Glycated haemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study

A. L. Christman · K. Matsushita · R. F. Gottesman ·
T. Mosley · A. Alonso · J. Coresh · F. Hill-Briggs ·
A. R. Sharrett · E. Selvin

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Abstract

Aims/hypothesis This study aimed to examine the association between diabetes and hyperglycaemia—assessed by HbA_{1c}—and change in cognitive function in persons with and without diabetes.

Methods This was a prospective cohort study of 8,442 non-diabetic and 516 diabetic participants in the Atherosclerosis

Risk in Communities (ARIC) study. We examined the association of baseline categories of HbA_{1c} with 6 year change in three measures of cognition: the digit symbol substitution test (DSST); the delayed word recall test (DWRT); and the word fluency test (WFT). Our primary outcomes were the quintiles with the greatest annual cognitive decline for each test. Logistic regression models were adjusted for demographic (age, sex, race, field centre, education, income), lifestyle (smoking, drinking) and metabolic (adiposity, blood pressure, cholesterol) factors.

Results The mean age was 56 years. Women accounted for 56% of the study population and 21% of the study population were black. The mean HbA_{1c} was 5.7% overall: 8.5% in persons with and 5.5% in persons without diabetes. In adjusted logistic regression models, diagnosed diabetes was associated with cognitive decline on the DSST (OR 1.42, 95% CI 1.14–1.75, $p=0.002$), but HbA_{1c} was not a significant independent predictor of cognitive decline when stratifying by diabetes diagnosis (diabetes, p trend=0.320; no diabetes, p trend=0.566). Trends were not significant for the DWRT or WFT in either the presence or the absence of diabetes.

Conclusions/interpretation Hyperglycaemia, as measured by HbA_{1c}, did not add predictive power beyond diabetes status for 6 year cognitive decline in this middle-aged population. Additional work is needed to identify the non-glycaemic factors by which diabetes may contribute to cognitive decline.

A. L. Christman (✉) · K. Matsushita · J. Coresh · A. R. Sharrett ·
E. Selvin
Department of Epidemiology, Bloomberg
School of Public Health, Johns Hopkins University,
615 North Wolfe Street,
Baltimore, MD 21205, USA
e-mail: andrea.christman@gmail.com

A. L. Christman · J. Coresh · F. Hill-Briggs · A. R. Sharrett ·
E. Selvin
Welch Center for Prevention, Epidemiology,
and Clinical Research, Johns Hopkins University,
Baltimore, MD, USA

R. F. Gottesman
Department of Neurology,
Johns Hopkins University School of Medicine,
Baltimore, MD, USA

T. Mosley
Department of Medicine,
University of Mississippi Medical Center,
Jackson, MS, USA

A. Alonso
Division of Epidemiology and Community Health,
School of Public Health, University of Minnesota,
Minneapolis, MN, USA

F. Hill-Briggs
Department of Medicine,
Johns Hopkins University School of Medicine,
Baltimore, MD, USA

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Abbreviations

ARIC Atherosclerosis Risk in Communities
DWRT Delayed word recall test
DSST Digit symbol substitution test
WFT Word fluency test

Diabetes is associated with an increased risk of cognitive decline and development of dementia [1–4]. However, the biological mechanisms linking diabetes to impaired cognition remain unclear. Individuals with diabetes are at increased risk for stroke, which is a risk factor for dementia, and it is also hypothesised that hyperglycaemia may contribute to microvascular changes and ischaemia in the brain [5, 6]. Nonetheless, it remains unclear if hyperglycaemia is a predictor of cognitive decline independent of diabetes diagnosis.

HbA_{1c} is an integrated measure of circulating glucose levels over the preceding 2 to 3 months. HbA_{1c} is central to the management of glucose control in individuals with diagnosed diabetes and it has recently been recommended for use in the diagnosis of diabetes [7]. Epidemiological studies have demonstrated that HbA_{1c} is a risk factor for cardiovascular disease and total mortality among persons with and without diabetes [6, 8, 9]. Several previous studies have also reported an association between higher values of HbA_{1c} and poor cognitive function in persons with type 1 or type 2 diabetes [1]. However, few studies have investigated the association of hyperglycaemia with cognitive decline across the spectrum of glycaemia in persons with and without diabetes [10]. Previous studies have not investigated the association of HbA_{1c} with cognitive decline in a community-based population of persons with and without diabetes.

