Diabetes Care
American Diabetes Association

An Examination of Whether Diabetes Control and Treatments Are Associated With Change in Frailty Index Across 8 Years: An Ancillary Exploratory Study From the Action for Health in Diabetes (Look AHEAD) TrialNoninvasive Hypoglycemia Detection in People With Diabetes Using Smartwatch Data

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Diabetes Care 2023;46(3):519–525 | https://doi.org/10.2337/dc22-1728

ARTICLE HIGHLIGHTS

- Diabetes is reported to accelerate aging processes. It is unknown whether better control of type 2 diabetes may slow biological aging.
- We assessed whether lower HbA_{1c}, use of diabetes medication classes, and weight loss may slow the progression of a deficit accumulation frailty index, a marker of biological aging, over 8 years.
- Maintaining lower HbA_{1c}, use of metformin, and weight loss were independently associated with slower progression of a frailty index.
- These results suggest that better diabetes control may slow aging processes.

An Examination of Whether Diabetes Control and Treatments Are Associated With Change in Frailty Index Across 8 Years: An Ancillary Exploratory Study From the Action for Health in Diabetes (Look AHEAD) Trial

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Diabetes Care 2023;46:519–525 | https://doi.org/10.2337/dc22-1728

ORIGINAL ARTICLE

OBJECTIVE

The aim of this study was to describe cross-sectional and longitudinal associations between glycated hemoglobin (HbA_{1c}) levels and strategies to control type 2 diabetes with baseline levels and 8-year changes in a deficit accumulation frailty index (FI), a commonly used marker of biological aging.

RESEARCH DESIGN AND METHODS

We conducted exploratory analyses from 4,169 participants, aged 45–76 years, who were followed in the Action for Health in Diabetes (Look AHEAD) randomized controlled clinical trial, pooling data across intervention groups. We related baseline and 8-year levels of HbA_{1c} with FI scores using analyses of variance and covariance. Associations between 8-year changes in FI and the use of diabetes medication classes and weight changes were assessed with control for HbA_{1c} levels. Inverse probability weighting was used to assess bias associated with differential follow-up.

RESULTS

Baseline and average HbA_{1c} levels over time of <7%, as compared with ≥8%, were associated with less increase in FI scores over 8 years (both $P \leq 0.002$). After adjustment for HbA_{1c}, use of metformin and weight loss >5% were independently associated with slower increases in frailty.

CONCLUSIONS

Lower HbA_{1c} levels among individuals with diabetes are associated with slower biological aging as captured by a deficit accumulation FI. Strategies to control diabetes through weight loss or metformin use may also slow aging.

Type 2 diabetes is reported to accelerate biological aging (1,2) and is associated with both higher levels and more rapid increases in deficit accumulation frailty indices (FIs) (3). These indices combine age-related measures of individual physical and cognitive limitations with comorbidities and are used as indicators of the aging

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Received 2 September 2022 and accepted 27 November 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.21657221.

This article is featured in a podcast available at diabetesjournals.org/journals/pages/diabetes-core-update-podcasts.

**A complete list of the members of the Look AHEAD Research Group can be found within the publicly available resources at https://www.lookaheadtrial.org.*

process (4). Among older individuals with type 2 diabetes, maintaining a lower FI is associated with fewer adverse health events (5,6), and increases in FIs are associated with subsequent increased risk for mortality and poorer trajectories of physical and cognitive function (7).

It is unclear whether better control of type 2 diabetes may slow increases in FI. While some have reported that lower glycated hemoglobin (HbA_{1c}) among individuals with type 2 diabetes is associated with lower FI scores (3,8,9), others have reported that low HbA_{1c} may be associated with higher FI scores and worse trajectories of FI over time (10,11). Associations may be complicated by clinical factors, including treatment with high hypoglycemia risk medications that may lower HbA_{1c} but can cause serious adverse effects.

To further explore this topic, we examined the association between glycemic control and trajectories of FI among adults with type 2 diabetes over 8 years of follow-up. We also examined whether associations varied depending on the strategies for achieving control (weight loss, use of metformin as a first-line strategy, and other pharmacological therapies) because others have reported evidence that both intentional weight loss and metformin use may slow biological aging (e.g., 12,13). We examined whether weight loss and use of metformin (compared with the use of other oral medication and insulin) are independently associated with better 8-year trajectories of FI scores. We analyzed data from the large, diverse, and well-characterized cohort assembled by the Look AHEAD (Action for Health in Diabetes) randomized controlled clinical trial of a multidomain intensive lifestyle intervention (ILI) (14). We previously reported that this intervention, relative to a control condition of diabetes support and education (DSE), resulted in smaller 8-year FI increases (9).

