The Association of Late-Life Diabetes Status and Hyperglycemia With Incident Mild Cognitive Impairment and Dementia: The ARIC Study

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OBJECTIVE

We sought to examine associations in older adults among diabetes, glycemic control, diabetes duration, and biomarkers of hyperglycemia with incident mild cognitive impairment (MCI) and incident dementia.

RESEARCH DESIGN AND METHODS

We conducted a prospective analysis of 5,099 participants from the Atherosclerosis Risk in Communities (ARIC) Study who attended the fifth (2011–2013) exam. Cognitive status was assessed during follow-up via telephone calls, death certificate codes, surveillance, and a follow-up examination (2016–2017). We defined incident cognitive impairment as incident MCI or incident dementia in persons dementia-free at the index examination; we also examined each outcome separately. Diabetes was defined using self-report, medications, or HbA$_{1c}$ ≥6.5%; poor glycemic control in persons with diabetes was defined as HbA$_{1c}$ ≥7%. We examined the following biomarkers of hyperglycemia: HbA$_{1c}$, fructosamine, glycated albumin, and 1,5-anhydroglucitol.

RESULTS

Mean age at baseline was 76 years, 59% were female, and 21% were black. Diabetes (hazard ratio [HR] 1.14 [95% CI 1.00, 1.31]), poor glycemic control in persons with diabetes (HR 1.31 [95% CI 1.05, 1.63]), and longer diabetes duration (≥5 vs. <5 years; HR 1.59 [95% CI 1.23, 2.07]) were significantly associated with incident cognitive impairment. We found a J-shaped association between HbA$_{1c}$ and incident dementia. Glycated albumin and fructosamine were also associated with incident dementia, independently of HbA$_{1c}$. HbA$_{1c}$ and fructosamine were also associated with incident MCI.

CONCLUSIONS

Diabetes status, poor glycemic control, and longer diabetes duration were associated with worse cognitive outcomes over a median follow-up of 5 years.

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The U.S. population is rapidly aging. In 2012, 14% of the U.S. population was 65 years and older, and this proportion is expected to climb to >20% by 2030, representing >70 million people (1). Among older adults, the prevalence of diabetes is 22%, and the prevalence of prediabetes is 24% (2). Studies have documented that persons with

diabetes, particularly in midlife, have greater cognitive decline and risk of dementia than those without diabetes (3–6). Results from studies examining diabetes assessed in late life with subsequent risk of cognitive decline and dementia have been consistent, though more mixed (7–9), likely due to small sample sizes or shorter duration of follow-up. Additionally, data related to diabetes severity and documented duration in late life are limited, and few studies have examined whether diabetes is a risk factor for mild cognitive impairment (MCI) or progression to dementia in persons with MCI.

Measures of hyperglycemia have been of particular interest in relation to cognitive impairments. HbA_{1c} is the standard measure used in clinical practice to monitor glycemic control. There is growing interest in fructosamine, glycated albumin (GA), and 1,5-anhydroglucitol (1,5-AG) as alternative or complementary biomarkers of hyperglycemia that may add additional prognostic information beyond HbA_{1c} (10–13). These markers may provide additional insights into the association of hyperglycemia, such as the role of glucose excursions (14,15), with cognitive impairment.

In this study, we sought to examine associations among late-life diabetes, glycemic control as measured by HbA_{1c}, diabetes duration, and biomarkers of hyperglycemia with incident MCI and incident dementia using data from the Atherosclerosis Risk in Communities (ARIC) Study.

RESEARCH DESIGN AND METHODS

Study Population

ARIC is a community-based, prospective study of adults from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Participants were initially recruited in 1987–1989 (visit 1) and examined in 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), 2011–2013 (visit 5), and 2016–2017 (visit 6). Participants received annual follow-up telephone calls to assess changes in health status.

