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Diabetes in Midlife and Cognitive Change Over 20 Years

A Cohort Study

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Background: Type 2 diabetes is associated with dementia risk, but evidence is limited for possible associations of diabetes and prediabetes with cognitive decline.

Objective: To determine whether diabetes in midlife is associated with 20-year cognitive decline and to characterize long-term cognitive decline across clinical categories of hemoglobin A_{1c} (HbA_{1c}) levels.

Design: Prospective cohort study.

Setting: The community-based ARIC (Atherosclerosis Risk in Communities) study.

Participants: 13 351 black and white adults aged 48 to 67 years at baseline (1990 to 1992).

Measurements: Diabetes was defined by self-reported physician diagnosis or medication use or HbA_{1c} level of 6.5% or greater. Undiagnosed diabetes, prediabetes, and glucose control in persons with diagnosed diabetes were defined by clinical categories of HbA_{1c} level. Delayed word recall, digit symbol substitution, and word fluency tests were used to assess cognitive performance and were summarized with a global *Z* score.

Results: Diabetes in midlife was associated with a 19% greater cognitive decline over 20 years (adjusted global *Z*-score difference, −0.15 [95% CI, −0.22 to −0.08]) compared with no diabetes. Cognitive decline was significantly greater among persons with prediabetes (HbA_{1c} level of 5.7% to 6.4%) than among those with an HbA_{1c} level less than 5.7%. Participants with poorly controlled diabetes (HbA_{1c} level ≥7.0%) had greater decline than those whose diabetes was controlled (adjusted global *Z*-score difference, −0.16; $P = 0.071$). Longer-duration diabetes was also associated with greater late-life cognitive decline (P for trend < 0.001). Rates of decline did not differ significantly between white and black persons (P for interaction = 0.44).

Limitation: Single HbA_{1c} measurement at baseline, 1 test per cognitive domain, and potential geographic confounding of race comparisons.

Conclusion: Diabetes prevention and glucose control in midlife may protect against late-life cognitive decline.

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The prevalence of diabetes has increased substantially over the past several decades to approximately 10%, and 21 million adults are affected in the United States (1). Type 2 diabetes is an established risk factor for heart disease, stroke, hypertension, blindness, and kidney disease (2–4). The association of diabetes with dementia risk is well-established (5–7), but the association of diabetes with cognitive decline is less well-characterized. Because cognitive decline is a precursor to dementia, strong risk factors for decline can help identify persons who may benefit from early intervention. The effects of diabetes and early hyperglycemic states assessed in midlife on long-term cognitive decline are relatively uncharacterized (6). Previous studies have been limited by short follow-up and a lack of rigorous adjustment for potential confounding variables, and most were limited to white persons and were done in elderly populations, where associations tend to be weaker (8, 9).

Hemoglobin A_{1c} (HbA_{1c}) level is a measure of the average circulating glucose level in the blood over the preceding 2 to 3 months. It is the standard measure used in the clinical management of diabetes, and its use is now recommended for diagnosis of diabetes and identification of persons at risk for the condition (10). Studies have shown cross-sectional associations between HbA_{1c} level and cognitive scores in persons with diabetes (11, 12). However, there is little evidence prospectively linking better glycemic control to slower cognitive decline, and few studies have examined whether chronic hyperglycemia below the threshold for a diagnosis of diabetes ("prediabetes") is associated with long-term cognitive impairment (13–15).

Our objective was to examine the association of diabetes assessed in middle age with subsequent 20-year cognitive decline in a community-based population of black and white adults. We also examined the associations of prediabetes and glycemic control in the setting of diabetes with 20-year cognitive decline. An inherent challenge to accurately quantifying the long-term risk factor associations in observational studies is that participants who are ill are less likely to return for study visits. In this study, we used methods to account for this attrition, which is important in quantifying the long-term associations of diabetes with cognitive decline.

METHODS

Study Population

The ARIC (Atherosclerosis Risk in Communities) study is a community-based, prospective cohort study of

See also:

Summary for Patients I-15

Context

Data are limited on the relationship of midlife glycemic control and long-term cognitive impairment.

Contribution

This prospective longitudinal study involved 13 351 adults living in 4 U.S. communities. Diabetes status was defined at baseline, and cognitive function was assessed at baseline and periodically during the 20-year follow-up.

Caution

The relationship between improvement in glucose control over time and cognitive decline could not be examined.

Implication

Diabetes and prediabetes in midlife were associated with a greater risk for cognitive decline over 20 years. Longer-duration diabetes had a stronger association with cognitive decline.

—The Editors

15 792 middle-aged adults from 4 U.S. communities: Washington County, Maryland; Forsyth County, North Carolina; and suburbs of Minneapolis, Minnesota, and Jackson, Mississippi. The field centers in all 4 communities selected participants by probability sampling; the Mississippi field center recruited only black persons, the Forsyth County site recruited black and white persons, and the racial distribution in the other locations resulted in a small percentage of nonwhite participants. Participants were seen at 4 visits approximately 3 years apart beginning in 1987 to 1989, and a fifth visit took place in 2011 to 2013. Cognitive function was evaluated at visit 2 (1990 to 1992), at visit 4 (1996 to 1998), and as part of the ARIC-NCS (ARIC Neurocognitive Study) at visit 5 (2011 to 2013). Detailed information about the ARIC study can be found elsewhere (16).

Baseline for the present analysis was visit 2, the first visit at which cognitive data were collected. Of the 14 348 participants who attended visit 2, we excluded participants who were neither white nor black and the small number of black persons in the Minnesota and Washington County cohorts ($n = 91$), those missing results from 1 or more cognitive function tests at baseline ($n = 217$), and those missing variables of interest ($n = 689$), resulting in a final sample size of 13 351 participants at baseline (93% of the visit 2 sample). A flow diagram of the study population and the pattern of visit attendance is provided in **Figure 1**.

Assessment of Cognitive Function

We used 3 neuropsychological tests to assess cognitive function: the delayed word recall test (DWRT) (17), the digit symbol substitution test (DSST) of the Wechsler Adult Intelligence Scale-Revised (18), and the word fluency test (WFT) (19). Protocols for the tests were standardized, and trained examiners administered the tests in a fixed order during 1 session in a quiet room.

The DWRT is a test of verbal learning and recent memory. Participants were asked to learn 10 common nouns by using each in a sentence. Two exposures to each word were given. After a 5-minute filled delay, participants had 60 seconds to recall the words. The score was equal to the number of words recalled.

The DSST is a test of executive function and processing speed. In this 90-second test, participants were asked to use a key to translate numbers to symbols. The score was equal to the count of numbers correctly translated to symbols, with possible scores ranging from 0 to 93.

The WFT is a test of executive function and language. Participants were given 60 seconds for each of the letters "F," "A," and "S" and were asked to generate as many words as possible beginning with each letter, excluding proper nouns. The score was equal to the total number of words generated for each letter.

To facilitate comparison across cognitive tests, Z scores standardized to visit 2 were calculated for each test by subtracting the participant's test score at each visit from the mean score at visit 2 and dividing by the SD of the visit 2 scores. A composite global cognitive Z score was calculated by averaging the Z scores of the 3 tests and was then standardized to visit 2 by using the mean and SD of the global Z scores at visit 2. Thus, a Z score of -1 would describe cognitive performance that is 1 SD below the mean score at visit 2. Composite global scores derived in this manner have been used in analyses of cognitive change in the ARIC study (20, 21) and elsewhere (22–24).

Assessment of Diabetes

We defined diabetes as self-reported physician diagnosis or diabetes medication use or HbA_{1c} level of 6.5% or greater.