RESEARCH DESIGN AND METHODS

The Look AHEAD protocol and Consolidated Standards of Reporting Trials (CONSORT) diagram have been published (14,15). It was a multisite, single-masked randomized controlled clinical trial that recruited 5,145 individuals (during 2001 to 2004) from 16 U.S. centers. All individuals had type 2 diabetes and met the following criteria: 45–76 years of age, BMI >25 kg/m^2 (>27 kg/m^2 if on insulin), HbA_{1c} <97 mmol/mol (11%), systolic/diastolic blood pressure $<160/<100$ mmHg, triglycerides <600 mg/dL, and a successful maximum graded exercise test. Protocols and consent forms were approved by local Institutional Review Boards.

Our descriptive analyses are based on data from the public use databases from Look AHEAD that are housed in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository (https://repository.niddk.nih.gov/studies/look-ahead/).

These include data on 4,906 of 5,145 Look AHEAD participants who agreed for their data to be shared. Of this subset, 4,174 (85%) had sufficient data to compute FIs at year 8 of follow-up and comprise our analysis data set. Supplementary Exhibit S5 provides a description of how these 4,147 participants differ from the 732 other repository participants who were excluded.

Interventions

Look AHEAD randomly assigned participants to ILI or DSE. The ILI targeted reducing caloric intake and increasing physical activity to induce weight loss $\geq$7% and maintaining this over time (16). Caloric consumption goals of 1,200 to 1,800 kcal/day were based on initial weight. Physical activity of >175 min/week through activities similar in intensity to brisk walking was targeted, as was improved diet (<30% calories from fat, <10% calories from saturated fat, and >15% calories from protein). During the first 6 months, ILI participants attended three group meetings and one individual session per month. For the remainder of the first year, they were provided two group meetings and one individual meeting per month. The intensity of the intervention gradually decreased thereafter.

DSE participants were invited to attend group sessions focused on diet, physical activity, and social support (17). Four meetings were offered during year 1, three per year during years 2–4, and one annually thereafter. Participants did not receive specific diet, activity, or weight goals or information on behavioral strategies. Both groups received feedback on cardiometabolic risk factors (lipids, HbA_{1c}, and blood pressure).

Interventions ended September 2012, when follow-up ranged from 8.4 to 11.1 years among participants. We used data from the first 8 years of follow-up to span the full time of intervention delivery for all participants.

Diabetes Control and Treatment

HbA_{1c} was assessed at baseline, annually through years 1–4, and at years 6 and 8 using standard protocols (14) by a central laboratory. We used the HbA_{1c} at baseline and the average HbA_{1c} across all assessments to characterize diabetes control for each individual and grouped individuals according to <7.0%, 7.0–7.9%, and $\geq$8%. The cut point of HbA_{1c} <7% was based on clinical recommendations during the administration of the Look AHEAD intervention (18). The cut point of 8% provided a reasonable number of participants with higher HbA_{1c} levels and has been used elsewhere in epidemiological research (e.g., O'Sullivan et al. [19]).

Participants were weighed annually by centrally trained and certified staff who were masked to intervention assignment (14). Participants were grouped into three categories according to weight changes from baseline: >5% decrease, no change in either direction of >5%, and >5% increase. A >5% weight loss has been defined as clinically significant (20), and cut points of >5% weight gains are often used in epidemiological studies (21).

Participants were asked to bring prescription medications to annual clinic visits for review. Diabetes medication use (grouped as insulins, metformin, and other oral medications) was summarized as the percent of these assessments (baseline through year 8) at which use of these medications was recorded and grouped as no use, <50% use, and $\geq$50% use.

Deficit Accumulation FI

We previously constructed a 38-item FI with components based on annual medical histories, clinic-based assessments, behaviors, functions, and abilities (9). Our original FI included two markers directly related to diabetes control (insulin use and fasting glucose): we eliminated these for the current analyses, resulting in a 36-component FI (see Supplementary Exhibit S7). Individual component scores range between 0 and 1, with higher scores reflecting health deficits. We calculated the total FI as the ratio of the sum of the individual component scores divided by the

number of components, expressed as a percentage ranging from 0 to 100.

