Original Contribution

Cognitive Impairment: An Increasingly Important Complication of Type 2 Diabetes

The Age, Gene/Environment Susceptibility–Reykjavik Study

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Persons with type 2 diabetes are at increased risk of cognitive dysfunction. Less is known about which cognitive abilities are affected and how undiagnosed diabetes and impaired fasting glucose relate to cognitive performance. The authors explored this question using data from 1,917 nondemented men and women (average age = 76 years) in the population-based Age, Gene/Environment Susceptibility–Reykjavik Study (2002–2006). Glycemic status groups included diagnosed diabetes (self-reported diabetes or diabetic medication use; $n = 163$ (8.5%)), undiagnosed diabetes (fasting blood glucose ≥ 7.0 mmol/L without diagnosed diabetes; $n = 55$ (2.9%)), and impaired fasting glucose (fasting blood glucose 5.6–6.9 mmol/L; $n = 744$ (38.8%)). Composites of memory, processing speed (PS), and executive function were constructed from a neuropsychological battery. Linear regression was used to investigate cross-sectional differences in cognitive performance between glycemic groups, adjusted for demographic and health factors. Persons with diagnosed diabetes had slower PS than normoglycemics ($\beta = -0.12$; $P < 0.05$); diabetes duration of ≥ 15 years was associated with significantly poorer PS and executive function. Undiagnosed diabetics had slower PS ($\beta = -0.22$; $P < 0.01$) and poorer memory performance ($\beta = -0.22$; $P < 0.05$). Persons with type 2 diabetes have poorer cognitive performance than normoglycemics, particularly in PS. Those with undiagnosed diabetes have the lowest cognitive performance.

cognition; diabetes mellitus, type 2

The incidence of type 2 diabetes mellitus is increasing worldwide, and the disease, common in older adults, has become a significant public health problem (1). Persons with diabetes are at high risk for macro- and microvascular damage leading to retinopathy, nephropathy, neuropathy, and cardiovascular and cerebrovascular disease. Epidemiologic studies suggest that cognitive impairment may be another complication experienced by older persons with diabetes (2–5). However, the American Diabetes Association (ADA) has not yet included cognitive impairment as a complication of type 2 diabetes in their 2008 treatment guidelines (6). Studies have suggested that duration of diabetes, use of glucose-lowering medications, and degree of glucose control may modulate the risk of cognitive impairment in older persons with type 2 diabetes (4, 7, 8).

Consistent with other complications of type 2 diabetes (9, 10), cognitive impairment might also be present in persons with undiagnosed diabetes and impaired fasting glucose, conditions that are very prevalent in the population (11, 12). While global cognitive dysfunction has been reported in persons with type 2 diabetes (4, 13), there is no consensus on the specific domains of cognition that may be affected by type 2 diabetes and thus which domains can be recommended for testing in diabetics. There have been few community-based studies that have provided data on the profile of cognitive impairment in persons with type 2

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diabetes (2, 14). Further, cognitive function has not been examined in undiagnosed type 2 diabetics, a group that represents approximately one-third of type 2 diabetes cases, indentified in epidemiologic studies on the basis of fasting glucose concentrations (11).

We examined the association of specific measures of cognitive function to 4 categories of glycemic status (normoglycemic, impaired fasting glucose, undiagnosed diabetes, and diagnosed diabetes) in a cohort of older men and women who participated in the Age, Gene/Environment Susceptibility–Reykjavik (AGES-Reykjavik) Study. In secondary analyses, we also examined the relation of cognitive performance to hemoglobin A1c levels, duration of clinically recognized type 2 diabetes, and medication use.

MATERIALS AND METHODS

The AGES-Reykjavik Study is investigating the contributions of environmental factors, genetic susceptibility, and their interactions to the aging of the neurocognitive, cardiovascular, musculoskeletal, and metabolic systems. Details on the study design and the baseline AGES-Reykjavik assessments have been given elsewhere (15, 16). In brief, participants were from the cohort of 30,795 men and women born in 1907–1935 and living in Reykjavik, Iceland, who were followed as part of the Reykjavik Study, initiated in 1967 by the Icelandic Heart Association (17). In 2002, cohort members were reinvited to participate in AGES-Reykjavik. At that time, 11,549 participants from the Reykjavik Study were still alive (38%). From these persons, recruitment order was randomly assigned.

