Research Paper

Frailty associates with respiratory exacerbations and mortality in the COPDGene cohort

Eleanor Kate Phillips[1,2], Yichen Huang[1], Elizabeth Regan[3], Barry Make[4], Matthew Strand[5], Abebaw Mengistu Yohannes[6], Nicola A. Hanania[7], Jessica Bon[8], Karin F. Hoth[9], James D. Crapo[4], Edwin K. Silverman[1,2,10], Dawn L. DeMeo[1,2,10]

[1]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA
[2]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA
[3]Division of Rheumatology, National Jewish Health, Denver, CO 80206, USA
[4]Division of Pulmonary, Critical Care, and Sleep Medicine, National Jewish Health, Denver, CO 80206, USA
[5]Division of Biostatistics and Bioinformatics, National Jewish Health, Denver, CO 80206, USA
[6]Department of Physical Therapy, University of Alabama at Birmingham, Birmingham, AL 35294, USA
[7]Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, TX 77030, USA
[8]Section of Pulmonary, Critical Care, Allergy, and Immunologic Diseases, Wake Forest University School of Medicine, Winston-Salem, NC 27101, USA
[9]Department of Psychiatry, University of Iowa Carver College of Medicine, Lowa City, IA 52242, USA
[10]Harvard Medical School, Boston, MA 02115, USA

Correspondence to: Dawn L. DeMeo; **email:** redld@channing.harvard.edu
Keywords: frailty, cigarette smoking, respiratory exacerbations, COPD, epigenetic aging
Received: February 26, 2025 **Accepted:** June 2, 2025 **Published:** July 3, 2025

ABSTRACT

Frailty is associated with respiratory exacerbations and mortality in individuals with Chronic Obstructive Pulmonary Disease (COPD). Among those with a smoking history and normal spirometry, frailty's association with respiratory outcomes is less defined.

COPDGene is a cohort study of individuals aged 45–80 with a minimum 10 pack-year smoking history. A modified Fried Frailty Phenotype was performed at 10-year follow-up; participants were categorized as frail, prefrail, or robust. Primary outcomes were respiratory exacerbations, epigenetic pace of aging, and all-cause mortality.

Among 2665 participants, 401 (15%) were frail and 1352 (51%) were prefrail. Adjusting for smoking and lung function, frailty was associated with prospective respiratory exacerbation rate (IRR 3.4, 95% CI 2.4–4.8), severe exacerbations (OR 2.8(1.8–4.2)), and frequent exacerbations (OR 5.5(3.2–9.3)). Prefrailty was also associated with exacerbation outcomes (rate IRR 1.8(1.4–2.3); severe OR 1.6(1.1–2.2); frequent OR 2.6(1.7–4.1)). Frailty and prefrailty were associated with increased all-cause mortality (AHR: frailty 4.5(2.4–8.5); prefrailty 2.5(1.5–4.2)). All frailty (and most prefrailty) findings persisted in those with normal spirometry. Baseline DunedinPACE of aging was associated with prospective frailty at 10-year follow-up.

Frailty associated with respiratory exacerbations and mortality; findings persisted among individuals with normal spirometry, highlighting the relevance of evaluating for frailty in people with a history of smoking.

INTRODUCTION

Frailty is a syndrome of decreased functional reserve and increased vulnerability to stressors. It has been associated with advanced age, chronic diseases including chronic obstructive pulmonary disease (COPD), and increased risk of disability and death [1]. A commonly used method for assessing frailty is the Fried Frailty Phenotype (FFP), a physiologic definition that categorizes individuals as frail, prefrail, or robust based on five components: shrinking, weakness, slowness, low activity level, and fatigue [1].

The reported prevalence of frailty in populations with COPD varies from 6–58% [2–10]. COPD is associated with increased odds of frailty and with increased rates of frailty progression [2, 11]. Among individuals with COPD, frailty increases the risk of hospitalizations and death [2, 5, 7]. Frailty (as well as handgrip weakness, a component of the frailty definition) has been associated with increased risk of COPD exacerbations [5, 12–15], although this association has not been consistently demonstrated [16]. Notably, in individuals with COPD, completing a pulmonary rehabilitation program may reverse the frailty phenotype [17].

Prefrailty, a potential 'subclinical' precursor to frailty, has also been linked to adverse outcomes [1, 18]. Among individuals with COPD, prefrailty has been associated with respiratory exacerbations as defined by electronic medical record codes and drug prescription data [5]. Its association with mortality in this population has been less consistent, although a recent meta-analysis demonstrated a pooled hazard ratio of 1.5 (0.9–2.4) of prefrailty on all-cause mortality [5, 19].

While cigarette smoking has been associated with prevalent frailty [20–22], the association between smoking and frailty development has been variable [23–28]. In particular, one study found that current smoking was associated with two-fold odds of incident frailty, but this effect was not observed after adjusting for COPD status [29]. The associations between smoking and frailty in the literature have not been consistently adjusted for lung function or COPD status, potentially contributing to this variability of findings.

The burden of smoking-related symptoms among individuals with normal spirometry is becoming increasingly recognized [30, 31]. Compared to never-smokers, populations with a cigarette smoking history and normal spirometry have demonstrated more respiratory exacerbations, higher dyspnea scores, higher airway wall thickness, and more evidence of radiographic emphysema [30, 31]. The relationship between frailty and respiratory exacerbations in this population remains unclear. While Verschoor and colleagues identified a cross-sectional association between history of respiratory symptoms (any cough, wheeze, or dyspnea in the past year) and frailty [32], this has not to our knowledge been studied prospectively, nor with a focus on exacerbations and with consideration of prefrailty.

Prior studies have demonstrated associations between a variety of epigenetic age acceleration measures and frailty [33–35]. DunedinPACE, a novel DNA methylation-based biomarker of the pace of aging, has been associated with subsequent (7-year) frailty in a small study of older adults (aged ≥70) [36, 37]. Another recent study suggested that a higher DunedinPACE may predate changes in frailty [38]. Given the extensive impact of current cigarette smoking on the epigenome, and noting that associations between smoking-related DNA methylation changes and frailty have been observed, we performed a smoking-stratified assessment of the association between DunedinPACE and frailty at 10-year follow up [21].

In this study, we determined the prevalence of frailty and prefrailty in a population with a smoking history and evaluated their associations with subsequent respiratory exacerbations and all-cause mortality. To elucidate the associations between frailty and outcomes independent of COPD, we adjusted for lung volume in regression models. We also performed subgroup analyses of individuals with normal spirometry, mild COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1), moderate to very severe COPD (GOLD 2–4), and Preserved Ratio Impaired Spirometry (PRISm). We additionally conducted post-hoc analyses comparing smoking intensity to frailty and evaluating frailty in a cohort of never-smoker controls. We hypothesized that frailty and prefrailty would increase the risk of adverse outcomes across spirometric subgroups, including among those with normal spirometry.

RESULTS

Demographics and baseline characteristics

Of 2665 participants, 401 (15%) were frail, and 1352 (51%) were pre-frail (Table 1). The mean age (standard deviation) of the study population was 70(8). The distribution of frailty category by age was similar for subjects between 50–80 years old; frailty prevalence was increased among individuals aged 80 and above (Supplementary Figure 1).

Frailty prevalence was higher among individuals with GOLD 2–4 COPD (24%) than in those with normal

Table 1. Participant characteristics.

Characteristic	*n*	Robust	Prefrail	Frail	*p**
n (%)	2,665	912 (34%)	1,352 (51%)	401 (15%)	
Age	2,665	68.6 (7.4)	69.7 (8.1)	71.5 (9.2)	**<0.001**
Sex	2,665				0.39
Male		450 (49.3%)	640 (47.3%)	204 (50.9%)	
Female		462 (50.7%)	712 (52.7%)	197 (49.1%)	
Race	2,665				**<0.001**
Non-Hispanic White		742 (81.4%)	933 (69.0%)	270 (67.3%)	
African American		170 (18.6%)	419 (31.0%)	131 (32.7%)	
BMI	2,665	28.6 (5.5)	28.5 (6.1)	30.1 (7.6)	**0.002**
Current Smoking	2,663	239 (26.2%)	462 (34.2%)	138 (34.4%)	**<0.001**
Smoking Pack-Years	2,663	39.3 (20.3)	43.0 (22.4)	52.7 (26.6)	**<0.001**
GOLD grade	2,646				**<0.001**
Normal Spirometry		473 (52.3%)	589 (43.7%)	108 (27.4%)	
1		115 (12.7%)	154 (11.4%)	27 (6.9%)	
2		160 (17.7%)	293 (21.8%)	68 (17.3%)	
3		56 (6.2%)	104 (7.7%)	85 (21.6%)	
4		9 (1.0%)	32 (2.4%)	52 (13.7%)	
Total GOLD 2–4 (Moderate-Severe COPD)		225 (24.9%)	429 (31.8%)	205 (52.0%)	**<0.001**
PRISm		92 (10.2%)	175 (13.0%)	54 (13.7%)	0.077
Comorbidity Count	2,665	1.1 (1.1)	1.4 (1.2)	2.0 (1.4)	**<0.001**

Total *N* = 2665. *N* with data available for each characteristic shown. Continuous variables reported as mean (standard deviation). Categorical variables reported as *n* (%). Abbreviations: BMI: body mass index (kg/m^2). GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: Chronic Obstructive Pulmonary Disease; PRISm: Preserved Ratio Impaired Spirometry. Comorbidity count is the sum of the following reported comorbidities: diabetes, coronary artery disease (including reported coronary artery disease, myocardial infarction, angina, angioplasty, or coronary artery bypass graft surgery), congestive heart failure, cerebrovascular disease (including reported stroke or transient ischemic attack), kidney disease, liver disease, cancer (excluding non-melanoma skin cancer), osteoarthritis, and osteoporosis. Expanded characteristics are available in Supplementary Table 1. **p*-values are calculated by the Kruskal-Wallis rank sum test for continuous variables and by Pearson's chi-squared test for categorical variables.

spirometry (9%) (Supplementary Figure 1). Comorbidities including cardiovascular disease and osteoarthritis were associated with frailty. Frailty distribution across BMI categories was U-shaped (Supplementary Figure 1). Frail subjects were more likely to report needing assistance with basic and independent activities of daily living (BADLs/IADLs); 25% of frail subjects reported needing help with IADLs, compared to less than 1% of robust subjects. Frailty category was also associated with probable cognitive impairment based on the Mini-Cog assessment (Supplementary Table 1).

Frailty category was associated with a higher Modified Medical Research Council (MMRC) dyspnea score and higher mean airway wall thickness (Pi10) on quantitative computed tomography (CT) scan across all respiratory subgroups (Table 2).

In this population of current and former smokers, current smoking and smoking pack-years were associated with frailty category (Table 2), including among individuals with normal spirometry. In a combined model adjusted for age, sex, and forced expiratory volume in one second (FEV1) % predicted, the association with frailty in individuals with normal spirometry persisted for current smoking (Odds Ratio (OR) 2.8 (95% CI 1.7–4.8), $p < 0.001$) but not smoking pack-years.

In the post hoc analysis of the 249 never-smoker controls with frailty assessments (mean age = 67),

Table 2. Respiratory characteristics and exacerbations by frailty category.

		All participants				Normal spirometry				GOLD 1			
(A)		**Robust**	**Prefrail**	**Frail**	***p****	**Robust**	**Prefrail**	**Frail**	***p***	**Robust**	**Prefrail**	**Frail**	***p***
Characteristic	*N*	912	1352	401		473	589	108		115	154	27	
Age	2665	69 (7)	70 (8)	71 (9)	**<0.001**	68 (7)	69 (8)	71 (9)	**<0.001**	71 (8)	73 (8)	74 (10)	0.27
FEV1 % pred	2646	85 (22)	81 (24)	65 (28)	**<0.001**	99 (13)	100 (14)	97 (12)	0.20	92 (11)	92 (10)	92 (7)	0.57
Current Smoking	2663	26.2% (239)	34.2% (462)	34.4% (138)	**<0.001**	22.8% (108)	31.6% (186)	34% (37)	**0.003**	(31%) 36	(37%) 57	(52%) 14	0.13
Smoking Pack-Years	2663	39 (20)	43 (22)	53 (27)	**<0.001**	35 (18)	38 (21)	42 (21)	**0.003**	43 (22)	48 (24)	56 (30)	0.055
BODE score†	2645	0 (0, 1)	1 (0, 2)	4 (2, 6)	**<0.001**	0 (0, 0)	0 (0, 1)	2 (1, 3)	**<0.001**	0 (0, 0)	1 (0, 2)	3 (2, 5)	**<0.001**
MMRC score†	2663	0 (0, 1)	0 (0, 2)	3 (1, 3)	**<0.001**	0 (0, 1)	0 (0, 1)	1 (0, 3)	**<0.001**	0 (0, 1)	0 (0, 2)	2 (0, 3)	**<0.001**
Pi10	2433	2.16 (0.50)	2.28 (0.55)	2.64 (0.61)	**<0.001**	1.95 (0.40)	1.99 (0.41)	2.14 (0.43)	**<0.001**	2.08 (0.36)	2.16 (0.42)	2.47 (0.45)	**<0.001**
(B)													
Outcome	*N*	793	1122	307		407	489	80		104	127	21	
Annual exacerbation rate	2222	0.14 (0.50)	0.28 (0.75)	0.67 (1.46)	**<.001**	0.10 (0.43)	0.19 (0.71)	0.39 (1.48)	0.173	0.22 (0.68)	0.20 (0.57)	0.71 (2.56)	0.78
Any severe exacerbation	2222	7.8% (62)	13.4% (150)	26.1% (80)	**<.001**	4.4% (18)	7.4% (36)	15.0% (12)	**.002**	12.5% (13)	12.6% (16)	24% (5)	0.34
Frequent exacerbations	2222	3.4% (27)	9.4% (105)	22.1% (68)	**<.001**	2.0% (8)	6.1% (30)	11.3% (9)	**<.001**	5.8% (6)	7.1% (9)	10% (2)	0.74

