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Changes in Glycemic Control are Associated with Changes in Cognition in Non-Diabetic Elderly

Ramit Ravona-Springer^{a,*}, Erin Moshier^b, James Schmeidler^c, James Godbold^b, Jimmy Akrivos^c, Michael Rapp^d, Hillel T. Grossman^{c,e}, Michael Wysocki^c, Jeremy M. Silverman^{c,e}, Vahram Haroutunian^{c,e}, and Michal Schnaider Beerⁱ

^aSheba Medical Center, Ramat-Gan, Israel

^bDepartment of Preventive Medicine, The Mount Sinai School of Medicine, New York, NY, USA

^cDepartment of Psychiatry, The Mount Sinai School of Medicine, New York, NY, USA

^dDepartment of Psychiatry, Humboldt University, Berlin, Germany

^eJames J. Peters Veterans Affairs Medical Center, Bronx, NY, USA

Abstract

The aim of the present study was to examine the relationship of changes in long term glucose levels as measured by Hemoglobin A1c (HbA1c) with simultaneous changes in cognition. The sample included in the present analysis consisted of 101 community dwelling non-diabetic elderly subjects participating in ongoing longitudinal studies of cognition. Subjects were included in this study if they were cognitively normal at baseline, had at least one co-temporaneous follow-up assessment of HbA1c and the Mini Mental State Exam (MMSE), and complete data on age, gender, race, and years of education. MMSE decline over time was the main outcome measure. In TOBIT mixed regression models, MMSE was the dependent variable and HbA1c the time-varying covariate. Sociodemographic (age, gender, and education), cardiovascular (hypertension and APOE4 status), and lifestyle (smoking and physical activity) covariates were included in the statistical model. After adjusting for age at follow-up, there was a decrease of 1.37 points in the MMSE ($p = 0.0002$) per unit increase in HbA1c. This result remained essentially unchanged after adjusting also for gender and education ($p = 0.0005$), cardiovascular factors ($p = 0.0003$), and lifestyle ($p = 0.0006$). Additionally, results remained very similar after excluding subjects with potentially incipient diabetes with HbA1c between 6 and 7. These findings suggest that in non-diabetic non-demented elderly subjects, an increase in HbA1c over time is associated with cognitive decline. Such results may have broad clinical applicability since manipulation of glucose control, even in non-diabetics, may affect cognitive performance, perhaps enabling preventive measures against dementia.

Keywords

Cognition; elderly; glucose control; HbA1c; non-diabetic

INTRODUCTION

Diabetes and even pre-diabetes stages have been demonstrated relatively consistently to be risk factors for cognitive decline [1], mild cognitive impairment (MCI) [2], and dementia [3]. Previous studies have addressed the association of several diabetes related factors (such as diabetes diagnosis across lifespan [3, 4], measures of long term glucose control at baseline [5], or insulin resistance at baseline [6]) with future cognitive decline, dementia, or structural brain changes. Yet, to the best of our knowledge, the association of changes in cognition as a function of long term changes in glucose control has not been addressed directly. Though several mechanisms have been proposed to explain the relationship between diabetes and cognition, there is still no consensus regarding the biological pathways or diabetes-related factors (glucose control, type of medication, presence and type of complications, etc.) by which diabetes affects cognition. Long term glucose levels in the blood, which are measured by hemoglobin A1c (HbA1c) and may be high or within normal range (reflecting good glucose control) in diabetic subjects, may represent a marker of neurotoxicity through as yet unidentified mechanisms [5]. Since HbA1c levels are a continuum, a relationship with cognitive performance in non-diabetic individuals, who are, by definition, limited to lower HbA1c levels, would reinforce its biological plausibility as a potential underlying risk factor for cognitive compromise. The aim of the present study was to assess the relationship of changes in HbA1c levels with concomitant changes in cognition in non-diabetic non-demented elderly individuals.

MATERIALS AND METHODS

Subjects

The sample consisted of 121 community dwelling elderly subjects participating in an ongoing prospective longitudinal study of risk factors for cognitive decline of the very elderly (≥ 75 years of age) at the Mount Sinai School of Medicine. They were recruited through talks, newspaper ads, and participating acquaintances and followed up at approximately yearly intervals. Subjects were included in this study if they were cognitively normal at baseline, as described below. Subjects with a diagnosis of stroke or other neuropsychiatric disease that could compromise cognition (such as history of stroke, Parkinson's disease, or schizophrenia) were excluded from the study. For the purposes of this analysis, subjects were included if they had at least one co-temporaneous follow-up assessment of HbA1c and the Mini Mental State Exam (MMSE) in addition to cotemporaneous baseline assessments, and complete data on sociodemographic (age, gender, years of education), cardiovascular (ApoE4 and hypertension status), and lifestyle (smoking and physical activity) variables. The number of diabetic subjects otherwise fulfilling inclusion criteria was too small ($n = 16$) for meaningful comparisons, so diabetic subjects were excluded from this analysis. Another four subjects were excluded because of missing data in one of the potential confounders. Thus, the final sample for analysis was of 101 subjects.

