Associations that Cardiorespiratory Fitness and Body Mass Index Loss Have with Deficit Accumulation Frailty

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ABSTRACT

OLSON, K., D. K. HOUSTON, J. ROSS, R. R. WING, F. R. SIMPSON, A. PANDEY, M. P. WALKUP, M. YANG, and M. A. ESPELAND. Associations that Cardiorespiratory Fitness and Body Mass Index Loss Have with Deficit Accumulation Frailty. *Med. Sci. Sports Exerc.*, Vol. 56, No. 4, pp. 717–724, 2024. **Introduction/Purpose:** Lower cardiorespiratory fitness and obesity may accelerate aging processes. The degree to which changes in fitness and body mass index (BMI) may alter the rate of aging may be important for planning treatment. We assessed cross-sectional and longitudinal associations that cardiorespiratory fitness and BMI had with a deficit accumulation frailty index (FI). **Methods:** Fitness, based on standardized graded exercise tests, and weight to calculate BMI at baseline and year 4 were collected from 3944 participants aged 45–76 yr in the Action for Health in Diabetes (Look AHEAD) randomized controlled clinical trial. A validated 38-item deficit accumulation FI was used as a marker of aging. Associations between baseline and changes in fitness and BMI with changes in FI were assessed using linear models. **Results:** Both baseline and 4-yr changes in fitness and BMI were independently associated with 4-yr changes in frailty (all $P < 0.001$). Mean (95% confidence interval) changes in FI ranged from −0.019 (−0.024, −0.013) for participants in the group with the greatest fitness increase and BMI loss to 0.029 (0.024, 0.034) for participants in the group with the greatest fitness loss and BMI gain. Associations of 4-yr changes in fitness and BMI with FI changes were similar across subgroups based on age, sex, baseline BMI, diabetes duration, and cardiovascular disease history. Increased fitness across 4 yr was associated with less FI accumulation independent of baseline fitness. **Conclusions:** Adults with type 2 diabetes and overweight or obesity may slow aging processes captured by an FI by increasing their cardiorespiratory fitness and losing weight. **Key Words:** WEIGHT LOSS, BIOLOGICAL AGING, LIFESTYLE INTERVENTION, TYPE 2 DIABETES MELLITUS, EPIDEMIOLOGY

Lower cardiorespiratory fitness and physical capacity accelerate aging (1). This can be seen with associations with increased mortality (2,3) and multimorbidity (4), shortened healthspan (1), and many biomarkers related to accelerated aging (3,5). Deficit accumulation frailty indices (FIs), which combine markers of age-related deficits in clinical characteristics, disease states, behaviors, and function, are increasingly used as markers of aging (6,7). Increases in FI scores are associated with subsequent increases in mortality and poorer trajectories of cognitive and physical function (8). Although these indices are known to have cross-sectional and longitudinal associations with cardiorespiratory fitness (9,10), it is unknown whether individuals who improve their cardiorespiratory fitness through lifestyle changes may thereby slow aging processes captured by FIs.

Increases in fitness through changes in lifestyle are often accompanied by weight loss, and intentional weight loss and caloric restriction may slow aging processes (11–13) and the progression of FI (14). The degree to which increases in fitness additionally slow FI progression separately from weight loss is unknown.

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We make use of data from the Action for Health in Diabetes randomized controlled clinical trial (15). Its participants had established type 2 diabetes and overweight or obesity, which placed them at increased risk for accelerated aging. Half were randomly assigned to an intensive lifestyle intervention (ILI) that was successful in inducing body mass index (BMI) loss and increased cardiorespiratory fitness compared with an intervention featuring diabetes support and education (DSE) (16). Our primary goal was to assess whether relative increases in fitness and BMI losses over 4 yr independently or synergistically slowed progression of FI. We also examined the consistency of our findings across important clinical subgroups.

METHODS

The Look AHEAD protocol and CONSORT diagram have been published (15,17). Look AHEAD was a multisite, single-masked randomized controlled clinical trial that recruited 5145 individuals (from 2001 to 2004) from 16 US centers. All had type 2 diabetes and met the following criteria: 45–76 yr of age, BMI >25 $kg \cdot m^{-2}$ (>27 $kg \cdot m^{-2}$ if on insulin), glycated hemoglobin (HbA_{1c}) <97 $mmol \cdot mol^{-1}$ (11%), systolic/diastolic blood pressure <160/<100 mm Hg, triglycerides <600 $mg \cdot dL^{-1}$, a successful maximum graded exercise test. Protocols and consent forms were approved by local institutional review boards, and written informed consent was obtained from all participants.

