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Research Article

Association of Baseline and Longitudinal Changes in Frailty Burden and Risk of Heart Failure in Type 2 Diabetes—Findings from the Look AHEAD Trial

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Abstract

Background: Individuals with diabetes have a high frailty burden and increased risk of heart failure (HF). In this study, we evaluated the association of baseline and longitudinal changes in frailty with risk of HF and its subtypes: HF with preserved ejection fraction (HFpEF), and HF with reduced ejection fraction (HFrEF).

Methods: Participants (age: 45–76 years) of the Look AHEAD trial without prevalent HF were included. The frailty index (FI) was used to assess frailty burden using a 35-variable deficit model. The association between baseline and longitudinal changes (1- and 4-year follow-up) in FI with risk of overall HF, HFpEF (ejection fraction [EF] ≥ 50%), and HFrEF (EF < 50%) independent of other risk factors and cardiorespiratory fitness was assessed using adjusted Cox models.

Results: The study included 5 100 participants with type 2 diabetes mellitus, of which 257 developed HF. In adjusted analysis, higher frailty burden was significantly associated with a greater risk of overall HF. Among HF subtypes, higher baseline FI was significantly associated with risk of HFpEF (hazard ratio [HR] [95% CI] per 1-*SD* higher FI: 1.37 [1.15–1.63]) but not HFrEF (HR [95% CI]: 1.19 [0.96–1.46]) after adjustment for potential confounders, including traditional HF risk factors. Among participants with repeat measures of FI at 1- and 4-year follow-up, an increase in frailty burden was associated with a higher risk of HFpEF (HR [95% CI] per 1-*SD* increase in FI at 4 years: 1.78 [1.35–2.34]) but not HFrEF after adjustment for other confounders.

Conclusions: Among individuals with type 2 diabetes mellitus, higher baseline frailty and worsening frailty burden over time were independently associated with higher risk of HF, particularly HFpEF after adjustment for other confounders.

Keywords: Diabetes, Frailty, Frailty index, Heart failure

Type 2 diabetes mellitus (T2DM) is a significant risk factor for cardiovascular disease (CVD), including heart failure (HF) (1–3). Specifically, T2DM and associated cardiometabolic abnormalities have been implicated in the growing burden of HF with preserved ejection fraction (HFpEF)—a subtype of HF that is unique to older adults, associated with a high burden of morbidity, mortality, and poor quality of life (1,4,5). Thus, novel approaches to prevent HF are needed among older individuals with T2DM.

Recent studies have demonstrated the excess risk of HF associated with T2DM persists despite optimal management of traditional cardiovascular risk factors (3). Besides the higher burden of traditional HF risk factors, older adults with T2DM also have a high prevalence of frailty (6). Frailty is a clinical syndrome characterized by accumulation of deficits, reduced physiological reserve, and associated impairment in functional status (7,8). Frailty can be quantified using the previously validated deficit accumulation model, in which health factors associated with aging are evaluated and summed to calculate a frailty index (FI) (9–12). While frailty has been previously associated with worse functional status, higher risk of hospitalization, and mortality in older adults, the association of frailty burden with the risk of overall HF and its subtypes—HFpEF and HF with reduced ejection fraction (HFrEF)—are not well characterized in patients with T2DM (8,13). Furthermore, it is unclear if longitudinal changes in frailty may modify the risk of HF independent of the baseline frailty burden. Accordingly, we evaluated the associations of baseline and longitudinal changes in FI with the risk of HF and its subtypes among participants of the Look AHEAD (Action for Health in Diabetes) trial. We hypothesized that higher frailty at baseline and worsening frailty burden over time would be associated with a higher risk of HF, particularly HFpEF. Our hypothesis is based on prior studies and observations that have demonstrated a substantial overlap in the pathophysiology of frailty and HFpEF in older adults (7,14).

Method

Look AHEAD Trial Design, Population, and Interventions

The Look AHEAD study design and primary results have been published previously (15,16). In brief, Look AHEAD was a multicenter, unblinded, randomized controlled trial which enrolled 5 145 participants with T2DM and overweight or obesity (body mass index [BMI] ≥ 25 or ≥27 kg/m^2 if taking insulin). Participants between 45 and 76 years old who could complete a maximal exercise test were included. The presence of T2DM was determined based on physician reports, use of medications for T2DM, or measured plasma glucose levels. Participants were randomized to either an intensive lifestyle intervention regimen or diabetes support and education. The multidomain intensive lifestyle intervention aimed to attain an average weight loss of ≥7% at 1 year and maintain this over time by dietary and physical activity modification (17). Targeted calorie intake was set as 1 200–1 800 kcal per day (<30% of total calories from fat and a minimum of 15% of calories from protein). Targeted physical activity was set as ≥175 min/wk of moderate-intensity exercise (15). Frailty was assessed at baseline and over 1- and 4-year follow-up as described below. Written informed consent was provided by all participants in the Look AHEAD trial, and the consent form and study protocol were approved by the institutional review board of each trial site.