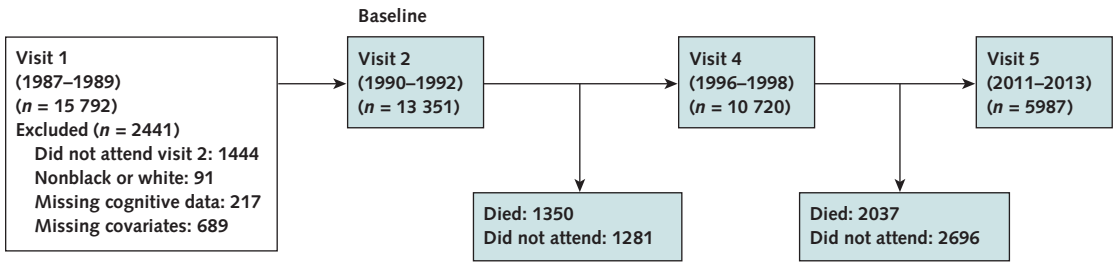
HbA_{1c} Measurement

We measured HbA_{1c} level in stored whole-blood samples by using high-performance liquid chromatography methods standardized to the Diabetes Control and Complications Trial assay (Tosoh A1c 2.2 Plus and G7 analyzers) (25). For analyses of the association between HbA_{1c} level and cognitive decline, HbA_{1c} level was categorized by using standard clinical cut points ($<5.7\%$, 5.7% to 6.4%, and $\geq 6.5\%$ in persons without a history of diabetes and $<7.0\%$ and $\geq 7.0\%$ in those with a history of diabetes) (10).

Covariates

All covariates used in the regression models were assessed at visit 2 except education, race, and sex, which were assessed at visit 1. We evaluated the following covariates as confounders: age; age squared; sex; race–field center (white persons from Minnesota, white persons from Washington County, white persons from Forsyth County, black persons from Forsyth County, and black persons from Mississippi); education (less than high school; high school, high

Figure 1. **Study flow diagram.**



	Visit 2	Visit 4	Visit 5	Total Count for Pattern
Pattern of visit attendance	X	X	X	5659
	X	X		5061
	X			2303
	X		X	328
Total count for visit	13 351	10 720	5987	

school equivalent, or vocational school; or college, graduate, or professional school); cigarette smoking status (current, former, or never); alcohol consumption (current, former, or never); body mass index (kg/m^2); hypertension, defined as use of blood pressure–lowering medication, systolic blood pressure greater than 140 mm Hg, or diastolic blood pressure greater than 90 mm Hg (yes or no); history of coronary heart disease (yes or no, with persons who were unsure of their history classified as "no"); history of stroke (yes or no); and apolipoprotein E ϵ4 genotype (0, 1, or 2 alleles). We also included interaction terms between each of these variables and time to allow for different rates of decline by these covariates. In sensitivity analyses, we treated cigarette smoking status, alcohol consumption, body mass index, hypertension, history of coronary heart disease, and history of stroke as time-varying and updated values at each study visit. We also adjusted for total cholesterol level and lipid-lowering medication use.

Statistical Analysis

We used linear models to estimate associations between diabetes and cognitive decline and fit them with generalized estimating equations to account for the within-person correlations of test scores arising from the repeated measures across time. We used unstructured correlation matrices and robust variance estimates. Time since baseline was modeled by using a linear spline with a knot at 6 years (the mean duration between visits 2 and 4). The spline term allowed for a nonlinear association between time and cognitive decline, more appropriately fit the study design than a quadratic term, and was supported by diagnostic Lowess smoothers. The primary coefficients of interest were the interactions between diabetes and the time spline terms, which address the hypothesis of greater decline among participants with diabetes after adjustment for age and the other covariates. To examine the role of stroke in mediating the association between diabetes and cognitive decline, we censored participant values at the time of stroke, thus excluding any poststroke cognitive information from our analyses. To test the robustness of our findings and to mitigate the differences in baseline characteristics between persons with and without diabetes, we reran analyses using propensity score matching. Propensity scores were developed by using logistic regression and included sex, age, race–field center, education, cigarette smoking status, alcohol consumption, hypertension status, prevalent coronary heart disease, prevalent stroke, and body mass index. All but 3 participants with diabetes were matched (details are provided in **Appendix 1**, available at www.annals.org).

We tested for effect modification between race and diabetes, and we tested for linear trend across categories of HbA_{1c} level by using variables assigned a value of 1 through 5 for each category.

In a separate analysis, we examined the association of diabetes duration with 14-year cognitive decline by using visit 4 as baseline and information from all prior visits to categorize diabetes duration. We calculated duration as the difference between the date of the visit 4 examination and the date of the visit when diabetes was first identified (based on a diagnosis or elevated glucose level at any prior visit) and categorized it as follows: no diabetes at visit 4 (reference), less than 3 years, 3 to 6 years, 6 to 9 years, or more than 9 years.

Table 1. **Baseline (Visit 2) Characteristics, by Diabetes Status**

Characteristic	Overall (*n* = 13 351)	Diabetes (*n* = 1779)	No Diabetes (*n* = 11 572)
Mean age (SD), *y*	57.0 (5.7)	58.2 (5.7)	56.8 (5.7)
Female, %	55.6	57.2	55.3
Visit 5 attendance, %			
Died before visit	25.4	46.4	22.1
Alive but did not attend	29.8	28.6	30.0
Attended	44.8	25.1	47.9
Race–field center, %			
White–Minneapolis, Minnesota	26.9	13.9	28.8
White–Washington County, Maryland	26.2	24.6	26.4
White–Forsyth County, North Carolina	23.3	16.5	24.4
Black–Forsyth County, North Carolina	2.7	4.9	2.4
Black–Jackson, Mississippi	21.0	40.1	18.0
Mean cognitive score (SD)			
Global *Z* score	0.00 (1.0)	−0.52 (1.0)	0.08 (1.0)
DWRT	6.6 (1.5)	6.1 (1.6)	6.7 (1.5)
DSST	44.7 (14.2)	36.9 (14.4)	45.9 (13.7)
WFT	33.2 (12.5)	29.3 (12.4)	33.8 (12.4)
Mean HbA_{1c} level (SD), %	5.8 (1.2)	8.0 (2.1)	5.4 (0.4)
Prevalent coronary heart disease, %	5.7	11.1	4.8
Prevalent stroke, %	1.7	4.4	1.3
Apolipoprotein E ε4 alleles, %			
0	69.2	69.4	69.2
1	28.1	27.8	28.2
2	2.6	2.9	2.6
Hypertension, %	35.6	59.0	32.0
Mean body mass index (SD), kg/m^2	28.0 (5.4)	31.4 (6.1)	27.4 (5.1)
Mean total cholesterol level (SD)			
mmol/L	5.43 (1.02)	5.57 (1.18)	5.41 (0.99)
mg/dL	210 (39.5)	216 (45.5)	209 (38.4)
Mean HDL cholesterol level (SD)			
mmol/L	1.28 (0.43)	1.11 (0.37)	1.30 (0.44)
mg/dL	49.4 (16.7)	43.1 (14.2)	50.4 (16.8)
Mean triglyceride level (SD)			
mmol/L	1.54 (1.02)	2.01 (1.53)	1.46 (0.90)
mg/dL	136 (90.3)	178 (135.3)	130 (79.4)
Education, %			
Less than high school	21.2	34.9	19.1
High school, GED, or vocational school	41.8	37.9	42.3
College, graduate, or professional school	37.0	27.2	38.6
Cigarette smoking status, %			
Current	22.3	20.8	22.5
Former	37.9	37.0	38.1
Never	39.8	42.2	39.4
Alcohol consumption, %			
Current	56.6	36.0	59.7
Former	20.8	33.2	18.9
Never	22.6	30.8	21.3

DSST = digit symbol substitution test; DWRT = delayed word recall test; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; WFT = word fluency test.

We used an inverse probability of attrition weighting (IPAW) approach (26, 27) to account for potential informative missingness effects (**Appendix 1**). Statistical analyses were done with SAS, version 9.3 (SAS Institute), and Stata, version 13.0 (StataCorp). PROC GENMOD was used for the generalized linear models, with a REPEATED statement to account for correlations between observations and a WEIGHT statement to incorporate the inverse probability weights.

Role of the Funding Source

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RESULTS

The mean age of participants at baseline was 57 years; 56% were female, 24% were black, and 13.3% had diabetes (**Table 1**). Participants with diabetes were older, had less education and lower cognitive scores, and had a more adverse cardiovascular risk factor profile at baseline than those without diabetes. Persons with diabetes at baseline were less likely to attend visit 5 (25% vs. 48%), which was largely due to the cumulative incidence of mortality (46%

vs. 22%) rather than study withdrawal (29% vs. 30%) (**Table 1**). Those with the lowest *Z* scores at visit 2 (below the fifth percentile) were also less likely to attend visit 5, with only 20% returning. Of the 13 351 participants who attended visit 2, 17% did not attend any follow-up visits. Among the remaining 83% of participants who had at least 1 follow-up visit (10 720 attended visit 4 and 5987 attended visit 5), the median follow-up was 19.3 years (interquartile range, 6.0 to 20.9 years).

