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RESEARCH ARTICLE

Glucose control and cognitive and physical function in adults 80+ years of age with diabetes

Oleg Zaslavsky[1] | Rod L. Walker[2] | Paul K. Crane[3] | Shelly L. Gray[4] | Eric B. Larson[2,3]

[1] Department of Biobehavioral Nursing and Health Informatics, University of Washington, Seattle, USA

[2] Kaiser Permanente Washington Health Research Institute, Seattle, USA

[3] Department of Medicine, University of Washington, Seattle, USA

[4] School of Pharmacy, University of Washington, Seattle, USA

Correspondence
Oleg Zaslavsky, Assistant Professor, Biobehavioral Nursing and Health Informatics Department, School of Nursing, University of Washington, Health Sciences Building, Box 357266, Seattle, WA, USA.
Email: ozasl@uw.edu

Abstract

Introduction: We modeled associations between glycated hemoglobin (HbA1c) levels (<7%, 7% to 8%, and >8%) and cognitive and physical function among adults 80+ years of age with diabetes and determined whether associations differ by frailty, multimorbidity, and disability.

Methods: A total of 316, adults with diabetes, 80+ years of age, were from the Adult Changes in Thought Study. **The** Cognitive Abilities Screening Instrument Item Response Theory (CASI-IRT) measured cognition. Short performance-based physical function (sPPF) and gait speed measured physical function. Glycosylated hemoglobin (HbA1c) levels were from clinical measurements. Analyses estimated associations between average HbA1c levels (<7%, 7% to 8%, and >8%) and functional outcomes using linear regressions estimated with generalized estimating equations.

Results: sPPF scores did not differ significantly by HbA1c levels. Gait speed did, but only for non-frail individuals; those with HbA1c >8% were slower (-0.10 m/s [95% CI, −0.16 to −0.04]) compared to those with HbA1c 7% to 8%. The association between HbA1c and CASI-IRT varied with age (interaction $P = 0.04$). At age 80, for example, relative to people with HbA1c levels of 7% to 8%, CASI-IRT scores were, on average, 0.18 points lower (95% CI, −0.35 to −0.02) for people with HbA1c <7% and 0.22 points lower (95% CI, −0.40 to −0.05) for people with HbA1c >8%. At older ages, these estimated differences were attenuated. Estimated associations were not modified by multimorbidity or disability.

Discussion: Moderate HbA1c levels of 7% to 8% were associated with better cognition in early but not late octogenarians with diabetes. Furthermore, HbA1c >8% was associated with slower gait speed among those without frailty. These results add to an evidence base for determining glucose targets for very old adults with diabetes.

KEYWORDS
cognitive abilities screening instrument, generalized estimating equations, longitudinal, octogenarian, performance-based physical function

1 | INTRODUCTION

Among U.S. adults 65 years of age and older, 9.9 million (20.8%) had diabetes in 2015,[1] and the number of people with diabetes is projected to increase 4.5-fold over the next 35 years.[2] Older adults with diabetes, in particular those who are 80 years of age and older, have the highest rate of diabetes complications.[3] Older people with diabetes also have double the rate of health care utilization compared to younger people with diabetes due to adverse treatment events.[4] Both the risk of diabetes complications and the risk of complications of therapy should be considered when setting therapeutic goals. However, the most appropriate glycemic targets for people 80 and older are ill defined.[5]

Several organizations, including the American Diabetes Association,[6] the US Department of Veterans Affairs,[7] and the American College of Physicians (ACP[8]), published recommendations for glycosylated hemoglobin (HbA1c) targets according to patient age and medical features. For example, most recently the ACP promulgated a recommendation of 7% to 8% HbA1c levels for most patients, but also stipulated that people older than 80 years of age might merit transitioning from specific HbA1c targets to symptom management.[8] Because of the ensued public debate[9-11] and because of the importance of enhancing research on optimal glucose targets in older adults by including person-valued outcomes,[12] additional evidence is needed. Historically, clinical trials that built evidence for glucose control focused on either intermediate end points such as albuminuria, worsening creatinine, or vascular outcomes. Although these end points are important for clinicians, cognitive and physical summative outcomes may be particularly salient for patients at advanced age because these functional outcomes reflect the capacity of older adults for independence. As such, we leveraged a well-characterized prospective cohort of the Adult Changes in Thought (ACT) study, to examine the relationship between HbA1c levels and cognitive and physical function in adults 80+ years of age with diabetes.