Exposure Variable of Interest—Frailty Index

The exposure variable of interest for this study was a deficit accumulation FI. The details regarding the development of the FI as a continuous measure of frailty burden in the Look AHEAD trial have been described previously (18,19). The FI model developed in the Look AHEAD cohort included 38 health factors that comprised participant characteristics across different domains, including self-rated health, quality of life, cardiovascular risk factor burden, noncardiac comorbidities, and functional status. Consistent with prior approaches, binary variables were assigned a score of 0 (absent) or 1 (present). Ordinal variables were coded by converting the number of possible ranks into equally spaced scores ranging from 0 to 1. Continuous variables were dichotomized as 0 (normal) or 1 (abnormal) based on established clinical thresholds, with 1 representing the most severe deficit. FI was calculated by dividing the total number of deficits present by the total number of deficits assessed. The components used to calculate FI were recorded at baseline and annual follow-up using standardized questionnaires. The details of baseline and follow-up assessment of different demographic, anthropometric, lifestyle, clinical characteristics, quality of life parameters, and condition-specific questionnaires have been reported previously (18,19). For the present study, we excluded 3 FI questions on the presence of HF and HF symptoms at baseline. The final FI model for the present analysis included 35 health factors as detailed in Supplementary Table 1. Participants were required to have data for at least 28 (80%) health factors to create a score.

Covariates

Among other covariates, baseline and follow-up assessment of clinical characteristics, anthropometric measures, and laboratory parameters were performed using previously reported standardized protocols (15,16). The cardiorespiratory fitness of participants was assessed using a maximal exercise test at baseline and submaximal exercise tests at 1 and 4 years using previously reported protocols (15,16). These tests were used to estimate peak metabolic equivalents (METs). Longitudinal change in cardiorespiratory fitness was calculated as the difference between baseline and follow-up measures.

Outcomes of Interest—Incident HF

The primary outcome of interest for this study was incident HF events on follow-up. Secondary outcomes of interest were HF subtypes: HFpEF and HFrEF. As reported previously, incident HF events (overall HF, HFpEF, and HFrEF) were adjudicated in the Look AHEAD trial over a median follow-up period of 12.4 years as part of an ancillary study (20). Briefly, HF outcome events on follow-up were identified by self-report or using administrative claims codes from hospitalization/clinic records and subsequently adjudicated using a well-established protocol (21). The adjudication was performed independently by two physicians who were unaware of the participant's treatment group assignment. The physicians reviewed clinical data (history, physical examination, test results, medications) to classify each case as "definite or possible acute HF," "chronic stable HF," "HF unlikely," or "unclassifiable." An outcome event classified as "definite or possible acute HF" classification was considered incident HF, and only the first HF hospitalization was adjudicated (20). HF subtypes

were determined based on available left ventricular ejection fraction data at the time of HF diagnosis. Consistent with established guideline recommendations, a HF event with a left ventricular ejection fraction ≥ 50% around the time of the index event was defined as HFpEF, and HF with left ventricular ejection fraction <50% was defined as HFrEF (22).

Statistical Analysis

The present study included participants of the Look AHEAD trial who did not have prevalent HF at baseline and had available data for calculation of FI (n = 5 100, Supplementary Figure 1). Participants without left ventricular ejection fraction data for an incident HF event were excluded from the HF subtype analysis. Participants who had follow-up data for calculation of FI at years 1 and 4 and were free of HF at the time of follow-up visit were included in the analysis evaluating the association of changes in FI and risk of HF (Supplementary Figure 1).

Participants were stratified into tertiles based on their baseline FI. Baseline characteristics were compared using chi-square tests for categorical variables and generalized linear models for continuous variables. Similarly, participants were stratified into tertiles based on the percentage change in FI at 1 and 4 years, and the baseline and follow-up characteristics were compared across tertiles of FI change. The association between continuous and categorical (tertiles [T1 to T3], referent group: T1) measures of baseline frailty and risk of overall HF, HFpEF, and HFrEF was evaluated using unadjusted cumulative incidence curves and adjusted Cox proportional hazards models with the following adjustments: *Model 1* adjusted for age, sex, race/ethnicity, and treatment arm; *Model 2* adjusted for all covariates in Model 1 as well as baseline estimated cardiorespiratory fitness (METs); *Model 3* adjusted for covariates in Model 2 and traditional HF risk factors (history of hypertension based on self-report and antihypertensive medication use, systolic blood pressure, smoking status, drinking status, history of CVD, HbA1c, glomerular filtration rate, body mass index). Separate models were constructed for overall HF and HF subtype outcomes with mortality and other HF subtype events treated as censoring events. Sensitivity analyses were performed to evaluate the association between FI at baseline and risk of HF excluding individuals who developed HF within the first 2 years of follow-up. Multiplicative interaction tests were performed to determine whether the association between the FI and risk of HF was modified by study intervention, gender, race, BMI, and baseline cardiorespiratory fitness. Stratified analyses were performed for any significant interactions or subgroups of interest.