Table 2 shows the estimated 20-year decline, by diabetes status, from our linear models for global cognitive *Z* score and DWRT, DSST, and WFT scores. Diagnosed diabetes was associated with significantly greater decline in the scores of all tests except the DWRT. The average decline over 20 years in global cognitive *Z* score was 0.78 in persons without diabetes and 0.92 in those with diabetes (difference, −0.15 [95% CI, −0.22 to −0.08]), a 19% greater decline among the latter (−0.15 / −0.78). The difference was similar in race-stratified analyses (*P* for interaction = 0.44) (**Appendix Tables 1** to **4**, available at www.annals.org). Adjustment for attrition by using the IPAW approach strengthened the magnitude of all associations by about 50%. To provide context for these results and because age-related decline in cognitive function is well-established, we used our linear model to estimate how much older a person without diabetes would need to be at baseline to have, on average, a *Z* score that was 0.15 SDs lower and estimated that a participant had to be 4.9 years older. In other words, a *Z* score that is 0.15 SDs lower is equivalent to the difference in cognitive performance of a 60-year-old person versus a 55-year-old person if they are otherwise similar (**Appendix 1**).

Our results were robust to an alternative analytic approach that used propensity score matching (**Appendix Tables 5** and **6** and the **Appendix Figure**, available at www.annals.org). Results were also unchanged when we adjusted for total cholesterol level and cholesterol-lowering medication use and when we used time-varying covariates. In our stroke mediation analysis, exclusion of poststroke cognitive scores reduced the 20-year difference in cognitive decline between persons with and without diabetes by 13%, although results remained significant (**Appendix Table 7**, available at www.annals.org).

Using visit 4 as the baseline showed that diabetes duration was associated with significantly greater subsequent 14-year cognitive decline (**Table 3**). The *P* value for linear trend across categories was significant for all tests.

Figure 2 shows differences in 20-year decline in global cognitive *Z* score by clinical categories of HbA_{1c} level. The *P* value for linear trend across all categories was significant (0.037 without adjustment for attrition and 0.006 with adjustment). Persons without diagnosed diabetes but with an HbA_{1c} level of 5.7% to 6.4% at baseline had significantly more cognitive decline over 20 years (adjusted difference in global cognitive *Z* score, −0.07; $P = 0.005$) than persons without diabetes and with an HbA_{1c} level less than 5.7%. Persons with undiagnosed diabetes (no diagnosis but HbA_{1c} level ≥6.5%) also had a greater decline in cognitive score than those in the reference group, but this difference was not statistically significant ($P = 0.105$). The greatest decline was found in patients with diabetes and an HbA_{1c} level of at least 7.0%, who had a larger decline than those with diabetes and an HbA_{1c} level less than 7.0% (adjusted difference in global cognitive *Z* score, −0.16;

Table 2. **Average Difference in 20-y Decline in Global Cognitive *Z* Score and DWRT, DSST, and WFT Scores Between Persons With a History of Diagnosed Diabetes and Those Without***

Test	20-y Decline (95% CI)		Difference (95% CI)†	Difference, %‡
	No Diabetes	Diabetes		
Not adjusted for attrition				
Global *Z* score	**−0.78 (−0.80 to −0.75)**	**−0.92 (−1.00 to −0.85)**	**−0.15 (−0.22 to −0.08)**	19
DWRT	**−0.98 (−1.02 to −0.94)**	**−1.04 (−1.15 to −0.92)**	−0.06 (−0.17 to 0.06)	6
DSST	**−0.69 (−0.71 to −0.67)**	**−0.82 (−0.87 to −0.77)**	**−0.13 (−0.18 to −0.08)**	19
WFT	**−0.17 (−0.19 to −0.14)**	**−0.28 (−0.35 to −0.22)**	**−0.12 (−0.18 to −0.06)**	71
Adjusted for attrition				
Global *Z* score	**−0.79 (−0.82 to −0.76)**	**−1.01 (−1.11 to −0.92)**	**−0.23 (−0.32 to −0.13)**	29
DWRT	**−1.01 (−1.05 to −0.96)**	**−1.09 (−1.22 to −0.96)**	−0.09 (−0.22 to 0.04)	9
DSST	**−0.70 (−0.72 to −0.68)**	**−0.87 (−0.94 to −0.81)**	**−0.18 (−0.24 to −0.11)**	26
WFT	**−0.17 (−0.20 to −0.14)**	**−0.37 (−0.47 to −0.28)**	**−0.21 (−0.31 to −0.10)**	124

DSST = digit symbol substitution test; DWRT = delayed word recall test; WFT = word fluency test.

* **Bold value** indicates $P < 0.05$. *Z* scores can be interpreted as the number of SDs above or below the mean. For example, a *Z*-score difference of −0.15 means that, on average, persons with diabetes declined an additional 0.15 SD compared with those without diabetes. Time since baseline was the time metric, and cognitive function was modeled by using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race–field center, sex, education, cigarette smoking status, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, apolipoprotein E ε4 genotype, and interactions between each of these covariates and time. There were 30 058 total records, with 13 351 participants at visit 2 (1779 with diabetes), 10 720 at visit 4 (1209 with diabetes), and 5987 at visit 5 (446 with diabetes).

† Difference in 20-y decline between persons without and those with diabetes (i.e., negative value indicates greater decline in those with diabetes).

‡ Percentage of decline in persons without diabetes—i.e., [decline in participants without diabetes − decline in participants with diabetes]/[decline in participants without diabetes]. Thus, a value of 19% indicates a 19% greater decline in persons with diagnosed diabetes than in those without. Differences and percentages were calculated before rounding of 20-y estimates.

Table 3. **Average Difference in 14-y Decline in Global Cognitive *Z* Score and DWRT, DSST, and WFT Scores Between Persons With Varying Diabetes Duration and Those Without***

Diabetes Duration, by Test	Not Adjusted for Attrition		Adjusted for Attrition	
	Absolute 14-y Decline (95% CI)	Difference (95% CI)†	Absolute 14-y Decline (95% CI)	Difference (95% CI)†
Global *Z* score				
No diabetes	**−0.67 (−0.70 to −0.64)**	Reference	**−0.68 (−0.71 to −0.65)**	Reference
<3 y	**−0.81 (−0.90 to −0.71)**	**−0.13 (−0.23 to −0.04)**	**−0.85 (−0.97 to −0.73)**	**−0.18 (−0.30 to −0.05)**
3–6 y	**−0.72 (−0.82 to −0.62)**	−0.05 (−0.14 to 0.05)	**−0.73 (−0.83 to −0.63)**	−0.05 (−0.15 to 0.05)
6–9 y	**−0.81 (−0.93 to −0.68)**	**−0.13 (−0.26 to −0.01)**	**−0.86 (−1.01 to −0.72)**	**−0.19 (−0.34 to −0.04)**
>9 y	**−0.85 (−0.95 to −0.74)**	**−0.18 (−0.28 to −0.07)**	**−0.91 (−1.02 to −0.79)**	**−0.23 (−0.34 to −0.12)**
P for trend	**0.001**	–	**0.002**	–
DWRT				
No diabetes	**−0.89 (−0.94 to −0.85)**	Reference	**−0.90 (−0.95 to −0.85)**	Reference
<3 y	**−0.98 (−1.11 to −0.84)**	−0.08 (−0.22 to 0.06)	**−1.02 (−1.19 to −0.86)**	−0.12 (−0.29 to 0.05)
3–6 y	**−0.96 (−1.10 to −0.81)**	−0.06 (−0.21 to 0.08)	**−0.97 (−1.13 to −0.82)**	−0.07 (−0.23 to 0.08)
6–9 y	**−0.99 (−1.18 to −0.81)**	−0.10 (−0.28 to 0.09)	**−1.01 (−1.20 to −0.82)**	−0.11 (−0.30 to 0.08)
>9 y	**−1.05 (−1.20 to −0.89)**	−0.16 (−0.31 to 0.00)	**−1.09 (−1.26 to −0.91)**	**−0.19 (−0.36 to −0.02)**
P for trend	**0.003**	–	**0.003**	–
DSST				
No diabetes	**−0.56 (−0.58 to −0.53)**	Reference	**−0.56 (−0.58 to −0.54)**	Reference
<3 y	**−0.68 (−0.75 to −0.61)**	**−0.12 (−0.19 to −0.05)**	**−0.70 (−0.78 to −0.62)**	**−0.14 (−0.22 to −0.06)**
3–6 y	**−0.62 (−0.69 to −0.55)**	−0.07 (−0.14 to 0.00)	**−0.62 (−0.68 to −0.55)**	−0.05 (−0.12 to 0.01)
6–9 y	**−0.65 (−0.74 to −0.55)**	−0.09 (−0.18 to 0.00)	**−0.68 (−0.77 to −0.58)**	**−0.11 (−0.21 to −0.02)**
>9 y	**−0.73 (−0.81 to −0.64)**	**−0.17 (−0.25 to −0.09)**	**−0.77 (−0.87 to −0.67)**	**−0.21 (−0.31 to −0.11)**
P for trend	**<0.001**	–	**<0.001**	–
WFT				
No diabetes	**−0.13 (−0.16 to −0.11)**	Reference	**−0.13 (−0.16 to −0.10)**	Reference
<3 y	**−0.20 (−0.29 to −0.12)**	−0.07 (−0.16 to 0.01)	**−0.23 (−0.33 to −0.13)**	**−0.10 (−0.20 to −0.00)**
3–6 y	**−0.14 (−0.23 to −0.05)**	−0.01 (−0.10 to 0.09)	**−0.13 (−0.23 to −0.03)**	0.00 (−0.10 to 0.11)
6–9 y	**−0.27 (−0.39 to −0.16)**	**−0.14 (−0.25 to −0.03)**	**−0.36 (−0.53 to −0.18)**	**−0.22 (−0.41 to −0.04)**
>9 y	**−0.24 (−0.33 to −0.15)**	**−0.11 (−0.20 to −0.02)**	**−0.29 (−0.39 to −0.18)**	**−0.15 (−0.26 to −0.05)**
P for trend	**<0.001**	–	**0.001**	–

