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Diabetes, Cognitive Decline, and Alzheimer's Disease: The Cache County Study on Memory, Health, and Aging

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DIABETES, COGNITIVE DECLINE, AND ALZHEIMER'S DISEASE: THE CACHE COUNTY STUDY ON MEMORY, HEALTH, AND AGING

by

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ABSTRACT

Diabetes, Cognitive Decline, and Alzheimer's Disease:

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Studies have reported mixed results for people with or without diabetes with cognitive decline or Alzheimer's disease (AD). Cognitive decline and AD among people with diabetes will be the focus of much discussion since results have been controversial.

The study examined whether diabetes is associated with cognitive decline and whether it is an independent risk factor for the development of AD among elderly residents of Cache County, Utah.

Results revealed an association between diabetes and a lower average Modified Mini Mental State Examination (3MS) score of nearly a point lower at baseline. Results also showed an association between diabetes and an increased risk of incident AD compared with non-diabetes for men but not for women. The interaction between diabetes, gender, and risk of AD should be explored further.

(85 pages)

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CHAPTER 1

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INTRODUCTION

Type 2 diabetes mellitus, the most common metabolic disorder, is highly associated with family history of diabetes, older age, obesity, and lack of exercise.[1] Its prevalence also increases with age.[2] Ninety percent to 95 percent of the people who have been diagnosed with type 2 diabetes mellitus usually develop the disease beyond age 20.[3]

Cognitive impairment represents a major public health burden: it has adverse psychosocial and economic consequences for affected person and their families and is a risk factor for increased home health care use, hospitalization, nursing home entry, and mortality.[4] Progressive loss of memory and other cognitive abilities is one of the most common problems affecting older person.[5, 6] Furthermore, since cognitive impairment is associated with significant morbidity and mortality, the identification of modifiable risk factors for cognitive decline is a major public health priority.[5]

Alzheimer's disease (AD) is the most common cause of dementia in elderly in elderly patients, accounting for 50% to 70% of all cases and more than 100,000 deaths annually.[7, 8]

The prevalence for diabetes increases with increasing age. More than 10 percent of the elderly suffer from diabetes.[9-11] When combined with dementia, the two are the most prevalent problems found in the elderly.[9] More than 10 percent of people over the age of 65 years develop dementia, and its prevalence increases to more than 50 percent for people over the age of 85.[8, 9, 12]

STUDY OBJECTIVES

Given the increased interest in research in this area, cognitive decline and AD among people with diabetes will be the focus of much discussion and debate. The present study was conducted to examine whether:

1. diabetes was independently associated with level of cognitive function as measured by the Modified Mini Mental State Examination (3MS) at baseline,
2. whether diabetes was independently associated with a decline in cognitive function, as measured by change in the 3MS score between baseline and at three follow-up interviews from a large population-based study, and
3. whether diabetes mellitus is an independent risk factor for the development of AD.

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CHAPTER 2

DIABETES MELLITUS, COGNITIVE DECLINE, AND ALZHEIMER'S DISEASE IN THE ELDERLY: A REVIEW

ABSTRACT

Diabetes mellitus, a common chronic disease characterized by high blood sugar due to total or relative impairment in insulin production, secretion, and action, is a major public health problem. Diabetes has been closely associated with numerous health problems, with cognitive impairment being one of them. Exactly how diabetes affects brain function is still unclear. Insulin crosses the blood-brain barrier and enters the brain via receptor-mediated active transport system. These receptors are widely distributed in the brain but their density decrease with advancing age. The possible association between diabetes and cognitive decline suggests that diabetes may also contribute to Alzheimer's disease. However, in some studies, the role of diabetes in cognitive decline remains controversial, with conflicting results from case-control, cross-sectional, and prospective studies. The probable associations between diabetes and risk of Alzheimer's disease in case-control, cross-sectional, and prospective studies also give conflicting results.

DIABETES

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin production, secretion, and action.[1] Several processes are involved in the development of diabetes mellitus. These range from autoimmune destruction of the β-cells of the pancreas with consequent absolute insulin deficiency (type 1) to abnormalities that result in resistance to insulin action (type 2).[1]

Type 1 diabetes mellitus usually occurs during early childhood or early teenage years, though less common, adults can develop type 1 as well.[2] Over 95 percent of the people who have been diagnosed with type 1 usually develop the disease before age 25.[3] People with type 1 do not produce enough insulin therefore they require daily insulin injections to maintain their insulin level.

Type 2 diabetes mellitus, the most common metabolic disorder, is highly associated with family history of diabetes, older age, obesity, and lack of exercise.[3] Its prevalence also increases with age.[4] Ninety percent to 95 percent of the people who have been diagnosed with type 2 diabetes mellitus usually develop the disease beyond age 20.[2]

Often, people don't know they have diabetes until their doctor tells them. Sometimes, the signs and symptoms do not exhibit themselves until much later, as in the case for type 2. Generally, the classic symptoms of diabetes are frequent thirst and increased urination. Other symptoms include hunger, unexplained weight loss or gain, flulike symptoms, including weakness and fatigue, blurred vision, irritability, slow-healing cuts or bruises, tingling or loss of feeling in hands or feet, recurring infections of gum or skin, and recurring vaginal or bladder infections.[2]

The number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity.[5] The number of cases of diabetes worldwide in 2000 among adults ≥ 20 years of age is approximately 171 million.[5] By the year 2030, it is projected that diabetes will rise to 366 million worldwide.[5] In developing countries, the majority of people with diabetes are in the 45- to 64- year age range, whereas, the majority of people with diabetes in developed countries are greater than 64 years of age.[5]

Diabetes affects between 6 percent and 7 percent of the U.S. population equating to about 17 million people.[6, 7] Fifteen to 16 million of these people have type 2 diabetes.[8] It is projected that there will be 800,000 new cases per year and a total of 23 million affected people within 10 years.[9] Increases were observed in both sexes, all ages, all ethnic groups, all educational levels, and in nearly all states (43 states).[7]

Diabetes and its complications are a significant cause of morbidity and mortality in the U.S accounting for more than 193,000 deaths in 1997.[6, 7, 10] Although deaths due to cancer, stroke, and cardiovascular disease are declining, the death rates due to diabetes have increased by about 30% in the past 12 years and life expectancy for persons with diabetes is approximately 15 years less than in those who do not have diabetes.[6] The major cause of death in individuals with type 2 is macrovascular disease (coronary artery, cerebrovascular and peripheral vascular), which accounts for at least two-thirds of type 2 diabetes-associated mortality.[11] Diabetes is proving itself to be clearly a growing public health threat in the U.S.[12]

COGNITIVE DECLINE

The study of cognitive function among older persons is usually thought of as having several components that focus on the areas of cognition most affected by common dementing illnesses, including memory, attention, language, visuospatial ability, and abstraction.[13] Cognitive function is generally defined as the functional components of cognition (attention, memory, learning, thinking, language, and visuospatial function).[14] It embraces the quality of knowing and thinking which includes all aspects of perception; recognition, conception, sensing, thinking, learning, comprehension, orientation, attention, reasoning, remembering and imagining.[15, 16]

Cognitive performance is an important indicator of health and functioning in elderly people and the ability to maintain cognitive function into old age is agreeably desired by most, if not all.[17] For most elderly, maintaining cognitive function is just as important in determining the quality of life in their later years as every other aspect of health. However, if or when cognitive function starts to decline, it can bring upon a degree of distress on the individual or the caregiver. The loss of cognitive function can range from simple memory deficit to profound dementia, such as AD or vascular dementia.[18] The causes of age-related cognitive decline are unknown, but some studies have suggested that it may be avoidable.[18] Therefore, a major challenge for investigators is to understand the extent to which cognitive dysfunction is preventable and, once cognitive decline has started, the degree to which it is reversible.[18]

Cognitive decline is worthy of study, both as an important outcome in its own right, and because of what it may tell us about future risk for dementia.[19] It is associated with a significant public health burden, as shown by strong associations with mortality.[20]

Cognitive impairment represents a major public health burden: it has adverse psychosocial and economic consequences for affected person and their families and is a risk factor for increased home health care use, hospitalization, nursing home entry, and mortality.[21] Progressive loss of memory and other cognitive abilities is one of the most common problems affecting older person.[22, 23] Furthermore, since cognitive impairment is associated with significant morbidity and mortality, the identification of modifiable risk factors for cognitive decline is a major public health priority.[22]

ALZHEIMER'S DISEASE

Among the elderly, dementing illnesses and their consequences are pressing concerns.[24] The World Health Organization (WHO) describe dementia as:[25] "a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment. Consciousness is not clouded. Impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation. This syndrome occurs in Alzheimer's disease (AD), in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain." Alzheimer's disease (AD) is the most common cause of dementia in elderly in elderly patients, accounting for 50% to 70% of all cases and more than 100,000 deaths annually.[26, 27]

AD, a degenerative brain disorder, is characterized by neuronal and synaptic degeneration, an increase in numbers of senile plaques and neurofibrillary tangles compared with non-demented individuals of the same age, decreased cholinergic

transmission and memory impairment, and progressive deterioration of cognitive function.[28, 29] Other description of AD is that it is also an irreversible, progressive brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks.[30] These losses are related to the breakdown of the connections between nerve cells in the brain and the eventual death of many of these cells.[31] The illness gradually progresses until, often after a decade or more, the individual is unable to speak or comprehend language, no longer controls his or her bowels, and requires assistance with all aspects of personal care.[29]

Current AD research have examined risk factors of AD and these risk factors are identified and categorized as non-modifiable (advanced age, family history, and genetic predisposition) and modifiable risk factors for AD (head injury, low education, cognitive inactivity, fat intake, high serum cholesterol, vascular disease, hypertension, diabetes, high homocysteine levels, estrogen, non-steroidal anti-inflammatory drugs, and metal exposure).[32]

There were a number of prevalence surveys conducted on dementia throughout the world. Some reports give slightly different results depending on the ages of the subjects sampled, methods of determining the presence, severity, and type of cognitive impairment and the regions or countries studied.[33] However, one thing they have in common—they show a steady rise in the prevalence of dementia with age. Thus, 1.4% of those aged 65-69 manifest a dementia syndrome, 2.8% of those aged 70-74, 5.6% of individuals aged 75-79, 11.1% of those aged 80-84, and 23.6% of those aged 85 and older.[34]

Data on the prevalence of dementia in less developed countries (ie. all regions of Africa, Asia [except Japan], Latin America, and the Caribbean, plus Melanesia, Micronesia, and Polynesia) is limited. Two studies from India and China revealed similar prevalence rates for dementia with the more developed countries (ie. Europe, Northern America, Australia/New Zealand, and Japan), but dementia is quite rare in Kashmir and among the Cree tribe of native American Indians.[35-38] Since very little is known about prevalence of dementia in the less developed countries, it is difficult to estimate the number of cases of dementia in the world.[39] However, it is possible to make an estimate for the more developed countries.[39]

In 1990, the United Nations (UN) reported the population of the more developed countries at 1,148 million, of which 144 million were aged 65 and over.[40] Based on current population projections, the UN estimates that by 2050 the number of individuals over 65 will increase to 1,181 million worldwide, of which 316 million will be aged 65 and over. Applying prevalence rates for various age groups by Jorm,[34] we arrive at an estimate of 7.4 million people with dementia in 1990.[39] By 2050, the number of individuals with dementia will reach 37 million people.[41] Now, since AD represents a major public health problem for more developed countries, it generally makes up the majority of dementia cases in these countries as well. We could estimate that more than half of these people would have AD (ie. at least 18.5 million people) by 2050.

