95	0.88-1.02	0.92*	0.85-0.98	0.91*	0.85-0.98
Unknown	0.88	0.67 - 1.61	0.88	0.67-1.16	0.88	0.67-1.16	0.88	0.67-1.16	0.86	0.65-1.13	0.84	0.64-1.11
Diabetes	1.31	1.21 - 1.42										
Kidney problems due to DM												
No DM			**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
DM without kidney problems			1.28**	1.18-1.39	1.23**	1.13-1.34	1.23**	1.14-1.34	1.21**	1.11-1.31	1.19**	1.1-1.29
DM with Kidney problems			1.72	1.36-2.16	1.58	1.25-1.99	1.56	1.23-1.96	1.41	1.12-1.78	1.39	1.1-1.75
Hypertension					1.09	1.03-1.16	1.07	1.02-1.16	1.08	1.02-1.15	1.09	1.02-1.16
Heart Problems					1.13*	1.05-1.21	1.11*	1.04-1.2	1.08*	1.01-1.16	1.07	0.99-1.15
Stroke					1.37**	1.22-1.53	1.36**	1.22-1.52	1.32**	1.18-1.48	1.30**	1.16-1.46
Arthritis							1.09*	1.02-1.16	1.04	0.97-1.11	1.03	0.97-1.1
Lung diseases							1.08	0.96-1.21	0.99	0.88-1.11	0.95	0.84-1.07

Cancer							0.94	0.86-1.02	0.94	0.86-1.03	0.94	0.86-1.02
Depressive Symptoms									1.28**	1.18-1.39	1.26**	1.16-1.37
ADL (any difficulties +1)									1.24**	1.13-1.35	1.21**	1.11-1.32
Hearing Loss									1.11*	1.03-1.2	1.11**	1.03-1.19
Vision Loss									1.18**	1.1-1.27	1.17**	1.08-1.26
Physical Activity (Active)											0.93*	0.87-0.99
Alcohol Consumption (drinks per day)												
None											**Ref.**	
1-2 drinks											0.83**	0.77-0.9
≥ 3 drinks											0.91	0.75-1.09
Smoking Status												
Never											**Ref.**	
Current											1.26**	1.15-1.39
Former											1.1	1.03-1.17

**** P-value <0.0001, * P-value <0.05.**

Moderation analysis

All interaction terms tested for effect moderation of chronic diseases, geriatric conditions, and lifestyle were not significant. Having diabetes and arthritis didn't increase the risk of incident Any-CI compared to those with diabetes alone (P-value=0.49). The only significant interaction term was for physical activity where non-diabetics who exercise have lower HR compared to non-diabetics who don't exercise (HR=0.89; 95% CI: 0.84-0.96; P-value = 0.02. Subjects with diabetes, with and without kidney problems, and exercise are not statistically different from diabetics whom don't exercise (diabetes with kidney problems HR= 1.09; 95% CI 0.94-1.27 and without kidney problems HR=1.34; 95% CI 0.8-2.7, respectively).

Mediation analysis

In order to explore if there was any possible mediation-moderation effect between exposure and mediator, macrovascular diseases interaction with diabetes were examined. Hypertension, heart diseases, and stroke (as individual variables and as one variable) interaction with diabetes were not statistically significant (P-value > 0.05). Thus, mediation analysis was done without including any interaction term between exposure and mediator in the model. The total association between macrovascular diseases and Any-CI was 1.25 (95% CI 1.16 – 1.36), 1.22 (95% CI 1.13 – 1.32) for direct association, and 1.03 (95% CI 1.01 – 1.04) for indirect association (Table 3.5). Only 12.21% of the association between diabetes and Any-CI was mediated through macrovascular diseases.

Table 3.5: Aim 1 Estimated direct, indirect, total effect and proportion mediated by macrovascular diseases for diabetes and Any-CI relationship.

Effect	Estimate	95% confidence interval	P- value
CDE	1.22	(1.13 – 1.32)	<0.001
NDE	1.22	(1.13 – 1.32)	<0.001
NIE	1.03	(1.01 – 1.04)	<0.001
Total effect	1.25	(1.16 – 1.36)	<0.001
Proportion mediated	0.1221		

***CDE=controlled direct effect; NDE=natural direct effect; NIE=natural indirect effect.**

Sensitivity analysis

Death can have a huge impact on cognitive decline observed rate, those whom died early before didn't live long enough to witness the event. Adjusting for death subdistribution hazard would minimize the impact of death. Competing risk model didn't change the point estimate (HR), however, diabetic subjects with kidney problems become insignificant (Table 3.6). Death rate among those with diabetes and kidney problems was higher (23.29%) than both diabetic and non-diabetic subjects (17.13% and 10.34% respectively). also, hypertension become non-significant in the competing risk model compared to the cox-regression model. Lung diseases become negatively associated with the risk of incident Any-CI. Accounting for interval censoring didn't change the estimates (Table 3.6). Restricting the sample to those 65 and above, only changed the significance level of diabetics with kidney problems (become non-significance). This could be explained that after excluding those under 65 years, sample power for this group was reduced (N= 67 vs. 146). Hearing loss became non-significant too.

Table 3.6: Aim 1 Sensitivity analysis result comparison for incident Any-CI.

	Model 5		**Competing risk**		**Interval censoring**		**Age ≥ 65** (N=6,535; Any-CI=3,203)	
	HR	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**
Age categories								
< 65	**Ref.**		**Ref.**		**Ref.**			
65-74.99	1.80	1.67-1.94	1.75	1.63-1.89	1.81	1.69-1.96	**Ref.**	
75-84.99	3.86	3.54-4.21	3.34	3.05-3.65	3.92	3.59-4.28	2.12	1.96-2.92
≥ 85	5.70	4.92-6.6	4.16	3.54-4.88	5.82	5.02-6.75	3.2	2.77-3.69
Female	0.83	0.77-0.89	0.86	0.80-0.93	0.83	0.78-0.89	0.85	0.78-0.93
Married/Partnered	1.02	0.95-1.1	1.06	0.98-1.14	1.03	0.96-1.12	1.02	0.93-1.11
Annual Household Income								
< $20,000	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
$20,000-39,999	0.81	0.75-0.88	0.82	0.76-0.89	0.8	0.74-0.89	0.81	0.74-0.89
≥ $40,000	0.66	0.6-0.72	0.68	0.62-0.74	0.65	0.60-0.72	0.69	0.62-0.77
BMI (kg/m2)**								
Normal <30	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Obese ≥30	0.91	0.85-0.98	0.92	0.86-0.99	0.92	0.85-0.99	0.87	0.79-0.95
Unknown	0.84	0.64-1.11	0.84	0.63-1.12	0.84	0.64-1.1	1.01	0.71-1.42
Kidney problems due to DM								
No DM	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
DM with no kidney problems	1.19	1.1-1.29	1.13	1.04-1.24	1.19	1.1-1.3	1.19	1.08-1.32
Kidney problems	1.39	1.1-1.75	1.22	0.95-1.58	1.4	1.12-1.77	1.24	0.89-1.71
Hypertension	1.09	1.02-1.16	1.04	0.89-1.21	1.09	1.02-1.16	1.11	1.03-1.2
Heart Problems	1.07	0.99-1.15	1.01	0.93-1.09	1.07	0.99-1.15	1.04	0.96-1.13
Stroke	1.30	1.16-1.46	1.24	1.1-1.4	1.31	1.17-1.47	1.29	1.13-1.46
Arthritis	1.03	0.97-1.1	1.02	0.96-1.09	1.03	0.97-1.1	0.99	0.92-1.07
Lung diseases	0.95	0.84-1.07	0.86	0.76-0.97	0.94	0.83-1.06	0.92	0.8-1.06
Cancer	0.94	0.86-1.02	0.89	0.82-0.98	0.94	0.86-1.02	0.89	0.8-0.98
Depressive Symptoms	1.26	1.16-1.37	1.25	1.14-1.36	1.27	1.17-1.39	1.23	1.11-1.36
ADL (any difficulties +1)	1.21	1.11-1.32	1.15	1.05-1.27	1.21	1.1-1.32	1.25	1.12-1.39
Hearing Loss	1.11	1.03-1.19	1.09	1.01-1.18	1.1	1.02-1.19	1.09	0.99-1.18
Vision Loss	1.17	1.08-1.26	1.15	1.06-1.24	1.18	1.09-1.27	1.12	1.02-1.22
Physical Activity (Active)	0.93	0.87-0.99	0.96	0.90-1.03	0.93	0.87-0.99	0.89	0.83-0.96
Alcohol Consumption(drinks per day)								
None	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
1-2 drinks	0.83	0.77-0.9	0.83	0.78-0.9	0.83	0.78-0.9	0.81	0.74-0.88
≥ 3 drinks	0.91	0.75-1.09	0.88	0.73-1.06	0.91	0.76-1.1	0.88	0.69-1.1
Smoking Status								
Never	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Current	1.26	1.15-1.39	1.16	1.05-1.28	1.26	1.14-1.39	1.12	1.05-1.37
Former	1.10	1.03-1.17	1.05	0.99-1.13	1.1	1.03-1.18	1.11	1.02-1.19

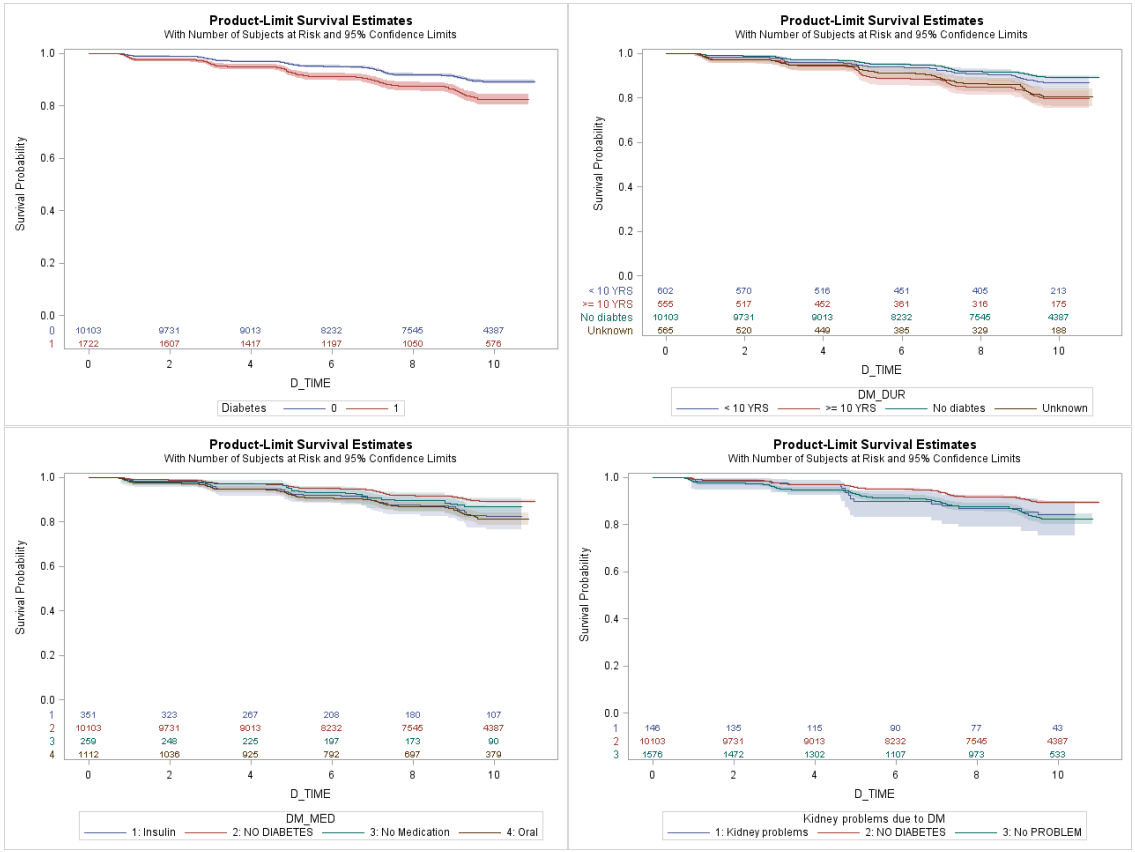
**** P-value <0.0001, * P-value <0.05.**

3.3.4Diabetes and risk of incident All-D

Kaplan-Meir analysis

Similar to Any-CI KM analysis, the incident dementia was significantly higher for participants with diabetes, long disease duration, and the presence of kidney problems (Figure 3.3). However, those on insulin medication show no statistical significant difference from those with diabetes and not taking any medication (P-value 0.12). The number of incident All-D increase with time as the survival curve had the steeper decline later in time rather than early on time as it for Any-CI.

Figure 3.3: Aim 1 Kaplan Meir survival curve for incident All-D.



Multivariable Cox proportion hazard

About 1,164 (9.84%) were developed dementia over a median of 8.4 years of follow up, interquartile range was 7.2 – 10.86. From 1,722 diabetic subjects about 236 (13.7%) and from 10,103 non-diabetic subjects about 928 (9.19%) were developed dementia. Association between diabetes, microvascular, and macrovascular complications and the development of All-cause dementia are shown in Table 3.7. Non-Hispanic Black and Hispanic had higher risk of All-D compared to Non-Hispanic White; HR 1.8 (95% CI 1.52-2.15) and 1.6 (95% CI 1.28-2.00) respectively. Education, income, and BMI were negatively associated with lower risk of All-D. Diabetes was associated with 55% (HR=1.55; 95% CI 1.33-1.79) higher risk of incident Any-CI compared to non-diabetics (Model 1), adjusting only for demographics variables. Among diabetics, subjects with kidney problems had even higher risk for Any-CI compared to those without diabetes. However, this significant association was diminish after adjusting for macrovascular diseases (from model 3 through 6). For macrovascular diseases, only stroke was significantly associated with higher risk of developing All-D in all models; HR=1.79 (95% CI 1.46-2.12) for model 6. None of the coexisting chronic diseases were significantly associated with All-D. Depression, ADL, and vision loss were positively associated with higher risk of All-D. Exercising and moderate alcohol consumption (1-2 drinks per week) were negatively associated with incident All-D; HR=0.84 (95% CI: 0.74-0.96) and 0.79 (95% CI: 0.68-0.92) respectively. Current smoking status had a higher risk of incident All-D compared to subjects whom never smoked, HR=1.3 (95% CI 1.06-1.59).

Table 3.7: Aim 1 Cox-proportional hazard models for incident All-D.

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Female	1.05	0.92-1.19	1.05	0.92-1.19	1.08	0.94-1.23	1.08	0.95-1.24	1.08	0.94-1.23	1.04	0.91-1.2
Race												
Non-Hispanic White	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Non-Hispanic Black	1.85	1.56-2.19	1.85	1.56-2.19	1.86	1.57-2.21	1.89	1.59-2.24	1.86	1.57-2.22	1.8	1.52-2.15
Hispanic	1.63	1.32-2.04	1.63	1.31-2.03	1.72	1.38-2.14	1.74	1.39-2.17	1.63	1.30-2.03	1.6	1.28-2.0
Others	0.97	0.58-1.62	0.97	0.58-1.62	1.02	0.61-1.69	1.01	0.60-1.68	0.98	0.59-1.63	0.95	0.57-1.58
Married/Partnered	1.05	0.92-1.21	1.05	0.92-1.21	1.05	0.91-1.21	1.05	0.92-1.21	1.08	0.94-1.25	1.09	0.95-1.26
Education												
≤ High school	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Some college	0.74	0.63-0.86	0.74	0.63-0.86	0.74	0.63-0.86	0.74	0.63-0.86	0.76	0.65-0.88	0.77	0.66-0.9
≥ College	0.68	0.57-0.82	0.68	0.57-0.82	0.7	0.58-0.83	0.7	0.58-0.84	0.72	0.6-0.86	0.75	0.63-0.9
Annual Household Income												
< $20,000	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
$20,000-39,999	0.79	0.68-0.91	0.79	0.68-0.91	0.79	0.68-0.91	0.79	0.68-0.92	0.82	0.70-0.95	0.83	0.72-0.97
≥ $40,000	0.49	0.41-0.58	0.49	0.41-0.58	0.5	0.42-0.6	0.5	0.42-0.6	0.53	0.44-0.64	0.56	0.47-0.71
BMI (kg/m**2)												
Normal <30	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Obese ≥30	0.87	0.75-1.00	0.87	0.75-1.002	0.86	0.74-0.99	0.86	0.74-0.99	0.83	0.71-0.96	0.81	0.7-0.94
Unknown	1.12	0.68-1.84	1.12	0.68-1.84	1.14	0.7-1.89	1.15	0.7-1.89	1.13	0.69-1.86	1.1	0.66-1.81
Diabetes	1.55	1.33-1.79										
Kidney problems due to DM												
No DM			**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
DM with no kidney problems			1.53	1.32-1.78	1.45	1.24-1.69	1.45	1.24-1.7	1.41	1.20-1.64	1.38	1.18-1.61
Kidney problems			1.77	1.09-2.88	1.57	0.97-2.56	1.55	0.96-2.53	1.36	0.84-2.23	1.33	0.82-2.17
Hypertension					1.12	0.86-1.56	1.16	0.86-1.56	1.12	0.85-1.54	1.12	0.85-1.55
Heart Problems					1.14	0.99-1.30	1.13	0.98-1.29	1.08	0.94-1.24	1.06	0.92-1.22
Stroke					1.88	1.56-2.26	1.87	1.55-2.25	1.81	1.5-2.18	1.76	1.46-2.12
Arthritis							0.97	0.86-1.1	0.91	0.81-1.04	0.91	0.81-1.03
Lung diseases							1.3	1.04-1.63	1.17	0.94-1.47	1.11	0.88-1.4

Cancer							0.94	0.79-1.11	0.94	0.79-1.11	0.93	0.79-1.11
Depressive Symptoms									1.5	1.28-1.76	1.47	1.26-1.72
ADL (any difficulties +1)									1.23	1.04-1.46	1.2	1.01-1.42
Hearing Loss									1.06	0.92-1.23	1.05	0.91-1.22
Vision Loss									1.21	1.04-1.39	1.18	1.03-1.37
Physical Activity (Active)											0.84	0.74-0.96
Alcohol Consumption (drinks per day)												
None											**Ref.**	
1-2 drinks											0.79	0.68-0.92
≥ 3 drinks											0.76	0.5-1.16
Smoking Status												
Never											**Ref.**	
Current											1.3	1.06-1.59
Former											1.08	0.95-1.23

**** P-value <0.0001, * P-value <0.05.**

Moderation analysis

There were no effect moderation of other chronic diseases, geriatric conditions, and lifestyle factors on the association between diabetes and incident All-cause dementia. As in Any-CI model, physical activity was significantly associated with lower risk of dementia among non-diabetics only. Among non-diabetic, those who exercise had a lower risk of incident All-D compared to those who don't exercise (HR 0.81; 95% 0.7-0.93). Among diabetics with and without kidney problems, those who exercise had non-significant lower risk of All-D (with kidney problems HR was 0.96; 95% CI 0.72-1.27 and without kidney problems HR was 0.74; 95% CI 0.21-2.58, respectively).