DSST = digit symbol substitution test; DWRT = delayed word recall test; WFT = word fluency test.

* **Bold value** indicates $P < 0.05$. Baseline for this analysis was visit 4, and visits 1, 2, and 3 were used to calculate diabetes duration. *Z* scores can be interpreted as the number of SDs above or below the mean. For example, a *Z*-score difference of −0.15 means that, on average, persons with diabetes declined an additional 0.15 SD compared with those without diabetes. Time since baseline was the time metric, and cognitive function was modeled by using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race–field center, sex, education, cigarette smoking status, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, apolipoprotein E ε4 genotype, and interactions between each of these covariates and time. There were 16 707 total records, with 10 720 at visit 4 (1209 with diabetes) and 5987 at visit 5 (446 with diabetes).

† Difference in 14-y decline between persons with no diabetes at either visit and those who had prevalent diabetes at visit 2 or developed diabetes between visits 2 and 4 (i.e., negative value indicates greater decline in those with prevalent or incident diabetes).

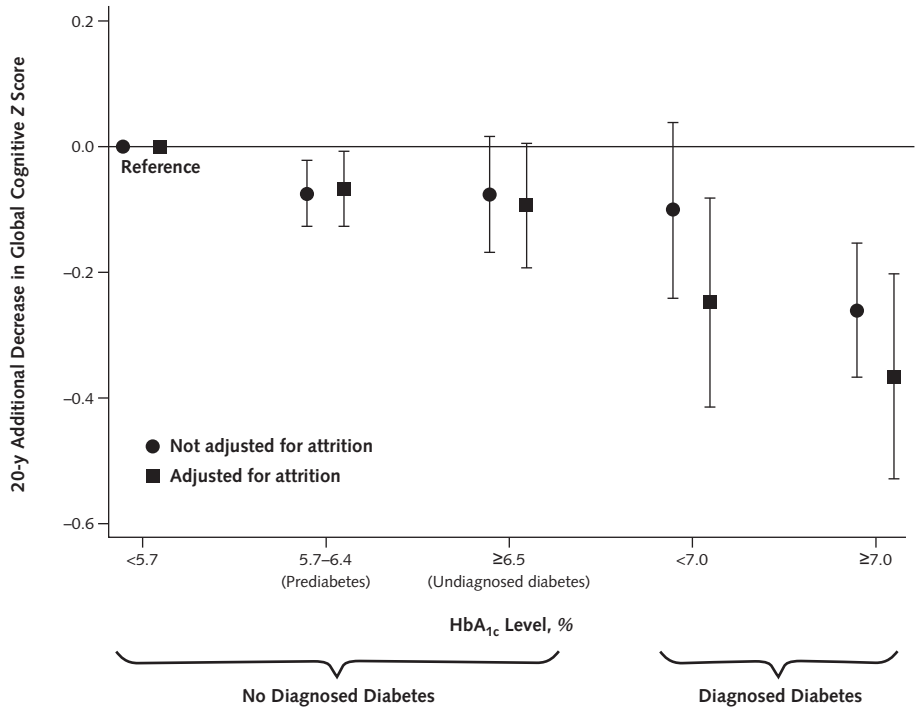
$P = 0.071$), which was borderline statistically significant. Adjustment for attrition strengthened the magnitude of all associations.

DISCUSSION

In this community-based population, we found significantly greater cognitive decline among black and white adults with diabetes than those without diabetes at baseline, with a 20-year cognitive decline that was 19% larger in this group for the global score, or 30% larger after we accounted for attrition. Diabetes duration seemed to be a factor, with a greater 14-year decline late in life for participants with longer-duration diabetes. We found trends of increased cognitive decline across clinical categories of HbA_{1c} level, even among persons without a history of diabetes; those with an HbA_{1c} level of 5.7% to 6.4% (prediabetes) and those with an HbA_{1c} level of at least 6.5% (undiagnosed diabetes) at baseline had larger declines over 20 years than those with an HbA_{1c} level less than 5.7%. Exclusion of persons who had stroke after baseline attenuated the results slightly, suggesting that stroke partially mediates the association between diabetes and cognitive decline.

The observed association of diabetes with decline in global cognitive function was primarily driven by decreases in the DSST and WFT scores, which reflect impairments in the domains of processing speed and executive function (28, 29). These results suggest that the association of diabetes with cognitive function may involve the subcortical microvasculature that damages white matter pathways or subcortical gray matter in other ways (30–32). However, we also found associations with memory after adjustment for attrition, but only in white persons. This may be because the DWRT, with only 10 words, is insensitive to small declines in memory.

Figure 2. **Difference in global cognitive *Z* score decline by clinical category of HbA_{1c} level compared with decline in persons without diabetes and HbA_{1c} level <5.7%.**



"Adjusted for attrition" refers to the inverse probability of attrition weighting used to account for participant death or dropout during follow-up. Estimates and 95% CIs are from generalized linear models fit using generalized estimating equations for global cognitive *Z* score, with adjustment for age; age^2; race–field center; sex; education; cigarette smoking status; alcohol consumption; hypertension; history of coronary heart disease; history of stroke; apolipoprotein E ϵ4 genotype; body mass index; interactions between each of these variables and time (except alcohol consumption and history of coronary heart disease, which were not significant); and interactions between race–field center and sex, hypertension, and education. HbA_{1c} level was categorized by using the standard clinical cut points based on American Diabetes Association criteria (<5.7% [n = 9031], 5.7% to 6.4% [n = 2365], and ≥6.5% [n = 711] in participants without a diagnosis of diabetes and <7.0% [n = 415] and ≥7.0% [n = 829] in those with diagnosed diabetes). HbA_{1c} = hemoglobin A_{1c}.

Previous studies of diabetes and cognitive decline have had short durations. A review by Cukierman and colleagues (6) included only 1 study with a mean follow-up of more than 6 years. Diabetes was associated with a 12-year decline in several tests in the Maastricht Aging Study (33); a 10-year decline in a global test, memory, and reasoning in 2 Whitehall II studies (15, 34); and an 8-year decline in 1 of 8 tests in the Framingham Offspring Study (35). However, only 1 of these reported associations with diabetes diagnosed before age 65 years.

