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Research

Diabetes Treatment Intensity and Accelerated Functional Decline in Older Adults: Evidence From the Health and Retirement Study

Zhang Wei, MS[1], Shuyang Fang, MD[2], Bing Yue, MD[3], Chayakrit Krittanawong, MD, FACC, FAHA, FSCAI[4], Erfan Darzi, PhD[5]

AFFILIATIONS

[1]Tsinghua University, China

[2]Endocrinology division, Kaiser Permanente Washington, Seattle, WA, United States

[3]PeaceHealth Southwest Medical Center, Vancouver, WA, United States

[4]HumanX, Delaware, DE, United States

[5]Harvard Medical School, Boston, MA, United States

BACKGROUND: Functional limitation and disability are major consequences of diabetes in older adults. Whether greater diabetes treatment intensity is associated with accelerated functional decline beyond diabetes status alone remains uncertain. This study examined the association between diabetes treatment intensity and the accumulation of activities of daily living (ADL) and instrumental activities of daily living (IADL) limitations in adults aged ≥50 years.

METHODS: This cohort study used the RAND HRS Longitudinal File 2022 (V1), derived from the nationally representative US Health and Retirement Study. A total of 43,553 respondents contributed 272,804 self-respondent and proxy interviews conducted biennially from 1994 to 2022. Time-varying diabetes treatment was categorized as no diabetes, non-insulin-treated diabetes, or insulin-treated diabetes. The primary outcome was the number of ADL limitations (0–5), with IADL limitations as a secondary outcome. The primary estimand was the excess ADL limitation slope per decade in each treatment state relative to the trajectory without diabetes.

RESULTS: During follow-up, 4,113 respondents reported insulin use and 9,340 reported non-insulin-treated diabetes. Each decade of insulin-treated diabetes was associated with 0.150 additional ADL limitations (95% CI: 0.076–0.224), compared with 0.048 (95% CI: 0.017–0.079) for non-insulin-treated diabetes (between-group difference: 0.102; P = 0.01). Insulin initiation coincided with 0.279 additional limitations. The 10-year cumulative incidence of a new ADL limitation was 27.3%, 41.7%, and 55.5% among respondents without diabetes, with non-insulin-treated diabetes, and with insulin-treated diabetes at baseline, respectively. Findings were robust across multiple sensitivity analyses but attenuated after adjustment for diabetes duration (0.075; P = 0.07). The association was not significant on a relative scale or for baseline-defined treatment and IADL outcomes. Estimates across 1994–2008 and 2010–2022 were imprecise and did not differ (P = 0.83).

CONCLUSIONS: Insulin-treated diabetes was associated with greater ADL limitation accumulation, including an increase coinciding with insulin initiation. This association was partly explained by diabetes duration. Insulin initiation may represent a clinically relevant opportunity for functional assessment.

KEYWORDS: Diabetes mellitus, insulin therapy, functional decline, activities of daily living, disability, older adults

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Introduction

Diabetes mellitus is a leading determinant of functional limitation and disability in older adults, with converging longitudinal evidence linking the condition to loss of independent living across diverse populations. A systematic review and meta-analysis confirmed a consistent association between diabetes and increased risk of physical disability.[1] Prospective data demonstrated that diabetes was associated with incident functional disability in older women,[2] and longitudinal analyses in an elderly urban cohort showed that diabetes independently predicts long-term disability.[3] Subclinical functional impairment attributable to diabetes has also been documented among initially nondisabled older adults, suggesting that deterioration begins before overt disability thresholds are reached.[4] These findings collectively establish diabetes as a major longitudinal predictor of declining physical function in the aging population.

While the diabetes–disability association is well established, substantially less is known about whether escalation of pharmacologic treatment intensity adds prognostic information about the rate of functional decline beyond diabetes status alone. Pharmacologic management of type 2 diabetes typically follows an intensity continuum, from no medication to oral antidiabetic agents to insulin, with transitions often reflecting worsening glycemic control and increasing disease severity. The METABOLIC Study demonstrated the feasibility of linking medication-exposure categories to multidimensional functional assessment in older patients with type 2 diabetes taking oral antidiabetic treatment,[5] and frailty has been found to be associated with pharmacologic therapy patterns among older adults with type 2 diabetes.[6] Evidence of potential overtreatment in older adults with tight glycemic control raises concern that treatment intensification may increase adverse-event risk without commensurate functional benefit.[7] However, no prior longitudinal study has directly tested whether progression through treatment-intensity stages predicts accelerated functional decline trajectories in a nationally representative older-adult cohort.

We addressed this gap using the RAND HRS Longitudinal File, a panel of United States adults aged 50 years and older drawn from a nationally representative survey and followed across up to 15 biennial interview waves (1994–2022).[8] At each interview, respondents who report diabetes are asked whether they take oral medication and whether they use insulin for it, which allows treatment intensity to be measured directly and updated over time. Prior work in the Health and Retirement Study by Bardenheier et al. demonstrated that functional decline predicts subsequent diabetes incidence, the reverse direction from our question, underscoring the bidirectionality of this relationship.[9] The present analysis tests the forward direction: whether time spent on insulin is associated with steeper trajectories of ADL and instrumental ADL (IADL) limitation accumulation.

Methods

This analysis used the RAND HRS Longitudinal File 2022 (Version 1), a user-friendly longitudinal file derived from the Health and Retirement Study (HRS), the premier longitudinal study of aging in the United States. The HRS is sponsored by the National Institute on Aging and conducted by the University of Michigan Survey Research Center. The RAND file is created and maintained by the RAND Center for the Study of Aging. This secondary analysis used deidentified public-use data and did not constitute human participants research requiring institutional review board review. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[10]

Study Design

The HRS uses a biennial panel design. Its age-eligible sample is adults older than 50 years, and spouses are interviewed regardless of age.[8] We used all interviews from waves 2–16 (1994–2022), including proxy interviews, which the HRS conducts when a respondent is unable to answer; excluding them would remove interviews from

respondents whose function had declined most. Each respondent's baseline was the first interview at which they were aged 50 years or older and diabetes status was known. The analytic cohort comprised respondents with at least 1 ADL measurement, and all counts in the text, tables, and figures refer to this cohort. The 50-year threshold follows the HRS sampling frame and prior HRS analyses of diabetes and function, which used thresholds of 50 or 51 years;[9,11,12,13] its effect was tested directly.

Exposures

Diabetes was defined from the first interview at which the respondent reported a physician diagnosis and carried forward thereafter. At each interview, respondents with diabetes reported whether they currently take oral medication for diabetes and whether they currently use insulin. The primary exposure was time-varying: at each interview, a respondent was classified as having no diabetes, diabetes without insulin (non-insulin), or insulin-treated diabetes, with insulin status carried forward from the first interview at which insulin use was reported. A missing insulin item was treated as no new report, so the respondent kept the state reported at earlier interviews. Because states change only at reported transitions, classification at any interview uses no information from later interviews. In a secondary specification, the non-insulin state was split into diabetes without medication and oral medication without insulin.

