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Association between baseline glycemic markers (HbA1c) and 8-year trajectories of functional disability

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Abstract

Background: This study assessed whether baseline 1) HbA1c (low [$<5.7\%$], intermediate [$5.7\%-6.4\%$] and high [$\geq 6.5\%$]), and 2) glycemic control (7% HbA1c cutoff) in participants with self-reported diabetes were associated with differential 8-year functional disability trajectories.

Methods: We used data from the 2006-2014 waves of the Health and Retirement Study (HRS) for adults 50 years and older. Latent class mixture modeling was used to identify distinct functional disability trajectory classes. Multinomial logistic regression analysis examined the association between the newly constructed trajectories and baseline HbA1c levels, and glycemic control respectively.

Results: All participants ($n=5966$) were classified into four functional disability trajectory classes (no disability, low disability, low-increasing, and high-increasing). Participants with elevated HbA1c were at greater risk of being classified into the high-increasing (RRR=1.63, 95% CI=1.25-2.11) trajectory class. Results showed significant effect modification by age and race. Three functional disability trajectories (no disability, low-increasing, and high-increasing) were identified for participants with self-reported diabetes ($n=1119$). There was no significant association between glycemic control in adults with self-reported diabetes and functional disability trajectory classes.

Conclusions: Participants with intermediate HbA1c and elevated HbA1c were more likely to be classified into the trajectories with progressing disability over the study period. More research is needed to better understand the association between glycemic markers and functional disability trajectories. Such research may provide insights into improvements for clinical care, self-management, and public health interventions for both conditions.

Key words: functional disability, prediabetes, diabetes, HbA1c, glycemic markers, trajectories

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Introduction

According to the Centers for Disease Control (CDC), over 25% of older adults in the U.S. have diabetes, and 48.3% have prediabetes (1). Further, glycemic markers such as glycosylated hemoglobin (HbA1c) and fasting plasma glucose have indicated that approximately one-third of older adults in the U.S. have undiagnosed diabetes (2).

Diabetes can lead to micro and macro vascular complications, which are known predictors of disability (3,4). Adults with a combination of diabetes and functional disability are at an increased risk of depression, comorbid chronic conditions, poorer quality of life, cognitive declines, and mortality (5,6). The association between diabetes and functional disability is well documented in the literature (3–5,7–11), however, knowledge gaps still exist partially because of variations in the ascertainment of diabetes and limited use of longitudinal measures of disability in previous research. Previous studies have mostly used self-reported diabetes measures (3,4,11). Self-reported diabetes may underestimate the true prevalence of the disease (8) as undiagnosed diabetes cannot be taken into account. Further, self-reports may incorrectly categorize prediabetes or exclude it entirely. This is problematic as research indicates that impaired glucose tolerance, and intermediate HbA1c levels are associated with an increased risk of disability even before progression to diabetes (9,12). The use of glycemic markers can decrease these concerns and provide a more accurate estimation of diabetes risk, prevalence and management in comparison to self-reports.

Evidence for the association between diabetes management using glycemic markers and functional disability have been inconsistent. Some studies have reported that poor glycemic control is associated with decreased functional ability, others have indicated a significant

association between tight (lower) glycemic control and functional disability, and one study reported that there was no significant association observed (6,13–15).

HbA1c is considered a gold standard to assess glycemic control and is often used to assess diabetes status (16), however, the breadth of information on the association between HbA1c and trajectories of functional disability is limited. While few studies have examined HbA1c and its association with functional disability, these studies examined cross-sectional data, or assessed functional decline over a brief (2 years) period of time (2,10). Examining trajectories of functional disability over many years is of great importance, as the evolution of functional status in later life may differentially vary due to intraperson factors (17). Sociodemographic factors, health status, and lifestyle behaviors may contribute to heterogeneity in the development and progression of functional disability over time (17,18). In addition, cross-sectional measures of functional disability may result in misclassification of individuals who may require assistance at the time of measurement due to short-term illness, hospitalization, or injury (18). Repeated measures examining functional disability, taking into account change over time, would allow for a better understanding how HbA1c levels and glycemic control impact inter- and intra-individual variability of disability over time.