ACCORD MIND (Action to Control Cardiovascular Risk in Diabetes Follow-Up Study—Memory in Diabetes Follow-Up Study), a randomized clinical trial, showed that tight glucose control in elderly diabetic persons with high cardiovascular risk did not reduce cognitive decline as measured by the DSST (13, 14). Some have postulated that the lack of benefit in ACCORD MIND may have been due to the older age of the participants (mean age, 63 years), the short treatment period (3.3 years), and a higher frequency of hypoglycemic episodes in the treatment group than in the control group. However, our observations that higher HbA_{1c} levels were associated with greater 20-year cognitive decline even in persons without a diagnosis of diabetes and that longer-duration diabetes was associated with greater cognitive decline suggest that a long-term trial, if one were feasible, could show the cognitive benefit of glycemic control. The potential benefit of early intervention warrants further study (36).

Some limitations of our study deserve consideration. We had only 1 test in each cognitive domain at each visit and only 1 HbA_{1c} measurement at baseline. Black persons in the ARIC study came from only 2 study sites, which limited our ability to separate the effects of race from those of geography. Attrition is a likely concern for any long-term study. However, our adjustment for attrition probably provided less biased estimates of the effect of diabetes on cognition than when attrition is ignored, as in most prior reports. Although we adjusted for attrition by using a broad set of available data, our method of adjustment may not have fully accounted for the effects of withdrawal, especially that directly related to low cognitive function, and our estimate of the association of diabetes with cognitive

decline may be conservative. Because this is an observational study, we cannot conclude that the link between diabetes and cognitive decline is causal and cannot rule out the possibility of residual confounding.

Strengths of this study include the large community-based population of black and white persons, the rigorous assessment of variables that might affect the association between diabetes and cognitive function, and our methods to reduce the effects of withdrawal. The evaluation of cognitive change over time, with 20 years of follow-up and cognitive function assessed at several time points, is also a strength. In contrast to assessing dementia or cognitive performance at a single time point, examining scores over time reduces the influence of confounding variables (20).

Maintaining cognitive function is a critical aspect of successful aging and ensuring a high quality of life. Diabetes and glucose control are potentially modifiable and may offer an important opportunity for the prevention of cognitive decline, thus delaying progression to dementia. At the population level, delaying the onset of dementia by even a couple of years could reduce its prevalence by more than 20% over the next 30 years (37).

This study documents that diabetes and prediabetes in middle age are associated with greater cognitive decline over the subsequent 2 decades. The association with cognitive decline was stronger for longer-duration diabetes, and our findings were similar in black and white adults. These data suggest that primary prevention of diabetes or glucose control in midlife may protect against later-life cognitive decline.

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Note: Ms. Rawlings had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Reproducible Research Statement: *Study protocol and data set:* Protocols and data for the parent ARIC-NCS may be obtained by approved persons through written agreements with the ARIC Steering Committee and the research sponsor (NHLBI). *Statistical code:* Available from Dr. Selvin (e-mail, eselvin@jhu.edu).

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Appendix 1: Supplemental Material

Summary of Propensity Score Methods

Persons with diabetes differ from those without it in many demographic, behavioral, and clinical characteristics. In studying diabetes as a risk factor, a lack of comparability in participant characteristics between the groups may reduce the effectiveness of controlling for confounding by using conventional statistical methods (such as regression), potentially leading to bias. An alternative to the conventional methods of controlling for confounding is propensity score matching, a method of treating observational data in an attempt to mimic characteristics of a randomized trial. That is, conditional on the propensity score, baseline characteristics will be similar between the groups. We used this approach to test the robustness of our findings.

In the propensity score analysis, we modeled diabetes as an outcome by using logistic regression and included sex, age, race–field center, education, cigarette smoking status, alcohol consumption, hypertension status, prevalent coronary heart disease, prevalent stroke, and body mass index. These variables are strongly associated with diabetes and differed between persons with and without diabetes in our study population (**Table 1**). For this analysis, we included an additional 415 participants with "not reported" apolipoprotein E $\epsilon 4$ at baseline, resulting in 13 766 available participants (1827 with diabetes). Using this model, we predicted the probability of diabetes (propensity score).

For the propensity score, we used nearest-neighbor matching without replacement, with a caliper of 0.05 (on the probability scale) to select matches among persons without diabetes. We chose a caliper of 0.05 because it is half of the SD of our propensity score, which has been indicated by prior research to remove a substantial portion of the initial bias (38). All but 3 participants with diabetes had a match, resulting in 1824 participants with diabetes compared with 1779 in our primary regression analysis.

The **Appendix Figure** shows the propensity score distributions for persons with and without diabetes in the full cohort of 13 766 participants (*top panel*) and among matched participants (*bottom panel*). In the full cohort, the propensity scores for persons with and without diabetes overlapped across the full range of probabilities, suggesting that the conventional regression approach was sufficient in this case.

After participants were matched, the propensity scores overlapped fully, suggesting that the propensity score matching performed well. In addition, **Appendix Table 5** shows baseline characteristics among matched participants. Visual inspection of the means and percentages shows that the matched variables were well-balanced; we found no significant differences between persons with and without diabetes ($P > 0.40$ for all).

When we used the matched sample to examine the relationship between diabetes and cognitive decline (**Appendix Table 6**), our results did not differ appreciably and our conclusions were unchanged from the primary regression analysis (**Table 2**).

IPAW Details

Persons with diabetes and those with substantial cognitive impairment were more likely to withdraw from the study or die before the next study visit, potentially biasing the estimated relationship between diabetes and cognitive decline. We used the IPAW method to account for this differential withdrawal.

We developed stabilized inverse probability of attrition weights for each person at each time point of participation and used weighted analyses to obtain estimates "adjusted" for attrition. These weights were calculated from predicted probabilities of attrition estimated from 2 sets of logistic models: one for dropout due to attrition and the other for dropout due to death.

For dropout due to death, we modeled the probability of death between visits 2 and 4, between visit 4 and a pseudovisit (based on annual telephone call data between visits 4 and 5), and between the pseudovisit and visit 5. For withdrawal not due to death, we modeled the probability of withdrawal between visits 2 and 4 and between visits 4 and 5. All models used the same covariates, updated to reflect current status or total history, which were selected for inclusion into prediction models by using a stepwise selection criterion. Models were run separately for black and white participants.

Covariates included age; sex; field center; education; diabetes; apolipoprotein E ϵ4 alleles (0, 1, or 2); history of stroke; history of coronary heart disease; cigarette smoking status; body mass index; height; hypertension medication use; global *Z* score (categorized into quintiles); self-reported poor health (assessed at visit 1); number of prior hospitalizations; retirement status; chronic lung disease; lung capacity; insurance status; leukocyte count; anemia; and interactions between age and global *Z* score, anemia, and lung volume.

To calculate the stabilized weights, we ran additional models to predict death and withdrawal by using a subset of covariates (age, sex, field center, education, and diabetes). The probabilities from these models were multiplied by the weights calculated earlier to create stabilized weights. Ideally, these weights have a mean of 1 and represent the distribution of the original population without inflating the sample size. Additional information on probability weighting has been published elsewhere (39).

Appendix Table 8 shows the distribution of the stabilized weights. For completeness, we show the unstabilized weights even though we did not use them in our analyses.

Transformation of Global *Z* Score Into an "Age Equivalent"

To provide context for our primary result of a global *Z*-score difference of −0.15, we calculated the age-related equivalent for this degree of decline. To do this, we used our final model to estimate how much older someone without diabetes would need to be at baseline to perform 0.15 *Z* scores lower, and we estimated that to be 4.9 years. That is, our model of *Z* scores included age, and at baseline older participants performed worse than younger participants (negative coefficient for age). The coefficient for age was −0.02998, so each additional year of age at baseline reduced *Z* scores by approximately 0.03. Thus, being about 5 years older at baseline (without diabetes) was "equivalent" to the amount of additional decline over 20 years among persons with diabetes.

Because a value of 0.15 may not be intuitive, we also categorized the decline as the percentage of additional decline among persons with diabetes. That is, persons without diabetes had a decrease of 0.78 in the *Z* score over 20 years, and those with diabetes had a decrease of 0.92 (**Table 2**). Therefore, persons with diabetes had a 19% greater decline (0.15/0.78) than those without diabetes.

