DIABETES AND COGNITIVE IMPAIRMENT

José A. Luchsinger, MD, MPH, Christopher Ryan, PhD, and Lenore J. Launer, PhD

Dr. José A. Luchsinger is Associate Professor of Medicine and Epidemiology, Columbia University Medical Center, New York, NY. Dr. Christopher Ryan is Director, Human Research Protection Program, University of California San Francisco, San Francisco, CA. Dr. Lenore J. Launer is Senior Investigator and Chief, Neuroepidemiology Section, Laboratory of Epidemiology and Population Sciences, National Institute on Aging, National Institutes of Health, Bethesda, MD.

SUMMARY

Cognitive impairment, ranging from mild cognitive impairment to dementia, is increasingly recognized as a potential complication of diabetes. The increase in the prevalence of diabetes along with the aging of the population may result in a large increase in the prevalence of cognitive impairment in persons with diabetes. Approximately one-third of the United States adult population has prediabetes or diabetes. However, about one-half of persons age ≥60 years, who are most at risk for cognitive impairment, have prediabetes or diabetes. The association of diabetes and cognitive impairment may reflect a direct effect on the brain of hyperglycemia or the effects of the diabetes-associated comorbidities, such as hypertension, dyslipidemia, or hyperinsulinemia. There is evidence for an effect of diabetes-related processes on both neurodegenerative and vascular processes, thus contributing to both Alzheimer's-like cognitive impairment, i.e., amnestic, and cerebrovascular-type cognitive impairment characterized by impairment in executive cognitive function.

This chapter reviews epidemiologic studies of the association between diabetes and cognitive impairment in large clinical or community-based studies, emphasizing studies in the United States. Type 1 diabetes is, in general, related to modest decrements in cognitive abilities, primarily in executive-frontal abilities. Type 2 diabetes seems to be more strongly related to vascular and non-amnestic forms of cognitive impairment, including non-amnestic mild cognitive impairment and vascular dementia, but it also seems to have a less strong association with amnestic forms of cognitive impairment, including amnestic mild cognitive impairment and Alzheimer's dementia.

The relation of diabetes to cognitive impairment has therapeutic implications. There is conflicting evidence from clinical trials of diabetes interventions examining the effects of better glucose control on cognition and the brain. Lifestyle interventions among persons with diabetes and prediabetes do not seem to be related to better cognitive outcomes in the long term.

Despite many studies documenting the association between diabetes and cognitive impairment, the causal nature and the mechanisms of this association have not been fully established and require further study.

INTRODUCTION

This chapter describes important concepts in cognitive impairment and epidemiologic data on cognitive impairment in the general U.S. population. Then, the relationship between diabetes and cognitive impairment is explored, including potential mechanisms and epidemiologic data linking the two conditions, as well as implications for treatment and prevention. The review of the epidemiologic data from diabetic cohorts emphasizes large longitudinal studies in the United States and Canada and clinical trials when available. Both type 1 diabetes and type 2 diabetes are covered in this chapter.

DESCRIPTION OF COGNITIVE IMPAIRMENT

To study cognitive impairment, persons with and without diabetes are compared in performance of cognitive tests and by the presence or absence of cognitive disorders, such as mild cognitive impairment (MCI) and dementia. A brief description of these types of cognitive impairment follows. Importantly, in this chapter, Alzheimer's disease (AD) is referred to as one pathologic process underlying cognitive impairment, characterized by the presence of amyloid plaques and neurofibrillary tangles on brain autopsy, and not the manifestation of cognitive impairment, a frequent source of confusion. Dementia, the most severe clinical manifestation of AD, is referred to as AD dementia.

Performance in Cognitive Tests

The most frequently studied cognitive domains broadly defined are memory and executive-frontal abilities. Memory can be defined as the ability to recall an experience after it has ended (1). Memory is tested by repetition of words usually delivered verbally as lists of several words or as a part of tests of global cognition, such as the 5-minute recall of three items in the Mini Mental Status Exam (2). Memory problems are probably the most frequent cognitive complaints that bring patients to medical attention. Several key processes are involved in the long-term maintenance of memories. Consolidation, primarily located in the hippocampal formation, enables the acquisition of new memories (1). Consolidation is the first

and most prominently affected process in AD dementia and its antecedent, amnestic MCI. Another key memory process is retrieval (1), which is most affected by lesions disturbing the frontal lobe-subcortical circuits in the brain. Retrieval deficits manifest as difficulty in recalling words or objects that can be aided by giving multiple choice options or cues (recognition).

Executive-frontal abilities include those skills that are used to plan and execute complex tasks and comprise different processes, such as attention, working memory, and impulse control. Executive-frontal abilities are most often affected by lesions that disrupt the frontal subcortical networks (3), the same network that supports memory retrieval. A common type of lesion that can affect frontal subcortical networks in diabetes is cerebrovascular disease. Commonly used tests of executive-frontal abilities include digits forward and backward (a test in which persons are asked to repeat a number series forward and backward), the attention items of the Mini Mental Status Exam (2), and the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale (4).

An important consideration about the evaluation of performance on cognitive tests as outcomes is the judgment of the clinical significance of differences found between groups, for example, between persons with diabetes and those without diabetes. Some studies will report that persons with diabetes perform less well in a test than persons without diabetes and provide a difference size or the score in performance in both groups. It can be concluded from such data that persons with diabetes will perform less well than persons without diabetes, but the clinical importance of such a difference is uncertain. One way to overcome this problem is by providing standardized differences. One common metric used is Cohen's d (5), which is calculated as the difference between the means divided by the pooled standard deviation. A Cohen's d of 0.2 is considered small, 0.5 is considered medium, and 0.8 is considered large. Some sections of this chapter make reference to Cohen's d in the interpretation of effect sizes.

Mild Cognitive Impairment

MCI is a diagnostic category used to capture the transitional state between normal cognitive function and dementia (6,7) and has become a target for interventions (8). The feature that differentiates MCI from dementia is functional impairment: individuals with MCI still have the ability to function in daily activities (7), while persons with dementia do not. In MCI, general cognitive performance is well preserved, but performance in one cognitive domain falls below expectations for age and education. Typically, it is defined following cutpoints of "pass/fail" results on neuropsychological tests (e.g., 1.5 standard deviations of established norms). This threshold is arbitrary, and the field of cognitive disorders has become interested in even milder forms of cognitive impairment (e.g., using a threshold of 1.0 standard deviations rather than 1.5), which some have termed pre-MCI (9).

MCI can be classified as amnestic and non-amnestic MCI. Amnestic MCI involves memory impairment, while non-amnestic MCI involves predominantly non-memory domains, such as frontal-executive abilities. Amnestic MCI is believed to be an early manifestation of AD and an antecedent of AD dementia, while non-amnestic MCI, such as executive MCI, may be a form of vascular cognitive impairment (VCI) (6). In VCI, cognitive impairment may present slowly and incrementally as subclinical cerebrovascular disease worsens (seen as white matter hyperintensities [WMH] on brain imaging, called mini-strokes by clinicians, and "silent infarcts"), or it may suddenly appear after an infarct. In general, VCI affects executive-frontal abilities and memory retrieval and, similar to amnestic MCI, may or may not progress to the syndrome of dementia. Some experts believe that the cognition field has paid more attention to cognitive impairment due to AD to the detriment of the identification of the other forms of cognitive impairment described here, particularly those related to executive abilities (10).

This relative lack of research is particularly relevant to persons with diabetes, who likely have cerebrovascular disease and, thus, are at high risk of cognitive impairment involving executive-frontal functions.

Dementia

Dementia is a syndrome characterized by impairment of memory and other cognitive abilities, as well as behavior disorder severe enough to impair the ability to live independently (11). Dementia is the most extreme form of cognitive impairment and the one most often identified in research and clinical practice due to its clinical significance. The most common cause of late-onset dementia is AD (12), comprising between 60% and 80% of cases. Vascular dementia is the second most common cause, comprising about 10% of cases, but approximately 50% of cases of dementia have a vascular component (12). Memory may be affected in vascular dementia, but the main cognitive domains affected are generally related to executive-frontal abilities. An important subgroup of dementia cases, the size of which likely differs across populations, has mixed pathology, having both neurodegenerative lesions typical of AD and cerebrovascular disease, which is "typical" of vascular dementia (13). This mixed dementia is particularly important when discussing cognitive impairment in diabetes, because diabetes is well known to be a risk factor for cerebrovascular disease (14), but whether it causes neurodegenerative disease is less clear (10). Other causes of dementia, such as frontotemporal dementia and Lewy body disease, are less common (15), are not known to be related to diabetes, and are thus not discussed in this chapter.