The baseline for the current study was visit 5, the first visit that included comprehensive cognitive measures. Of the 6,538 participants who attended visit 5, we excluded participants who were neither black nor white ($n = 18$) or were nonwhite from Minnesota or Maryland field centers ($n = 24$), were missing cognitive status ($n = 14$), had dementia ($n = 342$), were missing covariates of interest ($n = 563$), or had no follow-up time ($n = 478$), giving an analytic sample size of 5,099. For analyses of glycemic control, we additionally excluded persons missing HbA_{1c} ($n = 46$).

Categorization of Diabetes, Glycemic Control, and Diabetes Duration

At visit 5, we defined diabetes if a participant self-reported a physician diagnosis, reported using glucose-lowering medication, or had an HbA_{1c} of ≥6.5% (48 mmol/mol). Among persons with diabetes, we dichotomized HbA_{1c} at 7% (53 mmol/mol), a treatment goal recommended by the American Diabetes Association (ADA) Standards of Medical Care for many adults (16), while individuals with complex health may have less stringent glycemic goals (such as 8–8.5% and 64–69 mmol/mol), 73% of ARIC participants with diabetes had an HbA_{1c} <7% (53 mmol/mol). In secondary analyses, we examined associations across three levels of HbA_{1c}: <7%, 7–7.9%, and ≥8% (<53, 53–63, and ≥64 mmol/mol), respectively.

We used information from visits 1–4 and annual follow-up calls following visit 4 to identify the date of first reported diabetes. We calculated diabetes duration as the difference between this date and the visit 5 date. Self-reported diabetes in ARIC has been shown to be reliable and highly specific (17). Participants who reported no diabetes at any visit or phone call prior to visit 5 but who met our definition of diabetes at visit 5 were categorized as having diabetes with 0 duration; participants with undiagnosed diabetes at visit 5 (i.e., no self-reported diagnosis or medication use at any visit with HbA_{1c} ≥6.5% at visit 5) were excluded from this analysis. We dichotomized diabetes duration as <5 or ≥5 years.

Markers of Glycemia: HbA_{1c}, Fructosamine, Glycated Albumin, and 1,5-AG

HbA_{1c} was measured using a Tosoh G7 automated high-performance liquid chromatography analyzer (Tosoh Bioscience, South San Francisco, CA) standardized to the Diabetes Control and Complications Trial assay. Fructosamine was measured in serum on the Roche Modular P800 Chemistry Analyzer (Roche Diagnostics) using a colorimetric assay. GA was measured in serum using a complex method by Asahi Kasei Pharma adapted to the Roche Modular P800 Chemistry Analyzer (Roche Diagnostics). 1,5-AG was measured in serum using GlycoMark 1,5-AG reagent on a Roche Modular P800 Chemistry Analyzer (Roche Diagnostics). All assays were conducted in stored samples collected from ARIC participants at visit 5, which had been stored at −70°C in freezers at the University of Minnesota.

Categorization of Cognitive Status at Visit 5

ARIC participants' cognitive function at visit 5 was categorized by committee review as part of the ARIC Neurocognitive Study (ARIC-NCS) (18), which added dementia surveillance, and cognitive status to visit 5 of the parent ARIC Study. Briefly, cognitive status was categorized as normal, MCI, or dementia using information from proxy interviews, change in cognitive scores on three cognitive tests administered at study visits since midlife, and visit 5 results from the Mini-Mental State Examination, the Clinical Dementia Rating (CDR) form, the Functional Activities Questionnaire (FAQ), and Z scores from a full battery of 10 neuropsychological tests. An algorithmic diagnosis was assigned for all possible combinations of diagnostic elements; an expert committee reviewed the algorithmic diagnosis and assigned final cognitive status as normal cognition, MCI, or dementia. Etiologic classification was added to the MCI and dementia cases, but etiology was not considered in the current study.