In the U.S., there is growing concern and recognition that as the population ages, AD will place an enormous burden on the country because, not only is the cost of care for AD a financial one, it has such a huge impact on individuals, families, the health care system, and society it places great emotional and physical stress as they cope with the

physical and mental changes in their loved ones.[30, 42, 43] More than 34 million people are now age 65 or older,[30] which represents 13 percent of the total population of the U.S. In addition, the group of people over 85—the group with the highest risk of AD—is the fastest growing segment of the population.[30] In 1997, the prevalence of AD in the U.S. was 2.32 million.[42] Of these, approximately 68 percent were female and 32 percent were male. In 2000, there were 4.5 million persons with AD. By 2050, this number will increase by almost 3-fold, to approximately 14 million—if the current numbers hold and no preventive treatments become available.[44] However, from an interesting point of view of intervention, according to estimates in the U.S., delaying mean onset of AD by approximately 5 years correspond to a 50% reduction in risk, and would reduce the expected prevalence by 1.15 million people after 10 years (by 2007) and 4.04 million people after 50 years (by 2047).[42] If interventions could delay onset of the disease by 2 years, after 50 years there would be 1.94 million fewer cases than projected; if onset could be delayed by 1 year, there would be nearly 800,000 fewer prevalent cases.[42] This is a huge public health implication.

DIABETES MELLITUS, COGNITIVE DECLINE, AND ALZHEIMER'S DISEASE

The prevalence for diabetes increases with increasing age. More than 10 percent of the elderly suffer from diabetes.[9, 10, 45] When combined with dementia, the two are the most prevalent problems found in the elderly.[45] More than 10 percent of people over the age of 65 years develop dementia, and its prevalence increases to more than 50 percent for people over the age of 85.[27, 45, 46]

Cognitive impairment or decline among people with diabetes is the focus of much discussion and debate. Several longitudinal studies have demonstrated an association between history of diabetes and cognitive deficits[47, 48] and dementia.[49-51] The association between diabetes and AD is not so obvious, although a role for advanced glycated-end products (AGEs) in the pathogenesis of AD has been hypothesized.[52] AGEs are sugar-derived protein modifications formed through a series of non-enzymatic glycosylation reactions that are resistant to protease degradation.[53] AGEs have been detected in abundance in plaques and extracellular neurofibrillary tangles from AD brains.[53, 54] In diabetes mellitus, accelerated AGEs formation is likely a result of elevated circulating glucose.[53] The purpose of this paper is to review literature surrounding the probable associations between diabetes and the risk for cognitive decline and AD.

MECHANISMS OF ACTION: ROLE OF GLUCOSE AND INSULIN ON THE BRAIN

Glucose is the main metabolic fuel of the brain.[55] Because neurons in the brain are unable to store or synthesize glucose, brain glucose is obtained through the systemic circulation and subsequently transported across the blood-brain barrier.[56] Given the dependence of the brain on systemically supplied glucose, it is not surprising that conditions that affect glucose regulation, utilization, and metabolism may also affect cognitive function.[56]

Several studies have reported the memory-enhancing effects of glucose in animals and humans.[57-59] These studies suggests that circulating blood glucose levels modulate learning and memory processes and that this modulating action may be a natural memory-enhancing mechanism in many situations.[60] Evidence also suggests that a

primary disruption in glucose regulation accompanies AD and contributes to the severe memory impairment that is a hallmark of the disorder.[56] Positron Emission Tomography (PET) have been used by many studies to document reduced glucose metabolism in AD, particularly in the temporo-parietal and frontal association areas.[61]

Insulin, the primary modulator of glucose homeostasis, peripherally wears several hats in the central nervous system (CNS), including that of glucose metabolism, neurotrophic, signal transduction, and neuroendocrine functions.[62] Insulin, insulin receptors and insulin-sensitive glucose transporters (GLUTs) have been identified in the medial temporal structures, which support memory but are compromised early in the course of AD.[63] Furthermore, insulin has been shown to contribute to the regulation of β-amyloid (Aβ), a primary constituent of the senile plaques that characterize AD neuropathology.[63]

Until recently, the brain was not thought to be an insulin-sensitive organ.[63] For many years, insulin was considered to be incapable of crossing the blood-brain barrier, and therefore to be without impact on the brain.[64] Studies have now shown that insulin is transported into the central nervous system across the blood-brain barrier by a saturable, insulin receptor-mediated transport process.[63, 65-67] Although insulin and insulin receptors are abundant in the brain, they are selectively distributed, particularly in the cortex and hippocampus.[63, 64] In neurons, the binding of insulin to its receptor initiates tyrosine kinase mediated intracellular signaling.[53, 68] Frolich studied brain tissue samples from 21 subjects with AD compared with 8 middle-aged controls and 13 matched controls and found that their brain insulin concentration and insulin receptor densities both decrease with age, with tyrosine kinase reduced among the AD patients.[53, 69] In mice, disruptions

of the insulin receptor tyrosine kinase signaling leads to an accumulation of phosphorylated Tau in the hippocampus.[53, 70] Disruption of the insulin receptor or its signal transduction might then contribute to the development of Tau abnormalities and neurofibrillary tangles and account for the shared risk of AD and type 2 diabetes mellitus.[53]

Type 2 diabetes mellitus is the product of two abnormalities: insulin resistance (reduced ability of insulin to stimulate glucose utilization) and an insufficient compensatory insulin secretory response.[63] Insulin resistance, common among older adults, may lead to both peripheral and central nervous system changes that affect cognitive functioning.[63] In the CNS, the distribution of insulin, insulin receptors and insulin-sensitive GLUTs suggests that insulin resistance may alter glucose metabolism in selective brain regions, including those of the hippocampus and hypothalamic-pituitary-adrenal (HPA) axis, which support memory and regulate cortisol. Increase evidence supports the notion that insulin abnormalities may contribute to cognitive and neuropathological changes in patients with AD **(TABLE 2.1).**

ANIMAL AND HUMAN STUDIES

Evidence gathered from studies conducted approximately a decade ago indicated that modest increases in circulating glucose levels enhance the formation of new memories in rodents and humans.[57-59] In rats, systemic injections of glucose enhance learning and memory under many conditions.[57] Ragozzino et al demonstrated that acetylcholine (ACh) output in the hippocampal formation of rats is increased during spontaneous alternation testing in a cross maze, that glucose augments ACh output in the hippocampal formation under behavioral testing conditions, and that glucose enhances

spontaneous alternation performance in a four-arm maze. ACh is believed to play a role in learning and memory. The result of that study suggest that increased release of ACh in the hippocampal formation may contribute to glucose enhancement of memory on the cross maze, either by direct or indirect effects of glucose.[58] Studies that were conducted in humans have revealed similar results. A cross-sectional study suggested that diabetes, as well as impaired glucose tolerance and hyperinsulinaemia in non-diabetic subjects was associated with cognitive impairment.[71] A double-blind study by Messier et al.[72] measured the intake of glucose (50 g) among individuals. Their results showed that glucose improved the performance of cognitive tests for males.

CASE-CONTROL STUDIES: DIABETES AND COGNITIVE IMPAIRMENT

Two case-control studies reported significantly higher cognitive impairment among diabetics (cases) when compared to non-diabetics (controls) whereas one study found no significant differences among diabetic and control groups.[73-75] Asimakopoulou et al found evidence of limited cognitive dysfunction among people with uncomplicated type 2 diabetes mellitus (as diagnosed by a diabetes consultant) as evidenced by difficulties in remembering verbal logical sequences in the short term. However, after controlling for hypertension and cerebrovascular disease, Mukit et al later found no significant association between diabetes (blood sample collected and diagnosed according to WHO criteria). Both studies had few cases and controls, therefore the study sample size was too small to make any appropriate inferences. In addition, the study by Mukit was entirely conducted among males only. Cosway wanted to determine whether uncomplicated type 2 diabetes mellitus (ascertained through medical records) is

associated with impairment of cognitive function and information processing ability. The study found no significant differences in any are of cognitive functioning or information processing between the groups of patients with type 2 diabetes mellitus and non-diabetic controls.[75] It should be noted that the mean age of the diabetic cases and the non-diabetic controls were relatively low (57.7 and 55.9 years, respectively) than most studies.

CROSS-SECTIONAL STUDIES: DIABETES AND COGNITIVE IMPAIRMENT

Results from this type of study revealed contradicting findings.[71, 76-79] Two studies found significant association between diabetics and cognitive impairment while three studies found no association as to whether diabetics were at risk of developing cognitive impairments.

The Dutch study[71] found that diabetics had a rate ratio (rate ratio of the number of erroneous answers given on the MMSE by the index compared to the reference group) of 1.23 (95% CI: 1.04-1.46) which suggest that diabetics (as defined by oral glucose tolerance test and diagnosed with the WHO criteria) were associated with cognitive impairment. The study by Worrall et al.[78] found that diabetics had significantly poorer scores on two tests of cognitive function. However, the Worrall study did not specify how diabetic subjects were identified.

The studies by Ryan et al.,[76] Vanhanen et al.,[77] and Robertson-Tchabo et al.[79] showed no association between diabetics and cognitive decline. Ryan's study was conducted among middle-aged predominantly healthy individuals. Adults with type 2 diabetes mellitus were recruited from a diabetes research subject registry. The method for recruiting non-diabetic comparison subjects was by asking participants (diabetics) to

bring a non-diabetic friend or family member with them. This, however, could lead to selection bias. The Finnish study by Vanhanen showed an interesting contrast. They found that women with diabetes (as defined by oral glucose tolerance test and diagnosed according to the WHO criteria) performed better than the non-diabetic women in the MMSE. However, the study pointed out that cognitive impairment was found among diabetic women in the Trail-Making tests parts A and C. They explained that perhaps this could be a reflection of mildly affected frontal lobe/executive functions. The results of the Baltimore Longitudinal Study of Aging conducted by Robertson-Tchabo does not support the position that cognitive performance is poorer in men with type 2 diabetes mellitus. This type of study is subject to survivor bias; that is, those men who live and return for repeated measures generally were better performers at the first time of measurement, whereas those who did not return would have succumbed to illnesses.

PROSPECTIVE STUDIES: DIABETES AND COGNITIVE IMPAIRMENT

Prospective studies do have their share of contradicting results.[47, 48, 80-87] Studies by Rodriguez-Saldana et al.[82] and Scott et al.[86] showed no strong or consistent association between diabetics and cognitive decline. The study of older Mexicans by Rodriquez-Saldana did not find any difference among diabetics (diagnosis based on fasting blood glucose, self-report, and anti-diabetic drug use) and non-diabetics in cognitive decline. An interesting observation about this study was that the study population was heterogeneous (composed primarily of professionals). They reportedly received higher level of health care than the general population, which may lead to a form of survival bias. As mentioned above, the Rancho Bernardo Study by Scott did not show any

association between diabetics (upon confirmation of blood test, subjects were classified as diabetics according to the WHO criteria for fasting plasma glucose, post-challenge plasma glucose, or a history of diabetes as diagnosed by a doctor). The authors suggested that their results should be "reassuring" to older adults and to those recently diagnosed as diabetics. However, it is important to note that the Rancho Bernardo study subjects had a higher social economic status within their community.