EPIDEMIOLOGY AND BURDEN OF COGNITIVE IMPAIRMENT IN THE GENERAL U.S. POPULATION
Frequency

Major epidemiologic studies have shown that dementia prevalence increases logarithmically after age 70 years (16) and may reach 50% in persons age ≥85 years (17). According to the 2014 Alzheimer's Disease facts and figures report from the Alzheimer's Association (12), 11% of people age ≥65 years and one-third of

people age ≥85 years have late-onset AD dementia. Given the longer life expectancy of the population, cases of AD dementia in persons age ≥65 years are expected to increase by 40% from current numbers by 2025 (12). Estimates from the 2010 Census revealed that in 2010, there were 4.7 million cases of AD dementia, of whom 0.7 million were age 65–74 years, 2.3 million were 75–84 years, and 1.8 million were ≥85 years (18). Based on these estimates, the projected number of AD dementia cases in 2050 will be 13.8 million, with 7.0 million age ≥85 years. AD dementia is the sixth leading cause of death in the United States and the fifth leading cause for those age ≥65 years (15). As previously mentioned, vascular dementia is the second most common cause, comprising about 10% of cases, but approximately 50% of all cases of dementia have a vascular component (12).

The prevalence of amnestic MCI varies from 3% to 20% depending on the criteria applied (19) and the population studied. Estimates increase from about 1% in persons age 60 years to 25% at age 85 years (20). The Aging, Demographics, and Memory Study estimated the prevalence of cognitive impairment without dementia, similar to MCI, in a representative sample of 856 persons in the United States (21). Twenty-two percent of persons age ≥71 years met the study criteria for cognitive impairment without dementia. Among those, 8% died and 12% progressed to dementia on an annual basis. Persons with amnestic MCI may progress to AD dementia at the rate of nearly 10%–15% per year (6) compared to 1%–2% in elderly persons with normal cognition (7).

It is important to put the epidemiology of cognitive impairment in the context of the epidemiology of diabetes in the United States. Over 100 million U.S. adults have diabetes or prediabetes: 25 million have diabetes and 79 million have prediabetes (22), comprising one-third of the U.S. population. This high prevalence is accounted for in large part by the age group most at risk for cognitive impairment, persons age ≥60 years in whom the prevalence of prediabetes and diabetes is >50% (>60% in minorities) (22,23). A large proportion of this prevalence is accounted for by non-Hispanic blacks and Hispanics (22,24,25), who have about *twice* the prevalence of diabetes compared to non-Hispanic whites (22,24).

An interesting aspect of dementia is that it has ethnic differences similar to those found in type 2 diabetes. In a study from Northern Manhattan in New York City, Hispanics and non-Hispanic blacks had approximately double the prevalence of dementia compared to non-Hispanic whites (26,27). In the same cohort from Northern Manhattan, it was estimated that the higher prevalence of diabetes in minorities could account for some of the ethnic disparities in cognitive impairment, including MCI and dementia, among persons age ≥65 years (28).

Causes, Risk Factors, Prevention, and Treatment of Cognitive Impairment
The pathologic hallmark of AD is the presence of amyloid plaques and neuro-fibrillary tangles identified in brains that have come to autopsy (29). To date, the accumulation of amyloid and its

prevention (30) have received the most attention in studies of causes, prevention, and treatment of AD.

In 2010, an expert panel from the National Institutes of Health concluded that there was insufficient evidence to recommend treatment or prevention for AD dementia (31). The genetic causes of early-onset, familial AD dementia are known (32), but this form represents a minority of cases and is not the focus of this chapter. *APOE-ε4*, encoding a form of apolipoprotein E, is the only robust genetic susceptibility risk factor for late-onset AD dementia, occurring in up to 50% of cases. However, it has not proved useful for diagnosis, prevention, or treatment (33,34,35). In addition, *APOE-ε4* has lower predictive value in non-Hispanic blacks and Hispanics compared to non-Hispanic whites (27,33). Among nongenetic risk factors, older age, lower education, and diabetes (36) are the most robust. Studies of hypertension in relation to dementia have shown that mid-life exposure to risk factors may be a better indicator of future risk for dementia than measures obtained close to the time that cognitive impairment is detected (37,38). Other factors, such as smoking, dyslipidemia, diet, and physical activity, have been studied, but results are inconsistent (39). Risk factors for VCI (40) are mainly those associated with cerebrovascular disease, including diabetes and other vascular risk factors, such as hypertension and dyslipidemia (41).

## POTENTIAL MECHANISMS LINKING DIABETES AND COGNITIVE IMPAIRMENT

Diabetes and its related conditions, adiposity and hyperinsulinemia, and their clustering with other vascular risk factors, such as hypertension and dyslipidemia (42), are known to increase the risk for cerebrovascular disease (14,41,43,44,45,46). In addition, insulin or diabetes-related byproducts may affect the amyloid cascade that is thought to be responsible for AD (47). Thus,

potential mechanisms linking diabetes with cognitive impairment are classified as cerebrovascular and non-cerebrovascular.

CEREBROVASCULAR SUBSTRATES
Infarcts, ascertained by clinical history as strokes causing neurologic deficits (48) or identified as focal lesions on brain imaging (49), are related to a higher risk of AD dementia and vascular dementia.

The mechanisms for the association with AD dementia are not clear. However, the presence of infarcts in persons with AD neuropathology may result in an increase in brain injury and increase the likelihood of reaching a clinical dementia endpoint in the presence of such neuropathology (50,51).

FIGURE 24.1. Relation of Glycemia and Insulin Resistance to Risk of Alzheimer's Disease Neuropathology, the Hisayama Study, 1998–2003
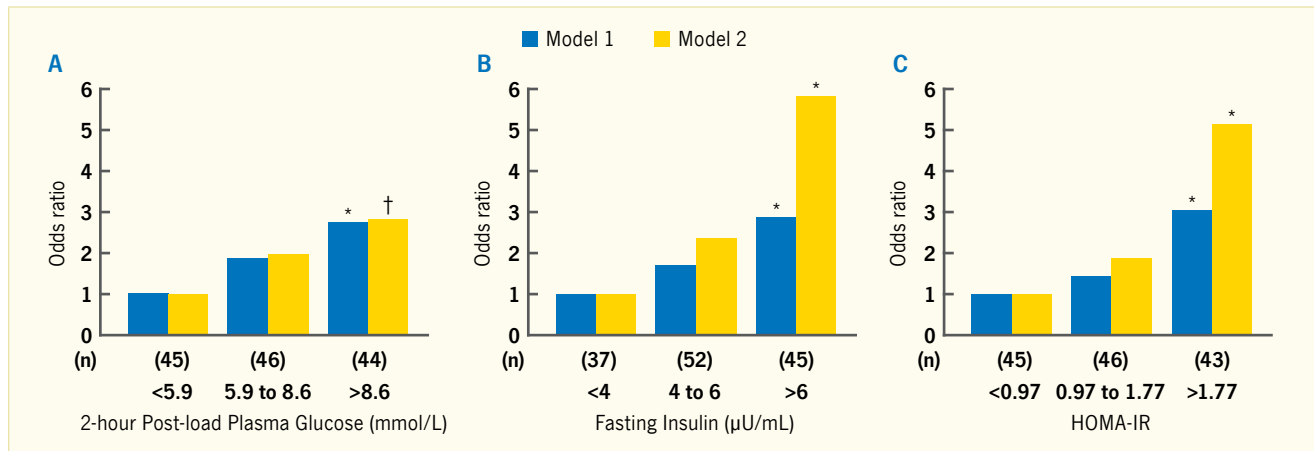
Odds ratios for each tertile of (A) glucose, (B) insulin, and (C) HOMA-IR versus the lowest tertile for the presence of neuritic plaques. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, systolic blood pressure, total cholesterol, body mass index, current smoking, regular exercise, and cerebrovascular disease. Conversions for glucose and insulin values are provided in *Diabetes in America Appendix 1 Conversions*. HOMA-IR, homeostasis model assessment of insulin resistance.
* p<0.05 versus the lowest tertile
† p<0.10 versus the lowest tertile

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White matter disease, called mini-strokes by clinicians, is ascertained as WMH, also known as leukoaraiosis, on brain imaging (40). WMH may represent microvascular disease in the brain or demyelination. However, the nature of WMH is still not well understood. WMH are thought to be ischemic in origin in the same way that infarcts are (52) and, thus, have been proposed as surrogate markers of cerebrovascular disease (52). However, WMH are common in AD dementia, and some may be related to cerebral amyloid angiopathy (53,54,55,56), a correlate of AD, inflammation, or other demyelinating processes. WMH are common correlates of cognitive impairment in diabetes (57), but it is unclear whether these WMH are markers of microvascular injury or if they represent a process related to amyloid deposition or another neurodegenerative process.

NON-CEREBROVASCULAR MECHANISMS

Hyperinsulinemia caused by insulin resistance is an important antecedent and companion of type 2 diabetes (58,59). Hyperinsulinemia is a plausible risk factor for AD dementia, independent of cerebrovascular disease for several reasons. Insulin can cross the blood brain barrier (60), and peripheral insulin infusions in the elderly may affect amyloid levels in cerebrospinal fluid (61), an indirect marker of AD risk. In addition, insulin receptors

in important brain structures, including the hippocampus and entorhinal cortex, are affected early in AD (62). Insulin and amyloid are competing substrates for insulin-degrading enzyme, which has been linked to clearance of amyloid in the brain (63). Insulin in the brain can increase the deposition of amyloid and Tau protein phosphorylation, which are central to the pathogenesis of AD (60). The pathways relating insulin in the periphery with amyloid clearance in the brain are multiple and complex (64). One potential pathway is that peripheral hyperinsulinemia downregulates insulin uptake in the blood brain barrier due to saturation over physiologic levels (65). This may result in reduction of insulin levels in the brain, as well as downregulation of the expression of insulin-degrading enzyme (66) and reduction in its related amyloid clearance function (63). This complex observation has been used to support the seemingly paradoxical use of rosiglitazone, an insulin sensitizer (67,68), and intranasal insulin (69) in the treatment of AD dementia.