The association between changes in FI at 1- and 4-year follow-up with downstream risk of HF was assessed in a subset of participants who did not have HF at the time of follow-up assessment of FI parameters (N = 4 751 for 1 year and N = 4 481 for 4-year follow-up). Separate Cox proportional hazards models were constructed evaluating the association of changes in FI at 1- and 4-year follow-up with risk of HF outcomes adjusting for the following covariates: *Model 1*—age, sex, race/ethnicity, treatment arm, baseline FI, and baseline cardiorespiratory fitness; *Model 2*—Model 1 + change in cardiorespiratory fitness (METs), percent change in HbA1c, and percent change in systolic blood pressure from baseline to year 1 or 4, respectively. Change in FI on follow-up was analyzed as a continuous and a categorical variable (data-derived tertiles) with separate models for each exposure and outcome variable (overall HF, HFpEF, and HFrEF) of interest. A 2-sided p-value < .05 was considered statistically significant. All the analyses were conducted using SAS statistical analysis software.

Results

Baseline Characteristics Across Frailty Strata

The current study included 5 100 participants (99.1% of the original Look AHEAD cohort, 59.6% women, 63.3% White participants). The baseline characteristics of the study participants stratified by their baseline FI are shown in Table 1. There were no meaningful differences in age or treatment assignment across the baseline FI categories. Participants with a higher frailty burden (FI Tertile 3) were more commonly women, less commonly of the self-reported White race, and had lower education levels and lower annual income. Participants with a higher frailty burden also had higher BMI, lower cardiorespiratory fitness levels, longer duration of T2DM, higher HbA1c, and greater use of insulin. The prevalence of traditional CV risk factors and prevalent CVD was also higher among participants with a higher frailty burden.

Association Between Baseline Frailty and Risk of HF

Over a median follow-up of 12.4 years (57 985 person-years), 257 HF events occurred in the overall cohort (4.43 events per 1 000 patient-years). Of these, 129 (50.2% of all HF events, 2.23 events per 1 000 person-years) were HFpEF, and 104 (40.5% of all HF events; 1.80 events per 1 000 person-years) were HFrEF, and 24 with HF and missing EF (9.3% of all HF events). In unadjusted analysis, higher baseline frailty was significantly associated with a higher risk of overall HF (Supplementary Figure 2; log-rank p-value < .001). In Cox models, higher frailty burden at baseline was associated with a significantly higher risk of overall HF after adjusting for demographic characteristics and treatment arm (hazard ratio [HR] [95% CI] per 1-*SD* higher FI: 1.70 [1.53–1.90], Model 1, Table 2). This association attenuated modestly but remained significant after further adjustment for baseline cardiorespiratory fitness and other traditional HF risk factors (HR [95% CI] per 1-*SD* higher FI: 1.28 [1.13–1.46] , Model 3, Table 2). Similar findings were noted using categorical measures of FI (tertiles) such that participants with the highest frailty burden (tertile 3) had a 61% higher risk of incident HF in the most adjusted model (HR [95% CI] T3 vs T1 [ref] = 1.61 [1.11-2.34], Model 3, Table 2).

Among HF subtypes, in unadjusted analysis, higher baseline FI was significantly associated with greater risk HFpEF and HFrEF (Supplementary Figure 3, log-rank p-value < .001 and .003, respectively). In adjusted Cox models, higher baseline frailty burden was significantly associated with greater risk of HFpEF in partially as well as fully adjusted models accounting for cardiorespiratory fitness and other traditional risk factors (HR [95% CI] per 1-*SD* higher FI: 1.37 [1.15–1.63] Model 3, Table 2). Higher frailty burden was also significantly associated with the risk of HFrEF after adjustment for demographic characteristics and baseline cardiorespiratory fitness. However, this association attenuated and was not significant after further adjustment for other traditional HF risk factors (HR [95% CI] per 1-*SD* higher FI: 1.19 [0.96–1.46], Model 3, Table 2). Similar patterns of association were noted using categorical measures of FI such that participants with the highest frailty burden (Tertile 3 vs Tertile 1) had a significantly higher risk of HFpEF (HR [95% CI] T3 vs T1 (ref) = 1.92 [1.11–3.32], Model 3, Table 2) but not HFrEF (HR [95% CI] T3 vs T1 (ref) = 1.23 [0.71–2.14], Model 3, Table 2) in the most adjusted analysis.