Three fixed classifications were analyzed for comparison: the highest treatment reported at any interview during follow-up (the exposure in the earlier version of this analysis), treatment at the baseline interview followed regardless of later change (a landmark design), and the highest stage of diabetes duration since first report (<10 vs ≥10 years). Agreement between the duration stage and reported insulin use was tabulated.

Outcomes

The primary outcome was the count of ADL limitations (0–5 scale; items: bathing, dressing, eating, transferring from bed, and walking across a room). The secondary outcome was the count of IADL limitations (0–5 scale; items: using the telephone, managing money, taking medications, shopping for groceries, and preparing meals). Both outcomes were assessed at each biennial interview; IADL data were available from wave 3 (1996) onward.

Statistical Analysis

Functional trajectories were estimated using linear regression with respondent-clustered robust standard errors. Time was defined as years since each respondent's baseline interview, scaled in decades (t_it). The primary model took the form:

$$Y_{it} = \beta_0 + \beta_1 t_{it} + \beta_2 S_{non,it} + \beta_3 S_{ins,it} + \gamma_1 T_{non,it} + \gamma_2 T_{ins,it} + \delta(t_{it} \times a_{0i}) + X_i' \theta + \varepsilon_{it}$$

where Y_it is the ADL (or IADL) limitation count for respondent i at interview t; S_non,it and S_ins,it indicate the current treatment state; T_non,it and T_ins,it are the decades spent in the non-insulin and insulin states since baseline; a_0i is baseline age, centered at 60 years and scaled per 10 years; and X_i is the vector of baseline covariates. The primary estimands were y_1 and y_2, the excess limitation slope per decade spent in each state relative to the trajectory without diabetes. B_2 and B_3 capture the difference in limitation count at entry into each state (or at baseline for respondents already in that state). We tested y_2 − y_1 to compare insulin with non-insulin treatment, and estimated a linear trend across the 4 ordered states (no diabetes, diabetes without medication, oral medication, insulin) by constraining the excess slope to increase by a common amount per step. Covariates were baseline age, sex, race, Hispanic ethnicity, education, BMI, hypertension, heart disease, stroke, chronic lung disease, arthritis, current smoking, alcohol use, and CES-D score. Missing binary covariates were coded as a separate category, and missing continuous covariates, including CES-D for respondents whose baseline interview was by proxy, were set to the median with a missingness indicator.

Sensitivity analyses addressed model specification, sample, and measurement. To adjust rates of change as well as baseline levels, all covariates

were interacted with time. Generalized estimating equations with an exchangeable working correlation and a linear mixed model with random intercepts and slopes reduced the weight given to respondents with many interviews. Nonlinear time was modeled with a natural cubic spline (4 df) for time since baseline and, separately, with squared terms for decades in each treatment state. A Poisson model with log link estimated excess slopes on a relative scale. Weighted analyses used baseline HRS respondent weights with standard errors clustered on sampling units (stratum × sampling error computation unit). We repeated the primary model restricted to self-respondent interviews; excluding respondents with diabetes who had any missing insulin item; ending follow-up in 2014, before the 2016 revision of the HRS diabetes module; excluding respondents whose reported year of diagnosis implied onset before age 30 years, as a proxy for type 1 diabetes; and restricting to respondents with no ADL limitation at baseline. To test whether treatment adds information beyond diabetes duration, a further model added a time-varying term for decades spent beyond 10 years of diabetes duration. As an absolute measure, we estimated the unadjusted Kaplan-Meier cumulative incidence of a first ADL limitation within 10 years among respondents without ADL limitations at baseline, by treatment at baseline. Deaths during follow-up and loss to follow-up (last interview before 2022 without a recorded death) were tabulated by group.

Because long-acting glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may have delayed or replaced insulin in recent years, changing who is classified as insulin-treated, we repeated the primary model separately for follow-up in 1994–2008 and 2010–2022. Liraglutide, the first once-daily long-acting GLP-1 RA, was approved in the United States in 2010. The HRS does not record GLP-1 RA use, so calendar period served as a marker of availability. Each period was analyzed as its own cohort with baseline reset to the first interview in the period; both periods were fitted in one model with all terms interacted with period, and the interaction for decades on insulin tested whether the insulin excess slope differed. We repeated this with a 2014 cut (approval of once-weekly dulaglutide) and with later follow-up ending in 2014. To assess the 50-year age threshold, we refitted the primary model with minimum baseline ages of 51 (the HRS age-eligibility threshold), 55, 60, and 65 years (the threshold used by American Diabetes Association guidance for older adults),[14] resetting baseline to the first interview at or above each threshold, and tested whether slopes differed between respondents aged 50–64 and ≥65 years at baseline. Statistical significance was defined at □ = .05 (two-sided); analyses beyond the primary model were not adjusted for multiple comparisons and should be interpreted as supportive. All models were estimated in Python (statsmodels 0.14) from a single analysis script.

Results

Study Population

The analytic cohort comprised 43,553 respondents with 272,804 person-wave observations (Figure 1); 43,095 respondents (263,355 observations) contributed to the IADL model. During follow-up, 30,100 respondents (69.1%) did not report diabetes, 9,340 (21.4%) had diabetes without insulin, and 4,113 (9.4%) reported insulin use at 1 or more interviews (Table 1). Median follow-up was 10 years without diabetes, 12 years with non-insulin diabetes, and 12 years with insulin; 56.8% of respondents who used insulin died during follow-up, compared with 42.2% without diabetes, and 11.0% and 24.3%, respectively, were lost to follow-up alive. Mean (SD) baseline age was 60.8 (10.1) years, and 55.8% were women. Respondents who used insulin more often had hypertension (65.9% vs 34.5%) and arthritis (45.4% vs 28.0%) at baseline, and fewer had no ADL limitation (74.6% vs 89.0%). Among respondents with diabetes, 22%–30% reported insulin use at each interview year (Figure 2; eTable 1 in Supplement 1).

Primary Outcome

For a respondent aged 60 years at baseline, ADL limitations increased by 0.227 per decade without diabetes. Each decade spent with non-insulin diabetes added 0.048 (95% CI, 0.017 to 0.079; P = .002), and each decade on insulin added 0.150 (95% CI, 0.076 to 0.224; P < .001) (Table 2; Figure 3). The insu