The characteristics of the 2,300 persons selected as compared with all Reykjavik Study participants have been previously described (15). Briefly, 1,310 men (27% of surviving men from the Reykjavik Study cohort) and 1,933 women (29% of surviving women from the Reykjavik Study cohort) were invited to participate in AGES-Reykjavik. Compared with all surviving Reykjavik Study men, those invited to participate in AGES-Reykjavik had higher cholesterol levels, lower triglyceride levels, higher systolic blood pressure, and lower body mass index (weight (kg)/height (m)) at the midlife examination. Compared with all surviving Reykjavik Study women, those invited to participate in AGES-Reykjavik had significantly lower triglyceride levels, lower fasting blood glucose levels, and lower body mass index and were less likely to smoke at the midlife examination. The response rate for AGES-Reykjavik was 75% for men and 68% for women. For both men and women, nonresponders were more likely to have a poor cardiovascular profile at midlife (e.g., higher systolic blood pressure, higher blood glucose) than those who participated in AGES-Reykjavik (15).

Here we report on the first 2,300 participants who completed the AGES-Reykjavik examination, which included a structured in-person questionnaire, a clinical examination, cognitive testing, and brain magnetic resonance imaging (MRI). The in-person questionnaire, clinical examination (including blood drawing), and cognitive testing were conducted during a single visit. MRI scans were taken at a separate visit conducted within 2 weeks of the clinical examination.

AGES-Reykjavik was approved by the Icelandic National Bioethics Committee, the Icelandic Data Protection Authority, and the institutional review board of the US National Institute on Aging, National Institutes of Health. Signed informed consent was given by all participants.

Definition of glycemic groups

Glycemic groups were defined using ADA cutpoints (18). Diagnosed type 2 diabetes mellitus was based on self-reported doctor's diagnosis of diabetes or use of diabetic medication (hypoglycemic medications and/or insulin), which was noted from medication vials brought to the clinic, as well as assessed by means of a standardized questionnaire. Undiagnosed type 2 diabetes mellitus was defined as no self-report of diabetes, no use of diabetes medication, and a fasting blood glucose level greater than or equal to 7.0 mmol/L at the baseline AGES-Reykjavik examination. The definition of impaired fasting glucose followed ADA criteria of no type 2 diabetes and a fasting blood glucose level of 5.6–6.9 mmol/L. In separate analyses, we also defined impaired fasting glucose according to World Health Organization criteria (fasting glucose levels of 6.1–7.0 mmol/L) (19). Hemoglobin A1c, as a measure of glucose control, was also examined in relation to cognitive performance. Measurement of hemoglobin A1c (%) was performed on a Hitachi 912 automatic clinical chemistry analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana), with a turbidimetric inhibition immunoassay for hemolyzed whole blood, traceable to the Diabetes Control and Complication Trial reference.

To further identify factors that may moderate the association between diabetes and cognitive function, we examined the effects of duration of disease, as assessed by questionnaire, and of diabetes-related medication use, assessed from vials the participants brought to the examination.

Neuropsychological testing

The cognitive test battery included multiple tests of 3 cognitive domains. Similarly to investigators in other population-based studies (20, 21), we constructed composite scores for memory, processing speed, and executive function based on a theoretical grouping of tests. The memory composite measure included the immediate- and delayed-recall portions of the California Verbal Learning Test (22). The processing speed composite measure included the Digit Symbol Substitution Test (23), the Figure Comparison Test (24), and the Stroop Test (25) Part I (word naming) and Part II (color naming). The executive function composite measure included the Digits Backward Test (23), the Spatial Working Memory Test of the Cambridge Neuropsychological Test Automated Battery (26), and the Stroop Test, Part III (word-color interference). Composite measures were computed by converting raw scores on each test to standardized z scores (mean $= 0$, standard deviation $= 1$) and averaging the z scores across the tests in each composite. A confirmatory factor analysis, the results of which have been previously reported, showed that the fit of the composites scores was good (27). Interrater reliability

was excellent (Spearman correlations ranged from 0.96 to 0.99 for all tests).