The operational definition of "cognitively normal status" was based on the MMSE at baseline (above the 10th percentile by age, gender, and education adjusted norms [7]), Clinical Dementia Rating (CDR) of zero (i.e., no dementia) [8], and subject's medical charts, all of which were discussed in multidisciplinary consensus conferences. The mean number of observations per subject was 3.00 (SD = 0.95, range 2 to 6). The mean follow-up duration was 32.03 months (SD = 14.80, range = 6.8 to 65.2). Follow-up assessment included HbA1c and MMSE measurements and was performed at approximately yearly intervals. The study was approved by the Mount Sinai institutional review board and all subjects signed informed consent.

Assessment procedures

MMSE—The MMSE was administered in this study at approximately yearly intervals. The MMSE is a commonly used 30 point scale assessing cognitive function in areas of orientation, registration, attention and calculation, recall, language, and praxis [9].

Clinical Dementia Rating (CDR)—The CDR scale was administered to each participant at baseline. The CDR is an established clinical and research instrument for the assessment of cognitive function and performance on a five point scale in six domains [8]: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. A score for each domain is established through semi-structured interviews with the participant, as well as a separate interview with an individual familiar with the participant (usually a family member, nurse, or certified nursing assistant). Scores are 0 (nondemented), 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).

HbA1c—Ion exchange, high performance liquid chromatography was used to assess HbA1c [10]. This assessment was usually performed on the same day as the MMSE. In exceptional cases, HbA1c assessment was performed within two weeks of the MMSE assessment.

Additional confounders

Diagnosis of hypertension and diabetes—Diagnosis of hypertension was determined by a consensus conference based on the presence of hypertension in the medical chart, blood pressure measurements from the chart implying hypertension based on the American Heart Association criteria [11], or medications for the treatment of hypertension. In addition to the medical charts, medication inventories were done at the participants' residences, where the interviewer recorded information directly from medication labels, providing good reliability of this data. Diagnosis of diabetes was determined similarly [12].

Physical activity—Physical activity was evaluated using a questionnaire that assessed the best description of physical activity level within the past year. A subject could be rated in one of six levels of physical activity ranging from: the lowest (1) = Mostly sitting, to the highest (6) = Strenuous exercise several times a week [13].

ApoE—A subject carrying at least one ApoE4 allele was considered ApoE4 positive. ApoE genotype was determined by PCR run from blood [14].

Smoking status—Subjects were questioned regarding present and past smoking. In this analysis, smoking was defined as never/ever smoked.

Lipid levels—Lipid levels (triglycerides and cholesterol) levels at baseline were extracted from the subjects' medical charts.

Statistical analysis

A TOBIT mixed regression model with a time-varying covariate which assesses the within-subject associations of changes over time was used to analyze longitudinal MMSE data. The TOBIT approach has long been used to model data where there is either a floor-effect or a ceiling-effect in the outcome. In the presence of a ceiling effect, for example, an ordinary regression model would give misleading results since the slope would be attenuated by the fact that many observations have reached the maximum value and are not changing as the independent variable changes. The TOBIT model accounts for this phenomenon and adjusts

the estimate of the slope appropriately. Recently, the classic TOBIT model has been extended to accommodate repeated measurements on subjects in the context of a longitudinal study (mirroring what has been done to extend classic regression models to mixed models). The extension of the TOBIT model allows for imbalanced data (not all subjects must have the same number of visits) as well as unequal spacings between visits [15], to accommodate ceiling effects [15] that can be common in the context of non-demented subjects. We felt TOBIT regression is well suited to the analysis of this data since it models both the probability of reaching either the floor or ceiling and the development over time between the floor and ceiling [15]. Additionally, the TOBIT addresses variable times between follow-up assessments. The primary predictor was HbA1c, which was entered as a time-varying covariate, i.e., varying simultaneously with the MMSE. In our TOBIT mixed model, the only random effect was “subject”; all other variables in the model were treated as fixed effects. In the classic TOBIT model, all variables (including latent variables) would be considered fixed; so in a mixed model extension, it is still only the subject variable that is considered as a random effect.