Categorization of Cognitive Status After Visit 5

Cognitive status after visit 5 was defined by expert committee review (19) using the same criteria as at visit 5, which has been previously described in detail (18). Briefly, dementia was categorized in a stepwise fashion based on five hierarchical, leveled dementia diagnosis variables (19) based on the availability of data: level 1 diagnosis was based on neuropsychological data collected from participants who attended visits 5 and/or 6; level 2a was based on the Telephone Interview for Cognitive Status and

retrospective dementia surveillance from visit 5; levels 2b and 2c were based on the Six-Item Screener (SIS) or Ascertain Dementia 8-item (AD8) (20–22) informant questionnaire, both captured from the annual telephone calls; and level 3 was based on ARIC surveillance of hospitalizations and deaths. The sequential order from available data sources considered for dementia ascertainment assignment were 1) reviewer diagnosis at visit 5 or visit 6, 2) algorithmic diagnosis at visit 5 or visit 6, 3) AD8 result, 4) two SIS results, 5) one SIS result if the participant is lost to follow-up or deceased, 6) hospitalization discharge codes, and 7) death certificate codes.

Each of the leveled diagnosis variables had an associated date of diagnosis. If the participant was categorized as having dementia, the date corresponded to the earliest date that dementia was detected. If the participant was categorized as not having dementia, the corresponding date came from the visit 5 date, visit 6 date, AD8 date, or SIS date.

Participants who attended visit 6 were categorized as cognitively normal if their neuropsychological test scores in each of three domains (memory, language, and executive function) were higher than −1.5 SDs expected for their age, race, and education level, or they had little or no cognitive decline in the full ARIC cognitive battery (decline of <0.055 SDs per year [ARIC visit 6 Manual 17 (23)]). MCI was defined only in persons examined at study visits. Diagnosis required having at least one failed domain score (defined as a score <1.5 SDs below the participant's expected score), a CDR sum of boxes between >0.5 and ≤3, an FAQ ≤5, and a decline on the full ARIC cognitive battery of >0.055 SDs per year. Dementia diagnoses in persons examined at visit 6 required cognitive decline >0.055 SDs/year, two or more failed cognitive domains and FAQ >5, or CDR sum of boxes >3.

Incident Cognitive Impairment
Incident cognitive impairment was defined to represent progression in cognitive status from visit 5 to visit 6 (median follow-up 5 years). The following two groups were categorized as having incident cognitive impairment: 1) persons categorized as cognitively normal at visit 5 and having MCI or dementia at visit 6 or

dementia from surveillance for those who did not attend visit 6, and 2) persons categorized as having MCI at visit 5 and as having dementia at or before visit 6.

Covariates
We included the following confounders based on a priori knowledge: age; race and field-center (categorized into five groups as white adults from Minneapolis, Washington County, or Forsyth County or black adults from Forsyth or Jackson); sex; education (less than high school education; high school graduate, high school equivalency, or vocational school; or college or above); drinking status (current, former, or never); cigarette smoking (current, former, or never); hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or blood pressure–lowering medication); apolipoprotein E genotype, number of e4 alleles (APOE4; zero or one or more alleles); history of stroke (yes/no); and history of coronary heart

disease (CHD; yes/no). All variables were assessed at visit 5 except for education, which was determined at visit 1. For analyses of glycemic markers, we also examined associations additionally adjusted for HbA$_{1c}$.

Statistical Analysis
We compared baseline characteristics by diabetes status using means (SD) and proportions. For analyzing incident events, we used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs. We verified the proportional hazards assumption using log-log plots. We present results unadjusted and fully adjusted using the covariates described above. We fit models for four separate cognitive outcomes: 1) incident dementia and 2) incident MCI, both among participants who were cognitively normal at baseline; 3) incident cognitive impairment among all baseline participants; and 4) incident dementia among participants with MCI at baseline.

