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High Hemoglobin A1c and Diabetes Predict Memory Decline in the Health and Retirement Study

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Abstract

Background—Type 2 diabetes (T2D) is an established risk factor for dementia, but evidence for T2D and memory decline is less consistent. Understanding how T2D and blood glucose relate to memory decline is crucial to elucidating the mechanisms linking T2D and dementia.

Methods—For 8,888 Health and Retirement Study participants aged 50+, glycosylated hemoglobin (HbA1c) was measured in either 2006 or 2008 and physician's diagnosis of diabetes was self-reported in the same year. Composite memory (z-scored) was assessed biennially through 2012 using immediate and delayed word list recall or the Informant Questionnaire for Cognitive Decline. Marginal mean regression models for repeated outcomes were specified to predict memory decline as a function of diabetes or HbA1c, using age as the timescale and adjusting for health and social confounders.

Results—Diabetes was associated with a 10% faster rate of memory decline ($\beta = -0.04$ per decade; 95% CI: $-0.06, -0.01$). A 1-unit increase in HbA1c corresponded with a 0.05 SD decrease in memory score per decade (95% CI: $-0.08, -0.03$). Even among individuals with HbA1c $< 6.5\%$ (threshold for diabetes), higher HbA1c was associated with memory decline ($\beta = -0.05$ per decade; 95% CI: $-0.08, -0.03$).

Discussion—Diabetes accelerated memory loss and higher HbA1c predicted memory decline even in non-diabetics.

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Conflicts of Interest

None of the authors have any conflicts of interest or financial disclosures.

Keywords

diabetes; blood glucose; glycosylated hemoglobin; memory; cognition; cognitive decline; memory decline; dementia

INTRODUCTION

The relationship between type 2 diabetes (T2D) and increased dementia risk is well-characterized¹⁻³, but the biological mechanisms linking the two are not well understood. Although memory loss is a hallmark of dementia, diagnostic criteria include both cognitive and functional indicators. Dementia incidence is therefore influenced by both *rate* of cognitive decline and pre-decline *level* of cognitive function. Risk factors for dementia may impact either level of cognitive function or rate of cognitive decline, or both. Since rate of memory decline is closely aligned with the development and progression of diseases such as Alzheimer's and cerebrovascular pathology⁴, understanding how T2D and blood glucose levels relate to memory decline is crucial to elucidating the mechanisms driving higher dementia rates among individuals with T2D. To date, some studies have found an association between diabetes and memory decline⁵⁻⁸, while others have not⁹⁻¹². Understanding this relationship is crucial for identifying people who would benefit from potential interventions.

Chronic hyperglycemia, measured via glycosylated hemoglobin (HbA1c), is one possible biological mechanism linking T2D with increased risk of dementia and memory decline (Figure 1). Other than hyperglycemia, possible explanations for the association between T2D and dementia include both causal and noncausal factors³. Proposed causal mechanisms include insulin dysregulation¹³, expression of insulin-degrading enzyme^{3,13}, and severe hypoglycemic events among individuals with T2D^{3,14}. The primary noncausal explanation is that shared determinants of T2D and dementia confound the association, including health behaviors, socioeconomic factors, as well as obesity, hypertension, and other comorbidities. Analyses of change in memory are less vulnerable to such potential confounders.

Similar to the evidence on diabetes and dementia risk and rate of cognitive decline, a relationship between blood glucose levels and dementia has been established¹⁵. However, the association between HbA1c and cognitive decline^{3,6,7,16-18}, and, specifically, memory decline^{3,6,17}, is less consistent. Therefore, whether glycemic control among diabetics, and even pre-diabetic blood glucose levels among non-diabetics, could predict the risk of memory decline remains unknown.

The majority of prior studies were limited due to short follow-ups, non-diverse and elderly populations, selective attrition and survival, and incomplete data on potential social and behavioral confounding factors. Short follow-ups are especially problematic in studies of cognitive decline because there is a low signal-to-noise ratio when identifying determinants of decline. Sample diversity is particularly important for research on diabetes because minority populations are disproportionately burdened and the association could differ in minorities versus whites¹⁹. Selective attrition and survival is common in longitudinal

studies of aging because sicker individuals are more likely to both drop out and die²⁰, but steps are rarely taken to minimize the potential bias²¹.