To our knowledge, there have not been any studies assessing whether the recommended HbA1c cut points for diagnosing prediabetes and diabetes, and poor glycemic control can predict class membership in functional disability trajectories. Accurate estimation of the differential effects of HbA1c on functional disability trajectories, and how these trajectories may differ between diabetic individuals with tight and poor glycemic control is pivotal to gauge the health needs of the US ageing population. Research into whether baseline HbA1c can predict longitudinal trajectories of functional disability may provide insights into appropriate clinical

practice, and public health interventions to inform optimal self and clinical management of older adults with these conditions.

The current study aimed to address these gaps in knowledge by examining the association between HbA1c and functional disability trajectories in older adults 50 years and older. The specific objectives of this study were to 1) identify distinct trajectory classes of functional disability over an 8-year period, as measured by activities of daily living (ADLs); 2) examine whether baseline HbA1c predicts class membership in functional disability trajectories, and 3) determine if glycemic control (tight vs poor, 7% HbA1c cutoff) in adults with a self-report of doctor diagnosed diabetes is associated with differential functional disability trajectories.

Methodology

Data Source: We used data from the 2006-2014 waves of the Health and Retirement Study (HRS). The HRS is a longitudinal cohort study of health and retirement among American adults 50 years and older, which collects data on health conditions, demographics, socioeconomic factors, and behavioral indicators biennially. Additional information on sampling procedures and study design for the HRS is available elsewhere (19).

The total HRS sample size in 2006 was 18,469. Response rates above 88.6% were reported in the 2006 and subsequent study waves (19). Relative to participants who remained in the study, those lost to follow-up were more likely to be in poorer health, less educated, and employed (20). The variables used for the current study were cleaned and processed to allow for comparability across waves by the RAND Center for the Study of Aging (21). Approximately 50% of the 2006 study sample was randomly selected for HRS Enhanced Face-to-Face Interview (EFTF) interviews. During these interviews' biomarker data including blood glycosylated

hemoglobin via dried blood spot were collected. Participants who conducted the interview by proxy or over the telephone and those who were institutionalized were excluded from the biomarker component of the study. Eighty-four percent of participants consented to the blood test and the HRS reported an overall completion rate of 81% (22).

The HRS was approved by the Institutional Review Board at the University of Michigan and all participants provided informed consent. HRS data are de-identified and publicly available, therefore review and approval was not required from the Internal Review Board at the University of Texas Medical Branch.

Inclusion and exclusion criteria: The inclusion criteria for the current study required participants to have provided a biological sample in 2006 (n= 6,735) during the EFTF interview and have two or more ADL measure including one at baseline (n=6,305). To reduce mortality or attrition bias, participants who dropped out entirely, or returned at a later wave, and those who died during the study period were included if they had two or more ADL measures. To allow for accurate longitudinal assessment of trajectories, we excluded 339 participants with only one ADL measure. Excluded participants were older, less educated, more likely to report ADL limitations at baseline, and had higher prevalence of intermediate and elevated HbA1c. Approximately 87% (n=294) were deceased by 2014. The final study sample had 5,966 participants. Of these, 1,119 participants self-reported a diabetes diagnosis.

Variables of interest: The predictor variable of interest was HbA1c, a measure of blood glucose concentration over the past 2-3 months. HbA1c is used to diagnose diabetes and assess disease management. As recommended by the HRS (22), we used the NHANES equivalent HbA1c value. HbA1c was classified into 3 categories reflecting the thresholds for a diabetes diagnoses i.e. no diabetes, prediabetes, and diabetes respectively: low (<5.7%), intermediate

(5.7%-6.4%) and elevated ($\geq 6.5\%$). The American Diabetes Association recommends HbA1c target of $< 7\%$ (23), among adults with type 2 diabetes. We therefore defined poor glycemic control in those with self-reported diabetes as HbA1c levels at or above 7%, and tight glycemic control as HbA1c below 7%. Self-reported diabetes was ascertained by a confirmatory response to the question “Has a doctor ever told you that you have diabetes or high blood sugar?”

