Published in final edited form as:

J Am Geriatr Soc. 2017 January ; 65(1): 137–145. doi:10.1111/jgs.14478.

Effects of Longitudinal Glucose Exposure on Cognitive and Physical Function: Results from the Action for Health in Diabetes Movement and Memory Study

Kristen M. Beavers, PhD¹, Iris Leng, PhD², Stephen R. Rapp, PhD³, Michael E. Miller, PhD², Denise K. Houston, PhD⁴, Anthony P. Marsh, PhD¹, Don G. Hire, BS², Laura D. Baker, PhD⁴, George A. Bray, MD⁵, George L. Blackburn, MD, PhD⁶, Andrea L. Hergenroeder, PhD⁷, John M. Jakicic, PhD⁸, Karen C. Johnson, MD⁹, Mary T. Korytkowski, MD¹⁰, Brent Van Dorsten, PhD¹¹, Stephen B. Kritchevsky, PhD⁴, and for the Action for Health In Diabetes (Look AHEAD) Movement and Memory Ancillary Study Research Group

¹Department of Health and Exercise Science, Wake Forest University, Winston-Salem, USA

²Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, USA

³Department of Psychiatry and Behavioral Medicine, Wake Forest School of Medicine, Winston-Salem, USA

⁴Department of Internal Medicine, Section on Gerontology and Geriatric Medicine, Winston-Salem, USA

⁵Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, USA

⁶Division of Nutrition, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, USA

⁷Department of Physical Therapy, University of Pittsburgh, Pittsburgh, USA

⁸Department of Health and Physical Activity, University of Pittsburgh, Pittsburgh, USA

⁹Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, USA

¹⁰Department of Medicine, University of Pittsburgh, Pittsburgh, USA

¹¹Department of Physical Medicine and Rehabilitation, University of Colorado Denver School of Medicine, Aurora, USA

Corresponding Author: Kristen M. Beavers, PhD, MPH, RD, Wake Forest University, Department of Health and Exercise Science, P.O. Box 7868, Winston-Salem, NC, 27109, USA, Phone: +1.336.758.5855 | Fax: +1.336.758.4680, beaverkm@wfu.edu.

Author Contributions: Kristen M. Beavers: data analysis and interpretation; Iris Leng: data analysis and interpretation; Stephen R. Rapp: study design and concept; Michael E. Miller: data analysis and interpretation; Denise K. Houston: study concept and design; Anthony P. Marsh: data analysis and interpretation; Don G. Hire: data analysis and interpretation; Laura D. Baker: data analysis and interpretation; George A. Bray: study concept and design, acquisition of subjects and data, data analysis and interpretation; George L. Blackburn: study concept and design, acquisition of subjects and data, data analysis and interpretation; Andrea L. Hergenroeder: data analysis and interpretation; John M. Jakicic: study concept and design, acquisition of subjects and data, data analysis and interpretation; Karen C. Johnson: study concept and design, acquisition of subjects and data, data analysis and interpretation; Mary T. Korytkowski: data analysis and interpretation; Brent Van Dorsten: study concept and design, acquisition of subjects and data, data analysis and interpretation, and Stephen B. Kritchevsky: study concept and design and data analysis and interpretation. All coauthors revised the article critically for important intellectual content and gave final approval of the version to be published.

Abstract

Objectives—To test whether average long-term glucose exposure is associated with cognitive and physical function in middle aged and young older adults with type 2 diabetes.

Design—Prospective cohort study.

Setting—Data obtained as a part of the Look AHEAD trial (NCT00017953) and Look AHEAD Movement and Memory ancillary study (NCT01410097).

Participants—879 overweight and obese individuals with type 2 diabetes, aged 45–76 years at baseline.

Measurements—Glycated hemoglobin (HbA1c) was measured at regular intervals over 7 years, and objective measures of cognitive function (Trail Making Test, Modified Stroop Color-Word Test, Digit Symbol-Coding, Rey Auditory Verbal Learning Test, and Modified Mini-Mental State Exam) and physical function (Short Physical Performance Battery [SPPB], expanded PPB, 400-m and 20-m gait speed) and strength (grip and knee extensor strength) were assessed at the year 8 or 9 follow-up exam.

Results—Average HbA1c exposure was $7.04 \pm 1.06\%$ (53 ± 11.6 mmol/mol), with 57%, 27%, and 16% of participants classified as having HbA1c levels of $<7\%$ (<53 mmol/mol), 7–8% (53 – 64 mmol/mol), and $>8\%$ (>64 mmol/mol), respectively. After adjustment for age, sex, race, education, smoking status, alcohol intake, knee pain physical fitness, body mass index, diabetes medication and statin use, ancillary year visit, study arm and site, higher HbA1c was associated with worse physical, but not cognitive, function. Further adjustment for prevalent diabetes-related comorbidities rendered all associations non-significant. Results did not differ when stratified by participant baseline age (<60 vs. ≥ 60 years).

Conclusion—Results presented here suggest that, in the absence of diabetes-related complications, longitudinal glucose exposure is not associated with future cognitive and physical function. Optimal management of diabetes-related comorbidities may prevent or reduce the burden of disability associated with type 2 diabetes.

Keywords

HbA1c, cognition; physical function; type 2 diabetes mellitus

INTRODUCTION

The prevalence of diagnosed type 2 diabetes mellitus in the United States has increased sharply over the past two decades,¹ with one in four adults aged 65 years and older currently manifesting the condition.² Type 2 diabetes is associated with exacerbation of age-related declines in cognitive³ and physical⁴ function. Indeed, the odds of experiencing frank dementia⁵ or lower extremity disability^{6,7} are at least 1.5 times higher for individuals with, compared to those without, type 2 diabetes. Importantly, such cognitive and physical limitations consistently predict loss of independence⁸ and consequent higher healthcare spending.^{9,10}

One hypothesis suggests that among those with type 2 diabetes, glucose dysregulation directly contributes to cognitive and physical impairment, as chronically elevated glucose is a hallmark of the condition. Data supporting this conjecture, however, are mixed. Some, but not all,¹¹ cross-sectional studies associate higher levels of glycated hemoglobin (HbA1c) with worse cognitive^{12,13} and physical^{7,14} function in individuals with type 2 diabetes. However, recent prospective studies suggest that poor glycemic control (i.e., HbA1c >7%; 53 mmol/mol) may^{15, 16} (or may not¹⁷) be associated with a decline in cognitive function, yet a paradoxical improvement in self-reported physical function.¹⁸ Thus, the true nature of the relationship between HbA1c and cognitive and physical function is unclear.