Appendix 2: ARIC-NCS Staff

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Appendix Table 1. **Average Difference in 20-y Decline in Global Cognitive *Z* Score and DWRT, DSST, and WFT Scores Between White Persons With a History of Diagnosed Diabetes and Those Without***

Test	20-y Decline (95% CI)		Difference (95% CI)†	Difference, %‡
	No Diabetes	Diabetes		
Not adjusted for attrition				
Global *Z* score	−0.81 (−0.84 to −0.78)	−0.96 (−1.05 to −0.88)	−0.16 (−0.24 to −0.07)	19
DWRT	−0.97 (−1.02 to −0.92)	−1.12 (−1.26 to −0.98)	−0.15 (−0.28 to −0.01)	15
DSST	−0.78 (−0.80 to −0.76)	−0.89 (−0.95 to −0.83)	−0.11 (−0.17 to −0.05)	14
WFT	−0.15 (−0.19 to −0.13)	−0.25 (−0.33 to −0.18)	−0.10 (−0.18 to −0.03)	66
Adjusted for attrition				
Global *Z* score	−0.83 (−0.86 to −0.79)	−1.11 (−1.22 to −1.00)	−0.28 (−0.39 to −0.17)	34
DWRT	−0.99 (−1.05 to −0.93)	−1.20 (−1.35 to −1.05)	−0.21 (−0.36 to −0.06)	22
DSST	−0.79 (−0.82 to −0.77)	−0.97 (−1.06 to −0.88)	−0.18 (−0.27 to −0.09)	22
WFT	−0.16 (−0.19 to −0.13)	−0.41 (−0.55 to −0.26)	−0.25 (−0.40 to −0.09)	154

DSST = digit symbol substitution test; DWRT = delayed word recall test; WFT = word fluency test.
* All *P* values were <0.05. *Z* scores can be interpreted as the number of SDs above or below the mean. For example, a *Z*-score difference of −0.15 means that, on average, persons with diabetes declined an additional 0.15 SD compared with those without diabetes. Time since baseline was the time metric, and cognitive function was modeled by using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race–field center, sex, education, cigarette smoking status, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, apolipoprotein E ε4 genotype, and interactions between each of these covariates and time.
† Difference in 20-y decline between persons without and those with diabetes (i.e., negative value indicates greater decline in those with diabetes).
‡ Percentage of decline in persons without diabetes (i.e., [decline in participants without diabetes − decline in participants with diabetes]/[decline in participants without diabetes]). Thus, a value of 19% indicates a 19% greater decline in persons with diagnosed diabetes than in those without.

Appendix Table 2. **Average Difference in 20-y Decline in Global Cognitive *Z* Score and DWRT, DSST, and WFT Scores Between Black Persons With a History of Diagnosed Diabetes and Those Without***

Test	20-y Decline (95% CI)		Difference (95% CI)†	Difference, %‡
	No Diabetes	Diabetes		
Not adjusted for attrition				
Global *Z* score	**−0.80 (−0.91 to −0.69)**	**−0.94 (−1.10 to −0.79)**	**−0.14 (−0.26 to −0.03)**	18
DWRT	**−0.94 (−1.16 to −0.73)**	**−0.88 (−1.14 to −0.61)**	0.07 (−0.11 to 0.25)	−7
DSST	**−0.62 (−0.69 to −0.55)**	**−0.80 (−0.90 to −0.70)**	**−0.18 (−0.26 to −0.10)**	29
WFT	**−0.29 (−0.38 to −0.20)**	**−0.41 (−0.54 to −0.28)**	**−0.13 (−0.22 to −0.03)**	44
Adjusted for attrition				
Global *Z* score	**−0.88 (−1.01 to −0.75)**	**−1.06 (−1.24 to −0.88)**	**−0.18 (−0.32 to −0.05)**	21
DWRT	**−1.00 (−1.23 to −0.76)**	**−0.91 (−1.21 to −0.60)**	0.09 (−0.12 to 0.30)	−9
DSST	**−0.64 (−0.71 to −0.56)**	**−0.86 (−0.98 to −0.75)**	**−0.23 (−0.31 to −0.14)**	36
WFT	**−0.33 (−0.43 to −0.24)**	**−0.50 (−0.65 to −0.36)**	**−0.17 (−0.28 to −0.06)**	51

DSST = digit symbol substitution test; DWRT = delayed word recall test; WFT = word fluency test.
* **Bold value** indicates $P < 0.05$. *Z* scores can be interpreted as the number of SDs above or below the mean. For example, a *Z*-score difference of −0.15 means that, on average, persons with diabetes declined an additional 0.15 SD compared with those without diabetes. Time since baseline was the time metric, and cognitive function was modeled by using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race–field center, sex, education, cigarette smoking status, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, apolipoprotein E ε4 genotype, and interactions between each of these covariates and time.
† Difference in 20-y decline between persons without and those with diabetes (i.e., negative value indicates greater decline in those with diabetes).
‡ Percentage of decline in persons without diabetes (i.e., [decline in participants without diabetes − decline in participants with diabetes]/[decline in participants without diabetes]). Thus, a value of 18% indicates an 18% greater decline in persons with diagnosed diabetes than in those without.

Appendix Table 3. **Average Difference in 14-y Decline in Global Cognitive *Z* Score and DWRT, DSST, and WFT Scores Between White Persons With Prevalent Diagnosed Diabetes at Visit 2 or Incident Diagnosed Diabetes at Visit 4 and Those Without Diabetes at Either Visit***

Diabetes Duration, by Test	Not Adjusted for Attrition		Adjusted for Attrition	
	Absolute 14-y Decline (95% CI)	Difference (95% CI)†	Absolute 14-y Decline (95% CI)	Difference (95% CI)†
Global *Z* score				
No diabetes	**−0.72 (−0.75 to −0.69)**	Reference	**−0.74 (−0.77 to −0.70)**	Reference
<3 y	**−0.92 (−1.02 to −0.82)**	**−0.20 (−0.30 to −0.10)**	**−0.92 (−1.03 to −0.80)**	**−0.18 (−0.29 to −0.06)**
3–6 y	**−0.87 (−0.99 to −0.76)**	−0.15 (−0.27 to 0.03)	**−0.90 (−1.02 to −0.77)**	**−0.16 (−0.29 to −0.03)**
6–9 y	**−0.82 (−0.98 to −0.66)**	−0.10 (−0.26 to 0.06)	**−0.92 (−1.13 to −0.72)**	−0.19 (−0.40 to 0.02)
>9 y	**−0.87 (−0.97 to −0.77)**	**−0.15 (−0.25 to −0.05)**	**−0.96 (−1.07 to −0.84)**	**−0.22 (−0.33 to −0.11)**
P for trend	**<0.001**	–	**<0.001**	–
DWRT				
No diabetes	**−0.91 (−0.97 to −0.86)**	Reference	**−0.92 (−0.98 to −0.87)**	Reference
<3 y	**−1.10 (−1.26 to −0.95)**	**−0.19 (−0.34 to −0.04)**	**−1.08 (−1.26 to −0.91)**	−0.16 (−0.34 to 0.02)
3–6 y	**−1.09 (−1.27 to −0.91)**	**−0.18 (−0.35 to −0.01)**	**−1.14 (−1.32 to −0.96)**	**−0.22 (−0.40 to −0.04)**
6–9 y	**−1.04 (−1.27 to −0.81)**	−0.13 (−0.36 to 0.10)	**−1.11 (−1.34 to −0.87)**	−0.18 (−0.42 to 0.05)
>9 y	**−1.06 (−1.21 to −0.90)**	−0.15 (−0.31 to 0.01)	**−1.13 (−1.30 to −0.95)**	**−0.21 (−0.38 to −0.03)**
P for trend	**0.004**	–	**<0.001**	–
DSST				
No diabetes	**−0.65 (−0.68 to −0.63)**	Reference	**−0.67 (−0.70 to −0.65)**	Reference
<3 y	**−0.78 (−0.86 to −0.70)**	**−0.13 (−0.20 to −0.05)**	**−0.80 (−0.88 to −0.72)**	**−0.13 (−0.21 to −0.05)**
3–6 y	**−0.73 (−0.82 to −0.65)**	−0.08 (−0.16 to 0.01)	**−0.74 (−0.83 to −0.65)**	−0.07 (−0.15 to 0.02)
6–9 y	**−0.70 (−0.84 to −0.56)**	−0.04 (−0.18 to 0.10)	**−0.72 (−0.85 to −0.59)**	−0.04 (−0.17 to 0.09)
>9 y	**−0.83 (−0.91 to −0.74)**	**−0.17 (−0.26 to −0.08)**	**−0.90 (−1.02 to −0.79)**	**−0.23 (−0.35 to −0.12)**
P for trend	**<0.001**	–	**<0.001**	–
WFT				
No diabetes	**−0.11 (−0.14 to −0.08)**	Reference	**−0.12 (−0.15 to −0.09)**	Reference
<3 y	**−0.22 (−0.30 to −0.13)**	**−0.11 (−0.19 to −0.02)**	**−0.22 (−0.31 to −0.13)**	**−0.10 (−0.19 to −0.01)**
3–6 y	**−0.21 (−0.32 to −0.09)**	−0.09 (−0.21 to 0.02)	**−0.18 (−0.31 to −0.04)**	−0.06 (−0.19 to 0.08)
6–9 y	**−0.20 (−0.35 to −0.06)**	−0.09 (−0.24 to 0.05)	**−0.38 (−0.68 to −0.09)**	−0.26 (−0.56 to 0.04)
>9 y	**−0.18 (−0.27 to −0.08)**	**−0.07 (−0.16 to 0.03)**	**−0.23 (−0.34 to −0.12)**	**−0.11 (−0.22 to −0.00)**
P for trend	**0.013**	–	**0.003**	–