	GOLD 2–4				PRISm			
	Robust	**Prefrail**	**Frail**	***p***	**Robust**	**Prefrail**	**Frail**	***p***
Characteristic	225	429	205		92	175	54	
Age	70 (7)	71 (8)	73 (9)	**0.008**	67 (8)	67 (8)	67 (8)	0.86
FEV1 % pred	59 (14)	56 (16)	43 (17)	**<0.001**	72 (8)	70 (8)	67 (10)	**0.01**
Current Smoking	27.6% (62)	32.9% (141)	30.7% (63)	0.38	34% (31)	44% (77)	39% (21)	0.26
Smoking Pack-Years	45 (20)	50 (23)	58 (27)	**<0.001**	40 (21)	38 (20)	52 (27)	**0.003**
BODE score†	1 (0, 3)	2 (1, 4)	6 (4, 7)	**<0.001**	0 (0, 1)	1 (0, 3)	3 (3, 5)	**<0.001**
MMRC score†	1 (0, 2)	2 (0, 3)	3 (3, 4)	**<0.001**	0 (0, 2)	1 (0, 3)	3 (2, 3)	**<0.001**
Pi10	2.54 (0.49)	2.69 (0.52)	2.91 (0.56)	**<0.001**	2.35 (0.50)	2.43 (0.50)	2.65 (0.55)	**0.003**
Outcome	198	358	160		78	145	42	
Annual exacerbation rate	0.18 (0.48)	0.45 (0.91)	0.88 (1.38)	**<.001**	0.18 (0.59)	0.20 (0.53)	0.42 (0.85)	**0.026**
Any severe exacerbation	12.6% (25)	22.6% (81)	33.1% (53)	**<.001**	8% (6)	11.7% (17)	21% (9)	0.087
Frequent exacerbations	4.0% (8)	15.9% (57)	31.9% (51)	**<.001**	6% (5)	6.2% (9)	12% (5)	0.44

(**A**) Cross-sectional respiratory characteristics. (**B**) Longitudinal follow-up exacerbations (mean follow-up time: 2.8 years). Note that 19 participants did not have spirometry data reported, and not all participants had longitudinal follow-up data (*N* reported separately for 2A and 2B). Continuous variables reported as mean (standard deviation) unless otherwise specified; categorical variables reported as % (*n*). Abbreviations: GOLD: Global Initiative for Chronic Obstructive Lung Disease; PRISm: Preserved Ratio Impaired Spirometry; FEV1 % pred: Forced expiratory volume in 1 second % predicted; BODE: Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity; MMRC: Modified Medical Research Council Dyspnea Scale; Pi10: standardized airway wall thickness on quantitative CT scan (mm). *p-value across frailty category (using Kruskal-Wallis rank sum test for continuous data, Pearson's chi-squared test for categorical data with cell counts >5, and Fisher's Exact test for categorical data with cell counts ≤5). †Median (IQR).

4 individuals (2%) were frail, and 84 individuals (34%) were prefrail (Supplementary Table 2).

Distribution of frailty components

Shrinking and weakness were the most common features in the study cohort. Among frail individuals with moderate to very severe COPD, slowness and low activity were the most common (Supplementary Table 3 and Supplementary Figure 2). Principal Component Analysis (PCA) demonstrated cross-loading between low activity, slowness, and fatigue, and Multiple Correspondence Analysis (MCA) demonstrated contributions of low activity, slowness, and fatigue to the primary dimension (with which frailty was highly correlated) (Supplementary Figure 3).

Respiratory characteristics and exacerbations

Exacerbation analyses included 2222 individuals with at least 180 days of follow-up (mean follow-up time = 2.8 years) (Supplementary Table 4 describes those without follow-up). Frail participants had significantly higher mean annual exacerbation rates compared to robust participants (0.67 events/year vs. 0.14 events/year, $p < 0.001$) and a higher unadjusted incidence of severe (26% vs. 8%, $p < 0.001$) and frequent (22% vs. 3%, $p < 0.001$) exacerbations (Table 2).

In adjusted models, frailty was associated with increased exacerbation rate (Incidence Rate Ratio [IRR] 3.4 (95% CI 2.4–4.8), $p < 0.001$) and with increased odds of severe (OR 2.8 (1.8–4.2), $p < 0.001$) and frequent (OR 5.5 (3.2–9.3), $p < 0.001$) exacerbations (Figure 1 and Supplementary Table 5). Prefrailty was likewise associated with increased exacerbation rate (IRR 1.8 (1.4–2.3), $p < 0.001$), severe exacerbations (OR 1.6 (1.1–2.2), $p = 0.005$), and frequent exacerbations (OR 2.6 (1.7–4.1), $p < 0.001$). The frailty associations (and most prefrailty associations) persisted in subgroups analyses of those with moderate-very severe COPD and of those with normal spirometry

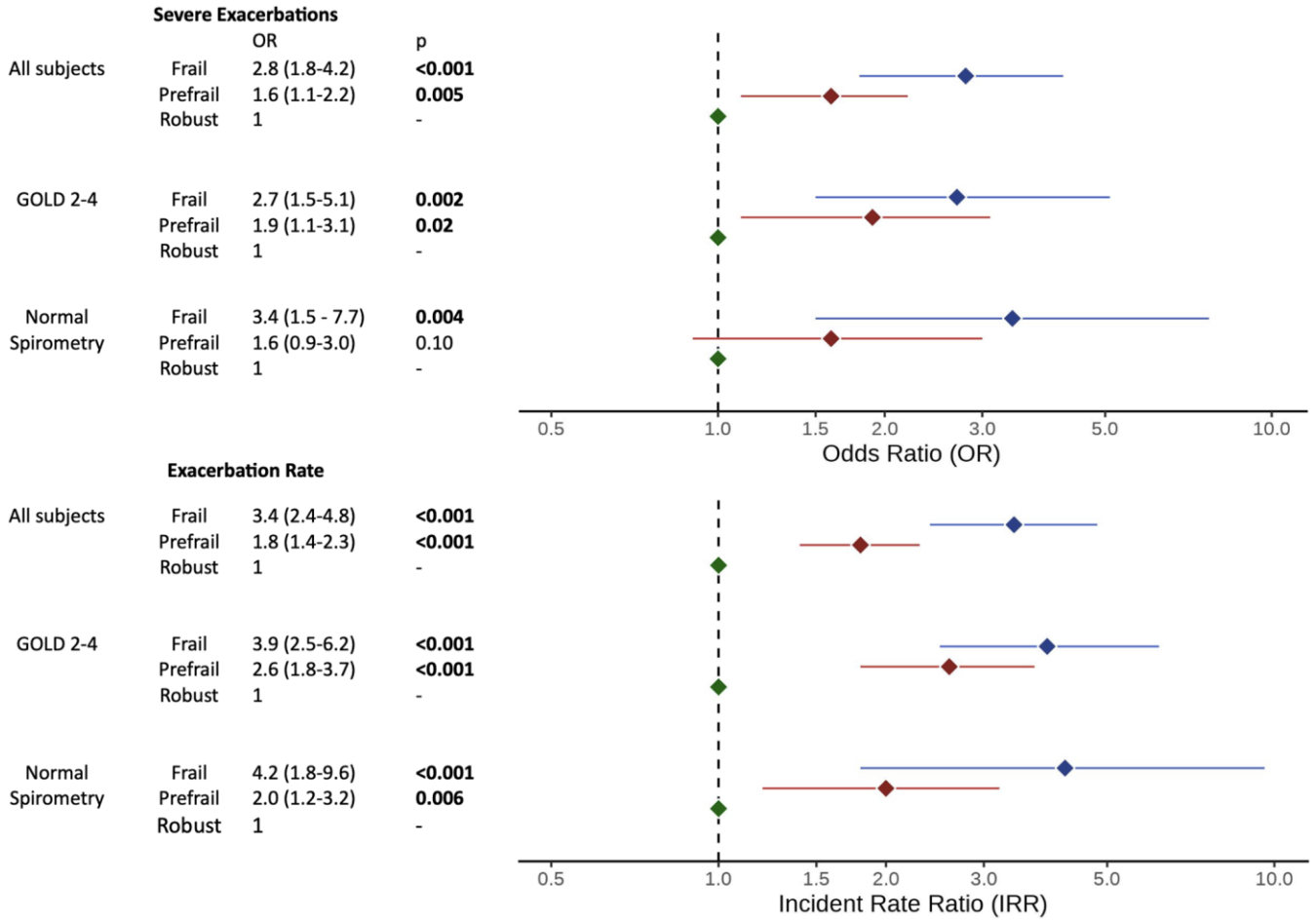


Figure 1. Forest plot of frailty category on respiratory exacerbations. Abbreviations: OR: odds ratio of frailty/prefrailty on severe exacerbations; IRR: incident rate ratio of frailty/prefrailty on annual exacerbation rate; GOLD: Global Initiative for Obstructive Lung Disease. OR/IRR and 95% confidence intervals (adjusted for age, sex, current smoking, and forced expiratory volume in one second (FEV1) %predicted) are shown on log-transformed x-axis. Full details in Supplementary Table 5.

(Figure 1). In the subgroups with fewer individuals (GOLD 1 and PRISm), associations between frailty and respiratory exacerbations did not consistently reach statistical thresholds, although effect estimates were in the same direction as in the overall analysis. Among individuals with PRISm, severe exacerbations were significantly associated with frailty (p = 0.047), and exacerbation rate had a trend towards association with frailty (p = 0.051) (Supplementary Table 5).

Survival analysis - results

For the 2512 participants with mortality and covariate data (mean follow-up time = 2.6 years), adjusted risk curves of frailty and prefrailty on mortality are shown in Figure 2. Both frail (Adjusted Hazard Ratio (AHR) 4.5, 95% CI 2.4–8.5, p < 0.001) and pre-frail (AHR 2.5 (1.5–4.2), p < 0.001) individuals had an increased risk of death. These findings persisted in subgroup analyses of participants with GOLD 2–4 COPD (frailty AHR 4.0 (1.7–9.3), p = 0.001; prefrailty AHR 2.1 (1.02–4.4), p = 0.045) and with normal spirometry (frailty AHR 7.9 (1.9–32.5), p = 0.004; prefrailty HR 4.2 (1.4–12.6), p = 0.01). Adjusted survival analyses for the PRISm and GOLD 1 subgroups were not performed due to low event counts (details in Supplementary Table 6).

Epigenetic pace of aging – results

Of 2104 subjects with DNA methylation data available at Phases 1 and 2 (Supplementary Table 7), analyses revealed associations between DunedinPACE of aging at Phase 1 and Phase 2 and frailty category (frail, prefrail, or robust) at Phase 3 (p < 0.001) (Supplementary Table 8 and Supplementary Figure 4). Associations persisted when stratified by smoking status at the time of blood draw, although unsurprisingly, individuals who were currently smoking tended to have higher DunedinPACE overall despite being chronologically younger (Supplementary Table 8 and Supplementary Figure 4). A sensitivity analysis of only those who did not report current smoking at Phase 1 nor at Phase 2 ("former-former" smoking) confirmed an association between DunedinPACE and frailty category. A sex-stratified sensitivity analysis of DunedinPACE on frailty status redemonstrated the association between DunedinPACE and frailty. Logistic regression demonstrated an association between baseline DunedinPACE and 10-year frailty (OR 2.8; 95% CI 2.3–3.4) and prefrailty (OR 1.9 (1.6–2.3)) (Supplementary Table 9 and Supplementary Figure 5). (Original DunedinPACE units were used, in which a value of one corresponds to one year of biological aging per year of chronological aging).

Secondary analyses

There was no evidence of effect modification of FEV1 % predicted on the relationship between frailty and prefrailty and longitudinal outcomes.

Evaluation of the relationship between the number of frailty components on longitudinal outcomes demonstrated higher exacerbations and increased risk of death in individuals with more components present (Supplementary Figures 6, 7 and Supplementary Table 10).

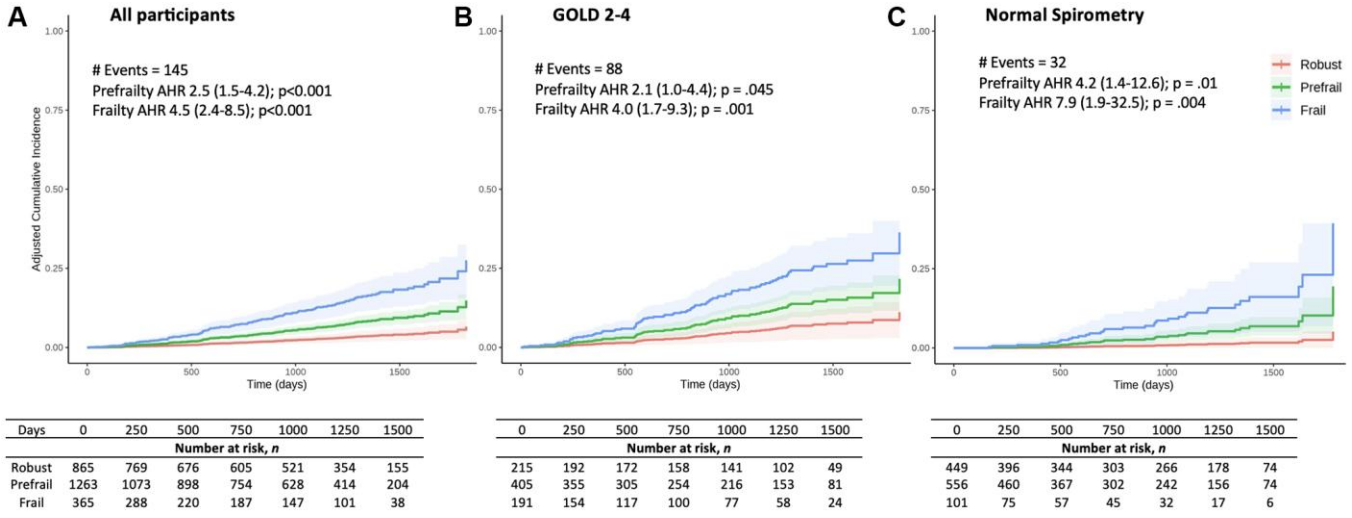


Figure 2. Adjusted all-cause mortality cumulative incidence curves by frailty category. Adjusted cumulative incidence (fraction) curves for (**A**) all participants, (**B**) individuals with GOLD 2–4 COPD, and (**C**) individuals with normal spirometry. The Cox adjusted Hazard Ratios (AHR) by frailty category (compared to robust group) are shown as: AHR (95% Confidence Interval); p-value. AHR was adjusted for age, sex, body mass index, smoking pack-years, FEV1 % predicted, diabetes, and heart disease (any of: coronary artery disease, myocardial infarction, angina, angioplasty, coronary artery bypass graft surgery, or congestive heart failure).