The characteristics of the cohort at baseline have been published (18). Briefly, at enrollment, the cohort was 60% women, with mean (SD) BMI of 36.0 (5.9) $kg \cdot m^{-2}$, age of 58.7 (6.8) yr, diabetes duration of 6.8 (6.5) yr, and HbA_{1c} of 7.3% (1.2%).

Interventions. Participants were randomly assigned to ILI or DSE. The ILI targeted reducing caloric intake and increasing physical activity to induce weight loss >7% and maintaining this over time (19). Caloric consumption goals of 1200–1800 $kcal \cdot d^{-1}$ were based on initial weight. Physical activity of >175 $min \cdot wk^{-1}$ through activities similar in intensity to brisk walking was targeted, as was improved diet (<30% calories from fat, <10% calories from saturated fat, >15% calories from protein). Cardiometabolic risk factors (lipids, HbA_{1c}, blood pressure) were monitored, and participants were provided with results. 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 with two group 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 (20). 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; however, the protocol for sharing risk factor information with participants and their physicians was the same as for ILI.

Cardiorespiratory fitness and BMI. A graded exercise treadmill test was used to assess cardiorespiratory fitness at baseline and years 1, 2 (25% subset), and 4 (16,21). In this report, we only use data from baseline and year 4 assessments. Cardiorespiratory fitness was defined as the estimated metabolic equivalent (MET) level based on the treadmill workload (speed and grade) using the criteria of attaining 80% of maximal heart rate for participants not taking a β-blocker or the criteria of attaining a rating of 16 on the rating of perceived exertion (RPE) scale. Change in cardiorespiratory fitness was defined as the difference in estimated submaximal METs attained at year 4 and the submaximal METs attained at baseline using the same termination criteria of attaining either 80% of maximal heart rate or attaining a rating of 16 on the RPE scale.

Assessment procedures involved setting the speed of the treadmill at 1.5, 2.0, 2.5, 3.0, 3.5, or 4.0 mph for the baseline test based on preferred speed of the participant and heart rate response during the first minute of the test, and this speed remained constant throughout the test. The grade of the treadmill was initially set at 0% and increased by 1% at 1-min intervals throughout the test. Heart rate was assessed at rest, during the last 10 s of each exercise stage, and at the point of test termination using a 12-lead ECG. RPE was assessed using the Borg 15-category scale (range is from 6 to 20) during the last 15 s of each stage and at the point of test termination. Blood pressure was assessed using a manual sphygmomanometer and stethoscope during the last 45 s of each even-minute stage (e.g., 2 and 4 min).

The baseline test was terminated at the point of volitional exhaustion or at the point when American College of Sports Medicine test termination criteria were observed. A baseline test was considered valid if the maximal heart rate was ≥85% of age-predicted maximal heart rate ($HR_{Max} = 220 - age$) if the participant was not taking a β-adrenergic blocking medication (β-blocker). If the participant was taking a β-blocking medication, the baseline test was considered valid if RPE was ≥18 at the point of termination. To be eligible for participation in Look AHEAD, participants needed to achieve ≥4 METs on the baseline graded exercise test, where one MET is equal to 3.5 $mL \cdot kg^{-1}$ per minute of oxygen uptake.

The test at year 4 to assess cardiorespiratory fitness was a submaximal test, performed at the same walking speed as the baseline assessment. This submaximal test was terminated when the participant first achieved or exceeded 80% of age-predicted maximal heart rate ($HR_{Max} = 220 - age$) if the participant was not taking a β-blocker at either the baseline or year 4 assessment period. If the participant was taking a β-blocker at either the baseline or year 4 assessment, the submaximal test was terminated at the point when the participant first reported achieving or exceeding a rating of 16 on the RPE scale.

Weight was measured at baseline and year 4 using a digital scale by masked staff. Height was measured at baseline using a standard stadiometer and used to calculate BMI at both baseline and year 4 so that percent change in BMI was equal to percent change in weight.