Other baseline measures of covariates in the model were sociodemographic variables (age at follow-up, gender, education), cardiovascular variables (hypertension, APOE4 genotype, and BMI), and lifestyle variables (physical activity and smoking). For descriptive purposes we performed Spearman correlations of pairs of variables included in the main analysis (Table 1). The Spearman correlation method was employed to highlight the presence of a ceiling effect in MMSE scores. For consistency, Spearman’s method was used to estimate correlations among all other variables as well (Table 1).

RESULTS

The sample included 101 subjects. As demonstrated in Table 2, mean age at baseline was 86. Approximately two thirds of the sample was female. The subjects were relatively highly educated (mean number of years of education = 15). The vast majority of the sample (94%) was Caucasians, 22.8% were ApoE4 positive, approximately two thirds of the sample had a diagnosis of hypertension, 59.1% had ever smoked, and 87% reported performing light or less physical activity in the last year. None of the subjects had a baseline diagnosis of diabetes and there were no incident cases of diabetes during the study period. As shown in Table 2, the average HbA1c at baseline was 5.5%, consistent with a non-diabetic status. Thirteen out of the 101 subjects (12.9%) participating in the study had HbA1c levels >6% and 7% (the highest HbA1c in the sample was 6.7%) but were not diagnosed with diabetes. The average MMSE at baseline was 28.1, consistent with a cognitively normal status.

Since the question of primary interest is the relationship between MMSE and HbA1c, the TOBIT regression model used for analysis relates the MMSE scores to the levels of HbA1c. In this model, the ordering of data along the x-axis is in terms of levels of HbA1c, not time. Although the descriptive statistics in Table 2 provide estimates of the changes in each of these variables over time, the fundamental relationship estimated by the TOBIT model relates MMSE scores to the HbA1c levels associated with these scores. The slope coefficient is interpreted as the change in MMSE per unit change in HbA1c; but it is to be noted that this fundamental relationship does not directly estimate the change in either of these variables over time aside from the fact that these variables were assessed at different times.

When considering the temporal change based on only the first and last assessments, the respective means of MMSE and HbA1c did not change in terms of clinical relevance (−0.12 and 0.03, respectively). However, when considering all assessments, there was statistically significant within-subject variability for both MMSE ($SD = 1.45$; $p < 0.0001$) and HbA1c ($SD = 0.23$; $p < 0.0001$). Thus, although the mean change from baseline to last assessment in

MMSE was only -0.12 , the average deviation within a subject from the grand mean MMSE of 28.11 was 1.45 units. Similarly, although the mean change in HbA1c from first to last visit was only 0.03, the average deviation within a subject from the grand mean HbA1c of 5.53 was 0.23 units. So, although temporally, from first to last assessment there does not appear to be any clinically relevant change in MMSE and HbA1c, there is significant variability among MMSE and HbA1c within subjects.

Table 1 shows zero-order correlations among the predictors entered in the regression equations as well as with the MMSE. Baseline MMSE was significantly correlated with last MMSE ($p < 0.0001$) and with changes in MMSE from first to last assessment ($p = 0.039$). Baseline HbA1c was significantly negatively correlated with baseline MMSE ($p = 0.0129$) and with changes in HbA1c from first to last assessment ($p = 0.0043$), and positively correlated with last HbA1c ($p < 0.0001$) and follow-up time ($p = 0.0196$). Age at baseline was significantly correlated with follow-up time ($p = 0.05$). All other correlations were not statistically significant.

As presented in Table 3, after adjusting for age at follow-up, there was a decrease of 1.37 points in MMSE ($p = 0.0002$, 95% CI -2.07 to -0.66) per unit increase in HbA1c. This result remained essentially unchanged after adjusting also for years of education and gender ($p = 0.0005$, 95% CI -1.98 to -0.57), cardiovascular factors ($p = 0.0004$, 95% CI -2.02 to -0.61), lifestyle variables ($p = 0.0006$, 95% CI -1.99 to -0.57), duration of follow-up ($p = 0.0008$, 95% CI -1.95 to -0.53), lipid levels ($p = 0.0003$, 95% CI -2.07 to -0.64), or BMI ($p = 0.0003$, 95% CI -2.05 to -0.63). In order to reduce the possibility that subjects who were at higher risk for developing diabetes were significant contributors to the results, we repeated the analysis after excluding subjects with HbA1c levels >6 . The results remained very similar: per each 1% increase in HbA1c levels, there was a decrease of 1.1 in the MMSE score (SE = 0.44, $p = 0.01$). This relationship is depicted in Fig. 1.