Our objective was to examine the association between HbA_{1c} and the 6 year change in cognitive function in middle-aged persons with and without diabetes in the Atherosclerosis Risk in Communities (ARIC) cohort. We sought to investigate if HbA_{1c} was an important determinant of cognitive function in both the overall population and in groups stratified by diabetes status. We also examined the association of HbA_{1c} with risk of hospitalisation with an ICD-9 code for dementia during 14 years of follow-up. We hypothesised that higher HbA_{1c} values in both persons with and without diabetes would be independently associated with the decline in cognitive function and risk of dementia hospitalisation.

Methods

Study population The ARIC study is an ongoing community-based prospective cohort of 15,792 middle-aged adults from four US communities. The first visit occurred between 1987 and 1989 and there were three subsequent visits, occurring approximately 3 years apart. Cognitive functioning was assessed at two time points: visit 2 (1990–92) and again at visit 4 (1996–98). In the present analysis visit 2 was considered the baseline visit. We examined change in cognition from baseline to visit 4 over

the 6 year period. Of the 11,656 participants who attended both visit 2 and visit 4, we excluded those who were missing HbA_{1c} or cognitive test data or had test scores recorded out of range, who self-identified as other than white or black race, who had a history of stroke, or who scored in the bottom fifth percentile of one of the three cognitive tests at visit 2 [3], leaving 8,948 participants to be included in the final sample.

Assessment of diabetes and measurement of HbA_{1c} Diabetes history was defined based on a self-reported physician diagnosis of diabetes, fasting glucose value ≥ 7 mmol/l, or diabetes medication use at or prior to visit 2 (baseline). Frozen whole-blood samples collected at ARIC visit 2 were thawed and assayed for HbA_{1c} measurement using high-performance liquid chromatography methods (Tosoh A_{1c} 2.2 Plus Glycohemoglobin Analyzer and Tosoh G7, Tosoh, Tokyo, Japan) [11]. We categorised HbA_{1c} using clinical cut-points set out in 2010 American Diabetes Association guidelines: in persons without a history of diabetes, $<5.7\%$, $5.7\text{--}<6.5\%$, $\geq 6.5\%$; and in persons with a history of diabetes, $<7.0\%$, $7.0\text{--}8.0\%$, and $\geq 8.0\%$ [7].

Measures of cognitive function Three neuropsychological tests were used to assess cognitive function: the digit symbol substitution test (DSST) from the Wechsler adult intelligence scale-revised (WAIS-R), the delayed word recall test (DWRT), and the word fluency test (WFT), also known as the controlled oral word association test of the multilingual aphasia examination. Using identical protocols at visit 2 and visit 4, trained examiners administered the neuropsychological tests in a standardised order during one session in a quiet room. Examiner performance was monitored by audiotape recordings, which were reviewed to ensure consistency.

The DSST is a test of executive function and processing speed. This is a timed test of translation of numbers to symbols using a key. The score is the total number of numbers correctly translated to symbols within 90 s. Scores can range from 0 to 93 [12].

The DWRT is a test of verbal learning and recent memory. The study participant is asked to learn ten common nouns by using each word in two sentences. After a 5-min interval, the participant is asked to recall the ten nouns. The score is the number of nouns correctly recalled. The range of possible scores is 0 to 10 [13].

The WFT is a test of executive function and expressive language. The test includes three 1 min trials where the participant is asked to generate words beginning with a particular letter, not including proper names or places. The three letters used were ‘F’, ‘A’ and ‘S’. The score is the total number of correct words generated for the three trials [14].