In an adjusted Cox model evaluating all five frailty components together, shrinking, weakness, and slowness remained independently associated with mortality. In sex-stratified analyses, frailty remained associated with exacerbation and mortality outcomes for both men and women, although the effect estimates for women tended to be higher (Supplementary Table 11).

Sensitivity analyses

When the frailty phenotype was operationalized using the slowness definition from the NETT trial [6], associations between frailty and prefrailty and primary outcomes (respiratory exacerbations and mortality) persisted. Two subgroup analyses (1. excluding individuals with probable cognitive impairment on the Mini-Cog, and 2. excluding those with body mass index (BMI) under 21) likewise demonstrated persistent associations between frailty and prefrailty and outcomes.

In an analysis excluding individuals who were frail or prefrail due to slowness (to rule out excessive influence of low six-minute walk distance (6MWD)), the associations between frailty and prefrailty and outcomes persisted. In analyses of the subgroup of only individuals who were frail or prefrail due to shrinking (since shrinking could represent successful dieting), frailty and prefrailty associations with mortality persisted, as did all frailty associations with exacerbation outcomes. Prefrailty's association with some exacerbation outcomes attenuated in the subgroup of individuals with prefrailty due to shrinking.

We conducted a sensitivity analysis of respiratory exacerbation outcomes stratified by the timing of the Phase 3 visit (before or after the onset of the Covid-19 pandemic in March 2020). 28% of participants had visits after March 2020. Mean follow-up time was 3.4 years (pre-pandemic) vs. 1.3 years (post-pandemic). Frailty associations with exacerbations persisted in both the pre- and post-pandemic groups (Supplementary Table 12), although prefrailty findings lost statistical significance in the post-pandemic group. We were unable to perform a similar stratified analysis of mortality outcomes due to the small event number in the group whose site visit was post-pandemic.

DISCUSSION

In this cohort of people with a history of cigarette smoking, frailty and prefrailty were prevalent regardless of spirometry. Current smoking status was associated with frailty, even among individuals with normal spirometry. The prevalence of frailty in our study cohort was within the range described in the literature; however, the frailty prevalence observed in post-hoc analysis of nonsmoker controls was low (2%), underscoring the connection between cigarette smoking and frailty.

Among participants 80 years of age or younger, age was not significantly associated with frailty, reinforcing that frailty is not simply a trait of chronologic aging. Frail individuals had increased need for support with activities of daily living and higher prevalence of probable cognitive impairment, highlighting the multisystem nature of this syndrome.

In models adjusted for lung function and smoking status/intensity, individuals with frailty had threefold higher exacerbation rates and fourfold higher hazard of death than robust individuals; findings persisted in subgroup analyses of individuals with normal spirometry and with moderate-very severe COPD.

The association between frailty and prospective respiratory exacerbations among people with normal spirometry has not to our knowledge been previously described. Frail individuals with normal spirometry also reported higher baseline dyspnea scores and had increased airway wall thickening, suggesting a potential inflammatory link between frailty and respiratory symptoms. These findings, combined with the emerging recognition of smoking-related respiratory pathology in people with normal spirometry, suggest that frailty should be considered in all people with a smoking history.

We did not observe significant associations between frailty and respiratory exacerbations among individuals with GOLD grade 1 COPD. Among the subgroup with PRISm, only severe exacerbations reached statistical significance for association with frailty, and a trend was observed for exacerbation rate. This may be related to the much smaller sample sizes in these two subgroups, in which we calculated lower power to detect differences. Further attention to these at-risk spirometric groups in follow-up studies is indicated.

This study underscores the risks associated with the prefrail state, as prefrail individuals had a roughly doubled exacerbation rates and increased mortality risk compared to robust individuals. On a more granular level, we identified that the presence of just one frailty component was associated with increased risk of adverse outcomes; which has previously been demonstrated for mortality but not for respiratory exacerbations [39].

These findings highlight the importance of recognizing frailty and prefrailty in the clinical setting and suggest a role for frailty screening in all adults with a smoking

history, even those with normal spirometry. Improved recognition of prefrailty may inform earlier intervention points for preventing frailty, such as protein supplementation or nutritional counseling among prefrail individuals [40, 41]. Pulmonary rehabilitation has been associated with improvements in frailty status among individuals with COPD [6]; the potential benefits of pulmonary rehabilitation in pre-frail individuals may warrant investigation in future clinical studies.

Other metrics such as the BODE score have been used to predict outcomes in COPD [42]. While the Fried Frailty Phenotype (FFP) overlaps with some features of the BODE score, it evaluates for a distinct phenotype. For example, the modified FFP can identify frailty in individuals without airflow obstruction or with a BMI above 21 and is thus generalizable to a broader population. This is relevant as we found frailty and prefrailty in such individuals.

Frailty has been described as a state of physiologic dysregulation and disrupted homeostasis at a metabolic and cellular level, which leads to the observed phenotype [43]. In keeping with this, epigenetic associations between cigarette smoking and frailty have been identified [21]. In this study, we demonstrated that DunedinPACE, a novel metric of epigenetic aging, was associated with frailty status at 5- and 10-year follow-up. To our knowledge, this is the largest such analysis to be conducted and the first in a population enriched for a history of cigarette smoking. While baseline (Phase 1) frailty assessments were not performed, this adds to a recent prior study suggesting that an increased pace of aging could pre-date clinical frailty manifestations [38]. Despite the myriad effects of cigarette smoking on the epigenome, these findings were robust to stratification by current smoking status. Further research into the epigenetic underpinnings of frailty in populations with a smoking history could provide insight into disease mechanisms.

The strengths of our study include the large, well-phenotyped cohort and the presence of longitudinal follow-up for respiratory exacerbations and mortality. Its limitations include the length of follow-up time (which spanned the Covid-19 pandemic) and lack of cause-specific mortality data. Future research into respiratory-specific mortality related to frailty is needed. Furthermore, some spirometric subgroups had a low number of events, leading to widened confidence intervals of effect estimates for these subgroup analyses. As our study population had a history of smoking, the generalizability to never-smokers is unclear.

In conclusion, in a population of adults with a smoking history, frailty and prefrailty are associated with increased respiratory exacerbations and increased risk of death. The association between frailty and adverse outcomes is present in individuals with moderate to very severe COPD and in those with normal spirometry (and in PRISm for some exacerbation outcomes). Cigarette smoking was associated with frailty prevalence, even among those with normal spirometry. Frailty prevalence did not vary significantly with age among individuals under age 80. These findings highlight the importance of assessing for frailty and prefrailty in all adults with a history of smoking, even in those without advanced age and with normal spirometry.

METHODS

Study design and population

The COPDGene study (clinicaltrials.gov ID NCT00608764) is an ongoing multicenter cohort study [44]. Non-Hispanic White (NHW) and African American adults with a reported age 45–80 and a minimum 10 pack-year smoking history were eligible. Exclusion criteria included pulmonary fibrosis and active cancer under treatment. Participants had on-site evaluations at baseline (Phase 1) and every 5 years (Phases 2 and 3). All participants provided informed consent, and study protocols were approved by the institutional review board at each site.

The current study is an analysis of the COPDGene cohort limited to participants who returned for the Phase 3 (10-year follow-up) visit (2018–2023) and had an assessment of all five frailty components (Figure 3). Data were also collected on a smaller number of never-smoker controls; frailty prevalence was assessed in a post hoc analysis of this group.

Measurements

Physiologic, spirometric, chest CT scan, and questionnaire data were collected by trained personnel at the Phase 3 visit. Hand grip strength (average of three efforts) was measured with Jamar dynamometers. Six-minute Walk tests (6MWT) were conducted in accordance with American Thoracic Society (ATS) guidelines [45]. Pre- and post-bronchodilator spirometry was performed using ndd EasyOne Spirometers (ndd Medical Technologies, Andover, MA, USA). Questionnaires included the 36-Item Short Form Survey (SF-36) and portions of the Center for Epidemiologic Studies Depression Scale (CES-D) [46, 47]. Additional details are in the Supplementary Methods.

We generated a modified FFP from the five frailty components: shrinking, weakness, low activity, fatigue,

and slowness (Figure 3) [1]. Shrinking was defined as weight loss ≥4.6 kg or ≥5% of body weight from the prior (Phase 2) visit [1]; weakness was based on hand grip strength (with sex- and BMI-stratified cutoffs [1]); fatigue was assessed with standard questions from the CES-D; slowness was defined by the lowest quintile of 6MWD in the baseline population (adjusted for sex and height); low activity was defined by the sex-stratified lowest quintile of baseline SF-36 Physical Functioning scores. Defining frailty components by the lowest

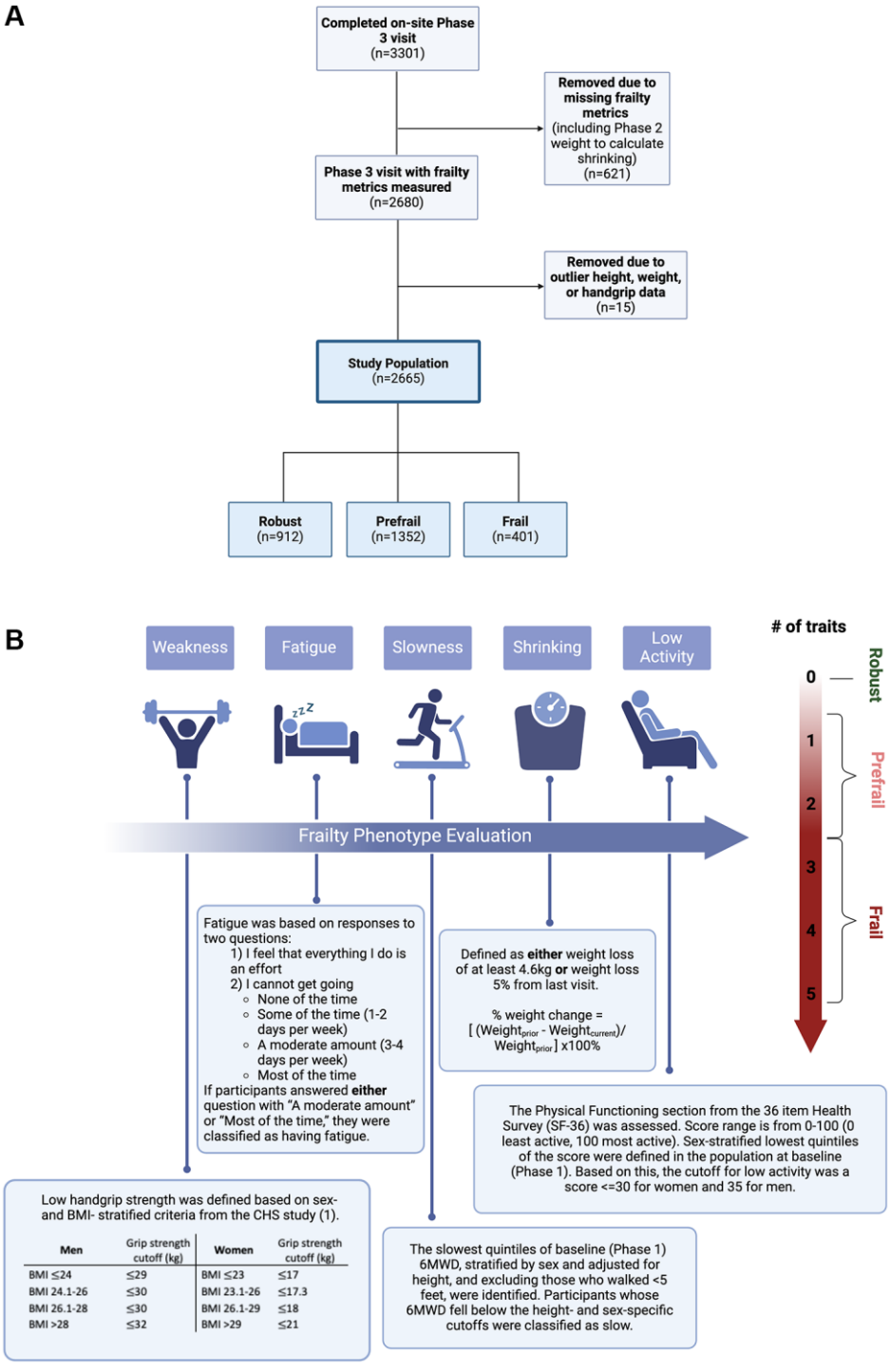


Figure 3. Methods. (**A**) CONSORT Diagram. (**B**) Frailty Phenotype Assessment. The frailty phenotype was evaluated based on five components: weakness, fatigue, slowness, shrinking, and low activity. Participants with three or more traits present were considered frail, those with one or two present were prefrail, and those without any traits present were classified as robust. Abbreviations: BMI: body mass index; 6MWD: six-minute walk distance; kg: kilograms; CHS: cardiovascular health study. Created in BioRender. Phillips, E. (2025) https://BioRender.com/6r3agi1 and https://BioRender.com/t42asu1.

quintile in the baseline population is established in the literature [1, 18]. Individuals were classified as frail if three or more of these components were present, prefrail if one or two were present, and robust if none were present [1].

Longitudinal outcome measurements

Longitudinal follow-up on respiratory exacerbations was collected at six-month intervals by telephone or web-based survey. Exacerbation data and unadjudicated all-cause mortality data are reported through July 2023.

Participants with fewer than 180 days of follow-up were excluded from exacerbation analyses. Exacerbations were defined as an episode of increased cough and phlegm or shortness of breath which lasted for at least 48 hours and required treatment with antibiotics, steroids, emergency room (ER) visit, or hospitalization. We evaluated annual exacerbation rate, presence of severe exacerbations, and presence of frequent exacerbations (defined in Supplementary Methods).