Our objectives were to determine associations between HbA1c levels (categories of <7%, 7% to 8% and >8%, in accordance with the ACP guidelines) and cognitive and physical function among people 80 and older with diabetes. We also sought to examine whether relationships between HbA1c and outcomes in this population differ across pre-specified groups defined by frailty, multimorbidity, and disability.

RESEARCH IN CONTEXT

1. Systematic review: Appropriate glycemic targets with respect to cognitive and physical functional outcomes for people age 80 and older are ill defined.
2. Interpretation: In this community-based sample of people 80+ with diabetes, we found that people with HbA1c levels of 7%-8% had higher cognitive scores, on average, then those with HbA1c levels <7% or >8%; however, the association was attenuated in older ages such that differences in cognition by HbA1c levels were not present among people in their late 80s and early 90s. We also found that HbA1c levels of >8% were associated with slower gait speed among those without frailty throughout all ages.
3. Future directions: The results of this observational study should not be assumed to be causal and instead should be viewed as contributing to an evidence base to inform larger future observational studies or clinical trials of glucose targets in the very old.

at least 65 years of age and without dementia, and then follows them with biennial study visits. At those visits, participants are screened for dementia using the Cognitive Abilities Screening Instrument (CASI), and those scoring 86 or lower receive an in-depth diagnostic workup including a clinical and cognitive evaluation, which is reviewed by a multidisciplinary committee that assigns dementia diagnoses according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.[13] Study staff also collect information on the health characteristics of numerous participants including measures of behavior and function at each biennial visit. In addition, because ACT participants are members of KPW, information on health care utilization, including prescription fills, clinic encounters, and diagnoses, is available on participants from their electronic health records, as are laboratory measures taken as part of their clinical care. Study procedures were approved by institutional review boards of KPW and the University of Washington, and participants provided written informed consent.

2 | METHODS

2.1 | Setting

This analysis used data from ACT, a prospective cohort study, to understand risk factors for development of incident dementia among older adults. ACT enrollment and follow-up began in 1994 to 1996 with an original cohort and has been ongoing, with new participants periodically added as part of expansion and replacement cohorts to replenish active participant numbers. The ACT study randomly samples and enrolls members from Kaiser Permanente Washington (KPW), an integrated health care delivery system in the state of Washington, who are

2.2 | Participants

Our analyses were limited to ACT participants 80 years or older who had ever been treated for diabetes. Specifically, we identified the first ACT visit at which a participant was at least 80 years of age, had a valid CASI score and did not have dementia, had been enrolled in KPW for at least the previous 2 years (to have potential to capture HbA1c measures), and had previously had at least two fills of insulin or a hypoglycemic medication within a year (Table S1 in the Supplement). We then included that visit (hereafter referred to as "baseline") and the participant's future biennial follow-up visits (up to September 30, 2016, the end of our study period) as part of our analytic sample. Per

ACT protocol, participants end biennial follow-up once they have a visit resulting in a dementia diagnosis (or die/disenroll).