Diagnosis of dementia

Ascertainment of dementia was performed in a 3-step process that has been described elsewhere (15). A consensus diagnosis of dementia based on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, guidelines (28) was made by a panel that included a geriatrician, a neurologist, a neuropsychologist, and a neuroradiologist. There were 128 cases of dementia diagnosed in the first 2,300 AGES-Reykjavik participants.

Potential confounders

We controlled for a number of demographic, health, and vascular risk factors, measured at the AGES-Reykjavik in-person visit, that are associated with both type 2 diabetes and cognitive function. Education and smoking history (never, former, current) were assessed by questionnaire. High depressive symptomatology was classified as a score of 6 or greater on the 15-item Geriatric Depression Scale (29). A cutpoint of 6 on the 15-item Geriatric Depression Scale has been shown to have a sensitivity of 0.91 for the diagnosis of a major depressive episode according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria (30). Visual acuity was measured by participants' responses to lines viewed on an autorefracting device; glasses were worn for the vision assessment, and the presenting visual acuity in each participant's better eye was used for analysis. For this analysis, visual acuity of 20/20 or better was compared with visual acuity worse than 20/20. Signs of retinopathy lesions were assessed on 2 45-degree digital images of the retina centered on the optic nerve and on the macula through the pharmacologically dilated pupil of both eyes. The digital retinal images were evaluated for the presence of retinal microvascular signs, including signs of retinopathy (microaneurysms and hemorrhages), by certified graders (31).

Hypertension was classified as a self-reported doctor's diagnosis of hypertension, use of hypertensive medication, or measured systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90. Body mass index was calculated from measured height and weight. History of myocardial infarction was defined as a self-reported doctor's diagnosis or detection by electrocardiogram.

Brain infarcts and white matter lesions were identified on MRI scans. The MRI protocol has been described previously (15, 27). Briefly, experienced neuroradiologists examined the MRI scan for the presence of cortical, subcortical, and cerebellar infarcts. White matter lesions were scored according to a scale with known properties (32). The top quartile of white matter lesions was classified as a high level of white-matter-lesion pathology. The reliability of the MRI readings was good. The weighted κ statistics were 0.71 for global white matter lesions and 0.66 cerebral infarcts.

Fasting insulin concentration was measured by electrochemiluminescence immunoassay on a Roche Elecsys 2010 automated analyzer (Roche Diagnostics K.K., Tokyo, Japan) using 2 monoclonal antibodies and a sandwich principle. The method was standardized using the World Health Organization's First International Reference Preparation 66/304 (National Institute for Biological Standards and Control, Potters Bar, United Kingdom). Apolipoprotein E genotype (possession of the apolipoprotein E ε4 genotype (yes/no)) was also included as a covariate (33).

Data analysis

Demographic and health characteristics were compared between the 4 glycemic groups using age-adjusted linear models for continuous variables and age-adjusted logistic regression for dichotomous outcomes. The cross-sectional association of cognitive performance and glycemic group was estimated using multivariate linear regression; normoglycemic subjects served as the reference group. Models were adjusted for demographic factors, health and vascular factors, apolipoprotein E genotype, visual acuity, and insulin level.

For the secondary analyses, we logarithmically transformed hemoglobin A1c levels to normalize the data distribution. Disease duration was categorized into 4 relatively equal-sized groups (<1 year, 1–6 years, 7–14 years, and ≥ 15 years); the test for trend by duration of diabetes excluded persons with undiagnosed type 2 diabetes and impaired fasting glucose. Finally, among persons with diagnosed type 2 diabetes, we compared cognitive performance in participants taking hypoglycemic medications or insulin with performance in those who were not taking these medications.