Epigenetic pace of aging measurement

Whole blood samples for assessment of DNA methylation were obtained at baseline (Phase 1) visit and at 5-year follow-up (Phase 2) visit. DNA methylation was assessed using the Illumina Infinium EPIC 850 k BeadChip array. After regression on correlated probes for bias correction and functional normalization, methylation beta values were used to calculate the DunedinPACE of Aging using the DunedinPACE package in R statistical software. Individuals who were missing either Phase 1 or Phase 2 methylation data were excluded from epigenetic pace of aging analyses.

Statistical analysis

Continuous variables are reported as mean (standard deviation) unless specified. Differences across frailty categories were assessed with Kruskal-Wallis rank sum test, Pearson's chi-squared test, and Fisher's Exact test.

To evaluate how the five frailty components combined to generate the frailty phenotype, we performed a PCA of the five continuous characteristics from which frailty components were derived and a complementary MCA of the five binary traits.

For longitudinal outcomes analyses, robust individuals were used as the comparator group for frail and prefrail individuals. Frequent and severe exacerbations were modeled using multivariable logistic regression. Exacerbation rate was modeled by multivariable negative binomial regression of total exacerbation count with an offset term of log(follow-up time) [48]. Exacerbation models were adjusted for participant age, sex, % predicted post-bronchodilator forced expiratory volume in 1 second (FEV1), and smoking status.

Multivariable Cox proportional hazards models adjusted for a priori covariates of age, sex, BMI, smoking pack-years, diabetes, and heart disease (defined in Supplementary Methods) were used to calculate adjusted hazard ratios (AHR) for frailty and prefrailty.

Subgroup analyses were performed by spirometric category (definitions in Supplementary Methods): normal spirometry, GOLD 1, GOLD 2–4, and PRISm. Secondary and sensitivity analyses (including evaluation of the interaction term between FEV1 %predicted and frailty on outcomes and evaluation of outcomes by the number of frailty components) are described in the Supplementary Methods.

The frequency of missing cross-sectional covariate data is reported, as are characteristics of subjects without longitudinal follow-up data and of those without epigenetic pace of aging data. In cases of missing data, complete case analysis was performed.

The association between epigenetic pace of aging (DunedinPACE) at baseline (Phase 1) and at 5-year follow-up (Phase 2) and frailty status at 10-year follow-up (Phase 3) was assessed. To evaluate for potential confounding epigenetic effects of current smoking, analyses were stratified by smoking status at the time of blood sample collection. Crude associations were assessed using Kruskal-Wallis rank sum test. Logistic regressions of Phase 1 and Phase 2 DunedinPACE of Aging on the outcome of Phase 3 frailty (vs. robustness) and prefrailty (vs. robustness) were performed. One unit of DunedinPACE can be interpreted as one year of biological aging per year of chronological aging; medians and interquartile ranges of these values (stratified by Phase and smoking status) are reported. A sensitivity analysis evaluating only former-former smokers (former at both Phase 1 and Phase 2) was conducted, as was a sensitivity analysis comparing DunedinPACE with frailty status when stratified by sex.

Statistical analyses were conducted in R 4.3.0 (with the exception of the calculation of DunedinPACE, which was conducted in R 4.2.0).

Abbreviations

AHR: Adjusted Hazard Ratio; BADLs: Basic Activities of Daily Living; BMI: Body Mass Index; BODE score: Body mass index, airflow Obstruction, Dyspnea, and

Exercise capacity score; CES-D: Center for Epidemiologic Studies Depression Scale; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; COPDGene: Genetic Epidemiology of COPD Study; CT: Computed Tomography; FEV1: Forced Expiratory Volume in one second; FFP: Fried Frailty Phenotype; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IADLs: Independent Activities of Daily Living; IRR: Incident Rate Ratio; MCA: Multiple Correspondence Analysis; mMRC: dyspnea score Modified Medical Research Council dyspnea score; OR: Odds Ratio; PCA: Principal Component Analysis; PRISm: Preserved Ratio Impaired Spirometry; SF-36: 36-Item Short Form Survey; 6MWD: Six Minute Walk Distance; 6MWT: Six Minute Walk Test.

AUTHOR CONTRIBUTIONS

EKP and DLD had full access to study data and take responsibility for the integrity of the data and accuracy of the data analysis. EKP and DLD contributed substantially to the study concept and design. DLD, ER, JDC, EKS, BM, and KH contributed to data collection. YH contributed to data analysis. EKP contributed to data analysis and writing of the manuscript. MS contributed to statistical analysis. All authors contributed to critical revision of manuscript for key scientific content.

ACKNOWLEDGMENTS

The authors would like to thank the COPDGene study coordinators and the COPDGene study participants. Molecular data for the Trans-Omics in Precision Medicine (TOPMed) program was supported by the National Heart, Lung and Blood Institute (NHLBI). DNA Methylation for "NHLBI TOPMed: COPDGene" (phs000951) was performed at Northwest Genomics Center (HHSN268201600032I). Core support including centralized genomic read mapping and genotype calling, along with variant quality metrics and filtering were provided by the TOPMed Informatics Research Center (3R01HL-117626-02S1; contract HHSN268201800002I). We gratefully acknowledge the studies and participants who provided biological samples and data for TOPMed.

CONFLICTS OF INTEREST

BM - AstraZeneca – received personal fees, consulting fees, payment or honoraria for presentation, serves on Medical Advisory Board, and research grant funds provided to and controlled by National Jewish Health. Baystate Medical Center – participation on Data Safety and Monitoring Board. Boehringer Ingelheim – received personal fees and participation on Medical Advisory Board. Glaxo Smith Kline – Advisory Board member and received personal fees. Optimum Patient Care Global Limited – received personal and consulting fees, payment or honoraria for presentations, and Advisory Board member. Spiration – received personal fees and participated in Data and Safety Monitoring Board. Third Pole – received personal and consulting fees. Verona – received consulting fees. Wolters Kluwer Health – received royalties. US Department of Defense – grant support. AMY - served as a consultant, on advisory board and received a consultation fee from Astra Zeneca. KH - is a member of the Medical and Scientific Advisory Board for the COPD Foundation (a not-for-profit) foundation. EKS - In the past three years, received grant support from Bayer and Northpond Laboratories. DLD - is a member of the Medical and Scientific Advisory Board for the COPD Foundation (a not-for-profit) foundation and in the past three years, received grant support from Bayer.

ETHICAL STATEMENT AND CONSENT

The study protocols were approved by the institutional review board at each site (Brigham and Women's Hospital IRB #2007P000554). All participants provided informed consent for participating in the COPDGene study, and written confirmation of the informed consent process was obtained. This included consent for publication of research results.

FUNDING

COPDGene Support: This work was supported by NHLBI grants U01 HL089897 and U01 HL089856 and by NIH contract 75N92023D00011. The COPDGene study (NCT00608764) has also been supported by the COPD Foundation through contributions made to an Industry Advisory Committee that has included AstraZeneca, Bayer Pharmaceuticals, Boehringer-Ingelheim, Genentech, GlaxoSmithKline, Novartis, Pfizer, and Sunovion. Author Financial Support: EKP is supported by NIH 5T32HL007427-42. KFH is supported by NIH R01 HL134822. EKS is supported by NIH R01 HL133135, R01 HL152728, and P01 HL114501. DLD is supported by NIH R01 HG011393, NIH K24 171900.

REFERENCES

1. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, and Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56:M146–56. https://doi.org/10.1093/gerona/56.3.m146

PMID:11253156

2. Lahousse L, Ziere G, Verlinden VJ, Zillikens MC, Uitterlinden AG, Rivadeneira F, Tiemeier H, Joos GF, Hofman A, Ikram MA, Franco OH, Brusselle GG, Stricker BH. Risk of Frailty in Elderly With COPD: A Population-Based Study. J Gerontol A Biol Sci Med Sci. 2016; 71:689–95. https://doi.org/10.1093/gerona/glv154 PMID:26355016

3. Dias LS, Ferreira ACG, da Silva Junior JLR, Conte MB, Rabahi MF. Prevalence of Frailty and Evaluation of Associated Variables Among COPD Patients. Int J Chron Obstruct Pulmon Dis. 2020; 15:1349–56. https://doi.org/10.2147/COPD.S250299 PMID:32606644

4. Galizia G, Cacciatore F, Testa G, Della-Morte D, Mazzella F, Langellotto A, Raucci C, Gargiulo G, Ferrara N, Rengo F, Abete P. Role of clinical frailty on long-term mortality of elderly subjects with and without chronic obstructive pulmonary disease. Aging Clin Exp Res. 2011; 23:118–25. https://doi.org/10.1007/BF03351076 PMID:21743290

5. Hanlon P, Lewsey J, Quint JK, Jani BD, Nicholl BI, McAllister DA, Mair FS. Frailty in COPD: an analysis of prevalence and clinical impact using UK Biobank. BMJ Open Respir Res. 2022; 9:e001314. https://doi.org/10.1136/bmjresp-2022-001314 PMID:35787523

6. Kennedy CC, Novotny PJ, LeBrasseur NK, Wise RA, Sciurba FC, Benzo RP. Frailty and Clinical Outcomes in Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2019; 16:217–24. https://doi.org/10.1513/AnnalsATS.201803-175OC PMID:30433830

7. Luo J, Zhang D, Tang W, Dou LY, Sun Y. Impact of Frailty on the Risk of Exacerbations and All-Cause Mortality in Elderly Patients with Stable Chronic Obstructive Pulmonary Disease. Clin Interv Aging. 2021; 16:593–601. https://doi.org/10.2147/CIA.S303852 PMID:33880018

8. Park SK, Richardson CR, Holleman RG, Larson JL. Frailty in people with COPD, using the National Health and Nutrition Evaluation Survey dataset (2003-2006). Heart Lung. 2013; 42:163–70. https://doi.org/10.1016/j.hrtlng.2012.07.004 PMID:23535142

9. Roberts MH, Mapel DW, Ganvir N, Dodd MA. Frailty Among Older Individuals with and without COPD: A Cohort Study of Prevalence and Association with Adverse Outcomes. Int J Chron Obstruct Pulmon Dis. 2022; 17:701–17. https://doi.org/10.2147/COPD.S348714 PMID:35411140

10. Marengoni A, Vetrano DL, Manes-Gravina E, Bernabei R, Onder G, Palmer K. The Relationship Between COPD and Frailty: A Systematic Review and Meta-Analysis of Observational Studies. Chest. 2018; 154:21–40. https://doi.org/10.1016/j.chest.2018.02.014 PMID:29477493

11. He D, Yan M, Zhou Y, Ge H, Zhang X, Xu Y, Liu C, Ying K, Zhu Y. Preserved Ratio Impaired Spirometry and COPD Accelerate Frailty Progression: Evidence From a Prospective Cohort Study. Chest. 2024; 165:573–82. https://doi.org/10.1016/j.chest.2023.07.020 PMID:37499976

12. Scarlata S, Finamore P, Laudisio A, Cardaci V, Ramaccia M, D'Alessandro F, Pedone C, Antonelli Incalzi R, Cesari M. Association between frailty index, lung function, and major clinical determinants in chronic obstructive pulmonary disease. Aging Clin Exp Res. 2021; 33:2165–73. https://doi.org/10.1007/s40520-021-01878-z PMID:34009526

13. Martinez CH, Diaz AA, Meldrum CA, McDonald MN, Murray S, Kinney GL, Hokanson JE, Curtis JL, Bowler RP, Han MK, Washko GR, Regan EA, and COPDGene Investigators. Handgrip Strength in Chronic Obstructive Pulmonary Disease. Associations with Acute Exacerbations and Body Composition. Ann Am Thorac Soc. 2017; 14:1638–45. https://doi.org/10.1513/AnnalsATS.201610-821OC PMID:29090990

14. Gale NS, Albarrati AM, Munnery MM, Hubbard RE, Tal-Singer R, Cockcroft JR, Shale DJ. Frailty: A global measure of the multisystem impact of COPD. Chron Respir Dis. 2018; 15:347–55. https://doi.org/10.1177/1479972317752763 PMID:29334783

15. Zou RH, Nouraie SM, Rossiter HB, McDonald ML, DeMeo DL, Mason S, Washko GR, Saha PK, Make BJ, Casaburi R, Regan EA, Bon J, and COPDGene Investigators. Associations Between Muscle Weakness and Clinical Outcomes in Current and Former Smokers. Chronic Obstr Pulm Dis. 2023; 10:112–21. https://doi.org/10.15326/jcopdf.2022.0365 PMID:36599111

16. Yee N, Locke ER, Pike KC, Chen Z, Lee J, Huang JC, Nguyen HQ, Fan VS. Frailty in Chronic Obstructive Pulmonary Disease and Risk of Exacerbations and Hospitalizations. Int J Chron Obstruct Pulmon Dis. 2020; 15:1967–76. https://doi.org/10.2147/COPD.S245505

PMID:32848382

17. Maddocks M, Kon SS, Canavan JL, Jones SE, Nolan CM, Labey A, Polkey MI, Man WD. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. Thorax. 2016; 71:988–95. https://doi.org/10.1136/thoraxjnl-2016-208460 PMID:27293209

18. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, Xue QL, Walston JD, Kasper JD. Frailty in Older Adults: A Nationally Representative Profile in the United States. J Gerontol A Biol Sci Med Sci. 2015; 70:1427–34. https://doi.org/10.1093/gerona/glv133 PMID:26297656

19. Xu J, Xu W, Qiu Y, Gong D, Man C, Fan Y. Association of Prefrailty and Frailty With All-Cause Mortality, Acute Exacerbation, and Hospitalization in Patients With Chronic Obstructive Pulmonary Disease: A Meta-Analysis. J Am Med Dir Assoc. 2023; 24:937–44.e3. https://doi.org/10.1016/j.jamda.2023.03.032 PMID:37150209

20. Hubbard RE, Searle SD, Mitnitski A, Rockwood K. Effect of smoking on the accumulation of deficits, frailty and survival in older adults: a secondary analysis from the Canadian Study of Health and Aging. J Nutr Health Aging. 2009; 13:468–72. https://doi.org/10.1007/s12603-009-0085-y PMID:19390755