Statistical Analysis

Differences in baseline characteristics across HbA_{1c} categories were assessed using χ^2 tests and analyses of variance. A scatterplot with an overlaid spline regression line was used to portray the association between baseline HbA_{1c} and FI. Associations between baseline HbA_{1c} and 8-year changes in FI were assessed using analyses of covariance, with adjustment for age (continuous), sex, diabetes duration, and intervention assignment. Associations between mean 8-year HbA_{1c} and 8-year FI changes were also based on ANCOVA with the same covariates. To examine the association between diabetes medication use (insulin, metformin, and other medications) and 8-year FI change, we used ANCOVA adjusted for mean HbA_{1c}. Additional adjustment for baseline age, sex, and diabetes duration had little impact on results and are not reported. We used the same approach to examine the association between BMI and FI change. This latter analysis was repeated for participants grouped according to baseline age to assess whether associations extended to relatively older participants. The potential impact of differential attrition was gauged using inverse probability of attrition weighting (22), with weights based on logistic regression with the following predictors at baseline: age, BMI, years of education, sex, smoking status, history of cardiovascular disease, history of diabetes among first-degree relatives, intervention assignment, general health and mental health component scores from the SF-36, and interactions between age and each of these factors.

Data and Resource Availability

As noted above, data from the Look AHEAD program, for participants who provided consent, are publicly available at the NIDDK Central Repository.

RESULTS

Table 1 describes characteristics of the cohort at baseline and cross-sectional associations with baseline HbA_{1c}. Overall, those in the group with the highest baseline HbA_{1c} levels were more likely to be younger with higher BMI and longer durations of diabetes and were more likely to use insulin. Random assignment to the Look AHEAD interventions was independent of baseline HbA_{1c}. Mean FI was greater among those with HbA_{1c} levels ≥8% (53 mmol/mol) compared with HbA_{1c} levels <7% (64 mmol/mol). Overall, the correlation between baseline HbA_{1c} and FI was modest (r = 0.08) and, based on spline regression, was approximately linear (Supplementary Exhibit S1).

Over 8 years of follow-up, those with greater mean HbA_{1c} were more likely to be younger and female and to have shorter diabetes durations, to not use insulin, to be assigned to ILI, and to have a lower baseline FI (Table 2).

Table 1—Baseline characteristics at Look AHEAD enrollment by baseline HbA_{1c} categories***

Baseline characteristic	Baseline HbA_{1c} (%) <7.0 (53 mmol/mol) (N = 1,944)	7.0–7.9 (N = 1,310)	≥8.0 (64 mmol/mol) (N = 915)	P value*
Age, years (%)				
45–54 (23.1)	390 (20.1)	288 (22.0)	291 (31.8)	<0.001
55–64 (56.9)	1,138 (58.5)	737 (56.3)	499 (54.5)	
65–76 (19.8)	416 (21.4)	285 (21.8)	125 (13.7)	
Sex (%)				
Female (59.1)	1,131 (58.2)	785 (59.9)	549 (60.0)	0.51
Male (40.9)	813 (41.8)	525 (40.1)	366 (40.0)	
BMI, kg/m^2 (%)				
25–29 (15.2)	330 (17.0)	183 (14.0)	121 (13.2)	0.01
30–39 (62.6)	1,215 (62.5)	824 (62.9)	571 (62.4)	
≥40 (22.2)	399 (20.5)	303 (23.1)	223 (24.4)	
Diabetes duration, years (%) (missing = 27)				
0–4 (46.6)	1,149 (59.5)	513 (39.5)	267 (29.2)	<0.001
≥5 (53.4)	782 (40.5)	785 (60.5)	646 (70.8)	
Diabetes medication (%) (missing = 41)				
Insulin (14.9)	132 (6.9)	225 (17.4)	257 (28.2)	<0.001
Metformin/no insulin (52.4)	991 (51.5)	704 (54.4)	468 (51.4)	
Other medications/no insulin (18.8)	403 (21.0)	231 (17.8)	144 (15.8)	
No medication (13.9)	397 (20.6)	135 (10.4)	41 (4.5)	
History of CVD (%)**				
No (86.9)	1,714 (88.2)	1,123 (85.7)	785 (85.8)	0.07
Yes (13.1)	230 (11.8)	187 (14.3)	130 (14.2)	
Intervention group (%)				
DSE (49.3)	947 (48.7)	656 (50.1)	453 (49.5)	0.74
ILI (50.7)	997 (51.3)	654 (49.9)	462 (50.5)	
FI	19.93 (0.15)	20.82 (0.19)	21.53 (0.22)	<0.001

Data are N (% of column) or mean (SE) unless otherwise indicated. *χ^2 test or ANOVA. **History of cardiovascular disease: self-report of prior myocardial infarction, coronary artery bypass, angioplasty/stent procedures, peripheral vascular disease, stroke, stable angina, or class I/II heart failure. ***N = 5 participants included in our analysis files did not have records of a baseline HbA_{1c} and did not contribute to this table.