DSST = digit symbol substitution test; DWRT = delayed word recall test; WFT = word fluency test.

* **Bold value** indicates $P < 0.05$. *Z* scores can be interpreted as the number of SDs above or below the mean. For example, a *Z*-score difference of −0.15 means that, on average, persons with diabetes declined an additional 0.15 SD compared with those without diabetes. Time since baseline was the time metric, and cognitive function was modeled by using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race–field center, sex, education, cigarette smoking status, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, apolipoprotein E ε4 genotype, and interactions between each of these covariates and time.

† Difference in 14-y decline between persons with no diabetes at either visit and those who had prevalent diabetes at visit 2 or developed diabetes between visits 2 and 4 (i.e., negative value indicates greater decline in those with prevalent or incident diabetes).

Appendix Table 4. **Average Difference in 14-y Decline in Global Cognitive *Z* Score and DWRT, DSST, and WFT Scores Between Black Persons With Prevalent Diagnosed Diabetes at Visit 2 or Incident Diagnosed Diabetes at Visit 4 and Those Without Diabetes at Either Visit***

Diabetes Duration, by Test	Not Adjusted for Attrition		Adjusted for Attrition	
	Absolute 14-y Decline (95% CI)	Difference (95% CI)†	Absolute 14-y Decline (95% CI)	Difference (95% CI)†
Global *Z* score				
No diabetes	**−0.74 (−0.86 to −0.63)**	Reference	**−0.78 (−0.90 to −0.66)**	Reference
<3 y	**−0.73 (−0.95 to −0.52)**	0.01 (−0.18 to 0.21)	**−0.83 (−1.09 to −0.56)**	−0.04 (−0.30 to 0.21)
3–6 y	**−0.58 (−0.77 to −0.39)**	**0.17 (0.01 to 0.32)**	**−0.63 (−0.82 to −0.43)**	0.16 (−0.01 to 0.32)
6–9 y	**−0.90 (−1.11 to −0.69)**	−0.15 (−0.33 to 0.03)	**−0.95 (−1.17 to −0.74)**	−0.17 (−0.35 to 0.01)
>9 y	**−1.06 (−1.41 to −0.72)**	−0.32 (−0.65 to 0.01)	**−1.11 (−1.46 to −0.75)**	−0.33 (−0.66 to 0.02)
P for trend	0.141	–	0.097	–
DWRT				
No diabetes	**−0.91 (−1.13 to −0.69)**	Reference	**−0.89 (−1.11 to −0.66)**	Reference
<3 y	**−0.80 (−1.14 to −0.45)**	0.11 (−0.18 to 0.40)	**−0.88 (−1.30 to −0.46)**	0.01 (−0.39 to 0.40)
3–6 y	**−0.72 (−1.04 to −0.41)**	−0.05 (−0.05 to 0.42)	**−0.66 (−0.98 to −0.34)**	0.23 (−0.02 to 0.48)
6–9 y	**−0.95 (−1.30 to −0.59)**	−0.10 (−0.32 to 0.25)	**−0.86 (−1.23 to −0.49)**	0.03 (−0.28 to 0.33)
>9 y	**−1.16 (−1.64 to −0.69)**	−0.16 (−0.69 to 0.18)	**−1.11 (−1.63 to −0.60)**	−0.23 (−0.71 to 0.25)
P for trend	0.84	–	0.81	–
DSST				
No diabetes	**−0.60 (−0.68 to −0.52)**	Reference	**−0.61 (−0.69 to −0.53)**	Reference
<3 y	**−0.70 (−0.85 to −0.55)**	−0.10 (−0.24 to 0.04)	**−0.75 (−0.94 to −0.57)**	−0.14 (−0.33 to 0.04)
3–6 y	**−0.61 (−0.75 to −0.48)**	−0.02 (−0.13 to 0.10)	**−0.62 (−0.76 to −0.48)**	−0.01 (−0.13 to 0.11)
6–9 y	**−0.76 (−0.91 to −0.62)**	−0.17 (−0.29 to −0.04)	**−0.81 (−0.97 to −0.64)**	**−0.20 (−0.35 to −0.05)**
>9 y	**−0.78 (−0.99 to −0.56)**	−0.18 (−0.39 to 0.03)	**−0.79 (−1.01 to −0.57)**	−0.18 (−0.39 to 0.03)
P for trend	**0.008**	–	**0.006**	–
WFT				
No diabetes	**−0.20 (−0.29 to −0.11)**	Reference	**−0.25 (−0.34 to −0.15)**	Reference
<3 y	−0.16 (−0.35 to 0.02)	0.04 (−0.14 to 0.22)	**−0.27 (−0.49 to −0.06)**	**−0.03 (−0.17 to −0.00)**
3–6 y	−0.07 (−0.23 to 0.09)	0.13 (−0.01 to 0.27)	−0.14 (−0.31 to 0.01)	0.10 (−0.04 to 0.24)
6–9 y	**−0.38 (−0.56 to −0.19)**	**−0.17 (−0.34 to −0.01)**	**−0.49 (−0.68 to −0.30)**	**−0.24 (−0.41 to −0.07)**
>9 y	**−0.45 (−0.67 to −0.23)**	**−0.25 (−0.46 to −0.05)**	**−0.49 (−0.71 to −0.27)**	**−0.24 (−0.43 to −0.05)**
P for trend	**0.049**	–	**0.009**	–

DSST = digit symbol substitution test; DWRT = delayed word recall test; WFT = word fluency test.

* **Bold value** indicates $P < 0.05$. *Z* scores can be interpreted as the number of SDs above or below the mean. For example, a *Z*-score difference of −0.15 means that, on average, persons with diabetes declined an additional 0.15 SD compared with those without diabetes. Time since baseline was the time metric, and cognitive function was modeled by using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race–field center, sex, education, cigarette smoking status, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, apolipoprotein E ε4 genotype, and interactions between each of these covariates and time.

† Difference in 14-y decline between persons with no diabetes at either visit and those who had prevalent diabetes at visit 2 or developed diabetes between visits 2 and 4 (i.e., negative value indicates greater decline in those with prevalent or incident diabetes).