Analytic sample

Among the 2,300 participants who completed the in-person examination, 128 were diagnosed with dementia and an additional 255 were missing information on 1 or more of the cognitive composite measures. The present study sample consists of 1,917 participants who were not demented and who had complete data on the cognitive tests.

RESULTS

Of the 1,917 subjects, 49.8% were normoglycemic ($n = 955$), 38.8% ($n = 744$) were classified as having impaired fasting glucose, 8.5% ($n = 163$) had diagnosed type 2 diabetes mellitus, and 2.9% ($n = 55$) had undiagnosed type 2 diabetes mellitus. Compared with normoglycemics, persons with impaired fasting glucose, diagnosed type 2 diabetes, and undiagnosed type 2 diabetes were more often male, were more likely to be hypertensive, and had a higher average body mass index (Table 1). Persons with diagnosed type 2 diabetes were more likely to have retinopathy, lower average total serum cholesterol levels, and poorer processing speed performance than normoglycemics. Persons with undiagnosed type 2 diabetes had significantly higher education, poorer memory and speed of processing performance and were less likely to have depressive symptoms than normoglycemics.

Glycemic groups and cognitive performance

In the initial and fully adjusted models, persons with impaired fasting glucose (ADA criteria) did not perform

Table 1.   Characteristics of the Study Sample According to Glycemic Status, AGES-Reykjavik Study, 2002–2006[a]

	Normoglycemia (*n* = 955)	Impaired Fasting Glucose (*n* = 744)	Diagnosed Type 2 Diabetes Mellitus (*n* = 163)	Undiagnosed Type 2 Diabetes Mellitus (*n* = 55)
Age, years	76.0 (5.7)	75.3 (5.4)	75.6 (5.4)	75.9 (4.9)
Low education, %	22.8	21.0	21.5	10.9**
Female sex, %	64.4	54.4***	44.2**	45.5**
Depressive symptomatology, %	7.8	5.5	6.0	2.0*
Memory (*z* score)	0.08 (0.89)	0.11 (0.90)	0.01 (0.76)	−0.18 (0.71)*
Speed of processing (*z* score)	0.05 (0.72)	0.12 (0.72)	−0.08 (0.73)*	−0.13 (0.81)*
Executive function (*z* score)	0.04 (0.65)	0.06 (0.66)	0.02 (0.64)	−0.07 (0.55)
Ever smoking, %	54.3	54.4	63.8*	50.9
Body mass index[b]	25.9 (4.1)	27.8 (4.4)***	28.7 (4.3)***	29.4 (5.3)***
Hypertension, %	73.9	80.5**	92.0***	90.9***
Being in top quartile of white matter lesion load, %	20.5	19.0	29.5*	27.3*
MRI cerebral infarct, %	24.6	27.8	39.3***	30.9
Visual acuity of 20/20, %	27.0	27.7	27.0	20.4
Retinopathy, %	19.1	16.0	39.7***	21.2
Apolipoprotein E ε4 genotype, %	27.6	26.9	21.5	23.6
Total cholesterol level, mmol/L	5.8 (1.1)	5.8 (1.2)	5.2 (1.1)***	5.7 (1.2)
Insulin level, μU/mL	7.4 (4.5)	11.5 (7.3)***	17.4 (21.1)***	16.8 (10.9)***
Median hemoglobin A1c level, %	5.6 (5.4–5.8)[c]	5.7 (5.5–5.9)	6.4 (6.0–7.1)***	6.2 (5.8–6.5)***
Median fasting glucose level, mmol/L	5.2 (5.0–5.4)	5.9 (5.7–6.2)***	7.3 (6.3–8.9)***	7.6 (7.2–8.1)***

Abbreviations: AGES-Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik; MRI, magnetic resonance imaging.

* $P < 0.05$; **$P < 0.01$; ***$P < 0.001$ (age-adjusted comparison with normoglycemic group).

[a] Glycemic groups were based on current American Diabetes Association criteria (18). All values are means with standard deviations in parentheses, unless otherwise noted.

[b] Weight (kg)/height (m)^2.