The outcome of interest was trajectories of functional disability from 2006 to 2014. Functional disability was defined using a modified version of the Katz ADL scale. The Katz ADL index (24) provided by Rand HRS includes five tasks 1) getting out of bed, 2) bathing, 3) dressing, 4) eating, and 5) toileting which give a 0–5 range of ADL limitations (21). This scale has been validated and widely used in studies of community-dwelling older adults (24).

Additional baseline covariates chosen for their association with measures of diabetes and ADL limitations were: race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White, other), age (< 65 , 65-57, > 75 years), educational attainment (< 12 years, 12 years, 13-15 years, ≥ 16 years), and marital status (married, not married), chronic conditions (none, 1, ≥ 2 of self-reported physician diagnosed hypertension, heart disease, lung disease, and cancer), duration with diabetes (for self-reported diabetes sample only), hospitalization in past 12 months (yes, no), health insurance coverage (no insurance plan, ≥ 1), alcohol use (days per week), depressive symptoms (≥ 4 cut off), cognitive functioning (≤ 11 cut off), body mass index (BMI), and exercise.

Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D) 8-item scale (25). Cognitive function was assessed using a modified version of the Telephone Interview for Cognitive Status (TICS), which includes 4 tasks (i) immediate (ii) and delayed verbal recall, (iii) serial 7s subtraction, and (iv) counting backwards

with scores ranging from 0-27 (26). BMI was treated as an ordinal variable with 4 categories: underweight/normal ($<24.9 \text{ Kg/m}^2$), overweight ($25.0\text{-}29.9 \text{ Kg/m}^2$), obese ($>30.0\text{-}34.9 \text{ Kg/m}^2$) and morbidly obese ($>35 \text{ Kg/m}^2$). Under and normal weight were combined as only 1.2% of participants had a BMI below 18.5 Kg/m^2 . In addition participants with missing BMI were treated as an unknown group and included in the analysis to reduce concerns of nonresponse bias (5). Exercise was defined as engaging in moderate or vigorous exercise two or more times a week.

Statistical Analysis: Sample characteristics were summarized using frequencies and means. Bivariate analysis between categories of HbA1c and functional disability trajectories were conducted. A two-step analytic approach was used, first, to identify trajectories, then to assess their association with baseline HbA1c. Separate trajectories were developed for 1) the entire study population and 2) only participants with self-reported diabetes at baseline ($n=1,119$). Distinct trajectories of functional disability were developed using latent class mixture models. Trajectories were modeled with their own linear functional form and direction simultaneously. Through latent class modeling, we were able to (a) estimate the number and size of the trajectories, and (b) assign probability of latent trajectory membership to individuals in the population. Trajectories were generated using a Stata Plugin “traj” for group-based trajectory modeling, and were modeled using Zero-Inflated Poisson, to account for the large proportion of participants who did not require assistance with their ADLs. Model selection was determined on the basis of Bayesian Information Criterion which allows for comparisons of both the number of trajectories and functional forms of each trajectory. Additional criteria included an assessment of confidence intervals, reasonable sample sizes in each identified trajectory, and average posterior probabilities with a value above .7 indicating a good fit (Supplemental Table 1) (27).

Multinomial logistic regression analysis for which we report relative risk ratios (RRR) and 95% confidence intervals (CI) examined the association between 1) HbA1c levels 2) glycemic control, and the newly constructed trajectories, while fully adjusting for participant baseline characteristics. To examine potential effect modification, interactions between HbA1c and demographic variables of interest (gender, education, marital status, and race/ethnicity) were tested. Significant interactions would call for stratified analyses. All analyses were performed using Stata15 MP Software (Stata, College Station, TX).

Results

Descriptive Baseline Participant Characteristics: Approximately 40.1% were men, 12.4% identified as non-Hispanic Black, and 8.0 % identified as Hispanic. The mean age was 67.5 years (SD = 67.2-67.4). Prevalence of elevated and intermediate HbA1c respectively was 14.3%, and 27.4%, compared to 58.1% low HbA1c (Table 1). Table 2 presents baseline characteristics for participants who self-reported diabetes in 2006. Approximately 15% of the participants had poor glycemic control. Prevalence of ADL limitations at baseline for the study population was 13%. By 2014 ADL incidence among those who had not been lost to follow-up or died during the 8-year follow-up period was 21%.