Incident dementia hospitalisation ARIC investigators conduct active community-wide surveillance for all hospitalisations and deaths. We defined time to first hospitalisation with an ICD-9 code for dementia using the following ICD-9 codes (listed anywhere in the hospital discharge record): Alzheimer's disease (331.0), vascular dementia (290.4) or dementia of other aetiology (290.0, 290.1, 290.2, 290.3, 290.9, 294.1, 294.2, 294.8, 294.9, 331.1, 331.2, 331.8, 331.9) (www.icd9data.com/2011/Volume1/290-319/290-294/290/default.htm) [3].

Covariates All covariates used in the regression models were assessed during visit 2 (1990–1992), except education, which was assessed during visit 1 (1987–1989). Covariates evaluated as potential confounders included: age, race, field centre, sex, education (<high school; high school or vocational school; college, graduate, or professional school), family income (<US\$35,000 per year; ≥US\$35,000 per year; not reported), BMI, cigarette smoking (current; former; never), drinking (current; former; never), systolic blood pressure, diastolic blood pressure, hypertension medication use and total cholesterol concentration.

Statistical analysis We computed the annual cognitive change for each person for each of the three tests. Change in cognitive function was calculated as the difference in days between the test scores at visit 4 and visit 2 divided by 365.25 to obtain the annual score change for each test. We then categorised the annual change in cognitive function into quintiles for each test. In our primary analyses, we compared the quintile with the largest annual decline with the other four quintiles.

Using multivariable linear regression, we estimated the cross-sectional associations between visit 2 cognitive test scores and HbA_{1c}. We estimated adjusted odds ratios for the top quintile of annual cognitive decline and their 95% confidence intervals using multivariable logistic regression. Cox regression models were used to estimate adjusted hazard ratios for dementia hospitalisation. We considered two models that were adjusted as follows: model 1 was adjusted for age, race, field centre, sex, education and income; and model 2 was adjusted for all variables in model 1 plus BMI, smoking, drinking, systolic and diastolic blood pressures, hypertension medication use and total cholesterol concentration. We formally tested for interactions with race, sex and education. All models were evaluated overall (across the entire study population) and stratified by diabetes status to examine the association of HbA_{1c} with cognitive decline separately among persons with and without a history of diagnosed diabetes. We tested for trend across the median of the diabetes–HbA_{1c} categories. The *p* value for trend represents linear trend of mean yearly change in test score across HbA_{1c} for no diabetes and

diagnosed diabetes groups separately. The *p* value for overall trend represents linear trend of mean yearly change in test score across HbA_{1c} categories for all participants (no diabetes and diagnosed diabetes combined).

In analyses of cognitive decline, we performed a sensitivity analysis excluding participants with incident stroke between visits 2 and 4 (*n*=81). To assess possible survival bias, we evaluated the proportion of participants who died between visits 2 and 4 by diabetes-specific HbA_{1c} categories.

All reported *p* values are two-sided and *p*<0.05 was considered statistically significant. Analyses were performed using Stata Version 11 [15].

Results

The demographic and clinical characteristics of the 8,958 study participants overall and stratified by diabetes–HbA_{1c} categories are shown in Table 1. The mean age was 56 years, 56% were women and 21% were black. The mean HbA_{1c} was 5.7% overall: 8.5% in persons with and 5.5% in persons without diabetes.

In cross-sectional analyses of visit 2 cognitive test scores with HbA_{1c}, an HbA_{1c} value higher by 1% was associated with a significantly lower score on DSST overall (−0.43, 95% CI −0.63, −0.23, *p*<0.001) and when stratified by diabetes status (no diabetes: *p*=0.02, diabetes *p*=0.05). An HbA_{1c} value higher by 1% was associated with a −0.03 lower score on DWRT overall (95% CI −0.06, −0.003, *p*=0.28) and with a −0.33 lower score on WFT overall (95% CI −0.55, −0.10, *p*=0.005). When stratified by diabetes status, cross-sectional associations between DWRT and WFT were not significantly associated with HbA_{1c} (*p* values >0.06).

The mean annual change in cognitive test score adjusted for age, race, sex and education by diabetes–HbA_{1c} category is shown for each of the three cognitive tests in Fig. 1. In analyses adjusted for age, race, sex and education, the mean annual change in cognitive test score increased with increasing diabetes–HbA_{1c} category for all three cognitive tests in the overall population (DSST *p* trend overall<0.001, DWRT *p* trend overall=0.032, WFT *p* trend overall=0.005), but not when stratified by diabetes diagnosis.