Table 1—Baseline (visit 5, 2011–2013) population characteristics by diabetes* status

	Total	No diabetes	Diabetes	
			HbA$_{1c}$ <7%	HbA$_{1c}$ ≥7%
N (%)	5,099	3,318 (65.7)	1,276 (25.3)	459 (9.1)
Age, years, mean (SD)	75.8 (5.0)	75.8 (5.0)	76.0 (5.1)	75.1 (4.7)
Female	59.2	60.0	58.3	55.3
Black	21.4	17.3	26.7	35.7
Education				
Less than high school	12.9	9.9	17.6	21.4
High school	42.5	41.9	44.0	42.5
Higher than high school	44.7	48.2	38.5	36.2
Current smoking	5.8	5.8	6.1	5.4
Current drinking	49.9	54.9	42.5	34.0
BMI, kg/m^2, mean (SD)	28.8 (5.7)	27.8 (5.2)	30.2 (5.8)	32.0 (6.2)
Hypertension	74.0	68.1	84.0	88.3
History of CHD	13.7	11.6	17.8	17.7
History of stroke	3.2	2.4	4.0	7.0
APOE e4 alleles				
0	72.3	72.2	72.3	72.5
1	25.7	25.9	25.2	25.5
2	2.1	1.9	2.5	2.0
Cognitive outcomes† after visit 5				
Dementia	11.1	10.0	12.5	15.5
MCI	16.8	16.2	16.6	23.2
Cognitive impairment	20.1	19.0	20.7	25.9

Data are percentages unless otherwise noted. The three-level categorization of diabetes and glycemic control excludes 46 persons missing HbA$_{1c}$ data. *Diabetes was defined based on self-reported diagnosis, use of glucose-lowering medication, or HbA$_{1c}$ of ≥6.5% (48 mmol/mol). HbA$_{1c}$ of 7% is equivalent to 53 mmol/mol. †Dementia was categorized using information from study visits, telephone calls with participants or their proxy, or surveillance of hospitalizations and deaths. MCI was defined only in persons examined at visit 6 based on neuropsychological testing. Cognitive impairment includes the following progression in cognitive status from visit 5 to 6: 1) cognitively normal at visit 5, MCI or dementia at visit 6, or dementia from surveillance, or 2) MCI at visit 5, dementia at visit 6, or dementia from surveillance.

To examine the association between each biomarker of hyperglycemia and incident dementia, we used restricted cubic splines (24) with knots at the 5th, 35th, 65th, and 95th percentiles; restricted cubic splines allow for potential nonlinear relationships between biomarker level and incident dementia. To allow for comparison across markers, we converted each participant's biomarker values to Z scores by subtracting the mean and dividing by the SD.

In secondary analyses, we examined incident dementia in persons with diabetes by tertiles of age and diabetes duration in an effort to examine whether associations between diabetes duration with dementia differ by baseline age. Because of small sample sizes, this secondary model was adjusted only for age at study baseline, race-center, sex, and education level.

All analyses were done using Stata/SE 14.2 (StataCorp, College Station, TX). We report 95% CIs, and P values <0.05 were considered statistically significant.

RESULTS

Study Characteristics
At study baseline (visit 5), the mean age of participants was 76 years, 59% were female, 21% were black, and 34% had diabetes (Table 1). Participants with diabetes were more likely to be black, to have lower levels of education, higher BMI, hypertension, a history of CHD, and history of stroke and were less likely to be current drinkers. Other characteristics were similar across the groups (Table 1).

Incident Dementia and MCI in Participants Cognitively Normal at Baseline
Median follow-up for incident events was ~5 years (mean 4.8 years, SD 0.8). In participants who were cognitively normal at visit 5, there were 275 incident dementia and 455 incident MCI cases. Diabetes was not associated with incident dementia, and differences in incident dementia by glycemic control were nonsignificant (Table 2). In contrast, diabetes was significantly associated with incident MCI (HR 1.23 [95% CI 1.00, 1.51]) (Table 2). Persons with HbA_{1c} <7% (53 mmol/mol) did not have significantly higher risk of developing MCI compared with persons without diabetes (HR 1.11 [95% CI 0.88, 1.40]). In contrast, those with HbA_{1c} ≥7% (53 mmol/mol) compared with those with no diabetes had 1.73 times higher risk of MCI (95% CI 1.26, 2.38) (Table 2); additionally, comparing the glycemic control groups among persons with diabetes, those with HbA_{1c} ≥7% (53 mmol/mol) had 1.56 times the risk of MCI (95% CI 1.10, 2.21) compared with persons with HbA_{1c} <7% (53 mmol/mol). Longer duration of diabetes was associated with incident dementia (HR 1.91 [95% CI 1.09, 3.35]) (Table 2) and incident MCI (HR 1.58 [95% CI 1.04, 2.41]) (Table 2).