21. Gao X, Zhang Y, Saum KU, Schöttker B, Breitling LP, Brenner H. Tobacco smoking and smoking-related DNA methylation are associated with the development of frailty among older adults. Epigenetics. 2017; 12:149–56. https://doi.org/10.1080/15592294.2016.1271855 PMID:28001461

22. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health. 2018; 3:e323–32. https://doi.org/10.1016/S2468-2667(18)30091-4 PMID:29908859

23. Ottenbacher KJ, Graham JE, Al Snih S, Raji M, Samper-Ternent R, Ostir GV, Markides KS. Mexican Americans and frailty: findings from the Hispanic established populations epidemiologic studies of the elderly. Am J Public Health. 2009; 99:673–9. https://doi.org/10.2105/AJPH.2008.143958 PMID:19197079

24. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, Masaki K, Murray A, Newman AB, and Women's Health Initiative. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. J Am Geriatr Soc. 2005; 53:1321–30. https://doi.org/10.1111/j.1532-5415.2005.53405.x PMID:16078957

25. Etman A, Kamphuis CB, van der Cammen TJ, Burdorf A, van Lenthe FJ. Do lifestyle, health and social participation mediate educational inequalities in frailty worsening? Eur J Public Health. 2015; 25:345–50. https://doi.org/10.1093/eurpub/cku093 PMID:25061232

26. Trevisan C, Veronese N, Maggi S, Baggio G, Toffanello ED, Zambon S, Sartori L, Musacchio E, Perissinotto E, Crepaldi G, Manzato E, Sergi G. Factors Influencing Transitions Between Frailty States in Elderly Adults: The Progetto Veneto Anziani Longitudinal Study. J Am Geriatr Soc. 2017; 65:179–84. https://doi.org/10.1111/jgs.14515 PMID:27861714

27. Lee JS, Auyeung TW, Leung J, Kwok T, Woo J. Transitions in frailty states among community-living older adults and their associated factors. J Am Med Dir Assoc. 2014; 15:281–6. https://doi.org/10.1016/j.jamda.2013.12.002 PMID:24534517

28. Pérez-Tasigchana RF, Sandoval-Insausti H, Donat-Vargas C, Banegas JR, Rodríguez-Artalejo F, Guallar-Castillon P. Combined Impact of Traditional and Nontraditional Healthy Behaviors on Frailty and Disability: A Prospective Cohort Study of Older Adults. J Am Med Dir Assoc. 2020; 21:710.e1–9. https://doi.org/10.1016/j.jamda.2019.08.025 PMID:31636035

29. Kojima G, Iliffe S, Jivraj S, Liljas A, Walters K. Does current smoking predict future frailty? The English longitudinal study of ageing. Age Ageing. 2018; 47:126–31. https://doi.org/10.1093/ageing/afx136 PMID:28985256

30. McKleroy W, Shing T, Anderson WH, Arjomandi M, Awan HA, Barjaktarevic I, Barr RG, Bleecker ER, Boscardin J, Bowler RP, Buhr RG, Criner GJ, Comellas AP, et al. Longitudinal Follow-Up of Participants With Tobacco Exposure and Preserved Spirometry. JAMA. 2023; 330:442–53. https://doi.org/10.1001/jama.2023.11676 PMID:37526720

31. Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JH, Grenier PA, Kauczor HU, Bailey WC, DeMeo DL, Casaburi RH, Friedman P, Van Beek EJ, Hokanson JE, et al, and Genetic Epidemiology of

COPD (COPDGene) Investigators. Clinical and Radiologic Disease in Smokers With Normal Spirometry. JAMA Intern Med. 2015; 175:1539–49. https://doi.org/10.1001/jamainternmed.2015.2735 PMID:26098755

32. Verschoor CP, Dales RE, Duong M, Bourque C, Mian O, Ma J, Griffith LE. Respiratory Symptoms Are Associated With Frailty in Older Adults With Normal Spirometry, Independent of Smoking, in the Canadian Longitudinal Study of Aging. Respir Care. 2021; 66:1848–57. https://doi.org/10.4187/respcare.09225 PMID:34610984

33. Gale CR, Marioni RE, Harris SE, Starr JM, Deary IJ. DNA methylation and the epigenetic clock in relation to physical frailty in older people: the Lothian Birth Cohort 1936. Clin Epigenetics. 2018; 10:101. https://doi.org/10.1186/s13148-018-0538-4 PMID:30075802

34. Seligman BJ, Berry SD, Lipsitz LA, Travison TG, Kiel DP. Epigenetic Age Acceleration and Change in Frailty in MOBILIZE Boston. J Gerontol A Biol Sci Med Sci. 2022; 77:1760–5. https://doi.org/10.1093/gerona/glac019 PMID:35037036

35. Verschoor CP, Lin DTS, Kobor MS, Mian O, Ma J, Pare G, Ybazeta G. Epigenetic age is associated with baseline and 3-year change in frailty in the Canadian Longitudinal Study on Aging. Clin Epigenetics. 2021; 13:163. https://doi.org/10.1186/s13148-021-01150-1 PMID:34425884

36. Belsky DW, Caspi A, Corcoran DL, Sugden K, Poulton R, Arseneault L, Baccarelli A, Chamarti K, Gao X, Hannon E, Harrington HL, Houts R, Kothari M, et al. DunedinPACE, a DNA methylation biomarker of the pace of aging. Elife. 2022; 11:e73420. https://doi.org/10.7554/eLife.73420 PMID:35029144

37. Phyo AZZ, Espinoza SE, Murray AM, Fransquet PD, Wrigglesworth J, Woods RL, Ryan J. Epigenetic age acceleration and the risk of frailty, and persistent activities of daily living (ADL) disability. Age Ageing. 2024; 53:afae127. https://doi.org/10.1093/ageing/afae127 PMID:38941117

38. Mak JKL, Karlsson IK, Tang B, Wang Y, Pedersen NL, Hägg S, Jylhävä J, Reynolds CA. Temporal Dynamics of Epigenetic Aging and Frailty From Midlife to Old Age. J Gerontol A Biol Sci Med Sci. 2024; 79:glad251. https://doi.org/10.1093/gerona/glad251 PMID:37889476

39. Xue QL, Bandeen-Roche K, Tian J, Kasper JD, Fried LP. Progression of Physical Frailty and the Risk of All-Cause Mortality: Is There a Point of No Return? J Am Geriatr Soc. 2021; 69:908–15. https://doi.org/10.1111/jgs.16976 PMID:33368158

40. Kwon J, Yoshida Y, Yoshida H, Kim H, Suzuki T, Lee Y. Effects of a combined physical training and nutrition intervention on physical performance and health-related quality of life in prefrail older women living in the community: a randomized controlled trial. J Am Med Dir Assoc. 2015; 16:263.e1–8. https://doi.org/10.1016/j.jamda.2014.12.005 PMID:25659620

41. Park Y, Choi JE, Hwang HS. Protein supplementation improves muscle mass and physical performance in undernourished prefrail and frail elderly subjects: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr. 2018; 108:1026–33. https://doi.org/10.1093/ajcn/nqy214 PMID:30475969

42. Marin JM, Carrizo SJ, Casanova C, Martinez-Camblor P, Soriano JB, Agusti AG, Celli BR. Prediction of risk of COPD exacerbations by the BODE index. Respir Med. 2009; 103:373–8. https://doi.org/10.1016/j.rmed.2008.10.004 PMID:19013781

43. Fried LP, Cohen AA, Xue QL, Walston J, Bandeen-Roche K, Varadhan R. The physical frailty syndrome as a transition from homeostatic symphony to cacophony. Nat Aging. 2021; 1:36–46. https://doi.org/10.1038/s43587-020-00017-z PMID:34476409

44. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, Curran-Everett D, Silverman EK, Crapo JD. Genetic epidemiology of COPD (COPDGene) study design. COPD. 2010; 7:32–43. https://doi.org/10.3109/15412550903499522 PMID:20214461

45. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002; 166:111–7. https://doi.org/10.1164/ajrccm.166.1.at1102 PMID:12091180

46. Ware JE Jr. SF-36 health survey update. Spine (Phila Pa 1976). 2000; 25:3130–9. https://doi.org/10.1097/00007632-200012150-00008 PMID:11124729

47. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psychol Meas. 1977; 1:385–401. https://doi.org/10.1177/014662167700100306

48. Gardner W, Mulvey EP, Shaw EC. Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models. Psychol Bull. 1995; 118:392–404.
https://doi.org/10.1037/0033-2909.118.3.392
PMID:7501743

SUPPLEMENTARY MATERIALS

Supplementary Methods

Study design and population

The COPDGene study (clinicaltrials.gov ID NCT00608764) is an ongoing multicenter cohort study [1]. Non-Hispanic White and African American adults with a reported age 45–80 and a minimum 10 pack-year smoking history were eligible to participate. Exclusion criteria included pulmonary fibrosis, active cancer under treatment, and history of chest radiation. Participants had on-site evaluations at baseline (Phase 1) and every 5 years (Phases 2 and 3). Participants provided written documentation of the informed consent process, and study protocols were approved by the institutional review board of each clinical center.

The current study is an analysis of the COPDGene cohort limited to the participants who returned for the Phase 3 (10-year follow-up) visit (2018–2023) and had an assessment of all five frailty components (Figure 3). Data were also collected on a small number of never-smoker controls; frailty prevalence was assessed in a post hoc analysis of this group.

Measurements

Physiologic, spirometric, questionnaire, and CT data were collected by trained personnel at the Phase 3 visit. Hand grip strength (average of three efforts) was measured with Jamar dynamometers. Six-minute walk tests (6MWT) were conducted in accordance with ATS guidelines [2].

Pre- and post-bronchodilator spirometry was performed using ndd EasyOne Spirometers. Post-bronchodilator forced expiratory volume in one second (FEV1) % predicted was defined based on NHANES III references [3]. COPD was defined as an FEV1/FVC (forced vital capacity) ratio of <0.7, and GOLD grade was defined according to standard criteria [4]. Preserved Ratio Impaired Spirometry (PRISm) was defined as an FEV1 of <80% predicted and an FEV1/FVC ratio of >0.7 [5].

Questionnaires included the 36-Item Short Form Survey (SF-36) and portions of the Center for Epidemiologic Studies Depression Scale (CES-D) [6, 7].

Two self-reported questions about need for assistance with basic and instrumental activities of daily living (ADLs) were asked based on recommendations by the Alzheimer's Association's Medicare Detection of Cognitive Impairment Workgroup [8]:

(1) "During the past 7 days, did you need help from others to perform everyday activities such as eating, getting dressed, grooming, bathing, walking, or using the toilet?" (Yes/No)
(2) "During the past 7 days, did you need help from others to take care of things such as laundry and housekeeping, banking, shopping, using the telephone, food preparation, transportation, or taking your own medications?" (Yes/No)

The Mini-Cog was administered as a brief standardized screen for cognitive impairment, with probable cognitive impairment defined as a total score ≤3. This cutoff was chosen based on prior literature examining the Mini-Cog sensitivity and specificity relative to the gold standard assessment [9, 10].

Comorbidities and smoking status were self-reported by survey. For this study, comorbidity count was defined as the sum of the following: congestive heart failure, coronary artery disease (CAD) composite, cerebrovascular disease, kidney disease, liver disease, diabetes, osteoarthritis, osteoporosis, and cancer (excluding non-melanoma skin cancers). CAD (composite) was defined by the presence of any of the following: self-reported CAD, myocardial infarction, angina, angioplasty, or coronary artery bypass graft surgery. Heart disease (composite) was defined if participants reported any of the following: CAD, myocardial infarction, angina, angioplasty, coronary artery bypass graft surgery, or congestive heart failure. Cerebrovascular disease (composite) was defined as the presence of reported stroke and/or transient ischemic attack (TIA).

Detailed protocols regarding CT scan data collection and analysis have been described previously [1]. Volumetric CT acquisitions were obtained, and images were reconstructed using sub-millimeter slice thickness. Quantitative CT measurement of the standardized airway wall thickness (Pi10) was calculated using Thirona software based on the average wall thickness of a hypothetical airway with a lumen perimeter of 10mm.

Frailty assessment

We generated a modified FFP from the five frailty components of shrinking, weakness, low activity, fatigue, and slowness (Figure 1) [11].

Shrinking was defined as weight loss ≥4.6kg or ≥5% of body weight from the prior (Phase 2) visit [11].

Weakness was based on hand grip strength (with sex- and body mass index (BMI)-stratified cutoffs [11]).

Fatigue was assessed with two questions from the CES-D:

(1) "I feel that everything I do is an effort"
(2) "I cannot get going"

Response options were "None of the time", "Some of the time (1–2 days per week)", "A moderate amount (3–4 days per week)", and "Most of the time." Individuals who answered "A moderate amount (3–4 days per week)" or "Most of the time" to either question were considered to have fatigue.

Slowness was defined by the lowest quintile of 6MWD in the baseline (Phase 1) population (stratified by sex and adjusted for height). Defining frailty components by the lowest quintile in the baseline population is established in the literature [11, 12].

Low activity was based on responses to the SF-36 survey Physical Functioning (PF) section. This section consists of 10 questions as follows:

"The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
(b) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
(c) Lifting or carrying groceries
(d) Climbing several flights of stairs
(e) Climbing one flight of stairs
(f) Bending, kneeling, or stooping
(g) Walking more than a mile
(h) Walking several hundred yards
(i) Walking one hundred yards
(j) Bathing or dressing yourself"

SF-36 PF response options were "Yes, limited a lot", "Yes, limited a little", and "No, not limited at all". Responses were scored 0 (not limited), 50 (somewhat limited), or 100 (limited a lot), and the mean of the responses was used as the PF section score [6]. Low activity was defined by the sex-stratified lowest quintile of baseline (Phase 1) SF-36 PF scores.

Individuals were classified as frail if three or more of these components were present, prefrail if one or two were present, and robust if none were present [11].

Longitudinal outcome measurements

Longitudinal follow-up on respiratory exacerbations was collected at six-month intervals by telephone or web-based survey. Exacerbation data and unadjudicated all-cause mortality data are reported through July 2023.