Expressing annual change in cognitive test scores in SD units enables comparison of the magnitude of the change across the tests. Participants experienced greater yearly decline on the DSST (−0.39±1.00 SDs) compared with the DWRT (−0.10±0.84 SDs) and the WFT (−0.10±1.0 SDs).

The adjusted odds ratios for the highest quintile of annual cognitive decline for each test are shown according to diabetes–HbA_{1c} categories in Table 2. In the total

Table 1 Characteristics of participants at ARIC visit 2 overall and by HbA_{1c} category and diabetes status

Characteristic	All participants (<i>N</i> =8,958)	Non-diagnosed diabetes			Diagnosed diabetes		
		HbA _{1c} <5.7% (<i>n</i> =6,589)	HbA _{1c} 5.7–6.5% (<i>n</i> =1,542)	HbA _{1c} ≥6.5% (<i>n</i> =311)	HbA _{1c} <7.0% (<i>n</i> =144)	HbA _{1c} 7.0–8.0% (<i>n</i> =107)	HbA _{1c} ≥8.0% (<i>n</i> =265)
Age (years)	56.5±5.6	56.2±5.6	57.4±5.7	57.3±5.5	58.7±5.4	58.4±5.9	57.0±5.7
Women, <i>n</i> (%)	5,015 (56.0)	3,726 (56.6)	825 (53.5)	181 (58.2)	74 (51.4)	54 (50.5)	155 (58.5)
Race, <i>n</i> (%)							
White	7,046 (78.7)	5,648 (85.7)	935 (60.6)	154 (49.5)	106 (73.6)	72 (67.3)	131 (49.4)
Black	1,912 (21.3)	941 (14.3)	607 (39.4)	157 (50.5)	38 (26.4)	35 (32.7)	134 (50.6)
Education, <i>n</i> (%)							
<High school	1,344 (15.0)	776 (11.8)	348 (22.6)	88 (28.3)	33 (22.9)	34 (31.8)	65 (24.5)
High school or vocational school	3,875 (43.3)	2,886 (43.8)	648 (42.0)	117 (37.6)	59 (41.0)	39 (36.5)	126 (47.6)
College, graduate, or professional school	3,739 (41.7)	2,927 (44.4)	546 (35.4)	106 (34.1)	52 (36.1)	34 (31.7)	74 (27.9)
Family income, <i>n</i> (%)							
<US\$35,000/year	4,087 (45.6)	2,717 (41.2)	850 (55.1)	199 (64.0)	82 (56.9)	66 (61.7)	173 (65.3)
≥US\$35,000/year	4,392 (49.0)	3,530 (53.6)	601 (39.0)	88 (28.3)	56 (38.9)	37 (34.6)	80 (30.2)
Missing	479 (5.4)	342 (5.2)	91 (5.9)	24 (7.7)	6 (4.2)	4 (3.7)	12 (4.5)
BMI (kg/m ²)	27.8±5.2	27.0±4.7	29.4±5.7	32.0±5.9	30.5±5.1	31.4±6.4	31.9±6.0
Cigarette smoking status, <i>n</i> (%)							
Current smoker	1,709 (19.1)	1,175 (17.8)	391 (25.4)	65 (20.9)	24 (16.7)	21 (19.6)	33 (12.5)
Former smoker	3,472 (38.8)	2,571 (39.0)	573 (37.2)	122 (39.2)	59 (41.0)	45 (42.1)	102 (38.5)