The remaining referenced prospective studies have significant associations between diabetics and cognitive decline. The Nurses' Health study conducted by Logroscino[80] identified diabetics if they had been diagnosed by a doctor before the baseline cognitive interview. Since this study was conducted among nurses, it was thought to represent a more "health-conscious" group, but that assumption was not necessarily the case. In fact, the relative homogeneity of the sample in terms of social economic status and their accessibility to health care should help minimize confounders. This study examined the association of type 2 diabetes with baseline cognitive function and cognitive decline over two years of follow-up on women living in the community and on the effects of treatments for diabetes. They found that women with type 2 diabetes had increased odds of poor cognitive function and substantial cognitive decline compared with women without diabetes on the telephone interview of cognitive status (OR: 1.34; 95% CI: 1.14-1.57) and the global composite score (OR: 1.26; 95% CI: 1.06-1.51). In addition, the study also found that women not taking medication for diabetes or those taking insulin had worse cognitive performance. This seem to be consistent with results from other studies of cognition.[47, 48] A major strength of this study was the large sample size. Published three years prior to Logroscino's study, another Nurses' Health Study by

Grodstein[85] reported that diabetes (confirmed or probable diagnoses based on information collected were ascertained and compared with medical records) was related to lower scores on several aspects of cognitive function. They also discovered that longer duration of diabetes may be associated with poorer scores, but hypoglycemic therapy may ameliorate scores. The main difference between the Logroscino's study and Grodstein's study was that the former had over 18,000 subjects participating in the study whereas the later had a little over 2,000 subjects. The SALSA study by Wu[81] found that baseline diabetes (diabetes was ascertained using a combination of self-report of a doctor's diagnosis, drug use, and fasting plasma glucose) was a significant predictor of major cognitive impairment in 3MS and word-list test. The Hispanic elderly study by Nguyen[83] found that people with diabetes (self-report doctor diagnosed diabetes) had an odds ratio of 1.45 (95% CI: 1.04-2.01) and had an increased risk for cognitive decline. The EVA French study by Fontbonne[84] found that after 4 years, diabetic subjects (self-reported diabetes as well as diagnosed by fasting blood glucose) had a lower performance on all cognitive tests, except for the MMSE. The Women's Osteoporotic Fracture study by Gregg[48] found that diabetes (self-report of physician's diagnosis and age at diagnosis) was associated with lower level of cognitive function and greater cognitive decline among older women. The Framingham study by Elias[47] reported that history and duration of diabetes (self-report of physician's diagnosis) were significant risk factors for poor cognitive performance. The Framingham study is one of the oldest and active on-going study available which adds to the power of the results.

CASE-CONTROL STUDIES: DIABETES AND AD

Four case-control studies reported relatively low rates of diabetes in patients with AD.[88-91] Nielson wanted to determine whether diabetes was rare in AD relative to other types of dementia and whether diabetics (ascertained by medical history records) with dementia had a low frequency of the Apolipoprotein-E E4 genotype. The study found diabetes to be rare among AD patients (0.8%) relative to vascular dementia (11.8%), mixed vascular/AD dementia (8.8%), and "other" dementia patients (8.8%).[88] Mortel conducted a study to determine relative contributions of first-degree familial and individual risk factors to clinical manifestations of two major age-related dementias. The study reported that among AD and ischemic vascular dementia subject, 6% and 23% respectively, had diabetes. A Swedish study by Landin tested possible differences between patients with AD and patients with other forms of dementia and the healthy population concerning body composition, blood pressure, metabolic data and leukoaraiosis (white matter lesions).[90] The study found no cases of diabetes in the AD group while the prevalence was 21% and 36% for diabetes in the unspecified dementia and vascular dementia groups. It is also worth noting that the study subjects included seventy-one patients. Wolf-Klein conducted an interesting observation from their study sample in New York. The study observed that Alzheimer patients appeared to have fewer physical ailments and medical problems than other patients in that particular geriatric care center. The study found less heart disease, cerebrovascular disease, hypertension, and diabetes mellitus (one person) among patients with AD than in either the normal or the abnormal non-Alzheimer groups.[91] This study brings into question the issue of survival bias. It seems that the Alzheimer patients studied represented the

healthier surviving population and that those who had more medical problems had died before they had ever been enrolled into the study.

CROSS-SECTIONAL STUDY: DIABETES AND AD

A cross-sectional study by Kuusisto reported a positive association between diabetes and AD.[92] This Finnish study determined the association between features of the insulin resistance syndrome and AD. The study analyzed the association between AD and hyperinsulinemia (defined as the highest insulin quintile >89.4 pmol/l) in non-diabetic subjects. It was reported that among subjects without the e4 allele (n=532) hyperinsulinemia was associated with an increased risk for AD (the prevalence of AD in hyperinsulinemic versus nomoinsulinemic subjects was 7.5% and 1.4%, respectively).

PROSPECTIVE STUDIES: DIABETES AND AD

The Religious Orders Study (the study of Catholic nuns, priests, and brothers) by Arvanitakis[87] discovered that using a proportional hazards model adjusted for age, sex, and educational level, those with diabetes (reported taking anti-diabetic drugs, self-report diabetes diagnosis, or both) had a 65 percent increase in the risk of developing AD compared with those without diabetes mellitus (hazard ratio, 1.65; 95% CI: 1.10-2.47). A major strength of the study was that the study included the availability of a mean of 5.5 years of follow-up data with annual structured evaluations. In another study of older Mexican Americans (SALSA study), Haan found that risk of dementia was nearly eight times higher among subjects with both type 2 diabetes and stroke.[93] Diabetes was ascertained by determining use of diabetic medication (obtained by medicine chest inventory at the interview), self-report of a physician's diagnosis, or fasting glucose of

126 mg/dL or greater. Forty-three percent of dementia was attributable to type 2 diabetes, stroke, or a combination of the two. An interesting observation about this study was that few cases in this study had previously been diagnosed with dementia—most were newly diagnosed, 90% of the sample had medical insurance and 88% had a regular doctor. However, it can be reasonably assumed that their healthcare source failed to identify their dementia. In the Rotterdam Study,[51] Ott found that people with diabetes had almost doubled the risk of dementia and AD (dementia: 1.9; 95% CI: 1.3-2.8; AD: 1.9; 95% CI: 1.2-3.1). Diabetes was defined according to the World Health Organization (WHO) criteria: use of antidiabetes medication or a random or postload serum glucose greater than 11 mmol/L. An interesting point in their findings was that people treated with insulin were at highest risk of dementia (RR: 4.3; 95% CI: 1.7-10.5). Since the Rotterdam Study involved a large number of people (n=6,370), selection bias was minimized by the population-based design. However, not all participants could be rescreened in person and this may have led to selective underdiagnosis of dementia. Three years prior to this study, Ott published another study to examine the association between diabetes and prevalent dementia.[49] Diabetes was diagnosed as use of anti-diabetes medications or random or post serum glucose over 11 mmol/L. In that study, they also found positive association between diabetes and dementia (OR: 1.3, 95% CI: 1.0-1.9). In particular, strong associations were found between dementia and diabetes treated with insulin (OR: 3.2, 95% CI: 1.4-7.5). In this study, as is many population-based studies of this nature, the issue of survival bias is yet another important aspect to be kept in mind. Leibson conducted a study in Rochester, New York, to estimate the risk of dementia and AD associated with diabetes (defined as diagnosis at age 20 years or

older).[50] The study reported persons with diabetes exhibited significantly increase risk of all dementia (RR: 1.66; 95% CI: 1.34-2.05). A Japanese study by Yoshitake wanted to determine the type-specific incidence of dementia and its risk factors.[94] The study found for persons with diabetes exhibited significant risk for vascular dementia (RR: 2.77; 95%CI: 2.59-2.97) and nearly significant risk for AD (RR: 2.18; 95% CI: 0.97-4.90).

In contrast with studies previously mentioned, there were also a few prospective studies that showed minimal or no association between diabetes and AD. Firstly, the Canadian Study of Health and Aging (CSHA) by MacKnight investigated the relationship between diabetes and incident dementia (including AD and vascular cognitive impairment) in a 5-year longitudinal study.[95] The study determined diabetes from four sources: a) the screening interview (self-report); b) the clinical interviews (self-report supplemented by informant and health records; c) the medication list (insulin or oral hypoglycemic drugs; d) laboratory testing (venous plasma glucose levels > 11.1 mmol/L. They found that diabetes was not associated with mixed dementia (RR: 0.87, 95% CI: 0.34-2.21), incident AD (RR: 1.30, 95% CI: 0.83-2.03), or all dementias (RR: 1.26, 95% CI: 0.90-1.76). However, diabetes was associated with incident vascular cognitive impairment (RR: 1.62; 95% CI: 1.12-2.33), vascular dementia (RR: 2.03; 95% CI: 1.15-3.57), and vascular cognitive impairment not dementia (RR: 1.68; 95% CI: 1.01-2.78). Even though there is increased understanding between the role of vascular factors in AD, this study did not find an association between diabetes and incident AD. The study also noted that insulin users were more likely to develop vascular cognitive impairment but not AD, which probably reflects the severity of the underlying disease, and not an adverse effect of insulin. The OCTO-Twin Study by Hassing was another example that

showed no increased risk of AD but more than twofold risk of vascular disease in persons with diabetes (RR: 2.54; 95% CI: 1.35-4.78).[96] Diabetes onset was recorded based on information from medical records and self-reports. A difference between this study and other longitudinal studies was that the higher age of studied sample (aged >80) and perhaps one reason for the no association between diabetes and AD could be a result of gender bias given that 70% of the subjects in this study were women. The Fremantle Diabetes Study by Bruce also found no association between probable dementia and diabetes duration, glycemic control, insulin treatment, hypoglycemia, dyslipidemia, or stroke.[97] A limitation of this study was the number of people included were small (n=63). Finally, Luchsinger wanted to determine the association between diabetes and the different types of dementia and also to examine whether the differences in prevalence of diabetes in Blacks and Hispanics is higher than in Whites could account for the higher risk of dementia reported in non-Whites.[45] The presence of diabetes was based on reported use of insulin or oral hypoglycemic agents or a clinical history of diabetes. The study found weak association between diabetes and AD (RR: 1.3; 95% CI: 0.84-1.88) and a strong association between diabetes and stroke-associated dementia (RR: 3.4; 95% CI: 1.70-6.91). The main limitations of this study were a lack of data on duration of diabetes, severity of diabetes, and the presence of undiagnosed diabetes.

COMMENT

Evidence is accumulating concerning an important role for type 2 diabetes mellitus in the etiology of cognitive decline and dementia in later life, with a variety of potential mechanisms by which this association may be mediated.[98] Case-control studies, cross-sectional studies, and prospective studies reported associations on diabetes with

cognitive impairment, probably involving both memory and executive function[98] while some studies showed no or weak associations. Similar results have also been found for diabetes and AD for cross-sectional studies and prospective studies where positive and weak associations have been found.

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Table 2.1 Summary of the possible roles of insulin and insulin resistance in the pathogenesis of Alzheimer's disease

Type 2 diabetes mellitus	Type 2 diabetes is the result of insulin resistance and inadequate compensatory insulin secretion. Abnormal insulin metabolism produces hyperglycemia, which is associated with an increase risk of cortical neuronal damage during cerebral vascular events and head trauma. Type 2 diabetes increases the risk of a number of serious events including large and small vessel vascular disease and neuropathy
CNS insulin receptors and glucose transport	Insulin, insulin receptors and insulin-sensitive GLUTs (4 and 8) are selectively distributed and co-localized in several brain regions, including the hippocampus and hypothalamus. Although insulin levels do not modulate glucose transport in to the CNS, these overlapping distributions suggest that insulin may influence selective brain functions subserved these regions, including memory and HPA axis regulation
APP and Aβ	Insulin may contribute to regulation of APP and Aβ (a neurotoxic derivative of APP found in senile plaques that define Alzheimer's disease neuropathology). Converging evidence suggests that insulin may influence both the intracellular trafficking and the clearance of Aβ

Aβ=β-amyloid; APP=amyloid precursor protein; GLUTs=glucose transporters; HPA=hypothalamic-pituitary-adrenal.

CHAPTER 3

DIABETES MELLITUS AND COGNITIVE DECLINE AMONG ELDERLY PARTICIPANTS IN THE CACHE COUNTY, UTAH, STUDY ON MEMORY, HEALTH, AND AGING

ABSTRACT

Previous studies have reported significantly higher cognitive impairment among diabetics when compared to non-diabetics while other studies have found no significant differences. Given the increased interest in research in this area, cognitive decline among people with diabetes will be the focus of much discussion and debate since epidemiologic findings on the associations of diabetes and cognitive decline are mixed.

To examine whether diabetes is independently associated with level of cognitive function at baseline and to determine whether diabetes is independently associated with a decline in cognitive function, as measured by change in the cognitive assessment score over baseline and at three follow-up interviews in a cohort of elderly men and women living in Cache County, Utah.