To help clarify the association, we used data from the Look AHEAD trial and Movement and Memory (M&M) ancillary study to test the hypothesis that chronically high levels of HbA1c are associated with age-related functional impairments in adults with type 2 diabetes. Using measures of HbA1c over 7 years (baseline-year 8) and cognitive and physical function assessments collected at the year 8 or year 9 (hereafter referred to as year 8/9) clinical exam, we examined whether longitudinal HbA1c exposure was associated with several objective cognitive and physical function measures, sensitive to age-related decline. Due to the rich characterization of the Look AHEAD cohort, we also examined whether the observed associations varied by age or were independent of diabetes-related comorbidities (i.e., cardiovascular disease [CVD], stroke, retinopathy, renal disease, neuropathy, hypertension, and depression). We hypothesized that average HbA1c would be inversely related to follow-up measures of cognitive and physical function, particularly in the oldest members of the cohort, and that this association would be driven by clinically manifested diabetes-related comorbidities.

METHODS

Look AHEAD Study Design

The design and methods of the Look AHEAD trial (NCT00017953) have been previously published.¹⁹ Briefly, in 16 study centers in the United States, 5145 overweight or obese patients with type 2 diabetes were randomized to participate in a 4 year intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity (intervention group) or to receive diabetes support and education (control group). The goal in the intensive lifestyle intervention arm was to induce a loss of at least 7% of participants' initial weight by dietary modification and increase physical activity to a minimum of 175 minutes per week.²⁰ The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years. The primary outcome paper is published, with no difference in the rate of cardiovascular events seen between groups.²¹

The Look AHEAD M&M ancillary study (NCT01410097) enrolled Look AHEAD participants at four clinical centers to assess cognitive and physical function during the weight maintenance phase of the trial at either their year 8 or 9 clinical examination. Only currently active Look AHEAD participants at the Baton Rouge, Denver, Memphis, and Pittsburgh clinics who provided separate informed consent were eligible to enroll. The Look AHEAD M&M protocol and consent forms were approved by local Institutional Review

Boards prior to use. Primary outcome papers were published, with modest treatment effects observed for physical, but not cognitive, function endpoints.^{22,23}

Current Study Sample

The four Look AHEAD M&M clinics enrolled 1,331 participants into the Look AHEAD trial at baseline. When Look AHEAD M&M enrollment started, 30 of the original participants had withdrawn from Look AHEAD, 65 had died, and 4 were lost to follow-up, leaving 1,232 participants who attended a Year 8 or 9 visit during the Look AHEAD M&M enrollment period. Of these, 1,092 (89%) consented to enroll in the Look AHEAD M&M ancillary study, of which 1,081 (Baton Rouge n=280; Denver n=303; Memphis n=220; Pittsburgh n=278) were seen either at the clinic (n = 979) or assessed by telephone (n = 102). Data for the function measures presented here are from 879 participants who had at least two measures of HbA1c and all relevant covariate information; 65% of the original Look AHEAD enrollees. Final sample sizes differed by outcome measure (see sections on *Assessment of Cognitive and Physical Function*).

Assessment of HbA1c

Blood specimens were collected annually after at least a 12-hour fast and were analyzed by the Central Biochemistry Laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle, WA) using standardized laboratory procedures for measuring HbA1c. In the Look AHEAD trial, HbA1c was assessed at baseline, annually during years 1–4, and then biannually thereafter. For all analyses, ‘HbA1c exposure’ represented the annual average of at least 24 months, and the distribution of annual HbA1c measurements was 2 (0.23%) participants with 3 values, 11 (1.25%) with 5 values, 68 (7.74%) with 6 values, and 798 (90.78%) with 7 values.

Assessment of Cognitive Function

Following a standardized protocol, the Look AHEAD M&M study assessed cognitive abilities sensitive to aging during a clinic exam at year 8/9 of the Look AHEAD trial. Per protocol, participants’ blood glucose was assessed prior to testing and required to be >70 mg/dL in order to proceed with the cognitive assessment. All tests were previously validated and administered by centrally trained and certified examiners who were masked to intervention assignment.²² The cognitive tests (and associated domains and sample sizes) included: Trail Making Test-Parts A and B²⁴ (simple attention, and executive function-set shifting, respectively; n=878); Modified Stroop Color-Word Test^{25,26} (executive function-response inhibition; n=860); Digit Symbol-Coding²⁷ (processing speed and executive function-working memory; n=878); Rey Auditory Verbal Learning Test²⁸ (episodic verbal learning and memory; n=879); and the Modified Mini-Mental State Exam²⁹ (global cognitive functioning; n=879).

Assessment of Physical Function

The Look AHEAD M&M study assessed objective measures of physical function using centrally trained and certified staff who were masked to intervention assignment during the year 8/9 clinic examination of the Look AHEAD trial.²³ Per protocol, participants’ blood

glucose was assessed prior to testing and required to be >70 mg/dL in order to proceed with the physical assessment. The Short Physical Performance Battery (SPPB) consisted of 3 hierarchical standing balance tasks held for 10 seconds each (side-by-side, semi- and full-tandem stands), a usual pace 4-meter walk, and 5 repeated chair stands.³⁰ Each performance measure was assigned a score ranging from 0–4, with 4 indicating the highest level of performance and 0 an inability to complete the tests. We calculated a summary score from 0 (worst performers) to 12 (best performers) by summing all test scores (n=852). In addition, we administered an expanded Physical Performance Battery (PPB) to circumvent the ceiling effect of the SPPB.³¹ The expanded PPB increased the standing balance tasks to 30 seconds and added a single leg stand. Scores were continuous and ranged from 0 to 3, with higher scores indicative of better performance (n=852). Usual walking speeds over 20 meters (20-m) and 400 meters (400-m) were also measured (n=840 and n=797 for the 20- and 400-m walk tests, respectively).³² Grip strength (kg) was measured twice per hand using an isometric Hydraulic Hand Dynamometer (Jamar, Bolingbrook, IL) and we analyzed the maximum force from two trials for the stronger hand (n=828). Finally, we assessed maximum knee extensor muscle strength (lbs; one repetition maximum) on a Nautilus One™ Leg Extension machine (n=641). We tested the right leg unless there was a contraindication (e.g., prior knee surgery).