Table 2—Baseline characteristics at Look AHEAD enrollment by mean HbA_{1c} over follow-up

Baseline characteristic	Mean HbA_{1c} (%) over 8 years			
	<7.0 (53 mmol/mol) (*N* = 2,181)	7.0–7.9 (*N* = 1,296)	≥8.0 (64 mmol/mol) (*N* = 697)	*P* value
Age, years (%)				
45–54 (23.1)	390 (17.9)	319 (24.6)	259 (37.2)	<0.001
55–64 (56.9)	1,268 (58.1)	737 (56.9)	375 (53.8)	
65–76 (19.8)	523 (24.0)	240 (18.5)	63 (9.0)	
Sex (%)				
Female (59.1)	1,264 (58.0)	760 (58.6)	445 (63.8)	0.02
Male (40.9)	917 (42.0)	536 (41.4)	252 (36.2)	
BMI, kg/m^2 (%)				
25–29 (15.2)	355 (16,3)	182 (14.0)	98 (14.1)	0.30
30–39 (62.6)	1,342 (61.5)	834 (64.4)	439 (63.0)	
≥40 (22.2)	484 (22.2)	280 (21.6)	160 (23.0)	
Diabetes duration, years (%) (missing = 27)				
0–4 (46.6)	1,216 (56.2)	487 (37.8)	229 (32.9)	<0.001
≥5 (53.4)	946 (34.8)	802 (62.2)	467 (67.1)	
Diabetes medication (%) (missing = 41)				
Insulin (14.9)	162 (7.5)	248 (19.3)	204 (29.4)	<0.001
Metformin/no insulin (52.4)	1,106 (51.3)	720 (56.0)	341 (49.2)	
Other medications/no insulin (18.8)	445 (20.6)	216 (16.8)	117 (16.9)	
No medication (13.9)	442 (20.5)	101 (7.9)	31 (4.5)	
History of CVD (%)				
No (86.9)	1,921 (88.1)	1,099 (84.8)	607 (87.1)	0.02
Yes (13.1)	260 (11.9)	197 (15.2)	90 (12.9)	
Intervention group (%)				
DSE (49.3)	984 (45.1)	697 (53.8)	379 (54.4)	<0.001
ILI (50.7)	1,197 (54.9)	599 (46.2)	318 (45.6)	
FI	20.22 (0.16)	20.60 (0.19)	21.49 (0.26)	<0.001

Data are *N* (% of column) or mean (SD) unless otherwise indicated.

As seen in Table 3, mean 8-year FI increased in a graded fashion with greater baseline HbA_{1c} levels ($P = 0.002$). FI increases were also larger among those with greater average HbA_{1c} levels over follow-up ($P < 0.001$), and this relationship was similar across participants grouped by baseline FI (interaction $P = 0.63$, data not shown). As seen in Supplementary Exhibit S2, associations were similar for participants grouped by baseline age (interactions $P > 0.20$).

Mean HbA_{1c} levels over time varied among participants grouped by diabetes medication use and BMI change (Supplementary Exhibit S3). Participants with mean HbA_{1c} levels ≥8% (64 mmol/mol) over time, as compared with those averaging lower HbA_{1c}, were less likely to have been assigned to ILI and more likely to use insulin. They were also less likely to use metformin or other oral diabetes medications or not use any medications. They also were less likely to have average weight losses of >5%.

As seen in Table 4, after adjustment for mean HbA_{1c} levels over follow-up, FI increases were smaller among individuals who were using metformin or no medications to treat their type 2 diabetes and were greater among individuals who were using insulin. There was little association between the use of other oral diabetes medications and FI changes. There was a graded relationship between weight loss and mean (SE) FI progression: 1.41 (0.32) for those with average weight losses >5%, 2.90 (0.27) for those with stable weight, and 6.05 (0.46) for those with weight gains >5%. As seen in Supplementary Exhibit S4, the relationship was fairly linear. This association was seen in both intervention groups. Compared with those with >5% average gains in weight, those with >5% weight losses among ILI participants had mean (SE) 5.19 (0.80) less FI accumulation (*N* = 99 >5% gainers vs. *N* = 923 >5% losers). Among DSE participants, the mean difference was 4.26 (0.64) (*N* = 238 >5% gainers vs. *N* = 385 >5% losers). Weight loss remained associated with less FI accumulation after adjustment for medication use ($P < 0.001$), and metformin use remained associated with less FI accumulation after adjustment for weight loss ($P = 0.008$).