Mediation analysis

In order to know if there was a mediation-moderation role of macrovsacular diseases, the interaction between diabetes and macrovascular diseases were tested. There was no statistically significant interaction between diabetes and macrovascular diseases (P-value >0.05). The total association between macrovascular diseases and All-D was 1.45 (95% CI 1.24-1.67), 1.39 (95% CI 1.19-1.61) for direct association, and 1.04 (95% CI 1.01-1.07) for indirect association (Table 3.8). Only 13.29% of the association between diabetes and All-D was mediated through macrovascular diseases.

Table 3.8: Aim 1 Estimated direct, indirect, total effect and proportion mediated by macrovascular diseases for the diabetes and All-D relationship.

Effect	Estimate	95% confidence interval	P- value
CDE	1.39	(1.19-1.61)	<0.001
NDE	1.39	(1.19-1.61)	<0.001
NIE	1.04	(1.01-1.07)	0.003
Total effect	1.45	(1.24-1.67)	<0.001
Proportion mediated	0.1329		

***CDE=controlled direct effect; NDE=natural direct effect; NIE=natural indirect effect.**

Sensitivity analysis

Competing risk model showed no difference from full model 6. Death has no impact on the risk of incident All-D development (Table 3.9). Accounting for interval censoring didn't change the estimates. Moreover, restricting the sample to those 65 and above didn't change the final results.

Table 3.9: Aim1 Sensitivity analysis result comparison for All-D model.

	Model 5		Competing risk		Interval censoring		Age ≥ 65	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Female	1.04	0.91-1.2	1.04	0.91-1.2	1.04	0.91-1.2	1.13	0.96-1.32
Race								
Non-Hispanic White	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Non-Hispanic Black	1.80	1.52-2.15	1.80	1.52-2.15	1.81	1.53-2.16	1.85	1.52-2.25
Hispanic	1.60	1.28-2.0	1.60	1.28-2.01	1.59	1.27-1.99	1.46	1.11-1.91
Others	0.95	0.57-1.58	0.95	0.56-1.59	0.95	0.57-1.59	1.03	0.59-1.79
Married/Partnered	1.09	0.95-1.26	1.09	0.94-1.26	1.09	0.95-1.26	1.09	0.94-1.28
Education								
≤ High school	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Some college	0.77	0.66-0.9	0.77	0.66-0.9	0.77	0.66-0.91	0.78	0.66-0.93
≥ College	0.75	0.63-0.9	0.75	0.62-0.9	0.75	0.63-0.91	0.79	0.65-0.96
Annual Household Income								
< $20,000	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
$20,000-39,999	0.83	0.72-0.97	0.83	0.72-0.97	0.83	0.72-0.97	0.90	0.76-1.06
≥ $40,000	0.56	0.47-0.71	0.56	0.46-0.68	0.55	0.46-0.67	0.64	0.52-0.79
BMI (kg/m**2)								
Normal <30	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Obese ≥30	0.81	0.7-0.94	0.81	0.7-0.94	0.82	0.7-0.95	0.78	0.66-0.93
Unknown	1.10	0.66-1.81	1.10	0.65-1.83	1.1	0.67-1.82	1.24	0.71-2.16
Kidney problems due to DM								
No DM	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
DM with no kidney problems	1.38	1.18-1.61	1.38	1.18-1.62	1.37	1.18-1.61	1.41	1.19-1.67
Kidney problems	1.33	0.82-2.17	1.33	0.82-2.15	1.33	0.81-2.16	0.92	0.46-1.87
Hypertension	1.15	0.85-1.55	1.12	0.85-1.56	1.21	0.99-1.27	1.07	0.83-1.62
Heart Problems	1.06	0.92-1.22	1.06	0.91-1.22	1.06	0.92-1.22	1.02	0.88-1.19
Stroke	1.76	1.46-2.12	1.76	1.45-2.14	1.74	1.44-2.1	1.69	1.38-2.07
Arthritis	0.91	0.81-1.03	0.91	0.81-1.03	0.91	0.8-1.03	0.91	0.79-1.04
Lung diseases	1.11	0.88-1.4	1.11	0.89-1.39	1.1	0.88-1.39	1.17	0.91-1.5
Cancer	0.93	0.79-1.11	0.93	0.78-1.11	0.93	0.79-1.11	0.89	0.74-1.07
Depressive Symptoms	1.47	1.26-1.72	1.47	1.25-1.72	1.47	1.26-1.72	1.45	1.21-1.72
ADL (any difficulties +1)	1.20	1.01-1.42	1.20	1.01-1.42	1.19	1.002-1.4	1.26	1.05-1.52

Hearing Loss	1.05	0.91-1.22	1.05	0.91-1.22	1.05	0.91-1.22	1.05	0.9-1.23
Vision Loss	1.18	1.03-1.37	1.18	1.02-1.37	1.18	1.02-1.36	1.17	0.998-1.37
Physical Activity (Active)	0.84	0.74-0.96	0.84	0.74-0.96	0.85	0.74-0.96	0.81	0.70-0.93
Alcohol Consumption (drinks per day)								
None	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
1-2 drinks	0.79	0.68-0.92	0.79	0.68-0.92	0.79	0.68-0.92	0.76	0.65-0.9
≥ 3 drinks	0.76	0.5-1.16	0.76	0.49-1.18	0.76	0.5-1.17	0.65	0.39-1.09
Smoking Status								
Never	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Current	1.30	1.06-1.59	1.30	1.07-1.58	1.3	1.06-1.59	1.10	0.85-1.42
Former	1.08	0.95-1.23	1.08	0.95-1.23	1.08	0.95-1.23	1.06	0.92-1.22

**** P-value <0.0001, * P-value <0.05.**

3.5 CHAPTER SUMMARY

In this study, diabetes was associated with higher risk of both any-cognitive impairment (Any-CI) and all cause of dementia (All-D). This is consistent across all models and sensitivity analyses, confirming the reliability of results. Measures associated with diabetes disease severity like longer disease duration, insulin treatment, and microvascular complications (kidney problems) also were significantly associated with a higher risk of cognitive decline. Very interestingly, diabetes and diabetes with nephropathy were stronger predictors of Any-CI compared with other vascular risk factors, supporting the possibility of a microvascular pathway as an explanation for cognitive impairment in patients with diabetes. However, this association was not significant for All-D model, suggesting that microvascular pathway maybe responsible for some cognitive decline but not severe enough to increase the risk to dementia level. These results should be interpreted with caution since microvascular disease indicators (nephropathy, retinopathy, and neuropathy) were not fully addressed in the data collection and analysis. Of note, stroke (macrovascular disease) was a stronger predictor for All-D than diabetes with nephropathy. Heart disease, on the other hand, didn't show as strong an association with cognitive impairment as did diabetes. Macrovascular diseases were responsible for only 12% and 10% of the association between diabetes and Any-CI and All-D, respectively. This contribution of macrovascular diseases to cognitive impairment in patients with diabetes is less than expected. There are many other factors that may explain diabetes association with cognitive decline that need to be explored.

Other chronic diseases were not significantly associated with Any-CI or All-D. Even the effect moderation of the co-occurrence of diabetes and other chronic diseases was not significant in both outcome analyses. Results did not suggest a shared underlying

pathology with diabetes. All Geriatric variables (depressive symptoms, mobility, hearing loss and vision loss) were associated with Any-CI and All-D. The strongest association was with depressive symptoms, and the risk of All-D in subjects with depressive symptoms was higher than that of Any-CI. However, depressive symptoms had a bidirectional association with diabetes and cognitive decline which made the interpretation of this association difficult. Hearing loss was significantly associated with Any-CI but not All-D. In sensitivity analysis, hearing loss was not significantly associated with Any-CI in those 65 and above. This suggests that hearing loss may impact individuals' cognitive reserve rather than acting as an early symptom of dementia. Vision loss among diabetic subjects was more likely related to diabetes. However, in HRS data it was not possible to distinguish between diabetes related vision impairment and impairment due to other causes.

There was a significant beneficial effect for lifestyle factors on reducing the risk of developing both Any-CI and All-D. Physical activity, moderate drinking and no smoking were associated with lower risk of developing both Any-CI and All-D. Physical activity showed to be beneficial in the case of non-diabetics only. Non-diabetics who were exercising had lower risk for incident cognitive impairment compared to non-diabetics who were not active. Moderate consumption of alcohol was associated with lower risk of both Any-CI and All-D. Active smoking was, in the other hand, associated with higher risk.

Chapter 4: Hyperglycemia, microvascular complications, and macrovascular diseases and the risk of incident Any-CI / All-D among those with diabetes

4.1 INTRODUCTION

The association between hyperglycemia (measured by A1c which reflects blood glucose level over 2-3 months[137]) and cognitive decline in those with diabetes mellitus has a mixed picture in the literature[138,139]. High A1c values were associated with increased risk of cognitive decline among individuals with diabetes[140,141] but not in nondiabetic individuals[142]. Lowering A1c to normal levels didn't improve cognitive performance[79,143]. Understanding the A1c relationship with cognition is essential for guideline improvement and risk reduction. Microvascular complications are associated with higher risk of cognitive decline among diabetics and diabetes is associated with more vascular dementia compared to other types of dementias[84]. Diabetes is known to contribute to both large vessel changes (macrovascular)[62], like stroke, and small vessel changes (microvascular), like retinopathy. Both stroke and retinopathy are linked to cognitive decline and dementia in people with type 2 diabetes[62,94]. Macrovascular diseases are a partial mediator for this association[111]. Microvascular complications also contributed to cognitive decline[94,112]. Other co-existed chronic diseases (like arthritis, depression, and emphysema) impact on cognition along with diabetes are not fully studied[101]. Most diabetes and cognition studies account for macrovascular complications but not microvascular complications, and they combined vascular complications with other co-morbidities. This approach makes it difficult to know the pathway by which diabetes may contribute to cognitive decline, through the microvascular or macrovascular

pathway. Also, the interaction between these different chronic complications and diseases are not well explored; whether they might be an additive or multiplicative effect that would accelerate the cognitive decline. The goal of this chapter is to examine the association between incidents any cognitive impairment (Any-CI) / all types dementia (All-D) with hyperglycemia, microvascular complications, macrovascular diseases, other chronic diseases, and geriatric conditions that may increase the risk of cognitive decline among diabetic subjects. Moreover, lifestyle factor effect in reducing the risk of incident Any-CI / All-D among diabetics will be explored.

4.2 SPECIFIC AIM 2

To examine the impact of hyperglycemia, microvascular and macrovascular complications, co-existing diseases, and geriatric conditions on the incidence of any-cognitive decline (Any-CI) / all-cause dementia (All-D) among diabetic subjects in a national representative sample followed prospectively for ten years.

Representative Hypotheses

To examine these relationships in more detail in the cohort of diabetes patients. Sub-aims are:

- Exposure for glycemia (diabetes duration, and A1c level at baseline) will increase the risk of incident Any-CI / All-D among diabetic patients adjusting for demographic characteristics (educational level, age, sex, ethnicity, income, and BMI).

- The presence of microvascular (retinopathy, nephropathy, and neuropathy) may mediate the association between hyperglycemia and cognitive function.
- The presence of macrovascular (hypertension, hyperlipidemia, heart diseases, stroke, and transient ischemic attack) may mediate the association between hyperglycemia and cognitive function.
- Other chronic diseases (arthritis, emphysema, depression) may associate with higher incidence cognitive impairment and dementia.
- Geriatric conditions (depressive symptoms, ADL, and hearing loss) may associate with higher risk of incident Any-CI / All-D.
- Examine the possible moderating effects of health behaviors (exercise, smoking, and alcohol drinking) on cognitive decline among diabetics.

4.3 METHODS

4.3.1 Dataset and Study sample

The baseline sample was based on the HRS 2003 Diabetes Study, a supplemental study on Diabetes was conducted by mail with persons who reported they had diabetes in the 2002 core wave (For more information, see http://hrsonline.isr.umich.edu). The main aim for 2003 diabetes study was to gather data on aspects related to diabetes treatment, self-management, and a biomarker of glucose control (glycosylated hemoglobin A1c). In the 2002 HRS 3,194 reported having diabetes, 680 were excluded from 2003 diabetes study at random due to their participation in other studies and 129 died before diabetes study started. Of the 2,385 remaining eligible cases, only 1,901 returned questionnaires, for a response rate of 79.7%[144]. 1,233 had a valid blood test for A1c which was 64.9% of those who returned questionnaires, and 51.8% of all eligible cases[144].

For this aim (Aim 2), 2003 diabetes survey was used to extract the baseline population and relevant diabetes variables. The sample was aligned with the 2002 HRS wave to have complete measures of cognition, other chronic diseases, geriatric conditions and lifestyle factors followed through 2012. The full description of HRS 2002 wave description is similar to aim 1 (For more information, see http://hrsonline.isr.umich.edu).

4.3.2 Key Measures

Specific aim 2 uses the same non-diabetes related measures as specific aim 1, cognition status, other chronic conditions, geriatric conditions, and health behaviors. Thus, descriptions of these measures will not be repeated below. However, diabetes related measures like A1c, medication, duration, microvascular diseases, hyperlipidemia

were based on 2003 diabetes study. Macrovascular diseases were reconstructed from a combined measure from 2003 diabetes study and 2002 HRS study.

Independent variables

Hyperglycemia

Diabetes duration was calculated as the difference between interview year and age at diagnosis (from 2003 file), and categorized as diabetes ≤ 10 years, diabetes >10 years, and unknown for missing values (N=150). Glycosylated hemoglobin (A1c) was used for hyperglycemia exposure in the diabetic cohort[145]. The 2003 Diabetes Study collected A1c data using the Flexsite Diagnostics A1c at Home Test Kit (Flexsite Diagnostics, Inc., Palm Beach, FL), U.S. Food and Drug Administration (FDA) approved kit for home use. According to American college of physicians[146], A1c level was categorized into three levels; normo-glycemia (A1c < 7%), and hyperglycemia (A1c ≥ 7), and unknown for missing values (N=353).

Indicators of Microvascular diseases

Retinopathy in the 2003 diabetes survey was assessed with the questions “Have you ever had diabetic eye disease or laser surgery on your eyes (for your diabetes)?”, and “How would you rate your vision (using your glasses or contacts, if you wear them)?”. Whose answer were yes to the first question or to have poor or fair vision to the second question were considered positive response for retinopathy. Neuropathy was assessed in 2003 diabetes study with the question “During the past 12 months, how often have you had any of the following problems with your legs and feet: Numbness or loss of feeling in your feet, tingling or burning sensation in your feet (especially at night), decreased ability to feel hot or cold with your hands or feet, or sores, infections or ulcers on your feet that

did not heal". Any response with 'All of the time' were coded as yes and the rest 'Most of the time; Some of the time; A little of the time; and None of the time' were ceded as no. For kidney problems, nephropathy, was assessed in 2003 diabetes study with the question of "Have you ever been told by a doctor that you have any of the following: Kidney failure (yes/no), protein in your urine (yes/no), or kidney dialysis (yes/no)" and from 2002 wave with the question "Have you ever been told by a doctor that you have any of the following: kidney failure or protein in urine?". Any positive answer on one of the three problems/questions was coded as yes for nephropathy. Missing data didn't exceed 5% on any of these variables, missing was assumed as a negative response except nephropathy which has been compared with 2002 wave diabetes kidney problem question and recoded accordingly.

Indicators of Macrovascular diseases

Self-reported macrovascular diseases at baseline (2002 wave) were assessed with the question "Has a doctor ever told you that you had …?". This included hypertension, stroke and heart diseases (Myocardial infarction, angina, congestive heart failure and other heart problems). Answers for this question were compared and corrected with 2003 diabetes study questions about macrovascular diseases, it was assessed with the question "In the past 12 months, have you been told by a doctor that you have any of the following problems related to your heart or circulation: Heart attack or previous heart attack, Congestive heart failure, Angina, Stroke or previous stroke, and Transient ischemic attacks (TIA or "mini-strokes")" (Yes/no). Any positive answer (yes) for each disease either in 2002 or 2003 study was coded as having the disease. For hypertension, those with positive answer on hypertension medication in either 2002 wave or 2003 diabetes study were re-coded as having hypertension too. Hypertesion medications were extracted

from the following question: in 2002 wave was “In order to lower your blood pressure, are you now taking any medication?”, and in 2003 study with the question “Do you now take medication for your high blood pressure?”. Hyperlipidemia were assessed only in 2003 diabetes study with the question “Has a doctor or nurse ever told you that you have high cholesterol?”. For hyperlipidemia medication use, “Do you now take medication for your high cholesterol?” was used. Missing in hyperlipidemia variable was less than 5%, thus, it was re-coded as negative response (No).