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Deficit accumulation FI. As we noted in the Introduction, FIs have become widely used measures of health status and aging. Although these indices vary depending on data sources, a standard algorithm has been adopted for creating FI, where the score is a fraction of 30–40 evaluable health-related deficits that are present of the total evaluated, ranging from a possible score of 0 to 1 (22). In practice, scores greater than 0.40 are fairly rare and identify individuals with very poor health prognoses. Although increases in FI over time are correlated with increases in calendar age, FIs are designed to align more with biologic aging than calendar age (23).

We previously constructed an FI with 38 components based on annual medical histories, clinic-based assessments, behaviors, functions, and abilities (11,24). This FI has been validated in the Look AHEAD cohort: changes in the FI are strongly predictive of subsequent trajectories of cognitive and physical function and mortality (8).

Statistical analysis. Our analyses are drawn from 3944 (77%) of the 5145 Look AHEAD participants who had graded exercise tests and FI scores at baseline and year 4. Compared with the 1201 not included in the analyses, this subset of participants comprising our analysis dataset tended to be younger, be less heavy, and have no history of cardiovascular disease (all $P < 0.001$; see Supplemental Table 1, Supplemental Digital Content, Comparison of baseline characteristics of Look AHEAD participants included and not included in our analytic database, http://links.lww.com/MSS/C976). There was a modest imbalance between intervention groups: 51% of those included had been assigned to ILI compared with 46% of those not included ($P = 0.006$). At baseline, those included had a mean (SE) FI of 0.201 (0.001), and those not included had a mean FI of 0.222 (0.002), $P < 0.001$.

We grouped baseline fitness and 4-yr changes in fitness according to tertiles. For baseline fitness, the tertile ranges were 3.3–6.1 METs tertile 1 (least fit), 6.2–7.8 METs tertile 2 (moderate fit), and 7.9–16.7 METs tertile 3 (most fit). For 4-yr percent changes in fitness, these tertiles's ranges were ≤−10.0% tertile 1 (fitness decline), −10.0% to 8.4% tertile 2 (fitness stable), and >8.4% tertile 3 (fitness increase). We grouped baseline BMI as 25–29, 30–39, and >40 $kg \cdot m^{-2}$, as has commonly been done in other Look AHEAD publications. We defined 4-yr changes in BMI within ±2.5% as stable. These correspond to changes of about ±2.5 kg, which others have used to define stable weight (25,26). We labeled decreases in BMI >2.5% as loss and increases in BMI >2.5% as gain. χ^2 and *t*-tests were used to compare these groups with respect to baseline characteristics, intervention assignment, and baseline FI scores.

Associations that baseline levels of fitness and BMI had with 4-yr changes in FI were assessed using analyses of covariance, first with adjustment for age and intervention assignment, and then with additional adjustment for baseline fitness or BMI. Associations that 4-yr changes in fitness and BMI had with changes in FI were assessed similarly. β-Blocker use necessitated using participant's RPE rather than the age-predicted maximal heart rate to define the threshold used for the submaximal exercise testing (16,27). To assess whether this influenced our findings, we repeated these analyses after removing all individuals taking β-blockers at baseline and year 4 from the datasets. The consistency of relationships among subgroups based on age, sex, diabetes duration, history of cardiovascular disease, and intervention assignment was assessed by including interaction terms in models. The consistency of associations between 4-yr changes in fitness and 4-yr changes in FI among subgroups based on baseline fitness levels was also assessed using interaction terms.

RESULTS

As seen in Table 1, baseline fitness tended to be greater among participants who were relatively younger, were male, had lower BMI, had shorter durations of diabetes, did not have a history of cardiovascular disease, and had lower FI scores. At baseline, those with the greatest level of obesity tended to be younger, female, and less fit. They also had higher mean FI scores. As expected, there was little difference in baseline fitness and BMI levels between intervention groups because of randomization.

Four-year increases in fitness tended to occur more often among participants who were younger and had higher BMI, lower fitness, and no history of cardiovascular disease at baseline (Table 2). Women tended to be more likely to have stable fitness than men. Random assignment to the ILI was associated with less decline in fitness. Four-year BMI gains were more common among younger individuals, those with longer durations of diabetes, and those assigned to DSE.