[c] Numbers in parentheses, interquartile range.

significantly differently than normoglycemics in any of the 3 cognitive domains (Table 2). Results were similar when the World Health Organization criteria for impaired fasting glucose were used (data not shown).

Compared with normoglycemics, persons with diagnosed type 2 diabetes had significantly slower processing speed but did not perform significantly differently in memory or executive function; those with undiagnosed type 2 diabetes had significantly poorer memory performance and slower processing speed than normoglycemics (Table 2).

Characteristics of disease severity

Hemoglobin A1c.   Log-transformed hemoglobin A1c level was not related to performance in the 3 cognitive abilities (for processing speed, fully adjusted $\beta = -0.10$, 95% confidence interval (CI): −0.49, 0.29; for memory, fully adjusted $\beta = -0.14$, 95% CI: −0.63, 0.35; for executive function, fully adjusted $\beta = -0.17$, 95% CI: −0.55, 0.20).

Duration of disease.   Of the 163 subjects with diagnosed type 2 diabetes, the median duration of disease was 9 years

(interquartile range, 3–19); 14.7% had had diabetes diagnosed during the past year, 28.8% had been diagnosed 1–6 years before the AGES-Reykjavik study examination, 27.0% had been diagnosed 7–14 years previously, and 29.5% had been diagnosed 15 or more years previously. Compared with participants diagnosed in the past year, those with type 2 diabetes of 15 or more years' duration had higher insulin levels (15.2 μU/mL vs. 22.4 μU/mL; $P < 0.05$). Otherwise, demographic and clinical factors did not vary by diabetes duration. Compared with normoglycemics, persons who had had diabetes diagnosed 15 or more years earlier had significantly slower processing speed and poorer executive function performance (Table 3).

Medication use.   Of the 163 subjects with diagnosed type 2 diabetes, 116 (71.2%) were taking diabetes-related medications. There were no differences in cognitive performance between participants taking medication and those not taking medication (for processing speed, fully adjusted $\beta = 0.03$, 95% CI: −0.22, 0.29; for memory, fully adjusted $\beta = 0.08$, 95% CI: −0.17, 0.36; for executive function, fully adjusted $\beta = -0.09$, 95% CI: −0.31, 0.13).

Table 2. Relation Between Cognitive Performance (z Score) and Glycemic Status, AGES-Reykjavik Study, 2002–2006[a]

Glycemic Status	No. of Subjects	Memory		Speed of Processing		Executive Function	
		β[b]	95% CI	β[b]	95% CI	β[b]	95% CI
Normoglycemia	955	0	Reference	0	Reference	0	Reference
Impaired fasting glucose	744	0.02	−0.06, 0.10	0.02	−0.04, 0.09	−0.01	−0.07, 0.05
Diagnosed type 2 diabetes mellitus	163	0.01	−0.14, 0.14	−0.12*	−0.24, −0.01	−0.01	−0.10, 0.11
Undiagnosed type 2 diabetes mellitus	55	−0.22*	−0.45, −0.01	−0.22**	−0.40, −0.05	−0.12	−0.29, 0.05

Abbreviations: AGES-Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik; CI, confidence interval.

* $P < 0.05$; ** $P < 0.01$.

[a] Glycemic groups were based on current American Diabetes Association criteria (18). Beta coefficients represent the difference in z score from the normoglycemic group reference score.

[b] Adjusted for age, education, sex, depressive symptomatology, body mass index, myocardial infarction, total cholesterol level, apolipoprotein E genotype, hypertension, smoking status, visual acuity, white matter lesion load, magnetic resonance imaging cerebral infarct, and insulin level.

DISCUSSION

In this study, we examined the relation of glycemic status to different domains of late-life cognitive function. Participants with impaired fasting glucose did not perform differently from normoglycemics in any of the cognitive domains examined. However, we found that while both diagnosed and undiagnosed type 2 diabetes were associated with slower processing speed, undiagnosed type 2 diabetes was also associated with poorer memory performance in comparison with normoglycemia. Cognitive performance in processing speed tests was negatively associated with duration of disease.