There was no significant interaction between baseline FI and treatment arm (p-interaction = .77), race (p-interaction = .67), BMI (p-interaction = .70), and baseline cardiorespiratory fitness (p-interaction = .27) for the risk of HF. A significant interaction

Table 1. Baseline Characteristics Stratified by Frailty Index Tertiles

Variable	FI Tertile 1 FI: 0.14 (0.02) (*n* = 1 710)	FI Tertile 2 FI: 0.20 (0.02) (*n* = 1 686)	FI Tertile 3 FI: 0.28 (0.05) (*n* = 1 704)	*p*-Value
Range of frailty index	0.034–0.174	0.174–0.230	0.231–0.518	—
Age, y	58.8 (6.8)	58.7 (7.0)	58.6 (6.8)	.81
Female, *n* (%)	957 (56.0)	1 018 (60.4)	1 066 (62.6)	<.001
White, *n* (%)	1 078 (63.0)	1 096 (65.0)	1 054 (61.9)	<.001
Education, (%)				<.001
<13 y	302 (17.7)	324 (19.2)	383 (22.5)	
13–16 y	555 (32.5)	654 (38.8)	693 (40.7)	
>16 y	817 (47.8)	670 (39.7)	588 (34.5)	
Missing	36 (2.1)	38 (2.3)	40 (2.4)	
Income, n (%)				<.001
<$20k	161 (9.4)	166 (9.9)	254 (14.9)	
$20k–$40k	257 (15.0)	331 (19.6)	389 (22.8)	
$40k–$60k	292 (17.1)	330 (19.6)	322 (18.9)	
$60k–$80k	272 (15.9)	244 (14.5)	229 (13.4)	
>$80	534 (31.2)	461 (27.3)	358 (21.0)	
Missing	194 (11.4)	154 (9.1)	152 (8.9)	
BMI, kg/m^2	34.5 (5.5)	36.1 (5.8)	37.3 (6.1)	<.001
Estimated fitness, METs	7.8 (2.0)	7.2 (1.9)	6.6 (1.8)	<.001
Systolic BP, mmHg	126.1 (15.2)	128.9 (17.1)	131.5 (18.4)	<.001
Diastolic BP, mmHg	69.9 (9.1)	70.0 (9.4)	70.5 (10.1)	.21
History of CVD, *n* (%)	113 (6.6)	201 (11.9)	361 (21.2)	<.001
History of hypertension, *n* (%)	1 332 (77.9)	1 401 (83.1)	1 505 (88.3)	<.001
Duration of diabetes, y	5.6 (5.5)	6.6 (6.3)	8.1 (7.4)	<.001
Smoking, *n* (%)				<.001
Never	1 022 (59.9)	801 (47.6)	733 (43.1)	
Past	656 (38.4)	813 (48.3)	840 (49.4)	
Present	29 (1.7)	69 (4.1)	127 (7.5)	
Alcohol, n (%)				.008
None/wk	1 119 (65.6)	1 144 (68.1)	1 185 (69.8)	
1–3/wk	330 (19.3)	332 (19.8)	325 (19.1)	
≥4+/wk	257 (15.1)	204 (12.1)	188 (11.1)	
HbA1c, %	7.0 (1.0)	7.2 (1.1)	7.6 (1.3)	<.001
GFR, mL/min per 1.73 m^2	89.9 (15.1)	89.8 (16.1)	89.4 (16.8)	.63
ILI treatment group, *n* (%)	836 (48.9)	848 (50.3)	859 (50.4)	.61
Insulin use, *n* (%)	81 (4.9)	213 (13.1)	489 (29.7)	<.001
LDL, mg/dL	113.0 (28.7)	112.2 (32.2)	111.0 (35.5)	.19

Notes: BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; ILI = intensive lifestyle intervention; LDL = low-density lipoprotein cholesterol; METs = metabolic equivalents.

was noted between FI and sex (*p*-interaction = .05 using a continuous measure of FI and *p* = .003 using FI tertiles) for the risk of HF. In the sex-stratified analysis, higher baseline FI was more strongly associated with the risk of HF and its subtypes in men versus women (Supplementary Tables 2 and 3). The association between higher baseline FI and HF risk was consistent across tertiles of BMI (Supplementary Table 4). In sensitivity analysis landmarking at 2 years of follow-up, the pattern of association between FI and risk of HF outcomes was similar to that observed in the primary analysis (Supplementary Table 5).