Table 3 describes associations that baseline fitness and BMI had with 4-yr changes in FI. With adjustment for baseline age and intervention assignment, baseline BMI and fitness levels were each associated with FI changes ($P < 0.001$). Compared with those in the highest tertile of baseline fitness, those in the lowest tertile had nearly three times greater 4-yr mean progression in FI. Similarly, compared with those with overweight (BMI 25–29 $kg \cdot m^{-2}$) at baseline, those with class 3 obesity (BMI ≥40 $kg \cdot m^{-2}$) had over twice the mean worsening of FI. Adjustment for baseline BMI attenuated the association between baseline fitness and 4-yr FI changes, but it still remained significant ($P < 0.001$). Similarly, adjustment for baseline fitness modestly attenuated the relationship between baseline BMI and 4-yr FI changes.

Four-year changes in fitness and BMI were correlated in both intervention groups ($r = -0.26$ for DSE and $r = -0.32$ for ILI, both $P < 0.001$). Table 4 describes associations that 4-yr percent changes in fitness and BMI had with changes in FI. There was a strong graded inverse association between change in fitness and change in FI scores ($P < 0.001$), which was essentially unchanged with adjustment for changes in BMI. FI scores were essentially stable over 4 yr among participants whose fitness increased. Four-year changes in BMI had a strong direct association with changes in FI, which was independent of changes in fitness. FI was also essentially stable over 4 yr among individuals whose BMI decreased by >2.5%.

TABLE 1. Baseline characteristics at Look AHEAD enrollment by fitness groups: *n* (percent) or mean (SD).

Baseline Characteristic	Baseline Fitness, METs 1st Tertile [3.3–6.1] *n* = 1181	2nd Tertile [6.2–7.8] *n* = 1400	3rd Tertile [7.9–16.7] *n* = 1363	*P*[a]	Baseline BMI, kg·m^{-2} 25–29 *n* = 622	30–39 *n* = 2497	40+ *n* = 825	*P*
Age, yr								
45–54	201 (19.8)	369 (36.4)	443 (43.7)		122 (12.0)	591 (58.3)	300 (29.6)	
55–64	639 (29.2)	800 (36.6)	748 (34.2)	<0.001	333 (15.2)	1425 (65.2)	429 (19.6)	<0.001
65–76	341 (45.8)	231 (31.1)	172 (23.1)		167 (22.5)	481 (64.7)	96 (12.9)	
Sex								
Male	285 (17.8)	510 (31.8)	810 (50.5)	<0.001	284 (17.7)	1062 (66.2)	259 (16.1)	<0.001
Female	896 (38.3)	890 (38.1)	553 (23.6)		338 (14.5)	1435 (61.4)	566 (24.2)	
BMI, kg·m^{-2}					NA	NA	NA	NA
25–29	101 (16.2)	165 (26.5)	356 (57.2)					
30–39	631 (25.3)	930 (37.2)	936 (37.5)	<0.001				
40+	449 (54.4)	305 (37.0)	71 (8.61)					
Fitness, METS	NA	NA	NA	NA				
Low fit: 1st tertile [3.3–6.1]					101 (8.6)	631 (53.4)	449 (38.0)	<0.001
Middle fit: 2nd tertile [6.2–7.8]					165 (11.8)	930 (66.4)	305 (21.8)	
Most fit: 3rd tertile [7.9–16.7]					356 (26.1)	936 (68.7)	71 (5.2)	
Diabetes duration, yr (missing = 31)								
0–4	492 (27.1)	631 (34.7)	696 (38.3)	<0.001	282 (15.5)	1128 (62.0)	409 (22.5)	0.30
>5	676 (32.3)	762 (36.4)	656 (31.3)		335 (16.0)	1349 (64.4)	410 (19.6)	
History of CVD[b]								
No	1003 (28.9)	1246 (35.9)	1226 (35.3)	<0.001	546 (15.7)	2181 (62.8)	748 (21.5)	0.04
Yes	178 (38.0)	154 (32.8)	137 (29.2)		76 (16.2)	316 (67.4)	77 (16.4)	
Intervention group								
DSE	575 (29.8)	677 (35.1)	677 (35.1)	0.80	296 (15.3)	1232 (63.9)	401 (20.8)	0.70
ILI	606 (30.1)	723 (35.9)	686 (34.0)		326 (16.2)	1265 (62.8)	424 (21.0)	
FI	0.22 (0.002)	0.20 (0.002)	0.18 (0.002)	<0.001	0.17 (0.06)	0.20 (0.07)	0.22 (0.07)	<0.001

[a] χ^2 Test or analysis of variance.
[b] 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.