Potential Risk Factors for Cognitive and Physical Limitations

Certified staff obtained all risk factor measurements. We used standardized questionnaires to collect self-reported baseline characteristics (i.e. age, gender, race, education, smoking status, alcohol use, and knee pain) and medical history. Baseline and incident diabetes-related comorbidities (noted during the follow-up examinations occurring prior to the year 8/9 testing session) include: CVD (i.e. myocardial infarction, PTCA, CABG, carotid endarterectomy, angioplasty of lower extremity artery, aortic aneurysm repair, heart failure, or congestive heart failure); stroke; retinopathy; renal disease; neuropathy; hypertension (systolic blood pressure > 140 mmHg and antihypertensive medication use); or depression (depressive symptoms were assessed year 8 using the Beck Depression Inventory [BDI]; total scores on the BDI range from 0 to 63, with higher scores indicating greater severity).³³ A maximal graded exercise test was administered at baseline and a submaximal graded exercise test at years 1 and 4 to estimate cardiorespiratory fitness in metabolic equivalents (METS).³⁴ Height was measured annually in duplicate using a stadiometer and body mass was measured using a digital scale throughout the Look AHEAD trial. Body mass index (BMI) was calculated as body mass in kilograms divided by height in meters squared at baseline, and years 1 and 8. Diabetic medication (including: thiazolidinediones, biguanides, insulins, meglitinides, sulfonylureas, alpha-glucans, and dipeptidyl peptidase 4 inhibitors) and statin use were collected via self-report at year 8. Lastly, relevant study-related covariates included ancillary visit year, randomization arm, and study site.

Statistical Analysis

We calculated average HbA1c exposure (%) using a time-weighted approach based on the amount of time elapsed between measurements from baseline to year 8. All values between baseline and ancillary date were weighed equally, with changes assumed to occur at the

midpoint between time points. The mean value was calculated after generating an HbA1c value for each day between measurements.

We classified participant according to 3 HbA1c categories: <7%, 7–8%, and >8% (<53 mmol/mol, 53–64 mmol/mol, and >64 mmol/mol) based on recent American Diabetes Association³⁵ and American Geriatrics Society recommendations.³⁶ Group differences were compared using the chi square test for proportions and ANOVA for continuous variables. Multiple linear regression models were used to assess associations between average HbA1c exposure over 7 years of follow-up and cognitive and physical function assessments. An initial unadjusted model (Model 1) was followed with two sets of adjusted models (Models 2 and 3), fitted for each outcome measure. The baseline covariates in the first adjusted model (Model 2) were age, sex, race, BMI, education level, smoking status, alcohol intake, knee pain, cardiorespiratory fitness (METS), randomization arm, and study site. Model 2 adjustments were also made for BMI at years 1 and 8, cardiorespiratory fitness at years 1 and 4, diabetes medication use at year 8, statin use at year 8, and visit year of the ancillary study (year 8 or 9). In Model 3, we further adjusted for diabetes-related comorbidities (i.e. CVD, stroke, retinopathy, renal disease, neuropathy, hypertension and depression) and hypoglycemic events. All presented parameter estimates are standardized to 1 standard deviation of each outcome measure to aid in comparability.

To elucidate the relative contributions of HbA1c and diabetes-related comorbidities on cognitive and physical performance, Model 3 was re-fit including diabetes-related comorbidities with and without HbA1c exposure. Lastly, using the covariates included in Model 2, we tested for the interaction between the HbA1c effect and an indicator of age (<60 vs. ≥60 years, determined *a priori*) to determine if the relationship between HbA1c and each outcome was consistent across age groups. All analyses were performed using SAS 9.4 (Cary, NC), with a significance level set at $p=0.05$.

RESULTS

Participant Characteristics

Average age of the study sample ($n=879$) at randomization was 58.9 ± 6.79 years (56% <60 years at baseline), 56.4% were women, and 19.3% were African American. Relevant participant characteristics, by average HbA1c exposure level over 7 years of follow-up, are shown in Tables 1 and 2. The majority of participants were categorized as having low (<7% or 53 mmol/mol; range: 4.75–6.96% or 28–53 mmol/mol; 57% of sample) HbA1c levels, followed by moderate (7–8% or 53–64 mmol/mol; 27% of sample) and high (>8% or 64 mmol/mol; range: 8.01–13.78% or 64–127 mmol/mol; 16% of sample) levels. The coefficient of variation of HbA1c over time was 10.6%, with higher levels of HbA1c associated with higher variability.

Younger age and African American race were associated with higher average HbA1c exposure (both $p<0.01$). Elevated HbA1c was also associated with higher BMI (years 1 and 8), year 8 BDI score, retinopathy, renal disease, hypertension, and diabetes medication use (all $p<0.01$). Among HbA1c exposure categories, there were no pairwise differences in education; smoking status; alcohol intake; knee pain; CVD, stroke, or neuropathy;

cardiorespiratory fitness; baseline BMI; statin use; ancillary visit year; randomization arm; or study site.

Although baseline cognitive and physical function were not assessed, unadjusted performance on the battery of functional tests performed at the year 8/9 visit, stratified by average HbA1c, are presented in Table 3 for descriptive purposes. No differences in any of the functional outcome measures were observed across HbA1c categories, although a trend was observed for the Modified Stroop Color-Word Test ($p=0.055$).

Associations between Cognitive and Physical Function by Average HbA1c

Model parameter estimates and 95% CIs between performance on cognitive and physical function tests at the year 8/9 visit and average HbA1c exposure over 7 years of follow-up are presented in Table 4. In separate unadjusted models, HbA1c was not associated with performance on any outcome measures at the year 8/9 visit (Model 1). After adjusting for age, sex, race, education, smoking status, alcohol intake, knee pain, METS, BMI, diabetes medication and statin use, ancillary year visit, study arm and site (Model 2), parameter estimates between HbA1c and cognitive function were unchanged. Average HbA1c exposure was more consistently associated with physical function in Model 2, however, with higher average HbA1c exposure associated with lower SPPB and expanded PPB scores, and slower 400- and 20-m gait speed (all $p < 0.05$). Interestingly, of covariates included Model 2, age appeared to be the most influential to physical function results and inversely correlated with HbA1c.