This is a prospective cohort study of health, cognitive impairment, prevalence and incidence of Alzheimer's disease and other dementias among residents (n=5092) of Cache County, Utah aged 65 years and older (mean age, 74.9 years for men and 76.5 years for women). Cognitive function was assessed in the baseline interview (1995) and at three follow-up interviews conducted during 1996-1997 (Telephone), 1998-1999 (Wave 2), and 2002-2003 (Wave 3). A mixed model was used to assess change in cognitive function over time.

The Modified Mini Mental State Examination (3MS) scores was used as the primary outcome measure for these analyses. Mean baseline 3MS scores for men and women were 88.8 and 89.4, respectively. Approximately 60 percent of the total population were female.

Baseline prevalence of self-reported physician diagnosed diabetes was 333 for men (16%) and 380 for women (14%). A mixed model analyses with control for potential confounding variables, revealed an association between diabetes and a lower average 3MS score (0.9 of a point less at baseline, p=.0014). With the addition of time interactions, diabetes was associated with an additional quarter of a point lower on the average 3MS score per year compared to non-diabetics (p=.0095).

Diabetes was associated with a lower baseline cognitive score (3MS) and greater cognitive decline over the six-year span of the study among the elderly participants in the Cache County Study on Memory, Health, and Aging.

INTRODUCTION

Type 2 diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin production, secretion, and action.[1] The number of people with diabetes is increasing due to population growth, urbanization, and increasing prevalence of obesity and physical inactivity.[2] The prevalence of diabetes also increases with age. More than 10 percent of the elderly suffer from diabetes.[3-5] When combined with dementia, the two are the most prevalent problems found in the elderly.[5] More than 10 percent of people over the age of 65 years develop dementia, and its prevalence increases to more than 50 percent for people over the age of 85.[5-7]

A number of studies have examined associations between cognitive impairment and diabetes and their findings have yielded inconsistent results.[8-17] The differences lies in the various methodologies imposed on the study (ie. types of cognitive screening used, selection and control for potential covariates, sample size, and type of study design—case-control, cross-sectional, or longitudinal studies). Published reports from the Nurses' Health Study revealed that women with type 2 diabetes had increased risk of poor cognitive function and substantial cognitive decline compared with women without diabetes on several cognitive screening tests (five cognitive tests).[13, 14] In contrast, the Rancho Bernardo study, using 12 cognitive function tests (634 men and 875 women), and the Baltimore Longitudinal Study of Aging, using 2 cognitive performance tests (men only: 662) found no relationship between diabetes and cognitive function.[12, 18]

Given the increased interest in research in this area, cognitive decline among people with diabetes will be the focus of much discussion and debate. The present study was conducted to examine whether diabetes was independently associated with level of cognitive function as measured by the Modified Mini Mental State Examination (3MS) at baseline and whether diabetes was independently associated with a decline in cognitive function, as measured by change in the 3MS score between baseline and at three follow-up interviews from a large population-based study.

METHODS

Study Population

The Cache County Study on Memory, Health, and Aging (CCMS) is a prospective cohort study of health, cognitive impairment, prevalence and incidence of Alzheimer's disease and other dementias among residents of Cache County, Utah aged

65 years and older. Details of the study protocol have been published previously.[19, 20] Briefly, all residents of the county aged 65 years and older as of January 1, 1995, were invited to participate (n=5677).[21] The institutional review boards of each collaborating site (Utah State University, Duke University, and Johns Hopkins University) approved the protocols of the study, and all participants and/or their collateral informants (spouses, companions, or others knowledgeable about the respondents) provided informed consent.[21]

Design Overview

Although our present study uses the CCMS study population for analysis, our study design was slightly modified to answer our research question of interest, mainly to determine whether diabetes was associated with cognitive decline. This study, therefore, limits its research scope to include in the present analysis individuals who have successfully completed the 3MS at four time points as well as those with some missing data. Also, each participant must not have had a history of a central nervous system disorder or current psychiatric disorder, and if indicated, must have completed dementia screening.[22]

Assessment of Cognitive Function and Decline

Participants' cognitive function was assessed with the 3MS.[23] The 100-point test included items that assessed personal information, such as date and place of birth, verbal fluency, and abstract verbal reasoning, as well as a second delayed recall trial.[22] The 3MS screenings were administered at baseline, in 1995 (Wave 1) and at three follow-up interviews: 1996-1997 (Telephone), 1998-1999 (Wave 2), and 2002-2003 (Wave 3). The

3MS scores used in the present analysis were sensory adjusted. In all analyses, total 3MS score at four different time points was the dependent variable. Participants underwent a multistage screening and assessment procedure to evaluate the presence of dementia at baseline. Dementia was defined using DSM-III-R criteria.[24] Data from these evaluations were used to classify participants at consensus conferences that were conducted by two geriatric psychiatrists, a board-certified neurologist, a senior neuropsychologist, and a cognitive neuroscientist.

Assessment of Diabetes History and Other Covariates

Diabetes status was assessed at baseline from the Medical History section of the Prevalence Wave Baseline Interview Questionnaire. The assessment of diabetes was based on self-report of a physician's diagnosis. The question was phrased: "Have you ever had diabetes, high blood sugar or sugar in your urine?" The responses were: "YES" and "NO." If the answer was YES, the following question was: "Did a doctor diagnose this condition?" The responses were: "YES" and "NO."

Covariates of interest used in the present analyses to adjust for their effects included age (in years), gender (male, female), education (less than high school, high school and greater), body mass index (BMI, weight in kg/height in m^2), smoker (never, ever/current), alcohol (never, ever/current), light physical activity (ie. walking). Health variables used included APOE genotype (no e4, 1 or 2 e4), stroke (no, yes), hypertension (no, yes), high cholesterol (no, yes), myocardial infarction (no, yes), and diabetes (no, yes).

Participant Sampling

Among the eligible study sample, a total of 5092 individuals (90%) were enrolled at baseline, Wave 1 (559 refused participation or were unable to locate and 26 were deceased). Prevalence of dementia was detected (356 individuals) and an additional 33 persons with dementia were later identified after Wave 1 but before Wave 2.

After Wave 1, those without prevalent dementia and had complete 3MS scores (n=4689) were followed 1-2 years after the study had begun. Participants were screened for cognitive impairment using the 3MS via telephone during 1996-1997. A total of 3412 individuals participated in this phase of the study (lowered figure due to lost to follow-up and refused follow-up). During 1998-1999, participants were followed once more (Wave 2). The 3MS was used again to assess cognitive impairment. Between Wave 1 and Wave 2, 599 participants had died, 175 had moved out of the area or were lost to follow-up, and 538 refused follow-up. A total of 3316 individuals had complete 3MS scores at Wave 2. Here, dementia was detected in 151 individuals and 32 additional individuals were found to be demented after Wave 2 put prior to Wave 3. At Wave 3 (2002-2003), 2243 study participants were followed with another 3MS. Between Wave 2 and Wave 3, an additional 546 participants died, 74 moved out of the area or were lost to follow-up, 367 refused follow-up, and 4 had other reasons for loss to follow-up.

Procedures

Trained personnel of the Epidemiology Center at Utah State University visited and interviewed participants in their homes. Beginning in 1995, participants were screened with the 3MS four times at approximately the following intervals: 0 years (baseline), 1.5 years, 3years, and 6 years.

Statistical Analyses

Firstly, baseline characteristics were analyzed and presented by gender. We report selected sociodemographic variables, medical, and behavioral characteristics of the participants.

Secondly, we use linear mixed models to assess the effects of diabetes on average 3MS scores over time while accounting for the correlation between repeated observations made on individuals.[25, 26] An advantage to using the mixed model is that it allows the inclusion of missing data into the model without decreasing its power. The correlation of the 3MS data were evaluated to determine the best model (Unstructured, Compound Symmetry, Autoregressive with different or equal variance).[25] Once model selection was established, we modeled the mean by assessing the effects of covariates (particularly the effects of time) on the mean 3MS scores. We modeled the effects of time in years.

In the present study, we determined the association between average 3MS decline with diabetes, controlling for age, gender, education, BMI, smoking status, alcohol intake, light physical activity, APOE genotype, stroke, hypertension, high cholesterol, and myocardial infarction. Repeated measurements of cognitive function were assessed with the sensory adjusted 3MS scores at Waves 1, telephone, and at Waves 2 and 3. Interactions between time and the potential confounding factors were examined and

controlled in subsequent models. P<.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.0 (SAS Institute Inc., Cary, NC).

RESULTS

Mean age for men and women were 74.9 years and 76.5 years, respectively. At baseline, approximately 60 percent of the total population were female **(TABLE 1)**. Over two thirds of men and women were between the ages of 65 to 79 years. The majority of the subjects had attained at least a high school education or greater (79% for men and 83% for women). Fifty-eight percent of men and 56 percent of women had a BMI of greater than or equal to 25 (mean BMI for men: 26.2, women: 26.0). Over 90 percent of women and approximately two thirds of men reported never having smoked cigarettes. Similar reports were obtained for alcohol consumption. Over 90 percent of women reported never consuming alcohol. In men, over 70 percent replied they had never drank alcohol. In terms of self-reported chronic diseases, approximately 50 percent of women reported having hypertension while approximately 40 percent of the men said that they were afflicted with that condition.

Physician diagnosed diabetes at baseline was reported by 333 men (16%) and 380 women (14%). The mean age of diabetic men and women were 74.1 and 75.3 years, respectively. Among diabetics, 57 percent of men and 64 percent of women had a BMI of greater than or equal to 25. Fifty-eight percent of men and 68 percent of women reported having both diabetes and hypertension.

Mean baseline sensory adjusted 3MS scores for men and women were 88.8 and 89.4, respectively **(TABLE 2)**. **FIGURE 1** demonstrates the distribution of the average

3MS score across all waves for all participants. During the Telephone interview and Wave 2 interview, there seem to be an elevated mean 3MS score. At Wave 3, the mean 3MS score is lowered.

In **FIGURE 2**, the distribution of the average 3MS scores across all waves for men and women illustrates that women, at baseline, had a higher 3MS score than men, but at Waves 2 and 3, their average 3MS scores were approximately the same as men.

FIGURE 3 shows the distribution of the average 3MS score across all waves for diabetics and non-diabetics. Non-diabetics, at baseline and across all waves, had a higher average 3MS scores than diabetics.

FIGURE 4 shows the distribution of the average 3MS scores across all waves for diabetics and non-diabetics, stratified by gender. Non-diabetic women, at baseline, had a higher mean 3MS score than diabetic women, non-diabetic men, and diabetic men. Among diabetic women, although their 3MS score at baseline were higher than diabetic men, their average 3MS scores decreased dramatically between the Telephone interview and Wave 3 (lower than diabetic men).

In our analysis, we selected the unstructured correlation model for our mixed model analyses because it was the more complex model and had the least –2(residual log likelihood) value among other correlation models. When we compared the fit of this model with other correlation models, its chi-square significance was $p<.05$, hence we rejected the null hypothesis that the more simple model is better. **TABLE 3** displays results of the linear mixed models estimate. The models displayed are Model 1: Basic (diabetes covariate only); Model 2: Basic + Time (interaction model between time and diabetes covariate); Model 3: Basic + Demographic covariates (gender, age, education,

smoking status, alcohol intake, APOE genotype, BMI, light physical activity); Model 4: Basic + Demographic covariates + Time (interaction model between Time and all the covariates listed in Model 3); Model 5: Full (all covariates in Model 3) + Cardiovascular covariates (stroke, hypertension, high cholesterol, and myocardial infarction); and Model 6: Full (all covariates in Model 5) + Time (interaction model between Time and all the covariates listed in Model 5).

In Model 1, diabetics were associated with an average 3MS score of 1.14 points lower at baseline than non-diabetics. When we include the interaction between time and diabetes, Model 2 showed that diabetics have on average a 1.13 points lower on the 3MS score than non-diabetics at baseline and they also have an additional 0.20 of a point lower on the average 3MS score per year since their 3MS was first measured. Clearly what this equates to would be that if the present condition holds and there were no other unforeseen health circumstances, then in 10 years, the average 3MS score for diabetics would decrease by 2 points.