Table 3—Eight-year changes in frailty scores by HbA_{1c} groupings

	Mean (SE)	*P* value
Baseline HbA_{1c} (%)		0.002
<7.0	2.43 (0.29)	
7.0–7.9	2.88 (0.31)	
≥8.0	3.54 (0.34)	
Mean HbA_{1c} over time (%)		<0.001
<7.0	1.99 (0.28)	
7.0–7.9	3.23 (0.31)	
≥8.0	4.47 (0.37)	

Table 4—Eight-year changes in FI for participants grouped by percent use of diabetes medications across annual visits and by mean percent change in BMI over time, with adjustment for mean HbA_{1c} across follow-up

	8-year changes in FI	
Diabetes control strategy	Mean (SE)	Mean (95% CI) difference from reference
Insulin		
Never (*N* = 2,616)	1.93 (0.27)	Reference
<50% (*N* = 749)	3.85 (0.37)	1.93 (1.29, 2.56)
≥50% (*N* = 809)	4.70 (0.37)	2.77 (2.11, 3.44)
Metformin		
Never (*N* = 866)	3.21 (0.35)	Reference
<50% (*N* = 1,111)	3.32 (0.32)	0.11 (0.55, 1.63)
≥50% (*N* = 2,197)	2.23 (0.28)	−0.98 (−1.57, −0.40)
Other oral medications		
Never (*N* = 269)	2.77 (0.28)	Reference
<50% (*N* = 1,114)	2.67 (0.32)	−0.10 (−0.62, 0.42)
≥50% (*N* = 361)	2.80 (0.45)	0.04 (−0.79, 0.86)
No medications		
Never (*N* = 2,940)	2.79 (0.27)	Reference
<50% (*N* = 816)	2.97 (0.62)	0.18 (−0.41, 0.77)
≥50% (*N* = 418)	1.83 (0.45)	−0.96 (−1.78, −0.15)
Mean percent change in BMI over time		
>5% gain (*N* = 338)	6.05 (0.46)	Reference
−5% to 5% (*N* = 2,507)	2.90 (0.27)	−3.14 (2.31, 3.78)
>5% loss (*N* = 1,329)	1.41 (0.32)	−4.63 (3.73, 5.53)

Supplementary Exhibit S5 describes differences in baseline characteristics between individuals in the Look AHEAD public use database (i.e., those who consented to have their data shared) who were included in our analyses versus those who were excluded because of missing 8-year data. Supplementary Exhibit S6 presents results from analyses parallel to those used for Table 4, but with inverse probability weighting to provide some protection against differential missing data. As can be seen, although there are minor differences in fitted means, the overall interpretation of these results closely mirrors those for Table 4.

CONCLUSIONS

Our descriptive analyses support that better diabetes control and specific approaches to diabetes treatment (weight loss and metformin use) might slow biological aging as captured by deficit accumulation FIs.

Others have reported that lower HbA_{1c} is associated with lower incidence of frailty and less progression of FIs (3). However, some have raised concerns that among individuals meeting criteria for frailty, low HbA_{1c} levels may accelerate its progression by increasing risks for functional deficits, falls, and mortality (11,23). This has led to recommendations that HbA_{1c} targets should be adjusted upwards as frailty develops (24,25). This drew us to examine whether relatively lower HbA_{1c} levels were associated with greater FI increases among Look AHEAD participants with higher baseline FI (i.e., those in the highest baseline tertile [FI >21]). Among these individuals, there was a graded relationship between 8-year subsequent increases in FI and average HbA_{1c} levels over time (P = 0.01). For those with average HbA_{1c} levels <7% (53 mmol/mol) over follow-up, mean (SE) increases in FI were 0.79 (0.47). For those with mean HbA_{1c} levels 7–7.9%, mean FI increases were 1.93 (0.49) and 3.04 (0.50) among those with mean HbA_{1c} levels ≥8% (64 mmol/mol). Thus, this suggests that among Look AHEAD participants with the greatest baseline FI, higher HbA_{1c} levels both at baseline and averaged over follow-up were associated with accelerated aging. It may be that Look AHEAD inclusion criteria (e.g., successful graded exercise test) and regular monitoring of HbA_{1c} and other metabolic risk factors altered relationships. In addition, there are reports that there may be different subtypes of diabetes related to frailty and HbA_{1c}, which may introduce heterogeneity in findings (26). We also note there is some evidence that among Look AHEAD participants with higher baseline FI, assignment to ILI was associated with a (nonsignificant but troubling) increased incidence of major cardiovascular events, with a hazard ratio of 1.29 (95% CI 0.94, 1.42) (6). This is despite ILI being equally successful in producing weight losses and fitness gains among participants with both relatively low and high baseline FI.