2.3 | Exposure and outcome measures

A participant's average HbA1c level (measured from electronic laboratory data) in the 2 years preceding each ACT study visit served as the time-varying exposure measure of interest. Primary outcomes, measured at the time of each study visit, included the CASI Item Response Theory (CASI-IRT) score and a short version of the Performance-based Physical Function (sPPF) test. A CASI score is based on a combination of items measuring features such as short and long-term memory, mental concentration, orientation, and language ability. The CASI score ranges from 0 to 100, with a lower score indicating worse cognitive function.[14] CASI-IRT is a complementary metric derived from the individual CASI items using IRT techniques that address shortcomings of the CASI by providing a score with linear scaling properties (a feature potentially lacked by the overall CASI score[15]). Thus, CASI-IRT scores are particularly well-suited for analyses of change over time across a wide range of cognitive abilities. CASI-IRT scores are defined such that the mean score is 0 and standard deviation is 1 among all individuals in ACT without dementia; mean scores and standard deviations (SDs) may be different from (0,1) in this 80+ sub-sample. CASI-IRT scores have been used in analyses of cognitive change in other ACT projects.[16-18] The sPPF score is based on a participant's objectively measured gait speed, grip strength, and time taken to complete five successful chair stands. Each of the three individual components is scored from 0 through 4, with lower values indicating worse physical function, and summed to generate the sPPF. This is the same as the original PPF construct except that the subscore from a standing balance test has been removed because it was frequently not administered in our sample; thus, scores range from 0 to 12 rather than from 0 to 16.[19] A secondary outcome of interest was gait speed alone (limited to those participants able to perform the gait test).

2.4 | Other measures

Other covariate information assessed from the ACT study visits included age, study cohort, sex, self-reported race/ethnicity (non-Hispanic white vs other), education (at least some college vs high school or less), body mass index (BMI), and self-reported comorbidity histories of coronary artery disease (myocardial infarction, coronary artery bypass grafting, angina, or coronary angioplasty) and cerebrovascular disease (stroke, transient ischemic attack, or carotid endarterectomy). A Charlson Comorbidity Score was also computed at each visit based on diagnoses found in the electronic health record in the year preceding each study visit.[20] ACT study questionnaires collected participants' current reported exercise behaviors at each visit and the number of difficulties they reported with activities of daily living (ADLs). At each visit, participants were also classified as frail if they had 3 or more points (out of 5) measured on a scale that included features of physical

activity, exhaustion, weight loss, weakness, and slowness. The criteria used to define frailty approximated the simplified Women's Health Initiative (sWHI) (Table S2) frailty phenotype. The sWHI was previously validated and compared to Fried phenotype.[22] Emergency department encounters due to hypoglycemia in the two years following the study baseline were summarized using a validated algorithm.[23]

2.5 | Missing data

To account for any missing data in predictors and outcomes in our analytic sample, we performed multiple imputations by chained equations to generate 10 imputed data sets with complete information for each of the planned analyses prior to estimation of our analytic (outcome) models.[24] In addition to including exposure, adjustment, outcome, and select interaction variables in the imputation equations, we also incorporated information on many auxiliary variables to help improve the imputation process (eg, random non-HbA1c glucose measures, difficulties with instrumental ADLs, self-rated health, smoking status, and co-morbidities such as depression, hypertension, and congestive heart failure). Analytic models (described in Analyses below) were then fit on each of the imputed data sets, and final parameter and variance estimates were used for inference were based on combining model estimates per Rubin's rules.[25] Information regarding the extent of missing data across observations is provided in Table S3.

2.6 | Analyses

We estimated the association between average HbA1c levels (<7%, 7% to 8%, and >8%) and each of the primary outcomes (CASI-IRT, sPPF), as well as the secondary outcome (gait speed), using separate linear regression models in which the unit of observation was an ACT person-visit. People could contribute analysis time across multiple measurement occasions. To account for the within-person correlation arising from repeated measures across time, we estimated model parameters using generalized estimating equations with an exchangeable working correlation matrix and computed standard errors using the Huber-White sandwich estimator.[26] Age at each ACT visit was the time-scale used to model the association between HbA1c levels and the primary and secondary outcomes. For each outcome, we first fit a model with main effects for average HbA1c level (categorized as <7%, 7% to 8%, and >8%) and age (continuous, measured as years beyond 80), and product terms representing the interaction between the two. Primary adjustment variables in this model included ACT study cohort, baseline age, sex, race/ethnicity, and education. We then performed a joint test of the interaction (HbA1c X age) parameters to assess whether evidence supported that differences in the outcomes by the HbA1c exposure categories varied over time. If the estimated omnibus P-value from this joint test was > 0.05, we re-estimated the model dropping the interaction terms; otherwise, we left the model unchanged. We then presented this final model with varying levels of adjustment to show the impact of additional potential confounder control (one model

additionally adjusted for BMI and exercise, and another additionally adjusted for history of cerebrovascular disease and coronary artery disease). All but the demographic variables (such as age at baseline, study cohort, sex, and race/ethnicity) were time-varying. As a sensitivity analysis, we also repeated the above primary analyses, excluding any follow-up visits at which a participant was determined to have dementia.