Functional Disability Trajectories: Four trajectory classes (no disability, low disability, low-increasing, and high-increasing) were identified for all participants (Figure 1). A brief overlap in confidence intervals was observed in 2010 due to the positive gradient of the low-increasing trajectory, however it was minimal, and the trajectories were distinct (Supplemental Table 1). A 3-class solution (no disability, low-increasing, and high-increasing) was determined using ADL scores for participants who self-reported diabetes at baseline (Figure 2).

Multinomial Models: In the pooled multinomial logistic regression analyses, relative to low HbA1c, high HbA1c was associated with greater risk of being classified into the high-increasing trajectory (RRR=1.63, 95% CI=1.25-2.11) only, while similar results were not observed for intermediate HbA1c (Table 3).

Interactions between HbA1c and demographic factors (age, gender, education, marital status, and race/ethnicity) were significant ($p < 0.05$) for age and race only. The results of the age and race stratified analyses are presented in Supplemental Table 2. Adults <65 years with elevated HbA1c were over twice (95% CI =1.17-3.47) as likely to be classified into the high-increasing trajectory, relative to those with low HbA1c. Relative to 65-75-year-old participants with low HbA1c, those with elevated HbA1c levels had a 96% (95% CI =1.26-3.04) increased likelihood of being classified in the high-increasing trajectory. Among the very old (>75 years) intermediate HbA1c predicted class membership for the low-increasing trajectory.

An increased risk of classification into the high-increasing trajectory was evident for non-Hispanic Black (RRR=1.83, 95%CI=1.02-3.29), Hispanic (RRR=4.17, 95%CI=1.75-9.91) and non-Hispanic White (RRR=1.60, 95% CI =1.15-2.21) participants with elevated HbA1c. In addition, Hispanic participants with intermediate HbA1c (2.38, 95%CI=1.01-5.69) were more likely to be classified into the high-increasing trajectory class.

After adjusting for all relevant co-variates, there was no significant association observed between glycemic control in adults with self-reported diabetes and the low-increasing (OR=1.00, 95%CI=.62-1.58) or high-increasing (OR=1.04, 95%CI=0.63-1.71) trajectory classes.

Discussion

The current study builds upon current literature by assessing the association between baseline HbA1c and longitudinal trajectories of functional disability. We identified four distinct

functional disability trajectories for the entire study sample, and three for those with a self-reported diabetes diagnosis and examined whether HbA1c levels, and glycemic control predicted differential membership into the trajectories. Our results corroborated previous findings that reported an association between diabetes or glycemic markers at or above the threshold for a diabetes diagnoses and functional disability (5,7–10,28). Specifically, our findings indicated that participants with elevated HbA1c had greater likelihood of being classified into the low-increasing and high-increasing trajectories, which showed increasing disability over the study period. Participants classified into these trajectories may represent individuals with an accelerated decline in health, with increased odds of using more health services and at risk of losing some economic self-sufficiency (29).

The relationship between intermediate glycemic markers and disability is inconclusive. Some studies have reported significant associations between intermediate glycemic markers and impaired functioning status (9,12), while other studies have found no association (7,28). In our study, intermediate HbA1c was associated with classification into trajectories with increasing disability in participants >75 years and among Hispanic participants. Among those >75 years, this finding may be explained by diagnostic efficiency and frailty. Some studies have indicated that HbA1c demonstrates limited sensitivity in detecting diabetes in the elderly, as diagnostic efficiency decreases with age, in part due to decreasing red blood cells count (30). In addition lower HbA1c levels have been associated with frailty, which is linked to impaired functional status (31,32). We postulate that increasing risk of frailty with age, along with decreasing diagnostic efficiency of HbA1c for diabetes with age, may render intermediate HbA1c more detrimental to health in the very old, without similar effects their younger counterparts.