Association Between Changes in Frailty Index and Risk of HF

The association between changes in FI and risk of HF was assessed in the subset of participants who were free of HF and had data available for repeat calculation of FI at 1-year (*n* = 4 751) and 4-year (*n* = 4 481) follow-up. The baseline and follow-up characteristics of study participants stratified across tertiles of FI change at 1- and 4-year change are shown in Supplementary Tables 6 and 7. At 1-year follow-up, participants in tertile 1 of FI change had a modest improvement in frailty burden, those in Tertile 2 had no meaningful change in FI, and those in tertile 3 had worsening frailty burden. Participants with worsening frailty burden (Tertile 3) were more commonly White, less commonly randomized to the intensive lifestyle intervention arm, had a longer duration of diabetes, and had less favorable improvement in cardiometabolic parameters and CV risk factors on follow-up, with less weight loss, fitness improvement, blood pressure, and HbA1c reduction on follow-up. Similar patterns in baseline and follow-up characteristics were noted across 4-year FI change categories.

In adjusted analysis, increasing FI burden at 1-year follow-up was significantly associated with a higher risk of overall HF after adjustment for baseline characteristics and interval change in cardiorespiratory fitness, HbA1c, and systolic blood pressure (HR [95% CI] per 1-*SD* increase in FI: 1.24 [1.03–1.50], Model 2, Table 3). Among HF subtypes, increasing frailty burden was significantly associated with higher risk of HFpEF (HR [95% CI] per 1-*SD*

Table 2. Multivariable Adjusted Association of Baseline Frailty Index With Risk of Incident Overall HF, HFpEF, and HFrEF

	Model 1		Model 2		Model 3	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Overall HF (*N* = 257 Events)						
Continuous frailty measure						
Per 1-*SD* (0.07) higher	1.70 (1.53–1.90)	<.001	1.53 (1.36–1.71)	<.001	1.28 (1.13–1.46)	<.001
Frailty categories (referent group: Tertile 1)						
Tertile 2	1.94 (1.34–2.81)	<.001	1.64 (1.13–2.37)	.01	1.30 (0.89–1.90)	.17
Tertile 3	3.51 (2.49–4.96)	<.001	2.61 (1.84–3.72)	<.001	1.61 (1.11–2.34)	.01
HFpEF (*N* = 129 events)						
Continuous frailty measure						
Per 1-*SD* (0.07) higher	1.81 (1.56–2.11)	<.001	1.62 (1.38–1.90)	<.001	1.37 (1.15–1.63)	<.001
Frailty categories (referent group: Tertile 1)						
Tertile 2	2.28 (1.32–3.94)	.003	1.91 (1.10–3.30)	.02	1.48 (0.85–2.60)	.17
Tertile 3	4.25(2.55–7.09)	<.001	3.11 (1.85–5.24)	<.001	1.92 (1.11–3.32)	.02
HFrEF (*N* = 104 events)						
Continuous frailty measure						
Per 1-*SD* (0.07) higher	1.54 (1.29–1.84)	<.001	1.44 (1.19–1.73)	<.001	1.19 (0.96–1.46)	.11
Frailty categories (referent group: Tertile 1)						
Tertile 2	1.48 (0.86–2.53)	.15	1.34 (0.78–2.30)	.30	1.08 (0.62–1.88)	.79
Tertile 3	2.44 (1.47–4.03)	<.001	2.02 (1.21–3.39)	.008	1.23 (0.71–2.14)	.46

Notes: BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; GFR = glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; HbA1c = hemoglobin A1c. Model 1: Adjusted for age, sex, race/ethnicity, and treatment arm. Model 2: Model 1 + baseline estimated fitness (METs). Model 3: Model 2 + history of hypertension, systolic blood pressure, smoking status, drinking status, history of CVD, HbA1c, GFR, BMI.

increase in FI: 1.39 [1.06–1.83], Model 2, Table 3) but not HFrEF (HR [95% CI] per 1-*SD* increase in FI: 1.15 [0.85–1.54], Model 2, Table 3) in the most adjusted model. Similar patterns of association were observed in adjusted analysis using frailty change categories. Individuals with worsening frailty burden had a significant 2-fold higher risk of HFpEF (HR [95% CI] T3 vs T1 [ref] = 2.01 [1.20–3.37], Model 2, Table 3) but not HFrEF (HR [95% CI] T3 vs T1 (ref) = 1.04 [0.58–1.88], Model 2, Table 2) on follow-up.