Further adjustment for the presence of diabetes-related comorbidities attenuated previously significant associations by 54% to 60%, such that they were no longer significant (Model 3). Addition of an indicator variable for hypoglycemic events occurring prior to the functional assessment visit ($n=35$) did not alter these results. Conversely, parameter estimates for diabetes-related comorbidity effects, which were significantly and inversely related to several functional outcome measures, did not materially change with the addition of HbA1c exposure level (see Supplementary Table 1 in Appendix). Lastly, exploratory analyses testing an interaction between age and HbA1c yielded largely non-significant results, with the exception of the Modified Stroop Color-Word Test (p for interaction=0.03).

DISCUSSION

Despite the interest in elevated glucose as a pro-aging factor, in this sample of middle aged and young older adults with type 2 diabetes, average HbA1c over 7 years of follow-up was not associated with cognitive function and only modestly associated with physical function. Moreover, the inverse relationship between HbA1c and physical function was not apparent after accounting for diabetes-related comorbidities. This suggests that, in the absence of diabetes-related complications, HbA1c does not contribute to the development of cognitive and physical dysfunction. However, given the inherent limitations of the study design (i.e. lack of baseline outcome measures, potential selection bias) findings should be interpreted cautiously and warrant replication using concurrent longitudinal HbA1c and function data.

In the past several years, numerous studies have demonstrated that type 2 diabetes is a risk factor for cognitive and physical decline. Multiple pathophysiologic processes are speculated to underlie this association, including both glucose dysregulation and microvascular complications and related comorbidities.^{4, 7, 37} One hypothesis linking glucose dysregulation to increased risk of age-related cognitive and physical impairment posits that chronically elevated glucose accelerates the accumulation of advanced glycation end products (AGEs), promoting reactions that denature proteins and thereby increase oxidative stress and inflammatory burden.³⁸ In support of this conjecture, positive associations between AGEs and advanced dementia³⁹ as well as reduced physical function⁴⁰ have been reported.

Although the AGEs hypothesis may be true, and some data implicate elevated HbA1c in functional decline,^{15,16} overall results from our study do not support an independent role of elevated HbA1c in lower performance on objective measures of cognitive function. This finding is echoed longitudinally in the Atherosclerosis Risk in Communities (ARIC) study,¹⁷ as well as in the Action to Control Cardiovascular Risk in Diabetes-Memory Study (ACCORD MIND),⁴¹ where randomization to intensive glycemic control (HbA1c<6%; 42 mmol/mol) in participants with type 2 diabetes did not improve cognitive function.

Alternatively, our findings suggest that common medical complications of type 2 diabetes, rather than glucose dysregulation itself, may be responsible for the association between type 2 diabetes and lower performance on objective tests of physical function. Type 2 diabetes-related comorbidities are independent predictors of long-term disability, and may contribute to disability via limited cardiopulmonary reserve, restricted physical movement and exercise intolerance, and/or inflammatory processes. Our findings are in agreement with other cross-sectional⁷ and longitudinal⁶ data suggesting a prominent role for comorbidities in explaining the association between type 2 diabetes and functional disability, even when compared to poor glycemic control.⁷

Although we did not observe a differential effect of HbA1c on function by age strata in our sample, these analyses were exploratory in nature and specific to relatively “younger” older adults (as over half of the study sample were under the age of 60 at baseline). More longitudinal and randomized controlled trial data are necessary to clarify the complex role of glucose regulation in predicting physical function in older populations, especially when considering provocative findings from the On Lok Lifeways Study, where HbA1c levels of 8–8.9% (64–74 mmol/mol) independently predicted *better* functional outcomes in nursing home eligible, older (80±9 years) adults.¹⁸

The primary limitation of the current study design is the measurement of cognitive and physical function at a single time-point. Additionally, despite the well-characterized nature of the Look AHEAD cohort, findings are limited to a study population comprised of adults with type 2 diabetes, who are perhaps too healthy (i.e. limited range of HbA1c measures, volunteer selection bias, able to complete a maximal graded exercise test at baseline) and young to see significant variability in follow-up cognitive and physical function measures. Thus, our results cannot exclude the possibility that HbA1c is an important independent predictor of functional decline at older ages, over a longer follow-up period, and at significantly higher or lower HbA1c levels. Several outcome measures were assessed as part

of the cognitive and physical function batteries, and may have inflated our Type 1 error rate. However, because outcome measures are not independent of one another and analyses were post hoc and largely exploratory, we did not adjust for multiple comparisons. Lastly, although we do adjust for intervention arm assignment, one inherent limitation of conducting a descriptive study of a randomized controlled trial is the potential for confounding, especially considering legacy effects of the treatment on outcome measures. Strengths include the administration of multiple, objective, well-validated tests associated with both age-related cognitive and physical function decline and a relatively large sample.

In conclusion, results from this study do not support the hypothesis that glucose dysregulation, per se, leads to impairments in cognitive and physical function in overweight and obese adults diagnosed with type 2 diabetes. Rather, it may hasten the onset of diabetes-related comorbidities, which in turn were associated with poorer function. Thus, optimal management of diabetes-related comorbidities may prevent or reduce the burden of physical disability associated with type 2 diabetes, especially in “younger” older adults who may be more responsive to intervention; however, more data are necessary to clarify best practice strategies for preventing or slowing functional decline in the oldest old with type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FUNDING AND SUPPORT

This ancillary study is supported by the National Institute on Aging, National Institutes of Health, Department of Health and Human Services, R01 AG03308701. The Action for Health in Diabetes is supported through the following cooperative agreements from the National Institutes of Health: DK57136, DK57149, DK56990, DK57177, DK57171, DK57151, DK57182, DK57131, DK57002, DK57078, DK57154, DK57178, DK57219, DK57008, DK57135, and DK56992. The following federal agencies have contributed support: National Institute of Diabetes and Digestive and Kidney Diseases; National Heart, Lung, and Blood Institute; National Institute of Nursing Research; National Center on Minority Health and Health Disparities; Office of Research on Women's Health; the Centers for Disease Control and Prevention; and the Department of Veterans Affairs. This research was supported in part by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases. The Indian Health Service (I.H.S.) provided personnel, medical oversight, and use of facilities. The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the I.H.S. or other funding sources.