We estimate the association between diabetes and memory decline, as well as the relationship between HbA1c and memory decline, among diabetics and non-diabetics aged 50+ in the U.S. Health and Retirement Study (HRS) while controlling for a comprehensive set of potential confounders. We also evaluated the possibility that HbA1c above the threshold for diabetes has worse consequences for memory than HbA1c levels in the normal or pre-diabetic range.

METHODS

Study population

HRS is a nationally representative cohort with a target population of all non-institutionalized adults age 50+ in the contiguous United States. Biomarker data was collected on two subsamples in 2006 and 2008. Participants aged 50+ at biomarker collection were eligible for inclusion into our study²². Biennial interviews (or proxy interviews for decedent participants) are available through 2012. Details of HRS are reported elsewhere²³. Original survey response rates varied across enrollment cohorts from 70-82%, and retention rates through 2008 ranged from 86% to 91%.

Of 12,186 possible respondents who were in the sample and age 50+ at biomarker collection (either 2006 or 2008), we excluded participants without a memory assessment at biomarker collection (N=1,094), who were missing diabetes status (N=11), or were nondiabetics with an HbA1c measure over 6.5 (the cut point for a diagnosis of diabetes²⁴) (N=345). In addition, we excluded anyone missing covariate information (N=1,848). These exclusions left a final analytic sample of 8,888, including 7,051 non-diabetics and 1,837 diabetics.

Memory Function and Decline Outcomes

Memory was assessed by immediate and delayed recall of a 10-word list and the Informant Questionnaire for Cognitive Decline (IQCODE). For individuals too impaired to directly participate in memory assessments, proxy informants, typically spouses, assessed the participants' memory on a 5-item Likert scale and completed a 16-item version of the IQCODE²⁵. We used a previously developed memory composite score combining proxy and direct memory assessments for longitudinal analyses²⁶. The composite score algorithm was developed in an 856-subject subsample who participated in a comprehensive neuropsychological battery as part of the Aging, Demographics, and Memory Study²⁷. We standardized the memory score by dividing each score by the 1995 standard deviation so that every unit change in memory score corresponds to approximately one standard deviation in the population. The potential for practice effects is minimal because everyone had taken at least one assessment prior to our baseline wave²⁸.

Diabetes

Diabetes is self-reported with the question: “Has a doctor ever told you that you have diabetes or high blood sugar?”²⁹, and we used the measure at the time of biomarker collection (2006 or 2008).

Glycosylated Hemoglobin (HbA1c)

Glycosylated hemoglobin (HbA1c) is a measure of blood glucose concentration over the past 2-3 months; it is used both for diagnosis of diabetes and for assessment of disease management among people with diagnosed diabetes²⁴. HbA1c was measured via dried blood spot (DBS) in either 2006 or 2008²². In the pooled sample including both diabetics and non-diabetics, HbA1c was centered at 6.5% (the cut point for diagnosis of diabetes), and at the mean for each group in analyses stratified by diabetes status.

Age

Age was calculated as the time between self-reported date of birth and interview date, measured continuously, centered at 70 years, and converted to decades.

Covariates

All models were adjusted for hypothesized confounders of the association between diabetes/HbA1c and memory decline. These include: race (white, black, or other), gender (male vs. female), childhood socioeconomic status (continuous composite score based on measures of human and financial capital), baseline marital status (married/partnered, separated/divorced, widowed, and never married), initiated smoking before age 18 (yes/no), childhood social capital composite scale (using measures of maternal investment and created via factor analysis, continuous composite score), father absent during childhood (yes/no), childhood and baseline self-rated health (very low/low, good, very good/excellent), high school completion (yes/no), college completion (yes/no), baseline household income (log transformed), baseline household wealth (log transformed), baseline smoking (yes/no), baseline drinking (drinks per day: 0, 1-2, 3+), baseline BMI (normal weight, overweight, obese), baseline physical activity level (active/inactive), ever had hypertension at baseline (yes/no), ever had a stroke at baseline (yes/no), baseline elevated depressive symptoms (measured by the 8-item CES-D³⁰, depressive symptoms score > 3), and ever had heart disease at baseline (yes/no). All covariates are based on self-reports, with the exception of depression. All “baseline” covariates are measured in 2004 so that they are temporally prior to diabetes and HbA1c assessment. In sensitivity analyses, we additionally adjusted for cholesterol medication use (yes/no in 2006).