Although the role of HbA1c changes on functional decline is of interest, due to the small number of subjects who converted from CDR = 0 to CDR = 0.5 ($n=6$) during the period of the study, a meaningful analysis investigating this relationship was not possible.

When a regression model with a 1-visit lag for HbA1c (excluding baseline MMSE, since there was no prior HbA1c) was examined, the lagged HbA1c was no longer significantly associated with MMSE 1-visit later. To examine whether the vanishing significance was due to a reduced sample size, we re-ran the model excluding baseline records. The parameter estimate and the significance level for the HbA1c variable was virtually unchanged from what was obtained using the full sample including baseline measurements. A model with the outcome and predictor variables interchanged was run, demonstrating a significant effect of MMSE on HbA1c. When the model was rerun for lagged MMSE predicting HbA1c, the p -value (0.5677) became non-significant, similar to the lagged HbA1c model.

Finally, a MMSE domain-specific analysis was conducted (Table 4). The “delayed recall” domain (outcome variable) showed significant association with concurrent HbA1c (independent variable) while the other domains were not associated with concurrent HbA1c. We also performed an analysis using a 1-visit lag for HbA1c and the odds ratio was rendered non-significant (results not shown).

DISCUSSION

The results of this study suggest that in non-diabetic non-demented elderly subjects, an increase in HbA1c is associated with concurrent cognitive decline as measured by the MMSE. These results remained significant even after controlling for demographic [16], cardiovascular [17], and lifestyle factors [18] which have previously been demonstrated to

be associated with cognition, or with length of follow-up which is inherently controlled for in the analysis.

The average changes in MMSE and HbA1c over the course of the study were negligible; however, there was enough within subject variability in MMSE and HbA1c to allow assessment of the association with changes in HbA1c. Therefore, despite changes in HbA1c [19, 20] and cognition [21] with aging, the presently observed relationship cannot be attributed merely to overall trends in both over time. Approximately 13% of the subjects participating in the study had baseline HbA1c levels above 6% (but below 7%). Although such HbA1c values are relatively common in the general population not diagnosed as suffering from diabetes, they may be indicative of impaired fasting plasma glucose [22] and precede the diagnosis of diabetes. In order to reduce the possibility that undiagnosed diabetic, or pre-diabetic subjects were the main contributors to these results, we performed an additional analysis which excluded subjects with baseline HbA1c >6%. The results did not change substantially and remained statistically significant despite the decrease in the sample size.

The present study advances beyond associations of baseline HbA1c with cognitive decline among non-diabetic persons to associations of simultaneous changes in HbA1c and cognitive performance over time. Our results may suggest that long-term peripheral glucose levels *per se* may be associated with biological mechanisms for neuronal dysfunction/neurodegeneration and subsequent cognitive compromise beyond their manifestation in diabetes. Interestingly, a lagged effect has not been found, i.e., HbA1c levels were associated with concurrent MMSE score but not with future MMSE scores. Similarly, MMSE scores correlated with concurrent HbA1c levels but not with future HbA1c levels. HbA1c levels at any point in time, reflect the average glycemic control over the previous 3 months, whereas MMSE scores are more subjected to short-term variations, especially in elderly subjects [23]. Thus, though the direction of the association between HbA1c and cognition cannot be elucidated based on the present data, it is plausible that cognitive performance is affected by glycemic control over the past months. The present results are consistent with those of previous studies showing that reduced glucose tolerance at a certain time point is associated with decreased general cognitive performance and memory impairment in middle aged and elderly non-diabetic non-demented individuals [24]. Others have demonstrated the long term association of HbA1c levels at baseline with incident MCI and dementia at follow-up in mostly non-diabetic elderly women [5]. In subjects with HbA1c levels within the range regarded as normal in clinical practice, higher HbA1c levels (but not cardiovascular risk factors such as diabetes) were also associated with smaller hippocampal volume and with accelerated rate of brain atrophy [25], both of which are biological measures associated with cognitive performance. Previous studies have shown that HbA1c levels are associated with cardiovascular disease [26], mortality [27, 28], and carotid artery plaques [29] even in nondiabetic subjects with modest levels of HbA1c. This may suggest the possible role of long-term glucose levels in vascular pathology, which may also affect cognition [30, 31]. Indeed, vascular brain pathology has been demonstrated to be an important contributor to cognitive compromise and dementia in the elderly [30]. In the present study, brain imaging data was not available, thus precluding the ability to evaluate the effect of changes in HbA1c on brain parenchyma and vasculature. Stroke was an exclusion criterion for participation in this study based on medical history, chart, and consensus conference. However, measurement of subclinical manifestations of cerebrovascular disease, which might have modulated our findings, was beyond the scope of this study. Chronic and acute hyperglycemia were associated with decrease in cerebral blood flow in animal models [31], particularly in the hippocampus [32, 33]. This phenomenon may be further stressed when confronting cognitive tasks, which in animal models have been demonstrated to be associated with depletion of extracellular glucose in the hippocampus