Never smoker	3,777 (42.1)	2,843 (43.2)	578 (37.5)	124 (39.9)	61 (42.4)	41 (38.3)	130 (49.0)
Alcohol use status, <i>n</i> (%)							
Current alcohol use	5,399 (60.3)	4,260 (64.7)	813 (52.7)	129 (41.5)	70 (48.6)	46 (43.0)	81 (30.6)
Former alcohol use	1,638 (18.3)	1,009 (15.3)	372 (24.1)	94 (30.2)	34 (23.6)	30 (28.0)	99 (37.4)
Never alcohol use	1,918 (21.4)	1,317 (20.0)	357 (23.2)	88 (28.3)	40 (27.8)	31 (30.0)	85 (32.1)
HbA _{1c} (%), median (IQR)	5.4 (5.2–5.8)	5.3 (5.1–5.5)	5.9 (5.8–6.1)	6.8 (6.6–7.2)	6.3 (5.8–6.6)	7.4 (7.2–7.7)	9.8 (8.9–10.9)
Glucose (mmol/l)	6.1±1.9	5.6±0.6	6.1±0.8	8.1±2.4	7.7±1.9	10.1±2.3	14.4±4.1
Total cholesterol (mmol/l)	5.4±1.0	5.4±1.0	5.5±1.0	5.5±1.0	5.3±1.0	5.3±1.0	5.6±1.1
LDL-cholesterol (mmol/l)	3.4±0.9	3.4±0.9	3.6±0.9	3.6±1.0	3.4±1.0	3.4±0.9	3.7±1.0
HDL-cholesterol (mmol/l)	1.3±0.4	1.3±0.4	1.2±0.4	1.1±0.3	1.1±0.4	1.1±0.3	1.1±0.4
Triacylglycerols (mmol/l)	1.4±0.7	1.4±0.7	1.5±0.7	1.7±0.8	1.7±0.8	1.8±0.8	1.9±0.9
Systolic blood pressure (mmHg)	120±17.6	118±17.2	123±17.8	127±17.8	129±19.2	127±18.3	127±18.9
Diastolic blood pressure (mmHg)	72.0±9.9	71.6±9.9	73.1±10.0	74.3±9.5	72.0±9.5	71.9±10.4	72.0±9.9
Hypertension, <i>n</i> (%)	2,847 (31.8)	1,737 (26.4)	641 (41.6)	168 (54.0)	87 (60.4)	69 (64.5)	146 (55.1)
Cognitive testing at visit 2							
Digit symbol substitution	47.4±12.8	49.4±12.0	42.9±13.5	39.3±13.1	44.6±12.6	40.9±13.6	38.7±13.7
Delayed word recall	6.9±1.4	7.0±1.3	6.7±1.3	6.5±1.4	6.5±1.3	6.3±1.3	6.5±1.5
Word fluency	35.4±11.5	36.3±11.4	33.4±11.6	32.0±11.9	34.3±11.5	31.9±12.7	31.0±10.6
Cognitive testing at visit 4							
Digit symbol substitution	44.7±12.9	46.7±12.0	40.4±13.3	36.9±13.2	41.0±12.8	36.5±15.1	35.5±14.4
Delayed word recall	6.7±1.5	6.8±1.5	6.5±1.5	6.1±1.6	6.1±1.5	6.0±1.8	6.2±1.7
Word fluency	34.6±12.0	35.5±11.8	32.6±12.2	31.5±11.4	33.3±11.5	29.0±13.7	28.6±11.2
Cognitive decline (visit 4–visit 2)							
Digit symbol substitution	−2.75±6.92	−2.70±6.75	−2.55±7.12	−2.43±7.10	−3.59±7.29	−4.42±9.13	−4.14±8.08
Delayed word recall	−0.18±1.52	−0.15±1.50	−0.19±1.54	−0.41±1.57	−0.36±1.40	−0.31±1.67	−0.33±1.69
Word fluency	−0.83±7.91	−0.75±7.96	−0.80±7.59	−0.55±8.35	−1.03±7.38	−2.88±8.01	−2.41±8.03