Statistical Analysis

Baseline (2004) characteristics were calculated for diabetics and non-diabetics. The present analysis includes memory function measured at biennial interviews from biomarker collection (2006 or 2008) until the end of the study period (2012) or until death or dropout, for up to 4 memory assessments.

In all models, we use generalized estimating equations (GEE) to model memory decline longitudinally via marginal mean regression models for repeated outcomes with age (in decades, centered at age 70) as the timescale. First, we assess the relationship between diabetes at the time of biomarker collection and subsequent memory decline with a diabetes-by-age interaction term (Eq 1).

$$Memory_{ij} = \hat{\beta}_0 + \hat{\beta}_1 Diabetes_i + \hat{\beta}_2 Age_{ij} + \hat{\beta}_3 Diabetes \cdot Age_{ij} + \hat{\beta}_4 Covariates_i \quad (1)$$

In the same sample, including both diabetics and non-diabetics, we investigated whether HbA1c predicts memory decline. We model HbA1c using two linear terms, to test whether the effect of increases in HbA1c differed above the 6.5% threshold: 1) a linear term for a percentage point increase in HbA1c; 2) a linear term for an additional effect of a percentage point increase in HbA1c for every unit greater than or equal to 6.5% (labeled HbA1cAbove6.5 in equation 2). We interacted each of these HbA1c variables with age (Eq 2). In sensitivity analyses, we estimated models that additionally controlled for self-reported cholesterol medication use since there is a hypothesis that statin use influences memory loss³¹.

$$\begin{aligned} Memory_{ij} &= \hat{\beta}_0 + \hat{\beta}_1 Diabetes_i \\ &+ \hat{\beta}_2 Age_{ij} \\ &+ \hat{\beta}_3 Diabetes \cdot Age_{ij} \\ &+ \hat{\beta}_4 HbA1c_i \\ &+ \hat{\beta}_5 HbA1c \text{ Above}6.5_i \\ &+ \hat{\beta}_6 HbA1c \cdot Age_{ij} \\ &+ \hat{\beta}_7 HbA1c \text{ Above}6.5 \cdot Age_{ij} \\ &+ \hat{\beta}_8 Covariates_i \end{aligned} \quad (2)$$

Next, we stratified by diabetes status and examined the relationship between HbA1c and memory decline separately among diabetics and non-diabetics using an HbA1c-by-age interaction term. Given our DAG in Figure 1, we concluded that stratification by diabetes diagnosis does not introduce substantial collider stratification bias because the variables that are likely to be in “u” are similar to the social and behavioral confounders we have already measured and included in the models³². Since there is uncertainty in the field about how to control for confounding in longitudinal studies of decline, we report models both with and without interaction terms between each covariate and age. All models use inverse probability weights (IPWs) to adjust for selective survival and attrition²¹. We used pooled logistic regression models to estimate the probability of mortality and attrition in order to calculate stabilized IPWs³³. Although we specified an independence working correlation structure for repeated outcomes as recommended by Tchetgen Tchetgen et al³⁴ in order to accommodate time updated weights, robust standard errors are reported which appropriately account for

the longitudinal design and all sources of variability. The HRS is drawn from a nationally representative sample, but we did not apply the sampling weights.

Further, we conducted a sensitivity analysis where we included the 345 individuals who had HbA1c values of 6.5% or higher (the cut point for diabetes diagnosis) but self-reported never being diagnosed with diabetes. In addition, we used natural log-transformed HbA1c to predict memory decline in order to test the non-linearity of the relationship. In this analysis, we used a log-HbA1c-by-age interaction term as the main parameter of interest, and controlled for diabetes, diabetes-by-age, and all covariates. The log-HbA1c-by-age interaction term divided by 10 is interpreted as the additional decrease in memory score per decade associated with a 10% increase in HbA1c (e.g. from 6% to 6.6%). Finally, we conducted a sensitivity analysis on a subset of the sample with data on APOE-4 status (6,187 non-diabetics and 1,562 diabetics) where we included a main effect for any APOE-4 alleles (yes/no) as well as interactions between APOE-4 and diabetes/HbA1c and age.