We repeated analyses underlying Tables 3 and 4, omitting the 29.6% of DSE participants and 29.1% of ILI participants ($P = 0.70$) who were recorded as taking β-blockers at baseline and/or year 4. As seen in Supplemental Tables 2 and 3 (Supplemental Digital Content, Relationship of baseline and 4-yr-change fitness and BMI, http://links.lww.com/MSS/C976), although table entries varied and some associations were attenuated, all remained statistically significant in this subset of participants who were not using β-blockers.

We examined whether there was an interaction between changes in fitness and BMI with respect to changes in FI. As seen in Figure 1, there was no evidence for an interaction

TABLE 2. Differences in 4-yr changes in fitness and BMI among participants grouped by baseline characteristics.

Baseline Characteristic	4-yr Change in Fitness Lowest Tertile *n* = 1317	Middle Tertile *n* = 1322	Highest Tertile *n* = 1305	*P*	4-yr Change in BMI Loss >2.5% *n* = 1903	Stable *n* = 1147	Gain >2.5% *n* = 894	*P*
Age, yr								
45–54	273 (26.9)	341 (33.6)	400 (39.4)		460 (45.4)	291 (28.7)	263 (25.9)	
55–64	750 (34.3)	733 (33.5)	706 (32.2)	<0.001	1034 (47.2)	666 (30.4)	489 (22.3)	<0.001
65–76	294 (39.7)	248 (33.5)	199 (26.9)		409 (55.2)	190 (25.6)	142 (19.2)	
Sex								
Male	554 (34.5)	497 (30.9)	555 (34.6)	0.02	778 (48.4)	492 (30.6)	336 (20.9)	0.05
Female	763 (32.6)	825 (35.3)	750 (32.1)		1125 (48.1)	655 (28.0)	558 (23.9)	
BMI, kg·m^{-2}								
25–29	214 (34.4)	202 (32.5)	206 (33.1)		272 (43.7)	207 (33.3)	143 (23.0)	
30–39	873 (35.0)	829 (33.2)	796 (31.9)	0.004	1205 (48.)	727 (29.1)	566 (22.7)	0.02
40+	228 (27.8)	291 (35.4)	302 (36.8)		425 (51.8)	212 (25.8)	184 (22.4)	
Fitness, METS								
Low fit: 1st tertile [3.3–6.1]	316 (26.8)	413 (35.1)	449 (38.1)	<0.001	590 (50.1)	316 (26.8)	272 (23.1)	0.02
Middle fit: 2nd tertile [6.2–7.8]	473 (33.8)	483 (34.5)	445 (31.8)		696 (49.7)	389 (27.8)	316 (22.6)	
Most fit: 3rd tertile [7.9–16.7]	528 (38.7)	426 (31.2)	411 (30.1)		617 (45.2)	442 (32.4)	306 (22.4)	
Diabetes duration, yr (missing = 31)								
0–4	577 (31.8)	609 (33.5)	631 (34.7)	0.06	896 (49.3)	557 (30.6)	364 (20.0)	<0.001
>5	732 (34.9)	700 (33.4)	664 (31.7)		989 (47.2)	583 (27.8)	524 (25.0)	
History of CVD								
No	1125 (32.4)	1156 (33.2)	1196 (34.4)	<0.001	1678 (48.3)	1016 (29.2)	783 (22.5)	0.79
Yes	192 (41.1)	166 (35.6)	109 (23.3)		225 (48.2)	131 (28.0)	111 (23.8)	
Intervention group								
DSE	751 (38.9)	633 (32.8)	546 (28.3)	<0.001	722 (37.4)	62 (32.8)	576 (29.8)	<0.001
ILI	566 (28.1)	689 (34.2)	759 (37.7)		1181 (58.6)	515 (25.6)	318 (15.8)	
FI	0.202 (0.069)	0.204 (0.069)	0.197 (0.064)	0.03	0.201 (0.07)	0.197 (0.07)	0.205 (0.07)	0.04

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TABLE 3. Relationship of baseline fitness and BMI with 4-yr changes in FI scores.