Incident Cognitive Impairment in All Study Participants and Incident Dementia in Persons With MCI
In analyses examining progression in cognitive status from visit 5 to visit 6, diabetes was significantly associated with incident cognitive impairment (HR 1.14 [95% CI 1.00, 1.31]) (Table 3). This was primarily driven by persons with diabetes and HbA_{1c} ≥7% (HR 1.38 [95% CI 1.12, 1.69]); persons with diabetes and HbA_{1c} <7% (53 mmol/mol) did not have significantly higher hazard of incident dementia compared with persons without diabetes (HR 1.05 [95% CI 0.91, 1.22]) (Table 3). Among persons with diabetes, those with diabetes duration of ≥5 years had 1.59 (95% CI 1.23, 2.07) times the hazard of cognitive impairment compared with persons of shorter diabetes duration (Table 3). Trends were similar for diabetes and glycemic control for incident dementia among persons with MCI at baseline (Table 3).

Glcyemic Markers and Incident Dementia
The continuous associations for each glycemic marker with incident dementia among participants dementia-free at baseline are shown in Fig. 1. For HbA_{1c}, low (less than ~5.8% and ~40 mmol/mol) and high (greater than ~7.5% and ~58 mmol/mol) values were significantly associated with higher risk of incident dementia. Higher values of GA and fructosamine, values predominately in the diabetes range, were associated with higher risk of incident dementia (Fig. 1) and persisted after additional adjustment for HbA_{1c} (Supplementary Fig. 1). We did not see an association with incident dementia for 1,5-AG. We found similar, though more modest, trends with incident MCI (Supplementary Fig. 2).

Table 2—Adjusted HRs (95% CI) for cognitive outcomes by diabetes status, glycemic control, and diabetes duration among participants who were cognitively normal at visit 5

	Incident dementia		Incident MCI	
	n/N‡ (%)	Adjusted HR (95% CI)	n/N‡ (%)	Adjusted HR (95% CI)
Diabetes				
No	164/2,690 (6.1)	1 (reference)	302/1,938 (15.6)	1 (reference)
Yes	111/1,317 (8.4)	1.08 (0.83, 1.39)	153/882 (17.4)	1.23 (1.00, 1.51)*
Diabetes and glycemic control				
No diabetes	164/2,690 (6.1)	1 (reference)	302/1,938 (15.6)	1 (reference)
Diabetes, HbA_{1c} <7%	77/968 (8.0)	1.01 (0.76, 1.35)	105/655 (16.0)	1.11 (0.88, 1.40)
Diabetes, HbA_{1c} ≥7% (compared with no diabetes)	32/336 (9.5)	1.16 (0.77, 1.74)	48/218 (22.0)	1.73 (1.26, 2.38)***
Diabetes, HbA_{1c} ≥7% (compared with HbA_{1c} <7%)	32/336 (9.5)	1.15 (0.75, 1.77)	48/218 (22.0)	1.56 (1.10, 2.21)*
Diabetes duration†				
<5 years	17/336 (5.1)	1 (reference)	30/226 (13.3)	1 (reference)
≥5 years	89/921 (9.7)	1.91 (1.09, 3.35)*	118/617 (19.2)	1.58 (1.04, 2.41)*

Models are adjusted for age, race-center, sex, education level, cigarette smoking status (current/former/never), drinking status (current/former/never), APOE e4 (zero, one, or two alleles), hypertension (yes/no), history of stroke (yes/no), and history of CHD (yes/no). Diabetes was defined based on self-reported diagnosis, use of glucose-lowering medication, or HbA_{1c} of ≥6.5% (48 mmol/mol). HbA_{1c} of 7% is equivalent to 53 mmol/mol. †Among persons with diabetes. ‡n/N: the number of incident cases (n) among the total number of participants in that group (N). *P < 0.05; ***P < 0.001.