Values are mean ± SD unless stated otherwise

IQR, interquartile range

Fig. 1 Mean yearly change in cognitive test scores by HbA_{1c} category and diabetes status adjusted for age, race, sex and education: **a** DSST, overall trend $p<0.001$; $^{\dagger}p=0.831$; $^{\ddagger}p=0.509$. **b** DWRT, overall trend $p<0.032$; $^{\dagger}p<0.055$; $^{\ddagger}p=0.722$. **c** WFT, overall trend $p=0.005$; $^{\dagger}p=0.231$ and $^{\ddagger}p=0.226$. The p value for trend represents the linear trend of mean yearly change in test score across HbA_{1c} for no diabetes and diagnosed diabetes groups, separately. The p value for overall trend represents the linear trend of mean yearly change in test score across HbA_{1c} categories for all participants (no diabetes and diagnosed diabetes combined). Error bars represent 95% CI

population, we observed a significant association between baseline HbA_{1c} and cognitive decline assessed by the DSST (model 2, p trend overall=0.011), which was probably driven by diagnosed diabetes. Diagnosed diabetes was associated with a 1.42 higher odds (95% CI 1.14–1.75, $p=0.002$) of cognitive decline on the DSST when comparing individuals with and without diagnosed diabetes. However, the association with HbA_{1c} was not significant when we stratified by diabetes status (diabetes, model 2, p trend=0.320; no diabetes, model 2, p trend 0.556). In the total population, HbA_{1c} was not significantly associated with cognitive decline assessed by either the DWRT or the WFT in adjusted analyses (DWRT model 2, p trend overall=0.235, WFT model 2, p trend overall=0.169). Similarly there was no significant association between cognitive decline and HbA_{1c} on the DWRT or WFT in analyses stratified by diabetes diagnosis (all p trend>0.2). There was no significant interaction between sex, race or education for any of the three cognitive tests (all p interaction >0.1). However, there was evidence of a stronger association between baseline HbA_{1c} and cognitive decline among blacks as compared with whites in this study. We observed borderline significant associations for both the DSST and DWRT in blacks in analyses stratified by race, although the p for interaction by race was not statistically significant (DSST p interaction model 2=0.822; DWRT p interaction model 2=0.103).

There were 165 cases of incident hospitalisation with dementia listed as an ICD-9 code during a median of 14 years of follow-up for this outcome. A diagnosis of diabetes was associated with a 2.80 (95% CI 1.83–4.30) times increased risk of dementia. Higher HbA_{1c} values at baseline were associated with an increased risk of dementia in the non-diabetes group (HR 0.92 [95% CI 0.59–1.44] and HR 2.68 [95% CI 1.46–4.91] for HbA_{1c} 5.7–<6.5% and $\geq 6.5\%$ compared with HbA_{1c} <5.7%, p trend=0.019), but not within the diabetes group (HR 0.97 [95% CI 0.37–2.55] and 1.13 [95% CI 0.43–2.98] for HbA_{1c} 7.0–<8.0% and $\geq 8.0\%$ compared with HbA_{1c} <7.0%, p trend=0.971).

In sensitivity analyses of cognitive decline where participants who experienced incident stroke between visits 2 and 4 were excluded ($n=81$), we found that the association for being in the top quintile of annual cognitive

Table 2 Adjusted odds ratios for top quintile of yearly cognitive decline

Variable	DSST		DWRT		WFT	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Diagnosed diabetes (yes vs no)	1.41 (1.15–1.74)	1.42 (1.14–1.75)	1.17 (0.94–1.44)	1.13 (0.91–1.41)	1.18 (0.95–1.46)	1.20 (0.96–1.50)
No diabetes						
HbA _{1c} <5.7% (reference)	1.00	1.00	1.00	1.00	1.00	1.00
HbA _{1c} 5.7–6.5%	0.94 (0.81–1.09)	0.94 (0.81–1.09)	0.92 (0.79–1.06)	0.90 (0.77–1.04)	0.94 (0.81–1.08)	0.95 (0.82–1.10)
HbA _{1c} ≥6.5%	0.95 (0.70–1.27)	0.94 (0.69–1.26)	1.35 (1.04–1.76)	1.30 (1.00–1.71)	0.97 (0.72–1.30)	0.99 (0.73–1.33)
<i>p</i> value for trend	0.485	0.566	0.258	0.462	0.478	0.589
Diagnosed diabetes						
HbA _{1c} <7.0%	1.07 (0.71–1.60)	1.04 (0.69–1.57)	1.02 (0.68–1.53)	1.01 (0.67–1.52)	0.89 (0.58–1.37)	0.93 (0.60–1.43)
HbA _{1c} 7.0–8.0%	1.82 (1.19–2.78)	1.78 (1.15–2.74)	1.46 (0.95–2.24)	1.40 (0.90–2.16)	1.37 (0.88–2.14)	1.41 (0.90–2.22)
HbA _{1c} ≥8.0%	1.41 (1.06–1.88)	1.34 (1.00–1.81)	1.14 (0.85–1.53)	1.08 (0.80–1.46)	1.22 (0.91–1.65)	1.22 (0.90–1.66)
<i>p</i> value trend	0.524	0.320	0.990	0.612	0.310	0.190
<i>p</i> value for overall trend	0.010	0.011	0.099	0.235	0.205	0.169