[34]. Since glucose levels in the blood exist along a continuum, relative high blood glucose levels (even within the range considered to be normal) may be associated with impaired cognitive function, as shown by other studies [24]. The susceptibility of the hippocampus to the effects of peripheral hyperglycemia is consistent with our finding that [9] delayed recall, the primary cognitive domain affected by hippocampal degeneration, amongst the different cognitive domains assessed by the MMSE, was the most strongly associated with HbA1c values.

The main strength of this study is the relatively long period with simultaneous assessments of HbA1c and MMSE, permitting examination of the association of their changes. The multidisciplinary consensus on the non-diabetic and cognitively normal status of the subjects is another strength. HbA1c levels in this study were consistent with those of other non-diabetic elderly cohorts, validating the applicability of the present results to non-diabetic elderly [22]. An additional advantage of this report is that in comparison to previous studies, which have based their conclusions on the association between glycemic control (or diabetes related characteristics) on baseline laboratory values or diagnosis [25, 35], the present study demonstrates an association between glycemic control and cognition as continuously measured over time. The study was focused on the oldest old, the fastest growing segment of the population [36] in the Western world and at the highest risk for dementia [37] but for whom little is known about risk factors for dementia. Extrapolation of the results of this study to younger elderly should be done with caution.

Limitations of this study are, as previously noted, lack of brain imaging data. Additionally, some of the potential confounders were based on self-report only (physical activity and smoking). We did not have consistent data on waist circumference, fasting blood glucose, or insulin levels. Data on BMI was available at baseline but not at follow-up. The subjects' relatively high educational level and homogenic race is similar to that of many other cohorts [38, 39], but limit the external validity of the results and their generalizability to populations with lower education or to non-Caucasians. Finally, the MMSE was used to measure overall cognitive performance; it withstood significant variability within a subject and was sensitive enough to capture the relationship between its changes and changes in glycemic control. In our sample, the rate of MMSE decline over time was in accordance with that observed in previous studies [40, 41] showing an initial increase in MMSE scores (attributed to a learning effect) and a progressive decrease in MMSE scores thereafter (results not shown). MMSE, therefore, may be an effective tool for the detection of cognitive deterioration in an aging population over long periods of time. However, a full neuropsychological assessment might provide useful information about specific cognitive domains that may be more affected by changes in glycemic control. Learning about the role of changes in HbA1c on elderly subjects' functional capacity would be of value. However, our study sample consisted of cognitively intact subjects at baseline (CDR = 0) and during the period of the study, only 6 subjects deteriorated to CDR = 0.5. Cognitive dysfunction leading to decline in the ability to function and maintain independence is one of the core criteria for diagnosis of dementia [42] and its presence as a criteria in the diagnosis of MCI is a topic of debate [43, 44]. Therefore, a meaningful analysis regarding the effect of increase in HbA1c on subjects' functional abilities in an a-priori cognitively intact sample was not possible. Although analyses of time co-varying variables has several advantages over prediction from baseline values only, one of its potential problems is reverse causality, which we cannot rule out: it is possible that cognitive performance was influencing glycemic control, either directly [45, 46], or indirectly, for example, through changes in dietary habits or physical activity as part of incipient cognitive decline, leading to increased levels of HbA1c. In order to address the possibility of reverse causality (i.e., that cognition drives changes in HbA1c rather than the opposite) between changes in HbA1c and changes in MMSE over time, we examined in secondary analyses (data not shown) whether the association between HbA1c and MMSE