Additional support was received from the University of Colorado Health Sciences Center General Clinical Research Center (M01RR00051) and Clinical Nutrition Research Unit (P30 DK48520); the University of Tennessee at Memphis General Clinical Research Center (M01RR0021140); and the University of Pittsburgh General Clinical Research Center (GCRC) (M01RR000056), the Clinical Translational Research Center (CTRC) funded by the Clinical & Translational Science Award (UL1 RR 024153) and NIH grant (DK 046204); and the Frederic C. Bartter General Clinical Research Center (M01RR01346)

The following organizations have committed to make major contributions to Look AHEAD: FedEx Corporation; Health Management Resources; LifeScan, Inc., a Johnson & Johnson Company; OPTIFAST® of Nestle HealthCare Nutrition, Inc.; Hoffmann-La Roche Inc.; Abbott Nutrition; and Slim-Fast Brand of Unilever North America.

Sponsor's Role: The National Institutes of Health had no role in the design or conduct of the study; in the data collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Conflict of Interest

Elements of Financial/Personal Conflicts	*Author 1 KMB		Author 2 IL		Author 3 SRR		Author 4 MEM	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X
Grants/Funds	X			X		X	X	
Honoraria		X		X		X		X
Speaker Forum		X		X		X		X
Consultant		X		X		X		X
Stocks		X		X		X		X
Royalties		X		X		X		X
Expert Testimony		X		X		X		X
Board Member		X		X		X		X
Patents								
Personal Relationship								

Elements of Financial/Personal Conflicts	Author 5 DKH		Author 6 APM		Author 7 DGH		Author 8 LDB	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X
Grants/Funds	X			X		X		X
Honoraria		X		X		X		X
Speaker Forum		X		X		X		X
Consultant		X		X		X		X
Stocks		X		X		X		X
Royalties		X		X		X		X
Expert Testimony		X		X		X		X
Board Member		X		X		X		X
Patents		X		X		X		X
Personal Relationship		X		X		X		X

Elements of Financial/Personal Conflicts	Author 9 GAB		Author 10 GLB		Author 11 ALH		Author 12 JMJ	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X
Grants/Funds	X			X		X	X	
Honoraria		X		X		X		X
Speaker Forum		X		X		X		X
Consultant		X		X		X	X	

Elements of Financial/Personal Conflicts	Author 9 GAB		Author 10 GLB		Author 11 ALH		Author 12 JMJ	
	Yes	No	Yes	No	Yes	No	Yes	No
Stocks		X		X		X		X
Royalties		X		X		X		X
Expert Testimony		X		X		X		X
Board Member								
Patents		X		X		X		X
Personal Relationship		X		X		X		X

Elements of Financial/Personal Conflicts	Author 13 KCJ		Author 14 MTK		Author 15 BVD		Author 16 SBK	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X
Grants/Funds		X		X		X		X
Honoraria		X		X		X		X
Speaker Forum		X		X		X		X
Consultant		X	X			X		X
Stocks		X		X		X		X
Royalties		X		X		X		X
Expert Testimony		X		X		X		X
Board Member		X		X		X		X
Patents		X		X		X		X
Personal Relationship		X		X		X		X

For “yes” x mark(s): give brief explanation below:

KMB, MEM, DKH, GAB, JMJ all report NIH grant funding. JMJ is a scientific advisor for Weight Watchers, Int. and also reports industry funding. MTK serves as consultants for Sanofi Aventis.

Appendix

The following clinical sites and personnel were involved in this study:

Pennington Biomedical Research Center George A. Bray, MD1; Kristi Rau2; Allison Strate, RN2; Frank L. Greenway, MD3; Donna H. Ryan, MD3; Donald Williamson, PhD3; Brandi Armand, LPN; Jennifer Arceneaux; Amy Bachand, MA; Michelle Begnaud, LDN, RD, CDE; Betsy Berhard; Elizabeth Caderette; Barbara Cerniauskas, LDN, RD, CDE; David Creel, MA; Diane Crow; Crystal Duncan; Helen Guay, LDN, LPC, RD; Carolyn Johnson, Lisa Jones; Nancy Kora; Kelly LaFleur; Kim Landry; Missy Lingle; Jennifer Perault; Cindy Puckett; Mandy Shipp, RD; Marisa Smith; Elizabeth Tucker.

University of Colorado Health Sciences Center James O. Hill, PhD1; Marsha Miller, MS, RD2; Brent Van Dorsten, PhD3; Judith Regensteiner, PhD3; Ligia Coelho, BS; Paulette Cohrs, RN, BSN; Susan Green; April Hamilton, BS, CCRC; Jere Hamilton, BA; Eugene Leshchinskiy; Lindsey Munkwitz, BS; Loretta Rome, TRS; Terra Worley, BA; Kirstie Craul, RD, CDE; Sheila Smith, BS.

The University of Tennessee Health Science Center

University of Tennessee East. Karen C. Johnson, MD, MPH1; Karen L. Wilson, BSN2; Mace Coday, PhD3; Beate Griffin, RN, BS; Donna Valenski; Polly Edwards; Brenda Fonda; Kim Ward. *University of Tennessee Downtown.* Helmut Steinburg, MD3; Carolyn Gresham, BSN2; Moana Mosby, RN; Debra Clark, LPN; Donna Green RN; Abbas E. Kitabchi, PhD, MD (retired).

University of Pittsburgh John M. Jakicic, PhD1; David E. Kelley, MD1; Jacqueline Wesche-Thobaben, RN, BSN, CDE2; Lewis H. Kuller, MD, DrPH3; Andrea Kriska, PhD3; Amy D. Otto, PhD, RD, LDN3; Lin Ewing, PhD, RN3; Mary Korytkowski, MD3, Daniel Edmundowicz, MD3; Monica E. Yamamoto, DrPH, RD, FADA3; Rebecca Danchenko, BS; Barbara Elnyczky; David O. Garcia, MS; George A. Grove, MS; Patricia H. Harper, MS, RD, LDN; Susan Harrier, BS; Nicole L. Helbling, MS, RN; Diane Ives, MPH; Juliet Mancino, MS, RD, CDE, LDN; Anne Mathews, PhD, RD, LDN; Tracey Y. Murray, BS; Joan R. Ritchea; Susan Urda, BS, CTR; Donna L. Wolf, PhD.