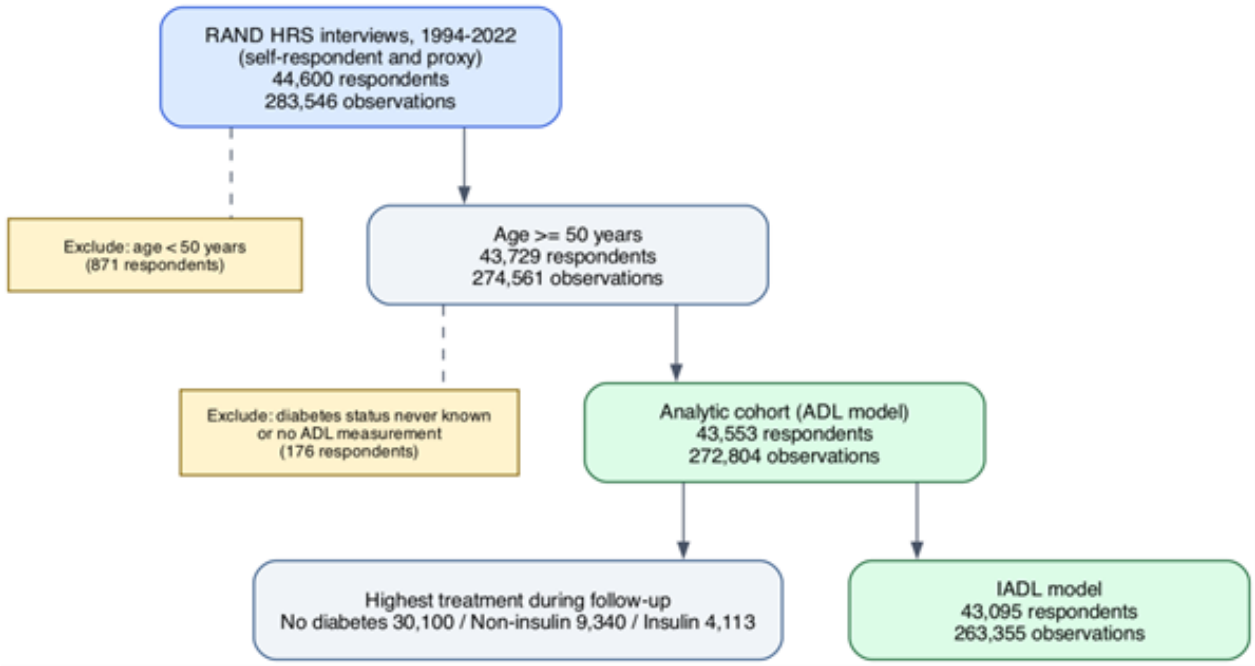


FIGURE 1. Study flow from RAND HRS interviews to the analytic cohort.

lin excess was larger than the non-insulin excess by 0.102 (95% CI, 0.023 to 0.181; P = .01). Entry into the insulin state coincided with 0.279 (95% CI, 0.235 to 0.322; P < .001) more ADL limitations, whereas entry into the non-insulin state did not (0.012 (95% CI, −0.007 to 0.031; P = .21)). Across ordered treatment steps, the excess slope was 0.004 (95% CI, −0.047 to 0.055; P = .87) for diabetes without medication, 0.067 (95% CI, 0.029 to 0.104; P < .001) for oral medication, and 0.152 (95% CI, 0.079 to 0.226; P < .001) for insulin (trend per step, 0.040 (95% CI, 0.025 to 0.055; P < .001)). Among respondents without ADL limitations at baseline, the 10-year cumulative incidence of a new ADL limitation was 27.3% (95% CI, 26.7%–27.9%) without diabetes, 41.7% (95% CI, 39.7%–43.7%) with non-insulin treatment, and 55.5% (95% CI, 51.7%–59.3%) with insulin at baseline.

Secondary Outcome

In the IADL model, the excess slope per decade was 0.108 (95% CI, 0.042 to 0.174; P = .001) for insulin and 0.056 (95% CI, 0.024 to 0.087; P < .001) for non-insulin treatment; the difference between them was not significant (0.053 (95% CI, −0.019 to 0.124; P = .15)).

Alternative Exposure Definitions

With respondents assigned to the highest treatment reported during follow-up, the insulin excess ADL slope was 0.152 (95% CI, 0.114 to 0.190; P < .001), similar to the primary estimate (Table 2). With treatment fixed at the baseline interview, the insulin excess was 0.143 (95% CI, 0.046 to 0.240; P = .004) for ADL but not significant for IADL (0.067 (95% CI, −0.015 to 0.149; P = .11)). The duration stage agreed poorly with reported treatment: 41.8% of respondents who reached ≥10 years of diabetes ever reported insulin, and 47.4% of insulin users never reached 10 years during follow-up. When decades beyond 10 years of diabetes duration were added to the primary model, the duration term was 0.169 (95% CI, 0.084 to 0.254; P < .001) and the insulin excess slope attenuated to 0.075 (95% CI, −0.006 to 0.157; P = .07). With fixed groups, insulin (0.110 (95% CI, 0.063 to 0.158; P < .001)) and duration of ≥10 years (0.085 (95% CI, 0.052 to 0.118; P < .001)) were each associated with a steeper slope.

Sensitivity Analyses

The insulin excess ADL slope was 0.134 (95% CI, 0.060 to 0.208; P < .001) with all covariates inter

TABLE 1. Baseline Characteristics by Highest Diabetes Treatment Reported During Follow-up

CHARACTERISTIC	OVERALL (N = 43,553)	NO DIABETES (N = 30,100)	DIABETES, NON-INSULIN (N = 9,340)	DIABETES, INSULIN (N = 4,113)
Demographic and socioeconomic				
Age, mean (SD), y	60.8 (10.1)	61.3 (10.6)	59.4 (8.8)	60.3 (9.0)
Female, No. (%)	24,310 (55.8)	17,013 (56.5)	5,060 (54.2)	2,237 (54.4)
Race, No. (%)[a]				
White	30,697 (71.4)	22,336 (75.2)	5,932 (64.2)	2,429 (59.5)
Black	8,641 (20.1)	5,235 (17.6)	2,177 (23.6)	1,229 (30.1)
Hispanic	5,665 (13.2)	3,208 (10.8)	1,718 (18.6)	739 (18.1)
Other	3,668 (8.5)	2,119 (7.1)	1,126 (12.2)	423 (10.4)
Education, No. (%)[a]				
Less than high school	10,755 (24.9)	6,806 (22.9)	2,583 (27.9)	1,366 (33.4)
GED	2,092 (4.9)	1,377 (4.6)	477 (5.1)	238 (5.8)
High school graduate	11,952 (27.7)	8,331 (28.0)	2,495 (26.9)	1,126 (27.5)
Some college	9,792 (22.7)	6,828 (23.0)	2,078 (22.4)	886 (21.6)
College or above	8,516 (19.8)	6,401 (21.5)	1,637 (17.7)	478 (11.7)
Married or partnered, No. (%)[a]	30,105 (69.1)	20,881 (69.4)	6,493 (69.6)	2,731 (66.4)
Clinical				
BMI, median [IQR][a]	27.0 [24.0, 30.7]	25.8 [23.3, 29.3]	29.0 [25.8, 32.9]	30.0 [26.6, 34.6]
Self-rated health fair or poor, No. (%)[a]	12,759 (29.3)	7,145 (23.7)	3,345 (35.9)	2,269 (55.1)
Hypertension, No. (%)[a]	16,599 (41.4)	9,612 (34.5)	4,474 (53.3)	2,513 (65.9)
Heart disease, No. (%)[a]	6,720 (15.5)	3,983 (13.3)	1,635 (17.6)	1,102 (26.9)
Stroke, No. (%)[a]	1,953 (4.5)	1,119 (3.8)	455 (4.9)	379 (9.3)
Chronic lung disease, No. (%)[a]	2,918 (6.8)	1,855 (6.3)	678 (7.4)	385 (9.5)
Arthritis, No. (%)[a]	12,556 (31.4)	7,736 (28.0)	3,068 (36.0)	1,752 (45.4)
Cancer, No. (%)[a]	3,658 (8.4)	2,529 (8.4)	794 (8.5)	335 (8.1)
Current smoker, No. (%)[a]	8,861 (20.4)	6,270 (20.9)	1,801 (19.3)	790 (19.3)
Ever smoker, No. (%)[a]	24,590 (56.8)	16,855 (56.3)	5,316 (57.2)	2,419 (59.3)
Drinks alcohol, No. (%)[a]	10,593 (41.0)	7,819 (46.4)	2,117 (34.7)	657 (22.6)
CES-D score (0-8), median [IQR][b]	1 [0, 2]	1 [0, 2]	1 [0, 3]	1 [0, 4]