and the direction of this association persisted after replacing the time varying HbA1c levels in the TOBIT model with only the baseline HbA1c level and its interaction with time. The reason for doing this is that if the results from the model looking only at baseline HbA1c (which we know cannot be tainted by reverse causality) agree with the results from the model using all measures of HbA1c then we can be reasonably confident that reverse causality is not adversely impacting our results. What we found was that although the interaction between baseline HbA1c and time was not statistically significant (The p -value for the interaction between that baseline HbA1c and time as linear was $p = 0.1787$); the direction of the association indicated that subjects with higher HbA1c levels at baseline had more of a decline in their MMSE over time than subjects with lower HbA1c levels at baseline. Therefore, the conclusion drawn from the analysis restricted to only baseline HbA1c data is consistent with the conclusion drawn from the analysis using all available time varying HbA1c data, namely increased levels of HbA1c are associated with decreased MMSE scores. We think the agreement between the two approaches lends credibility to our results; however, we acknowledge that statistical models do not establish causality or reverse causality.

Future studies should prospectively examine populations with broader sociodemographic characteristics and the interaction of long term glucose control, peripheral insulin levels, cognition, and neuropathologic findings. Another critical extension is replication of this study in a diabetic sample, particularly in light of recent findings suggesting that diabetes medications may reduce AD neuropathology [47]. Additionally, the effect of factors potentially associated with glucose control (such as diet and medications) on cognition should be assessed. Findings from such studies are expected to advance understanding of the underlying mechanisms relating poor glycemic control to increased risk of dementia as well as future planning and implementation of dementia prevention strategies in diabetic as well as in non-diabetic individuals.

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Fig. 1.

Fitted line from a TOBIT Regression model of MMSE scores regressed on HbA1c (adjusting for age, gender, APOE4, physical activity, years of education, smoking status, and hypertension) overlaid on the observed MMSE scores and corresponding HbA1c measures. This line was computed based on specific values of the aforementioned covariates, in particular an 87 year old smoking female, performing light physical activity with 15 years of education, no hypertension and APOE4 genotype. Other values of these covariates would generate a line with a different intercept and the same slope.

Table 1

Zero-order Spearman correlations among variables

	Baseline HbA1c	Baseline MMSE	Last MMSE	Last HbA1c	Δ MMSE	Δ HbA1c	Age at baseline	Follow-up time
Baseline HbA1c	Spearman r 1.0000	-0.2466	-0.1366	0.7374	0.1072	-0.2818	-0.0826	0.2320
	p -value	0.0129	0.1733	<0.0001	0.2859	0.0043	0.4118	0.0196
Baseline MMSE	Spearman r -0.2466	1.0000	0.4095	-0.1086	-0.4718	0.2051	-0.1814	0.0130
	p -value	0.0129	<0.0001	0.2795	<0.0001	0.0396	0.0695	0.8974
Last MMSE	Spearman r -0.1366	0.4095	1.0000	-0.2379	0.5540	-0.1486	-0.1057	-0.0310
	p -value	0.1733	<0.0001	0.0166	<0.0001	0.1382	0.2927	0.7583
Last HbA1c	Spearman r 0.7374	-0.1086	-0.2379	1.0000	-0.0738	0.3650	-0.1472	0.2032
	p -value	<0.0001	0.2795	0.0166	0.4631	0.0002	0.1418	0.0415
Δ MMSE	Spearman r 0.1072	-0.4718	0.5540	-0.0738	1.0000	-0.2847	0.0689	-0.0488
	p -value	0.2859	<0.0001	0.4631		0.0039	0.4933	0.6283
Δ HbA1c	Spearman r -0.2818	0.2051	-0.1486	0.3650	-0.2847	1.0000	-0.1582	0.0247
	p -value	0.0043	0.0396	0.1382	0.0039		0.1140	0.8062
Age at baseline	Spearman r -0.0826	-0.1814	-0.1057	-0.1472	0.0689	-0.1582	1.0000	-0.1955
	p -value	0.4118	0.0695	0.2927	0.4933	0.1140		0.0500
Follow-up time	Spearman r 0.2320	0.0130	-0.0310	0.2032	-0.0488	0.0247	-0.1955	1.0000
	p -value	0.0196	0.8974	0.7583	0.6283	0.8062	0.0500	

1 unit change in HbA1c = change in 01 (1%) HbA1c.