The patterns of association between changes in frailty burden at 4-year follow-up and risk of HF were comparable to those noted for 1-year change. Sustained increase in frailty burden at 4-year follow-up was associated with a significantly higher risk of overall HF (HR [95% CI] per 1-*SD* increase in FI at 4 year: 1.47 [1.21–1.79], Model 2, Table 4), which was driven by an increased risk of incident HFpEF (HR [95% CI] per 1-*SD* increase in FI at 4 years: 1.78 [1.35–2.34], Model 2, Table 4) but not HFrEF (HR [95% CI] per 1-*SD* increase in FI at 4 years: 1.13 [0.84–1.53], Model 2, Table 4). Similar pattern of results was observed using tertiles of change in FI as the exposure variable of interest (Table 4). There was no significant interaction between FI change (at 1 and 4 years) and treatment arm, sex, or race for the risk of HF (*p*-interaction > .20 for all).

Discussion

In this post hoc analysis of the Look AHEAD trial, we report several important findings. First, among adults with T2DM, higher baseline frailty was significantly associated with increased risk of HF and its subtypes—HFpEF and HFrEF. Second, the association between frailty and risk of HFrEF was driven mainly by the high burden of traditional HF risk factors. In contrast, the increased risk of HFpEF among individuals with high frailty burden was independent of baseline cardiorespiratory fitness levels and other HF risk factors. Third, the worsening burden of frailty on follow-up was also associated with an increased risk of HFpEF but not HFrEF independent of baseline cardiorespiratory fitness and changes in fitness on follow-up. Our findings suggest that higher frailty at baseline and worsening frailty burden contribute to the increased risk of HFpEF among older adults with T2DM.

Frailty is common among older adults with T2DM with its prevalence ranging from ~10% to 50% across studies. In a recent meta-analysis of 32 such studies, the pooled prevalence of frailty among individuals with T2DM was reported as ~20% (95% CI: 16%–24%) (6). The variability in frailty prevalence across studies is related to the differences in the frailty assessment tool and geographic location of the study population (6). The two most common tools used to assess frailty are the Fried phenotype and the Rockwood Index. The Fried phenotype, which is the most widely accepted standard tool for frailty assessment, assesses impairment in physiologic reserve across 5 domains of physical function namely, weakness, loss of endurance, weight loss, slowness, and low physical activity levels (12). While the Fried phenotype is considered the gold standard, it requires prospective assessment and is time and resource intensive and is often not available in large cohort studies. In contrast, the Rockwood FI assesses frailty as an accumulation of health deficits across multiple domains and can be assessed using clinical and health status data on signs and symptoms, comorbidities, laboratory data, activities of daily living, and patient-reported symptoms (9). The FI allows for a more granular assessment of frailty burden on a continuous scale and has been previously used in several large cohort studies retrospectively including in the Look AHEAD cohort (18,19). While frailty burden estimated by Fried phenotype is lower than that reported based on FI (6), prior studies have demonstrated comparable association of Fried phenotype-based frailty burden and Rockwood FI with gold standard measures of impairment in physical function (23). In a recent study among community-based senior adults, Lim et al. demonstrated both Fried phenotype and FI were comparable in identifying impaired physical function as determined by the Short Physical Performance Battery score (Fried vs

Table 3. Multivariable Adjusted Association of Change in Frailty Index at 1 Year With Risk of Incident Overall HF, HFpEF, and HFrEF

	Model 1		Model 2	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Overall HF				
Continuous frailty change				
Per 1-*SD* increase	1.28 (1.09–1.49)	.002	1.24 (1.03–1.50)	.03
Frailty change categories (referent group: Tertile 1)				
Tertile 2 for change in FI	1.04 (0.73–1.47)	.84	1.06 (0.73–1.52)	.77
Tertile 3 for change in FI	1.54 (1.11–2.15)	.01	1.43 (0.99–2.06)	.06
HFpEF				
Continuous frailty change				
Per 1-*SD* increase	1.48 (1.21–1.82)	<.001	1.39 (1.06–1.83)	.02
Frailty change categories (referent group: Tertile 1)				
Tertile 2 for change in FI	1.02 (0.61–1.72)	.94	0.91 (0.52–1.61)	.74
Tertile 3 for change in FI	2.16 (1.36–3.43)	.001	2.01 (1.20–3.37)	.008
HFrEF				
Continuous frailty change				
Per 1-*SD* increase	1.04 (0.80–1.35)	.76	1.15 (0.85–1.54)	.37
Frailty change categories (referent group: Tertile 1)				
Tertile 2 for change in FI	1.16 (0.70–1.91)	.56	1.37 (0.80–2.33)	.25
Tertile 3 for change in FI	1.00 (0.58–1.71)	.99	1.04 (0.58–1.88)	.90

Notes: CI = confidence interval; FI = frailty index; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; HbA1c = hemoglobin A1c. Model 1: Adjusted for age, sex, race/ethnicity, treatment arm, baseline frailty index and baseline estimated fitness (METs). Model 2: Model 1 + Change in baseline estimated fitness (METs) from baseline to year 1, percent change in HbA1c, and percent change in systolic blood pressure from baseline to year 1.