Appendix Table 5. **Baseline (Visit 2) Characteristics, by Diabetes Status: Propensity Score–Matched Cohort**

Characteristic	Overall (n = 3648)	Diabetes (n = 1824)	No Diabetes (n = 1824)
Mean age (SD), *y**	58.3 (5.7)	58.2 (5.7)	58.4 (5.7)
Female, %*	56.6	57.1	56.1
Visit 5 attendance, %			
Died before visit	40.3	46.7	33.3
Alive but did not attend	30.5	28.3	32.9
Attended	29.2	25.0	33.8
Race–field center, %*			
White–Minneapolis, Minnesota	14.9	14.3	15.6
White–Washington County, Maryland	16.1	16.4	15.0
White–Forsyth County, North Carolina	39.8	40.2	40.7
Black–Forsyth County, North Carolina	4.8	4.8	4.7
Black–Jackson, Mississippi	24.3	24.2	24.1
Mean cognitive score (SD)			
Global *Z* score	−0.45 (1.0)	−0.52 (1.0)	−0.38 (1.0)
DWRT	6.2 (1.6)	6.1 (1.6)	6.4 (1.6)
DSST	37.5 (14.6)	36.9 (14.5)	38.5 (14.8)
WFT	29.3 (12.5)	29.3 (12.4)	29.6 (12.5)
Mean HbA_{1c} level (SD), %	6.8 (1.9)	8.0 (2.1)	5.6 (0.4)
Prevalent coronary heart disease, %*	11.2	11.0	11.3
Prevalent stroke, %*	3.9	4.3	3.8
Apolipoprotein E ε4 alleles, %			
0	66.0	67.6	63.4
1	28.2	27.0	30.3
2	3.1	2.8	3.3
Not reported	2.7	2.6	3.0
Hypertension, %*	59.0	58.9	59.8
Mean body mass index (SD), kg/m^2*	31.2 (6.3)	31.4 (6.1)	30.9 (6.5)
Mean total cholesterol level (SD)			
mmol/L	5.54 (1.12)	5.59 (1.18)	5.46 (1.05)
mg/dL	214 (43.1)	216 (45.4)	211 (40.4)
Mean HDL cholesterol level (SD)			
mmol/L	1.18 (0.39)	1.12 (0.37)	1.25 (0.41)
mg/dL	45.7 (15.2)	43.1 (14.2)	48.4 (15.8)
Mean triglyceride level (SD)			
mmol/L	1.76 (1.30)	2.02 (1.54)	1.49 (0.89)
mg/dL	156 (114.7)	179 (136.0)	132 (79.2)
Education, %*			
Less than high school	36.4	35.0	36.5
High school, GED, or vocational school	37.2	37.8	37.0
College, graduate, or professional school	26.5	27.2	26.5
Cigarette smoking status, %*			
Current	22.2	20.8	22.0
Former	36.8	37.4	37.0
Never	41.0	41.8	41.0
Alcohol consumption, %*			
Current	36.3	36.2	35.9
Former	33.1	33.3	33.2
Never	30.6	30.4	30.9

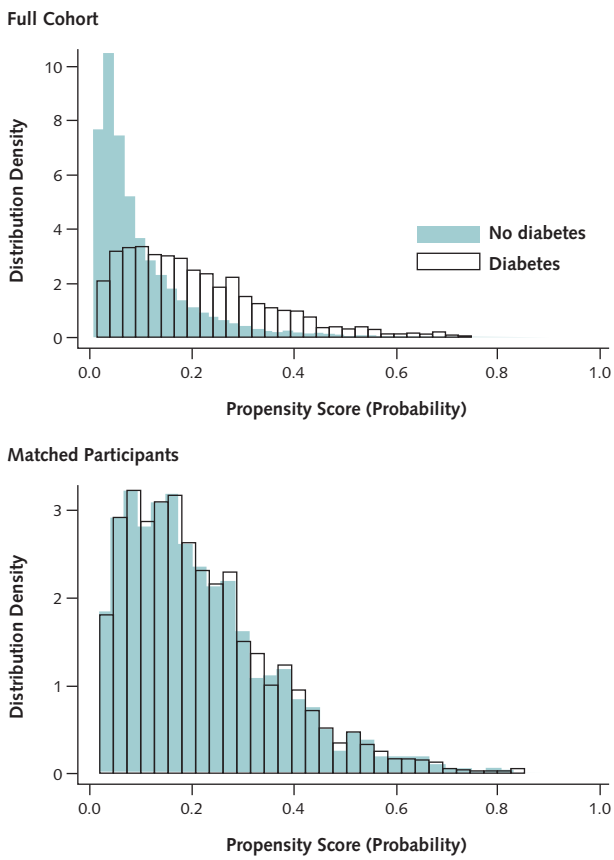
DSST = digit symbol substitution test; DWRT = delayed word recall test; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; WFT = word fluency test.
* Matching was done. Persons with and without diabetes did not differ significantly on these variables.

Appendix Table 6. **Average Difference in 20-y Decline in Global Cognitive *Z* Score and DWRT, DSST, and WFT Scores Between Persons With a History of Diagnosed Diabetes and Those Without: Propensity Score–Matched Cohort***

Test	20-y Decline (95% CI)		Difference (95% CI)†
	No Diabetes	Diabetes	
Global *Z* score	**−0.82 (−0.89 to −0.75)**	**−0.96 (−1.04 to −0.87)**	**−0.14 (−0.23 to −0.06)**
DWRT	**−1.11 (−1.22 to −0.99)**	**−1.10 (−1.23 to −0.97)**	0.00 (−0.13 to 0.14)
DSST	**−0.70 (−0.75 to −0.65)**	**−0.83 (−0.89 to −0.78)**	**−0.13 (−0.19 to −0.07)**
WFT	**−0.17 (−0.23 to −0.10)**	**−0.28 (−0.35 to −0.21)**	**−0.12 (−0.19 to −0.04)**

DSST = digit symbol substitution test; DWRT = delayed word recall test; WFT = word fluency test.
* **Bold value** indicates $P < 0.05$. *Z* scores can be interpreted as the number of SDs above or below the mean. For example, a *Z*-score difference of −0.15 means that, on average, persons with diabetes declined an additional 0.15 SD compared with those without diabetes. Time since baseline was the time metric, and cognitive function was modeled by using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race–field center, sex, education, cigarette smoking status, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, apolipoprotein E ε4 genotype, and interactions between each of these covariates and time. There were 7455 total records, with 3640 participants at visit 2, 2663 at visit 4, and 1152 at visit 5.
† Difference in 20-y decline between persons without and those with diabetes (i.e., negative value indicates greater decline in those with diabetes).

Appendix Figure. **Propensity score distribution for persons with and without diabetes, in the full cohort (*top*) and among matched participants (*bottom*).**



Propensity scores were calculated from logistic models that included sex, age, race–field center, education, cigarette smoking status, alcohol consumption, hypertension status, prevalent coronary heart disease, prevalent stroke, and body mass index.

Appendix Table 7. **Average Difference in 20-y Decline in Global Cognitive *Z* Score and DWRT, DSST, and WFT Scores Between Persons With a History of Diagnosed Diabetes and Those Without: Cognitive Values Censored for Participants With Stroke***

Test	20-y Decline (95% CI)		Difference (95% CI)†
	No Diabetes	Diabetes	
Global *Z* score	**−0.77 (−0.79 to −0.74)**	**−0.90 (−0.97 to −0.83)**	**−0.13 (−0.20 to −0.06)**
DWRT	**−0.97 (−1.01 to −0.93)**	**−1.02 (−1.13 to −0.91)**	−0.05 (−0.16 to 0.07)
DSST	**−0.69 (−0.71 to −0.67)**	**−0.82 (−0.87 to −0.77)**	**−0.13 (−0.18 to −0.08)**
WFT	**−0.16 (−0.18 to −0.13)**	**−0.25 (−0.31 to −0.19)**	**−0.10 (−0.16 to −0.04)**

DSST = digit symbol substitution test; DWRT = delayed word recall test; WFT = word fluency test.
* **Bold value** indicates $P < 0.05$. *Z* scores can be interpreted as the number of SDs above or below the mean. For example, a *Z*-score difference of −0.15 means that, on average, persons with diabetes declined an additional 0.15 SD compared with those without diabetes. Time since baseline was the time metric, and cognitive function was modeled by using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race–field center, sex, education, cigarette smoking status, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, apolipoprotein E ε4 genotype, and interactions between each of these covariates and time. There were 30 655 total records, with 13 729 participants at visit 2, 10 944 at visit 4, and 5982 at visit 5.
† Difference in 20-y decline between persons without and those with diabetes (i.e., negative value indicates greater decline in those with diabetes).

Appendix Table 8. **Distribution of Stabilized and Unstabilized Weights, by Race**

Race	Mean	SD	Minimum	5th Percentile	95th Percentile	Maximum
Black						
Unstabilized	1.504	1.652	1.000	1.000	2.790	82.18
Stabilized	1.010	0.273	0.125	0.770	1.301	9.123
White						
Unstabilized	1.320	1.999	1.000	1.000	2.200	243.0
Stabilized	1.002	0.296	0.282	0.830	1.159	19.24