The reduced model shown in Model 3 included additional background covariates (gender, age, and education) and some other covariates such as smoking, alcohol, APOE, BMI, light physical activity, and diabetes. After controlling for these covariates, diabetes was associated with a decrease of about a point lower in the average 3MS score at baseline. Another striking finding was APOE genotype. The results showed that for those who either had one or two copies of the e4 allele, there was an average decrease of 1.15 points lower on the 3MS at baseline than those who don't have those alleles. When we include time interactions into Model 4, we observed diabetes resulted in an additional quarter of a point lower on the average 3MS score per year. This was in addition to the

fact that after controlling for the covariates, having diabetes was still associated with decline in the average 3MS score of nearly a point at baseline.

In Model 5, we added more health covariates into the model. The results still show an association between diabetes and the decrease of the average 3MS score of 0.9 of a point at baseline. In the final model, Model 6, we observed that with time interactions, diabetes was associated with an additional quarter of a point lower on the average 3MS score per year. This simply equates to nearly 2.5 points lower on the average 3MS score for those who have diabetes, assuming they live for 10 years.

COMMENT

Findings from the linear mixed model analyses provide evidence to suggest a lower baseline 3MS scores for diabetes compared to non-diabetes, and an association of an accelerated cognitive decline in the elderly with diabetes. Few studies have used the mixed model in their analyses.[17, 27, 28] Statistical analyses conducted in this type of study have included logistic regression and a generalized estimating equation (GEE).[14 13, 15, 29] The strength to using the mixed model is that it allows the inclusion of participants with missing data into the model, thus enhancing statistical power.

Hassing et al used the mixed model in their analyses on a study of 274 elderly participants (36 with diabetes and 238 without diabetes).[27] What they found was that diabetes was a significant predictor of rate of decline for many of their 11 cognitive tests. The strengths of their study included a fairly long study period and follow-up. They also incorporated numerous cognitive assessment tools in their study. The limitation they have was the small sample size of diabetic cases.

In the Cache County study, we examined whether diabetes was independently associated with level of cognitive function as measured by the 3MS at baseline and whether diabetes was independently associated with a decline in cognitive function, as measured by change in the 3MS score between baseline and at three follow-up interviews. The findings revealed that there was an association between diabetes and cognitive decline at baseline as well as an association between diabetes and cognitive decline between baseline and at three follow-up interviews. Our study revealed a decrease in the average 3MS scores at baseline among subjects who were diabetics in addition to an accelerated decline in the average 3MS score per year, when we took time into account. Gregg et al also found an accelerated cognitive decline among women with diabetes who had lower baseline scores than those without diabetes on the MMSE and Digit-Symbol.[17] According to our results, the magnitude of decline due to diabetes when compared with APOE, age, and cardiovascular diseases (stroke, hypertension, high cholesterol, and myocardial infarction) remained significant even when controlling for these covariates. Simply stated, diabetes has an effect independent of cardiovascular diseases. This result could further highlight the importance of diabetes research on future funding in the area of chronic diseases.

Limitations of our study should be acknowledged. Firstly, we relied on self-reported doctor diagnosed diabetes to represent diabetes status for that individual. During data analysis, we came across 83 participants who answered NO for self-reported doctor diagnosed diabetes but were in fact prescribed with diabetic medications (as confirmed by the medication drug list). Therefore, we added this group of people and include them together with those who answered YES. Another limitation in the diabetes

aspect of this study was the lack of information as to when a doctor first diagnosed diabetes at Wave 1, Telephone, and Wave 2 interviews. Question on duration of diabetes was available in Wave 3 interviews. Thirdly, there were no biochemical assessments for blood glucose level collected at Wave 1 and Wave 2. In Wave 3, HbA1c (test that measures the amount of glycosylated hemoglobin in blood and gives a good estimate of how well diabetes is being managed over time) was collected.[30]

Despite these limitations, a major strength of this study was the large sample size for determining the association between cognitive decline and diabetes.

Future research directions include analyzing HbA1c blood samples collected at Wave 3 to help further explain the association of diabetes, cognitive function, and glycemic control. An interesting finding from the present study was the association between APOE genotype and cognitive decline. What was notable from the findings was that the magnitude of cognitive decline for the diabetes effect was similar to the APOE effect. For future studies, we can look into the association of APOE genotype and cognitive decline in much greater detail.

The number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity. It is proving itself to be clearly a growing public health threat. Cognitive performance, on the other hand, is an important indicator of health and functioning in elderly people and the ability to maintain cognitive function into old age is agreeably desired by most, if not all. Cognitive decline represents a major public health burden: it has adverse psychosocial and economic consequences for affected person and their families and is a risk factor for increased home health care use, hospitalization, nursing home entry, and mortality.

Ultimately, more research is needed to understand the interrelationship between diabetes and cognitive function so that prevention of cognitive impairment may be enhanced if future research determines the underlying mechanisms for the association between diabetes and cognitive decline.[17]

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Table 3.1 Selected Baseline Characteristics (N=5092)

Characteristic	n (%) Male	Female
1. Gender	2163 (42.5)	2929 (57.5)
2. Mean age, in years (SD)	74.9 (6.9)	76.5 (7.5)
3. Mean 3MS scores (SD)	88.8 (9.5)	89.5 (9.7)
4. Education		
- Less than High School	456 (21.1)	493 (16.9)
- High School and Greater	1701 (78.9)	2428 (83.1)
5. Mean BMI (SD)	26.2 (4.5)	26.0 (4.4)
6. Smoker		
- Never	1312 (64.1)	2513 (92.1)
- Ever/Current	736 (35.9)	217 (7.9)
7. Alcohol		
- Never	1494 (72.0)	2547 (92.0)
- Ever/Current	582 (28.0)	220 (8.0)
8. APOE		
- No E4	1438 (68.1)	1920 (67.3)
- 1 E4/2 E4	673 (31.9)	931 (32.7)
9. Stroke		
- No	1886 (93.7)	2531 (94.4)
- Yes	126 (6.3)	151 (5.6)
10. Hypertension		
- No	1222 (60.7)	1328 (49.5)
- Yes	791 (39.3)	1353 (50.5)
11. High Cholesterol		
- No	1433 (71.6)	1705 (64.1)
- Yes	568 (28.4)	956 (35.9)
12. Myocardial Infarction		
- No	1622 (80.9)	2432 (91.3)
- Yes	384 (19.1)	233 (8.7)
13. Diabetes		
- No	1683 (83.5)	2307 (85.9)
- Yes	333 (16.5)	380 (14.1)

Table 3.2 Mean 3MS Scores for Diabetics and Non-Diabetics, Stratified by Gender

Waves	Men[1]		Women[1]	
	Diabetes	No Diabetes	Diabetes	No Diabetes
1. Wave 1	88.8 (8.4) n=333	89.7 (7.7) n=1681	89.4 (8.1) n=377	90.6 (7.2) n=2298
2. Telephone	90.1 (6.9) n=218	90.1 (7.9) n=1163)	89.9 (7.9) n=261	91.0 (7.3) n=1770
3. Wave 2	90.5 (8.2) n=212	91.3 (8.1) n=1167	89.9 (10.0) n=243	91.7 (8.2) n=1694
4. Wave 3	89.4 (9.7) n=108	89.8 (8.4) n=820	89.3 (13.2) n=141	89.7 (11.1) n=1174

[1]In Mean (SD)

Table 3.3 Mixed Model Results of Fixed Effects

Independent Variable	Model Estimate	P-value
A. Model 1: Basic		
1. Diabetes	-1.138	.0002
B. Model 2: Basic + Time		
1. Diabetes	-1.130	.0002
2. Time	-0.469	<.0001
3. Time * Diabetes	-0.189	.0225
C. Model 3: Basic + Demographics		
1. Gender	-1.231	<.0001
2. Age	-0.422	<.0001
3. Education	4.009	<.0001
4. Smoking	-0.263	.3929
5. Alcohol	0.656	.0392
6. APOE	-1.149	<.0001
7. BMI	-0.004	.8488
8. Light Physical Activity	0.763	<.0001
9. Diabetes	-1.078	<.0001
D. Model 4: Basic + Demographics + Time		
1. Gender	-1.340	<.0001
2. Age	-0.385	<.0001
3. Education	3.932	<.0001
4. Smoking	-0.233	.4575
5. Alcohol	0.637	.0476
6. APOE	-1.033	<.0001
7. BMI	-0.004	.8335
8. Light Physical Activity	0.746	.0002
9. Diabetes	-0.981	.0002
10. Time	5.086	<.0001
11. Time * Gender	0.066	.3025
12. Time * Age	-0.069	<.0001
13. Time * Education	0.162	.0741
14. Time * Smoking	-0.054	.5220
15. Time * APOE	-0.177	.0054
16. Time * BMI	0.002	.7684
17. Time * Light Physical Act.	0.099	.0977
18. Time * Diabetes	-0.234	.0083

Table 3.4 Mixed Model Results of Fixed Effects "cont"

Independent Variable	Model Estimate	P-value
E. Model 5: Full (Model 3) + CVD covariates		
1. Gender	-1.053	<.0001
2. Age	-0.402	<.0001
3. Education	3.924	<.0001
4. Smoking	-0.224	.4683
5. Alcohol	0.616	.0523
6. APOE	-1.162	<.0001
7. BMI	-0.008	.7036
8. Light Physical Activity	0.713	.0002
9. Diabetes	-0.870	.0014
10. Stroke	-2.169	<.0001
11. Hypertension	-0.082	.6711
12. High Cholesterol	0.916	<.0001
13. Myocardial Infarction	-0.488	.0988
F. Model 6: Full (Model 5) + Time		
1. Gender	-1.168	<.0001
2. Age	-0.364	<.0001
3. Education	3.847	<.0001
4. Smoking	-0.168	.5927
5. Alcohol	0.524	.1059
6. APOE	-1.029	<.0001
7. BMI	-0.008	.7117
8. Light Physical Activity	0.698	.0004
9. Diabetes	-0.767	.0058
10. Stroke	-2.064	<.0001
11. Hypertension	-0.077	.6922
12. High Cholesterol	0.887	<.0001
13. Myocardial Infarction	-0.298	.3229
14. Time	4.869	<.0001
15. Time * Gender	0.093	.1545
16. Time * Age	-0.066	<.0001
17. Time * Education	0.158	.0827
18. Time * Smoking	-0.122	.2305
19. Time * Alcohol	0.183	.0773
20. Time * APOE	-0.199	.0019
21. Time * BMI	0.001	.9335
22. Time * Light Physical Activity	0.104	.0877
23. Time * Diabetes	-0.234	.0095
24. Time * Cardiovascular Disease	-0.273	.0923
25. Time * Hypertension	0.038	.5371
26. Time * High Cholesterol	0.103	.1064
27. Time * Myocardial Infarction	-0.361	.0003

CVD: cardiovascular diseases

Figure 3.1 Cognitive Decline for All Participants (Mean 3MS at Four Time Points)

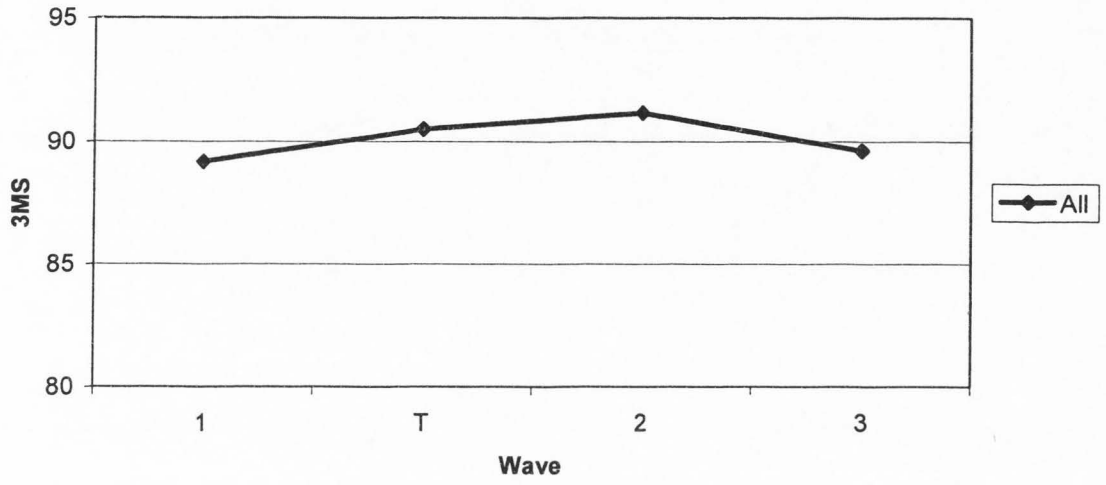


Figure 3.2 Cognitive Decline Stratified by Gender (Mean 3MS at Four Time Points)