Wake Forest University (coordinating center) Stephen B. Kritchevsky, PhD1; Denise K. Houston, PhD3; Jeff D. Williamson, MD3; Stephen R. Rapp, PhD3; Mark A. Espeland, PhD3; Xiaoyu (Iris) Leng, MD, PhD3; Gary Miller, PhD3; Kristen M. Beavers, PhD3; Amelia Hodges, BS, CCRP2; Michelle Gordon, MS; Jennifer Walker; Tara Beckner; Jason Griffin, BS; Lea Harvin, BS; Kathy Lane, BS; Rebecca H. Neiberg, MS.

¹Principal Investigator

²Program Coordinator

³Co-Investigator

All other Look AHEAD staffs are listed alphabetically by site.

REFERENCES

1. Increasing prevalence of diagnosed diabetes--United States and Puerto Rico, 1995–2010. MMWR Morb Mortal Wkly Rep. 2012; 61:918–921. [PubMed: 23151951]
2. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States. Atlanta, GA: 2011. 2011. Report No
3. van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. Biochim Biophys Acta. 2009; 1792:470–481. [PubMed: 18848880]
4. Gregg EW, Beckles GL, Williamson DF, et al. Diabetes and physical disability among older U.S. adults. Diabetes Care. 2000; 23:1272–1277. [PubMed: 10977018]

5. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. *Diabetologia*. 2005; 48:2460–2469. [PubMed: 16283246]
6. Volpato S, Blaum C, Resnick H, Ferrucci L, Fried LP, Guralnik JM. Comorbidities and impairments explaining the association between diabetes and lower extremity disability: The Women's Health and Aging Study. *Diabetes Care*. 2002; 25:678–683. [PubMed: 11919124]
7. Kalyani RR, Saudek CD, Brancati FL, Selvin E. Association of diabetes, comorbidities, and A1C with functional disability in older adults: results from the National Health and Nutrition Examination Survey (NHANES), 1999–2006. *Diabetes Care*. 2010; 33:1055–1060. [PubMed: 20185736]
8. von BM, Rantanen T, Laukkanen P, Suutama T, Heikkinen E. Mobility limitations and cognitive deficits as predictors of institutionalization among community-dwelling older people. *Gerontology*. 2006; 52:359–365. [PubMed: 16905887]
9. Hill J, Fillit H, Thomas SK, Chang S. Functional impairment, healthcare costs and the prevalence of institutionalisation in patients with Alzheimer's disease and other dementias. *Pharmacoeconomics*. 2006; 24:265–280. [PubMed: 16519548]
10. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc*. 2004; 52:80–85. [PubMed: 14687319]
11. Saczynski JS, Jonsdottir MK, Garcia ME, et al. Cognitive impairment: an increasingly important complication of type 2 diabetes: the, age, gene/environment susceptibility--Reykjavik study. *American journal of epidemiology*. 2008; 168:1132–1139. [PubMed: 18836152]
12. Nguyen HT, Grzywacz JG, Arcury TA, et al. Linking glycemic control and executive function in rural older adults with diabetes mellitus. *J Am Geriatr Soc*. 2010; 58:1123–1127. [PubMed: 20722846]
13. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. *Diabetes Care*. 2009; 32:221–226. [PubMed: 19171735]
14. De Rekeneire N, Resnick HE, Schwartz AV, et al. Diabetes is associated with subclinical functional limitation in nondisabled older individuals: the Health, Aging, and Body Composition study. *Diabetes Care*. 2003; 26:3257–3263. [PubMed: 14633811]
15. Yaffe K, Falvey C, Hamilton N, et al. Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. *Arch Neurol*. 2012; 69:1170–1175. [PubMed: 22710333]
16. Kanaya AM, Barrett-Connor E, Gildengorin G, Yaffe K. Change in cognitive function by glucose tolerance status in older adults: a 4-year prospective study of the Rancho Bernardo study cohort. *Arch Intern Med*. 2004; 164:1327–1333. [PubMed: 15226167]
17. Christman AL, Matsushita K, Gottesman RF, et al. Glycated haemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia*. 2011; 54:1645–1652. [PubMed: 21360189]
18. Yau CK, Eng C, Cenzer IS, Boscardin WJ, Rice-Trumble K, Lee SJ. Glycosylated hemoglobin and functional decline in community-dwelling nursing home-eligible elderly adults with diabetes mellitus. *J Am Geriatr Soc*. 2012; 60:1215–1221. [PubMed: 22702660]
19. Ryan DH, Espeland MA, Foster GD, et al. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials*. 2003; 24:610–628. [PubMed: 14500058]
20. Wadden TA, West DS, Delahanty L, et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)*. 2006; 14:737–752. [PubMed: 16855180]
21. Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013; 369:145–154. [PubMed: 23796131]
22. Espeland MA, Rapp SR, Bray GA, et al. Long-term impact of behavioral weight loss intervention on cognitive function. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2014; 69:1101–1108.