Table 4. Multivariable Adjusted Association of Change in Frailty Index at 4-Year Follow-up With Risk of Incident Overall HF, HFpEF, and HFrEF

	Model 1		Model 2	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Overall HF				
Continuous frailty change				
Per 1-*SD* increase	1.48 (1.27–1.73)	<.001	1.47 (1.21–1.79)	<.001
Frailty change categories (referent group: Tertile 1)				
Tertile 2 for change in FI	1.16 (0.76–1.76)	.49	1.02 (0.63–1.65)	.95
Tertile 3 for change in FI	1.97 (1.36–2.87)	<.001	1.72 (1.09–2.70)	.02
HFpEF				
Continuous frailty change				
Per 1-*SD* increase	1.76 (1.42–2.17)	<.001	1.78 (1.35–2.34)	<.001
Frailty change categories (referent group: Tertile 1)				
Tertile 2 for change in FI	1.36 (0.72–2.56)	.35	1.10 (0.51–2.36)	.81
Tertile 3 for change in FI	2.91 (1.67–5.06)	<.001	2.53 (1.28–4.99)	.008
HFrEF				
Continuous frailty change				
Per 1-*SD* increase	1.19 (0.93–1.52)	.18	1.13 (0.84–1.53)	.41
Frailty change categories (referent group: Tertile 1)				
Tertile 2 for change in FI	1.04 (0.57–1.88)	.90	0.85 (0.44–1.64)	.63
Tertile 3 for change in FI	1.22 (0.68–2.17)	.51	0.98 (0.51–1.88)	.94

Notes: CI = confidence interval; FI = frailty index; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; HbA1c = hemoglobin A1c. Model 1: Adjusted for age, sex, race/ethnicity, treatment arm, baseline frailty index, and baseline estimated fitness (METs). Model 2: Model 1 + Change in baseline estimated fitness (METs) from baseline to year 4, percent change in HbA1c, and percent change in systolic blood pressure from baseline to year 4.

SPPB: sensitivity—92%, AUC—0.77; FI vs SPPB: sensitivity—95%, AUC—0.72) (23). Furthermore, prior studies have also highlighted the prognostic importance of frailty, assessed by Fried phenotype as well as Rockwood FI, as a risk marker to identify individuals with a poor biological reserve at an increased risk of adverse clinical events, including HF (14,19,23,24). Findings from the present study add to the existing literature by evaluating the association of baseline frailty and longitudinal changes in frailty burden— assessed by FI— with the risk of HF. We observed that baseline frailty and changes in frailty on follow-up were associated with HF risk, particularly

HFpEF, independent of other HF risk factors. Our study provides important insights into the role of frailty as a potentially modifiable risk factor—and not just a risk marker—for HF, particularly HFpEF, among patients with T2DM.

Our study findings have important clinical implications. HF, particularly HFpEF, represents an important cardiovascular complication among patients with T2DM. Our study findings have established frailty as an independent risk factor for HF, particularly HFpEF, among middle-aged individuals with T2DM. These findings highlight the need to incorporate frailty assessment in routine care of older individuals with T2DM as a strategy to identify individuals who may be at an increased risk of HFpEF. Such strategies could range from prospective assessment of frailty using the Fried phenotype or incorporation of frailty index tools such as the one used in the present study into the electronic medical record to identify individuals with high FI (7). Our study also demonstrated that worsening frailty burden over time is implicated in the development of HFpEF independent of other risk factors. Several interventions have been studied to reverse frailty, including physical function interventions, nutritional supplementation, hormone supplementation, health education, and counseling (25–29). A 2019 systematic review concluded that a combination of muscle strength training and protein supplementation was the most effective intervention for delaying or reversing frailty (25). However, few interventions have been specifically tested in patients with T2DM and overweight or obesity. Prior work in the Look AHEAD trial by Simpson et al. has also demonstrated that lifestyle interventions, characterized by diet and physical activity modification, significantly improve the frailty burden on follow-up (18). In a recent study among older patients with HF and high burden of frailty, a multidomain physical function intervention was associated with significant improvement in physical function and frailty burden, with a more substantial benefit noted among patients with HFpEF (30). Future studies are needed to determine if such multidomain physical function interventions may be effective in lowering the risk of HF, particularly HFpEF, among frail at-risk individuals with T2DM (18,19).