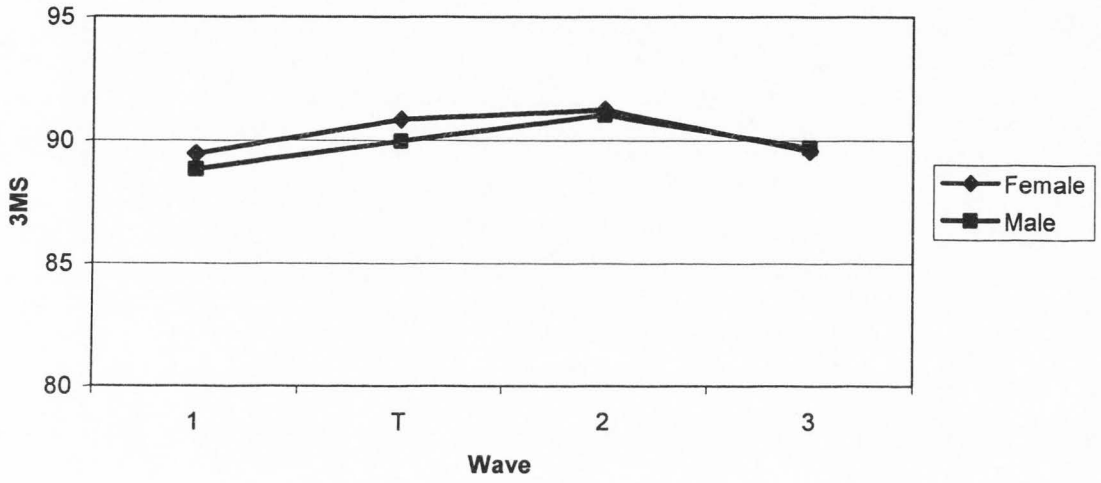


Figure 3.3 Cognitive Decline for Diabetics and Non-Diabetics (Mean 3MS at Four Time Points)

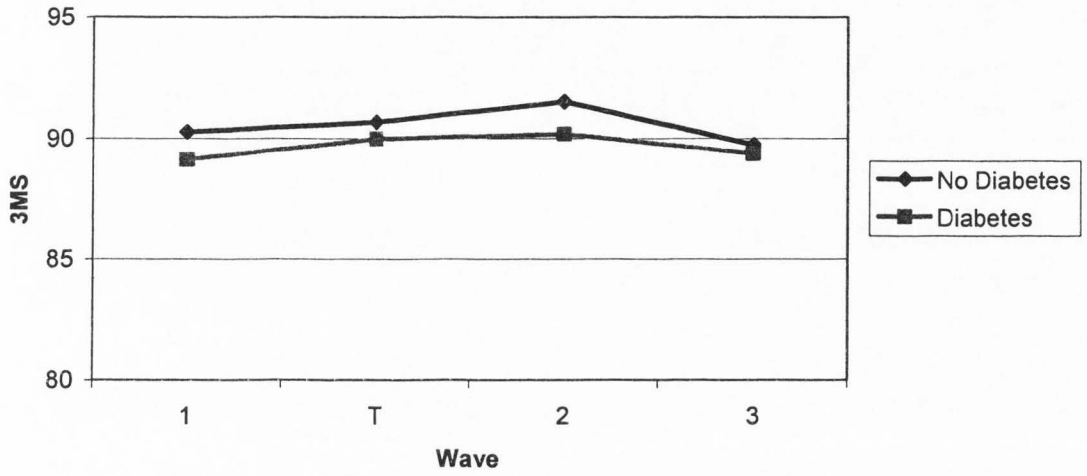
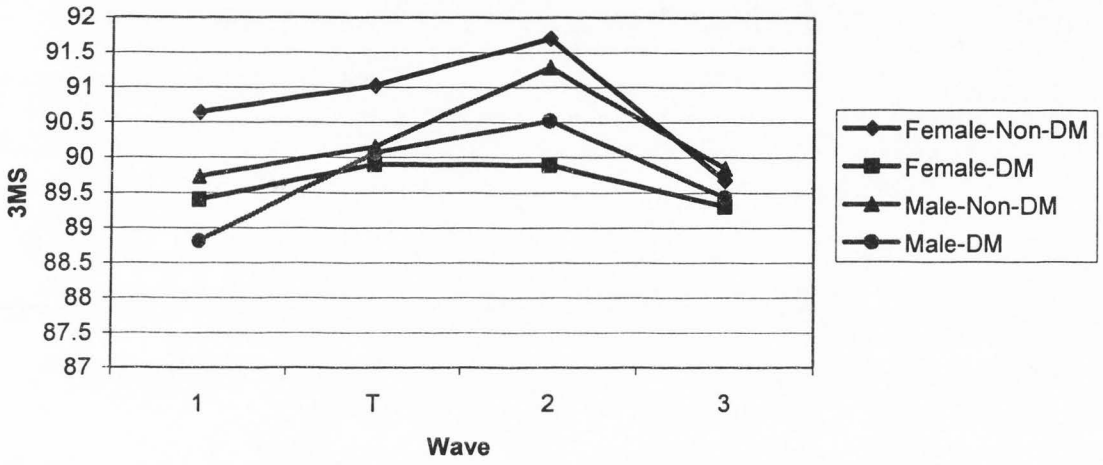


Figure 3.4 Cognitive Decline for Diabetics and Non-Diabetics Stratified by Gender (Mean 3MS at Four Time Points)



DM: Diabetics

CHAPTER 4

DIABETES MELLITUS AND RISK OF ALZHEIMER'S DISEASE IN THE CACHE COUNTY, UTAH, STUDY ON MEMORY, HEALTH, AND AGING

ABSTRACT

Some studies have reported minimal or no association between diabetes and Alzheimer's disease (AD) while other studies have observed positive association between diabetes and AD. Given the increased interest in research in this area, AD and diabetes will be the focus of much discussion and debate for years to come since epidemiologic findings on the associations of diabetes and AD are mixed.

To examine whether diabetes mellitus is an independent risk factor for the development of AD at the first follow-up wave from a large population-based study.

This is a prospective cohort study of health, cognitive impairment, prevalence and incidence of AD and other dementias among residents (n=5092) of Cache County, Utah aged 65 years and older (mean age, 74.9 years for men and 76.5 years for women). Cognitive function was assessed in the baseline interview (Wave 1) and at the first follow-up study 1998-1999 (Wave 2).

We found evidence of an association between a history of diabetes at baseline and an increased risk of incident AD compared with non-diabetics (Relative Risk (RR)=1.92 95% confidence interval (CI):1.03-3.43). After controlling for covariates (age, education, body mass index, smoking status, alcohol intake, APOE genotype, stroke, hypertension, high cholesterol, myocardial infarction, and diabetes) and stratifying by gender, the

association was observed in men (RR=3.71, 95% CI:1.54-8.58) but not in women (RR=1.01, 95% CI:0.35-2.48).

These results suggest that diabetes may be associated with increased risk for developing incident AD among men but not women in our study cohort of elderly residents of Cache County, Utah.

INTRODUCTION

Type 2 diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin production, secretion, and action.[1] The number of people with diabetes is increasing due to population growth, urbanization, and increasing prevalence of obesity and physical inactivity.[2] The prevalence of diabetes also increases with age. More than 10 percent of the elderly suffer from diabetes.[3-5] When combined with dementia, the two are the most prevalent problems found in the elderly.[3]

For most elderly, maintaining cognitive function is just as important in determining the quality of life in their later years as every other aspect of health. However, if or when cognitive function starts to decline, it can bring upon a degree of distress to the individual or the caregiver. The loss of cognitive function can range from simple memory deficit to profound dementia, such as Alzheimer's disease (AD) or vascular dementia (VaD, a complex neuropsychiatric disorder with cognitive and behavioral manifestations resulting from multiple infarctions, ischemic brain injury, or occasionally, hemorrhagic intracranial events).[6, 7] AD is the most common cause of dementia in elderly patients, accounting for 50% to 70% of all cases and more than 100,000 deaths annually.[8, 9]

Alzheimer's disease is a degenerative brain disorder, characterized by neuronal and synaptic degeneration, an increase in numbers of senile plaques and neurofibrillary tangles, decreased cholinergic transmission, memory impairment, and progressive deterioration of cognitive function.[10, 11] AD among people with diabetes is the focus of much discussion and debate. Many studies have reported conflicting results[3, 12-25]

In an outpatient dementia assessment center in Irvine, California, Neilson et al observed diabetes to be rare among AD patients (0.8%) relative to vascular dementia (11.8%), mixed vascular/AD dementia (8.8%), and "other" dementia patients (8.8%).[12] In Texas, Mortel et al found diabetes in only 6% of AD and 23% of ischemic vascular dementia subjects.[13] A Swedish study by Landin et al, on the other hand, found no cases of diabetes in the AD group.[14] Wolf-Klein et al reported less heart disease, cerebrovascular disease, hypertension, and diabetes mellitus (one person) among patients with AD than in either the normal mental status group or the abnormal non-AD group in a sample of 348 elderly patients at a large outpatient center in New York.[15] The Canadian Study of Health and Aging (CSHA) by MacKnight et al reported that diabetes was not associated with mixed dementia (Relative Risk (RR)=0.87, 95% confidence interval (CI):0.34-2.21), incident AD (RR=1.30, 95% CI:0.83-2.03), or all dementias (RR=1.26, 95% CI:0.90-1.76).[16] The OCTO-Twin Study by Hassing et al, a study of 702 Swedish elderly individuals, and the Fremantle Diabetes Study by Bruce et al, a study of 63 elderly patients in Australia, also observed no increased risk of AD in persons with diabetes.[17, 18]

In contrast, Arvanitakis et al and Haan et al reported positive associations between diabetes and AD.[20, 21] Arvanitakis et al, in a study conducted among elderly

Catholic nuns and priests in the U.S., reported that people with diabetes had a 65 percent increase in the risk of developing AD compared with people without diabetes (hazard ratio=1.65; 95% CI:1.10-2.47).[20] Haan found that the risk of dementia among elderly Latino population in California was nearly eight times higher among subjects with both type 2 diabetes and stroke.[21] In the Rotterdam Study, Ott et al found diabetes had almost double the risk of dementia and AD (dementia, RR=1.9; 95% CI:1.3-2.8; AD, RR=1.9; 95% CI:1.2-3.1) compared to non-diabetes.[22] However, when stratified by gender, women were found to have nearly twice the risk of developing AD (dementia, RR=1.9, 95% CI:1.2-3.0) than men (dementia, RR=1.8, 95% CI:0.8-4.1). Leibson et al conducted a study in Rochester, New York, and observed that diabetes exhibited significantly increased risk for all dementia (RR=1.66; 95% CI:1.34-2.05), while Yoshitake reported significant risk for vascular dementia (RR=2.77; 95% CI:2.59-2.97) among elderly Japanese people.[24, 25]

Given the increased interest in research in this area, AD and diabetes will be the focus of much discussion and debate for years to come. The Cache County Study on Memory, Health, and Aging provided an opportunity to examine whether diabetes mellitus is an independent risk factor for the development of AD.