Data are OR (95% CI)

Model 1 adjusted for age, race, sex, education, income and centre

Model 2 adds smoking, drinking, BMI, systolic blood pressure, diastolic blood pressure, hypertension medication use and total cholesterol

p value for trend represents linear trend of mean yearly change in test score across HbA_{1c} for no diabetes and diagnosed diabetes groups separately

p value for overall trend represents linear trend of mean yearly change in test score across HbA_{1c} categories for all participants (no diabetes and diagnosed diabetes combined)

decline for the DSST remained significant (adjusted OR 1.38 [95% CI 1.02–1.88]), comparing persons with diabetes and HbA_{1c} ≥8.0 to persons without diabetes and HbA_{1c} <5.7, *p* trend overall=0.045. Our results for the DWRT and the WFT were not appreciably altered and remained non-significant (DWRT model 2, *p* trend overall=0.313, WFT model 2, *p* trend overall=0.293, data not shown).

There were 769 ARIC participants who died between visits 2 and 4 and there were 1,228 individuals who did not attend visit 4 and were not included in our analysis. In sensitivity analyses where the outcome was the top quintile of cognitive decline or death or loss to follow-up, there was no association with HbA_{1c} category for any of the three cognitive tests (all *p*>0.5). There were significantly higher percentages of deaths as the HbA_{1c} increased (5.0%, 9.2%, 9.6%, 12.8%, 16.6% and 21.8% for HbA_{1c} categories <5.7%, 5.7–<6.5%, ≥6.5%, <7.0%, 7.0–8.0%, and ≥8.0%).

Discussion

To our knowledge, this is the first study of HbA_{1c} and cognitive decline in a community-based population of middle-aged adults. In the overall population (patients with and without diabetes combined), we found that HbA_{1c} was significantly associated with an increased risk of cognitive decline measured by the DSST, and this result appeared to

be driven by a diagnosis of diabetes. That is, we did not observe an association between HbA_{1c} and cognitive decline when stratifying by diabetes history. Our findings are consistent with numerous studies that have demonstrated the association of diabetes with cognitive impairment [1] and with a prospective study of over 8,000 older adults in Europe, in which an association between baseline fasting glucose and 5 year cognitive change in non-diabetic adults was not observed [16]. Our study suggests that hyperglycaemia per se may not be the most important determinant of the elevated risk of cognitive impairment seen in diabetes.

Consistent with the literature and a previous ARIC report [3], we found that diabetes status was associated with decline on DSST, which reflects impairment in the executive function and processing speed domains of cognition [1, 4, 17]. Van den Berg et al. [18] also used the DSST and found decrements in information-processing speed, psychomotor speed and attention and executive functions in persons with diabetes compared with those without diabetes over 4 years of follow-up. A recent systematic review of diabetes and cognition found that 63% of studies that assessed the processing speed domain reported an association of diabetes with impairment in this domain [19]. Diabetes appears to strongly affect the processing speed, psychomotor speed and executive functioning, indicating that these domains may be particularly

sensitive to the cognitive changes seen in diabetes [19]. The tests used in this study measure functions performed by different parts of the brain, with the DSST measuring subcortical function and the WFT and DWRT measuring cortical functions, indicating that hyperglycaemia may have a greater impact on the subcortical brain [19].