4.3.3 Covariates

Self-reported age, sex, race/ethnicity, marital status, education, and BMI in the 2002 HRS wave were included as covariates in all models similar to Aim1. However, education was re-categorized as (“high school and less”, and “more than high school”). Income was re-categorized as less than $40,000 and equal or greater than $40,000. Body Mass Index (BMI) (kg/m2) was dichotomized as not obese <30 kg/m2 and obese ≥30 kg/m2. In addition, medical history variables relevant to diabetes treatment were controlled for. Diabetes treatment was assessed with two questions about oral medication and insulin. It was combined as a single measure, no-medication, oral medication only, and insulin medication with or without oral medication.

4.3.4Statistical analysis

Censoring

The 2003 diabetes study was aligned with 2002 HRS study since cognitive measure was only available for 2002 wave. Thus, time calculation was based 2002 HRS

interview date rather than 2003 study in a similar way to aim 1. Participants were followed from 2002 through 2012, including 6 waves. Interview beginning date (2002) was used to calculate time to event; incident Any-CI or All-D. The incident date for Any-CI/All-D was calculated as halfway point between the interview date at which Any-CI/All-D was first reported and the previous wave; survival time calculation. Participants who didn't get the event were censored at their last interview date, death or at the end of the study period, 10 years, whichever time point was first.

Bivariate analysis

Descriptive statistics were created for each variable used in the analysis. For categorical variables, counts and percentages were reported, while for continuous (age) variables, means and standard deviations were reported. Bivariate relationships were compared between diabetic and non-diabetic individuals for all individual predictors, covariates and outcome variables using chi-square and ANOVA. The unadjusted survival curve for the incidence of Any-CI / All-D was examined by Kaplan- Meier method (KM) for the entire sample. Groups in KM were compared using log rank test.

Multivariable analysis: Cox proportional hazard

The incidence of Any-CI and All-D were evaluated separately. Eight models were run that added progressively more variables as shown below:

- Model 1: Demographic variables (Age, sex, race, education, marital status, income, BMI, and diabetes medication), and the incident Any-CI/All-D outcome.
- Model 2: Model 1 + diabetes duration, and hyperglycemia (A1c).

- Model 3: Model 2 + microvascular complications (retinopathy, nephropathy, and neuropathy).
- Model 4: Model 3 + macrovascular diseases (hypertension, hyperlipidemia, heart diseases, stroke, and TIA).
- Model 5: Model 4 + other chronic diseases (arthritis, lung diseases, and cancer).
- Model 6: Model 5 + geriatric problems (depressive symptoms, ability to perform ADLs, and hearing difficulty).
- Model 7: Model 6 + lifestyle factors (physical activity, alcohol drinking, and smoking status).
- Model 8: Effect moderation (interaction terms) of other chronic diseases, geriatric conditions, and life style factors with A1c on the incidence of Any-CI/All-D.

Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) of incident Any-CI and All-D. Tied events were handled using Exact method for all models. Results were reported as hazard ratio (HR) and their 95% confidence intervals (95% CI). Model assumptions and diagnostics were checked for all models used in the analysis. Model diagnostics were assessed using Martingale residual plot to evaluate the proportionality assumption. There was no severe violation of the proportional assumption. About 8 outliers were identified using Deviance residual; models estimates were evaluated with and without outliers. The effect of outliers didn't severely impact the model estimates, they kept in the analysis. The overall model fit was evaluated using Cox-Snell residual plot; no major problem with all models (See Appendix A.2). Non-

informative censoring was evaluated using competing risk model where death was considered as a competing event.

Moderation and Mediation analysis

The interaction of A1c with other chronic diseases, geriatric conditions, and lifestyle factors were evaluated in the full model (model 7) as individual term then were introduced all in one model. The hypothesis of no excess hazard due to interaction was considered significant at P-value <0.05. Only significant interactions were reported. The potential mediating role of microvascular complications and macrovascular diseases on the relationship between A1c and cognitive decline was examined similar to Aim 1, using a method developed by Vanderweele and Valeri[130-132], see eAppendix (http://links.lww.com/EDE/A877) for more details[130]. Automated macro software for mediation for survival data for SAS 9.3 is available for download at the authors' websites (https://www.hsph.harvard.edu/tyler-vanderweele/tools-and-tutorials). The interaction terms between glycemia and macrovascular variable were not significant, thus, mediation analysis didn't include any interaction term.

Sensitivity analysis

In survival analysis, subject were censored for more than one reason, end of the study, death, event of interest, and drop out. Regular cox hazard model treat these different modes of study exist the same in estimating the hazard; the variable relationship with these different modes were assumed to be equal which could be not always the case. Some variable could be more associated with, for example death, than the event of interest. This will take subjects out of the study, or risk pool, early enough not to observe

the event, compete with the event of interest. The presence of competing events may biased study estimates. In competing risk, each mode of study exist were treated individually and the cumulative incidence of the event (Any-CI/All-D) represents the rate of the event as well as the influence of competing events (death)[147]. On the other hand, the covariate effect on the event of interest may have a direct effect of making the event of interest more likely or less likely to occur, or have an indirect effect of making competing events more or less likely to occur, or both[147]. In order to account for the impact of death on the incident Any-CI/All-D risk, competing risk model was examined using Fine and Gray's extension of cox-regression model[136]. The result consistency and reliability were tested by several sensitivity analyses: first, competing risk model was used to account for death during study follow up which may impede the observation of cognitive decline. Second, the effect of interval censoring due to non-response fluctuation (subjects didn't have a continuity of response for all waves; they in and out of the study at different time point) through follow up period was adjusted for. Finally, the study sample was restricted to those 65 and above in order to examine results reliability and wither it changed for elderly.

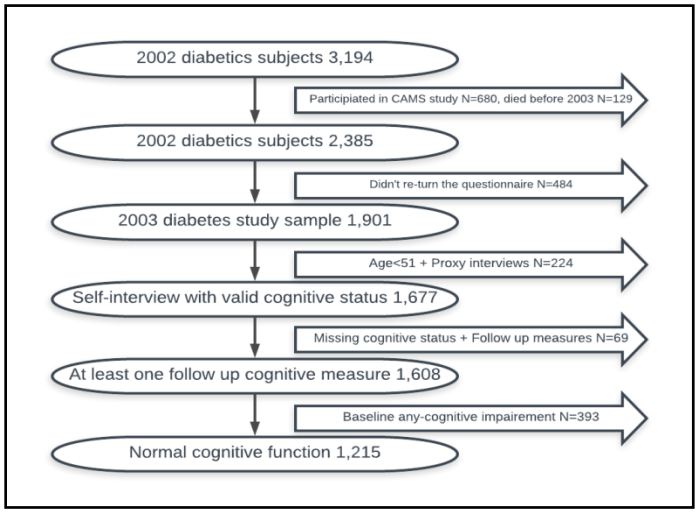
4.4 RESULTS

4.4.1 Analytic sample and Missing Data

This study included those 51 years old and above. Exclusions included: subjects living in nursing home, baseline proxy interviews, missing baseline cognition, or missing follow up interview or cognition status (Figure 4.1). From the 1,901 respondents to the diabetes survey, 1,215 had normal cognition at baseline and were available for analysis. Since our study goal is to study incidence of Any-CI/ All-D, subjects with cognitive

impairment at baseline were excluded from the study. The total final analytic sample size was 1,215 subjects (this is about 38.0% of 2002 diabetic subjects sample, 50.94% from 2003 study eligible cases, and 63.9% from those whom returned the questionnaire of 2003 study). Missing data in A1c were re-categorized as 'unknown' category for A1c. For microvascular complications and hyperlipidemia missing rate were less than 5% of the analytical sample, thus, they were re-coded as negative responses (No).

Figure 4.1:Flow chart from the complete, eligible Health and Retirement Study 2003 diabetes sub-study to study analytic sample (Aim 2).



4.4.2 Descriptive statistics

The total sample used for aim 2 analysis was 1,215 subjects with an average age at baseline of 68.73 years old (Table 4.1). The majority of the sample was Non-Hispanic White, female and married or partnered (>50%). About 40% had an annual income $40,000 and above and finished his high school. Those with Any-CI were more likely to

be older, Non-Hispanic Black or Hispanic, not married, less educated and lower annual income compared to cognitively normal subjects. Meanwhile, those with All-D were more likely to be female, Non-Hispanic white, not married, less educated and lower annual income.

Table 4.1. Baseline demographic characteristics for Aim 2 study participants.

	Any cognitive impairment				All cause dementia				Total	
	Normal (N=669)		Any-CI (N=546)		No D (N=1,052)		All-D (N=163)		(N=1,215)	
	%	N	%	N	%	N	%	N	%	N
Age; mean(std)	66.38	7.45	71.59*	8.16	67.94	7.99	73.74	7.72	68.73	8.2
Female	53.66	359	56.04	306	53.23	560	64.42*	105	54.73	665
Race										
Non-Hispanic White	79.52	532	69.23*	378	70.55	115	75.57*	795	74.9	910
Non-Hispanic Black	11.81	79	19.78	108	14.72	24	15.49	163	15.39	187
Hispanic	5.53	37	10.07	55	13.5	22	6.65	70	7.57	92
Others	3.14	21	0.92	5	1.23	2	2.28	24	2.14	26
Married/Partnered	72.2	483	63.55*	347	69.77	734	58.9*	96	68.31	830
Education (> High School)	50.52	338	26.92*	147	42.21	444	25.15*	41	39.92	485
Annual income (≥ $40,000)	49.03	328	28.39*	155	42.68	449	20.86*	34	39.75	483

*** P-value <0.05.**

The majority of diabetics subjects were taking medication, approximately 19.42% were not taking any medication, 61.07% taking only oral medication, and 19.5% on insulin (Table 4.2). Almost have of the sample (46.83%) had diabetes duration less than 10 years and 40.8% had it more than 10 years. Subjects with controlled hyperglycemia (A1c < 7%) was 38.77% of the sample while 32.18% with A1c greater than 7%. The most prevalent microvascular disease in this sample was retinopathy (27.82%) followed by nephropathy (20.66%). Vascular risk factors, hypertension and hyperlipidemia were very common, 79.42% and 62.72% respectively. Also, heart diseases had a higher

percentage from retinopathy (35.72%). Arthritis was the most prevalent co-existed chronic disease (59.51%). Hearing loss percentage in the sample was higher from depressive symptoms, 20.25% vs 15.72%. More than 30% of the sample was exercising, not drinking alcohol and never smoked.

Those with Any-CI were more likely to be on insulin medication (21.25%) and had disease duration 10 years or more (45.6%). There was no statistical difference between cognitively normal A1c level and cognitively impaired subjects. All microvascular complications and macrovascular diseases were more prevalent in cognitively impaired group compared to normal. Retinopathy was significantly higher in Any-CI group 32.6% compared to normal subjects 23.92%. Heart diseases and stroke percentage among Any-CI group was significantly higher, almost the double, in Any-CI compared to cognitive normal group, 43.22% VS 29.6% and 15.02% VS 8.03% respectively. Lung diseases percentage was significantly lower in Any-CI group. Arthritis and all geriatric conditions were significantly higher among Any-CI subjects.

Only alcohol drinking was different between two groups, Any-CI were more likely not to drink. Subjects with dementia were more likely to have diabetes duration ≥ 10 years compared to those without dementia, 50.31% VS 39.35%. Similarly, retinopathy was significantly higher among All-D group. Other microvascular complications and A1c were not differed between two groups. Surprisingly, Hyperlipidemia was significantly less common among All-D group compared to non-demented group, 51.53% VS 64.45%. Stroke was significantly higher in All-D group, 19.63% VS 9.89%. Depressive symptoms, hearing loss, and not drinking alcohol were significantly higher in All-D group.

Table 4.2. Baseline clinical characteristics for Aim 2 study participants.

	Any cognitive impairment				All cause dementia				Total	
	Normal (N=669)		Any-CI (N=546)		No D (N=1,052)		All-D (N=163)		(N=1,215)	
	%	N	%	N	%	N	%	N	%	N
Diabetes medication										
No medication	21.82	146	16.48*	90	19.58	206	18.4	30	19.42	236
Oral med. Only	60.09	402	62.27	340	60.84	640	62.58	102	61.07	742
Insulin med.	18.09	121	21.25	116	19.58	206	19.02	31	19.51	237
DM duration										
<10 years	51.87	347	40.66*	222	48.67	512	34.97*	57	46.83	569
≥ 10 years	36.92	247	45.6	249	39.35	414	50.31	82	40.82	496
Unknown	11.21	75	13.74	75	11.98	126	14.72	24	12.35	150
A1c %										
< 7%	42.9	287	33.7	184	40.11	422	30.06	49	38.77	471
≥ 7%	30.19	202	34.62	189	32.51	342	30.06	49	32.18	391
Unknown	26.91	180	31.68	173	27.38	288	39.88	65	29.05	353
Retinopathy	23.92	160	32.6*	178	26.81	282	34.36*	56	27.82	338
Nephropathy	19.88	133	21.61	118	20.44	215	22.09	36	20.66	251
Neuropathy	11.66	78	12.27	67	12.17	128	10.43	17	11.93	145
Hypertension	78.48	525	80.59	440	79.56	837	78.53	128	79.42	965
Hyperlipidemia	63.98	428	61.17	334	64.45	678	51.53*	84	62.72	762
Heart diseases	29.6	198	43.22*	236	35.27	371	38.65	63	35.72	434
TIA	3.44	23	7.33*	40	5.04	53	6.13	10	5.19	63
Stroke	8.07	54	15.02*	82	9.89	104	19.63*	32	11.19	136
Arthritis	56.35	377	63.37*	346	58.65	617	65.03	106	59.51	723
Lung diseases	9.27	62	6.04*	33	7.7	81	8.59	14	7.82	95
Cancer	13.15	88	15.75	86	14.26	150	14.72	24	14.32	174
Depressive Symptoms	12.71	85	19.41*	106	14.83	156	21.47*	35	15.72	191
ADL (any difficulties +1)	16.59	111	21.43*	117	18.54	195	20.25	33	18.77	228
Hearing Loss	16.44	110	24.91*	136	18.92	199	28.83*	47	20.25	246
Physical Activity (Active)	37.97	254	38.1	208	38.21	402	36.81	60	38.02	462
Alcohol Consumption (drinks per day)										
None	73.39	491	82.05*	448	75.76	797	87.12*	142	77.28	939
1-2 drinks	24.22	162	15.93	87	21.86	230	11.66	19	20.49	249
≥ 3 drinks	2.39	16	2.01	11	2.38	25	1.23	2	2.22	27
Smoking Status										
Never	42.3	283	38.1	208	40.02	421	42.94	70	40.41	491
Current	10.46	70	10.07	55	10.46	110	9.2	15	10.29	125
Former	47.23	316	51.83	283	49.52	521	47.85	78	49.3	599

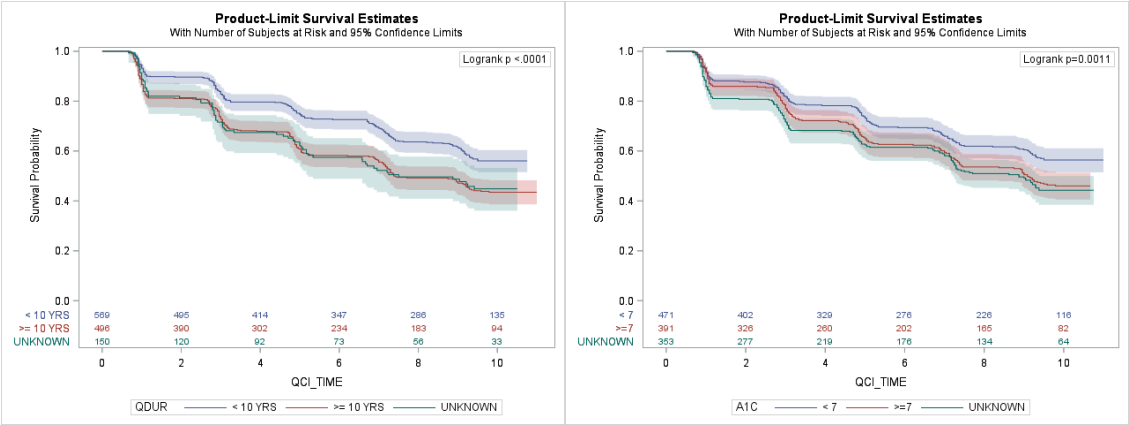
*** P-value <0.05.**

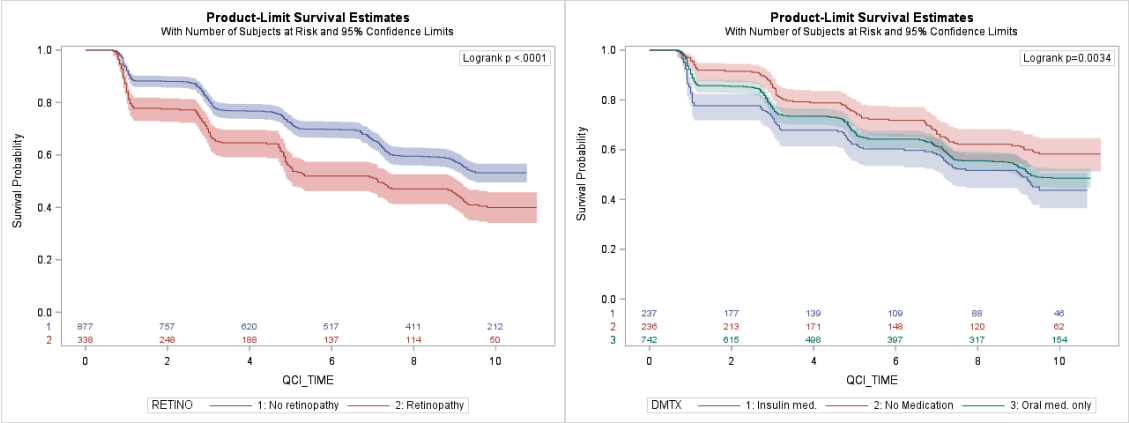
4.4.3 Hyperglycemia, microvascular complications and incident Any-CI

Kaplan-Meir analysis

In Kaplan-Meir analysis, those with diabetes duration 10 years or more had significantly higher rate of Any-CI compared to diseases duration less than 10 years (Figure 4.2). Hyperglycemia (A1c ≥ 7) had significantly higher rate of incident Any-CI than those less than 7%. Insulin use had the highest rate of incident Any-CI compared to oral medication group and who doesn't take any medication for diabetes. From microvascular complications, only retinopathy was significantly associated with higher rate of incident Any-CI.