Participants with fewer than 180 days of follow-up were excluded from exacerbation analyses. Exacerbations were defined as an episode of increased cough and phlegm or shortness of breath which lasted for at least 48 hours and which required treatment with antibiotics, steroids, emergency room (ER) visit, or hospitalization. Exacerbations requiring an ER visit or hospitalization were classified as severe. The exacerbation outcomes evaluated were annual exacerbation rate, presence of severe exacerbations, and presence of frequent exacerbations (annual rate of ≥1/year).

Epigenetic pace of aging measurement

Whole blood samples for assessment of DNA methylation were obtained at baseline (Phase 1) visit and at 5-year follow-up (Phase 2) visit. DNA methylation was assessed using the Illumina Infinium EPIC 850k BeadChip array. After regression on correlated probes for bias correction and functional normalization, methylation beta values were used to calculate the DunedinPACE of Aging using the DunedinPACE package in R statistical software. Individuals who were missing either Phase 1 or Phase 2 methylation data were excluded from epigenetic pace of aging analyses.

Statistical analysis

Continuous variables are reported as mean (standard deviation) unless otherwise specified. Differences across frailty categories were assessed with Kruskal-Wallis rank sum test (continuous data), Pearson's chi-squared test (categorical data), and Fisher's exact test (categorical data with cell counts ≤5).

To evaluate how the five frailty components combined to generate the frailty phenotype, we performed a principal component analysis (PCA) of the five continuous underlying characteristics from which frailty traits were derived. PCA was performed on scaled data using the variance-covariance method. A complementary multiple correspondence analysis (MCA) of the five binary frailty traits was conducted using an indicator matrix.

For analyses of exacerbation data, robust individuals were used as the comparator group for frail and prefrail individuals. Frequent and severe exacerbations were

modeled using multivariable logistic regression. Exacerbation count was analyzed using multivariable negative binomial regression of total exacerbation count with an offset term for the log(follow-up time) [13]. Exacerbation models were adjusted for participant age, sex, % predicted post-bronchodilator forced expiratory volume in 1 second (FEV1), and smoking status.

Multivariable Cox proportional hazard models adjusted for a priori covariates of age, sex, BMI, smoking pack-years, diabetes, and heart disease (defined above) were used to calculate adjusted hazard ratios (AHR) for frailty and prefrailty. Robust individuals were used as the comparison group. Linearity was tested using likelihood ratios comparing the model used to model with covariate terms including second order poly-nomials. A sensitivity analysis was performed using a parametric (Weibull) multivariable model to confirm persistence of frailty and prefrailty effects. Covariates were selected based on factors that had been (clinically or scientifically) associated with both frailty and mortality and thus could potentially confound analyses. For this reason, covariate selection differed slightly between exacerbation and mortality analyses (for example, diabetes was included in the model for mortality but not in those for respiratory exacerbations). Adjusted cumulative incidence curves were obtained using the G-formula method [14].

Subgroup analyses were performed by spirometric category (normal spirometry, GOLD 1, GOLD 2–4, and PRISm; defined above), with a focus on the two subgroups with the largest number of participants (normal spirometry and GOLD 2–4).

The association between epigenetic pace of aging (DunedinPACE) at baseline (Phase 1) and at 5-year follow-up (Phase 2) and frailty status at 10-year follow-up (Phase 3) was assessed. To evaluate for potential confounding epigenetic effects of current smoking, analyses were stratified by smoking status at the time of blood sample collection. Crude associations were assessed using Kruskal-Wallis rank sum test. Logistic regressions of Phase 1 and Phase 2 DunedinPACE of Aging on the outcome of Phase 3 frailty (vs robustness) and prefrailty (vs robustness) were performed. One unit of DunedinPACE can be interpreted as one year of biological aging per year of chronological aging; medians and interquartile ranges of these values (stratified by Phase and smoking status) are reported.

Statistical analyses were conducted in R 4.3.0 (with the exception of the calculation of DunedinPACE, which was conducted in R 4.2.0). Software packages used included survival, adjustedCurves, methylCIPHER, and FactoMineR. A two-sided p-value of <0.05 was considered statistically significant unless otherwise specified.

Missing data

The frequency of missing cross-sectional covariate data is reported. Characteristics of subjects with and without missing follow-up and methylation data are reported. In cases of missing data in regression models, complete case analysis was performed.

Secondary analyses

To explore the observed cross-sectional associations between cigarette smoking and frailty category, we performed exploratory post-hoc multivariable logistic regressions of outcomes of frailty and prefrailty against covariates of age, sex, FEV1 % predicted, smoking status, and smoking pack-years. The purpose of this was to evaluate if the association between frailty and prefrailty and smoking persisted after adjusting for age and lung function. These were performed on the entire study population and for each spirometric subgroup (normal spirometry, GOLD 1, GOLD 2–4, and PRISm).

For longitudinal outcomes, we evaluated for effect modification of lung function on frailty/prefrailty's association with outcomes by adding an interaction term for FEV1% predicted * frailty (or FEV1 % predicted *prefrailty) to above models.

We also evaluated the association between the number of frailty traits (0–5, categorical) and respiratory exacerbations (exacerbation rate, severe exacerbations, and frequent exacerbations) and with mortality (collapsing the groups with 4 and 5 traits due to low event counts).

To assess if any one frailty component was overly influential to mortality risk, we separately performed a Cox proportional hazard model (adjusted for covariates in primary mortality model) including all five individual frailty components (instead of frailty category) as predictors.

We also performed sex-stratified analyses of the associations between prefrailty and frailty and longitudinal outcomes.

Lastly, we characterized the prevalence of frailty and prefrailty in the non-smoker control group.

Sensitivity analyses

We performed several sensitivity analyses of the associations between frailty and prefrailty and the

primary outcomes of exacerbations and mortality (of the primary effects only; not respiratory subgroup analyses).

(1) We used an alternative frailty and prefrailty definition based on the slowness criteria used in the NETT trial, which defined slowness as a 6MWD of ≤770 feet for men 173 cm or shorter and women 159cm or shorter, and otherwise as a 6MWD of ≤900 feet [15].
(2) We excluded individuals with a Mini-Cog score of 3 or lower from analyses (since frailty status ascertainment involved self-reported measures).
(3) To assess for overly influential effects of underweight subjects, we performed a subgroup analysis on only those with BMI over 21.
(4) To confirm that frailty effects were not simply driven by low 6MWD, we *excluded* individuals who were frail due to slowness (that is, had exactly 3 frailty components, one of which was slowness) or who were prefrail due to slowness (that is, had only one frailty component: slowness).
(5) We *looked only at the subgroup* of individuals who were frail and prefrail due to shrinking to see if associations with adverse outcomes persisted in this group as well (since successful dieting could be classified as shrinking). Individuals who were considered frail "due to shrinking" had exactly three frailty components, one of which was shrinking. Individuals who were prefrail "due to shrinking" had only one frailty component present (shrinking).
(6) We performed stratified analyses based on whether participants had their Phase 3 visit before or after 2020 to assess for pandemic effects.

For epigenetic pace of aging analyses, a sensitivity analysis evaluating only former-former smokers (former at both Phase 1 and Phase 2) was conducted, as was a sensitivity analysis comparing DunedinPACE with frailty status when stratified by sex.

Supplementary References

1. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, Curran-Everett D, Silverman EK, Crapo JD. Genetic epidemiology of COPD (COPDGene) study design. COPD. 2010; 7:32–43. https://doi.org/10.3109/15412550903499522 PMID:20214461

2. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002; 166:111–7. https://doi.org/10.1164/ajrccm.166.1.at1102 PMID:12091180

3. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999; 159:179–87. https://doi.org/10.1164/ajrccm.159.1.9712108 PMID:9872837

4. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, Bourbeau J, Han MK, Martinez FJ, Montes de Oca M, Mortimer K, Papi A, Pavord I, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Eur Respir J. 2023; 61:2300239. https://doi.org/10.1183/13993003.00239-2023 PMID:36858443

5. Wan ES, Fortis S, Regan EA, Hokanson J, Han MK, Casaburi R, Make BJ, Crapo JD, DeMeo DL, Silverman EK, and COPDGene Investigators. Longitudinal Phenotypes and Mortality in Preserved Ratio Impaired Spirometry in the COPDGene Study. Am J Respir Crit Care Med. 2018; 198:1397–405. https://doi.org/10.1164/rccm.201804-0663OC PMID:29874098

6. Ware JE Jr. SF-36 health survey update. Spine (Phila Pa 1976). 2000; 25:3130–9. https://doi.org/10.1097/00007632-200012150-00008 PMID:11124729

7. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psychol Meas. 1977; 1:385–401. https://hdl.handle.net/11299/98561.

8. Cordell CB, Borson S, Boustani M, Chodosh J, Reuben D, Verghese J, Thies W, Fried LB, and Medicare Detection of Cognitive Impairment Workgroup. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. Alzheimers Dement. 2013; 9:141–50. https://doi.org/10.1016/j.jalz.2012.09.011 PMID:23265826

9. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. J Am Geriatr Soc. 2003; 51:1451–4. https://doi.org/10.1046/j.1532-5415.2003.51465.x PMID:14511167

10. Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry. 2000; 15:1021–7. https://doi.org/10.1002/1099-1166(200011)15:11<1021::aid-gps234>3.0.co;2-6 PMID:11113982

11. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, and Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56:M146–56.
https://doi.org/10.1093/gerona/56.3.m146
PMID:11253156

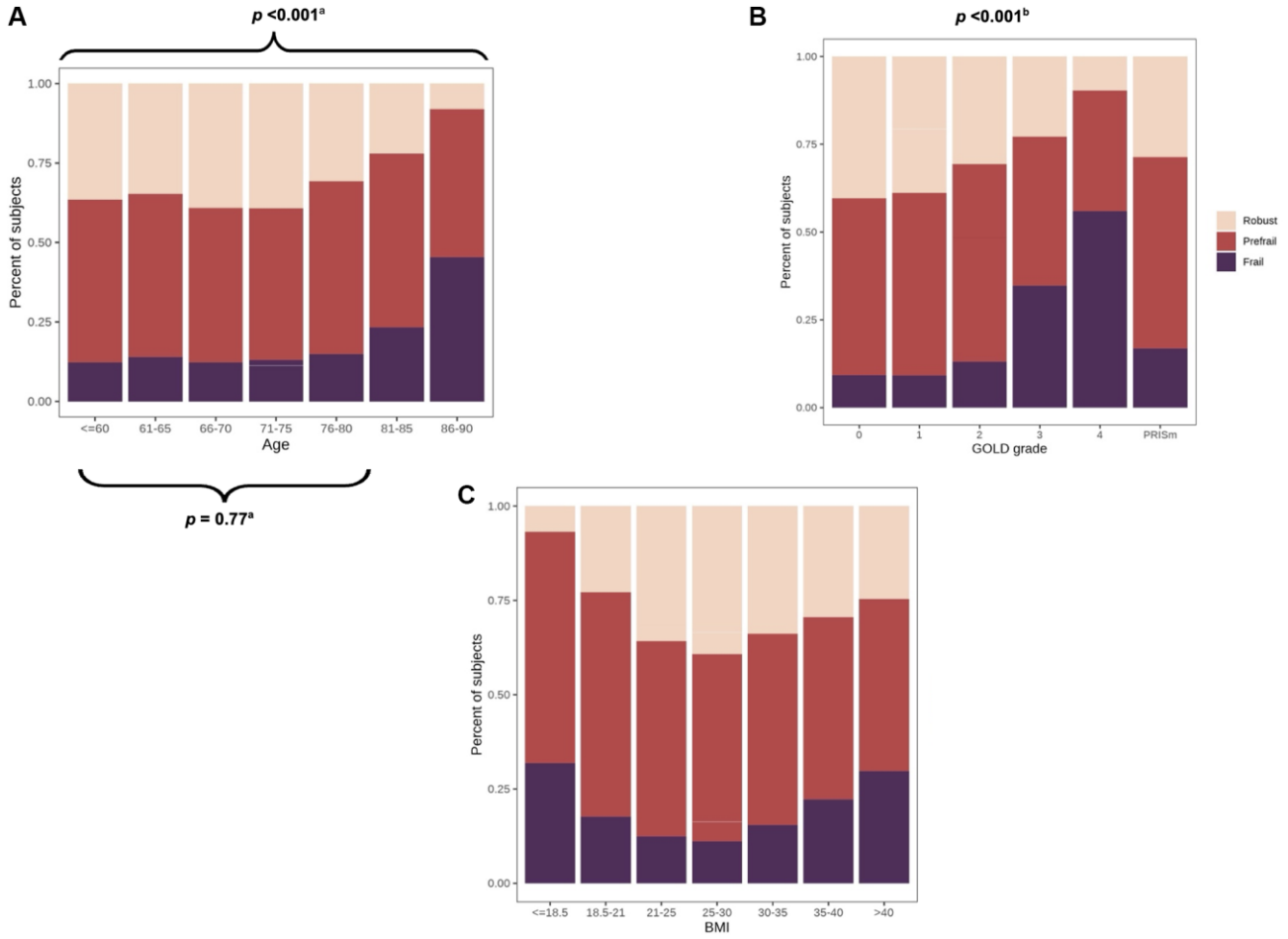
12. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, Xue QL, Walston JD, Kasper JD. Frailty in Older Adults: A Nationally Representative Profile in the United States. J Gerontol A Biol Sci Med Sci. 2015; 70:1427–34.
https://doi.org/10.1093/gerona/glv133
PMID:26297656

13. Gardner W, Mulvey EP, Shaw EC. Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models. Psychol Bull. 1995; 118:392–404.
https://doi.org/10.1037/0033-2909.118.3.392
PMID:7501743