Most studies assessing the relationship between HbA_{1c} and cognitive function have been limited to persons with diabetes and have been cross-sectional, while our community-based prospective study included both persons with and without diabetes. Cukierman-Yaffe et al. [20] found a cross-sectional association whereby each 1% higher HbA_{1c} value was associated with a 1.75 point lower DSST score in the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD-MIND) study baseline population (mean age 63 years). We observed a similar cross-sectional association on the DSST in the ARIC population of middle-aged adults with and without diabetes, both overall and when stratified. We did not, however, observe an independent association between HbA_{1c} and 6 year cognitive decline in our prospective analyses stratified by diabetes status. This null result may partially reflect the middle-aged population and short duration of follow-up. Indeed, the absolute levels of cognitive change over this 6 year period were small. In addition, differential survival may have also biased our results toward the null, as the 769 ARIC participants who died between visits 2 and 4 were more likely to have higher baseline HbA_{1c}, a history of diagnosed diabetes, and may have had greater cognitive declines prior to death.

None of race, sex or education significantly modified the associations between HbA_{1c} and cognitive decline in our study. However, in analyses stratified by race, we observed borderline significant associations between cognitive decline on both the DSST and DWRT in blacks only.

We did not find any significant association between diabetes or HbA_{1c} and cognitive decline on either the WFT or the DWRT. Our weaker results for WFT and DWRT may reflect the short duration of follow-up and the small absolute changes in cognition in this population of middle-aged adults. Our results cannot exclude the possibility that HbA_{1c} is an important predictor of cognitive decline at older ages and/or over longer follow-up.

Previous analyses of ARIC data demonstrated a strong association of diabetes and cognition with incident dementia hospitalisation [3]. We also found that in participants without a history of diabetes, HbA_{1c} ≥ 6.5% was associated with incident dementia hospitalisation, probably driven by the extremely high cumulative incidence (>80%) of a subsequent diagnosis of diabetes in this group [9, 21]. Among individuals with diagnosed diabetes, HbA_{1c} was not independently associated with risk of dementia hospitalisation in this study.

A number of mechanisms have been postulated to explain how diabetes and hyperglycaemia contribute to cognitive decline. First, AGEs accumulate both during the normal ageing process and more rapidly with hyperglycaemia and diabetes [22]. AGEs cause tissue damage generally, and perhaps in cerebral vessels specifically, both by forming cross-links that disrupt the structure and function of proteins and lipids and by interacting with AGE surface receptors, leading to oxidative stress and inflammation [23]. Hyperinsulinaemia may also increase the risk of cognitive impairment and dementia by interfering with amyloid precursor protein metabolism, and possibly promoting the cerebral β -amyloid deposits characteristic of Alzheimer's disease. Hyperinsulinaemia may contribute to microvascular damage leading to cerebral infarcts and atrophy [23].

Important limitations of our study include a limited cognitive test battery, lack of data on hypoglycaemic events, and the reliance on a single measurement of HbA_{1c} at baseline. We may have had limited power to detect associations between HbA_{1c} and cognitive decline as we did not observe large changes in cognition during the 6 year period in this community-based middle-aged population [24]. Although our study population had a mean age of 56 years and the prevalence of substantial cognitive decline in this community-based population was low, other studies using this cohort have found significant associations with other vascular risk factors and cognitive decline over this time period [3].

The strengths of this study include the comprehensive assessment of diabetes risk factors, large sample size, and two assessments of cognition. This study adds to our knowledge of the association of HbA_{1c} with cognition across the entire spectrum of glycaemia in persons with and without diabetes.

In summary, hyperglycaemia, as measured by HbA_{1c}, did not predict 6 year cognitive decline beyond diabetes status in this middle-aged community-based population. In this prospective study, diabetes itself was associated with decline in one cognitive domain (executive function and processing speed) but higher values of baseline HbA_{1c} were not independently associated with cognitive decline over a 6 year period in persons either with or without diabetes. Future studies should help identify the non-glycaemic risk factors by which diabetes contributes to cognitive decline.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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