RESULTS

Sample characteristics from 2004 are shown for the 1,837 diabetics and 7,051 non-diabetics included in our models (Table 1). Average follow-up was 5.2 years (out of 6 possible) overall, 5.3 years among non-diabetics, and 5.0 years among diabetics. Overall average number of memory assessments was 3.6 (out of 4 possible). Mean HbA1c among non-diabetics was 5.5% (SD=0.4%), and 6.8% (SD=1.3%) among diabetics. Median HbA1c among nondiabetics was 5.6%, and 6.5% among diabetics. There were 386 self-reported strokes over the follow-up period, with diabetics almost twice as likely to report a stroke.

In a pooled sample including diabetics and non-diabetics, in the model without adjustment for covariate-by-age interaction terms, the average rate of memory decline was 0.443 memory score units per decade for people without diabetes and 0.480 memory score units per decade for people with diabetes (β for the difference=-0.037; 95% CI: -0.064, -0.010; $p=0.007$) (Table 2, Model 1). The association between diabetes and decline remained when the covariate-by-age interactions were included. We tested whether the relationship between HbA1c and memory decline differed for individuals with HbA1c greater than and less than 6.5% (the cutoff for diabetes diagnosis). A percentage point increase in HbA1c corresponded to an estimated 0.052 unit decrease in memory per decade (95% CI: -0.078, -0.026; $p<0.0001$) (Table 2, Model 2). Figure 2 depicts linear memory decline curves for diabetics and non-diabetics at different levels of HbA1c. Although results without covariate-by-age interaction terms suggested effects of HbA1c were smaller for individuals with HbA1c greater than 6.5% ($\beta=0.044$ for the difference in slope for a percentage point increase in HbA1c; 95% CI: 0.005, 0.082; $p=0.026$), in a fully adjusted model with covariate-by-age interaction terms, there was no evidence of a difference in slope for individuals with an HbA1c over 6.5% ($p=0.440$). Diabetes did not predict memory decline once HbA1c was included in the model. Estimated associations were qualitatively similar when cholesterol medication use was included in the model (Table 2, Model 3).

Results restricted to non-diabetics were similar to the pooled estimates, but we found no evidence of an association between HbA1c and memory decline among diabetics alone

(Table 3). However, point estimates among diabetics were suggestive of an association large enough to be clinically relevant, if we were powered to detect one of this magnitude. Results were similar in sensitivity analyses where we included the 345 individuals who had HbA1c values of 6.5% or higher (the cut point for diabetes diagnosis) but self-reported never being diagnosed with diabetes. In models controlling for APOE-4 status, while there was a main effect of APOE-4 on memory decline, we found no evidence of an interaction with either diabetes ($\beta=0.045$; 95% CI: $-0.020, 0.110$; $p=0.173$ for the interaction of APOE-4, diabetes, and age) or HbA1c ($\beta=0.019$; 95% CI: $-0.044, 0.082$; $p=0.554$ for the interaction of APOE-4, HbA1c, and age) in a pooled sample.

Since the pooled models showed a possible smaller association between a percentage point increase in HbA1c and memory decline among individuals with T2D (i.e., HbA1c $> 6.5\%$), we conducted a sensitivity analysis investigating the relationship between log-transformed HbA1c and memory decline. A 10% increase in HbA1c (e.g. from 6.0% to 6.6%) was associated with approximately a 0.02 faster memory score decline per decade ($p<0.001$). Model fit was extremely similar for this model compared to a model using non-transformed HbA1c (QIC = 28082.01 vs. 28081.96). Applying IPWs to adjust for selective survival and attrition did not qualitatively change the results of any models.

DISCUSSION

Our results suggest that both diabetes and HbA1c predict memory decline in a national sample after controlling for a comprehensive set of social, behavioral, and health-related confounders. Diabetes was associated with a 0.037 unit faster decline in memory score per decade, which is about 8% of the estimated magnitude of association between a 10-year increase in age and decline. A percentage point increase in HbA1c was associated with a 0.052 unit decrease in memory score per decade, about 10% of the association between a 10-year increase in age and rate of decline. We found no consistent evidence that the association between HbA1c and decline differed based on HbA1c level or diabetes status, although point estimates for a percentage point increase in HbA1c were attenuated among individuals with T2D (i.e., HbA1c $> 6.5\%$). Adjustment for cholesterol medication use did not meaningfully alter the results, consistent with a recent meta-analysis that showed no adverse effects of statin use on cognition³⁵. Our findings suggest that 1) among diabetics, poor management and higher HbA1c levels may adversely impact rate of memory decline; and 2) among non-diabetics, higher HbA1c levels – even below the threshold for diabetes diagnosis (i.e., “prediabetes” levels) – predict faster memory decline.