Advanced glycation endproducts (AGEs) are closely linked with glycemia and diabetes and have also been related to AD. Glycated hemoglobin (A1c), used by clinicians to track diabetes control, is the most common example of an AGE. With hyperglycemia, diabetic animal and human tissues increase both AGEs and

their receptors (RAGE) (70,71,72), and AGEs are known to be related to the traditional microvascular complications of type 2 diabetes (73,74,75,76,77,78). Increased expression of RAGE is also observed in AD dementia (79,80,81), and expression of RAGE is enhanced in blood vessels near amyloid deposits in AD brains (79,82).

Several studies have examined the relation between diabetes and dementia mechanisms, particularly surrogate markers of AD, and found conflicting results. These markers have included neuropathology studies, brain imaging studies, and studies of other biomarkers. Neuropathology studies from 233 participants in the Religious Orders Study, a study of deceased older Catholic nuns, priests, and brothers from across the United States (83), and from a study of 385 nursing home residents who underwent autopsy (84) found that a history of diabetes was not related to AD neuropathology, similar to a study in a Finnish population (85). However, a study of Japanese Americans in Hawaii found that diabetes was associated with higher prevalence of AD neuropathology (86). The most compelling neuropathology study to date found, in a Japanese sample, that increased glycemia and insulin resistance measured 10 years before autopsy were related to increased risk of AD neuropathology (Figure 24.1) (87). One

brain imaging study in the United States found that insulin resistance was related to a profile of brain metabolism on brain positron emission tomography (PET) that is consistent with AD (88). Similarly, another brain imaging study from the United States among 749 persons with a mean age of 79 years found that diabetes was associated with a brain metabolism pattern similar to AD, but not with increased amyloid brain accumulation, as ascertained with brain PET with an amyloid ligand (Figure 24.2) (89). A study from the Baltimore Longitudinal Study of Aging (BLSA) (90) found among 197 persons with autopsy at a mean age of 88 years that hyperglycemia, insulin resistance, and diabetes assessed approximately at age 66 years were not associated with increased brain AD pathology. The same study had data on 53 subjects with brain amyloid PET acquired at a mean age of 79 years and also found no evidence of a relation with brain amyloid.

The conflicting results of these studies do not help resolve the question of whether diabetes is related to brain amyloid accumulation. The limitations of the neuropathology studies include survival bias and selection bias and the lack of proper ascertainment of diabetes status compared with the previously mentioned Japanese study with detailed data on glycemia and insulin resistance

FIGURE 24.2. Patterns of Brain Metabolism and Amyloid Brain Accumulation by Positron Emission Tomography, by Diabetes Status and Cognitive Impairment, Mayo Clinic Study of Aging, 2006–2012
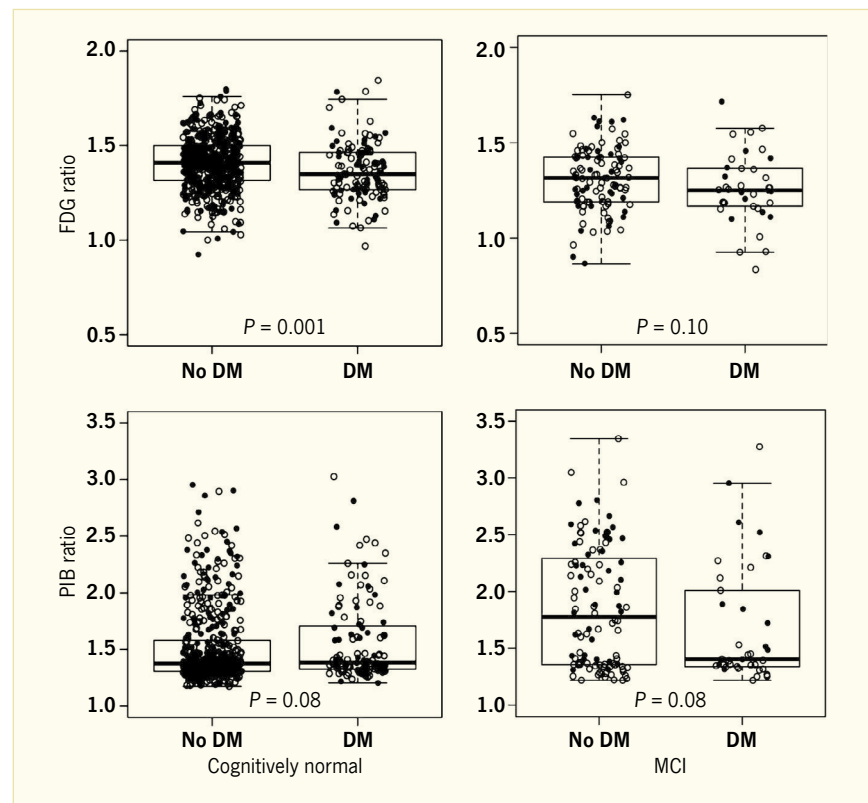
Box plots for 18F-FDG and 11C-PiB retention ratio in Alzheimer's disease signature regions by diabetes mellitus (DM) in cognitively normal subjects and those with mild cognitive impairment (MCI). ● = women; ○ = men.

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that found that hyperglycemia and insulin resistance were related to AD pathology (87). The limitations of the few amyloid brain imaging studies include old age and small clinic samples, which also suffer

from survival and selection biases (i.e., persons with diabetes may have a higher mortality risk that could result in survival bias and affect the study of dementia and neuropathology outcomes).

TYPE 1 DIABETES AND COGNITIVE IMPAIRMENT

Historically, most research on the relationship between type 1 diabetes and cognitive impairment was conducted on relatively small "convenience" samples, and was restricted to children or young and middle-aged adults. Cognitive status was typically measured with a battery of neuropsychological tests that assessed multiple cognitive domains, including attention/concentration, learning and memory, mental and motor speed, visual perceptual skills, and reasoning or "executive function" (91,92). Because the focus was on identifying mild to moderate decrements in cognitive functioning, dysfunction was operationally

defined in terms of performance differences between demographically similar subjects with and without diabetes. Most recent studies have expressed these as standardized differences (e.g., z score differences; Cohen's d) (93). With very few exceptions (94,95), researchers have not made formal ratings of clinically significant impairment like dementia or MCI, largely because it is quite unusual to find clinical evidence of serious cognitive impairments in this patient population. Drawing on results from 15 studies comprising 1,029 subjects with diabetes and 751 control subjects, Gaudieri et al. (96) found modestly poorer performance

among those children and adolescents with diabetes. Effects were largest for measures of "crystalized intelligence"— factual information about the world, verbal learning, and visual and motor integration. Because a number of studies have consistently indicated that children with an "early onset" of diabetes—usually diagnosis before age 6 or 7 years—perform more poorly than those with a later onset of diabetes (97), the meta-analysis was repeated, but comparing early-onset with later-onset subjects. The magnitude of the cognitive differences was found to be somewhat larger in persons with early onset of diabetes compared with

later onset, with more domains equal to or greater than an effect size (Cohen's d) of 0.15, considered a small difference as compared with controls. Taken together, these results support the view that in children and adolescents, diabetes is associated with modest decrements on a range of cognitive skills, with these effects being greatest in those youngsters who were diagnosed with diabetes early in life. Another meta-analysis, adding several newer studies (24 studies published between 1980 and 2005), identified a generally similar pattern of results (98), with modest differences between diabetic and nondiabetic samples (Cohen's d 0.15–0.30) evident on tests of verbal and performance intelligence, as well as on measures of visuospatial ability, motor speed, attention, and reading and writing.