Secondary analyses evaluated whether associations between average HbA1c levels and the outcomes of interest that were estimated in the above primary analyses differed across pre-specified groups defined by features of interest: frailty status, disability (as measured by difficulty with three or more ADLs), and multimorbidity (as measured by a Charlson Comorbidity Score of 3+). For each of these analyses, we re-estimated the primary models including main effects for the feature of interest and interaction terms between that main effect and the model terms corresponding to the groups defined by HbA1c levels. As before, a joint test of interaction parameters (in this case, the HbA1c X feature terms) at the 0.05 level dictated whether the interaction terms were retained in final models. All data analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata 15.0 (StataCorp LLC, College Station, TX, USA).

3 | RESULTS

A total of 316 ACT participants 80+ years of age who had ever been treated for diabetes and who met other study inclusion criteria were included in analyses. Of these, 62 (20%) contributed a single visit, 72 (23%) contributed two visits, 79 (25%) contributed three visits, and 103 (33%) contributed four or more visits to analyses; the total number of visits across all these participants was 940. Across all of the follow-up, 83 participants experienced the ACT study end point of a dementia diagnosis. Of the 233 who did not, 126 died and 39 withdrew or did not return during follow-up. More than 4000 HbA1c measures were available across time to inform the primary exposures of interest; average HbA1c levels in the 2 years prior to each ACT visit were, on average, based on four measures (median 4, interquartile range IQR 3 to 6) per person per visit. The relative proportion of people in each of the HbA1c categories (<7%, 7% to 8%, >8%) at each visit tended to remain stable across follow-up.

Participant characteristics at the time of their first eligible study visit are shown in Table 1, stratified according to their average HbA1c levels in the 2 years preceding the visit. Although the age distribution was similar across groups, higher proportions of people with HbA1c levels of 7% to 8% were female, non-Hispanic white, and had higher educational attainment than those with higher and lower HbA1c levels. They also had lower prevalence of coronary artery disease and overall comorbidity (as measured by Charlson). Frailty prevalence was highest among people with HbA1c levels >8%. Outcomes of interest at this first visit are also shown in Table 1. Specifically, CASI, CASI-IRT, and sPPF scores were slightly higher in the HbA1c 7% to 8% group compared to other HbA1c groups at this first visit. More than 90% of people in each group were able to complete the gait test.

The estimated association between HbA1c levels and CASI-IRT is presented in Table 2 and Figure 1. Because we found evidence that this association varied with age (interaction P = .04), we provide model estimates of mean CASI-IRT scores by HbA1c level across a range of ages. In both Table 2 and Figure 1, we present point estimates (and 95% CIs) that represent the estimated difference in CASI-IRT scores at select ages between people with average HbA1c levels <7% and >8% relative to those with levels of 7% to 8%, holding other primary adjustment variables constant. At the youngest ages in our sample, higher (>8%) and lower (<7%) HbA1c levels tended to be associated with the lowest cognitive scores. At age 80, for example, relative to people with HbA1c levels of 7% to 8%, CASI-IRT scores were estimated to be, on average, 0.18 points lower (95% CI, −0.35 to −0.02] for people with HbA1c <7% and 0.22 points lower (95% CI, −0.40 to −0.05) for people with HbA1c >8%. At older ages, however, these estimated differences in cognitive scores between HbA1c groups were attenuated. For example, at age 88, these estimated differences were 0.06 (95% CI, −0.07 to 0.20) for people with HbA1c <7% and −0.02 (95% CI, −0.17 to 0.13) for people with HbA1c >8%. We did not detect modification of the estimated HbA1c-CASI-IRT association in subgroup analyses conducted based on frailty, disability, and multimorbidity (interaction P-values = 0.852, 0.180, and 0.718, respectively).