METHODS

Study Population

The Cache County Study on Memory, Health, and Aging (CCMS) is a prospective cohort study of health, cognitive impairment, prevalence and incidence of Alzheimer's disease and other dementias among residents of Cache County, Utah aged 65 years and older. Details of the study protocol have been published previously.[26, 27]

Briefly, all residents of the county aged 65 years and older as of January 1, 1995, were invited to participate (n=5677).[28] Data was collected at baseline, in 1995 (Wave 1) and at two other time points: 1998-1999 (Wave 2) and 2002-2003 (Wave 3). The institutional review boards of each collaborating site (Utah State University, Duke University, and Johns Hopkins University) approved the protocols of the study, and all participants or their collateral informants (spouses, companions, or others knowledgeable about the respondents) or both provided informed consent.[28]

Design Overview

Although our present study uses the CCMS study population for analysis, our study design was slightly modified to answer our research question of interest, mainly to determine whether diabetes is an independent risk factor for the development of incident AD at the first follow-up examination (Wave 2). The present study, therefore, limits its research scope to examine only incident AD cases at Wave 2.

Assessment of Cognitive Function, Decline, and Alzheimer's Disease

Participants' cognitive function was screened with the Modified Mini-Mental State Examination (3MS, a 100-point test that assessed personal information, such as date and place of birth, verbal fluency, and abstract verbal reasoning, as well as a second delayed recall trial).[29, 30] If participants were unable to participate, an informant questionnaire was completed[31] **(APPENDIX ONE)** followed by the Dementia Questionnaire (DQ).[32] Participants with screening results suggesting a cognitive disturbance then underwent a multistage screening and assessment procedure to evaluate the presence of dementia at baseline. Dementia was defined using DSM-III-R criteria.[33]

Data from these evaluations were then considered by a panel of experts comprising two geriatric psychiatrists, a board-certified neurologist, a senior neuropsychologist, and a cognitive neuroscientist at a consensus conference who then assigned diagnoses of AD and other disorders using standard criteria.[28]

Assessment of Diabetes History and Other Covariates

Diabetes status was assessed at baseline from the medical history section of the baseline interview questionnaire. The assessment of diabetes was based on self-report of a physician's diagnosis. The question was phrased: "Have you ever had diabetes, high blood sugar or sugar in your urine?" The responses were: "YES" and "NO." If the answer was YES, the following question was: "Did a doctor diagnose this condition?" The responses were: "YES" and "NO."

Covariates of interest that were used in the present analyses to adjust for their effects included age, gender, education, body mass index (BMI, weight in kg/height in m^2), smoking status, and alcohol intake. Selected health variables included APOE genotype, stroke, hypertension, high cholesterol, myocardial infarction, and diabetes. These covariates were selected based upon their associations with diabetes (ie. obesity and cardiovascular diseases).

Participant Sampling

Among the eligible study sample, a total of 5,092 individuals (90%) were enrolled at baseline, (559 refused participation or were unable to be located and 26 were deceased). Prevalence of dementia was detected in 356 individuals and an additional 33

persons with dementia were later identified after baseline but before the first follow-up examination (Wave 2) and were not included in the present study.

Approximately 3-4 years after baseline, the first follow-up interview began. Between baseline and Wave 2, 599 participants had died, 175 had moved out of the area or were lost to follow-up, and 538 refused follow-up. At Wave 2, 302 participants were given a diagnosis that was not AD (ie. mild ambiguous, other cognitive impairments, other dementias, etc.) and were removed from the present analysis (in order to study and compare between those who had AD diagnosis only and those who were non-AD diagnosis) while 248 had missing diabetes data. A total of 3,230 participants had complete diabetes and dementia data at Wave 2.

Statistical Analyses

Baseline characteristics were compared for participants with and without AD as well as the sociodemographic, medical, and behavioral characteristics of dementia-free participants and those with AD.

We estimated the relative risk of incident AD among diabetes and non-diabetes using logistic regression models while controlling for potential covariates including gender, age, education, smoking status, alcohol intake, APOE genotype, BMI, stroke, hypertension, high cholesterol, and myocardial infarction. All statistical analyses were performed using SAS software, version 9.0 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics are shown in **TABLE 4.1**. Mean age for men and women were 74.9 years and 76.5 years, respectively. At baseline, approximately 60 percent of the total population were female. Over two thirds of men and women were between the ages of 65 to 79 years. The majority of the subjects had attained at least a high school education or more (79% for men and 83% for women). Fifty-eight percent of men and 56 percent of women had a BMI of greater than or equal to 25 (mean BMI for men: 26.2, women: 26.0). Over 90 percent of women and approximately two thirds of men reported never having smoked cigarettes. Similar reports were obtained for alcohol consumption. Over 90 percent of women responded that they never consumed alcohol. In men, over 70 percent replied that they had never drank alcohol. In terms of self-reported chronic diseases, approximately 50 percent of women reported having hypertension while approximately 40 percent of the men said that they were afflicted with that condition.

At Wave 2, from a total of 3230 participants, 107 individuals were diagnosed with AD and the rest did not have AD or any other dementia diagnosis.

The results of the logistic regression estimates of the relative risk of incident AD are shown in **TABLE 4.2**. The models presented were the Half Model (adjusted for gender, age, education, smoking, alcohol intake, and diabetes) and the Full Model (adjusted for gender, age, education, smoking, alcohol intake, APOE, BMI, stroke, hypertension, high cholesterol, and myocardial infarction). In the Half Model, after controlling for some demographic covariates, diabetes at baseline was not significantly associated with increased risk for developing incident AD (RR=1.70, 95% CI:0.98-2.85) when compared with non-diabetes. In the Full Model, after additional covariates were

added into the model, we observed APOE and diabetes at baseline were associated with increased risk for developing incident AD when compared with non-diabetes. Individuals who have either 1 or 2 alleles of the APOE 4 increased the risk for incident AD by 2.5 times (RR=2.52, 95% CI:1.59-3.97) compared to those who don't have the APOE 4 alleles. In the Full Model, diabetes at baseline nearly doubled the risks for developing incident AD (RR=1.92, 95% CI:1.03-3.43) compared to non-diabetes.

The results of the logistic regression for the relative risk of incident AD, stratified by gender are shown in **TABLE 4.3**. In the Half Model, diabetes at baseline was associated with 4 times greater risk for developing incident AD among men (RR=4.05, 95% CI:1.84-8.65) than non-diabetics. We did not observe any association between diabetes and risk of incident AD among women in the Half Model. APOE was associated with increased risk for developing incident AD in women (RR=3.06, 95% CI:1.73-5.45) but not for men (RR=1.90, 95% CI:0.82-4.27) in the Full Model. Diabetes, however, was associated with increased risk for incident AD after controlling for selected demographic and chronic disease covariates, among men (RR=3.71, 95% CI:1.54-8.58) but not in women (RR=1.01, 95% CI:0.35-2.48).

COMMENT

This study was conducted to examine whether diabetes mellitus is an independent risk factor for the development of AD at the first follow-up wave (1998-1999) from a large population-based study. In our study of elderly people in Cache County, Utah, we found evidence of an association between diabetes at baseline and risk for developing incident AD when compared with non-diabetes (RR=1.92, 95% CI:1.03-3.45). After controlling for covariates and stratifying by gender, the association was observed in men

(RR=3.71, 95% CI:1.54-8.58) but not in women (RR=1.01, 95% CI:0.35-2.48). These results suggest that diabetes may be associated with increased risk of incident AD among men but not women in the Cache County cohort.

These results are consistent with findings from some studies.[22, 34] The Rotterdam Study reported that diabetes almost doubled the risk of AD during an average 2.1 years of follow-up in more than 6000 elderly participants.[22] Since the study involved a large number of people, selection bias was minimized by the population-based design as in the Cache County Study. However, not all participants could be rescreened in person and this may have led to selective underdiagnosis of dementia. The Honolulu-Aging Study of 2500 Japanese-American elderly men living in Hawaii reported that diabetes had almost doubled the risk of AD (RR=1.8, 95% CI:1.1-2.9) compared to non-diabetes.[34] This study also found individuals with diabetes and the APOE e4 allele had 5.5 times the risk (CI:2.2-13.7) for AD compared with those without the risk factor.[34] In our study, we found an association with APOE (RR=2.52, 95% CI:1.59-3.97) and AD. However, when stratified by gender, the association was only observed in women and not in men. Due to a small number of studies that have looked at stratification by gender, more insights on gender differences and the role of APOE genotype will need to be further addressed. However, a probable explanation could be the importance of duration of diabetes on gender differences. This is beyond the scope of the present study and would need to be investigated further.

Limitations of our study should be acknowledged. First, we relied on self-report of physician diagnosed diabetes to represent diabetes status for that individual. During data analysis, we came across 83 participants who answered NO for self-reported doctor

diagnosed diabetes but were in fact prescribed with diabetic medications (as confirmed by the medication drug list). Therefore, we added this group of people and included them in the diabetic group. In a way, this could also be regarded as a strength of the study since, we had the participants' medication drug list available and we were able to use that data to confirm diabetes status according to self-report of physician diagnosed diabetes. Another limitation in the diabetes aspect of this study was the lack of information as to when diabetes was first diagnosed at Wave 1 and Wave 2 interviews. Third, there were no biochemical assessments for blood glucose level collected at baseline and Wave 2 to confirm diabetes status. Finally, as with many studies of this nature, we included people who were able to successfully complete the study. Therefore, the participants were in generally good health at the start of the study. Those who were frail and had other underlying health conditions may not have participated in the study, thus it is important to recognize this type of selection bias in our study (Left-censoring or truncation bias).

Despite these limitations, a major strength of this study was the large sample size for determining the association between diabetes and incident AD, the control on many covariates, and the stratification of results by gender.

Future research directions include further exploring the association of APOE genotype, duration of diabetes, and other cardiovascular covariates and examine whether they reveal any independent risks for the development of AD.

There is growing concern and recognition that as the population ages, AD will place an enormous burden on the country because, not only is the cost of care for AD a financial one, it has such a huge impact on individuals, families, the health care system, and society.[35, 36] AD places great emotional and physical stress on families as they cope

with the physical and mental changes in their loved ones.[37] According to estimates in the U.S., delaying mean onset of AD by approximately 5 years would correspond to a 50% reduction in risk, and would reduce the expected prevalence by 1.15 million people after 10 years (by 2007) and 4.04 million people after 50 years (by 2047).[36] If interventions could delay onset of the disease by 2 years, after 50 years there would be 1.94 million fewer cases than projected; if onset could be delayed by 1 year, there would be nearly 800,000 fewer prevalent cases.[36] This is a huge public health implication.