Although there is robust association linking diabetes and dementia, there is inconsistent evidence on the association between diabetes and cognitive decline. Many studies test the association between diabetes and rate of change in multiple cognitive domains and find an association between diabetes and one or two cognitive domains assessed, but there is no reliable association in any individual domain across studies³. For example, memory is among the most commonly assessed cognitive domains and is of particular interest because it is a hallmark of Alzheimer's disease. While some researchers have found an association between diabetes and rate of memory decline⁵⁻⁸, others have not⁹⁻¹². In particular, one study by Wu et al. used earlier data from the same cohort (HRS) and our memory scores as

one of their outcomes, but did not find an association between diabetes and memory decline. However, the authors only included individuals over the age of 65. The difference may also reflect chance, as the 95% CIs reported by Wu et al., include our point estimates.

Other domains of cognition that have been assessed in multiple studies – with no consistent finding – in relation to T2D include processing speed, executive function, and verbal fluency^{5,7,8,10-12,16}. These discrepant findings may be due to an underlying weak association between T2D and rate of cognitive decline, high signal-to-noise ratios, or may reflect methodological differences between the studies. For example, the range of cognitive domains and neuropsychological tests used, how rate of cognitive decline was modeled, the varied length of follow-up, potential bias due to differential attrition or mortality, or differences in sample characteristics.

Establishing that diabetes predicts longitudinal change in cognition is central for ruling out confounding as the explanation for the diabetes-dementia link. Numerous social or behavioral factors that potentially influence diabetes risk, for example educational quality, may also predict lower average cognitive reserve. The previously documented association between diabetes and incident dementia may therefore reflect either confounding or mechanisms mediated by early life cognitive development and cognitive reserve. Indeed, previous Mendelian Randomization studies showed that a polygenic score combining all genetic variants confirmed to be associated with Type 2 Diabetes does not predict dementia risk^{36,37}. Findings in Walter et al., suggested that genetic variants related to insulin sensitivity, as opposed to polymorphisms affecting adiposity or β -cell function, might have a distinct relationship with dementia risk, however. Our finding that blood glucose levels predict longitudinal memory loss therefore substantially bolsters the evidence for an etiologic role of diabetes in dementia pathology and is consistent with the previous results on insulin sensitivity.

There is even less research investigating the relationship between HbA1c and cognitive decline to date. Many studies have been restricted to individuals diagnosed with diabetes^{16,18,38,39}, while others included both diabetics and non-diabetics with stratification by diabetes diagnosis^{6,7,17}. Prior studies have found more consistent associations between blood glucose levels and decline in other domains of cognition, such as processing speed and executive function, compared to decline in memory⁶. Only one other study adjusted for attrition⁶, and none adjusted for selective survival; however, since our use of IPWs did not qualitatively change results, bias due to selective survival and attrition may be small. Additionally, our analyses included all participants with available data, regardless of baseline cognitive status. This approach has the advantage of allowing us to more accurately identify long-term consequences of diabetes-related processes.

Possible biological mechanisms linking T2D and cognition include chronic hyperglycemia as well as hyperinsulinemia and functional insulin deficiency in the brain. In addition, some risk factors for dementia, such as severe hypoglycemic events and depression, are more common in individuals with T2D and could explain the association³. This study lends support to the hypothesis that chronic hyperglycemia is a key pathway linking diabetes and memory decline, most likely via microvascular injury. It is possible that other mechanisms

contribute to the explanation of the diabetes-memory relationship and they may also link diabetes with other domains of cognition. Each of these proposed mechanisms could impact cognitive decline and dementia via either contributing to Alzheimer's disease pathogenesis or vascular disease. Thus, we cannot discern whether HbA1c is associated with memory loss in our study because of chronic hyperglycemia influencing vascular disease or AD pathology.