Estimated associations between HbA1c levels and the outcomes of sPPF and gait speed based on all included study visits are presented in Table 3. We did not detect evidence that the associations differed by age (HbA1c-by-age interaction P-values = .70 and .31 for the two outcomes, respectively); therefore, point estimates (and 95% CIs) in this table represent the estimated differences in sPPF scores and gait speed between people with average HbA1c levels <7% and >8% relative to those with levels of 7% to 8%, holding age and other primary adjustment variables constant. sPPF scores did not differ significantly between HbA1c groups but gait speeds did. Among participants who could perform the gait test, those with HbA1c levels >8% were 0.05 m/s slower, on average, relative to those with HbA1c levels of 7% to 8% (−0.05| 95% CI, −0.10 to −0.01]). No difference in gait speed was observed between the <7% and 7% to 8% groups (0.00; 95% CI, −0.04 to 0.04]). Our subgroup analysis of the HbA1c-gait speed association by frailty status (interaction P = 0.02) suggested that the estimated association of slower gait speeds in people with HbA1c levels >8% (compared to 7% to 8%) appeared limited to non-frail individuals. In non-frail people, that difference was −0.10 m/s (95% CI, −0.16 to −0.04); whereas, among frail people, there was no such difference (0.01, 95% CI, −0.05 to 0.06). Other subgroup analyses (by disability and multimorbidity) did not find significant differences in the estimated HbA1c-sPPF or HbA1c-gait speed associations by subgroup (all interaction P-values > 0.05).

Sensitivity analyses in which we included additional model adjustment for factors such as BMI, exercise, and cerebrovascular and cardiovascular disease did not substantively change results for our primary and secondary outcome models (Table S4). Sensitivity analyses that repeated model estimation after excluding any follow-up study visits at which a participant was determined to have dementia also

TABLE 1 Characteristics and outcome measures among 316 participants at time of first eligible study visit, stratified by average HbA1c levels in the prior 2 years

	Average HbA1c level[a]		
	<7%	7% to 8%	>8%
Characteristics	%	%	%
Row percent	39	41	20
Age, mean (SD)	83 (3)	83 (3)	83 (3)
ACT cohort			
Original	53	61	52
Expansion	24	18	36
Replacement	23	21	12
Female	55	66	55
Non-Hispanic White	79	85	80
At least some college	64	67	52
Regular exercise	59	53	56
Body mass index, mean (SD)	28 (5)	29 (5)	29 (5)
Coronary artery disease	36	30	47
Cerebrovascular disease	25	21	19
Frail	50	51	57
Charlson score of 3+	43	39	47
Difficulty with 3+ ADLs	11	12	6
CASI, mean (SD)	91.0 (6.9)	93.3 (4.8)	91.3 (4.3)
CASI-IRT, mean (SD)	0.0 (0.7)	0.2 (0.7)	-0.1 (0.6)
Short PPF, mean (SD)	6.2 (3.1)	6.4 (2.9)	6.0 (2.8)
% able to perform gait test	93	98	98
Gait speed in m/s among those able, mean (SD)	0.75 (0.26)	0.72 (0.23)	0.70 (0.25)

Note: ACT, Adult Changes in Thought; ADL, activities of daily living; CASI, Cognitive Abilities Screening Instrument; IRT, Item Response Theory; PPF, Performance-based Physical Function
[a]Unless otherwise specified, values shown are column %.

TABLE 2 Estimated differences in Cognitive Abilities Screening Instrument Item Response Theory (CASI-IRT) scores by age and HbA1c levels[a]

Average HbA1c level	Differences in CASI-IRT (95% CI) at:			
	Age 80	Age 84	Age 88	Age 92
<7%	**−0.18 (-0.35, -0.02)**[b]	-0.06 (−0.17, 0.05)	0.06 (−0.07, 0.20)	0.19 (−0.03, 0.40)
7%-8%	Reference	Reference	Reference	Reference
>8%	**−0.22 (-0.40, −0.05)**[b]	**−0.12 (−0.24, -0.01)**[†]	−0.02 (−0.17, 0.13)	0.08 (−0.16, 0.32)

[a]Estimates are based on models using age at each study visit as the time-scale and adjusting for ACT study cohort, baseline age, sex, self-reported race/ethnicity, and education. We found evidence that associations differed by age; therefore the table provides the estimated differences in scores between groups at select ages.
[b]**Bold values** indicate $P < 0.05$.

yielded results that were comparable to those of the primary analyses (Table S5).