Figure 4.2. Aim 2 Kaplan Meir survival curve for incident Any-CI.





Multivariable Cox proportion hazard for incident Any-CI

Over a median of 7.08 years of follow up (interquartile range, 3.04 – 9.92), Any-CI developed in 546 of the 1,215 respondents (44.94%) at the end of follow up. Among those with hyperglycemia at baseline (A1c ≥ 7%, N=391), 189 developed Any-CI (48.34%); among those with A1C less than 7% at baseline (N=471), 184 developed Any-CI (39.07%); and among those with unknown A1c level (N=353), 173 developed Any-CI (49.01%). The association between diabetes medication, disease duration, hyperglycemia, and microvascular complications is shown in Table 4.3. Non-Hispanic Blacks had significantly higher risk of incident Any-CI compared to Non-Hispanic Whites in all models (HR 1.72; 95% CI 1.36-2.17) (Table 4.3). In model 7, Hispanic became non-significantly associated with higher risk when the model adjusted for geriatric conditions. Higher education and annual income were consistently associated with lower risk of incident Any-CI in all models (HR 0.54(95% CI 0.44-0.67) and 0.76 (95% CI 0.62-0.94), respectively).

In all model 1-7, oral and insulin diabetes medications were significantly associated with higher risk of incident Any-CI compared to those who weren't taking any diabetes medication. In the full model 7, the risk associated with insulin medication had higher HR from oral medication, HR= 1.45 (95% CI 1.05-2.01) VS 1.32 (95% CI 1.03-1.69) respectively. Baseline longer diabetes duration and hyperglycemia (A1c ≥ 7%) were not statistically significant, in contrast to KM analysis, even though they were associated with higher risk of incident Any-CI. Unknown group for A1c variable was marginally insignificant (HR 1.24 (95% CI 0.99-1.55), P-value = 0.06 in model 7) and was higher HR value compared to other A1c levels. This phenomenon could be explained by lack of power in this study and subjects in unknown category may have a higher risk for Any-CI. The effect of diabetes medication and duration was attenuated by the addition of microvascular diseases in model 3; HR for diabetes oral medication in model 1 was 1.37 (95% CI 1.08-1.73) and reduced to HR=1.30 (95% CI 1.02-1.67) in model 3 after microvascular diseases were included in the model. Similarly, insulin use was associated with HR=1.71 (95% CI 1.3-2.27) in model 1 that attenuated in model 3 to HR value 1.46 (95% CI 1.06-2.01). Surprisingly, retinopathy that was significant in the KM analysis was marginally insignificant in model 3 (HR=1.18; 95% CI 0.98-1.42, P-value=0.089) and remained non-significant in all models, even when macrovascular diseases were included in the model (in model 7 HR= 1.1; 95% CI 0.91-1.34; P-value=0.2). In a similar way to retinopathy, neuropathy was marginally insignificantly associated with 28% higher risk of Any-CI in model 3 (HR=1.28; 95% CI 0.98-1.68; P-value 0.07). Nephropathy wasn't significantly associated with incident Any-CI in all model, in model 7 HR=1.09 (95% CI 0.88-1.35). The insignificant association of microvascular complications could simply be due to lack of sample power, taking in the note the marginal insignificant association of retinopathy and neuropathy.

In model 4, controlling for demographic characteristics, hyperglycemia, and microvascular complications, heart diseases (myocardial infarction, congestive heart failure, angina, and other heart problems) were significantly associated with 38% higher risk of incident Any-CI (HR 1.38; 95% CI 1.15-1.66). Stroke was significantly associated with 42% higher risk of Any-CI (hr 1.42; 95% CI 1.07-1.89). This association was not attenuated by further adjusting for other variables, HR in the full model (7) for heart diseases and stroke was 1.36 and 1.38, respectively. Mini stroke (TIA) showed no risk of incident Any-CI but wasn't significant, HR= 1.00 (95% CI 0.67-1.47). TIA was only measured in diabetes study, thus it lack of power in the presence of missing data. Hypertension and hyperlipidemia were not significantly associated with incident Any-CI and they had a negative association sign (in the full model β were (-0.1) and (-0.14) respectively) with the outcome.

In model 5, the additions of other chronic diseases (arthritis, lung diseases, and cancer) were not significantly associated with incident Any-CI. Surprisingly, lung diseases were became significantly associated with lower risk of incident Any-CI in model 6 and 7, HR in model 7 was 0.64 (95% CI 0.44-0.92). For Geriatric conditions (depressive symptoms, ADL, and hearing loss), only hearing loss was significantly associated with higher incident Any-CI (HR in model 7 was 1.27; 95% CI 1.03-1.56). Depressive symptoms were marginally insignificant in the full model, HR 1.27 (95% CI 0.999-1.62; P-value= 0.051). Current smoking status had the highest risk of Any-CI (HR=1.64; 95% CI 1.19-2.26) compared to never smoked group. Even it was not significant, former smoke had higher risk of Any-CI, HR=1.17 (95% CI 0.96-1.41).

In summary, in the full model (model 7), macrovascular diseases, hearing loss, and current smoking status increased the risk of incident any-cognitive impairment and lung diseases reduced the risk. Heart diseases were associated with 36% increase and stroke with a 38% increase in Any-CI. Diabetes medication (oral and insulin) was associated with higher risk of incident Any-CI but exposure to glycemia (longer disease duration, and baseline hyperglycemia), and microvascular complications were not significant. Lung diseases were associated with lower risk of Any-CI, while current smoking status was associated with higher risk of Any-CI. Hearing loss was associated with increased risk of Any-CI.

Table 4.3. Aim 2 Cox proportional hazard models for incident Any-CI.

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Age	1.08	1.06-1.09	1.07	1.06 - 1.09	1.08	1.06 - 1.09	1.07	1.06 -1.8	1.07	1.06 - 1.08	1.07	1.06 - 1.08	1.07	1.06 -1.9
Female	0.95	0.79-1.14	0.94	0.79 - 1.13	0.94	0.78 - 1.12	0.97	0.81 - 1.17	0.97	0.80 - 1.17	0.99	0.82 -1.2	1.04	0.85 - 1.27
Race														
Non-Hispanic White	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Non-Hispanic Black	1.76	1.41-2.2	1.65	1.31 - 2.07	1.61	1.28 - 2.02	1.73	1.37 - 2.18	1.69	1.34 - 2.13	1.7	1.34 - 2.14	1.72	1.36 - 2.17
Hispanic	1.46	1.09-1.95	1.38	1.03 - 1.85	1.37	1.01 - 1.84	1.43	1.06 - 1.93	1.41	1.04 - 1.90	1.32	0.97 - 1.79	1.32	0.97 - 1.78
Others	0.62	0.26-1.5	0.64	0.26 - 1.55	0.65	0.27 - 1.57	0.67	0.28 - 1.64	0.64	0.26 - 1.57	0.67	0.27 - 1.63	0.63	0.26 - 1.55
Married/ Partnered	1.02	0.83-1.24	1.01	0.83 - 1.24	1.01	0.83 - 1.23	1	0.82 - 1.22	1	0.82 - 1.23	1.03	0.84 - 1.26	1.07	0.87 - 1.31
Education (> High School)	0.52	0.43-0.63	0.53	0.43 - 0.65	0.53	0.43 - 0.64	0.54	0.44 - 0.66	0.54	0.44 - 0.66	0.53	0.43 - 0.65	0.54	0.44 - 0.67
Annual income (≥ $40,000)	0.72	0.59-0.89	0.72	0.58 - 0.88	0.74	0.6-0.91	0.74	0.60 - 0.92	0.74	0.6-0.91	0.76	0.62 - 0.94	0.76	0.62 - 0.94
Obese (BMI ≥30 kg/m**2)	0.92	0.77-1.1	0.92	0.77 -1.1	0.91	0.76 - 1.09	0.9	0.75 - 1.08	0.88	0.73 - 1.06	0.86	0.71 - 1.03	0.88	0.72 - 1.06
Diabetes medication														
No medication	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Oral med. only	1.37	1.08-1.73	1.34	1.05 - 1.71	1.3	1.02 - 1.67	1.29	1.00 3-1.65	1.3	1.02 - 1.68	1.29	1.00 4-1.65	1.32	1.03 - 1.69
Insulin med.	1.71	1.3-2.27	1.55	1.13 - 2.12	1.46	1.06 - 2.01	1.38	1.00 - 1.91	1.4	1.02 - 1.94	1.41	1.02 - 1.95	1.45	1.05 - 2.01
DM duration														
<10 years			**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
≥ 10 years			1.13	0.92 - 1.38	1.08	0.88 - 1.33	1.08	0.88 - 1.32	1.07	0.87 - 1.31	1.05	0.86 - 1.29	1.04	0.85 - 1.28
Unknown			1.19	0.91 - 1.56	1.18	0.90 - 1.55	1.19	0.91 - 1.56	1.19	0.91 - 1.56	1.13	0.86 - 1.49	1.12	0.85 - 1.47
A1c %														
< 7%			**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
≥ 7%			1.18	0.95 -	1.18	0.95 -	1.16	0.94 -	1.16	0.94 -	1.15	0.93 -	1.11	0.9-1.38

				1.46		1.46		1.44		1.44		1.43		
Unknown			1.28	1.03 - 1.59	1.3	1.04 - 1.62	1.28	1.03 - 1.59	1.3	1.04 - 1.62	1.31	1.05 - 1.63	1.24	0.99 - 1.55
Retinopathy					1.18	0.98 - 1.42	1.13	0.94 - 1.37	1.15	0.95 - 1.39	1.1	0.90 - 1.34	1.1	0.91 - 1.34
Nephropathy					1.08	0.87 - 1.33	1.06	0.86 - 1.32	1.07	0.89 - 1.33	1.07	0.87 - 1.32	1.09	0.88 - 1.35
Neuropathy					1.28	0.98 - 1.68	1.24	0.94 - 1.62	1.22	0.93 -1.6	1.17	0.89 - 1.54	1.17	0.89 - 1.54
Hypertension							0.9	0.72 - 1.12	0.88	0.7- 1.1	0.88	0.70 - 1.11	0.9	0.72 - 1.13
Hyperlipidemia							0.87	0.73 - 1.04	0.87	0.73 - 1.04	0.86	0.72 - 1.03	0.87	0.73 - 1.04
Heart diseases							1.38	1.15 - 1.66	1.39	1.15 - 1.68	1.35	1.12 - 1.63	1.36	1.12 - 1.64
TIA							1	0.68 - 1.48	1.03	0.7- 1.51	1.02	0.69 -1.5	1	0.67 - 1.47
Stroke							1.42	1.07 - 1.89	1.44	1.08 - 1.91	1.41	1.07 - 1.88	1.38	1.04 - 1.84
Arthritis									1.11	0.92 - 1.34	1.05	0.87 - 1.27	1.06	0.87 - 1.28
Lung diseases									0.7	0.49 - 1.01	0.66	0.46 - 0.95	0.64	0.44 - 0.92
Cancer									1	0.79 - 1.26	1.02	0.81 -1.3	1	0.79 - 1.27
Depressive Symptoms											1.27	0.99 6- 1.62	1.27	0.99 9- 1.62
ADL (any difficulties +1)											1.12	0.89 - 1.41	1.12	0.89 - 1.41
Hearing Loss											1.26	1.03 - 1.56	1.27	1.03 - 1.56
Physical Activity (Active)													1.14	0.95 - 1.38
Alcohol Consumption (drinks per day)														
None													**Ref.**	
1-2 drinks													0.85	0.66 - 1.09
≥ 3 drinks													1.21	0.65 - 2.26
Smoking Status														

Never													**Ref.**	
Current													1.64	1.19 - 2.26
Former													1.17	0.96 - 1.41

Moderation and Mediation analysis for incident Any-CI

All interaction terms tested for possible effect moderation of other chronic diseases, geriatric conditions, and lifestyle with hyperglycemia (A1c) association on incident Any-CI were not significant. The three way interaction between A1c ≥ 7%, hypertension, and hyperlipidemia was significant. Those with A1c ≥ 7%, , hypertension, and hyperlipidemia was marginally significantly associated with higher risk of Any-CI compared to those with A1c < 7%, hypertension, and hyperlipidemia, HR=1.35 (95% CI 1.01-1.79; P-value=0.046). There were no significant interaction between A1c and microvascular diseases; retinopathy, nephropathy, and neuropathy (P-value >0.05). Moreover, there were no interaction between A1c and macrovascular diseases, heart diseases, stroke and TIA. Since A1c wasn't statistically significant, it becomes hard to test any possible mediation role of microvascular complications or macrovascular diseases between A1c and Any-CI.

Sensitivity analysisfor incident Any-CI

The influence of death on the cumulative incidence of Any-CI, a competing risk model was examined (Table 2.4). About 205 died before the end of the study, competing event, and 464 were censored. Hazard ratios of the competing risk model were similar to the full model (model 7), there were no difference in significance level or point estimates for most of the variables. However, some variables that were significant in model 7 became insignificant in the competing risk model; diabetes medication, stroke, and hearing loss. The point estimates for these variables didn't change that much, they still had a higher risk of incident-CI regardless of the effect of death on the incidence of Any-

CI. For example, stroke was associated with higher risk of death as well as cognitive decline. Whether stroke association with death impact its' association with cognitive impairment in our study is not known. The HR for stroke in cox-model was 1.38 and in the competing risk model was 1.32 which directly associated with increased risk of incident Any-CI regardless to stroke impact on death risk ,that may indirectly impact the incidence rate of Any-CI (Those didn't die were lived long enough to develop Any-CI). Similarly, diabetes medication and hearing loss had similar HR result in both cox-model and competing risk model. Accounting for interval censoring, due to changing non response during 10 year of follow up, resulted in similar estimates as the full model. The only difference was depressive symptoms association with incident Any-CI became more prominent and significant (HR 1.3; 95% CI 1.02-1.66). Restricting the sample to those 65 years old and above (N=806) revealed similar point estimates of the full model. Insulin medication, stroke, and hearing loss lost their significance which is plausible due to sample size reduction. Oral medications, heart diseases, and smoking remain main predictors for higher risk meanwhile lung diseases persistently associated with lower risk of Any-CI.

Table 4.4: Aim 2 sensitivity analyses for incident Any-CI.