Baseline Fitness or BMI	4-yr Change in FI With Adjustment for Baseline Age and Intervention Assignment		4-yr Change in FI With Adjustment for Baseline Age, Intervention Assignment, and Either BMI or Fitness	
	Mean	95% CI	Mean	95% CI
Fitness, METS				
Low fit: 1st tertile [3.3–6.1]	0.017	0.013–0.020	0.014	0.010–0.018
Middle fit: 2nd tertile [6.2–7.8]	0.013	0.009–0.016	0.013	0.009–0.016
Most fit: 3rd tertile [7.9–16.7]	0.006	0.003–0.010	0.009	0.005–0.013
P	<0.001	—	<0.001	—
BMI, kg·m^{-2}				
25–29	0.009	0.004–0.014	0.011	0.006–0.016
30–39	0.010	0.007–0.012	0.010	0.008–0.012
>40	0.021	0.016–0.025	0.018	0.014–0.022
P	<0.001	—	<0.001	—

($P = 0.30$). FI increased more slowly among individuals with better profiles of fitness, irrespective of the benefits associated with BMI loss. Similarly, FI increased more slowly among individuals who had BMI loss, irrespective of changes in fitness. Mean (95% confidence interval (CI)) changes in FI ranged from −0.019 (−0.024 to −0.013) for participants in the group with the highest fitness increase and BMI loss to 0.029 (0.024 to 0.034) for participants in the group with the greatest fitness loss and BMI gain.

There was no evidence that the associations between changes in fitness and FI varied among subgroups at baseline based on sex, cardiovascular disease history, age, fitness, BMI, and intervention assignment (all interaction terms, $P > 0.05$; Table 5). As seen in Table 6, associations between changes in BMI and FI did not vary between these subgroups ($P > 0.05$), with one exception: the association between BMI loss and FI changes appeared to be steeper among ILI compared with DSE participants ($P = 0.02$).

With adjustment for baseline BMI and 4-yr changes in BMI, improvements in cardiorespiratory fitness slowed FI progression similarly across all baseline levels of fitness ($P = 0.89$), as seen in Figure 2.

DISCUSSION

At baseline, both cardiorespiratory fitness and BMI were strongly correlated in the Look AHEAD cohort (28), and poorer levels of both were associated with elevated FI at baseline and worsening in FI over time. These associations were to be expected based on prior reports, as noted in the Introduction (9,10,14). The finding that changes in BMI and fitness were both independently associated with changes in FI over 4-yrs is more novel: few studies have examined these associations over time. There are important clinical implications of this finding because it suggests that individuals who increase their fitness or decrease their BMI can slow the progression of FI. Because the benefits appear to be additive (given the lack of a significant interaction), the greatest benefit would be expected in those who have positive changes in both fitness and BMI. It is noteworthy that increases in fitness appeared to benefit FI for individuals irrespective of their level of fitness at baseline and even after statistical adjustment for both baseline and 4-yr change in BMI. It follows that prevention of either condition may contribute to slowing aging processes; however, prevention of either low fitness or obesity does not make up for the deficits associated with the other condition, as is similar to what has been reported about all-cause mortality (29).

TABLE 4. Relationship of 4-yr changes in fitness and BMI with 4-yr changes in frailty—with adjustment for baseline age and intervention assignment.

Change in Fitness and BMI	4-yr Change in FI With Adjustment for Baseline Age and Intervention Assignment		4-yr Change in FI With Adjustment for Baseline Age, Intervention Assignment, and Either BMI or Fitness	
	Mean	95% CI	Mean	95% CI
4-yr change in fitness, METS				
Decline: 1st tertile (<–10%)	0.017	0.013 to 0.020	0.017	0.014 to 0.021
Stable: 2nd tertile (–10% to 8%)	0.007	0.003 to 0.010	0.006	0.003 to 0.010
Increase: 3rd tertile (>8%)	–0.001	–0.005 to 0.002	–0.001	[–0.005 to 0.002]
P	<0.001	—	<0.001	—
4-yr change in BMI				
Loss: >2.5% loss	–0.005	–0.008 to –0.001	–0.005	–0.008 to –0.002
Stable: ±2.5% change	0.012	0.009 to 0.015	0.013	0.009 to 0.016
Gain: >2.5% gain	0.028	0.025 to 0.031	0.028	0.024 to 0.031
P	<0.001	—	<0.001	—

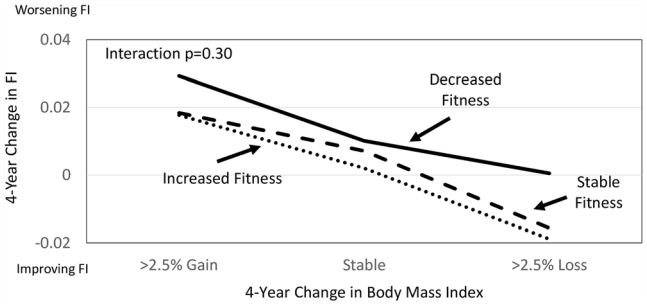

FIGURE 1—Mean 4-yr change in deficit accumulation frailty by change in fitness and BMI.