4 | DISCUSSION

In this population-based sample of people over 80 or older with diabetes, we found that among people in their early 80s, those with

HbA1c levels of 7% to 8% had higher cognitive scores, on average, than those with HbA1c levels <7% or >8%. Cognitive functioning at age 80 among those with HbA1c levels of 7% to 8% was estimated to be approximately 0.2 points higher on the CASI-IRT scale than those with HbA1c <7% and people with HbA1c >8%. To put the magnitude of this difference into context, 0.2 points roughly amounts to the difference in cognitive scores associated with a 2- to 3-year difference in age in this population. This association of moderate levels of glucose control
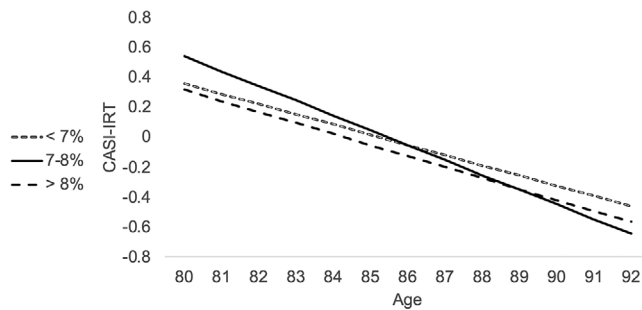
FIGURE 1 Estimated average Cognitive Abilities Screening Instrument Item Response Theory (CASI-IRT) scores by age and glycosylated hemoglobin (HbA1c) levels[a]. [a]Estimates are based on models using age at each study visit as the time-scale and adjusting for ACT study cohort, baseline age, sex, self-reported race/ethnicity, and education. We found evidence that associations differed by age; therefore, the graph presents estimates of mean CASI-IRT scores by average HbA1c level (<7%; 7% to 8%; >8%) across a range of ages

(ie, HbA1c 7% to 8%) with better cognition at the younger ages in our sample persisted when controlling for potential confounders that included demographics, anthropometrics, physical activity, and vascular disease; however, the association was attenuated in older ages such that differences in cognition by HbA1c levels were not present among people in their late 80s and early 90s. These findings also persisted in sensitivity analyses that accounted for change in cognition due to transitioning to dementia, thereby extending previous results on glucose control and brain health[27] to non-dementia outcomes.

We also found that elevated HbA1c levels of >8% were associated with worse functioning in terms of slower gait speed and that this association did not vary with age. We did not find an association, however, between HbA1c levels and a *composite* functional measure that includes both upper and lower extremity components. Additional analyses that examined modification by frailty showed evidence that HbA1c >8% was associated with lower extremity function among people without frailty rather than those with frailty; people who were not frail with HbA1c >8% had about 0.10 m/s slower gait speed on average than people who were not frail with HbA1c 7% to 8%. The 0.10 m/s difference is close to the minimal clinically important difference for change in gait speed in adult clinical populations.[28]

Previous prospective studies of glycemic control in people age 65 and older with diabetes with respect to cognitive and physical func-

tional outcomes showed mixed results. One study found that glycemic control of HbA1c >7% was associated with worse cognitive decline among Health ABC study participants,[29] whereas another report from community-dwelling nursing home eligible individuals showed that these HbA1c levels were associated with decreased risks of functional decline.[30] These studies were limited, however, by protocol to sparsely obtained HbA1c measures that may have obscured important dynamics in glucose observed in clinical care. Our approach that utilized thousands of clinically collected HbA1c measures preceding functional assessments provided unique insights into relationships between glucose and function in very old age.