	Model 7		**Competing risk**		**Interval censoring**		**Sample ≥65 (N=806)**	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Age	1.07	1.06-1.9	1.06	1.05-1.08	1.07	1.06-1.09	1.08	1.06-1.09
Female	1.04	0.85-1.27	1.02	0.83-1.26	1.04	0.85-1.28	1.05	0.83-1.32
Race								
Non-Hispanic White	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Non-Hispanic Black	1.72	1.36-2.17	1.78	1.40-2.26	1.75	1.38-2.22	1.43	1.08-1.91
Hispanic	1.32	0.97-1.78	1.42	1.04-1.94	1.30	0.96-1.77	1.01	0.68-1.49
Others	0.63	0.26-1.55	0.56	0.22-1.43	0.63	0.26-1.54	0.61	0.22-1.69
Married/Partnered	1.07	0.87-1.31	1.11	0.9-1.38	1.08	0.88-1.32	1.10	0.88-1.39
Education (> High School)	0.54	0.44-0.67	0.57	0.46-0.69	0.54	0.44-0.66	0.60	0.48-0.75
Annual income(≥ $40,000)	0.76	0.62-0.94	0.74	0.59-0.92	0.76	0.61-0.94	0.78	0.61-0.998
Obese (BMI ≥30 kg/m**2)	0.88	0.72-1.06	0.90	0.74-1.1	0.90	0.74-1.08	0.90	0.72-1.12
Diabetes medication								
No medication	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Oral med. Only	1.32	1.03-1.69	1.24	0.96-1.6	1.30	1.01-1.67	1.39	1.05-1.84
Insulin med.	1.45	1.05-2.01	1.30	0.92-1.84	1.41	1.02-1.96	1.38	0.95-2.02
DM duration								
<10 years	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
≥ 10 years	1.04	0.85-1.28	1.06	0.87-1.31	1.05	0.85-1.29	1.10	0.87-1.39
Unknown	1.12	0.85-1.47	1.14	0.86-1.5	1.13	0.86-1.49	1.09	0.8-1.48
A1c %								
< 7%	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
≥ 7%	1.11	0.9-1.38	1.14	0.91-1.43	1.12	0.90-1.4	1.07	0.84-1.37
Unknown	1.24	0.99-1.55	1.21	0.96-1.53	1.22	0.97-1.53	1.24	0.96-1.59
Retinopathy	1.10	0.91-1.34	1.05	0.86-1.29	1.10	0.91-1.34	1.05	0.84-1.32
Nephropathy	1.09	0.88-1.35	1.07	0.86-1.32	1.11	0.89-1.37	1.06	0.86-1.37
Neuropathy	1.17	0.89-1.54	1.07	0.8-1.45	1.14	0.86-1.5	1.13	0.82-1.56
Hypertension	0.90	0.72-1.13	0.86	0.68-1.08	0.90	0.72-1.13	0.85	0.66-1.1
Hyperlipidemia	0.87	0.73-1.04	0.92	0.76-1.11	0.87	0.73-1.04	0.83	0.68-1.02
Heart diseases	1.36	1.12-1.64	1.32	1.09-1.61	1.37	1.13-1.66	1.33	1.07-1.65
TIA	1.00	0.67-1.47	1.07	0.68-1.66	1.01	0.68-1.49	0.86	0.54-1.35
Stroke	1.38	1.04-1.84	1.32	0.97-1.81	1.40	1.05-1.88	1.34	0.97-1.86
Other diseases								
Arthritis	1.06	0.87-1.28	1.06	0.87-1.29	1.05	0.87-1.27	1.04	0.84-1.29
Lung diseases			0.60	0.87-0.88	0.62	0.43-0.9	0.60	0.38-0.95
Cancer	1.00	0.79-1.27	0.90	0.87-1.16	1.02	0.8-1.29	0.99	0.76-1.28

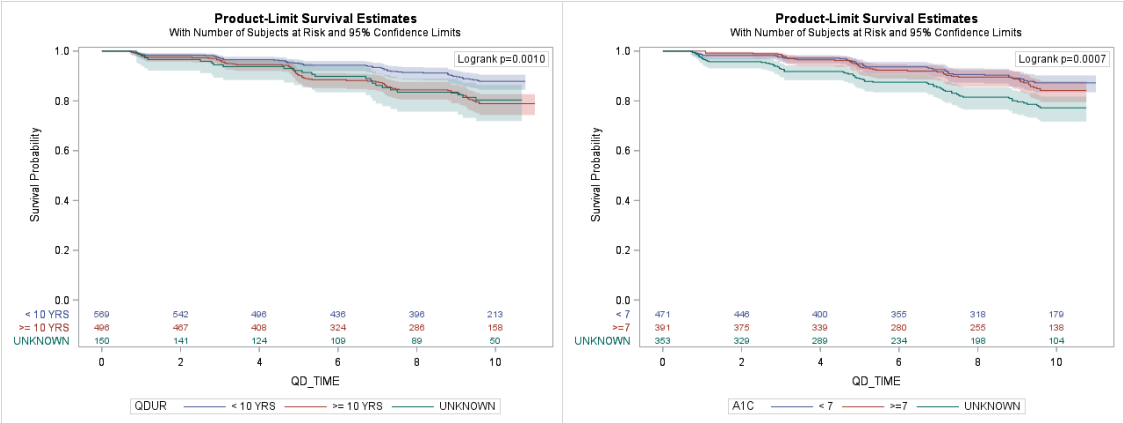
Geriatric Conditions								
Depressive Symptoms	1.27	0.999-1.62	1.20	0.94-1.54	1.30	1.02-1.66	1.22	0.92-1.62
ADL (any difficulties +1)	1.12	0.89-1.41	1.15	0.9-1.47	1.12	0.89-1.41	1.14	0.88-1.49
Hearing Loss	1.27	1.03-1.56	1.23	0.98-1.54	1.25	1.02-1.54	1.25	0.99-1.58
Life style and health Behaviors								
Physical Activity (Active)	1.14	0.95-1.38	1.16	0.95-1.41	1.15	0.95-1.39	1.04	0.85-1.29
Alcohol Consumption (drinks per day)								
None	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
1-2 drinks	0.85	0.66-1.09	0.83	0.64-1.07	0.85	0.66-1.09	0.78	0.58-1.03
≥ 3 drinks	1.21	0.65-2.26	1.12	0.6-2.1	1.26	0.67-2.36	1.25	0.60-2.59
Smoking Status								
Never	**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Current	1.64	1.19-2.26	1.47	1.04-2.06	1.62	1.17-2.24	2.00	1.33-3.01
Former	1.17	0.96-1.41	1.16	0.95-1.41	1.18	0.97-1.43	1.18	0.95-1.46

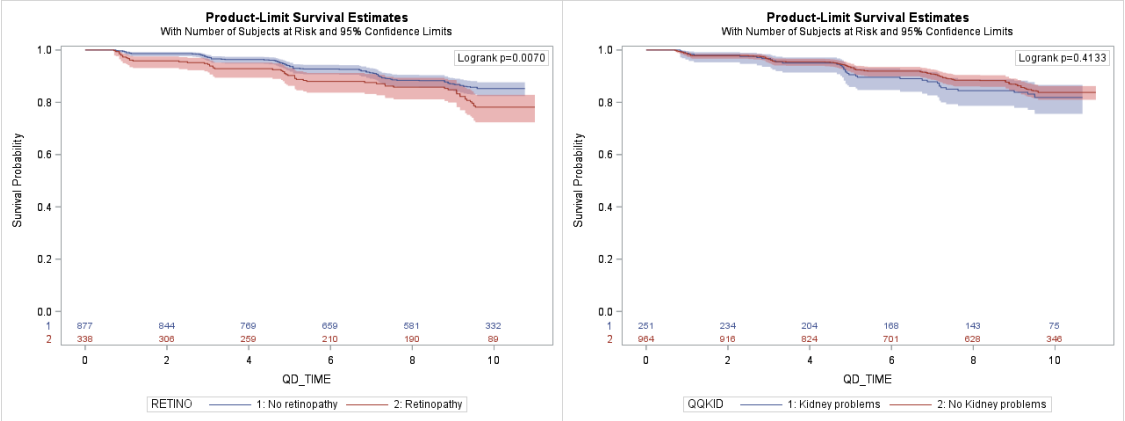
4.4.4 Hyperglycemia, microvascular complications and incident All - D

Kaplan-Meir analysis

Similarly to Any-CI outcome, Kaplan-Meir analysis showed that longer diabetes duration (≥10 years) had a significantly higher rate of incident All-D compared to diseases duration less than 10 years (Figure 4.3). Hyperglycemia at baseline (A1c ≥ 7%) wasn't significantly different from those with A1c less than 7%. Retinopathy was significantly associated with higher risk of incident All-D especially in the last years as the steepest decline of the KM curve occurred in the last years of the study. Other microvascular complications, neuropathy and nephropathy weren't significant.

Figure 4.3. Aim 2 Kaplan Meir survival curve for incident All-D.





Multivariable Cox proportion hazard for incident All-D

Over a median of 9.83 years of follow up (interquartile range, 5.9 – 10.08), All-D developed in 163 of the 1,215 respondents (13.42%) at the end of follow up. Among those with hyperglycemia (A1c ≥ 7%) subjects, about 49/391 developed All-D (12.53%); 49/471 among those less than 7% subjects (10.4%); and among those with unknown A1c level 65/353 developed Any-CI (18.41%). Similarly to Any-CI, higher education and annual income were associated with lower risk of incident All-D (Table 4.5). However, education became insignificant in model 2. Being a female was not significant in the first model, but starting from model 4 it became statistically significant with higher risk of All-D (HR=1.55; 95%CI 1.05-2.29). Non-Hispanic black and Hispanic didn't show higher risk of All-D. This could be also returned to the lack of power in this study especially that the sample majority was Non-Hispanic White.

In all model, diabetes medication, duration and hyperglycemia weren't significantly associated with incident All-D. Those with unknown A1c level was significantly associated with higher risk of All-D, in model 7 HR was 2.04 (95% CI 1.37-

3.06). This association was persistent in all models which suggest that unknown A1c group had the higher risk of incident All-D compared to those with A1c <7%. In model 3, nephropathy (or kidney problem) was marginally insignificantly associated with higher risk of incident All-D (P-value 0.084). This association increased in the fully adjusted model but still insignificant, HR 1.47 (95% CI 0.998- 2.17, P-value 0.051). In contrast to KM analysis, retinopathy wasn't significantly associated with the outcome in all models. Although, diabetes related measures were not significant, they associated with higher risk of incident All-D which could be related to sample power that wasn't enough to show the significance.

In model 4, Stroke was the strongest predictors of incident All-D, HR was 2.19 (95% CI 1.41-3.41). This association was persistent in all model and it didn't attenuated with further adjustment for other variables, in model 7 the HR was 2.17 (95% CI 1.39-3.4). heart diseases wasn't statistically significant with higher risk of All-D as Any-CI model, HR in model 7 was 1.1 (95% CI 0.76-1.58). Hypertension and hyperlipidemia were associated with lower risk of All-D. It was significant for hyperlipidemia only; with 43% decrease in All-D risk, HR in model 7 was 0.57 (95% CI 0.41-0.9).This association was surprising, thus, this low HR of these well-known high risk factors of dementia. It could be due to outcome rate was very low, small sample size, unreliable responses, or it could be the effect of hypertension or hyperlipidemia medication. In order to explore the later, hypertension medication were included in model 7. Hypertension becomes positively associated with higher risk of All-D (β=0.22) meanwhile medication variable were negatively associated (β=-0.29). Both hypertension and hypertension medication were not significant and there interaction term were not significant (P-value=0.53). For hyperlipidemia, the inclusion of hyperlipidemia medication didn't change the association

sign or significance, hyperlipidemia remained negatively associated with All-D (β=-1.03). On the other hand, hyperlipidemia medication was associated with higher risk of All-D, HR= 1.59 (95% CI 0.87-2.92), β=0.46, P-value=0.134. Also, the interaction between hyperlipidemia and hyperlipidemia medicine was not significant (P-value=0.14). These results should be carefully interpreted since the study sample under power and had a big confidence interval estimates. This is out of the study scope and further exploration maybe addressed in the future. None of the other chronic diseases, geriatric conditions, and lifestyle factors was significantly associated with incident All-D.

In summary, stroke was the strongest predictor of incident All-D. Heart diseases weren't significantly associated with higher risk of All-D. Hyperlipidemia was associated with reduced risk of incident All-D. This association should be carefully interpreted in the light of possible sample power problem. None of microvascular complications, hyperglycemia exposure, or diabetes medication was significantly associated with higher risk of All-D. Only nephropathy was close to significance that was persisting in all models.

Table 4.5. Aim 2 Cox proportional hazard models for incident All-D.

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95 % CI**	**HR**	**95 % CI**	**HR**	**95 % CI**	**HR**	**95 % CI**
Age	1.1	1.08-1.13	1.1	1.08 - 1.12	1.1	1.08-1.13	1.1	1.08 - 1.12	1.1	1.08 - 1.13	1.1	1.08 - 1.13	1.11	1.08 - 1.13
Female	1.41	0.99-1.99	1.39	0.98 - 1.98	1.4	0.99-1.99	1.49	1.04 - 2.13	1.45	1.01 - 2.08	1.55	1.07 - 2.23	1.55	1.05 - 2.29
Race														
Non-Hispanic White	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Non-Hispanic Black	1.11	0.71-1.75	0.91	0.57 - 1.45	0.88	0.55-1.4	0.85	0.53 - 1.38	0.88	0.54 - 1.42	0.91	0.56 - 1.47	0.91	0.56 - 1.48
Hispanic	1.75	1.09-2.82	1.58	0.98 - 2.57	1.51	0.92-2.47	1.52	0.93 - 2.49	1.56	0.95 - 2.56	1.47	0.89 - 2.42	1.48	0.89 - 2.44
Others	0.74	0.18-3.01	0.87	0.21 - 3.57	0.85	0.21-3.5	0.7	0.17 - 2.92	0.7	0.17 - 2.92	0.74	0.18 - 3.12	0.69	0.16 - 2.91
Married /Partnered	1.13	0.80-1.61	1.13	0.79 -1.6	1.13	0.79-1.61	1.16	0.81 - 1.66	1.2	0.83 - 1.71	1.24	0.86 - 1.79	1.26	0.87 - 1.82
Education (> High School)	0.65	0.44-0.94	0.7	0.48 - 1.03	0.7	0.48-1.03	0.76	0.52 - 1.12	0.76	0.52 - 1.12	0.75	0.51 -1.1	0.77	0.53 - 1.14
Annual income (≥ $40,000)	0.59	0.39-0.89	0.58	0.38 - 0.88	0.6	0.39-0.91	0.59	0.39 -0.9	0.6	0.39 - 0.90	0.6	0.4-0.91	0.62	0.41 - 0.95
Obese (BMI ≥30 kg/m**2)	0.93	0.66-1.35	0.93	0.66 - 1.31	0.93	0.66-1.31	0.97	0.69 - 1.37	0.95	0.67 - 1.35	0.92	0.65 - 1.31	0.92	0.64 - 1.31
Diabetes medication														
No medication	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Oral med. only	1.2	0.79-1.82	1.19	0.77 - 1.83	1.15	0.75-1.78	1.27	0.82 - 1.97	1.3	0.83 - 2.02	1.3	0.83 - 2.02	1.32	0.84 - 2.06
Insulin med.	1.4	0.84-2.35	1.2	0.68 - 2.14	1.12	0.62-2.00	1.11	0.62 - 1.99	1.13	0.63 - 2.04	1.2	0.66 - 2.18	1.23	0.67 - 2.26
DM duration														
<10 years			**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
≥ 10 years			1.26	0.87 - 1.83	1.21	0.83-1.76	1.18	0.81 - 1.71	1.18	0.81 - 0.17	1.15	0.79 - 1.68	1.12	0.77 - 1.64
Unknown			1.25	0.77 - 2.04	1.25	0.76-2.03	1.24	0.75 - 2.03	1.23	0.75 - 2.02	1.18	0.72 - 1.95	1.15	0.7-1.9
A1c %														

< 7%			**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
≥ 7%			1.15	0.76 - 1.73	1.15	0.76-1.74	1.2	0.79 - 1.82	1.2	0.79 - 1.82	1.18	0.78 - 1.79	1.12	0.73 - 1.71
Unknown			2.02	1.37 - 2.99	2.05	1.38-3.03	2.06	1.39 - 3.06	2.09	1.21 - 3.11	2.15	1.45 - 3.21	2.04	1.37 - 3.06
Retinopathy					1.14	0.81-1.62	1.13	0.79 - 1.61	1.11	0.78 - 1.59	1.06	0.74 - 1.53	1.06	0.74 - 1.52
Nephropathy					1.41	0.96-2.07	1.44	0.98 - 2.12	1.45	0.98 - 2.14	1.45	0.98 - 2.14	1.47	0.998-2.17
Neuropathy					1.06	0.63-1.78	1.01	0.6-1.72	1.02	0.6-1.172	1.03	0.6-1.76	1.03	0.60 - 1.77
Hypertension							0.74	0.5-1.10	0.73	0.49 - 1.08	0.73	0.49 - 1.09	0.74	0.5-1.11
Hyperlipidemia							0.57	0.41 - 0.79	0.57	0.41 -0.8	0.57	0.41 - 0.79	0.57	0.41 -0.9
Heart diseases							1.18	0.83 - 1.67	1.12	0.78 - 1.61	1.1	0.76 - 1.58	1.1	0.76 - 1.58
TIA							0.66	0.32 - 1.37	0.66	0.32 - 1.37	0.7	0.34 - 1.47	0.67	0.32 - 1.42
Stroke							2.19	1.41 - 3.41	2.25	1.44 - 3.52	2.22	1.42 - 3.46	2.17	1.39 -3.4
Other diseases														
Arthritis									1.21	0.85 - 1.71	1.17	0.82 - 1.67	1.2	0.84 - 1.72
Lung diseases									1.34	0.76 - 2.37	1.36	0.76 - 2.41	1.35	0.76 -2.4
Cancer									0.88	0.56 - 1.37	0.94	0.60 - 1.48	0.95	0.61 -1.5
Geriatric Conditions														
Depressive Symptoms											1.24	0.81 -1.9	1.26	0.82 - 1.92
ADL (any difficulties +1)											0.85	0.55 - 1.29	0.83	0.54 - 1.27
Hearing Loss											1.43	0.99 - 2.06	1.42	0.99 - 2.06
Life style and health Behaviors														
Physical Activity (Active)													1.1	0.78 - 1.55
Alcohol Consumption (drinks per day)														
None													**Ref.**	

1-2 drinks													0.69	0.41 - 1.16
≥ 3 drinks													0.88	0.21 - 3.69
Smoking Status														
Never													**Ref.**	
Current													1.48	0.81 - 2.71
Former													1.1	0.78 - 1.55

Moderation and Mediation analysis for incident All-D

Similar to Any-CI outcome, there were no significant interaction between A1c and other chronic diseases, geriatric conditions and lifestyle factors. The only positive interaction was between hearing loss and A1c, those with both high A1c (≥ 7%) and hearing loss had higher risk of All-D compared to those with low A1c (< 7%) and hearing loss, HR=2.28 (95% CI 1.03-5.05; P-valu=0.03). The three way interaction between A1c, hypertension, and hyperlipidemia was insignificant too, HR 1.2 (95% CI 0.68-2.11; P-valu=0.63). There was no interaction between microvascular complications and hyperglycemia (A1c), P-value >0.05. The mediation effect of microvascular and macrovascular diseases of the association between A1c couldn't be tested since this association wasn't significant in the first place.