Table 2

Description of the sample

Variable	n	Mean	Between subject std dev	Within subject std dev	Median	Minimum	Maximum
Age at baseline	101	85.89	5.42		87.07	68.01	95.97
Education	101	15.09	2.85		15.00	6.00	20.00
HbA1c	303	5.53	0.35	0.23	5.50	4.20	6.80
HbA1c (Last – baseline)	101	0.03	0.31		0.10	-1.20	0.70
MMSE	303	28.11	1.13	1.45	29.00	18.00	30.00
Δ MMSE (Last – baseline)	101	-0.12	2.01		0.00	-7.00	6.00
Follow-up time (months)	101	32.03	14.80		34.10	6.77	65.18
# of visits	101	3.00	0.95		3.00	2.00	6.00
BMI	101	25.12	3.97		24.5	16.15	41.15
CDR did not worsen	94	0.03	0.32		0.10	-1.20	0.70
CDR worsened	6	0.02	0.15		0.05	-0.20	0.20

Table 3

Association of changes in HbA1c and changes in MMSE (DF = 100). TOBIT regression estimates including *T*-values, confidence limits, DF and goodness of fit statistic

Model	Estimate	SE	DF	<i>t</i> -value	<i>p</i> -value	Lower 95% CL	Upper 95% CL	# subjects/ # Obs	-2 log likelihood
Intercept	45.0989	3.4247	100	13.1700	<0.0001	38.3045	51.8933	101/303	1112.7
HA1C	-1.3682	0.3554	100	-3.8500	0.0002	-2.0733	-0.6631		
Age at baseline	-0.1057	0.0319	100	-3.3100	0.0013	-0.1690	-0.0424		
Intercept	43.8347	3.4267	100	12.7900	<0.0001	37.0363	50.6331	101/303	1107.3
HA1C	-1.2799	0.3556	100	-3.6000	0.0005	-1.9853	-0.5745		
Age at baseline	-0.1164	0.0318	100	-3.6600	0.0004	-0.1794	-0.0533		
Education	0.1208	0.0567	100	2.1300	0.0357	0.0083	0.2333		
Gender	-0.3697	0.3465	100	-1.0700	0.2885	-1.0571	0.3177		
Intercept	44.2012	3.3873	100	13.0500	<0.0001	37.4809	50.9215	101/303	1103.2
HA1C	-1.3123	0.3552	100	-3.6900	0.0004	-2.0169	-0.6076		
Age at baseline	-0.1162	0.0314	100	-3.7100	0.0003	-0.1784	-0.0540		
Education	0.1250	0.0563	100	2.2200	0.0287	0.0133	0.2366		
Gender	-0.4958	0.3470	100	-1.4300	0.1562	-1.1843	0.1927		
HTN	-0.0703	0.3364	100	-0.2100	0.8350	-0.7376	0.5971		
APOE4	-0.7722	0.3827	100	-2.0200	0.0463	-1.5316	-0.0129		
Intercept	43.4661	3.5063	100	12.4000	<0.0001	36.5096	50.4225	101/303	1102.7
HA1C	-1.2783	0.3589	100	-3.5600	0.0006	-1.9904	-0.5662		
Age at baseline	-0.1119	0.0317	100	-3.5300	0.0006	-0.1748	-0.0491		
Education	0.1166	0.0575	100	2.0300	0.0454	0.0024	0.2307		
Gender	-0.5161	0.3459	100	-1.4900	0.1388	-1.2022	0.1701		
HTN	-0.0511	0.3388	100	-0.1500	0.8803	-0.7232	0.6210		
APOE4	-0.7852	0.3823	100	-2.0500	0.0426	-1.5437	-0.0268		
Smoker	-0.0319	0.3300	100	-0.1000	0.9231	-0.6867	0.6228		
Physical activity	0.1211	0.1596	100	0.7600	0.4498	-0.1955	0.4378		
Intercept	43.1785	3.4990	100	12.3401	0.0000	36.2365	50.1205	101/303	1098.1
HA1C	-1.2385	0.3573	100	-3.4661	0.0008	-1.9473	-0.5296		
Age at baseline	-0.1137	0.0316	100	-3.5970	0.0005	-0.1765	-0.0510		