Table 3—HRs (95% CI) for incident cognitive impairment and dementia by baseline cognitive status

	Incident cognitive impairment§ among participants dementia-free at baseline		Incident dementia among participants with MCI at baseline	
	n/N‡ (%)	Adjusted HR (95% CI)	n/N‡ (%)	Adjusted HR (95% CI)
Diabetes				
No	638/3,344 (19.1)	1 (reference)	169/639 (26.5)	1 (reference)
Yes	390/1,755 (22.2)	1.14 (1.00, 1.31)*	125/434 (28.8)	1.15 (0.90, 1.47)
Diabetes and glycemic control				
No diabetes	638/3,344 (19.1)	1 (reference)	169/639 (26.4)	1 (reference)
Diabetes, HbA$_{1c}$ <7%	264/1,276 (20.7)	1.05 (0.91, 1.22)	81/305 (26.6)	1.02 (0.78, 1.35)
Diabetes, HbA$_{1c}$ ≥7% (compared with no diabetes)	119/459 (25.9)	1. 38 (1.12, 1.69)**	39/122 (32.0)	1.38 (0.96, 2.00)
Diabetes, HbA$_{1c}$ ≥7% (compared with HbA$_{1c}$<7%)	119/459 (25.9)	1.31 (1.05, 1.63)*	39/122 (32.0)	1.35 (0.91, 2.00)
Diabetes duration†				
<5 years	75/441 (17.0)	1 (reference)	27/103 (26.2)	1 (reference)
≥5 years	302/1,234 (24.5)	1.59 (1.23, 2.07)***	95/311 (30.6)	1.40 (0.88, 2.20)

Models are adjusted for age, race-center, sex, education level, cigarette smoking status (current/former/never), drinking status (current/former/never), APOE e4 (zero, one, or two alleles), hypertension (yes/no), history of stroke (yes/no), and history of CHD (yes/no). Diabetes was defined based on self-reported diagnosis, use of glucose-lowering medication, or HbA$_{1c}$ of ≥6.5% (48 mmol/mol). HbA$_{1c}$ of 7% is equivalent to 53 mmol/mol. †Among persons with diabetes. ‡n/N: the number of incident cases (n) among the total number of participants in that group (N). §Cognitive impairment includes incident MCI in persons cognitively normal at baseline and incident dementia in persons cognitively normal or MCI at baseline. *P < 0.05; **P < 0.01; ***P < 0.001.

Secondary Analyses

Our secondary analyses of incident dementia in dementia-free individuals with diabetes by age and diabetes duration are shown in Supplementary Table 1. Age appeared to be a stronger driver of associations rather than duration. After adjusting for demographic variables, persons who were older at baseline had a higher absolute risk of incident dementia, regardless of their diabetes duration (Supplementary Table 1). In the first tertile of baseline age (<72.8 years), persons in the highest tertile of diabetes duration had 2.49 times the risk of dementia compared with persons in the lowest tertile of duration (95% CI 1.23, 5.06). In persons in the middle tertile of age (72.9–77.9 years), those with the longest duration of diabetes had 1.47 times the risk of dementia compared with persons with shorter duration (95% CI 0.80, 2.72). There was no appreciable association with diabetes duration in the highest tertile of baseline age. Results from analyses examining three levels of HbA$_{1c}$ for glycemic control are shown in Supplementary Tables 2 and 3; trends across the three HbA$_{1c}$ groups were similar to when HbA$_{1c}$ was dichotomized.

CONCLUSIONS

In this study of older adults without dementia, we found that diabetes, poor glycemic control, and longer diabetes duration were associated with incident cognitive impairment; persons with well-controlled diabetes (HbA$_{1c}$ <7%, 53 mmol/mol) did not have significantly higher risk of cognitive impairment compared with persons without diabetes. We also found that GA and fructosamine were associated with incident cognitive impairment, even after adjustment for HbA$_{1c}$. In persons who were cognitively normal at baseline, diabetes and glycemic control were strongly associated with incident MCI.