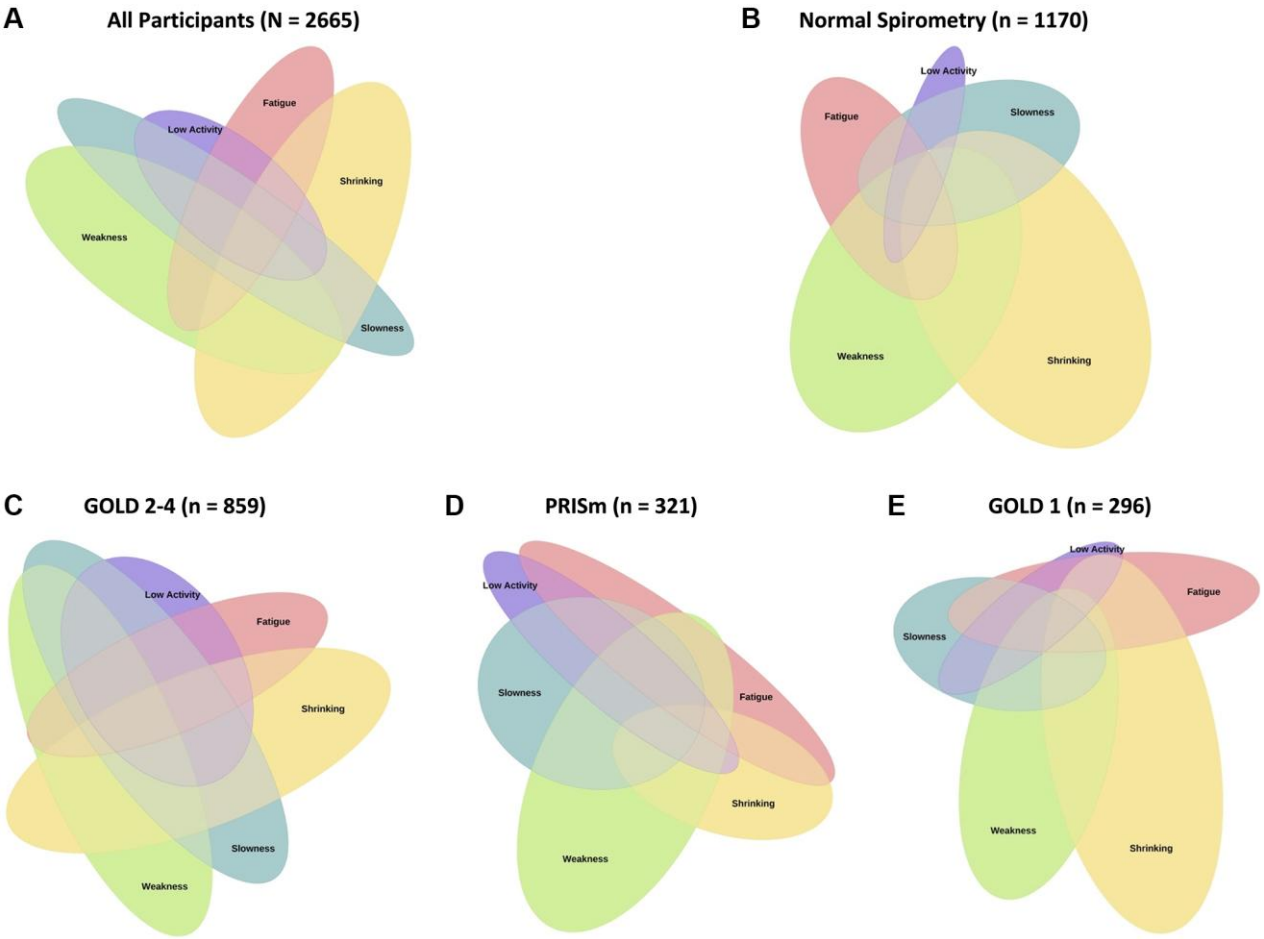
14. Denz R, Klaaßen-Mielke R, Timmesfeld N. A comparison of different methods to adjust survival curves for confounders. Stat Med. 2023; 42:1461–79.
https://doi.org/10.1002/sim.9681
PMID:36748630

15. Kennedy CC, Novotny PJ, LeBrasseur NK, Wise RA, Sciurba FC, Benzo RP. Frailty and Clinical Outcomes in Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2019; 16:217–24.
https://doi.org/10.1513/AnnalsATS.201803-175OC
PMID:30433830

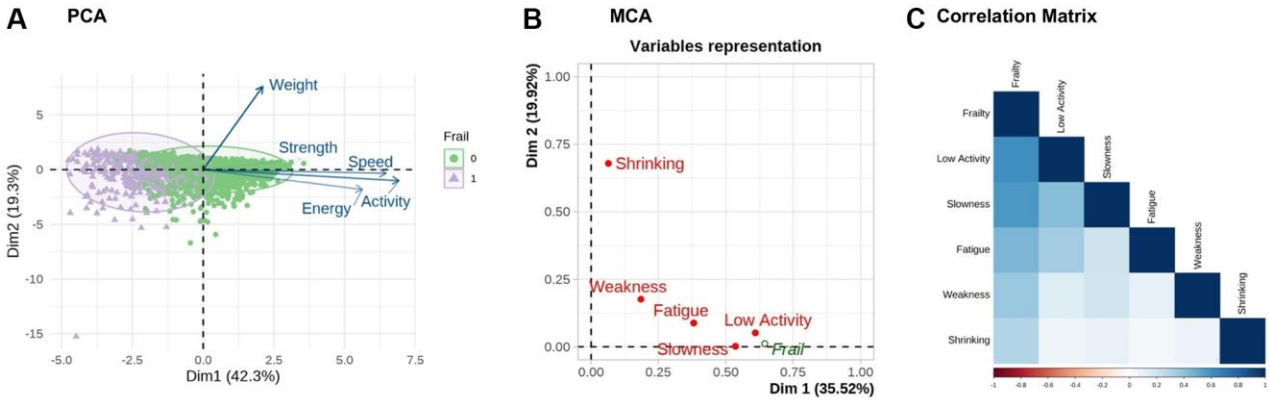
Supplementary Figures



Supplementary Figure 1. Frailty prevalence by age group, GOLD grade, and BMI category. Stacked bar graphs demonstrating the prevalence of frailty category (frail, prefrail, and robust) (**A**) across age categories (**B**) within each GOLD grade and (**C**) by BMI stratum. [a]*p*-values by Kruskal-Wallis rank sum test of participant age (continuous) across frailty category (frail, prefrail, robust) for all subjects (upper) and for subjects aged 80 or younger (lower). [b]Pearson's chi-squared *P*-value across all 6 categories (GOLD 0–4 and PRISm) shown. Abbreviations: GOLD: Global Initiative for Chronic Obstructive Lung Disease; PRISm: Preserved Ratio Impaired Spirometry; BMI: Body Mass Index (kg/m^2).

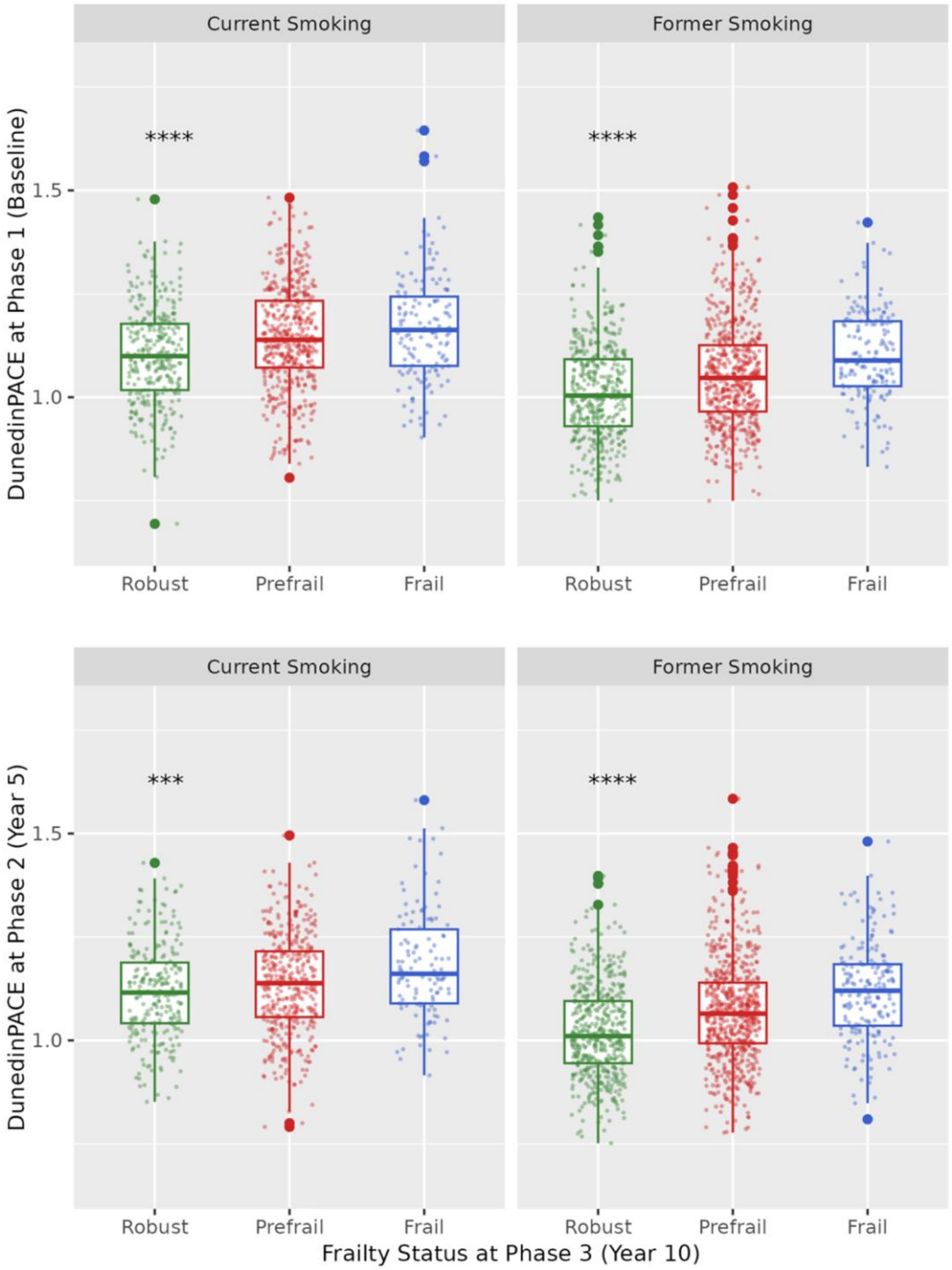


Supplementary Figure 2. Loading of frailty components. Proportional Euler diagrams of frailty components, (**A**) for all participants and (**B**–**E**) by spirometric category (in order of group size). Participants with 3 or more components present were frail, those with one or two present were prefrail. Number of participants with missing spirometry = 19. Abbreviation: GOLD: Global Initiative for Chronic Obstructive Lung Disease.

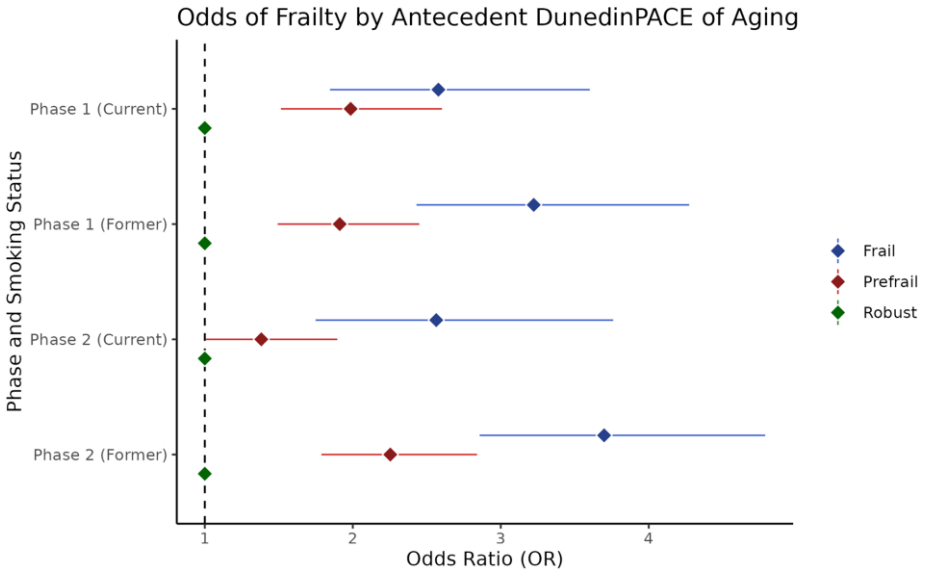


All subjects	PC 1	PC 2	PC 3	PC 4	PC 5
Eigenvalue	2.1	.97	.93	.63	.36
Variance %	42	19	19	13	7
Cum. var. %	42	62	80	93	100
Speed	.80	-.04	.08		
Activity	.86	-.13	-.15		
Energy	.70	-.23	-.36		
Weight	.26	.94	-.21		
Strength	.43	.12	.86		

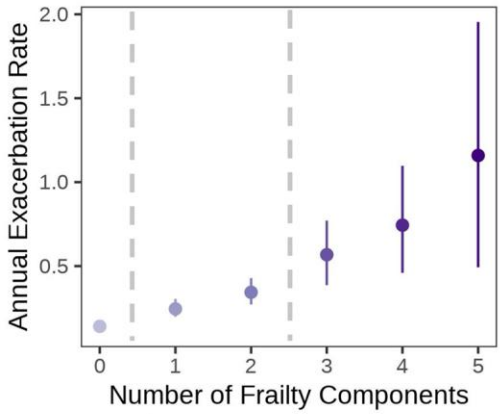
Supplementary Figure 3. Correlation of frailty characteristics. (**A**) Principal Component Analysis (PCA) biplot with table of eigenvalues and principal component loadings. The intensity of a variable (arrow) color is based on the strength of its contribution. Speed: 6-minute walk distance, Activity: 36-Item Short Form Survey Physical Function Score, Energy: inverse score of fatigue questions on the Center for Epidemiologic Studies Depression Scale (CES-D), Strength: grip strength (kilograms), Weight: inverse weight loss (or 0 if weight gain). Note that for the underlying characteristics, higher levels indicate a more robust status. Cum. var. %: cumulative variance %. (**B**) Multiple Correspondence Analysis (MCA) variable map of individual frailty traits (red) and the supplementary variable of overall frailty (green) against the two principal dimensions. (**C**) Correlation matrix of frailty components (degree of shading is Pearson's correlation coefficient between components).