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TABLE 1. Baseline Characteristics by Highest Diabetes Treatment Reported During Follow-up (cont)

CHARACTERISTIC	OVERALL (N = 43,553)	NO DIABETES (N = 30,100)	DIABETES, NON-INSULIN (N = 9,340)	DIABETES, INSULIN (N = 4,113)
Diabetes diagnosed before age 30 y, No. (%)	284 (0.7)	14 (0.0)	96 (1.0)	174 (4.2)
Function at baseline ADL limitations, No. (%)[a]				
0	37,803 (86.8)	26,802 (89.0)	7,931 (84.9)	3,070 (74.6)
1	2,839 (6.5)	1,729 (5.7)	671 (7.2)	439 (10.7)
≥2	2,911 (6.7)	1,569 (5.2)	738 (7.9)	604 (14.7)
IADL limitations, No. (%) [c]				
0	37,195 (86.3)	26,114 (88.0)	7,945 (85.2)	3,136 (76.3)
1	3,220 (7.5)	1,963 (6.6)	745 (8.0)	512 (12.5)
≥2	2,680 (6.2)	1,587 (5.3)	630 (6.8)	463 (11.3)
Total cognition score (0-35), mean (SD)[c]	22.6 (5.1)	22.9 (5.1)	22.4 (5.0)	21.4 (5.3)
Follow-up				
Baseline interview year, median [IQR]	1998 [1994, 2010]	1998 [1994, 2010]	1998 [1994, 2010]	1998 [1994, 2010]
Proxy interview at baseline, No. (%)	2,756 (6.3)	1,946 (6.5)	527 (5.6)	283 (6.9)
Follow-up, median [IQR], y	10 [4, 18]	10 [4, 16]	12 [6, 18]	12 [6, 18]
Interviews per respondent, median [IQR]	6 [3, 9]	5 [3, 9]	7 [4, 10]	6 [3, 10]
Died during follow-up, No. (%)	18,675 (42.9)	12,699 (42.2)	3,639 (39.0)	2,337 (56.8)
Lost to follow-up alive before 2022, No. (%)	9,466 (21.7)	7,300 (24.3)	1,715 (18.4)	451 (11.0)

Abbreviations: ADL, activities of daily living; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; GED, general educational development; IADL, instrumental activities of daily living; IQR, interquartile range.

[a] Percentages among respondents with non-missing values; at least 96% complete except hypertension (92%), arthritis (92%), and alcohol use (59%; drinking frequency is not available in this file for 1994).

[b] Not collected in proxy interviews.

[c] IADL items were first fielded in 1996; the cognition score is available in this file for 1996-2016 and is not collected in proxy interviews.

TABLE 2. Excess Functional Decline per Decade by Diabetes Treatment, Relative to No Diabetes

EXPOSURE DEFINITION AND GROUP	ADL LIMITATIONS[A] - B(95% CI)	P VALUE	IADL LIMITATIONS[B] - B(95% CI)	P VALUE
Current treatment, time-varying (primary)[c]				
Non-insulin	0.048 (0.017 to 0.079)	.002	0.056 (0.024 to 0.087)	<.001
Insulin	0.150 (0.076 to 0.224)	<.001	0.108 (0.042 to 0.174)	.001
Insulin minus non-insulin	0.102 (0.023 to 0.181)	.01	0.053 (-0.019 to 0.124)	.15
Current treatment step, time-varying[d]				
No diabetes medication	0.004 (-0.047 to 0.055)	.87	—	
Oral medication only	0.067 (0.029 to 0.104)	<.001	—	
Insulin	0.152 (0.079 to 0.226)	<.001	—	
Linear trend per treatment step	0.040 (0.025 to 0.055)	<.001	—	
Highest treatment during follow-up[e]				
Non-insulin	0.037 (0.018 to 0.057)	<.001	0.025 (0.005 to 0.044)	.02
Insulin	0.152 (0.114 to 0.190)	<.001	0.129 (0.092 to 0.166)	<.001
Insulin minus non-insulin	0.114 (0.074 to 0.155)	<.001	0.105 (0.065 to 0.144)	<.001
Treatment at baseline interview (landmark)[f]				
Non-insulin	0.106 (0.063 to 0.148)	<.001	0.095 (0.051 to 0.139)	<.001
Insulin	0.143 (0.046 to 0.240)	.004	0.067 (-0.015 to 0.149)	.11
Diabetes duration, highest stage during follow-up[g]				
<10 y	0.004 (-0.023 to 0.032)	.75	-0.008 (-0.035 to 0.019)	.55
≥10 y	0.120 (0.097 to 0.142)	<.001	0.108 (0.085 to 0.131)	<.001
Treatment and duration in one model, time-varying[h]				
Insulin	0.075 (-0.006 to 0.157)	.07	—	
Diabetes duration ≥10 y	0.169 (0.084 to 0.254)	<.001	—	

ABBREVIATIONS: ADL, activities of daily living; CI, confidence interval; IADL, instrumental activities of daily living.[a] N=43,553 respondents; 272,804 person-wave observations; 4,113 reported insulin at 1 or more interviews and 9,340 had diabetes without insulin. [b] N=43,095 respondents; 263,355 person-wave observations; IADL data available from 1996.[c] Excess change in limitation count per decade spent in each treatment state, relative to the no-diabetes trajectory. Treatment state is updated at each interview (diabetes once reported; insulin once reported), so no information from later interviews is used. Models adjust for baseline age, sex, race, Hispanic ethnicity, education, BMI, hypertension, heart disease, stroke, chronic lung disease, arthritis, current smoking, alcohol use, and CES-D score, and include time × baseline age, with respondent-clustered robust standard errors.[d] Diabetes without medication, oral medication without insulin, and insulin, each time-varying. Trend: common increment per step (0 = no diabetes to 3 = insulin). Oral minus no medication, 0.063 (0.001 to 0.125), P = .05; insulin minus oral, 0.085 (0.003 to 0.167), P = .04. [e] Exposure of the previous version: each respondent assigned to the highest treatment reported at any interview (non-insulin, 9,340; insulin, 4,113). Uses information from later interviews.[f] Treatment at the baseline interview, followed regardless of later change (non-insulin, 4,584; insulin, 1,803); respondents who developed diabetes later remain in the reference group.