In terms of cognition in adults with type 1 diabetes, Brands *et al.* (99) published a meta-analysis of 33 studies published between 1980 and 2004 that included adults age >18 years and a comparison group of subjects without diabetes. In virtually all studies, subjects were age <50 years at the time of the cognitive assessment. As illustrated in Figure 24.3 (99), adults with type 1 diabetes performed consistently more poorly than controls on measures of overall cognition, intelligence, psychomotor efficiency, speed of information processing, cognitive flexibility, attention, and visual perceptual skills. The largest effect sizes (Cohen's d 0.5–0.7) were found on measures of crystalized intelligence, fluid intelligence (e.g., problem-solving, reasoning), psychomotor efficiency, and cognitive flexibility, which fall under the umbrella of non-amnestic cognitive function. It is noteworthy that with the exception of measures of crystalized intelligence, the other cognitive domains that were most affected by diabetes tended to be those that required rapid responding or were otherwise time-limited. Despite the relatively small sample sizes of the studies included in this analysis, as well as the wide range of measures used by the different researchers, these results are remarkably consistent with those reported in studies

FIGURE 24.3. Meta-Analysis of Cognitive Performance Among Adults With Type 1 Diabetes
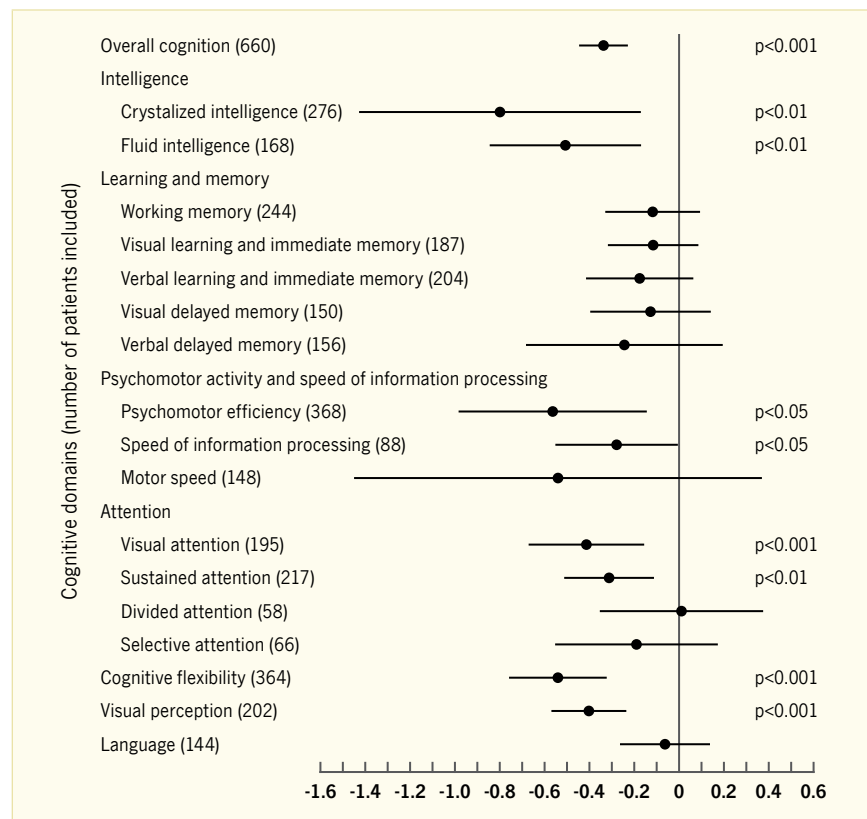
Standardized effect sizes (Cohen's d) and 95% confidence intervals for the cognitive domains in patients with type 1 diabetes compared with nondiabetic control subjects. Number of patients included in each domain is listed between parentheses. Nonsignificant p-values are not shown. Points to the left of 0 indicate worse cognitive performance in persons with type 1 diabetes compared to controls without diabetes.

SOURCE: Reference 99, copyright © 2005 American Diabetes Association, reprinted with permission from The American Diabetes Association. References for individual studies are available from Reference 99.

of children and adolescents: intelligence, as measured by formal IQ tests, is consistently lower—by about 3 to 5 points on average (the majority of the general population is between 85 and 115 points of IQ)—and performance is slower—by 5%–15%—on tasks that require attention and rapid responding.

The only large-scale study to comprehensively assess adolescents and adults with type 1 diabetes over time is the Diabetes Control and Complications Trial (DCCT), conducted in 29 sites in the United States and Canada (100). This clinical trial, which compared the effects of intensive insulin therapy (multiple daily injections) with conventional therapy (one or two daily injections), was designed to test the hypothesis that intensive therapy delayed or prevented the development of microvascular and neuropathic complications. Because intensive therapy was known to increase the incidence of

severe hypoglycemia and because earlier studies had demonstrated that severe hypoglycemia could adversely affect the structural and functional integrity of the brain, the DCCT study group developed a comprehensive battery of neurocognitive tests that was administered at study entry and repeated at years 2, 5, 7, and/or study end. Data from 1,441 subjects, followed for an average of 6.5 years, demonstrated that intensive insulin therapy did not differentially disrupt functioning on any of the eight cognitive domains studied. Despite high rates of hypoglycemia in the study group, there was no relationship between moderately severe hypoglycemia and performance on any cognitive test (95,101). Use of an innovative clinical rating procedure (102) showed very low rates of clinically significant worsening over time (by year 5, only 23 of 1,383 subjects showed significant cognitive decline), and these effects were unrelated to hypoglycemia.

The Epidemiology of Diabetes Interventions and Complications (EDIC) study, a follow-up assessment of the DCCT cohort (N=1,144), studied a mean of 18 years following study entry, also showed no between-group differences on any cognitive domain nor any relationship between recurrent episodes of hypoglycemia and change in cognitive functioning over time (Figure 24.4) (103). However, poorer metabolic control, operationalized as a time-weighted A1c value of ≥8.2% (≥66 mmol/mol), was associated with consistently poorer performance over time on two cognitive domains: psychomotor efficiency and motor speed.

Subsequent analyses, focusing on predictors of cognitive changes over time, demonstrated that after controlling for age and education, proliferative retinopathy, renal complications, and time-weighted A1c values were each independently and significantly associated with declining performance on measures of psychomotor efficiency (104). This work is consistent with earlier longitudinal studies (105) that link the development of microvascular complications to psychomotor slowing in adults with type 1 diabetes.

FIGURE 24.4. Effects of DCCT Treatment Group, Severe Hypoglycemia, and Glycated Hemoglobin on Changes in Cognition, From Entry Into DCCT to Year 12 in the EDIC Study

A. Original treatment assignment

B. Number of severe hypoglycemic events

C. Degree of metabolic control
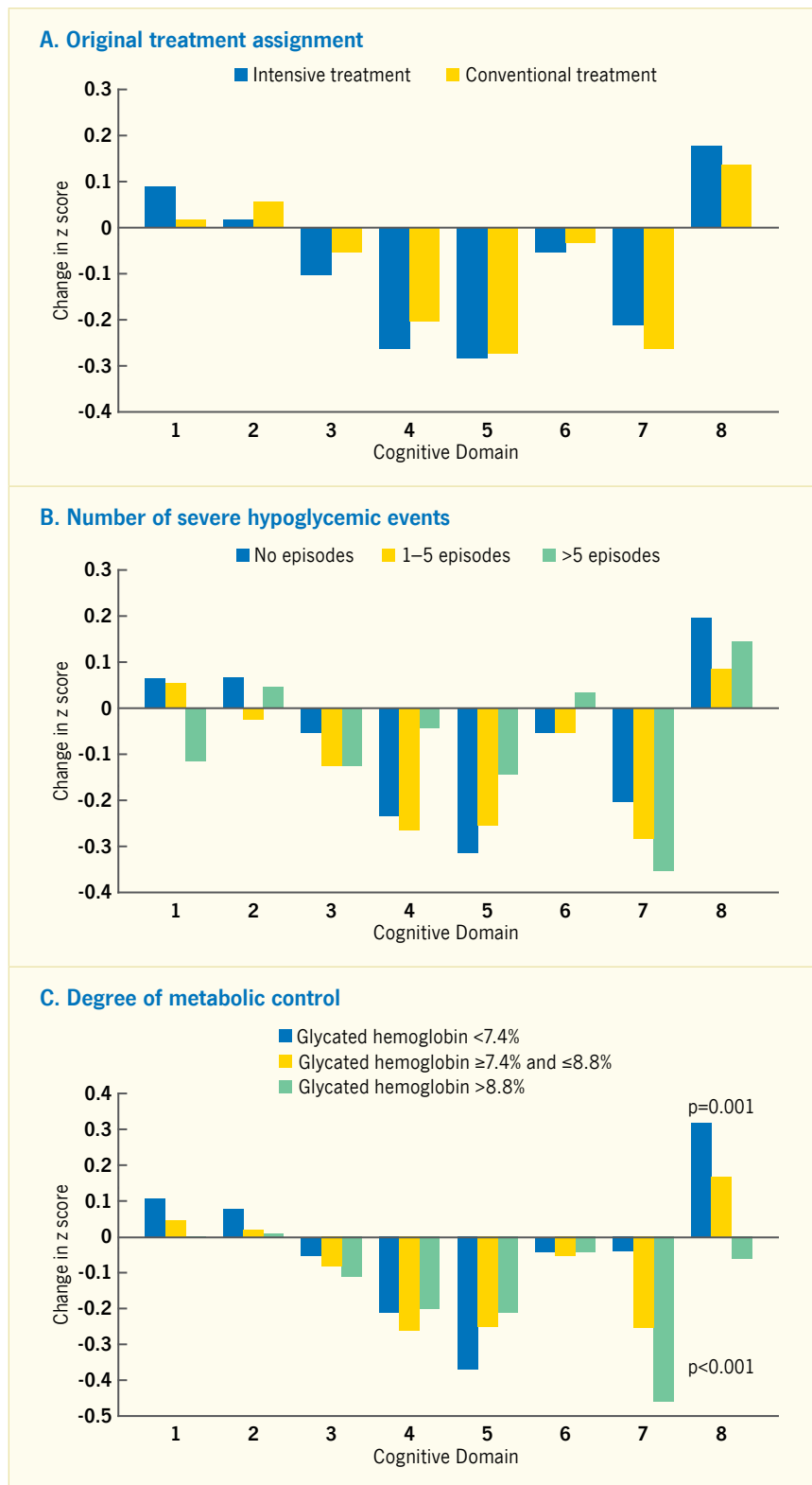
The bars show the changes within cognitive domains between cognitive testing at baseline in DCCT and follow-up testing (a mean of 18 years after baseline) expressed as (A) changes in z scores for intensive versus conventional treatment, (B) frequency of episodes of severe hypoglycemia (coma or seizure), and (C) mean glycated hemoglobin values. Across the three groups, higher levels of glycated hemoglobin were associated with moderate declines in psychomotor efficiency (p<0.001) and motor speed (p=0.001), but no other cognitive domain was affected significantly. Cognitive domains are numbered as follows: 1, problem solving; 2, learning; 3, immediate memory; 4, delayed recall; 5, spatial information; 6, attention; 7, psychomotor efficiency; and 8, motor speed. Conversions for glycated hemoglobin values are provided in *Diabetes in America Appendix 1 Conversions*. DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications study.