Look AHEAD participants who did not use diabetes medications were almost exclusively those with well-controlled HbA_{1c} (Supplementary Exhibit S3). These included some participants for whom diabetes was reversed (i.e., who maintained HbA_{1c} levels <6.5% [48 mmol/mol] with no medications during follow-up after meeting criteria for diabetes at baseline) (27). As we note, FI tended to increase relatively slowly among individuals who were most often not using diabetes medications

Increases in FI tended also to be slower among individuals using metformin. There is a growing appreciation that metformin use may slow both increases in frailty (28–30) and, underlying this, biological aging (31–34). Metformin may target multiple pathways in aging (e.g., inflammation, senescence, and immunity), both intra- and extracellularly (13,34,35). In some mouse models, long-term treatment with metformin starting at middle age extended both health span and life span (36). However, in a study of adults in the Diabetes Prevention Program clinical trial, an average of 2.8 years of randomization to metformin versus placebo was found to be ineffective in reducing frailty (37) or reducing mortality (38). Perhaps a longer duration of use is necessary for benefits, or differences may be due to the random assignment to metformin in the Diabetes Prevention Program. Clinical trials to assess the association between frailty and metformin are currently underway, including one studying metformin use in older adults with obesity (28). Others are planned (34,39). The potential benefits we see for metformin do not appear to extend to other diabetes medications, including insulin. Of note, this does not apply to sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists, which were not approved and available to participants over the time course of this study.

As noted in the introduction, we have previously examined the association that

8-year changes in FI have with subsequent (over up to 10 years) trajectories of walking speed, cognitive function, and mortality in the Look AHEAD cohort (7). Compared with participants with essentially no 8-year progression of FI (lower tertile), those with FI increases of ≥5.4 units (upper quartile) had significantly poorer profiles of subsequent walking speed and cognitive function and greater rates of mortality: hazard ratio 2.32 (95% CI 1.84, 2.94). Individuals with intermediate increases in FI (mid-tertile: midrange = 2.61) also had worse profiles of functions and increased mortality compared with those in the lower tertile of FI increases. Thus, the strength of associations seen in Table 4 may have important clinical implications.

Limitations

We report data from eligible volunteers for a randomized clinical trial of weight loss who may not represent general populations. We cannot rule out causation by indication in that medication use was not randomly assigned: a randomized clinical trial would be required to rule out reverse causation. In addition, our analyses of associations with weight loss are not based on intention to treat but instead are based on achieved weight loss. We have documented that individuals excluded from our analyses due to missing data differed from those who were included according to many baseline characteristics; however, based on our inverse probability weighting analyses, this did not appear to materially bias our findings.

Summary

Among adults with type 2 diabetes, poorer glycemic control is associated with greater frailty and worse profiles of frailty over time. Frailty progressed more slowly among individuals achieving weight loss and those treated with metformin, which may reflect slower biological aging.

Funding. This research was funded by two diversity supplements to the Action for Health in Diabetes Extension Study Biostatistics Research Center (NIDDK grants 3U01DK057136-19S1 and 3U01DK057136-19S2) and by the parent award U01DK057136. Support was also provided by National Institute on Aging grants R01AG058571, U01AG073697, and P30AG021332. Additional funding sources for the Look AHEAD study group are listed in Supplementary Exhibit S8.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. F.R.S. conducted statistical analyses and collaborated on drafting the manuscript. J.N.J., S.J.P., S.B.K., E.J.B., M.N.M., and C.K.F. reviewed and edited the manuscript and contributed to the discussion. M.A.E. obtained funding, conceived the research, and drafted the manuscript. All authors approved the final version of the manuscript. F.R.S. 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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