Sensitivity analysis for incident All-D

Competing risk model accounting for death sub-hazard distribution gave the same results of the full model (Table 4.6). The only difference was Hispanic who became significantly associated with higher risk of All-D. In both model of interval censoring and Age 65 and above, nephropathy became significantly associated with higher risk of All-D, HR 1.48 (95% CI 1.004-2.19) and 1.56 (95% CI 1.02-2.39), respectively. Hearing loss association with higher risk of All-D became significant when sample were restricted into 65 years old and above, HR 1.5 (95% CI 1.01-2.23). In order to understand the effect of missing A1c value on the association of hyperglycemia exposure on All-D incidence, missing baseline A1c were removed from the sample. Nephropathy, which was marginally insignificant, became significantly associated with increased risk of incident

All-D, HR 1.77 (95% CI 1.08-2.91). The lower risk associated with hypertension became significant (HR 0.55; 95% CI 0.33-0.92) and hyperlipidemia was insignificant (HR 0.72; 95% CI 0.47-1.12). Arthritis was associated with significant higher risk, HR was 1.81 (95% CI 1.09-3.01). Stroke and hearing loss across different sensitivity analyses models was persistently associated with higher risk of incident All-D.

Table 4.6. Aim 2 sensitivity analyses for incident All-D.

	Model 7		Competing risk		Interval censoring		Sample ≥65 (N=806)		A1c Not missing(N=862)	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Age	1.11	1.08-1.13	1.08	1.06-1.11	1.11	1.08-1.13	1.08	1.05-1.12	1.13	1.09-1.16
Female	1.55	1.05-2.29	1.53	1.02-2.31	1.54	1.04-2.27	1.66	1.09-2.51	1.41	0.86-2.31
Race										
Non-Hispanic White	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Non-Hispanic Black	0.91	0.56-1.48	1.09	0.67-1.76	0.92	0.57-1.5	1.04	0.63-1.73	0.89	0.41-1.94
Hispanic	1.48	0.89-2.44	1.93	1.18-3.18	1.44	0.87-2.38	1.10	0.60-2.01	1.83	0.96-3.5
Others	0.69	0.16-2.91	0.77	0.17-3.52	0.69	0.16-2.74	0.81	0.18-3.52	0.44	0.06-3.34
Married/Partnered	1.26	0.87-1.82	1.23	0.84-1.81	1.26	0.87-1.83	1.29	0.87-1.9	1.31	0.82-2.11
Education (> High School)	0.77	0.53-1.14	0.82	0.56-1.18	0.77	0.52-1.13	0.74	0.49-1.12	0.76	0.47-1.22
Annual income (≥ $40,000)	0.62	0.41-0.95	0.64	0.45-0.99	0.62	0.40-0.94	0.69	0.44-1.09	**0.60**	**0.35-1.00**
Obese (BMI ≥30 kg/m**2)	0.92	0.64-1.31	0.97	0.67-1.4	0.92	0.65-1.32	0.95	0.65-1.38	1.31	0.82-2.09
Diabetes medication										
No medication	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Oral med. only	1.32	0.84-2.06	1.16	0.73-1.85	1.30	0.83-2.04	1.22	0.76-1.94	1.01	0.56-1.85
Insulin med.	1.23	0.67-2.26	0.97	0.51-1.84	1.22	0.66-2.23	0.97	0.51-1.87	1.33	0.6-2.91
DM duration										
<10 years	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
≥ 10 years	1.12	0.77-1.64	1.25	0.85-1.83	1.13	0.77-1.65	1.22	0.81-1.82	1.44	0.87-2.37
Unknown	1.15	0.7-1.9	1.21	0.74-1.98	1.16	0.70-1.92	1.18	0.7-1.98	0.88	0.39-2.01
A1c %										
< 7%	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
≥ 7%	1.12	0.73-1.71	1.13	0.74-1.73	1.13	0.74-1.73	1.14	0.73-1.77	1.03	0.65-1.63
Unknown	2.04	1.37-3.06	1.78	1.18-2.69	2.04	1.36-3.06	1.98	1.3-3.02		
Retinopathy	1.06	0.74-1.52	0.96	0.67-1.39	1.07	0.74-1.54	0.93	0.63-1.36	1.12	0.7-1.8
Nephropathy	1.47	0.998-2.17	1.34	0.9-1.99	1.48	1.004-2.19	1.56	1.02-2.39	1.77	1.08-2.91
Neuropathy	1.03	0.60-1.77	0.91	0.52-1.59	1.03	0.6-1.77	0.87	0.47-1.61	1.08	0.55-2.1
Hypertension	0.74	0.5-1.11	0.77	0.50-1.18	0.74	0.5-1.11	0.70	0.45-1.09	0.55	0.33-0.92
Hyperlipidemia	0.57	0.41-0.9	0.64	0.46-0.91	0.58	0.41-0.8	0.54	0.38-0.77	0.72	0.47-1.12
Heart diseases			0.96	0.67-1.38	1.11	0.77-1.59	1.17	0.8-1.73	0.88	0.55-1.4
TIA	0.67	0.32-1.42	0.84	0.39-1.79	0.66	0.31-1.38	0.62	0.28-1.35	0.38	0.13-1.08
Stroke	2.17	1.39-3.4	2.00	1.23-3.25	2.14	1.37-3.36	2.48	1.54-3.99	2.95	1.67-5.19
Other diseases										

Arthritis	1.20	0.84-1.72	1.23	0.86-1.76	1.20	0.84-1.71	1.29	0.87-1.9	1.81	1.09-3.01
Lung diseases	1.35	0.76-2.4	1.23	0.67-2.25	1.32	0.74-2.36	1.62	0.9-2.92	1.39	0.63-3.07
Cancer	0.95	0.61-1.5	0.87	0.53-1.44	0.96	0.61-1.51	0.91	0.57-1.46	1.47	0.86-2.52
Depressive Symptoms	1.26	0.82-1.92	1.24	0.80-1.91	1.25	0.82-1.92	1.15	0.73-1.81	0.91	0.5-1.66
ADL (any difficulties+1)	0.83	0.54-1.27	0.80	0.52-1.23	0.81	0.53-1.25	1.01	0.65-1.59	0.89	0.51-1.54
Hearing Loss	1.42	0.99-2.06	1.42	0.98-2.05	1.42	0.98-2.05	1.50	1.01-2.23	1.22	0.75-1.52
Physical Activity (Active)	1.10	0.78-1.55	1.14	0.80-1.62	1.09	0.77-1.54	1.04	0.72-1.5	1.29	0.82-2.03
Alcohol Consumption (drinks per day)										
None	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
1-2 drinks	0.69	0.41-1.16	0.68	0.41-1.13	0.69	0.41-1.16	0.69	0.4-1.12	0.62	0.33-1.18
≥ 3 drinks	0.88	0.21-3.69	0.63	0.15-2.64	0.90	0.21-3.77	1.05	0.25-4.46	1.25	0.29-5.45
Smoking Status										
Never	**Ref.**		**Ref.**		**Ref.**		**Ref.**		**Ref.**	
Current	1.48	0.81-2.71	1.30	0.71-2.37	1.50	0.82-2.75	1.31	0.64-2.65	1.88	0.81-4.37
Former	1.10	0.78-1.55	1.11	0.77-1.59	1.11	0.78-1.57	1.16	0.80-1.68	1.03	0.66-1.61

4.5 CHAPTER SUMMARY

High income (≥ $40,000) was significantly associated with lower risk for both Any-CI and All-D outcome (HR 0.76 VS 0.62). Diabetes medication in a dose response way was significantly associated with higher risk of incident Any-CI but not with incident All-D. Long diabetes duration (≥10 years) was significantly associated with both outcomes in KM analysis. However, in Cox-models it wasn't significant for Any-CI and All-D. Hyperglycemia presented by A1c value ≥7% was associated with lower survival curve in KM analysis for both Any-CI and All-D. This wasn't the case in cox proportional hazard models where A1c was not statistically significant in all models. The group with missing A1c value were significantly associated with higher risk of incident Any-CI and All-D. This indicates that this group may have the highest risk for cognitive decline and missing data had a high impact on the study result. Similar to A1c, retinopathy in KM analysis was significantly associated with higher risk for both outcomes but not in Cox proportional hazard model. Nephropathy was marginally insignificant for All-D in model 7 (HR=1.46; 95% CI 0.998-2.17). This association turned to be significant in sensitivity analysis; when interval censoring (HR=1.48; 95% CI 1.004-2.19), sample age criteria was restricted to those ≥ 65 years old (HR=1.56; 95% CI 1.02-2.39), and missing A1c values were removed from the analysis (HR=1.77; 95% CI 1.08-2.91). Neuropathy wasn't significant for all models, in model 7 HR=1.03 (95% CI 0.6-1.77).

For incident Any-CI heart diseases and stroke were significantly associated with higher risk meanwhile for All-D only stroke remained significant. Stroke was the strongest predictors for both outcomes, in model 7 for Any-CI outcome HR was 1.38

(95% CI 1.04-1.84) and for All-D outcome HR was even higher 2.17 (95% CI 1.39-3.4). Hypertension and hyperlipidemia were associated with lower risk of both Any-CI and All-D, this was only significant for hyperlipidemia in All-D model HR=0.57 (95% CI 0.41-0.9). This association was surprising since both factors are known to be risk factors for cognitive decline. Many reasons could be behind such result; lack of power due to small sample size or it could be a proxy for possible protective effect for hypertension and hyperlipidemia medication.

Other chronic diseases were not association with any outcome. Depressive symptoms became associated with higher risk of incident Any-CI in sensitivity analysis both in age restricted model and interval censoring model. Hearing loss was significantly associated with increasing risk of Any-CI and insignificant with high risk of All-D (HR 1.27 VS 1.42).Higher risk of All-D associated with hearing loss became significant among those 65 and above, in sensitivity analysis in age restricted model. Regarding lifestyle factors, current smoking status was strong predictors for incident Any-CI, HR=1.64 (95% CI 1.19-2.26). In model 7 for incident All-D, also smoking had high risk of All-D but it wasn't significant, HR=1.48 (95% CI 0.81-2.7). Of note, all variables could be underestimated due to lack of power especially that the cox proportional hazard model is dependent on number of events in calculating the HR rather than time.

Chapter 5: Discussion, Limitations, and conclusion

This chapter covers three main topics, first: discussion of the results for each specific aim separately. Second: the strengths and limitations of this study, and finally: a brief conclusion of overall observations.

5.1 DISCUSSION

The whole purpose of this study was to evaluate the impact of diabetes microvascular complications, macrovascular diseases, co-existing chronic diseases, geriatric conditions, and life style factors on the incidence of any-cognitive decline (Any-CI) and all-cause dementia (All-D) among elderly paients with diabetes in order to determine possible pathways. This was evaluated with two cohorts: (1) in the whole 2002 wave HRS sample (general population), focusing on incident risk of Any-CI and All-D in diabetics and non-diabetics, and (2) within the 2003 diabetes study sample (diabetic population).

Demographic characteristics were controlled for in all analyses. Higher education level (above high school) and high income (≥ $40,000) were consistently associated with lower risk in all models testing for Any-CI and All-D outcomes. This finding was consistent with other studies; high education and high annual income were associated with lower risk of cognitive decline[148,149]. There were several possible explanations for income association with better cognition; it may simply reflect better health, better health behaviors, and better education[148]. Education in return, may play a similar role in terms of better health and health behaviors and may have a direct effect on early life

development and on brain cognitive reserve (individual brain ability to cope with any failures or declines it face due to massive storage of lifetime education, work and challenges)[26,149]. Although educational level was only significant in the general population (Aim 1) and not among diabetic sub-population (Aim 2), obesity was associated with lower risk of cognitive impairment and dementia for both; the general population and the diabetic subsample. This observation aligned with the reversed role of obesity – a protective role - among the elderly; an 'obesity paradox'[150].

Diabetes was independently increased the risk of both Any-CI and All-D. This was consistent across all models including sensitivity analyses models, confirming the reliability of results. This finding was similar to the conclusion of many previous studies[42,43,46,47] including studies that focused on older adults in the health and retirement study (HRS)[55]. Wu Q. *et al.* (2015)[55] reported that prevalent diabetes was associated with higher odds of dementia and memory decline compared to non-diabetics, OR=1.27 (95% CI 1.03-1.58) and z-score was -0.06 (95% CI -0.1 to 0.02), respectively. Newly diagnosed diabetes, incident diabetes, within 8 years of follow up was not associated with an increased risk. This study was across sectional study that evaluate prevalent diabetes measure was evaluated based on the same year of the outcome (2000 wave)[55]. It did take into account the time-varying effect of macrovascular risk factors and diseases that would be associated with prevalent diabetes by going back in time 8 years (1992 wave). It also used ADAMS study cognitive definition for dementia screening, however, this definition was validated to be used on those 70 years old and above while Wu Q. et al. study included all HRS eligible participant (that may include a big segment of those < 70 years old)[55,151]. This study is a longitudinal study design which adds a great value in dementia and cognitive impairment risk assessment. It also overcome the problem of cognitive

scale validity for those under 65 years old by using Crimmins *et al.*[122] definition and classification.

The observed associations between diabetes and incident Any-CI and All-D were independent of microvascular, macrovascular complications, co-existing chronic diseases, or geriatric conditions. The risk associated with diabetes per se was attenuated when nephropathy included in the model. The overall population risk of 1.31 for any-CI dropped to 1.23 for diabetic patients without kidney problems, but increased to 1.58 for those with kidney problems. Similarly, The overall population risk of 1.55 for All-D dropped to 1.45 for diabetic patients without kidney problems, but increased to 1.57 for those with kidney problems. Further adjustment for risk factors and diseases emphasizes this pattern; risk for any-CI decreased from 1.28 to 1.19 for diabetics without kidney problems and was 1.39 with kidney problems. Risk for All-D decreased from 1.53 to 1.38 for diabetics without kidney problems and was 1.33 with kidney problems. This suggests a possible microvascular pathway behind the association between diabetes and cognitive decline. Marseglia et al.[102], reported that prediabetes and diabetes associated with smaller brain volume that may reflect smaller white matter hyper-intensities volume which is a proxy of white matter microvascular lesions. These findings of Marseglia et al. study was consistent with other studies and contradicted with other ones[152]. Microvascular pathway for cognitive decline among diabetes was not confirmed yet.

Exposure to hyperglycemia (longer diabetes disease duration, A1c value ≥7%, and insulin treatment) also were significantly associated with higher risk of cognitive decline in bivariate KM analysis in the general population and diabetic population. However, in aim 2 multivariable cox proportional hazard model only diabetes medication

was associated with higher risk of any-cognitive impairment but not dementia. Diabetes duration and treatment modality has mixed results in the literature, some studies reported significant association with higher risk while the other failed to achieve significant association[53-55]. Similarly, longitudinal studies reported an increased risk of cognitive decline associated with high levels of A1c [141,153], while clinical trials failed to observe any beneficial effect of glycemic control on cognition[75,80]. Two longitudinal studies in HRS reported that high A1c level was associated with memory decline based on sample starting from 2006 wave through 2012 wave[58,154]. Both studies differ in their study sample definition, methodology, and outcome definition. On the other hand, ACCORD-MIND reported that controlling A1c under 7% didn't protect against cognitive decline associated with diabetes[75]. This study was based on other clinical trial designed to prevent macrovascular complications among diabetics' ≥66 years old and with high risk profile of cardiovascular diseases[155]. Systematic reviews and meta-analysis of different clinical trials confirmed these findings[79,156].

Very interestingly, diabetes with kidney problems, nephropathy, was significantly associated with higher risk of any cognitive impairment in general population only. In the diabetic subsample where these variables were better reported, none of the microvascular diseases were statistically significant likely due to a lack of statistical power. Nephropathy had a 47% increase in dementia that was marginally insignificant. The previously done studies on the association of nephropathy with cognitive impairment in patients with diabetes using cystatin C, a biomarker of kidney function, and albumin / creatinine ratio, a measure of microvascular endothelial disease, reached the same conclusion but did not clearly address the difference in relationship between kidney disease with Any-CI versus All-D as we did in our study[91,92]. Moreover, previous studies

reported that retinal microvascular abnormalities are linked to cognitive decline and dementia in people with and without diabetes[94,95] and severe diabetic retinopathy had higher risk of incident dementia compared to diabetic patients without retinopathy[97]. However, this study failed to show any significant association between microvascular complications (as a proxy of microvascular pathology) and cognitive decline. However, lack of study power in aim 2 and small nephropathy group in aim 1 may explain some of this discrepancy between study results.

Hypertension association with cognitive decline in general population has a different direction from diabetic population. Although it was not significant, hypertension increased cognitive impairment and dementia risk in general population and decreased risk in the diabetic sub-population. In addition, hyperlipidemia was associated with lower risk of cognitive decline among diabetic population. These findings should be interpreted with caution, since diabetic population sample was underpowered. Both hypertension and hyperlipidemia known to be risk factors of both cognitive impairment and dementia[157]. The contribution of hypertension and hyperlipidemia treatment on the observed lower risk of cognitive decline among diabetics needs to be explored.