SOURCE: Reference 103, copyright © 2007 Massachusetts Medical Society, reprinted with permission

TYPE 2 DIABETES AND COGNITIVE IMPAIRMENT

DIABETES, COGNITIVE DECLINE, AND MILD COGNITIVE IMPAIRMENT

The difference in cognitive function between those with and without diabetes is relatively robust across cohort studies, although results vary in terms of which specific functions differ between the two groups. Over 4 years, a cohort of 999 individuals age 44–89 years was followed in the Rancho Bernardo Study, a population-based study conducted in suburban southern California. Diabetes, ascertained by glucose tolerance testing, was associated with faster decline in a verbal fluency test (a test of executive-frontal abilities), but not a decline in the Mini Mental Status Exam (a test of global cognition) or Trail Making Tests (another test of executive-frontal abilities) (106). The Atherosclerosis Risk in Communities Study (ARIC) was a prospective epidemiologic study of 10,963 persons age 47–70 years in four U.S. communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis, Minnesota). ARIC showed that diabetes, ascertained by self-report or fasting glucose, was a strong predictor of decline in the DSST of the Wechsler Adult Intelligence scale and the word fluency test, both tests of executive-frontal abilities, after 6 years of follow-up (107).

Self-reported diabetes was related to a twofold higher risk of developing MCI among 7,027 osteoporotic post-menopausal women with a mean age of 66 years participating in a clinical trial of the osteoporosis medication raloxifene in 25 countries, including the United States (108). A multiethnic study of 1,088 subjects age ≥65 years in New York City found that diabetes was related to a higher risk of cognitive impairment-without dementia with stroke, but not of cognitive impairment-without dementia without stroke, after adjusting for demographic variables and the presence of the *APOE-ε4* allele (26). A Canadian prospective study in 5,574 persons age ≥65 years similarly found that diabetes was related only to VCI-without dementia (109). Another study in 918 subjects age ≥65 years in New York City found that diabetes was related to a higher risk of both amnestic and non-amnestic MCI, highlighting the importance of diabetes for both AD and VCI (110). A study of 1,640 subjects age 70–80 years from Olmstead County, Minnesota, reported that longer diabetes duration and treatment with insulin, a surrogate marker of diabetes severity, were related to higher MCI risk (111).

DIABETES AND DEMENTIA

Numerous studies conducted in a wide range of ethnic groups have examined the relation between diabetes and dementia (112,113). Table 24.1 shows the results of representative prospective studies in the United States. In general, the association between diabetes and dementia seems to be strongest for vascular dementia or AD dementia with vascular comorbidity, paralleling the findings for studies examining cognitive performance and non-dementia cognitive impairment as outcomes. One of the most compelling reports documenting the association between diabetes and dementia came from a study of 2,067 subjects age ≥65 years from Washington State with repeated measures of glycemia (114). In this study, increased glucose levels were related to a higher risk of dementia both among persons with and without diabetes. For example, for an average glucose level of 190 mg/dL (10.55 mmol/L) compared with 160 mg/dL (8.88 mmol/L), there was a 40% increased risk of dementia (Figure 24.5) (114). Some studies have also reported a greater risk of dementia among persons with diabetes and the *APOE-ε4* allele compared to persons with one of these risk factors or others (86,115), suggestive of gene-environment interaction.

TABLE 24.1. Summary of Epidemiologic Studies From North America Relating Type 2 Diabetes and Dementia

| YEARS (REF.)	POPULATION	SAMPLE	STUDY CHARACTERISTICS	STATISTICS
1970–1984 (153)	Historical cohort in Rochester, Minnesota	1,455 persons with diabetes; age ≥45 years	Dementia ascertained by medical record abstraction. Standardized morbidity ratios calculated using expected age- and sex-specific dementia rates.	Persons with diabetes exhibited significantly increased risk of all dementia (RR 1.66, 95% CI 1.34–2.05) and Alzheimer's disease (AD) dementia (for men, RR 2.27, 95% CI 1.55–3.31; for women, RR 1.37, 95% CI 0.94–2.01).
1991–1996 (26)	Multiethnic cohort from New York City recruited between 1992 and 1994	1,262 subjects without dementia at baseline; mean age 75.6 years	Diabetes diagnosed by self-report or use of diabetes medications. Dementia and dementia subtype diagnosed by standard research criteria.	The adjusted relative risk of AD dementia among persons with diabetes compared to those without diabetes was 1.3 (95% CI 0.8–1.9). The adjusted relative risk of stroke-associated dementia in persons with diabetes was 3.4 (95% CI 1.7–6.9).
1991–1992 (109)	Canadian Study of Health and Aging	5,574 subjects; mean age 74±6.4 years	Diabetes diagnosed by self-report. Dementia diagnosed by research criteria.	Diabetes at baseline was associated with incident vascular dementia (RR 2.03, 95% CI 1.15–3.57), but not with mixed AD/vascular dementia (RR 0.87, 95% CI 0.34–2.21), or AD dementia (RR 1.30, 95% CI 0.83–2.03), or all dementias (RR 1.26, 95% CI 0.90–1.76).
1991 and 1994 (86)	Population-based cohort of Japanese American men enrolled in the Honolulu-Asia Aging Study	2,574 subjects; mean age 76.9 years	Diabetes ascertained by interview and direct glucose testing. Dementia assessed by research criteria.	Diabetes was associated with total dementia (RR 1.5, 95% CI 1.01–2.2), AD dementia (RR 1.8, 95% CI 1.1–2.9), and vascular dementia (RR 2.3, 95% CI 1.1–5.0). Individuals with both type 2 diabetes and the *APOE-ε4* allele had a relative risk of 5.5 (95% CI 2.2–13.7) for AD dementia compared with those with neither risk factor.

TABLE 24.1. (continued)

YEARS (REF.)	POPULATION	SAMPLE	STUDY CHARACTERISTICS	STATISTICS
1994–2003 (154)	Religious Orders Study across the United States	824 nuns, priests, and brothers; mean age 75 years	Diabetes ascertained by self-report or use of medications. AD ascertained by research criteria.	Diabetes was related to higher risk of AD dementia (HR 1.65, 95% CI 1.10–2.47).
1964–1973 and 1994–2003 (155)	Participants of a health maintenance organization in Northern California	8,845 subjects	Diabetes ascertained when participants were between ages 40 and 44 years. Dementia ascertained when participants were between ages 70 and 74 years. Both diabetes and dementia ascertained from medical records.	Diabetes was related to a higher risk of dementia (HR 1.46, 95% CI 1.19–1.79).
1992–2000 (115)	Cardiovascular Health Study	2,547 subjects; mean age 74.67 years	Diabetes ascertained by fasting blood glucose or clinical history. AD ascertained by research criteria.	Diabetes was only related to dementia (HR 1.44, 95% CI 1.03–2.01), AD dementia (HR 1.62, 95% CI 0.98–2.67), and mixed AD (HR 1.75, 95% CI 1.00–3.04), but not vascular dementia (HR 0.80, 95% CI 0.30–2.09). Compared with those who had neither diabetes nor APOE-ε4, those with both factors had a significantly higher risk of AD dementia (HR 4.58, 95% CI 2.18–9.65) and mixed AD (HR 3.89, 95% CI 1.46–10.40).
1999–2007 (156)	Cohort from New York City recruited between 1999 and 2001	1,488 subjects; mean age 76.0 years	Diabetes ascertained by self-report. Dementia ascertained by research criteria.	Diabetes associated with a higher risk of AD dementia (HR 1.6, 95% CI 1.0–2.6) and vascular dementia (HR 5.4, 95% CI 0.3–95.0).
1994–2004 (114)	Cohort from the Group Health Cooperative in Washington State	2,067 subjects; mean age 76 years	Glycemia measured with glucose or glycated hemoglobin (A1c).	Among participants without diabetes, higher average glucose levels within 5 years before baseline were related to an increased risk of dementia (p=0.01). For a glucose level of 115 mg/dL compared with 100 mg/dL, the adjusted hazard ratio for dementia was 1.18 (95% CI 1.04–1.33). Among participants with diabetes, higher average glucose levels were also related to an increased risk of dementia (p=0.002); for a glucose level of 190 mg/dL compared with 160 mg/dL, the adjusted hazard ratio was 1.40 (95% CI 1.12–1.76).