Tighter glucose control may contribute to impaired cognition through more frequent episodes of hypoglycemia.[4] Higher glucose levels, on the other hand, may contribute to impaired cognition through several potential mechanisms including overall and spatially specific brain abnormalities. Magnetic resonance imaging (MRI) data of participants from the ACCORD MIND study demonstrated preservation of brain volume and certain cortical areas in intensely treated study participants.[31,32] Although in the ACCORD study these structural brain changes did not extend into improved cognition, very old people with diabetes might have lower cognitive reserves that, in turn, might render them less resilient to neuropathological changes. This assertion, however, warrants further research. Similarly, higher glucose levels might lead to poorer lower extremity muscle strength due to effects on peripheral nerve function.[33] In the Baltimore Longitudinal Study, the association of hyperglycemia and muscle strength was at least in part mediated by peripheral neuropathy.[34]

We acknowledge some limitations. Given the study's preponderance of white participants, any results may not be broadly generalizable. We relied on imputation models to address missing data in predictors and outcomes across person-visits. In addition, although our glycemia exposure was based on multiple clinical laboratory measurements of HbA1c, these varied in number and timing across participants due to measurements being obtained at irregular intervals depending on patients' patterns of clinical encounters. Glycated hemoglobin measures also may be inaccurate when measured during anemic states. Finally, it is possible that change in function might lead to diabetes management being altered in important ways. For example, decreased functional capacity and its accompanying reduction in ability to self-manage care might lead to increased risk of low glucose levels. Conversely, fear of the potential for hypoglycemia in such individuals might

TABLE 3 Estimated differences in short Performance-based Physical Function (sPPF) scores and gait speed by HbA1c levels[a]

Average HbA1c level	Differences in sPPF (95% CI) All participants	Differences in gait speed in m/s (95% CI) All participants	Non-frail participants	Frail participants
<7%	0.05 (−0.36, 0.46)	0.00 (−0.04, 0.04)	0.01 (−0.05, 0.06)	−0.01 (−0.06, 0.04)
7% to 8%	Reference	Reference	Reference	Reference
>8%	−0.40 (−0.91, 0.11)	**−0.05 (−0.10, −0.01)**[†]	**−0.10 (−0.16, −0.04)**[b]	0.01 (−0.05, 0.06)

[a]Estimates are based on models using age at each study visit as the time-scale and adjusting for ACT study cohort, baseline age, sex, self-reported race/ethnicity, and education. We did not detect evidence that the associations differed by age; therefore, presented estimates represent differences in sPPF scores and gait speed between HbA1c groups, holding age and other primary adjustment variables constant.
[b]**Bold values** indicate $P < 0.05$.

lead to looser or more permissive glucose control and thus more hyperglycemia. As such, the results of this observational study should not be assumed to be causal and instead should be viewed as contributing to an evidence base that could help inform potential larger future studies or clinical trials of glucose targets in the very old.

The strengths of this study include the prospective population-based design, the access to extensive clinical laboratory data, and the use of psychometrically robust functional measures. The results are clinically meaningful as they provide observational data to support the ACP recommendations of moderate diabetes management in people 80+ years of age.[8] Furthermore, our results suggest potential associations between HbA1c levels of 7% to 8% and better cognitive and physical function, especially for younger octogenarians. We also highlight the importance of patient-valued outcomes such as cognitive and physical function in diabetes research, especially in the very old.

CONFLICT OF INTEREST

There are no potential conflicts of interest relevant to this article.

AUTHOR CONTRIBUTIONS

Oleg Zaslavsky and Rod L. Walker designed the study, wrote the analyses plan, and interpreted the results. Rod L. Walker performed analyses with feedback from Oleg Zaslavsky, Paul K. Crane, Shelly L. Gray, and Eric B. Larson. Oleg Zaslavsky and Rod L. Walker wrote the first draft of the manuscript with critical feedback and revisions from Paul K. Crane, Shelly L. Gray, and Eric B. Larson. Oleg Zaslavsky, Rod L. Walker, Paul K. Crane, Shelly L. Gray, and Eric B. Larson gave final approval of the version to be published. Oleg Zaslavsky is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.