[g] Highest stage of diabetes duration since first report (≥10 y, 5,176; <10 y, 8,277). Of respondents reaching ≥10 years, 41.8% ever reported insulin; 47.4% of insulin users never reached 10 years.[h] Primary model with an added time-varying term for decades spent beyond 10 years of diabetes duration. In the fixed-group version, insulin 0.110 (0.063 to 0.158) and duration ≥10 y 0.085 (0.052 to 0.118).

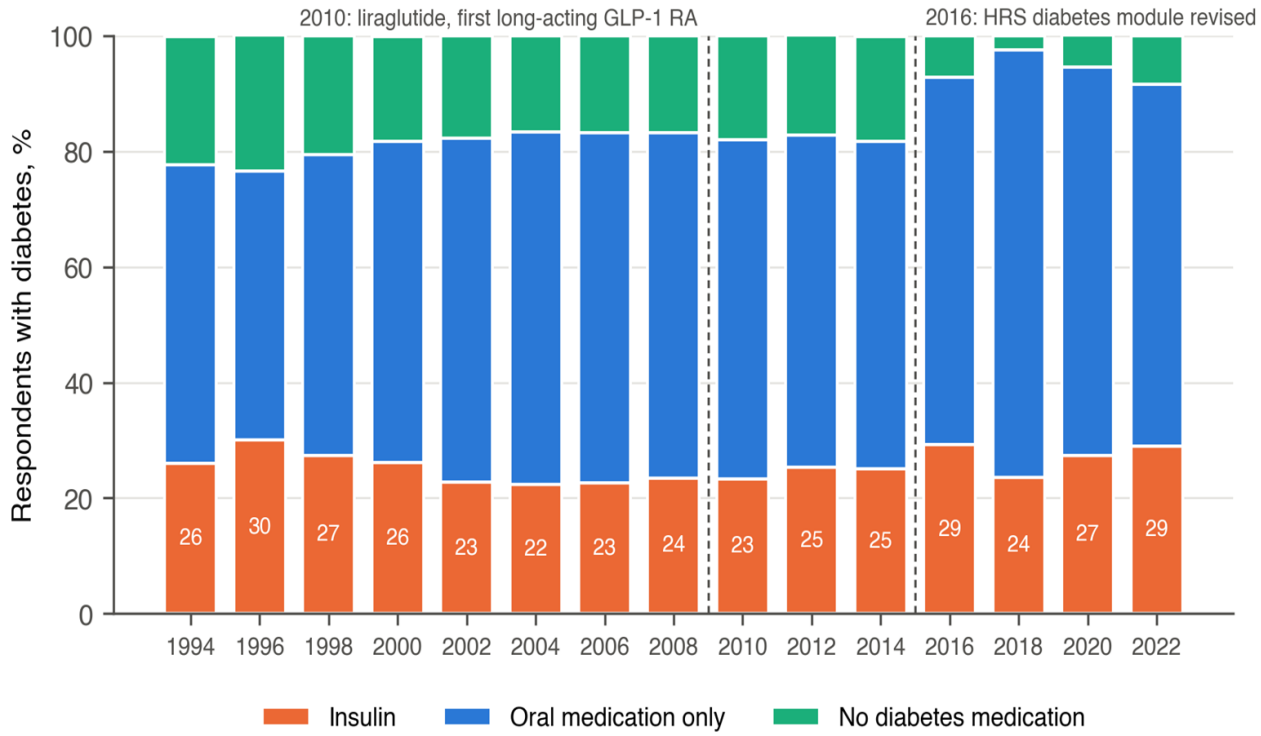


FIGURE 2. Study flow from RAND HRS interviews to the analytic cohort. Diabetes treatment reported by respondents with diabetes, by HRS interview year. Bars show the percentage reporting insulin (with or without oral medication), oral medication only, or no diabetes medication among respondents with non-missing treatment items; numbers in bars are the insulin percentage. Dashed lines mark US approval of liraglutide (2010) and the 2016 revision of the HRS diabetes module, after which the insulin item was missing more often.

TABLE 3. Sensitivity Analyses for the Excess ADL Slope (Time-Varying Exposure)

ANALYSIS	RESPONDENTS, NO.	INSULIN - □ (95% CI)	P VALUE	NON-INSULIN - □ (95% CI)	P VALUE
Primary model	43,553	0.150 (0.076 to 0.224)	<.001	0.048 (0.017 to 0.079)	.002
Model specification					
Covariate × time interactions[a]	43,553	0.134 (0.060 to 0.208)	<.001	0.029 (-0.002 to 0.060)	.07
GEE, exchangeable correlation	43,553	0.284 (0.221 to 0.347)	<.001	0.070 (0.043 to 0.097)	<.001
Mixed model, random intercept and slope (model-based SE)	43,553	0.503 (0.461 to 0.545)	<.001	0.150 (0.126 to 0.174)	<.001
Spline for time[b]	43,553	0.151 (0.078 to 0.225)	<.001	0.043 (0.012 to 0.074)	.006
Quadratic excess slopes[c]	43,553	0.132 (-0.009 to 0.274)	.07	—	
Poisson model, rate ratio per decade[d]	43,553	0.941 (0.876 to 1.010)	.09	0.960 (0.912 to 1.010)	.12

TABLE 3. Sensitivity Analyses for the Excess ADL Slope (Time-Varying Exposure) (cont)

ANALYSIS	RESPONDENTS, NO.	INSULIN - B (95% CI)	P VALUE	NON-INSULIN - B (95% CI)	P VALUE
HRS survey weights and design[e]	35,495	0.151 (0.043 to 0.259)	.006	0.024 (-0.006 to 0.054)	.12
Sample and measurement					
Self-respondent interviews only	42,141	0.128 (0.060 to 0.196)	<.001	0.022 (-0.005 to 0.050)	.11
Complete treatment data[f]	39,407	0.163 (0.075 to 0.251)	<.001	0.009 (-0.029 to 0.047)	.64
Follow-up through 2014[g]	35,983	0.162 (0.070 to 0.254)	<.001	0.041 (-0.001 to 0.083)	.06
Excluding diabetes diagnosed before age 30 y[h]	43,269	0.149 (0.073 to 0.225)	<.001	0.052 (0.021 to 0.083)	<.001
No ADL limitation at baseline	37,673	0.231 (0.152 to 0.311)	<.001	0.086 (0.056 to 0.116)	<.001
Covariate × time interactions, IADL outcome[a]	43,095	0.099 (0.031 to 0.166)	.004	0.043 (0.011 to 0.074)	.009

Abbreviations: ADL, activities of daily living; GEE, generalized estimating equations; HRS, Health and Retirement Study; IADL, instrumental activities of daily living.[a] All baseline covariates interacted with time, so that they adjust the rate of change as well as baseline level.[b] Natural cubic spline for time since baseline (4 df) in place of the linear time term.[c] Linear term from a model adding squared decades in each treatment state; joint P for the squared terms = .08.[d] Poisson regression with log link and respondent-clustered robust standard errors; ratio of expected limitation counts per decade in each state.[e] Baseline respondent weights with standard errors clustered on 160 sampling units (stratum × sampling error computation unit); respondents with zero weight at baseline (nursing home residents) excluded.[f] Excludes 4,146 respondents with diabetes who had a missing insulin item at any interview.[g] Ends before the 2016 revision of the HRS diabetes module.[h] Excludes 284 respondents whose reported diagnosis year implied onset before age 30 years, as a proxy for type 1 diabetes.