Model	Estimate	SE	DF	t-value	p-value	Lower 95% CL	Upper 95% CL	# subjects/ # Obs	-2 log likelihood
Education	0.1212	0.0575	100	2.1077	0.0376	0.0071	0.2353		
Gender	-0.4815	0.3454	100	-1.3938	0.1665	-1.1668	0.2039		
HTN	-0.0273	0.3384	100	-0.0808	0.9358	-0.6988	0.6441		
APOE4	-0.8106	0.3816	100	-2.1241	0.0361	-1.5678	-0.0535		
Smoker	-0.0402	0.3293	100	-0.1220	0.9031	-0.6935	0.6131		
Physical activity	0.1383	0.1596	100	0.8667	0.3882	-0.1783	0.4550		
Month of FU	0.3845	0.2355	100	1.6329	0.1056	-0.0827	0.8518		
Month of FU ²	-0.1163	0.0579	100	-2.0100	0.0471	-0.2312	-0.0015		
Intercept	43.3350	3.4622	99	12.5200	<0.0001	36.4652	50.2048	100/301	1080.6
HA1C	-1.3563	0.3588	99	-3.7800	0.0003	-2.0683	-0.6444		
Age at baseline	-0.1008	0.0307	99	-3.2800	0.0014	-0.1617	-0.0398		
Education	0.1402	0.0557	99	2.5200	0.0134	0.0297	0.2506		
Gender	-0.4236	0.3773	99	-1.1200	0.2642	-1.1723	0.3250		
HTN	-0.2586	0.3346	99	-0.7700	0.4413	-0.9225	0.4052		
APOE4	-0.7457	0.3741	99	-1.9900	0.0490	-1.4880	-0.0034		
Smoker	-0.0095	0.3200	99	-0.0300	0.9763	-0.6444	0.6253		
Physical activity	0.1224	0.1551	99	0.7900	0.4322	-0.1855	0.4302		
Glucose	-0.0156	0.0089	99	-1.7400	0.0842	-0.0333	0.0021		
Triglycerides	0.0082	0.0033	99	2.5000	0.0140	0.0017	0.0146		
HDL	0.0052	0.0096	99	0.5500	0.5859	-0.0138	0.0242		
LDL	-0.0036	0.0045	99	-0.8200	0.4167	-0.0125	0.0052		
Month of FU	0.4052	0.2376	99	1.7100	0.0913	-0.0663	0.8766		
Month of FU ²	-0.1194	0.0583	99	-2.0500	0.0431	-0.2350	-0.0038		
Intercept	44.0493	3.5981	98	12.2424	0.0000	36.9091	51.1896	99/299	1070.6
HA1C	-1.3444	0.3588	98	-3.7473	0.0003	-2.0564	-0.6325		
Age at baseline	-0.1066	0.0307	98	-3.4667	0.0008	-0.1676	-0.0456		
Education	0.1394	0.0552	98	2.5261	0.0131	0.0299	0.2490		
Gender	-0.5117	0.3790	98	-1.3501	0.1801	-1.2639	0.2404		
HTN	-0.3154	0.3363	98	-0.9378	0.3506	-0.9828	0.3520		
APOE4	-0.6812	0.3742	98	-1.8205	0.0717	-1.4237	0.0614		
Smoker	-0.0937	0.3226	98	-0.2905	0.7720	-0.7338	0.5464		

Model	Estimate	SE	DF	t-value	p-value	Lower 95% CL	Upper 95% CL	# subjects/ # Obs	-2 log likelihood
Physical activity	0.1929	0.1606	98	1.2012	0.2326	-0.1258	0.5116		
Glucose	-0.0143	0.0089	98	-1.6099	0.1106	-0.0320	0.0033		
Triglycerides	0.0083	0.0032	98	2.5728	0.0116	0.0019	0.0147		
HDL	0.0029	0.0096	98	0.3017	0.7635	-0.0161	0.0219		
LDL	-0.0026	0.0045	98	-0.5769	0.5654	-0.0114	0.0063		
Month of FU	0.4125	0.2393	98	1.7241	0.0879	-0.0623	0.8874		
Month of FU ²	-0.1229	0.0587	98	-2.0951	0.0387	-0.2393	-0.0065		
BMI	-0.0187	0.0394	98	-0.4748	0.6360	-0.0968	0.0594		

Table 4

Association of changes in HbA1c and changes in specific domains of the MMSE

	Odds ratio	95% CI	p-value	Denominator DF	F-value
Delayed recall	4.44	[2.14, 9.19]	<0.0001	175	16.30
Immediate recall	0.43	[0.04, 5.27]	0.5057	177	0.77
Attention	1.97	[0.85, 4.57]	0.1138	172	2.53
Language	1.03	[0.45, 2.33]	0.9455	176	0.00
Orientation time/place	1.60	[0.68, 3.75]	0.2792	176	1.18
Praxis	1.07	[0.47, 2.44]	0.8669	177	0.03
Total MMSE	3.09	[1.50, 6.35]	0.0024	168	9.52