Our findings suggest that type 2 diabetes is associated with certain cognitive systems but not others. We found that diabetes was associated with processing speed and memory but not with executive function. Our findings were particularly strong for processing speed, which was impaired in participants with both diagnosed and undiagnosed diabetes. These results are consistent with previous work in population-based studies that identified specific cognitive abilities, namely processing speed and specific types of memory, that were associated with late-life type 2 diabetes (2, 14). In both previous studies, processing speed was most strongly associated with type 2 diabetes. Arvanitakis et al. (2) found that both processing speed and semantic memory, but not episodic or

Table 3. Relation Between Cognitive Performance (z Score) and Duration of Type 2 Diabetes Mellitus, AGES-Reykjavik Study, 2002–2006[a]

Glycemic Status and Duration of Diabetes, years	No. of Subjects	Memory		Processing Speed		Executive Function	
		β[b]	95% CI	β[b]	95% CI	β[b]	95% CI
Normoglycemia	955	0	Reference	0	Reference	0	Reference
Type 2 diabetes							
<1	24	−0.04	−0.37, 0.27	−0.05	−0.30, 0.22	0.14	−0.11, 0.39
1–6	47	0.17	−0.05, 0.41	0.03	−0.15, 0.22	−0.01	−0.19, 0.17
7–14	44	−0.03	−0.27, 0.22	−0.11	−0.31, 0.09	0.02	−0.18, 0.22
≥15	48	−0.16	−0.39, 0.08	−0.39***	−0.58, −0.19	−0.23*	−0.43, −0.03
P_{trend}			NS		0.009		0.06

Abbreviations: AGES-Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik; CI, confidence interval; NS, not significant.

* $P < 0.05$; *** $P < 0.001$.

[a] Diabetes classification was based on current American Diabetes Association criteria (18). Beta coefficients represent the difference in z score from the normoglycemic group reference score.

[b] Adjusted for age, education, sex, depressive symptomatology, body mass index, myocardial infarction, total cholesterol level, apolipoprotein E genotype, hypertension, smoking status, visual acuity, white matter lesion load, magnetic resonance imaging cerebral infarct, and insulin level.

working memory, were impaired in participants with type 2 diabetes and suggested that the association between type 2 diabetes and impaired cognition may reflect a vascular process, rather than Alzheimer's pathology. Our composite measure of memory was made up of tests that reflect verbal or episodic memory. Thus, our findings suggest that type 2 diabetes may be associated with cognitive impairment through both vascular processes and Alzheimer's pathology. Indeed, type 2 diabetes is associated with an increased risk of both vascular dementia and Alzheimer's disease, although there is evidence suggesting that the association may be stronger for Alzheimer's disease with cerebrovascular disease (34).

There are a number of vascular and neurodegenerative mechanisms through which type 2 diabetes may affect cognitive function. Chronic hyperglycemia, atherosclerosis, and hemodynamic changes in persons with type 2 diabetes may lead to small vascular changes that are associated with cognitive impairment, including lacunae and microinfarcts (35–38). Hyperglycemia may also be directly toxic to the neuron, leading to its degeneration (39), as reflected in global and hippocampal atrophy (36, 40, 41) as well as neuropathologic markers of Alzheimer's disease (34). More data are presently becoming available on how the comorbid conditions associated with type 2 diabetes, including hyperinsulinemia and hypertension, may contribute, in independent pathways, to vascular disease and neurodegeneration (37, 41). Duration of diabetes represents a composite measure of the physiologic insult of hyperglycemia and other diabetes comorbidities.