TABLE 4. Excess ADL Slope by Calendar Period and Age Threshold (Time-Varying Exposure)

ANALYSIS	RESPOND	INSULIN - B (95% CI)	P VALUE	NON-INSULIN - B (95% CI)	P VALUE	P FOR DIFFERENCE[A]
Calendar period of follow-up[b]						
1994-2008	29,207	0.112 (-0.008 to 0.233)	.07	0.057 (-0.003 to 0.117)	.06	
2010-2022	30,126	0.095 (-0.004 to 0.194)	.06	0.001 (-0.042 to 0.044)	.97	.83
2010-2014[c]	22,521	0.060 (-0.165 to 0.286)	.60	-0.007 (-0.113 to 0.099)	.90	.69
1994-2012	35,588	0.139 (0.042 to 0.236)	.005	0.033 (-0.012 to 0.079)	.15	
2014-2022	26,430	0.087 (-0.045 to 0.219)	.20	-0.036 (-0.094 to 0.023)	.23	.54
Minimum baseline age[d]						
≥50 y (primary)	43,553	0.150 (0.076 to 0.224)	<.001	0.048 (0.017 to 0.079)	.002	
≥51 y	43,298	0.152 (0.079 to 0.226)	<.001	0.049 (0.018 to 0.080)	.002	

TABLE 4. Excess ADL Slope by Calendar Period and Age Threshold (Time-Varying Exposure) (cont)

ANALYSIS	RESPOND	INSULIN - B (95% CI)	P VALUE	NON-INSULIN - B (95% CI)	P VALUE	P FOR DIFFERENCE[A]
≥55 y	40,635	0.155 (0.080 to 0.231)	<.001	0.053 (0.021 to 0.086)	.001	
≥60 y	35,179	0.133 (0.049 to 0.217)	.002	0.061 (0.023 to 0.100)	.002	
≥65 y	29,250	0.116 (0.015 to 0.217)	.02	0.078 (0.032 to 0.125)	.001	
Age at baseline, stratified[e]						
50-64 y	30,635	0.187 (0.106 to 0.267)	<.001	0.045 (0.013 to 0.077)	.006	
≥65 y	12,918	0.051 (-0.125 to 0.227)	.57	0.105 (0.019 to 0.192)	.02	.20

Abbreviations: ADL, activities of daily living; CI, confidence interval.[a] Test that the insulin excess slope differs from the earlier period (calendar analyses) or from respondents aged 50-64 years (age strata).[b] Each period analyzed as its own cohort with baseline reset to the first interview in the period; periods fitted jointly with all terms interacted with period and standard errors clustered by respondent. Respondents reporting insulin: 1994-2008, 2,035; 2010-2022, 2,903; 1994-2012, 2,781; 2014-2022, 2,501. The HRS does not record GLP-1 receptor agonist use; 2010 marks US approval of liraglutide, the first once-daily long-acting agent, and 2014 marks approval of once-weekly dulaglutide.[c] Ends before the 2016 revision of the HRS diabetes module. Respondents reporting insulin, 1,783. [d] Baseline reset to the first interview at or above the stated age.[e] Separate models within each stratum; P for difference from a model in the full cohort with treatment-state slope terms interacted with baseline age ≥65 years (non-insulin slope, P = .13).

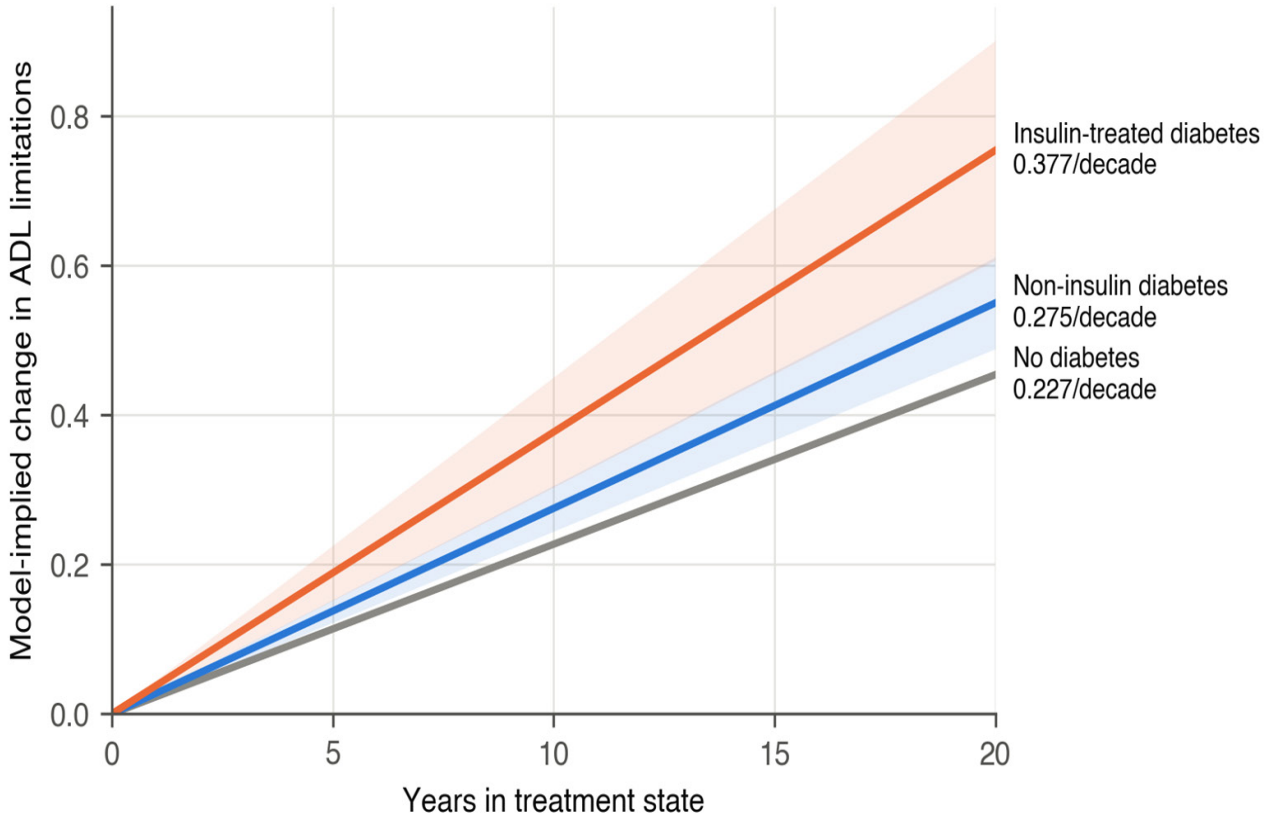


FIGURE 3. Study Model-implied change in ADL limitations for a respondent aged 60 years at baseline who spends the whole period without diabetes, with non-insulin diabetes, or on insulin, from the primary time-varying model. Shaded bands show 95% CIs for the excess slopes; the step change at insulin initiation is not shown. See Table 2 for estimates.