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions.* AD, Alzheimer's disease; CI, confidence interval; HR, hazard ratio; RR, relative risk.
SOURCE: References are listed within the table.

FIGURE 24.5. Risk of Incident Dementia Associated With the Average Glucose Level During the Preceding 5 Years, According to the Presence or Absence of Diabetes, Adult Changes in Thought Study, 1994–2004
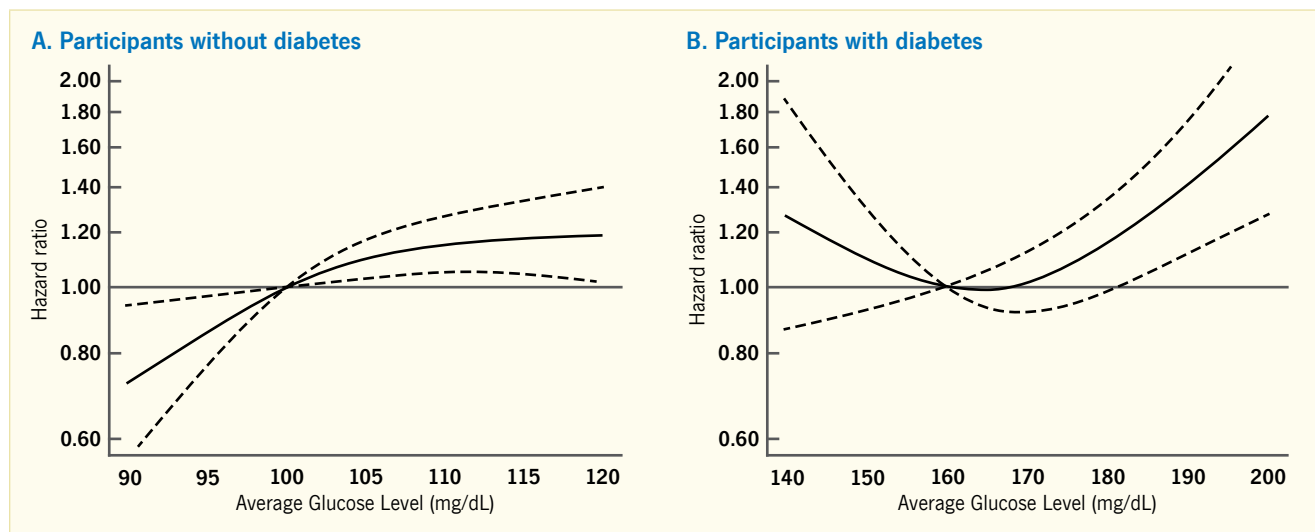
Solid curves represent estimates of the hazard ratios for the risk of incident dementia across average glucose levels relative to a reference level of 100 mg/dL for participants without diabetes (Panel A) and 160 mg/dL for participants with diabetes (Panel B). The dashed lines represent pointwise 95% confidence intervals. Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*.
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Caveats in the Epidemiologic Study of Diabetes and Dementia

The study of diabetes and dementia in older age is affected by competing risks of morbidity and mortality, which may limit the participation of persons with diabetes at baseline or follow-up studies. In other words, since diabetes is an important cause of morbidity and mortality, persons with diabetes may not live long enough or be healthy enough to participate in prospective studies examining the association between diabetes and cognitive impairment, which usually involve populations age ≥65 years. This issue is illustrated by a new analysis of the National Nursing Home Survey 2004 conducted for *Diabetes in America, 3rd edition*. This analysis, based on International Classification of Diseases, Ninth Revision (ICD-9), medical record coding of dementia, showed the prevalence of dementia was lower in persons with diabetes (13.8%) compared to persons without diabetes (21.7%) (Table 24.2). This difference was consistent in all age groups, both sexes, and across race/ethnicity groups (Table 24.2) and among dementia cases residing inside or outside of a dementia care unit (data not shown). This type of bias could also explain the conflicting results of studies examining the association of diabetes and markers of AD pathology on autopsy and brain imaging mentioned previously.

TABLE 24.2. Prevalence of Dementia in Nursing Home Residents, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 2004

CHARACTERISTICS	PERCENT (STANDARD ERROR)	
	Diabetes	No Diabetes
Overall	13.8 (0.73)	21.7 (0.62)
Age (years)		
<20	[2]	[2]
20–44	[2]	[2]
45–54	[2]	5.2 (1.56)
55–64	3.6 (1.21)[1]	10.2 (1.61)
65–74	9.3 (1.46)	16.0 (1.40)
75–84	15.0 (1.29)	25.7 (1.03)
85–94	19.5 (1.55)	24.8 (0.90)
≥95	14.4 (3.89)	19.3 (1.55)
Sex		
Male	11.8 (1.17)	17.4 (1.00)
Female	14.7 (0.88)	23.4 (0.69)
Race/ethnicity		
Non-Hispanic white	15.1 (0.89)	22.6 (0.68)
Non-Hispanic black	10.5 (1.50)	17.6 (1.49)
Hispanic	7.5 (2.23)	18.0 (2.90)

Diabetes is based on ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Dementia is based on ICD-9 codes 290, 294.1, 294.2, and 331. ICD-9, International Classification of Diseases, Ninth Revision.
[1] Relative standard error >30%–40%
[2] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.
SOURCE: National Nursing Home Survey 2004

THERAPEUTIC AND PREVENTION IMPLICATIONS

The association between diabetes and cognitive impairment has three main practical implications: first, diabetes treatment may alter the trajectory to cognitive impairment; second, interventions that prevent diabetes could prevent cognitive impairment; and third, specific diabetes medications could be used in the treatment and prevention of cognitive impairment.

DIABETES TREATMENT AND COGNITIVE IMPAIRMENT

The Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) study (n=2,790) was designed to examine the difference between therapeutic strategies in the rate of cognitive decline and related structural brain changes (116). MIND was embedded in the 2 by 2 factorial ACCORD therapeutic strategy trial that randomized 10,251 persons with longstanding type 2 diabetes, age 55–80 years, and who were at high risk for cardiovascular events in 77 sites in the United States and Canada. All participants were randomized to receive either the intensive glycemic control strategy (target A1c <6.0% [<42 mmol/mol]) or a standard glycemic control strategy (A1c 7.0%–7.9% [53–63 mmol/mol]), with the hypothesis that the more intensive therapeutic strategy would reduce the rate of cardiovascular events more than the standard strategy. The trial also had embedded in it a lipid trial (n=5,518), which tested whether within the context of good glycemic and lipid control (target low-density lipoprotein [LDL] cholesterol level <100 mg/dL [<2.59 mmol/L]) participants receiving a fibrate had fewer cardiovascular events than those receiving placebo. Also embedded was a blood pressure trial that compared cardiovascular events between a therapeutic strategy that followed standard guidelines (systolic blood pressure <140 mmHg) and one that aimed to lower systolic blood pressure goals (<120 mmHg).

The primary outcomes analysis of the MIND substudy focused on the glycemia trial and whether the intensive therapeutic strategy compared to the standard strategy reduced the risk of cognitive decline, measured with three tests covering memory and executive function, in the subset of MIND participants (mean age 62.5 years) (116). This analysis also assessed total brain volume, the primary brain structure outcome, on a subset of MIND participants who underwent brain magnetic resonance imaging. No differences were found between the treatment groups for the cognitive outcomes, but participants in the intensive treatment arm showed larger (better) total brain volumes (TBV). At 40 months, the TBV declined in all participants, but the decline was 0.41% per year in the intensive treatment arm compared with 0.57% per year in the standard treatment arm (Table 24.3) (116). Similarly, there were no differences in the cognitive outcomes in the blood pressure

TABLE 24.3. Cognitive and MRI Primary and Secondary Outcomes, by Glycemia Arm, ACCORD-MIND Study

ENDPOINT	TIME POINT	LEAST SQUARES MEAN (95% CONFIDENCE INTERVAL)		DIFFERENCE IN MEANS†
		Glycemia Intervention		
		Intensive*	Standard*	
DSST	Baseline‡	52.55	52.55	
	20 months	51.51 (51.09–51.93)	50.98 (50.57–51.39)	0.53 (-0.06–1.12), p=0.0756
	40 months	50.93 (50.50–51.35)	50.61 (50.19–51.03)	0.32 (-0.28–0.91), p=0.2997§
	40-month change	-1.62 (-2.05– -1.20)	-1.94 (-2.36– -1.52)	
RAVLT	Baseline‡	7.51	7.51	
	20 months	7.87 (7.77–7.96)	7.85 (7.76–7.94)	0.02 (-0.11–0.15), p=0.7897
	40 months	7.98 (7.88–8.08)	7.99 (7.90–8.08)	-0.01 (-0.14–0.12), p=0.8929
	40-month change	0.47 (0.37–0.57)	0.48 (0.39–0.57)	
Stroop	Baseline‡	32.0	32.0	
	20 months	30.87 (30.16–31.57)	31.46 (30.77–32.16)	-0.60 (-1.59–0.40), p=0.2375
	40 months	31.45 (30.73–32.17)	32.06 (31.34–32.77)	-0.61 (-1.62–0.40), p=0.2383
	40-month change	-0.55 (-1.27–0.17)	0.06 (-0.66–0.77)	
MMSE	Baseline‡	27.39	27.39	
	20 months	27.26 (27.14–27.38)	27.27 (27.15–27.39)	-0.01 (-0.18–0.16), p=0.9268
	40 months	27.05 (26.93–27.17)	27.06 (26.93–27.18)	-0.01 (-0.18–0.16), p=0.9328
	40-month change	-0.34 (-0.46– -0.22)	-0.33 (-0.46– -0.21)	
MRI-TBV	Baseline‡	927.5	927.5	
	40 months	914.4 (912.5–916.4)	909.8 (908.0–911.6)	4.6 (2.0–7.3), p<0.0007§
	40-month change	-13.0 (-15.0– -11.1)	-17.7 (-19.5– -15.9)	