Stroke (macrovascular disease) was a very strong predictor for any cognitive impairment and dementia in both general population and diabetic population. It was more prominent among diabetic population. Note: for Any-CI stroke was 1.30 in the general population and 1.38 in the diabetic cohort. Heart diseases was also more important for the diabetic subsample (1.36), pointing to the important role of vascular disease in the development of cognitive impairment. For dementia this was even more dramatic: stroke increased risk of All-D 1.76, but in the diabetic cohort this was 2.17. This can be

explained by the fact that vascular dementia occurs secondary to multiple strokes resulting from macrovascular occlusions secondary to thrombotic changes on top of atherosclerosis or embolic phenomena[23]. Diabetes contributes to atherosclerotic changes in cerebral vasculature[88]. Feinkohl I, et al. in the Edinburgh Type 2 Diabetes Study found a strong association between stroke and cognitive decline in patients with type 2 diabetes[58]. Besides, the study found that multiple markers of subclinical macrovascular disease (carotid intima-media thickness (cIMT), ankle brachial index (ABI), and serum N-terminal probrain natriuretic peptide (NT-proBNP) were significantly associated with cognitive decline[58]. In contrast to stroke, heart diseases, didn't show strong persistent association with cognitive impairment and dementia in general population and was only significantly associated with any cognitive impairment and not dementia in the diabetic cohort. Stroke and heart diseases are known to be the underlying causes of vascular dementia[85], which is the second most common type of dementias. Diabetes was also associated with vascular dementia in a higher degree (by contributing to large vessel atherosclerosis) than other types of dementia[84]. This study showed that stroke was the single largest risk factor for dementia in the general population and the diabetic cohort compared to other macrovascular diseases.

The cluster of multiple chronic conditions was shown to increase the risk of cognitive decline and dementia[36]. Some of these chronic diseases, arthritis and lung diseases were independently associated with higher risk of cognitive decline and dementia[108,115]. They characterized by shared underlying pathological pathway; inflammation. Chronic hyperglycemia also had a higher level of inflammatory markers[158]. Inflammation could be a possible mechanism that may explain the association between diabetes and cognitive decline[23]. The co-existence of these chronic diseases

together effect on cognition, whether they act as confounder or effect moderator, is unknown. On the other hand, cancer is associated mortality that may indirectly affect, or confound, diabetes association with cognitive decline and dementia rate in the study sample[159]. In addition, cancer was directly linked to cognitive decline in both brain tumor and other cancers that doesn't involve brain[160]. Other chronic diseases (arthritis, lung diseases, and cancer) were not significantly associated with any cognitive impairment and dementia in both general population and diabetic population. Moreover, the effect moderation of the co-existence of diabetes and other chronic diseases was not significant in both outcome analyses. Shared underlying inflammatory diseases pathology with diabetes was not suggested here and they didn't affect the risk level of cognitive decline associated with diabetes. This finding is not consistent with previous studies which suggested that the presence of multiple chronic diseases (like COPD, arthritis among others) was associated with an increased risk of cognitive decline and dementia[36-37]. These studies differ in their definition of cognitive decline and covariate set that account only for macrovascular diseases and diabetes without adjustment for microvascular diseases or geriatric conditions.

All Geriatric variables (depressive symptoms, mobility, hearing loss and vision loss) were associated with 11% to 25% increased risk in the general population with any cognitive impairment, although they were higher for dementia (18%-47% increased risk). In contrast, geriatric conditions were not significantly associated with higher risk of cognitive decline among diabetic subjects (27% increase from depression and 27% increase from hearing loss). Hearing loss had a 42% non-significant increase in dementia in the diabetic population. A stronger association between hearing loss and cognitive decline was reported by previous studies; a recent meta-analysis of 15,521 individuals

found that hearing impairment was associated with increased risk of MCI and dementia; RR of 1.3 (95% CI 1.12-1.51) for MCI and 2.39 (95% CI 1.58-3.61) for dementia[30]. Recent debate about the higher rate of hearing loss among diabetic subjects compared to non-diabetics is to be a disease complication that has similarities with neuropathy associated with diabetes[161,162]. In general population, depressive symptoms had the strongest association with cognitive decline. This finding was consistent with previous reports from literature[38,110]. However, the interpretation of depressive symptoms whether it was a risk factor or an early symptoms of cognitive decline is hard in the light of bidirectional association of depression with cognitive decline, dementia and diabetes. There was no interaction between diabetes and depressive symptoms, which was inconsistent with other work that reported positive interaction between depression and diabetes[110].

A final pathway that was explored concerned lifestyle and healthy behaviors. Smoking was the single most important lifestyle risk factor. In the general population, smoking increased risk 26% for cognitive impairment and 30% for dementia. In the diabetic cohort, smoking increased risk 64% for cognitive impairment and 48% for dementia. This risk factor is extremely important as it is a modifiable risk factor – it is a behavior that can be changed. Risk was highest for current smokers and non-significant for former smokers. There also was a significant beneficial effect for lifestyle factors (Physical activity and moderate drinking) on reducing the risk of cognitive decline, although these factors made only moderate reductions in risk of All-CI and All-D in general population but had a negligible effect among diabetics. This is consistent with the previous studies[33,34,163]. In general population, testing for possible effect moderation of physical activity on the association of diabetes and cognitive decline revealed to be in the

case of non-diabetics only. This was consistent with findings from diabetic population; physical activity didn't show any beneficial role in preventing cognitive decline among diabetics. Moderate consumption of alcohol was associated with lower risk of both Any-CI and All-D, however, it was significant in general population and not significant for diabetic population.

5.2 STRENGTHS

Strengths of this study include the use of: a national sample, statistical approaches to minimize bias and assure reliability of results, and a validated measure of cognitive performance. The use of cox-proportional hazard along with competing risk model did account for possible attrition bias due to death or drop out. HRS study is a national representative sample that covers a wide range of topics. HRS included a validated cognitive battery for cognitive impairment and dementia screening in general population. Cognitive measures included both self-respondent tests and proxy questionnaires. This combined method in measuring cognition was showed to minimize bias associated with cognitive outcome by reducing the effect of attrition bias impact on cognition[118,124]. Moreover, RAND v.P file included imputation for self-respondent missing cognitive tests which also minimize bias associated with no-response[125].

5.3 LIMITATIONS

The greatest limitation of this study is in the use of a survey not specifically designed to accurately measure health-related variables. There were no microvascular etc. questions for the general pop, only one time survey for the diabetics. Another limitation for this study was the omission of sampling weights for the general population. The HRS

study sample is a multi-stage probabilistic sample that included geographic stratification, clustering and oversampling of minorities. Thus, using sampling weights in the analysis will minimize sampling error and produce more accurate estimates that are representative for general U.S. population. The use of Crimmins et al. definition and classification of cognitive decline didn't include a state-of-the-art cognitive assessment, which may come at some cost of cognitive battery representativeness; limiting its ability to assess some cognitive functions like orientation. The impact of survey mode of administration (telephone based vs face to face) and factors (like hearing loss, and test language) may impact respondent performance.

Another issue is selection bias due to left truncation; those already have baseline any cognitive impairment were excluded from study. This will produce underestimated point estimates. It can be remedied by combining these cross-sectional data with longitudinal data, converting left truncation into left censoring problem, in order to have less biased, more accurate and robust estimates[164]. Missing data in key variables, especially for aim 2, severely reduced the study sample size. In specific aim 2, about 30% of those with valid A1c values were excluded due to missing in cognitive measures. Even this problem was addressed in sensitivity analysis but the impact of missing data on results needs to be explored more. Baseline exposure measures were included in the model. Later exposure and time varying covariates, like A1c, for these variables wasn't accounted for in the analysis. Thus, results could be underestimated and some of non-significant associations, A1c as an example, could be due to the inclusion of baseline measure rather than time dependent variable. Un-measured confounders like hyperlipidemia in general population, hypoglycemic event, and APOE ε_4.

5.4 CONCLUSION AND FUTURE DIRECTIONS

This study confirmed that diabetes was associated with higher risk of both cognitive impairment and dementia. This association was significant even after other complications and diseases were accounted for. Macrovascular diseases, mainly stroke, were the strongest predictor of cognitive decline that showed an increased risk among diabetic population compared to general population. Possible role of microvascular pathology were suggested but not confirmed. Nephropathy showed a significant higher risk of cognitive decline in general population and among diabetics but was not significant for the last. The diabetic study was under-powered, small sample size with missing data in microvascular diseases. As a result possible role of microvascular complications was not statistically significant; sometimes you can see the effect, like nephropathy on dementia for the diabetic cohort, but it was not significant. Other diseases that had been reported to be associated with higher or increased diabetes risk of cognitive decline had no risk in general population or diabetic population. This doesn't support the notion of possible underlying inflammatory mechanisms in cognitive decline development. The association between diabetes and cognitive decline wasn't completely explained by our model. The impact of diabetes risk factors management, mainly hypertension and hyperlipidemia, needs further exploration. Out of clinical characteristics of diabetes disease, there were several possible areas still unexplored. Social determinants could contribute to the diabetes and cognitive decline relationship.

References

1. Knickman JR, Snell EK. The 2030 Problem: Caring for Aging Baby Boomers. *Health Services Research.* 2002;37(4):849-884.

2. Centers for Disease Control and P. The state of aging and health in America 2013. *Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services.* 2013.

3. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med.* 2013;29(4):737-752.

4. Heron M. Deaths: Leading Causes for 2014. *Natl Vital Stat Rep.* 2016;65(5):1-96.

5. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol.* 2014;10(11):634-642.

6. Small SA, Stern Y, Tang M, Mayeux R. Selective decline in memory function among healthy elderly. *Neurology.* 1999;52(7):1392-1396.

7. Roberts R, Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med.* 2013;29(4):753-772.

8. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2018;90(3):126-135.

9. Petersen RC, Roberts RO, Knopman DS, et al. Prevalence of mild cognitive impairment is higher in men The Mayo Clinic Study of Aging. *Neurology.* 2010;75(10):889-897.

10. Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *The Lancet.* 1997;349(9068):1793-1796.

11. Palmer K, Bäckman L, Winblad B, Fratiglioni L. Mild cognitive impairment in the general population: occurrence and progression to Alzheimer disease. *The American Journal of Geriatric Psychiatry.* 2008;16(7):603-611.

12. Canevelli M, Grande G, Lacorte E, et al. Spontaneous reversion of mild cognitive impairment to normal cognition: A systematic review of literature and meta-analysis. *Journal of the American Medical Directors Association.* 2016;17(10):943-948.

13. Geerlings MI, Jonker C, Bouter LM, Ader HJ, Schmand B. Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. *Am J Psychiatry.* 1999;156(4):531-537.

14. Wahlund LO, Pihlstrand E, Jonhagen ME. Mild cognitive impairment: experience from a memory clinic. *Acta Neurol Scand Suppl.* 2003;179:21-24.

15. Ganguli M, Snitz BE, Saxton JA, et al. Outcomes of mild cognitive impairment by definition: a population study. *Arch Neurol.* 2011;68(6):761-767.

16. Koepsell TD, Monsell SE. Reversion from mild cognitive impairment to normal or near-normal cognition: risk factors and prognosis. *Neurology.* 2012;79(15):1591-1598.

17. Roberts RO, Knopman DS, Mielke MM, et al. Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. *Neurology.* 2014;82(4):317-325.

18. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):263-269.

19. Alzheimer's A. 2017 Alzheimer's disease facts and figures. *Alzheimer's & Dementia.* 2017.

20. 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. *Alzheimer's & Dementia.* 2017;13(1):28-37.

21. Langa KM, Larson EB, Crimmins EM, et al. A comparison of the prevalence of dementia in the United States in 2000 and 2012. *JAMA Internal Medicine.* 2017;177(1):51-58.

22. Winblad B, Amouyel P, Andrieu S, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *The Lancet Neurology.* 2016;15(5):455-532.

23. Mayeda ER, Whitmer RA, Yaffe K. Diabetes and cognition. *Clin Geriatr Med.* 2015;31(1):101-115, ix.

24. Kochhann R, Camozzato AL, Godinho C, Cerveiro MO, Forster LMK, Chaves MLF. Cognitive complaints compared to performance on a mental state screening test in elderly outpatients. *Dement Neuropsychol.* 2008;2(1):46-51.

25. Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. *Qjm.* 2007;100(8):469-484.

26. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet.* 2017;390(10113):2673-2734.

27. Langa KM, Llewellyn DJ, Lang IA, et al. Cognitive health among older adults in the United States and in England. *BMC geriatrics.* 2009;9(1):23.

28. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. *Clinics in geriatric medicine.* 2014;30(3):421-442.

29. Pase MP, Satizabal CL, Seshadri S. Role of improved vascular health in the declining incidence of dementia. *Stroke.* 2017;48(7):2013-2020.

30. Wei J, Hu Y, Zhang L, et al. Hearing Impairment, Mild Cognitive Impairment, and Dementia: A Meta-Analysis of Cohort Studies. *Dementia and geriatric cognitive disorders extra.* 2017;7(3):440-452.

31. Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology.* 2010;75(1):27-34.

32. Singh-Manoux A, Dugravot A, Fournier A, et al. Trajectories of depressive symptoms before diagnosis of dementia: a 28-year follow-up study. *JAMA psychiatry.* 2017;74(7):712-718.

33. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *Journal of internal medicine.* 2011;269(1):107-117.

34. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *American journal of epidemiology.* 2007;166(4):367-378.

35. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev.* 2011;10(4):430-439.

36. Vassilaki M, Aakre JA, Cha RH, et al. Multimorbidity and Risk of Mild Cognitive Impairment. *J Am Geriatr Soc.* 2015;63(9):1783-1790.

37. Baker NA, Barbour KE, Helmick CG, Zack M, Al Snih S. Arthritis and cognitive impairment in older adults. *Rheumatology International.* 2017:1-7.

38. Rotkiewicz-Piorun AM, Al Snih S, Raji MA, Kuo YF, Markides KS. Cognitive decline in older Mexican Americans with diabetes. *J Natl Med Assoc.* 2006;98(11):1840-1847.

39. Dodd JW, Getov SV, Jones PW. Cognitive function in COPD. *European Respiratory Journal.* 2010;35(4):913-922.

40. Group UKPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet.* 1998;352(9131):837-853.

41. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. *Jama.* 2015;314(10):1021-1029.

42. Center for Disease Control and Prevention (CDC).DiabetesDataand Statistics, National Data website.http://www.cdc.gov/diabetes/statistics/prevalence_national.htm. Accessed February 23, 2016.

43. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes.* 2004;53(2):474-481.

44. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology.* 1999;53(9):1937-1942.

45. Ahtiluoto S, Polvikoski T, Peltonen M, et al. Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. *Neurology.* 2010;75(13):1195-1202.

46. Centers for Disease Control and P. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. *Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention.* 2011;201.

47. Heron M. Deaths: Leading Causes for 2013. *Natl Vital Stat Rep.* 2016;65(2):1-95.

48. Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MM. Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia.*39(11):1392-1397.

49. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J.* 2012;42(5):484-491.

50. Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med.* 2000;160(2):174-180.

51. Wilson V. Cognitive impairment in patients with diabetes. *Nurs Stand.* 2012;27(15-17):44-49.

52. Bordier L, Doucet J, Boudet J, Bauduceau B. Update on cognitive decline and dementia in elderly patients with diabetes. *Diabetes Metab.* 2014;40(5):331-337.

53. Xu W, Caracciolo B, Wang H-X, et al. Accelerated progression from mild cognitive impairment to dementia in people with diabetes. *Diabetes.* 2010;59(11):2928-2935.

54. 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.

55. Wu Q, Tchetgen Tchetgen EJ, Osypuk T, et al. Estimating the cognitive effects of prevalent diabetes, recent onset diabetes, and the duration of diabetes among older adults. *Dement Geriatr Cogn Disord.* 2015;39(3-4):239-249.

56. Tuligenga RH, Dugravot A, Tabak AG, et al. Midlife type 2 diabetes and poor glycaemic control as risk factors for cognitive decline in early old age: a post-hoc analysis of the Whitehall II cohort study. *Lancet Diabetes Endocrinol.* 2014;2(3):228-235.

57. Xu W, Qiu C, Winblad B, Fratiglioni L. The effect of borderline diabetes on the risk of dementia and Alzheimer's disease. *Diabetes.* 2007;56(1):211-216.

58. Marden JR, Mayeda ER, Tchetgen Tchetgen EJ, Kawachi I, Glymour MM. High Hemoglobin A1c and Diabetes Predict Memory Decline in the Health and Retirement Study. *Alzheimer Dis Assoc Disord.* 2017;31(1):48-54.

59. Ma F, Wu T, Miao R, Xiao YY, Zhang W, Huang G. Conversion of mild cognitive impairment to dementia among subjects with diabetes: a population-based study of incidence and risk factors with five years of follow-up. *Journal of Alzheimer's Disease.*43(4):1441-1449.

60. Luchsinger JA, Lehtisalo J, Lindstrom J, et al. Cognition in the Finnish diabetes prevention study. *Diabetes Res Clin Pract.* 2015;108(3):e63-66.

61. Lindstrom J, Louheranta A, Mannelin M, et al. The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care.* 2003;26(12):3230-3236.

62. Feinkohl I, Keller M, Robertson CM, et al. Clinical and subclinical macrovascular disease as predictors of cognitive decline in older patients with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetes Care.* 2013;36(9):2779-2786.

63. Aung PP, Strachan MW, Frier BM, Butcher I, Deary IJ, Price JF. Severe hypoglycaemia and late-life cognitive ability in older people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabet Med.* 2012;29(3):328-336.

64. Riby LM, Riby DM. Raised blood glucose as a predictor of dementia risk in adults with and without diabetes. *Evid Based Med.* 2014;19(3):112.

65. Ramirez A, Wolfsgruber S, Lange C, et al. Elevated HbA1c is associated with increased risk of incident dementia in primary care patients. *J Alzheimers Dis.* 2015;44(4):1203-1212.