23. Houston DK, Leng X, Bray GA, et al. Long-term intensive lifestyle intervention and physical function: The Look AHEAD Movement and Memory Study. *Obesity* (Silver Spring). 2015; 23:77–84. [PubMed: 25452229]
24. Reitan RM. The validity of the Trail Making Test as an indicator of organic brain damage. *Percept Motor Skills* [Internet]. 1958; 8:271–276.
25. Stroop JR. Studies of interference in serial verbal reactions. *Exp Psychol* [Internet]. 1935; 18:643–662.
26. Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop Color-Word Test. *Exp Aging Res*. 1993; 19:209–224. [PubMed: 8223823]
27. Wechsler, D. Adult Intelligence Scale-III Manual. New York: Psychological Corporation; 1997. 1981
28. Lesak, MD. Neuropsychological Assessment. New York: Oxford University Press; 1995.
29. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987; 48:314–318. [PubMed: 3611032]
30. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994; 49:M85–M94. [PubMed: 8126356]
31. Simonsick EM, Newman AB, Nevitt MC, et al. Measuring higher level physical function in well-functioning older adults: expanding familiar approaches in the Health ABC study. *J Gerontol A Biol Sci Med Sci*. 2001; 56:M644–M649. [PubMed: 11584038]
32. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA*. 2014; 311:2387–2396. [PubMed: 24866862]
33. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961; 4:561–571. [PubMed: 13688369]
34. Jakicic JM, Jaramillo SA, Balasubramanyam A, et al. Effect of a lifestyle intervention on change in cardiorespiratory fitness in adults with type 2 diabetes: results from the Look AHEAD Study. *Int J Obes (Lond)*. 2009; 33:305–316. [PubMed: 19153582]
35. Standards of medical care in diabetes-2012. *Diabetes Care*. 2012; 35:S11–S63. [PubMed: 22187469]
36. Brown AF, Mangione CM, Saliba D, Sarkisian CA. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc*. 2003; 51:S265–S280. [PubMed: 12694461]
37. Cukierman-Yaffe T. Diabetes, dysglycemia and cognitive dysfunction. *Diabetes/metabolism research and reviews*. 2014; 30:341–345. [PubMed: 24339052]
38. Semba RD, Nicklett EJ, Ferrucci L. Does accumulation of advanced glycation end products contribute to the aging phenotype? *The journals of gerontology Series A, Biological sciences and medical sciences*. 2010; 65:963–975.
39. Valente T, Gella A, Fernandez-Busquets X, Unzeta M, Durany N. Immunohistochemical analysis of human brain suggests pathological synergism of Alzheimer's disease and diabetes mellitus. *Neurobiology of disease*. 2010; 37:67–76. [PubMed: 19778613]
40. Haus JM, Carrithers JA, Trappe SW, Trappe TA. Collagen, cross-linking, and advanced glycation end products in aging human skeletal muscle. *Journal of applied physiology*. 2007; 103:2068–2076. [PubMed: 17901242]
41. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol*. 2011; 10:969–977. [PubMed: 21958949]

Table 1

Descriptive participant characteristics by average HbA1C exposure over 7 years of follow up: The Look AHEAD Memory and Movement Ancillary Study.

Participant Characteristics *	Average HbA1c Exposure (%) [†]			p-value
	<7% (n=500)	7–8% (n=237)	>8% (n=142)	
Age (years)	59.79±6.73	59.00±6.72	55.75± 6.23	<0.01
<60	257 (51)	126 (53)	105 (74)	<.01
60	243 (49)	111 (47)	37 (26)	
Female, n (%)	278 (56)	124 (52)	94 (66)	0.03
Race, n (%)				<0.01
African American/Black	75 (15)	52 (22)	43 (30)	
White	393 (79)	166 (70)	85 (60)	
Other/Mixed	32 (6)	19 (8)	14 (10)	
Education, n (%)				0.52
HS or less	86 (17)	36 (15)	25 (18)	
Post HS	189 (38)	102 (43)	62 (44)	
College/Graduate	225 (45)	99 (42)	55 (39)	
Smoking Status, n (%)				0.06
Never	258 (52)	110 (46)	81 (57)	
Former	225 (45)	117 (49)	51 (36)	
Current	17 (3)	10 (4)	10 (7)	
Alcohol Intake, n (%)				0.19
None	136 (27)	67 (28)	50 (35)	
<1 drink/day	336 (67)	155 (65)	89 (63)	
1 drink/day	28 (6)	15 (6)	3 (2)	
Knee Pain: Yes, n (%)	234 (47)	95 (40)	53 (37)	0.06

Data are presented as mean±SD or n (%).

* All participant characteristics were collected at baseline, unless otherwise indicated.

[†] HbA1c categories of <7%, 7–8%, and >8% correspond to <53 mmol/mol, 53–64 mmol/mol, and >64 mmol/mol, respectively.

Table 2

Descriptive participant characteristics by average HbA1c exposure over 7 years of follow up: The Look AHEAD Memory and Movement Ancillary Study.

Participant Characteristics*	Average HbA1c Exposure (%) [†]			p-value
	<7% (n=500)	7–8% (n=237)	>8% (n=142)	
Diabetes-related comorbidities [‡] , n (%)				
Cardiovascular disease	109 (22)	70 (30)	36 (25)	0.07
Stroke	23 (5)	9 (4)	8 (6)	0.71
Retinopathy	86 (17)	56 (24)	46 (32)	<0.01
Renal disease	59 (12)	52 (22)	23 (16)	<0.01
Neuropathy	184 (37)	98 (41)	65 (46)	0.12
Hypertension	216 (43)	119 (50)	81 (57)	<0.01
Beck Depression Inventory (year 8), n (%)				
<11	460 (92)	207 (87)	115 (81)	<0.01
11	40 (8)	30 (13)	27 (19)	
Cardiorespiratory Fitness (METS)				
Baseline	5.25 (1.60)	5.29 (1.61)	5.27 (1.46)	0.96
Year 1	5.26 (1.63)	5.28 (1.63)	5.29 (1.45)	0.98
Year 4	5.28 (1.62)	5.35 (1.61)	5.27 (1.44)	0.83
Body Mass Index (kg/m ²)				
Baseline	35.38 (5.89)	35.77 (5.49)	36.33 (5.82)	0.21
Year 1	33.02 (6.17)	34.36 (5.91)	35.07 (5.68)	<.01
Year 8	33.43 (5.93)	34.54 (5.98)	35.35 (6.22)	<.01
Diabetes Medication Use [€] , n (%)	416 (83)	222 (93)	135 (95)	<0.01
Statin Medication Use, n (%)	362 (72)	173 (73)	100 (70)	0.86
Ancillary Year 8 Visit (vs. 9), n (%)	484 (97)	233 (98)	139 (98)	0.45
Intensive Lifestyle Intervention Arm, n (%)	269 (54)	116 (49)	66 (46)	0.21
Study Site, n (%)				0.40
Baton Rouge	138 (28)	50 (21)	35 (25)	
Denver	138 (28)	73 (31)	38 (27)	
Memphis	96 (19)	47 (20)	29 (20)	
Pittsburgh	127 (25)	66 (28)	39 (27)	

Data are presented as mean±SD or n (%).

* All participant characteristics were collected at baseline, unless otherwise indicated.