Potential reasons for this association in Hispanics are less clear. One study reported that a prediabetes diagnosis among Hispanic women but did not motivate preventive lifestyle changes (33). Further, Hispanics have less access to diabetes prevention programs (34,35). These factors may have increased risk of intermediate HbA1c progressing to elevated levels after baseline, resulting in the negative outcomes associated with elevated HbA1c. Hispanics with elevated HbA1c also had a 4-fold increased risk of being classified in the high-increasing trajectory. In comparison to non-Hispanic whites, Hispanics with diabetes reportedly have poorer glycemic control and higher rates of both diabetes complications and uninsured persons (36,37), factors that may increase risk of disability.

Several studies have indicated that poor glycemic control as measured by HbA1c is associated with an increased risk of disability in older adults (6). In our study however, poor glycemic control in adults with self-reported diabetes was not associated with trajectories of functional disability. These findings are corroborated by previous reports which either did not find any statistically significant association between glycemic control and disability, or reported an increase in ADL limitations and poorer lower extremity functioning with tighter glycemic control (13–15). While the reasons for this are unclear, one article postulated that tighter glycemic control may be of most benefit and can positively impact subsequent outcomes in newly diagnosed diabetes patients only (38).

Our study should be viewed in light of several limitations. First, using a one-time measure of HbA1c does not take into account short-term variations in glucose levels induced by effects of food or medication, which may result in hypoglycemia, hyperglycemia and ketoacidosis (16), factors associated with adverse health outcomes and complications. Second, our use of baseline HbA1c makes it challenging to estimate the impact of disease progression.

Changes in diabetes as it progresses may affect how individuals recover or progress from functional disability. Third, excluding 339 participants with one ADL assessment may have impacted the slopes of the identified trajectories, as the excluded participants were older and in worse health. The longitudinal methods we selected did not allow us to observe their trajectories, which may have had steeper slopes. Despite these shortcomings, our findings are strengthened by use of a large, representative, longitudinal cohort of community-dwelling Americans. HbA1c is widely used to assess glycemic control and is a surrogate for diabetes-associated complications (16), and our study benefits from its use in lieu of self-reported diabetes only.

The disablement process postulates that a relationship between functional disability and diabetes is dependent on sociodemographic, intra-individual, and extra-individual factors (39). Future research should examine the mediating effects of these factors and assess how HbA1c trajectories may interact and impact the development and progression of disability. A better understanding of the association between glycemic markers and functional disability trajectories could potentially provide improved estimations of the health needs of the population and help reduce costs associated with both conditions and improve the quality of life of the elderly.

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Conflict of Interest

None declared.

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Table 1: Baseline Characteristics by HbA1c (2006 wave, N =5966)

	<5.7		5.7-6.4		>6.5	
	N	%	N	%	N	%
Baseline Characteristics	3,465	58.08	1,640	27.49	861	14.43
Age Category***						
<65	1,560	45.02	519	31.65	303	35.19
65-75	1,223	35.30	688	41.95	360	41.81
>75	682	19.68	433	26.40	198	23.00
Gender**						
Male	1,450	41.85	620	37.80	371	43.09
Female	2,015	58.15	1,020	62.20	490	56.91
Education***						
< 12 years	527	15.21	356	21.71	229	26.60
12 years	1,237	35.70	614	37.44	328	38.10
13-15 years	818	23.61	369	22.50	165	19.16
≥16	883	25.48	301	18.35	139	16.14
Race***						
Hispanic	208	6.00	149	9.09	122	14.17
Non-Hispanic Black	306	8.83	270	16.46	167	19.40
Non-Hispanic White	2,897	83.61	1,186	72.32	547	63.53
Other	54	1.56	35	2.13	25	2.90
Marital Status***						
Married	2,353	67.91	1,014	61.83	551	64
Not Married	1112	32.09	626	38.17	310	36.00
Health Insurance Plan***						
No Plan	1,069	30.85	620	37.80	382	44.37
≥1	2,396	69.15	1,020	62.20	479	55.63
Exercise***						
≥2 days	941	27.16	359	21.89	127	14.75
≤ 1 day	536	15.47	228	13.90	106	12.31
Never	1,988	57.37	1,053	64.21	628	72.94
BMI***						
Underweight/Normal	1,174	33.88	430	26.22	126	14.63
Overweight	1,371	39.57	604	36.83	288	33.45
Obese	582	16.80	372	22.68	251	29.15
Morbidly Obese	300	8.66	215	13.11	184	21.37
Missing BMI	38	1.10	19	1.16	12	1.39
CESD***						
No	3,022	87.22	1,401	85.43	694	80.60