The overall association between diabetes and dementia has been well described (25,26); however, less is known about the association of diabetes in older
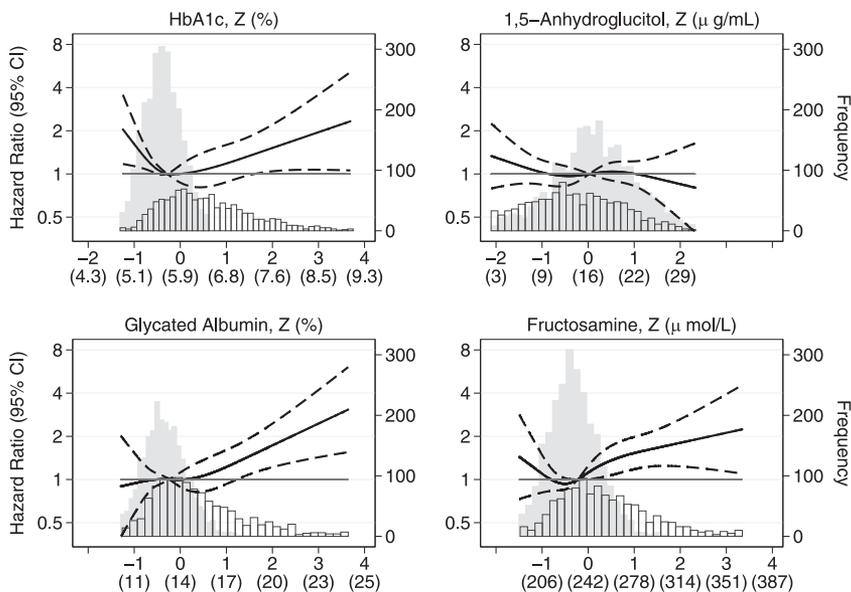

Figure 1—Adjusted HRs (95% CI) for standardized (actual) HbA$_{1c}$, 1,5-AG, GA, and fructosamine with incident dementia among persons dementia-free at baseline. Biomarker values are shown as Z scores (original units). HRs (solid line) and 95% CIs (dashed lines) are from Cox proportional hazard regression, adjusted for age, race, sex, education level, cigarette smoking status (current/former/never), drinking status (current/former/never), APOE e4 (zero, one, or two alleles), hypertension (yes/no), history of stroke (yes/no), and history of CHD (yes/no). Each biomarker was modeled using a restricted cubic spline, with knots at the 5th, 35th, 65th, and 95th percentiles, and centered at the median. Histograms of each biomarker are shown separately for persons without (solid bars) and with (outlined bars) diabetes.

adults on late-life incident MCI and progression to dementia from MCI. In our study, in which the median age was 76 years, we found relatively weak associations of diabetes and glycemic control with incident dementia in cognitively normal individuals over a median follow-up of 5 years. However, the strong associations with incident MCI and with progression in cognitive status imply that the effects of diabetes, glycemic control, and diabetes duration may have an impact on cognitive function along the continuum from normal cognition to MCI to dementia. These estimated overall associations between diabetes and incident dementia were similar to results reported in cognitively normal adults aged 65 and older with similar length of follow-up (27,28).

Studies have generally found stronger associations when vascular risk factors are ascertained in midlife compared with late life (7,9,29,30). In ARIC, diabetes measured in midlife (mean age 52 years) was associated with 1.77 times the risk of dementia (95% CI 1.53, 2.04) over 25 years compared with persons without diabetes (31). The ability in ARIC to examine both mid- and late-life exposures extends the literature by showing that late-life onset of diabetes, though associated with worse cognitive outcomes, is a weaker risk factor for dementia compared with midlife onset of diabetes. Our finding that longer diabetes duration was associated with higher risk of dementia only in the youngest tertile supports this hypothesis, though sample sizes were small, and survival bias may be contributing to these findings; more research in larger studies is needed to clarify these findings.