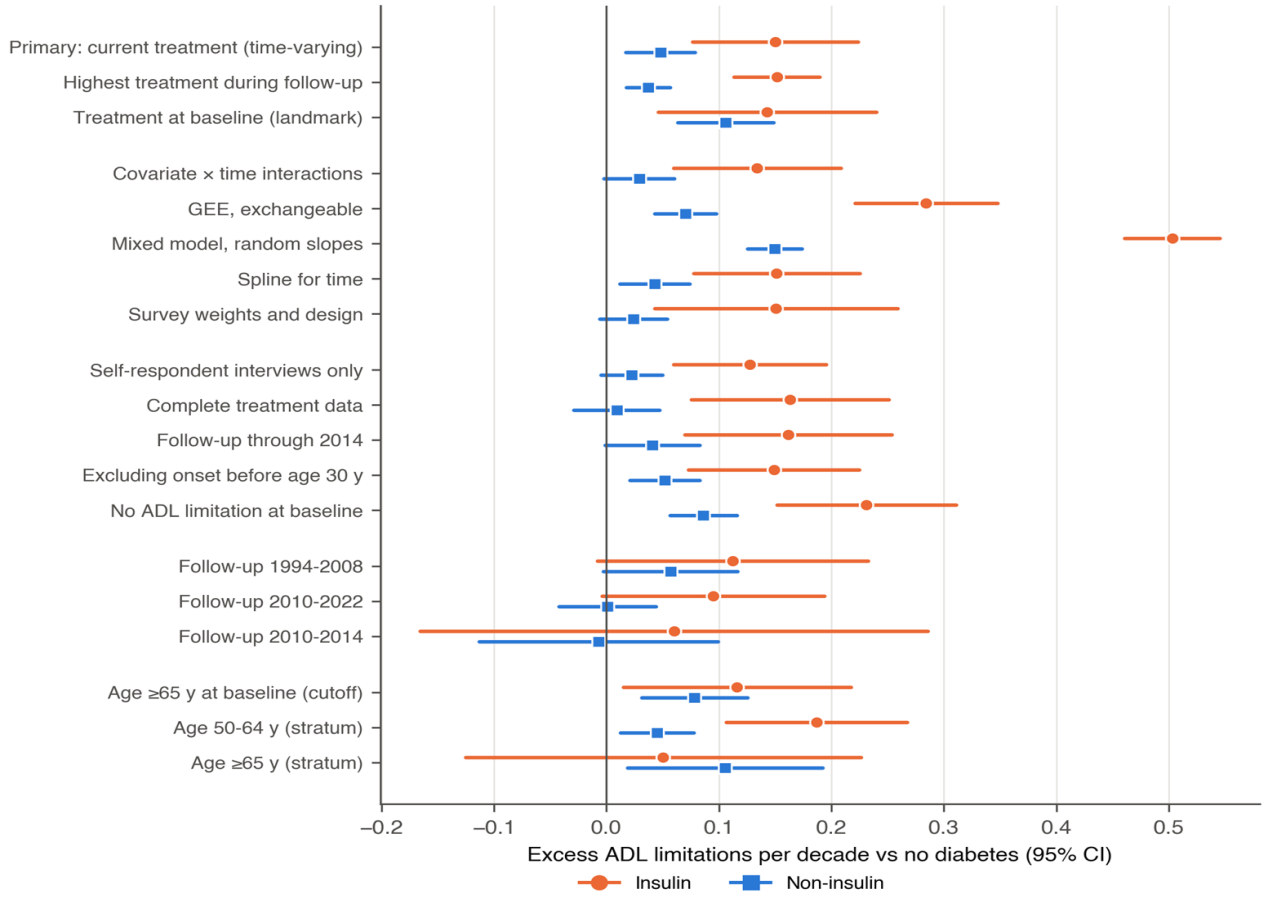


FIGURE 4. Excess ADL limitation slope per decade relative to no diabetes across exposure definitions, model specifications, samples, calendar periods, and age groups. Circles show insulin and squares show non-insulin treatment; lines are 95% CIs.

acted with time, 0.151 (95% CI, 0.043 to 0.259; P = .006) with survey weights and design, 0.128 (95% CI, 0.060 to 0.196; P < .001) in self-respondent interviews only, 0.163 (95% CI, 0.075 to 0.251; P < .001) among respondents with complete treatment data, 0.149 (95% CI, 0.073 to 0.225; P < .001) after excluding likely type 1 diabetes, and 0.231 (95% CI, 0.152 to 0.311; P < .001) among respondents with no ADL limitation at baseline (Table 3; Figure 4). Models that give less weight to respondents with many interviews gave larger estimates (generalized estimating equations, 0.284 (95% CI, 0.221 to 0.347; P < .001); mixed model, 0.503 (95% CI, 0.461 to 0.545; P < .001)). A spline for time left the estimate unchanged (0.151 (95% CI, 0.078 to 0.225; P < .001)), and squared terms did not improve fit (joint P = .08). On the relative scale of the Poisson model, the rate ratio per decade on insulin was 0.941 (95% CI, 0.876 to 1.010; P = .09): limitations accumulated faster in absolute terms but at a similar proportional rate, because insulin users started from more limitations.

Calendar Period and Age Threshold

The insulin excess ADL slope was 0.112 (95% CI, −0.008 to 0.233; P = .07) for follow-up in 1994–2008 and 0.095 (95% CI, −0.004 to 0.194; P = .06) for follow-up in 2010–2022; neither period estimate was significant on its own, and they did not differ (P = .83; Table 4). A 2014 cut (P = .54) and later follow-up ending in 2014 (0.060 (95% CI, −0.165 to 0.286; P = .60)) gave similar conclusions. The proportion of respondents with diabetes reporting insulin did not fall after 2010, whereas the insulin item was missing for 26%–38% of respondents with diabetes after the 2016 module revision, compared with 14% or less earlier (eTable 1 in Supplement 1).

The insulin excess slope was 0.152 (95% CI, 0.079 to 0.226; P < .001) with a minimum baseline age of 51 years, 0.155 (95% CI, 0.080 to 0.231; P < .001) at 55

years, 0.133 (95% CI, 0.049 to 0.217; P = .002) at 60 years, and 0.116 (95% CI, 0.015 to 0.217; P = .02) at 65 years. In respondents aged ≥65 years at baseline, the estimate was imprecise (0.051 (95% CI, −0.125 to 0.227; P = .57)) compared with 0.187 (95% CI, 0.106 to 0.267; P < .001) at ages 50–64 years (P = .20 for interaction).