One main limitation to this study is the lack of assessment of many important domains of cognition, other than memory. Additionally, we cannot distinguish the cause of memory decline, e.g. Alzheimer's disease versus vascular disease. Our measure of diabetes status is self-reported physician diagnosis, and therefore could suffer from bias if individuals cannot accurately report whether they have been diagnosed with diabetes. However, we excluded people whose HbA1c levels were inconsistent with their self-reported diabetes status. Further, we only have one measure of HbA1c per person, so we cannot examine trends in HbA1c levels or how time-updated HbA1c levels affect memory decline. We do not characterize duration of diabetes or duration of exposure to chronic hyperglycemia, which may be etiologically relevant. Since we did not time-update diabetes status, some individuals may have become diabetic during the follow-up period. This misclassification might have slightly attenuated effect estimates; however, we anticipate any such bias would be small because the effects of HbA1c on cognition probably take many years to manifest. Finally, we do not have as long a follow-up as Rawlings et al⁶, although we averaged a greater number of cognitive assessments for each participant.

The strengths of the HRS sample for evaluating this research question outweigh the above limitations. The HRS is a national sample, not a multi-site study, so we were able to control for birth region instead of only field site. Since our sample includes individuals aged 50+ at DBS collection, our younger population avoids possible bias due to selective survival²¹. Finally, HRS has rich social variables, so we were able to control for a battery of hypothesized social confounders. Most other studies only include high school completion as their adjustment for SES, but childhood SES, college completion, and later life income and wealth may still confound after high school completion is included in the model⁴⁰.

In conclusion, diabetes and higher levels of HbA1c both predicted faster memory decline after controlling for an extensive battery of potential social confounders in a large, U.S. dataset. Our results add support for a causal pathway from blood glucose levels to development of dementia, although precise biological mechanisms are still unknown. Even without diabetes, elevated blood glucose appears to have adverse neurocognitive consequences.

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Figure 1.

Directed Acyclic Graph (DAG) of the hypothesized relationship between diabetes, HbA1c, and cognitive decline.

We show HbA1c at two different time points (subscripts 1 and 2) to clarify that for some people we have a measure of HbA1c that precedes self-reported diabetes diagnosis and for others we have a measure that follows self-reported diabetes diagnosis. Diabetes pathology may influence cognitive decline either via chronic hyperglycemia (HbA1c) or via other mechanisms, such as hyperinsulinemia. Alternatively, it is possible that unmeasured confounders induce a spurious, non-causal association between diabetes *diagnosis* and decline, such as socioeconomic factors like late life income. If there were many unmeasured “u” variables, we would be concerned about collider stratification bias, but we believe that most of the variables in “u” are likely to be the same social and behavioral confounders already included in the study.

Figure 2. Linear memory decline curves based on Model 2 in Table 2 (with no confounder*age interactions) for diabetics and non-diabetics at different levels of HbA1c.

Table 1

Characteristics of our Health and Retirement Study sample in 2004.

	Diabetics N=1,837	Non-Diabetics N=7,051
Male (%)	848 (46%)	2753 (39%)
Race (ref=White)		
Black (%)	375 (20.41%)	737 (10.45%)
Other (%)	56 (3.05%)	123 (1.74%)
Age (mean, std)	67.4 (8.8)	66.9 (9.6)
Southern birth place (%)	347 (18.89%)	1008 (14.3%)
Started smoking before age 18 (%)	1649 (25.53%)	1649 (25.53%)
Childhood self-rated health (ref=good)		
Low (%)	167 (9.09%)	530 (7.52%)
High (%)	619 (33.7%)	2235 (31.7%)
Rural childhood (%)	3657 (56.62%)	3657 (56.62%)
Father absent (%)	525 (8.13%)	525 (8.13%)
Childhood Social Capital (mean, std)	-0.01 (1.14)	0.01 (1.05)
Not physically active (%)	1527 (83.12%)	5149 (73.03%)
Drinks per day (ref=0)		
1-2 drinks (%)	1726 (93.96%)	6202 (87.96%)
3+ drinks (%)	27 (1.47%)	225 (3.19%)
Current smoker (%)	247 (13.45%)	1131 (16.04%)
Body mass index (ref=normal)		
Overweight (%)	658 (35.82%)	2798 (39.68%)
Obese (%)	893 (48.61%)	1549 (21.97%)
Current hypertension (%)	1300 (70.77%)	3281 (46.53%)
Current stroke (%)	176 (9.58%)	388 (5.5%)
Current heart disease (%)	589 (32.06%)	1364 (19.34%)
Current depression (%)	329 (17.91%)	769 (10.91%)
Current self-rated health (ref=good)		
Low (%)	718 (39.09%)	1276 (18.1%)
High (%)	399 (21.72%)	3555 (50.42%)
Current marital status (ref=married)		
Divorced/separated	196 (10.67%)	712 (10.1%)
Widowed	343 (18.67%)	1217 (17.26%)
Never married	44 (2.4%)	185 (2.62%)
Childhood SES (mean, std)	-0.09 (0.93)	0.15 (1.03)
High school completion (%)	1356 (73.82%)	5843 (82.87%)
College completion (%)	330 (17.96%)	1699 (24.1%)
Household income (median, IQR)	\$23,669 (\$13,461-\$41,296)	\$29,792 (\$16,958-\$53,076)