ACCORD-MIND, Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes Study; DSST, Digit Symbol Substitution Test; MMSE, Mini Mental Status Exam; MRI-TBV, magnetic resonance imaging-total brain volume; RAVLT, Rey Auditory Verbal Learning Test.
* For DSST, RAVLT, and MMSE, a negative change value represents a decline in cognitive score. For the Stroop test, a positive change value represents a worsening score. For TBV, a negative change value represents a decline in volume.
† Difference calculated as intensive minus standard arm means.
‡ Baseline mean is the overall mean for both groups combined as measured prerandomization. This value is used to obtain the least squares means estimates at follow-up. Models are adjusted for baseline cognitive score and the factors used to stratify randomization: second trial assignment (BP or Lipid); randomized group allocation within the blood pressure (BP) and lipid trials, respectively; clinical center network; and history of cardiovascular disease.
§ Test of prespecified co-primary outcome.

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or lipid trials. However, one of the earlier analyses explored the relationship between the degree of hyperglycemia and cognitive status through a cross-sectional examination of baseline glycemic control and the cognitive scores obtained on the cognitive tests at baseline. It was reported that higher A1c levels were, indeed, associated with lower cognitive function in these patients (117). Another set of analyses found that depression in the MIND patients was associated with accelerated cognitive decline irrespective of which cognitive domains, treatment arms, or patient subgroups were assessed (118).

The Informatics in Diabetes Education and Telemedicine Study (IDEATel) was a randomized trial of telemedicine versus usual care in 2,169 elderly persons with diabetes conducted in two sites in New York, a rural upstate site and an urban downstate site (119). The telemedicine intervention comprised a telemedicine unit with videoconferencing, email, and clinical data entry capabilities for patients

FIGURE 24.6. Effect of a Telemedicine Intervention Versus Usual Care on Global Cognitive Decline, Informatics for Diabetes Education and Telemedicine Study, 2000–2007
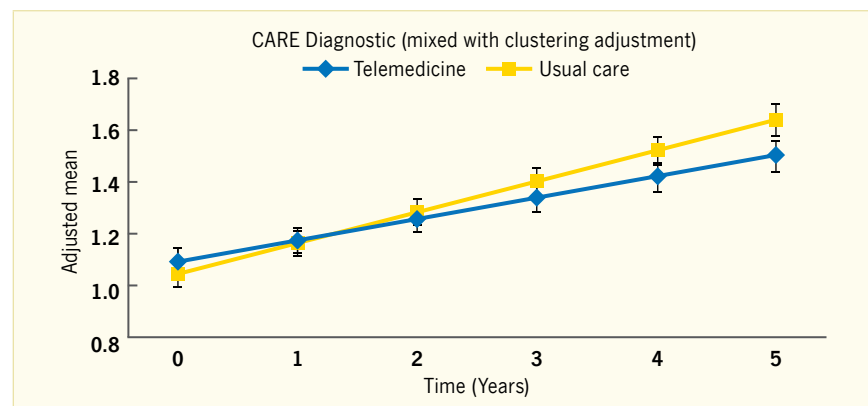
Comparison of changes in adjusted means in the Comprehensive Assessment and Referral Evaluation (CARE) Diagnostic Scale between the intervention and control from mixed models (adjusted for clustering) during a maximum follow-up of 5 years.

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who interacted with nurse care managers to improve their diabetes control. Persons in the IDEATel intervention group showed better diabetes control parameters compared to usual care (120). Estimated differences between the groups at year 5 were 0.29% for A1c, 3.84 mg/dL for LDL, and 4.32 mmHg for systolic blood pressure,

all statistically significant and favoring the telemedicine intervention. Persons in the telemedicine intervention had less global cognitive decline during a maximum of 5 years of follow-up (Figure 24.6) (121). Importantly, the glycemic control goals of IDEATel followed glycemic guidelines (target A1c <7.0%) that were less stringent

than the goals in ACCORD (A1c <6.0%), which showed increased mortality in its intensive glycemic control arm (122). Although the outcome of this study was global cognitive decline, memory was the strongest correlate of global cognitive function in a subset of patients with detailed neuropsychological testing. A mediation analysis demonstrated that among diabetes control parameters, lower glycemia measured with A1c, but not systolic blood pressure or LDL, was the main mediator for the association between improved control and cognitive performance (Figure 24.7) (121). Other analyses from this study restricted to the urban cohort in New York City found that mild memory or executive cognitive impairment (defined as cognitive performance worse than 1.0 standard deviations for the norms for age, sex, and education) were not associated with longitudinal diabetes control (123). Depression was also not associated with diabetes control, whether accompanied or not by mild executive or memory impairment (123). However, these studies did not measure whether persons with cognitive impairment received more assistance for their diabetes care, which could have underestimated the detrimental effects of cognitive impairment on diabetes control.

The Action for Health in Diabetes (Look AHEAD) clinical trial, conducted in 21 sites in the United States, found that a lifestyle intervention among 978 persons with diabetes was not related to cognitive performance 8.1 years after trial enrollment (124), despite clinically significant weight loss in the intervention arm (125).

FIGURE 24.7. Path Diagram Depicting the Direct and Indirect Effects of the Telemedicine Intervention Through Hemoglobin A1c on Cognition, Informatics for Diabetes Education and Telemedicine Study
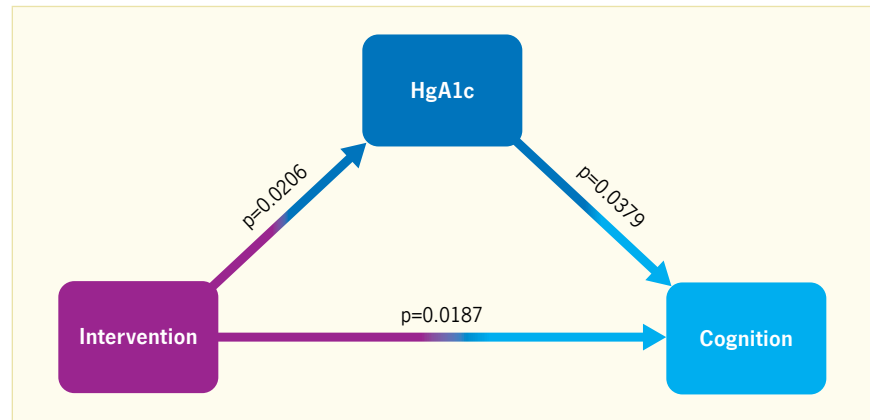
SAS PROC Mixed with a compound symmetry covariance structure was used in the cognition analyses with an adjustment for clustering within primary care provider clusters. HgA1c was treated as a time-varying covariate in the cognition analyses. SAS PROC Mixed was used to predict HgA1c and included adjustments for clustering and heterogeneity of variances in group and residual variances and exponential terms to model the nonlinear distribution of HgA1c over time. A first order auto-regressive covariance structure was used for the HgA1c analyses. Up to six waves of data (baseline plus five follow-up) were included in the analyses. n=2,169. HgA1c, glycated hemoglobin.

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HYPOGLYCEMIA AND COGNITIVE IMPAIRMENT

One of the main complications of diabetes treatment is hypoglycemia, which has long been hypothesized to be a potential mechanism explaining the presence of cognitive impairment in diabetes. A large longitudinal epidemiologic study in 16,667 enrollees in a managed care health plan in Northern California showed that persons with diabetes with reported hypoglycemic events were more likely to develop dementia (Table 24.4) (126). Persons with one episode of hypoglycemia had approximately a 26% increased risk of dementia, while persons with three or more episodes had nearly a doubling in risk of dementia. However, this study did not have information on cognitive performance at the time of hypoglycemia. Thus, the investigators could not rule out that persons who had the type of cognitive impairment that precedes dementia (i.e., MCI) were taking their diabetes medications inappropriately, making them more prone to hypoglycemia. Analysis of the ACCORD-MIND data showed that persons with poor performance at baseline in the DSST, a test of frontal-executive abilities, were more likely to have a hypoglycemic event (127). A 5-point poorer baseline score in the DSST (mean score 52.55) had a 13% increased risk of a first episode of hypoglycemia during a mean follow-up of 3.25 years. These results suggest that cognitive impairment could lead to hypoglycemia, presumably because of inappropriate

TABLE 24.4. Hypoglycemia and Risk of Incident Dementia

NUMBER OF HYPOGLYCEMIC EPISODES†	NUMBER OF DEMENTIA CASES	HAZARD RATIO (95% CONFIDENCE INTERVAL)*		
		Adjusted for Age (as Time Scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes	Additionally Adjusted for Comorbidities‡	Additionally Adjusted for 7-Year Mean A1c Level, Diabetes Treatment, and Years of Insulin Use
1 or more	250	1.68 (1.47–1.93)	1.48 (1.29–1.70)	1.44 (1.25–1.66)
1	150	1.45 (1.23–1.72)	1.29 (1.10–1.53)	1.26 (1.10–1.49)
2	57	2.15 (1.64–2.81)	1.86 (1.42–2.43)	1.80 (1.37–2.36)
3 or more	43	2.60 (1.78–3.79)	2.10 (1.48–2.73)	1.94 (1.42–2.64)

A1c, glycated hemoglobin; BMI, body mass index.
* Analyses combined using Cox proportional hazard models.
† The 1 or more group is compared to 0. The 3 or more group is compared to 0.
‡ Adjustment made using a comorbidity composite scale.