TABLE 5. Consistency of association that 4-yr changes in fitness have with 4-yr changes in FI across subgroups defined by characteristics at baseline: mean (SE) and interaction *P* value.

Subgroup	Tertile 4-yr Changes in Fitness: Decline Lowest Tertile <–10% *n* = 1311	Stable Mid-Tertile –10% to 8% *n* = 1309	Increase Highest Tertile >8% *n* = 1296	Interaction *P* Value
Age, yr				
45–54	0.017 (0.004)	0.005 (0.003)	–0.001 (0.003)	0.94
55–64	0.016 (0.002)	0.005 (0.002)	–0.002 (0.002)	
65–76	0.019 (0.004)	0.012 (0.004)	0.001 (0.004)	
Sex				
Female	0.017 (0.002)	0.008 (0.007)	–0.000 (0.002)	0.73
Male	0.017 (0.003)	0.004 (0.003)	–0.002 (0.003)	
BMI, kg·m^{-2}				
25–29	0.015 (0.004)	0.004 (0.004)	–0.001 (0.004)	0.19
30–39	0.013 (0.002)	0.004 (0.002)	–0.002 (0.002)	
>40	0.032 (0.004)	0.014 (0.004)	0.002 (0.004)	
Diabetes duration, yr				
<5	0.014 (0.003)	0.005 (0.003)	–0.000 (0.003)	0.35
>5	0.019 (0.002)	0.008 (0.002)	–0.002 (0.002)	
CVD history				
No	0.016 (0.002)	0.007 (0.002)	–0.002 (0.002)	0.25
Yes	0.021 (0.005)	0.001 (0.005)	0.004 (0.006)	
Intervention				
DSE	0.024 (0.002)	0.011 (0.002)	0.008 (0.003)	0.17
ILI	0.010 (0.003)	0.002 (0.002)	–0.010 (0.002)	

TABLE 6. Consistency of association that 4-yr changes in BMI have with 4-yr changes in FI across subgroups defined by characteristics at baseline: mean (SE) and interaction *P* value.

	Tertile 4-yr Changes in BMI			
Subgroup	Loss >2.5% Loss	Stable ±2.5% Change	Gain >2.5% Gain	Interaction *P* Value
Age, yr				
45–54	−0.008 (0.003)	0.009 (0.005)	0.021 (0.003)	0.97
55–64	−0.008 (0.002)	0.010 (0.003)	0.024 (0.002)	
65–76	0.001 (0.003)	0.017 (0.006)	0.030 (0.004)	
Sex				
Female	−0.005 (0.002)	0.012 (0.003)	0.024 (0.002)	0.88
Male	−0.007 (0.002)	0.009 (0.004)	0.024 (0.003)	
BMI, $kg \cdot m^{-2}$				
25–29	−0.008 (0.004)	0.005 (0.006)	0.026 (0.004)	0.18
30–39	−0.007 (0.002)	0.011 (0.003)	0.020 (0.002)	
>40	−0.001 (0.003)	0.018 (0.006)	0.037 (0.004)	
Diabetes duration, yr				
<5	−0.004 (0.002)	0.009 (0.003)	0.020 (0.003)	0.10
>5	−0.007 (0.002)	0.014 (0.003)	0.027 (0.002)	
CVD history				
No	−0.006 (0.002)	0.010 (0.003)	0.024 (0.002)	0.72
Yes	−0.004 (0.004)	0.019 (0.007)	0.025 (0.005)	
Intervention				
DSE	0.007 (0.002)	0.015 (0.003)	0.032 (0.002)	0.02
ILI	−0.008 (0.002)	0.015 (0.003)	0.024 (0.003)	

There is considerable evidence linking lower cardiorespiratory fitness to accelerated aging. For example, Kokkinos et al. (3) report that among US veterans aged 30–95 yr, being in the lowest quintile of fitness based on a standardized treadmill test was associated with a hazard ratio of 4.09 (95% CI, 3.90–4.20) for mortality across 10.2 yr of follow-up compared with being in the highest quintile. Poorer fitness based on exercise tests is associated with increased vascular aging (30), greater levels of multimorbidity (4), poorer profiles of brain structure and function (31–33), and poorer biomarkers of aging (5). More generally, markers related to greater physical capacity are associated with many biomarkers of aging (1). Separately, there is a vast literature establishing that obesity is related to accelerated aging (34,35). The Look AHEAD study has contributed to this. Within this cohort, participants with obesity at baseline had greater increases in FI scores over time (8,14).