66. Ravona-Springer R, Moshier E, Schmeidler J, et al. Changes in glycemic control are associated with changes in cognition in non-diabetic elderly. *J Alzheimers Dis.* 2012;30(2):299-309.

67. Wang F, Zhao M, Han Z, et al. Long-Term Subclinical Hyperglycemia and Hypoglycemia as Independent Risk Factors for Mild Cognitive Impairment in Elderly People. *The Tohoku Journal of Experimental Medicine.* 2017;242(2):121-128.

68. Sanz CM, Ruidavets JB, Bongard V, et al. Relationship between markers of insulin resistance, markers of adiposity, HbA1c, and cognitive functions in a middle-aged population-based sample: the MONA LISA study. *Diabetes Care.* 2013;36(6):1512-1521.

69. Ma F, Wu T, Miao R, Xiao YY, Zhang W, Huang G. Conversion of mild cognitive impairment to dementia among subjects with diabetes: a population-based study of incidence and risk factors with five years of follow-up. *J Alzheimers Dis.* 2015;43(4):1441-1449.

70. Gao L, Matthews FE, Sargeant LA, Brayne C. An investigation of the population impact of variation in HbA1c levels in older people in England and Wales: from a population based multi-centre longitudinal study. *BMC Public Health.* 2008;8:54.

71. Luchsinger JA, Palmas W, Teresi JA, et al. Improved diabetes control in the elderly delays global cognitive decline. *The journal of nutrition, health & aging.* 2011;15(6):445-449.

72. Lehtisalo J, Lindström J, Ngandu T, et al. Diabetes, glycaemia, and cognition—a secondary analysis of the Finnish Diabetes Prevention Study. *Diabetes/metabolism research and reviews.* 2016;32(1):102-110.

73. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol.* 2011;10(11):969-977.

74. Abbatecola AM, Paolisso G. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial: response to Cukierman-Yaffe et al. *Diabetes Care.*32(8):e102; author reply e103.

75. Murray AM, Hsu FC, Williamson JD, et al. ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. *Diabetologia.* 2017;60(1):69-80.

76. Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care.* 2010;33(5):983-990.

77. Strachan MW, Price JF. Diabetes. Cognitive decline and T2DM--a disconnect in the evidence? *Nature Reviews Endocrinology.*10(5):258-260.

78. Lehtisalo J, Lindstrom J, Ngandu T, et al. Diabetes, glycaemia, and cognition-a secondary analysis of the Finnish Diabetes Prevention Study. *Diabetes Metab Res Rev.* 2016;32(1):102-110.

79. Tuligenga RH. Intensive glycaemic control and cognitive decline in patients with type 2 diabetes: a meta-analysis. *Endocrine connections.* 2015;4(2):R16-R24.

80. Penaherrera-Oviedo C, Moreno-Zambrano D, Palacios M, et al. Does Intensive Glucose Control Prevent Cognitive Decline in Diabetes? A Meta-Analysis. *Int J Chronic Dis.* 2015;2015:680104.

81. Luchsinger JA, Ma Y, Christophi CA, et al. Metformin, Lifestyle Intervention, and Cognition in the Diabetes Prevention Program Outcomes Study. *Diabetes Care.* 2017;40(7):958-965.

82. Koekkoek PS, Ruis C, van den Donk M, et al. Intensive multifactorial treatment and cognitive functioning in screen-detected type 2 diabetes--the ADDITION-

Netherlands study: a cluster-randomized trial. *Journal of the Neurological Sciences.*314(1-2):71-77.

83. Kivimäki M, Singh-Manoux A. Prevention of dementia by targeting risk factors. *The Lancet.* 2018;391(10130):1574-1575.

84. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Internal medicine journal.* 2012;42(5):484-491.

85. Roman GC, Sachdev P, Royall DR, et al. Vascular cognitive disorder: a new diagnostic category updating vascular cognitive impairment and vascular dementia. *J Neurol Sci.* 2004;226(1-2):81-87.

86. Feinkohl I, Aung PP, Keller M, et al. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 diabetes study. *Diabetes Care.* 2014;37(2):507-515.

87. Rafnsson SB, Deary IJ, Smith FB, Whiteman MC, Fowkes FG. Cardiovascular diseases and decline in cognitive function in an elderly community population: the Edinburgh Artery Study. *Psychosom Med.* 2007;69(5):425-434.

88. Turner RC, Millns H, Neil HAW, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *Bmj.* 1998;316(7134):823-828.

89. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet Diabetes Endocrinol.* 2015;3(2):105-113.

90. Biessels GJ, Strachan MW, Visseren FL, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. *Lancet Diabetes Endocrinol.* 2014;2(3):246-255.

91. Fan YC, Hsu JL, Tung HY, Chou CC, Bai CH. Increased dementia risk predominantly in diabetes mellitus rather than in hypertension or hyperlipidemia: a population-based cohort study. *Alzheimers Res Ther.* 2017;9(1):7.

92. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. *Nat Rev Endocrinol.* 2011;7(2):108-114.

93. Larsson SC, Markus HS. Does Treating Vascular Risk Factors Prevent Dementia and Alzheimer's Disease? A Systematic Review and Meta-Analysis. *J Alzheimers Dis.* 2018;64(2):657-668.

94. Lesage SR, Mosley TH, Wong TY, et al. Retinal microvascular abnormalities and cognitive decline: the ARIC 14-year follow-up study. *Neurology.* 2009;73(11):862-868.

95. Ding J, Patton N, Deary IJ, et al. Retinal microvascular abnormalities and cognitive dysfunction: a systematic review. *Br J Ophthalmol.* 2008;92(8):1017-1025.

96. Hugenschmidt CE, Lovato JF, Ambrosius WT, et al. The cross-sectional and longitudinal associations of diabetic retinopathy with cognitive function and brain MRI findings: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care.* 2014;37(12):3244-3252.

97. Exalto LG, Biessels GJ, Karter AJ, Huang ES, Quesenberry CP, Jr., Whitmer RA. Severe diabetic retinal disease and dementia risk in type 2 diabetes. *J Alzheimers Dis.* 2014;42 Suppl 3:S109-117.

98. Zhang JB, Geng N, Li ZG, Qiao HJ, Sun HR, Li F. Biomarkers of Renal Function in Type 2 Diabetic Patients with Cognitive Impairment. *Neurosci Lett.* 2016;610:19-23.

99. Murray AM, Barzilay JI, Lovato JF, et al. Biomarkers of renal function and cognitive impairment in patients with diabetes. *Diabetes Care.* 2011;34(8):1827-1832.

100. Buchman AS, Tanne D, Boyle PA, Shah RC, Leurgans SE, Bennett DA. Kidney function is associated with the rate of cognitive decline in the elderly. *Neurology.* 2009;73(12):920-927.

101. Kuo SC, Lai SW, Hung HC, et al. Association between comorbidities and dementia in diabetes mellitus patients: population-based retrospective cohort study. *J Diabetes Complications.* 2015;29(8):1071-1076.

102. Marseglia A, Fratiglioni L, Kalpouzos G, Wang R, Bäckman L, Xu W. Prediabetes and diabetes accelerate cognitive decline and predict microvascular lesions: A population-based cohort study. *Alzheimer's & Dementia.* 2018.

103. Mehta HB, Mehta V, Goodwin JS. Association of Hypoglycemia With Subsequent Dementia in Older Patients With Type 2 Diabetes Mellitus. *J Gerontol A Biol Sci Med Sci.* 2017;72(8):1110-1116.

104. De Galan BE, Zoungas S, Chalmers J, et al. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. *Diabetologia.* 2009;52(11):2328-2336.

105. Punthakee Z, Miller ME, Launer LJ, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care.* 2012;35(4):787-793.

106. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. *Lancet.* 2010;375(9713):481-489.

107. Feinkohl I, Price JF, Strachan MW, Frier BM. The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. *Alzheimers Res Ther.* 2015;7(1):46.

108. Veeranki SP, Downer B, Jupiter D, Wong R. Arthritis and Risk of Cognitive and Functional Impairment in Older Mexican Adults. *J Aging Health.* 2017;29(3):454-473.

109. Luijks H, Schermer T, Bor H, et al. Prevalence and incidence density rates of chronic comorbidity in type 2 diabetes patients: an exploratory cohort study. *BMC Med.* 2012;10:128.

110. Katon W, Pedersen HS, Ribe AR, et al. Effect of depression and diabetes mellitus on the risk for dementia: a national population-based cohort study. *JAMA psychiatry.* 2015;72(6):612-619.

111. Santos CY, Snyder PJ, Wu WC, Zhang M, Echeverria A, Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. *Alzheimers Dement (Amst).* 2017;7:69-87.

112. McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. *The Lancet.* 2012;379(9833):2291-2299.

113. Ding J, Strachan MWJ, Reynolds RM, et al. Diabetic retinopathy and cognitive decline in older people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetes.* 2010.

114. Sullivan MD, Katon WJ, Lovato LC, et al. Association of depression with accelerated cognitive decline among patients with type 2 diabetes in the ACCORD-MIND trial. *JAMA Psychiatry.* 2013;70(10):1041-1047.

115. Zhang X, Cai X, Shi X, et al. Chronic Obstructive Pulmonary Disease as a Risk Factor for Cognitive Dysfunction: A Meta-Analysis of Current Studies. *J Alzheimers Dis.* 2016;52(1):101-111.

116. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort profile: The health and retirement study (HRS). *International journal of epidemiology.* 2014;43(2):576-585.

117. Juster FT, Suzman R. An overview of the Health and Retirement Study. *Journal of Human Resources.* 1995:S7-S56.

118. Weir D, Faul J, Langa K. Proxy interviews and bias in the distribution of cognitive abilities due to non-response in longitudinal studies: a comparison of HRS and ELSA. *Longitudinal and life course studies.* 2011;2(2):170.

119. RAND HRS Longitudinal File 2014 (V2). Produced by the RAND Center for the Study of Aging, with funding from the National Institute on Aging and the Social Security Administration. Santa Monica, CA. In:2018.

120. Health and Retirement Study, RAND HRS 2002 Fat File (V2C) . public use dataset. Produced and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740). Ann Arbor, MI, (2002). In:2002.

121. Brandt J, Spencer M, Folstein M. The telephone interview for cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol.* 1988;1(2):111-117.

122. Crimmins EM, Kim JK, Langa KM, Weir DR. Assessment of cognition using surveys and neuropsychological assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences.* 2011;66(suppl 1):i162-i171.

123. Langa KM, Kabeto M, Weir D. Report on race and cognitive impairment using HRS in, 2010 Alzheimer's disease facts and figures 2010. *Alzheimer's Disease Facts and Figures.* 2010.

124. Wu Q, Tchetgen EJT, Osypuk TL, White K, Mujahid M, Glymour MM. Combining direct and proxy assessments to reduce attrition bias in a longitudinal study. *Alzheimer disease and associated disorders.* 2013;27(3):207.

125. Weir DR. Health and Retirement Study Imputation of Cognitive Functioning Measures. 2017.

126. Steffick DE. Documentation of affective functioning measures in the Health and Retirement Study. *Ann Arbor, MI: University of Michigan.* 2000.

127. Rist PM, Marden JR, Capistrant BD, Wu Q, Glymour MM. Do physical activity, smoking, drinking, or depression modify transitions from cognitive impairment to functional disability? *Journal of Alzheimer's Disease.* 2015;44(4):1171-1180.

128. Moldoff M, Meijer E, Chien S, et al. RAND HRS income and wealth imputation, Version M. *Rand Center for the Study of Aging.* 2013.

129. Jenkins KR, Ofstedal MB, Weir D. Documentation of health behaviors and risk factors measured in the Health and Retirement Study (HRS/AHEAD). *Ann Arbor, MI: Survey Research Center, University of Michigan.* 2008.

130. Valeri L, VanderWeele TJ. eAppendix for:" SAS macro for causal mediation analysis with survival data".

131. VanderWeele TJ. Causal mediation analysis with survival data. *Epidemiology.* 2011;22(4):582-585.

132. Valeri L, VanderWeele TJ. Mediation analysis allowing for exposure–mediator interactions and causal interpretation: Theoretical assumptions and

implementation with SAS and SPSS macros. *Psychological methods.* 2013;18(2):137.

133. Pearl J. Interpretation and identification of causal mediation. *Psychological methods.* 2014;19(4):459.

134. Pearl J. Direct and indirect effects. 2001.

135. VanderWeele TJ. A Three-way Decomposition of a Total Effect into Direct, Indirect, and Interactive Effects. *Epidemiology (Cambridge, Mass).* 2013;24(2):224-232.

136. So Y, Lin G, Johnston G. Using the PHREG procedure to analyze competing-risks data. 2014.

137. 2. Classification and Diagnosis of Diabetes. *Diabetes Care.* 2016;39 Suppl 1:S13-22.

138. Mayeda ER, Whitmer RA, Yaffe K. Diabetes and cognition. *Clinics in geriatric medicine.* 2015;31(1):101-115.

139. Geijselaers SL, Sep SJ, Stehouwer CD, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. *Lancet Diabetes Endocrinol.* 2015;3(1):75-89.

140. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors. *Diabetes care.* 2009;32(2):221-226.

141. Yaffe K, Falvey C, Hamilton N, et al. Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. *Arch Neurol.* 2012;69(9):1170-1175.

142. Christman AL, Matsushita K, Gottesman RF, et al. Glycated haemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia.* 2011;54(7):1645-1652.

143. Murray AM, Hsu FC, Williamson JD, et al. ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. *Diabetologia.* 2016.

144. Health and Retirement Study. 2003 Diabetes Study, Version 2.0. (Sensitive Health Data) Data Description and Usage. Available at: hrsonline.isr.umich.edu/meta/diabetes/desc/diab2003dd.pdf . Published Apr,2007. Accessed ،April,11, 2017.

145. Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW. Diabetes and Cognitive Impairment. *Curr Diab Rep.* 2016;16(9):87.

146. Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA. Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. *Ann Intern Med.* 2018.

147. Dignam JJ, Zhang Q, Kocherginsky MN. The use and interpretation of competing risks regression models. *Clinical Cancer Research.* 2012:clincanres-2097.

148. Lee S, Buring JE, Cook NR, Grodstein F. The Relation of Education and Income to Cognitive Function among Professional Women. *Neuroepidemiology.* 2006;26(2):93-101.

149. Lee S, Kawachi I, Berkman LF, Grodstein F. Education, Other Socioeconomic Indicators, and Cognitive Function. *American Journal of Epidemiology.* 2003;157(8):712-720.

150. Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Archives of neurology.* 2009;66(3):336-342.

151. Gould CE, Beaudreau SA, Salman H. Diabetes is associated with cognitive impairment no dementia in the Aging, Demographics, and Memory Study (ADAMS). *International Psychogeriatrics.*25(1):167-168.

152. Roberts RO, Knopman DS, Przybelski SA, et al. Association of type 2 diabetes with brain atrophy and cognitive impairment. *Neurology.* 2014:10-1212.

153. Crane PK, Walker R, Hubbard RA, et al. Glucose levels and risk of dementia. *N Engl J Med.* 2013;369(6):540-548.

154. Pappas C, Andel R, Infurna FJ, Seetharaman S. Glycated haemoglobin (HbA1c), diabetes and trajectories of change in episodic memory performance. *J Epidemiol Community Health.* 2017;71(2):115-120.

155. Williamson JD, Miller ME, Bryan RN, et al. The Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND): rationale, design, and methods. *Am J Cardiol.* 2007;99(12a):112i-122i.

156. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *Bmj*. 2011;343:d6898.

157. Van den Berg E, Kloppenborg RP, Kessels RPC, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: a systematic comparison of their impact on cognition. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease.* 2009;1792(5):470-481.

158. De Rekeneire N, Peila R, Ding J, et al. Diabetes, hyperglycemia, and inflammation in older individuals: the health, aging and body composition study. *Diabetes care*. 2006;29(8):1902-1908.

159. Centers for Disease Control and Prevention (CDC). Leading Causes of Death. In. *Health United States, 2016*2016.

160. Pendergrass JC, Targum SD, Harrison JE. Cognitive Impairment Associated with Cancer: A Brief Review. *Innovations in Clinical Neuroscience.* 2018;15(1-2):36-44.

161. Ren H, Wang Z, Mao Z, et al. Hearing Loss in Type 2 Diabetes in Association with Diabetic Neuropathy. *Archives of Medical Research.* 2017;48(7):631-637.

162. Kakarlapudi V, Sawyer R, Staecker H. The effect of diabetes on sensorineural hearing loss. *Otol Neurotol.* 2003;24(3):382-386.

163. Anstey KJ, Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. *The American journal of Geriatric psychiatry.* 2009;17(7):542-555.

164. Cain KC, Harlow SD, Little RJ, et al. Bias Due to Left Truncation and Left Censoring in Longitudinal Studies of Developmental and Disease Processes. *American Journal of Epidemiology.* 2011;173(9):1078-1084.

Vita

Ola Ali Soudah was born in Dubai, United Arab Emirates in 1983 to Ali Saleh Soudah and Amal Ismael Zwawi. She grew up in Al-Ain, United Arab emirates and graduated from Al-Mereejib Secondery School in 2001. Then she obtained her bachelor's degree in Medical Laboratory Sciences and Master's degree in Diagnostic Molecular Biology and Human Genetics from Jordan University of Science and Technology (JUST), Jordan. She worked as medical technologist at King Abdullah University Hospital (KAUH) for 4 years before she left Jordan. In 2011, she came to United States with her husband and from there she pursued her studies in Clinical Sciences at University of Texas Medical Branch.

Permanent address: Faculty of Medicine, Yarmouk University, Irbid, Jordan. P.O.Box 566. ZIP code 21163.

This dissertation was typed by Ola A. Soudah.