[†] HbA1c categories of <7%, 7–8%, and >8% correspond to <53 mmol/mol, 53–64 mmol/mol, and >64 mmol/mol, respectively.

[‡] Presence of comorbidities include baseline, follow-up prior to ancillary study visit date, and SAE prior to ancillary study visit date.

[€] Diabetes medications include thiazolidinediones, biguanides, insulins, meglitinides, sulfonylureas, alpha-glucans, and dipeptidyl peptidase 4 inhibitors

Table 3

Year 8/9 cognitive and physical function by average HbA1c exposure over 7 years of follow-up: The Look AHEAD Memory and Movement Ancillary Study.

Functional Assessments	Average HbA1c Exposure (%)			<i>p</i> -value
	<7%	7–8%	>8%	
Cognitive Function Tests				
Trail Making Test				
Psychomotor Speed: Part A (range: 0–300 sec)	35.63 (12.55)	36.24 (12.42)	36.43 (11.28)	0.72
Set Shifting: Part B (range: 0–300 sec)	100.17 (55.70)	107.22 (63.12)	97.05 (49.41)	0.17
Modified Stroop Color-Word Test (score; sec + errors)	36.90 (13.45)	39.37 (14.93)	36.55 (13.33)	0.05
Digit Symbol-Coding (score; range 0–133)	41.69 (10.83)	40.92 (10.17)	42.15 (9.85)	0.50
Rey Auditory Verbal Learning Test				
Short Delay Recall (score; range: 0–15)	7.75 (3.01)	7.54 (3.00)	8.05 (2.94)	0.27
Long Delay Recall (score; range 0–15)	7.47 (3.30)	7.11 (3.18)	7.75 (3.20)	0.16
Modified Mini-Mental State Exam (score; range: 0–100)	92.37 (6.25)	91.73 (6.47)	92.99 (5.57)	0.15
Physical Function Tests				
SPPB Summary Score (range 0–12)	10.16 (1.78)	10.30 (1.66)	10.13 (1.74)	0.55
Expanded PPB Summary Score (range: 0–3)	1.68 (0.35)	1.68 (0.34)	1.67 (0.34)	0.98
400-m Gait Speed (m/s)	1.07 (0.17)	1.07 (0.17)	1.05 (0.16)	0.60
20-m Gait Speed (m/s)	1.15 (0.19)	1.15 (0.19)	1.13 (0.18)	0.62
Grip Strength (kg)	30.78 (9.52)	31.90 (9.98)	29.90 (9.19)	0.14
Knee Extensor Strength (lbs)	51.27 (24.93)	53.03 (24.81)	48.11 (24.60)	0.27

Data are presented as mean±SD.

Table 4

Associations between average HbA1c exposure over 7 years of follow-up and performance on cognitive and physical function tests administered at the year 8/9 visit: The Look AHEAD Memory and Movement Ancillary Study.

Standardized Functional Test Outcome Measure (1 Standard Deviation)	Unadjusted (Model 1)		Adjusted (Model 2)		Adjusted + Comorbidities (Model 3)	
	β Estimate* (95% CI)	p-value	β Estimate* (95% CI)	p-value	β Estimate* (95% CI)	p-value
Cognitive Function Tests						
Trail Making Test						
Psychomotor Speed: Part A (12.3 seconds)	0.03 (−0.03,0.10)	0.28	0.05 (−0.01,0.11)	0.12	0.02 (−0.04,0.08)	0.50
Set Shifting: Part B (56.5 seconds)	−0.01 (−0.07,0.06)	0.85	0.00 (−0.06,0.06)	0.91	−0.02 (−0.08,0.04)	0.49
Modified Stroop Color-Word Test Score (13.9)	0.04 (−0.84,0.92)	0.93	0.08 (−0.78,0.94)	0.85	−0.26 (−1.14,0.62)	0.56
Digit Symbol-Coding Score (10.5)	−0.01 (−0.08,0.05)	0.67	−0.05 (−0.11,0.01)	0.09	−0.02 (−0.07,0.04)	0.55
Rey Auditory Verbal Learning Test						
Short Delay Recall Score (3.0)	0.00 (−0.06,0.07)	0.92	−0.03 (−0.09,0.03)	0.34	−0.03 (−0.10,0.03)	0.30
Long Delay Recall Score (3.3)	−0.00 (−0.07,0.06)	0.90	−0.04 (−0.10,0.02)	0.17	−0.05 (−0.11,0.01)	0.11
Modified Mini-Mental State Exam Score (6.2)	0.02 (−0.05,0.08)	0.59	0.02 (−0.04,0.08)	0.41	0.03 (−0.03,0.09)	0.37
Physical Function Tests						
SPPB Summary Score (1.7)	−0.03 (−0.09,0.04)	0.42	−0.07 (−0.13, −0.01)	0.03	−0.03 (−0.09,0.03)	0.32
Expanded PPB Summary Score (0.3)	−0.03 (−0.09,0.03)	0.38	−0.07 (−0.13, −0.02)	0.01	−0.03 (−0.09,0.03)	0.27
400-m Gait Speed (0.2 m/s)	−0.05 (−0.11,0.02)	0.15	−0.07 (−0.12, −0.01)	0.03	−0.03 (−0.09,0.03)	0.39
20-m Gait Speed (0.2 m/s)	−0.05 (−0.11,0.01)	0.13	−0.07 (−0.13, −0.01)	0.02	−0.03 (−0.09,0.03)	0.34
Grip Strength (9.6 kg)	−0.02 (−0.08,0.04)	0.52	−0.03 (−0.08,0.01)	0.13	−0.02 (−0.06,0.03)	0.49
Knee Extensor Strength (24.9 lbs)	−0.00 (−0.08,0.07)	0.93	−0.01 (−0.07,0.04)	0.66	0.01 (−0.05,0.06)	0.82

Adjusted (Model 2) covariates: age, sex, race, education, smoking status, alcohol intake, knee pain, METS (baseline, year 1, year 4), BMI (baseline, year 1, year 8), diabetes medication and statin use (year 8), ancillary year visit, study arm and site. Fully Adjusted (Model 3) covariates: Model 2 + presence of type 2 diabetes-related comorbidities (CVD, stroke, retinopathy, renal disease, neuropathy, hypertension, depression).

* Parameter estimates are expressed per 1 unit (%) increment in average HbA1c.