Previous research suggests that weight loss without increased physical activity may lead to losses in cardiorespiratory fitness relative to weight loss with increased physical activity (36). However, we found that weight loss and cardiorespiratory fitness in Look AHEAD were correlated in both intervention groups, as has been reported earlier (21), suggesting that individuals in both intervention groups were following recommendations to maintain adequate levels of physical activity. Despite this correlation, both increases in fitness and BMI loss over 4 yr were independently associated with slower increases in FI, even after covariate adjustment for intervention assignment and age. Both appear to be important strategies for slowing the accumulation of health-related deficits. The benefits of BMI loss on FI may be larger than those for increased fitness, as seen in Figure 1 and Table 4; however, benefits for slowing the progression of FI associated with increased fitness were similar among those with BMI losses and BMI gains (based on the nonsignificant interactions). Across the full cohort, FI increased at a mean of about 0.01 units per year (37). Thus, the 4-yr differences seen in Figure 1, which range from about −0.02 to 0.03 units, may translate to 5-yr differences in "usual" aging in the Look AHEAD cohort.

Weight loss in older individuals can be a marker of impending age-related chronic diseases (38,39). Although we found benefit for BMI loss in slowing increases in FI scores, this may relate to the cohort's age range (45–76 yr) and the intentionality of weight loss advocated within both intervention groups. Importantly, the benefits of both increases in cardiorespiratory fitness and BMI loss on FI were statistically similar across the subgroups based on age, sex, baseline BMI, diabetes duration, and history of cardiovascular disease. Even among individuals in the highest age range (65–76 yr) of the Look AHEAD cohort, benefits of both BMI decreases and cardiorespiratory fitness gains were evident. We have previously reported that these older participants assigned to ILI achieved weight losses and increases in fitness that were at least as large as those achieved by younger participants (40).

Limitations. Our study benefited from the size of the cohort and standardized assessments in the Look AHEAD study. We acknowledge several limitations. As volunteers who met the eligibility criteria for a clinical trial of behavioral weight loss, the findings may not generalize to other cohorts and extend to individuals without type 2 diabetes and/or overweight or obesity. The analyses we report were not prespecified in the study protocol and thus should be viewed as exploratory. The study utilized submaximal fitness testing to assess cardiorespiratory fitness, which is less accurate than maximal graded fitness testing but considered safer, particularly in participants with musculoskeletal impairments, cardiovascular risk factors, and older adults (41). Furthermore, the current study assessed within subject change in cardiorespiratory fitness, which can be adequately quantified despite the limitations of the submaximal approach. The FI index that we use, although validated in the Look AHEAD cohort, is not replicated elsewhere. We describe associations that changes in fitness and BMI have with changes in FI but cannot rule out the possibility of reverse causality.

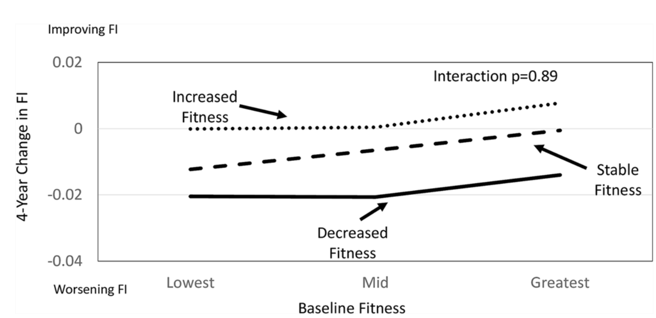

FIGURE 2—Mean 4-yr changes in frailty for participants grouped by baseline fitness tertile and 4-yr change in fitness tertile, with covariate adjustment for baseline BMI and 4-yr change in BMI.

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CONCLUSIONS

Among adults with type 2 diabetes and overweight or obesity, losing weight and increasing aerobic fitness may slow the rate of aging as captured by an FI.

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