Discussion

In this cohort of 43,553 adults aged 50 years and older followed for up to 28 years, time spent on insulin was associated with a steeper absolute accumulation of ADL limitations than time without diabetes, and insulin initiation coincided with a step increase in limitations. The excess rose with each treatment step, and 10-year incidence of a new ADL limitation was roughly twice as high among adults using insulin at baseline as among adults without diabetes. These findings extend evidence linking diabetes to disability,[1,2] with three qualifications that the sensitivity analyses make clear: the insulin excess was partly shared with longer diabetes duration, it was not present on a relative scale, and it was weaker for IADL than for ADL.

Prior observational studies have documented that diabetes is a consistent predictor of functional limitation. Prospective evidence established diabetes as a risk factor for incident functional disability in older women,[2] and longitudinal analyses in an elderly urban cohort demonstrated that diabetes independently predicts long-term disability.[3] The Health, Aging, and Body Composition study documented subclinical ADL limitation among initially nondisabled older adults with diabetes,[4] and cross-sectional analyses in NHANES linked diabetes, comorbidity burden, and hemoglobin A1c to functional disability.[15] Community-based work further connected diabetes and hyperglycemia to functional disability burden,[16] and a meta-analysis confirmed the consistency of the diabetes–disability association across study designs.[1] In the HRS, diabetes has been associated with fewer disability-free life-years from age 50 years[12] and with geriatric conditions that develop from middle age onward.[13] The present analysis asks a different question: whether the intensity of diabetes treatment is associated with the rate of limitation accumulation. Several mechanisms may explain why insulin-treated diabetes predicts worse function. Insulin is usually started after other agents fail, so it marks longer disease duration, greater cumulative metabolic burden, and more microvascular and macrovascular complications; the attenuation of the insulin slope after adjustment for duration is consistent with this. Insulin and sulfonylureas carry the highest risk of hypoglycemia,[17] and diabetes has been associated with hospitalized fall injury,[18] while sulfonylureas have been associated with falls and fractures among nursing home residents with type 2 diabetes.[19] Beyond hypoglycemia and frailty,[6] insulin therapy causes weight gain, which was greater with insulin than with other intensive regimens in the UK Prospective Diabetes Study,[20] and obesity has become increasingly associated with disability in older US adults.[21] Insulin also requires dose adjustment, injection technique, and glucose monitoring; lower health literacy is associated with worse glycemic control,[22] and patients with low diabetes-related numeracy commonly misread glucose meters and miscalculate medication doses.[23] Difficulty managing a complex regimen may both reflect and add to early cognitive and functional decline. These pathways could not be tested directly in the HRS. Decision-analytic modeling has demonstrated that expected benefits of intensive glucose control depend on comorbid illness and functional status,[24] and multimorbidity patterning may further accelerate functional decline beyond the contribution of diabetes alone.[11]

The pattern across scales helps interpret the size of the association. On the additive scale, insulin users accumulated more limitations per decade; on the relative scale, they did so at a proportional rate similar to that of adults without diabetes. Because insulin users started from more limitations, both statements hold: the absolute burden grows faster, which is what matters for care needs, but the data do not show that insulin use multiplies the underlying rate of decline. Models that weight each respondent more equally gave larger estimates than the pooled model, so the primary estimate is conserva-

tive in magnitude.

Since 2010, long-acting GLP-1 RAs may have allowed some patients with type 2 diabetes to delay or avoid insulin, which could change who is classified as insulin-treated. The HRS does not record GLP-1 RA use, so we examined calendar period instead. Period-specific estimates were imprecise and did not differ, and the proportion of respondents with diabetes reporting insulin did not fall over the study period. These data therefore neither show nor exclude a change in the insulin association after GLP-1 RAs became available. Concerns about overtreatment in older adults with tight glycemic control are relevant,[7] as are descriptions of insulin use and discontinuation among adults aged 75–79 years with type 2 diabetes.[25]

The 50-year threshold matches the HRS sampling frame and prior HRS studies of diabetes and function.[9,11,12,13] Estimates were similar when the cohort was restricted to adults aged 65 years and older, the threshold used in American Diabetes Association guidance for older adults,[14] but imprecise when respondents aged ≥65 years at baseline were analyzed alone. The larger estimate at ages 50–64 years is consistent with HRS evidence that diabetes-related geriatric conditions appear in middle age.[13] The bidirectional relationship between function and diabetes is also germane: functional decline was associated with subsequent diabetes incidence in the HRS,[9] raising the possibility that reverse causation partially explains the observed associations. Psychosocial context, including loneliness and functional limitation, may further shape these relationships in ways not captured by the current covariate adjustment.[26]

For clinical care, the step increase in limitations at insulin initiation and the faster absolute accumulation afterward suggest that starting insulin is a natural point to assess ADL and IADL function, falls risk, and the ability to self-manage injections, and to reassess at follow-up visits. Adults who already need help with daily activities may need simplified regimens, caregiver involvement in insulin administration, or glycemic targets relaxed in line with guidance for older adults.[14] De-intensification strategies for elderly patients[27] and deintensification of insulin and sulfonylurea therapy after severe hypoglycemia[17] are being actively investigated, and the trajectories documented here support patient-centered goals that include maintenance of ADL independence. Next steps include HRS data linked to Medicare Part D claims, which would distinguish GLP-1 RAs, sodium-glucose cotransporter 2 inhibitors, sulfonylureas, and insulin and allow active-comparator designs; cohorts with hemoglobin A1c, hypoglycemia, weight, and health literacy measures to test the mechanisms above; and trials of whether functional assessment at insulin initiation, or de-intensification, changes functional trajectories.

Limitations

This analysis has several limitations. First, treatment was self-reported as current oral medication or insulin use at biennial interviews, without dose, adherence, glycemic, weight, or hypoglycemia measures; the insulin item was missing more often after the 2016 HRS diabetes-module revision, although restriction to respondents with complete treatment data or to follow-up through 2014 gave similar results. Second, the HRS does not distinguish type 1 from type 2 diabetes; excluding respondents with onset before age 30 years did not change the findings, but misclassification remains possible. Third, the HRS does not identify GLP-1 RAs or other non-insulin injectable agents, which respondents may have reported as insulin or omitted, and the calendar-period analysis cannot isolate their effect. Fourth, diabetes duration was counted from the first HRS report, which understates duration for respondents with diabetes at entry, so the duration-adjusted model may not fully separate duration from treatment. Fifth, as an observational cohort study, the analysis is susceptible to residual confounding and to reverse causation, and analyses beyond the primary model were not adjusted for multiple comparisons. Sixth, respondents who used insulin were more likely to die during follow-up; selective survival would tend to attenuate observed differences. Finally, primary estimates are unweighted; weighted estimates were similar.

Conclusions

In this cohort of adults aged 50 years and older from the Health and Retirement Study (1994–2022), insulin-treated diabetes was associated with more ADL limitations at insulin initiation and with faster absolute accumulation of limitations thereafter, compared with no diabetes, with a graded association across treatment steps. The excess was partly shared with longer diabetes duration, was not present on a relative scale, and was weaker for IADL, so it should be read as a marker of advanced disease rather than evidence that insulin causes decline. Insulin initiation may be a practical point at which to assess function and plan support for independence in daily activities.

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