Studies examining diabetes in relation to MCI incidence and progression from MCI to dementia are more limited. One study examining MCI incidence in older adults (mean age 78 years) estimated an unadjusted risk of MCI over 4 years of 1.51 (95% CI 1.04, 2.20) in persons with diabetes compared with those without (32). In the Singapore Longitudinal Ageing Study (mean age 65 years), the estimated risk of MCI and progression to dementia in persons with diabetes were 2.84 (95% CI 1.92, 4.19) and 2.47 (95% CI 1.92, 4.19), respectively (33).

The association between HbA_{1c} and cognitive impairment is complex. We have previously shown in ARIC that higher midlife HbA_{1c} values in both persons with and without diabetes were associated with greater cognitive decline over 20 years (6). In the current study, higher HbA_{1c} was associated with incident dementia at values in the diabetic range, though low levels ($<5.8\%$, 40 mmol/mol) also appeared associated with higher risk of incident dementia. This contrasts with prior studies that found associations between HbA_{1c} and brain atrophy in cognitively normal individuals (34) and with higher risk of MCI (35), though not all studies have found associations, particularly when HbA_{1c} was assessed in combination with other markers of glycemia and insulin resistance (36,37). This may be in part related to J-shaped associations between HbA_{1c} and death (and other outcomes) in adults with (38) and without (39) diabetes, which has been shown in a number of prior studies. Lastly, tight glycemic control increases the likelihood of hypoglycemic events. Prior work (40,41) has shown associations between severe hypoglycemia (identified through hospitalizations) and cognitive deficits, though the association is likely bidirectional. In our study, 73% of participants with diabetes had an $HbA_{1c} <7\%$, a treatment goal recommended by the ADA as a reasonable target for healthy adults. Although we observed similar trends in incident cognitive outcomes when we considered three categories of HbA_{1c}, our sample sizes in these groups were small, and we were unable to identify mild cases of hypoglycemia. More research is needed to elucidate the association of HbA_{1c} with cognitive function in older adults with complex health and to identify optimal targets that balance the risks and benefits of tight glycemic control with respect to cognition and other health outcomes.

In our study, fructosamine and GA, biomarkers that are positively correlated with HbA_{1c}, were also strongly associated with incident dementia, even after additional adjustment for HbA_{1c}. Fructosamine and GA can be used to better estimate short-term (2–3 weeks) glycemic control because the glycation of hemoglobin occurs more slowly than the glycation of albumin (13). Glycated albumin levels have also been shown to be higher in persons with diabetes and decreased insulin secretion (15); low insulin levels have been associated with incident dementia in a pathway suggested to be independent of diabetes and hyperinsulinemia (42,43).

The additional prognostic value of these biomarkers for dementia, above and beyond HbA_{1c}, suggests the complementary nature of these measures and the possible utility of measuring multiple glycemic biomarkers in a single blood sample to better classify hyperglycemia in older adults.

Our study has several strengths, including the large, well-characterized population-based cohort and the inclusion of both cognitively normal individuals and participants with MCI. Additionally, we were able to use a wealth of data to categorize diabetes, diabetes duration, and glycemic control, and cognitive status was adjudicated via expert committee review. There are a few notable limitations to our study. First, we lacked imaging and cerebrospinal fluid biomarkers to define dementia and MCI etiologic subtypes. Second, most dementia cases occurred in participants who did not attend visit 6; however, persons with cognitive impairments are more likely to drop out, so access to telephone interviews with participants and proxies provided opportunities to capture case subjects who would otherwise have been missed. Prior work in ARIC has shown this approach may not be prone to ascertainment or diagnostic bias (J.A. Deal, A. Alonso, K. Bandeen-Roche, P. Palta, K. Perryman, M.C.P., A.L.C. Schneider, A.R.S., L.M. Wruck, unpublished observations).

In conclusion, diabetes status, poor glycemic control, and longer diabetes duration remain associated with worse cognitive outcomes over a median follow-up of 5 years in persons evaluated at ages 66–90 years. In older adults with diabetes, maintaining glycemic control is an important avenue for mitigating cognitive impairments into older age.

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