	Diabetics N=1,837	Non-Diabetics N=7,051
Household wealth (median, IQR)	\$93532 (\$26,164-\$266,368)	\$173,242 (\$60,741-\$411,074)
Baseline HbA1c (mean, std)	6.8 (1.3)	5.5 (0.42)

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Table 2

Diabetes and HbA1c predicting memory decline in a pooled sampled (i.e. both diabetics and non-diabetics).

	Model 1		Model 2		Model 3	
	No Confounder*Age Interactions	Confounder*Age Interactions	No Confounder*Age Interactions	Confounder*Age Interactions	No Confounder*Age Interactions	Confounder*Age Interactions
Diabetes	0.0001 (−0.016, 0.016)	−0.013 (−0.027, 0.001)	−0.010 (−0.028, 0.009)	−0.019 (−0.036, −0.002)	−0.016 (−0.035, 0.004)	−0.021 (−0.039, −0.004)
Age (centered at 70, in decades) [‡]	−0.443 (−0.456, −0.430)	−0.527 (−0.575, −0.479)	−0.494 (−0.521, −0.467)	−0.556 (−0.609, −0.502)	−0.509 (−0.541, −0.477)	−0.588 (−0.647, −0.528)
Age*Diabetes	−0.037 (−0.064, −0.010)	−0.030 (−0.057, −0.004)	0.001 (−0.032, 0.035)	−0.006 (−0.038, 0.026)	0.010 (−0.025, 0.045)	−0.003 (−0.036, 0.031)
HbA1c (centered at 6.5)			0.027 (0.012, 0.043)	0.020 (0.006, 0.035)	0.021 (0.004, 0.038)	0.017 (0.001, 0.032)
Age*HbA1c			−0.052 (−0.078, −0.026)	−0.028 (−0.053, −0.004)	−0.051 (−0.080, −0.023)	−0.034 (−0.062, −0.007)
HbA1c_2 (spline term for those with HbA1c >= 6.5)			−0.044 (−0.067, −0.022)	−0.036 (−0.057, −0.015)	−0.034 (−0.059, −0.01)	−0.030 (−0.053, −0.008)
Age*HbA1c_2			0.044 (0.005, 0.082)	0.014 (−0.021, 0.049)	0.045 (0.003, 0.088)	0.025 (−0.015, 0.064)
Cholesterol medication use					0.026 (0.012, 0.040)	0.016 (0.004, 0.029)
Age*Cholesterol medication use					0.014 (−0.009, 0.038)	0.023 (0.001, 0.045)

All models are weighted to adjust for survival and participation.

Bold indicates p<0.05

[‡] All age main effects and interaction terms are measured in decades.

Table 3

HbA1c predicting memory decline in diabetes-stratified samples.

	Diabetics		Non-Diabetics	
	No Confounder*Age Interactions	Confounder*Age Interactions	No Confounder*Age Interactions	Confounder*Age Interactions
HbA1c (centered at mean)	−0.011 (−0.022, 0.0003)	−0.011 (−0.021, −0.0002)	0.032 (0.014, 0.05)	0.022 (0.005, 0.038)
Age (centered at 70, in decades [†])	−0.492 (−0.521, −0.464)	−0.667 (−0.783, −0.551)	−0.439 (−0.453, −0.426)	−0.513 (−0.567, −0.460)
Age*HbA1c	−0.016 (−0.034, 0.003)	−0.013 (−0.030, 0.004)	−0.053 (−0.082, −0.025)	−0.023 (−0.051, 0.004)

All models are weighted to adjust for survival and participation.

[†] All age main effects and interaction terms are measured in decades.