Findings on the association between impaired fasting glucose and cognitive function are inconsistent, with some studies showing significantly lower performance in participants with impaired fasting glucose (5) while other investigators report no significant difference in cognitive performance between normoglycemic participants and those with impaired fasting glucose (14, 42). Differences in the ADA criteria for impaired fasting glucose (6.0 mmol/L vs. 5.6 mmol/L or 110 mg/dL vs. 100 mg/dL) may explain some differences between studies conducted before and after 2003, when the criteria changed (43). However, using both current ADA guidelines for impaired fasting glucose (5.6–6.9 mmol/L) and World Health Organization guidelines (6.1–6.9 mmol/L), we did not find a significant difference in performance between participants with impaired fasting glucose and those who were normoglycemic. Decreasing performance from normoglycemia to impaired fasting glucose to type 2 diabetes has been reported in several studies (5, 14); however, significant differences in performance between participants with impaired fasting glucose and those classified as normoglycemic were found in only 1 of these studies (5). The cognitive testing batteries also vary considerably among published studies, potentially contributing to inconsistent findings for cognitive performance. Despite inconsistent findings, impaired fasting glucose is a prediabetic state with a high rate of conversion to type 2 diabetes (44) and is a critical period for interventions designed to prevent or delay the onset of the disease. Thus, the association between impaired fasting glucose and cognitive function warrants further investigation.

We extended the findings of previous studies of type 2 diabetes and cognitive function by distinguishing patients with diagnosed type 2 diabetes from those with undiagnosed type 2 diabetes (2–5, 7, 8, 13, 14, 42). Undiagnosed diabetics represent approximately one-third of patients with type 2 diabetes (11) and have diabetes-related cardiovascular risk factors, including obesity, hypertension, dyslipidemia, and smoking, at rates equal to or higher than those of diagnosed diabetics (9, 10, 45, 46). Complications of type 2 diabetes, including retinopathy (47), neuropathy (47), and peripheral artery disease (48), are present in newly diagnosed cases. In our sample, patients with undiagnosed diabetes had poorer cognitive performance than diagnosed diabetics but a similar cardiovascular risk profile.

Among persons with diagnosed type 2 diabetes, there are a number of factors that may modify the risk of cognitive impairment, including disease control and medication regimens. In this cohort, we did not find an association between medication use or hemoglobin A1c levels and cognitive function. However, diabetes in this study sample was relatively well controlled, as evident from the participants' hemoglobin A1c levels. Thus, the results of the hemoglobin A1c analysis should be interpreted with caution and may not be generalizable to other diabetic populations whose diabetes is less well controlled. To determine how cognitive impairment can be modulated within a diabetic population, larger studies of treatment and long-term glycemic control in type 2 diabetics, such as the Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND) (49), are needed.

This study had several strengths. First, we report results from a large population-based sample that was well characterized with regard to health factors and was nondemented. We were able to separately examine the association of cognitive function to diagnosed and undiagnosed type 2 diabetes. Further, with composite scores, we could robustly identify specific cognitive abilities that may be vulnerable to the biologic changes that accompany type 2 diabetes. However, the results should be interpreted in the context of the limitations of cross-sectional data: Directionality could not be assessed, and survival bias may have occurred. Diabetics with longer durations of disease may have had milder diabetes, and those with the most serious disease may have died prior to follow-up. Further, although we controlled for a number of diabetes-associated comorbid conditions, including hypertension, MRI infarcts, and myocardial infarction, we cannot completely exclude the possibility of their making a contribution to cognitive impairment (50). The cutpoint used for the classification of high depressive symptomology may have been insufficiently sensitive to depression in this sample; thus, depression may have contributed to the cognitive impairment observed in participants with type 2 diabetes. In addition, the executive function composite was comprised primarily of tests of working memory, and the memory composite was comprised of tests from only 1 measure (the California Verbal Learning Test), although both immediate and delayed memory were included in the composite.

Evidence continues to accumulate suggesting that cognitive dysfunction is an important complication of type 2

diabetes. We found that both diagnosed and undiagnosed type 2 diabetes were associated with poor cognitive performance—slower processing speed in particular. The duration of diabetes may modulate the risk of cognitive impairment for certain cognitive abilities. Cognitive impairment in persons with type 2 diabetes has implications for diabetes management and self-care (51). Given the increasing prevalence of type 2 diabetes in older adults and the complexity of disease management in these high-risk individuals, future treatment protocols should be developed with the cognitive status of patients with type 2 diabetes in mind.

ACKNOWLEDGMENTS

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