Yes	443	12.78	239	14.57	167	19.40
Chronic Conditions***						
None	1,343	38.76	435	26.52	190	22.07
1	1,423	41.07	732	44.63	390	45.30
≥ 2	699	20.17	473	28.84	281	32.64
Cognitive Functioning***						
No	2,944	84.96	1,297	79.09	651	75.61
Yes	521	15.04	343	20.91	210	24.39
Days/week alcohol consumption***						
None	2,041	58.90	1,186	72.32	682	79.21
1-3	818	23.61	298	18.17	140	16.26
>3	606	17.49	156	9.51	39	4.53
Hospitalized in past year***						
No	2,697	77.84	1,191	72.62	593	68.87
Yes	768	22.16	449	27.38	268	31.13
Self-reported diabetes***						
Yes	3,313	95.72	1,290	78.90	235	27.29
No	148	4.28	345	21.10	626	72.71

* < 0.05; ** < 0.01; *** < 0.001

Table 2: Baseline Characteristics of Participants with Self-Reported Diabetes by Glycemic Control (2006 wave, N =1,119)

	Good Glycemic Control (A1C <7)		Poor Glycemic Control (A1C ≥ 7)	
	N	%	N	%
Baseline Characteristics	949	84.81	170	15.19
Age Category***				
<65	304	32.03	87	51.18
65-75	410	43.20	65	38.24
>75	235	24.76	18	10.59
Gender				
Male	404	42.57	68	40.00
Female	545	57.43	102	60.00
Education*				
< 12 years	237	24.97	56	32.94
12 years	348	36.67	63	37.06
13-15 years	201	21.18	23	13.53
≥16	163	17.18	28	16.47
Race***				
Hispanic	109	11.49	33	19.41
Non-Hispanic Black	164	17.28	46	27.06
Non-Hispanic White	656	69.13	84	49.41
Other	20	2.11	7	4.12
Marital Status				
Married	619	65.23	100	58.82
Not Married	330	34.77	70	41.18
Health Insurance Plan***				
No Plan	394	41.52	87	51.18
≥1	555	58.48	83	48.82
Exercise***				
≥2 days	150	15.81	15	8.82
≤ 1 day	122	12.86	17	10.00
Never	677	71.34	138	81.18
BMI				
Underweight /Normal	124	13.07	25	14.71
Overweight	317	33.40	47	27.65
Obese	292	30.77	48	28.24
Morbidly Obese	208	21.92	48	28.24

Missing BMI	8	21.92	2	1.18
CESD*				
No	772	81.35	125	73.53
Yes	177	18.65	45	26.47
Chronic Conditions**				
None	136	14.33	39	22.94
1	437	46.05	75	44.12
≥2	376	39.62	56	32.94
Cognitive Functioning				
No	731	77.03	121	71.18
Yes	218	22.97	49	28.82
Days/week alcohol consumption*				
None	748	78.82	148	87.06
1-3	151	15.91	19	11.18
≥3	50	5.27	3	1.76
Hospitalized in past year				
Yes	609	64.17	104	61.18
No	340	35.83	66	38.82
Diabetes Duration, Mean (SE)	16.27	(0.30)	19.70	(0.66)

* < 0.05; ** < 0.01; *** < 0.001

Table 3: Association between HbA1c and ADL Trajectories

	Low disability	Low-increasing	High-increasing
	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
HbA1c (<5.7 ref)			
5.7-6.4	1.06 (0.87-1.30)	1.19 (0.94-1.51)	.95 (0.75-1.20)
≥6.5	1.11 (0.86-1.44)	1.34 (0.98-1.85)	1.63 (1.25-2.11)

^a “No ADL limitations” was the base outcome in multinomial regression analysis.

^b Fully adjusted for all covariates.

Figure 1

Accepted

Figure 2

Accepted