We observed that individuals with higher frailty burden had higher BMI and lower fitness levels, two key factors that may play a role in mediating the association between frailty and risk of HF. Obesity, physical inactivity and low fitness—an objective measure of cardiopulmonary reserve—have all been associated with a higher risk of HF, particularly HFpEF (20,31–35). In the present study, we observed a significant association between frailty and risk of HFpEF independent of cardiorespiratory fitness levels, BMI, and other HF risk factors. Furthermore, the association between frailty and HF was not modified by baseline levels of BMI. Thus, high baseline frailty and worsening frailty burden over time may predispose individuals to increased risk of HFpEF through impairments in global physiologic reserves that are not limited to cardiovascular performance reserve and obesity-related cardiometabolic dysfunction.

Several factors may underlie the observed risk of HF, particularly HFpEF, among frail individuals. The pathophysiology of frailty and HFpEF are intertwined (7). Frailty is often preceded by advancing age, multi-morbidity, and metabolic abnormalities leading to upregulation of pro-inflammatory pathways, loss of muscle mass, endothelial dysfunction, impairment in mitochondrial function, capillary loss, skeletal muscle myopathy, and cardiovascular structural and functional abnormalities (36). These multisystem deficits lead to impairment in the global physiologic reserve among frail individuals and contribute to the risk of HF. To this end, even subclinical abnormalities in physical function and pre-frailty have been associated with increased risk of HF, particularly HFpEF (37). Another potential explanation for the observed association between frailty and risk of HF could be reverse causation such that subclinical HF at baseline may contribute to increased frailty burden at baseline and later manifest as clinical HF. However, in landmarked analysis excluding individuals who developed HF within 2 years after baseline frailty assessment, we found a similar pattern of association such that higher frailty was consistently associated with higher risk of developing HF. Furthermore, reverse causation due to subclinical HF contributing to increased baseline frailty burden would be nondifferential for HF subtypes and we observed a stronger association of frailty with risk of HFpEF versus HFrEF highlighting the unique biological contribution of frailty to HF development.

We also observed a significant interaction between sex and baseline frailty burden for the risk of HF. The association between higher frailty index and risk of HF was more robust in men versus women. The biological factors that may explain observed effect modification by sex are unclear and may be a chance finding from multiple testing or related to the higher incidence of HF in men versus women in the present study. Future studies are needed to confirm the effect modification by sex on the frailty-associated risk of HF and better understand the potential underlying mechanisms.

Our findings must be interpreted in the context of certain key limitations. First, the present study included participants enrolled in the Look AHEAD trial who could complete a maximal exercise treadmill test. Thus, there is a possibility of selection bias, as extremely frail patients may have been excluded due to the noncompletion of the exercise test. Second, there is a potential for reverse causation such that subclinical heart disease at baseline may contribute to a high frailty burden and the associated downstream risk of HF. However, we observed a consistent pattern of significant association between frailty and risk of HF in analysis landmarked at 2 years that excluded individuals who developed HF early in the follow-up and may have had subclinical HF at the time of baseline assessment. These findings suggest that the observed associations between frailty, changes in frailty burden, and risk of HF are not driven by reverse causation. Third, data on Fried phenotype of frailty assessment were not performed in the Look AHEAD cohort at baseline or year 1 and 4 visits. Accordingly, we could only estimate frailty using the Rockwood FI. However, both FI and Fried phenotype are well-accepted measures of frailty and prior studies have demonstrated comparable association of both frailty phenotypes with gold standard measures of physical function (23). Furthermore, FI has been previously estimated in the Look AHEAD trial cohort as a metric of frailty (18,19). Finally, given the observational nature of the present study, there is a possibility for residual bias and unmeasured confounding in the observed associations.

In conclusion, among individuals with T2DM, higher frailty burden was independently associated with a higher risk of HF, particularly HFpEF, independent of cardiorespiratory fitness levels. Furthermore, an increase in frailty burden over time was associated with higher risk of HF, particularly HFpEF. Future studies are needed to determine if effective multidomain physical function interventions targeting improvement in frailty burden may significantly lower the risk of HF in patients with T2DM.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

A.P. received grant funding outside the present study from Applied Therapeutics; has received honoraria outside of the present study as an advisor/consultant for Tricog Health Inc and Lilly, USA, Rivus, Roche Diagnostics, and has received nonfinancial support from Pfizer and Merck. A.P. is supported by the Texas Health Resources Clinical Scholarship, Gilead Sciences Research Scholar Program, the National Institute of Aging GEMSSTAR Grant (1R03AG067960-01), and grant support from Applied Therapeutics. The other authors declare no conflict.

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