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compliance with diabetes treatment that leads to hypoglycemia, and not the other way around. The lack of an effect of hypoglycemia on cognition is supported by an analysis of the DCCT and its follow-up EDIC study in persons with type 1 diabetes, who are at high risk of hypoglycemic episodes due to insulin treatment and autonomic dysfunction (103). Severe hypoglycemia, which occurred in 40% of this cohort, was not related to cognitive decline during 18 years of follow-up, albeit in relatively young participants.

DIABETES PREVENTION AND COGNITIVE IMPAIRMENT

The landmark Diabetes Prevention Program Outcomes Study (DPPOS) (128), conducted across 25 sites in the United States, measured cognition during follow-up at two time points 2 years apart (129). The Diabetes Prevention Program, the clinical trial preceding the DPPOS, compared lifestyle and metformin interventions with placebo among 3,234 persons with impaired glucose tolerance and showed that both lifestyle and metformin reduced diabetes incidence compared to placebo. During the DPPOS, participants originally randomized to metformin continued the drug, and a group lifestyle intervention was offered to all. Cognition was assessed (n=2,344) in years 8 and 10 of the DPPOS. Memory was assessed with the Spanish English Verbal Learning Test (SEVLT), the DSST, animal (AF) and letter fluency (LF), and a composite score with z scores of these tests. Cognition was similar across the Diabetes Prevention Program arms in Year 8. However, in mixed models adjusted for age at randomization and assessment year, the composite cognitive score was inversely associated with A1c (p=0.0002), indicating that while the interventions that prevented diabetes were not related to cognitive performance, worse glycemia was related to worse cognitive performance cross-sectionally.

DIABETES MEDICATIONS AND COGNITIVE IMPAIRMENT

As reviewed above, the findings that diabetes is related to an increased risk of AD dementia in epidemiologic studies (113), that peripheral hyperinsulinemia may impair amyloid clearance in the brain (47), and that decreased insulin signaling is a feature of AD brains (130) have prompted the testing of diabetes medications for the treatment or prevention of AD dementia.

The thiazolidinediones are powerful insulin sensitizers used in diabetes treatment (131) and have been tested as possible drugs to prevent or slow dementing processes. The thiazolidinedione rosiglitazone was tested for secondary prevention of cognitive decline in mild AD dementia among 511 persons without diabetes and was found to be nonefficacious (68) after promising results in a pilot study of 30 persons with mild AD dementia and MCI (67). However, it seems possible that the negative vascular effects of rosiglitazone (132) could have eclipsed the beneficial effects on AD pathology (133). The thiazolidinedione pioglitazone seems to have a lower risk of myocardial infarction compared to rosiglitazone (edema and congestive heart failure are class-specific and not lower) (134). However, a trial of pioglitazone in 78 adults with MCI found that pioglitazone improved insulin resistance, but there was no effect on cognitive performance after 6 months (135). It should be noted these drugs have concerning side effects, including edema, congestive heart failure, and in the case of rosiglitazone, myocardial infarction (136). The U.S. Food and Drug Administration issued a warning indicating that rosiglitazone carries cardiovascular risks and restricting its use to patients who cannot control their blood glucose by other means (132).

Metformin, a diabetes medication belonging to the biguanide class (137,138) and the most widely used diabetes medication (139), prevents diabetes by suppressing hepatic glucose output, increasing insulin-mediated glucose disposal, increasing intestinal glucose use, and decreasing fatty acid oxidation (140). These actions are accompanied by reduced pancreatic insulin secretion and lower insulin levels in blood in response to glucose loads. Metformin

is usually the first step in pharmacologic treatment of type 2 diabetes (141). There are conflicting data from cell and animal models suggesting that metformin may both increase (142) and decrease (143) AD pathology. Retrospective epidemiologic studies are also conflicting, suggesting that metformin use is associated with both higher (144,145) and lower (146) dementia risk. The DPPOS is the largest study to have examined the effects of metformin among persons with diabetes and those at risk. Metformin exposure over 14.0 years in the DPPOS was not related to cognition (129), suggesting at the very least that it is safe from a cognitive standpoint. A pilot trial of metformin in 80 persons with amnestic MCI without treated diabetes (147) showed that persons in the treatment arm had better memory performance at one year compared with placebo (148). Both the placebo and metformin arms showed improvement in words recalled in a memory test at one year, but the metformin arm showed a significant mean difference of four more words recalled (mean recall at baseline was 34.2 words in the metformin arm and 36.1 in the placebo arm, p=0.32). These results needs to be tested in a larger clinical trial and should be interpreted with caution given the small sample size of the pilot study and the possibility of chance findings. However, these results support those of the DPPOS showing that metformin is at the very least safe from a cognitive standpoint.

Intranasal insulin, used with the purpose of increasing brain insulin (not peripheral insulin), showed preliminary evidence of a cognitive benefit in a pilot study of 25 persons with mild AD dementia (149) randomized to intranasal insulin or placebo. Persons in the treatment group had increased memory savings scores compared to persons in the placebo arm.

The diabetes medication class of glucagon-like peptide agonists (150) increases both insulin secretion and sensitivity and has been hypothesized to be of benefit in AD dementia (151), but this has not been tested in clinical trials.

FUTURE DIRECTIONS AND CONCLUSIONS

An extensive body of research ranging from experimental, clinical, epidemiologic, and patient care studies suggests that diabetes is associated with cognitive impairment from mild to severe forms and including vascular and neurodegenerative forms. The association of diabetes with vascular and non-amnestic forms of cognitive impairment seems to be stronger than that for AD-related and amnestic forms of cognitive impairment. Elucidating the relation between diabetes and cognitive impairment is still an active area of research in many different fields that investigate links among neurodegenerative, vascular, and metabolic processes. Longitudinal studies documenting diabetes onset and cognitive performance at earlier ages than in current studies (most of which use elderly cohorts) are needed. Also important is the development of markers of preclinical cognition that can be used as an outcome in trials of diabetes treatment and prevention. Another important area for more research is the impact of cognitive impairment on diabetes treatment. New reports of an association between diabetes and dementia continue to suggest increased risk of dementia for persons with diabetes. However, the causality of this association has not been established and needs to be further studied. It is possible that processes that underlie both diabetes and AD, such as SorCS1 (152), could explain a link that is not causal. It is also possible that diabetes decreases brain resilience—that is, the brain's ability to resist neurodegenerative and other brain insults—but does not directly cause AD.

Establishing causality is important because it is necessary to know whether diabetes treatment and prevention strategies can be used to prevent dementia. Also, it is important to know whether Alzheimer's-based dementia treatment and prevention strategies that are being tested could be useful in persons with diabetes, or whether other strategies should be pursued. In the meantime, the co-occurring epidemics of diabetes and dementia mean that persons with diabetes are very likely to have cognitive impairment that will affect their ability to take care of themselves, which could result in more adverse dementia and diabetes outcomes. This may have a negative impact on health care systems worldwide.

LIST OF ABBREVIATIONS

A1c . . . . glycated hemoglobin
ACCORD-MIND . . . . Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes study
AD . . . . Alzheimer's disease
AGE . . . . advanced glycation endproduct
APOE . . . . apolipoprotein E
ARIC . . . . Atherosclerosis Risk in Communities Study
DCCT . . . . Diabetes Control and Complications Trial
DPPOS . . . . Diabetes Prevention Program Outcomes Study
DSST . . . . Digital Symbol Substitution Test
IDEATel . . . . Informatics for Diabetes Education and Telemedicine Study
LDL . . . . low-density lipoprotein
MCI . . . . mild cognitive impairment
PET . . . . positron emission tomography
RAGE . . . . receptor of advanced glycation endproducts
TBV . . . . total brain volume
VCI . . . . vascular cognitive impairment
WMH . . . . white matter hyperintensities

CONVERSIONS

Conversions for A1c, glucose, and LDL cholesterol values are provided in *Diabetes in America Appendix 1 Conversions*.

DUALITY OF INTEREST

Drs. Luchsinger, Ryan, and Launer reported no conflicts of interest. Dr. Luchsinger receives honoraria from Springer for his role as co-editor of the book *Diabetes and the Brain*. He also receives a stipend from Wolters Kluwer for his role as Editor-in-Chief of the journal *Alzheimer's Disease and Associated Disorders*.

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