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Table 4.1 Selected Baseline Characteristics (N=5092)

Characteristic	n (%)	
	Male	Female
1. Gender	2163 (42.5)	2929 (57.5)
2. Mean age, in years (SD)	74.9 (6.9)	76.5 (7.5)
3. Mean 3MS scores (SD)	88.8 (9.5)	89.5 (9.7)
4. Education		
- Less than High School	456 (21.1)	493 (16.9)
- High School and Greater	1701 (78.9)	2428 (83.1)
5. Mean BMI (SD)	26.2 (4.5)	26.0 (4.4)
6. Smoker		
- Never	1312 (64.1)	2513 (92.1)
- Ever/Current	736 (35.9)	217 (7.9)
7. Alcohol		
- Never	1494 (72.0)	2547 (92.0)
- Ever/Current	582 (28.0)	220 (8.0)
8. APOE		
- No E4	1438 (68.1)	1920 (67.3)
- 1 E4/2 E4	673 (31.9)	931 (32.7)
9. Stroke		
- No	1886 (93.7)	2531 (94.4)
- Yes	126 (6.3)	151 (5.6)
10. Hypertension		
- No	1222 (60.7)	1328 (49.5)
- Yes	791 (39.3)	1353 (50.5)
11. High Cholesterol		
- No	1433 (71.6)	1705 (64.1)
- Yes	568 (28.4)	956 (35.9)
12. Myocardial Infarction		
- No	1622 (80.9)	2432 (91.3)
- Yes	384 (19.1)	233 (8.7)
13. Diabetes		
- No	1683 (83.5)	2307 (85.9)
- Yes	333 (16.5)	380 (14.1)

Table 4.2 Adjusted Relative Risk for Incident Alzheimer's Disease (AD)

	RR (CI)
1. Half Model[1]	
- Gender	0.67 (0.41-1.08)
- Age	2.29 (1.97-2.67)
- Education	1.37 (0.81-2.43)
- Smoking	1.69 (0.79-3.38)
- Alcohol intake	0.30 (0.09-0.74)
- Diabetes	1.70 (0.98-2.85)
2. Full Model[2]	
- Gender	0.58 (0.33-0.97)
- Age	2.29 (1.94-2.72)
- Education	1.31 (0.74-2.44)
- Smoking	1.77 (0.76-3.84)
- Alcohol intake	0.36 (0.11-0.95)
- APOE 4	2.52 (1.59-3.97)
- BMI	1.02 (0.98-1.07)
- Stroke	0.72 (0.17-2.12)
- Hypertension	0.48 (0.29-0.77)
- High Cholesterol	0.41 (0.21-0.76)
- Myocardial infarction	1.33 (0.63-2.61)
- Diabetes	1.92 (1.03-3.43)

[1] Adjusted for gender, age, education, smoking, alcohol intake, and diabetes
[2] Adjusted for gender, age, education, smoking, alcohol intake, APOE, BMI, stroke, hypertension, high cholesterol, and myocardial infarction
RR=Relative Risk
CI=Confidence Interval

Table 4.3 Relative Risk for Incident Alzheimer's Disease (AD), Stratified by Gender

	RR (CI)	
	Male	Female
1. Half Model[1]		
- Age	1.78 (1.38-2.31)	2.55 (2.11-3.10)
- Education	0.58 (0.25-1.39)	2.40 (1.15-5.68)
- Smoking	1.68 (0.69-3.88)	0.67 (0.04-3.50)
- Alcohol intake	0.29 (0.08-0.88)	0.21 (0.01-1.08)
- Diabetes	4.05 (1.84-8.65)	0.85 (0.34-1.83)
2. Full Model[2]		
- Age	1.71 (1.30-2.26)	2.77 (2.22-3.51)
- Education	0.50 (0.21-1.24)	2.57 (1.12-6.84)
- Smoking	1.37 (0.52-3.39)	1.08 (0.06-6.19)
- Alcohol intake	0.35 (0.09-1.08)	0.29 (0.01-1.56)
- APOE 4	1.90 (0.82-4.27)	3.06 (1.73-5.45)
- BMI	0.98 (0.90-1.07)	1.04 (0.98-1.10)
- Stroke	0.52 (0.03-2.87)	0.89 (0.13-3.50)
- Hypertension	0.79 (0.32-1.85)	0.36 (0.19-0.65)
- High Cholesterol	0.72 (0.26-1.78)	0.33 (0.12-0.75)
- Myocardial infarction	1.93 (0.75-4.56)	0.76 (0.17-2.40)
- Diabetes	3.71 (1.54-8.58)	1.01 (0.35-2.48)

[1] Adjusted for gender, age, education, smoking, alcohol intake, and diabetes
[2] Adjusted for gender, age, education, smoking, alcohol intake, APOE, BMI, stroke, hypertension, high cholesterol, and myocardial infarction
RR=Relative Risk
CI=Confidence Interval

CHAPTER 5

SUMMARY AND CONCLUSION OF THE DIABETES, COGNITIVE DECLINE, AND ALZHEIMER'S DISEASE STUDY IN THE CACHE COUNTY STUDY ON MEMORY, HEALTH, AND AGING

ABSTRACT

Numerous studies have reported mixed results for people with or without diabetes with cognitive decline or Alzheimer's disease (AD). Cognitive decline and AD among people with diabetes will be the focus of much discussion and research in the coming years since results have been controversial.

The study examined whether diabetes is associated with cognitive decline and whether it is an independent risk factor for the development of AD among elderly residents of Cache County, Utah.

DIABETES MELLITUS AND COGNITIVE DECLINE

This is a prospective cohort study of health, cognitive impairment, prevalence and incidence of Alzheimer's disease and other dementias among residents (n=5092) of Cache County, Utah aged 65 years and older (mean age, 74.9 years for men and 76.5 years for women). Cognitive function was assessed in the baseline interview (1995) and at three follow-up interviews conducted during 1996-1997 (Telephone), 1998-1999 (Wave 2), and 2002-2003 (Wave 3). A mixed model was used to assess change in cognitive function over time.

Results demonstrated an association between diabetes with a lower average Modified Mini Mental State Examination (3MS) score of nearly a point lower at baseline. Results also showed an association between diabetes and an increased risk of incident AD compared with non-diabetes for men but not for women.

The Modified Mini Mental State Examination (3MS) scores was used as the primary outcome measure for these analyses. Mean baseline 3MS scores for men and women were 88.8 and 89.4, respectively. Approximately 60 percent of the total population were female.

A mixed model analyses with control for potential confounding variables, revealed an association between diabetes and a lower average 3MS score (0.9 of a point less at baseline, p=.0014). With the addition of time interactions, diabetes was associated with an additional quarter of a point lower on the average 3MS score per year compared to non-diabetics (p=.0095).

Diabetes was associated with a lower baseline cognitive score (3MS) and greater cognitive decline over the six-year span of the study among the elderly participants.

In the Cache County study, the findings revealed that there was an association between diabetes and cognitive decline at baseline as well as an association between diabetes and cognitive decline between baseline and at three follow-up interviews. Our study revealed a decrease in the average 3MS scores at baseline among subjects who were diabetics in addition to an accelerated decline in the average 3MS score per year, when we took time into account. According to our results, the magnitude of decline due to diabetes when compared with APOE, age, and cardiovascular diseases (stroke, hypertension, high cholesterol, and myocardial infarction) remained significant even

when controlling for these covariates. Simply stated, diabetes has an effect independent of cardiovascular diseases. This result could further highlight the importance of diabetes research on future funding in the area of chronic diseases.

DIABETES MELLITUS AND ALZHEIMER'S DISEASE

This is a prospective cohort study of health, cognitive impairment, prevalence and incidence of AD and other dementias among residents (n=5092) of Cache County, Utah aged 65 years and older (mean age, 74.9 years for men and 76.5 years for women). Cognitive function was assessed in the baseline interview (Wave 1) and at the first follow-up study 1998-1999 (Wave 2).

This study was conducted to examine whether diabetes mellitus is an independent risk factor for the development of AD at the first follow-up wave (1998-1999). In our study, we found evidence of an association between diabetes at baseline and risk for developing incident AD when compared with non-diabetes (RR=1.92, 95% CI:1.03-3.45). After controlling for covariates (age, education, body mass index, smoking status, alcohol intake, APOE genotype, stroke, hypertension, high cholesterol, myocardial infarction, and diabetes) and stratifying by gender, the association was observed in men (RR=3.71, 95% CI:1.54-8.58) but not in women (RR=1.01, 95% CI:0.35-2.48).

In our study, we also found an association with APOE (RR=2.52, 95% CI:1.59-3.97) and AD. However, when stratified by gender, the association was only observed in women and not in men. Due to a small number of studies that have looked at stratification by gender, more insights on gender differences and the role of APOE genotype will need to be further addressed. However, a probable explanation could be

the importance of duration of diabetes on gender differences. This is beyond the scope of the present study and would need to be investigated further.

Future research directions include further exploring the association of APOE genotype, duration of diabetes, and other cardiovascular covariates and examine whether they reveal any independent risks for the development of AD.

COMMENT

The number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity. It is proving itself to be clearly a growing public health threat. Cognitive performance, on the other hand, is an important indicator of health and functioning in elderly people and the ability to maintain cognitive function into old age is agreeably desired by most, if not all. Ultimately, more research is needed to understand the interrelationship between diabetes and cognitive function so that prevention of cognitive impairment may be enhanced if future research determines the underlying mechanisms for the association between diabetes and cognitive decline.[1]

There is also a growing concern and recognition that as the population ages, AD will place an enormous burden on the country because, not only is the cost of care for AD a financial one, it has such a huge impact on individuals, families, the health care system, and society.[2, 3] According to estimates in the U.S., delaying mean onset of AD by approximately 5 years would correspond to a 50% reduction in risk, and would reduce the expected prevalence by 1.15 million people after 10 years (by 2007) and 4.04 million people after 50 years (by 2047).[3] If interventions could delay onset of the disease by 2 years, after 50 years there would be 1.94 million fewer cases than projected; if onset

could be delayed by 1 year, there would be nearly 800,000 fewer prevalent cases.[3] This is a huge public health implication.

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EDUCATION

2000-present	Ph.D.	Utah State University, Logan, UT Department of Nutrition and Food Sciences Emphasis: Nutritional Epidemiology Graduation date: Dec. 2006 Dissertation: Diabetes, cognitive decline, and Alzheimer's disease: The Cache County Study on Memory, Health, and Aging Major Professor: Ronald G. Munger, Ph.D., M.P.H.
1994-1997	M.Sc.	Institute of Nutrition Mahidol University, Salaya, Thailand Major: Food and Nutrition for Development
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PROFESSIONAL EXPERIENCE

2005-2006	Academic Lecturer (Ajarn); Institute of Nutrition Mahidol University (INMU) Member of The Global Alliance for the Prevention of Chronic Diseases; Thailand Taskforce Research-Track Faculty, INMU, Salaya, **THAILAND** Thai Muslim Health Survey project, co-investigator, INMU, **THAILAND** A Research Project on Integration Health Strategies for Well Being among Elderly : Pilot Project in Nakhon Pathom Province; co-investigator, INMU, **THAILAND**

NUFN 601: Perspectives in Human Nutrition, INMU, **THAILAND**

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RANU 607: Nutrition Problem, INMU, **THAILAND**

RANU 610: Nutrient Roles and Functions, INMU, **THAILAND**

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2000-2005	Graduate Research Assistant, Cache County Study on Memory, Health, and Aging, Center for Epidemiologic Studies, Utah State University, Logan, UT, **U.S.A.**
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PROFESSIONAL PRESENTATIONS

Charoonruk G, Munger R, Wengreen H, Corcoran C, Hayden K, Bastian J, Tschanz J, Norton M, Breitner J, Welsh-Bohmer K. Prospective Study of Diabetes, Gender, and Subsequent Risk of Alzheimer's Disease: The Cache County Study on Memory, Health, and Aging. SER/CSEB Joint Meeting: Epidemiology without Borders, Toronto, Ottawa, **CANADA**, June 2005. **[Oral Presentation]**

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INTERNATIONAL MEETINGS, CONGRESSES,

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Sixth International Conference on Dietary Assessment Methods, Copenhagen, **DENMARK**; April 27-29, 2006

Society for Epidemiologic Research: Epidemiology Without Borders, Toronto, **CANADA**; June 27-30, 2005

Ninth International Conference on Alzheimer's Disease and Related Disorders, Philadelphia, Pennsylvania, **U.S.A.**, July 17-22, 2004

Second Congress of International Academy Nutrition and Aging, Albuquerque, New Mexico, **U.S.A.**, July 10-12, 2003

Fourth Meeting of the Inter-Agency Working Group on Food Insecurity and Vulnerability Information Mapping System Meeting (FIVIMS). Bali, **INDONESIA**; February 7-11, 2000.

Second International Conference on Nutrition and Aging. Tokyo, **JAPAN**; September 20-22, 1995

INTERNATIONAL TRAINING

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PROFESSIONAL MEMBERSHIP OF SCIENTIFIC SOCIETIES AND JOURNALS

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PUBLICATIONS

Hayden KM, Zandi PP, Lyketsos CG, Khatchaturian AS, Bastian LA, **Charoonruk G**, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia. Alzheimer Dis Assoc Disord 2006; 20: 93-100.

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