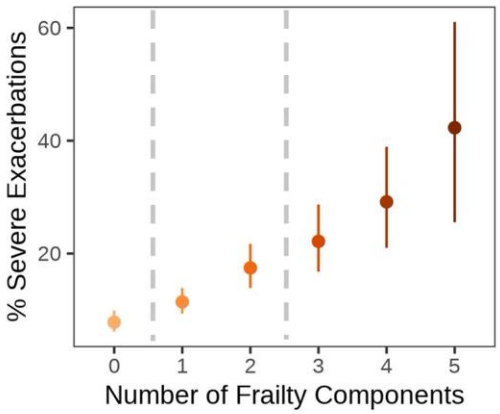


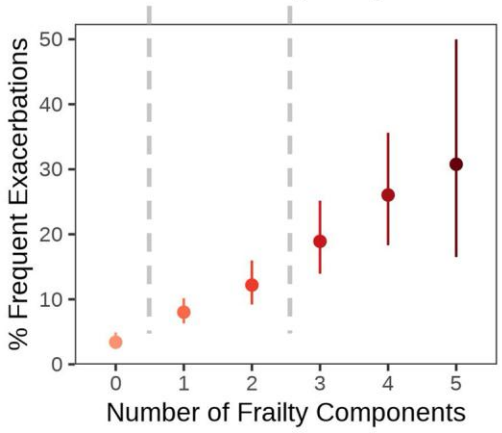
Supplementary Figure 4. Scatter plot of DunedinPACE (Phase 1 and Phase 2) by frailty status (Phase 3). DunedinPACE values at Phase 1 (baseline, top) and Phase 2 (5-year follow-up, bottom), stratified by smoking status (current, left; former, right) are displayed by frailty category at Phase 3 (10-year follow-up). Stars indicate Kruskal-Wallis rank sum test *p*-value across frailty category for that phase and stratum (***$p < .001$, ****$p < .0001$). Tabular format of this data is in Supplementary Table 8.



Supplementary Figure 5. Forest plot of DunedinPACE (Phase 1 and Phase 2) by frailty status (Phase 3). Odds ratios (OR) and 95% Confidence Intervals (95% CI) of DunedinPACE levels at Phase 1 (baseline) and Phase 2 (5-year follow-up) on frailty and prefrailty at Phase 3 (10-year follow-up) are shown. These are stratified by smoking status. The original units of DunedinPACE are used (one unit = one year of biological aging per year of chronological aging). Tabular format of this data is in Supplementary Table 9.

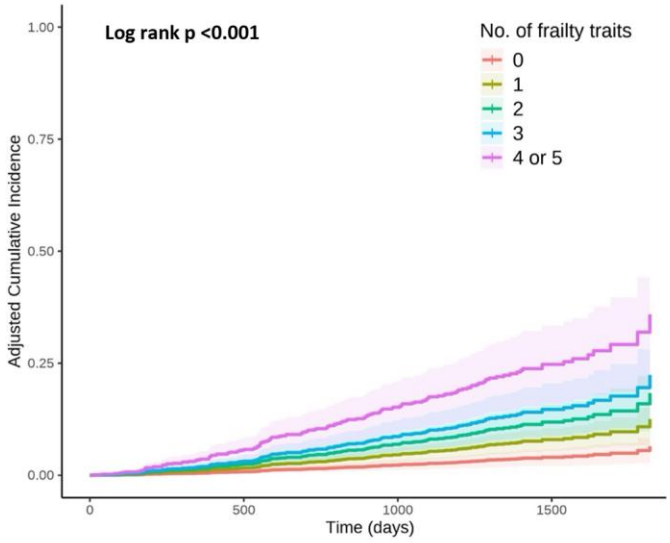






	# of Frailty Traits (n)					
	0 (793)	1 (761)	2 (361)	3 (185)	4 (96)	5 (26)
Mean Annual Exacerbation Rate (SD)	0.14 (0.50)	0.25 (0.74)	0.34 (0.78)	.57 (1.29)	.74 (1.60)	1.16 (1.98)
Severe Exacerbations (%) (95% CI)	7.8 (6.1-9.9)	11.4 (9.4-13.9)	17.5 (13.9-21.7)	22.2 (16.8-28.7)	29 (21-39)	42 (26-61)
Frequent Exacerbations (%) (95% CI)	3.4 (2.4-4.9)	8.0 (6.3-10.2)	12.2 (9.2-16.0)	18.9 (13.9-25.1)	26 (18-36)	31 (17-50)

Supplementary Figure 6. Respiratory exacerbations by number of frailty components. Top left: unadjusted annual exacerbation rate and 95% bootstrap confidence intervals among participants with *n* frailty components. Top right: % of subjects with severe exacerbations with 95% Wilson confidence intervals. Bottom left: % of subjects with frequent exacerbations with 95% Wilson confidence intervals. Dashed lines indicate the cutoffs between frailty categories (robust: 0, prefrail: 1–2, frail: 3–5). Bottom right: source data for figures.



#Frailty components	AHR (95% CI)	*p*
0	-	-
1	2.1 (1.2-3.6)	**0.012**
2	3.2 (1.8-5.7)	**<0.001**
3	4.1 (2.1-7.8)	**<0.001**
4 or 5	7.6 (4.0-14.3)	**<0.001**

#Frailty components	***n* at risk**			
	Day 0	Day 500	Day 1000	Day 1500
0	865	676	521	155
1	843	607	428	132
2	420	291	200	72
3	218	140	91	23
4 or 5	147	80	56	15

Supplementary Figure 7. Mortality by number of frailty components. Adjusted all-cause mortality risk curve by the number of frailty components present. Models adjusted for age, sex, body mass index, smoking pack-years, FEV1 % predicted, diabetes, and heart disease (presence of any of: coronary artery disease, myocardial infarction, angina, angioplasty, coronary artery bypass graft surgery, or congestive heart failure). Individuals with 4 and 5 frailty components are plotted together due to small size of individuals with 5 components. Risk table is displayed beneath the cumulative incidence curve. Cox adjusted Hazard Ratios (AHR), 95% confidence intervals (95% CI), and *P*-values are displayed to the right (comparator group is robust individuals with 0 frailty traits).

Supplementary Tables

Supplementary Table 1. Expanded participant characteristics.

Characteristic	*N*	Robust	Prefrail	Frail	*p*[a]
n (%)	2,665	912 (34%)	1,352 (51%)	401 (15%)	
Age	2,665	68.6 (7.4)	69.7 (8.1)	71.5 (9.2)	**<0.001**
Sex	2,665				0.39
Male		450 (49.3%)	640 (47.3%)	204 (50.9%)	
Female		462 (50.7%)	712 (52.7%)	197 (49.1%)	
Race	2,665				**<0.001**
Non-Hispanic White		742 (81.4%)	933 (69.0%)	270 (67.3%)	
African American		170 (18.6%)	419 (31.0%)	131 (32.7%)	
Married or Partnered	2,660	476 (52.4%)	565 (41.8%)	145 (36.3%)	**<0.001**
BMI	2,665	28.6 (5.5)	28.5 (6.1)	30.1 (7.6)	**0.002**
Current Smoking	2,663	239 (26.2%)	462 (34.2%)	138 (34.4%)	**<0.001**
Smoking Pack-Years	2,663	39.3 (20.3)	43.0 (22.4)	52.7 (26.6)	**<0.001**
GOLD grade	2,646				**<0.001**
Normal Spirometry		473 (52.3%)	589 (43.7%)	108 (27.4%)	
1		115 (12.7%)	154 (11.4%)	27 (6.9%)	
2		160 (17.7%)	293 (21.8%)	68 (17.3%)	
3		56 (6.2%)	104 (7.7%)	85 (21.6%)	
4		9 (1.0%)	32 (2.4%)	52 (13.7%)	
Total GOLD 2–4 (Moderate-Severe COPD)		225 (24.9%)	429 (31.8%)	205 (52.0%)	**<0.001**
PRISm		92 (10.2%)	175 (13.0%)	54 (13.7%)	0.08
BADL Assistance	2,664	3 (0.3%)	24 (1.8%)	34 (8.5%)	**<0.001**
IADL Assistance	2,665	6 (0.7%)	55 (4.0%)	102 (25.4%)	**<0.001**
Probable Cognitive Impairment by Mini-Cog	2,654	144 (15.9%)	325 (24.1%)	124 (31.1%)	**<0.001**
Comorbidity Count	2,665	1.1 (1.1)	1.4 (1.2)	2.0 (1.4)	**<0.001**
Diabetes		113 (12.4%)	289 (21.4%)	149 (37.2%)	**<0.001**
Coronary Artery Disease		133 (14.6%)	247 (18.3%)	118 (29.4%)	**<0.001**
Congestive Heart Failure		21 (2.3%)	54 (4.0%)	40 (10.0%)	**<0.001**
Cerebrovascular Disease		45 (4.9%)	121 (8.9%)	57 (14.2%)	**<0.001**
Kidney Disease		24 (2.6%)	61 (4.5%)	36 (9.0%)	**<0.001**
Liver Disease		36 (3.9%)	82 (6.1%)	31 (7.7%)	**0.013**
Cancer		171 (18.8%)	265 (19.6%)	91 (22.7%)	0.25
Osteoarthritis		307 (33.7%)	535 (39.6%)	204 (50.9%)	**<0.001**
Osteoporosis		132 (14.5%)	202 (14.9%)	64 (16.0%)	0.78

Total *N* = 2665. *N* with data available for each characteristic shown. Continuous variables reported as mean (standard deviation). Categorical variables reported as *n* (%). Abbreviations: BMI: body mass index (kg/m^2); GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: Chronic Obstructive Pulmonary Disease; PRISm: preserved ratio impaired spirometry; BADL Assistance: required assistance with basic activities of daily living in the past 7 days; IADL: required assistance with independent activities of daily living in the past 7 days. Probable cognitive impairment: score of 3 or lower on the Mini-Cog screening tool. Coronary artery disease (CAD) defined as reporting any of the following: CAD, myocardial infarction, angina, angioplasty, or coronary artery bypass graft surgery. Cerebrovascular disease defined as reporting a history of stroke or transient ischemic attack (TIA). Comorbidity count is the sum of the following reported comorbidities: diabetes, coronary artery disease, congestive heart failure, cerebrovascular disease, kidney disease, liver disease, cancer (excluding non-melanoma skin cancer), osteoarthritis, and osteoporosis. [a]*p*-values for continuous variables are calculated by the Kruskal-Wallis rank sum test; for categorical variables by Pearson's chi-squared test.

Supplementary Table 2. Characteristics of never-smoker control group.

Characteristic	Never smoked (control population) (*n* = 249)	Smoking history (study population) (*N* = 2,665)	*p*[a]
Age	66.7 (10.0)	69.6 (8.1)	**<0.001**
Sex			0.34
Male	113 (45.4%)	1,294 (48.6%)	
Female	136 (54.6%)	1,371 (51.4%)	
Race			**<0.001**
Non-Hispanic White	215 (86.3%)	1,945 (73.0%)	
African American	34 (13.7%)	720 (27.0%)	
BMI	27.7 (4.8)	28.8 (6.1)	**0.02**
FEV1 (% predicted)	102.3 (14.9)	80.2 (24.7)	**<0.001**
Comorbidity Count	0.7 (0.9)	1.4 (1.2)	**<0.001**
Diabetes	21 (8.4%)	551 (20.7%)	**<0.001**
Coronary Artery Disease	10 (4.0%)	498 (18.7%)	**<0.001**
Congestive Heart Failure	1 (0.4%)	115 (4.3%)	**0.003**
Cerebrovascular Disease	6 (2.4%)	223 (8.4%)	**<0.001**
Kidney Disease	2 (0.8%)	121 (4.5%)	**0.005**
Liver Disease	2 (0.8%)	149 (5.6%)	**0.001**
Cancer	43 (17.3%)	527 (19.8%)	0.34
Osteoarthritis	69 (27.7%)	1,046 (39.2%)	**<0.001**
Osteoporosis	28 (11.2%)	398 (14.9%)	0.12
Frailty Category			**<0.001**
Robust	161 (64.7%)	912 (34.2%)	
Prefrail	84 (33.7%)	1,352 (50.7%)	
Frail	4 (1.6%)	401 (15.0%)	

Characteristics of the never-smoker group (evaluated in a post hoc analysis) compared with the study population. Continuous variables reported as mean (standard deviation). Categorical variables reported as *n* (%). [a]*p*-values for continuous variables are calculated by the Wilcoxon rank sum test; for categorical variables by Pearson's chi-squared test.

Supplementary Table 3. Prevalence of frailty components.

	Prevalence (%)																			
	All subjects				Normal Spirometry				GOLD 1				GOLD 2–4				PRISm			
	All	Rob	Pre	Frail	All	Rob	Pre	Frail	All	Rob	Pre	Frail	All	Rob	Pre	Frail	All	Rob	Pre	Frail
N	2665	912	1352	401	1170	473	589	108	296	115	154	27	859	225	429	205	321	92	175	54
Fatigue	19.5	–	19.9	62.8	15.6	–	18.3	69.4	17.2	–	20.8	70	23.5	–	19.1	58.5	24.3	–	25.1	63
Slowness	23.0	–	21.4	80.5	13.8	–	16.1	62.0	15.9	–	16.2	81	34.5	–	27.0	87.8	30.8	–	29.1	89
Weakness	29.7	–	37.6	70.8	25.6	–	36.7	77.8	25.0	–	36.4	67	34.0	–	36.1	66.8	37.4	–	46.3	72
Low Activity	15.1	–	9.7	67.6	8.0	–	6.6	50.9	8.8	–	6.5	59	25.5	–	14.2	77.1	18.4	–	12.0	70
Shrinking	33.1	–	45.5	66.6	33.4	–	51.6	80.6	32.8	–	52.6	59	37.3	–	43.8	64.4	21.5	–	23.4	52

Prevalence of the five frailty components among prefrail and frail participants. For robust participants, the prevalence is 0% by definition. Prevalence is reported in the entire study cohort and by spirometric subgroup. *N* with frailty measurements but missing spirometry = 19. Rob = robust, Pre = prefrail. GOLD = Global Initiative for Chronic Obstructive Lung Disease. PRISm = Preserved Ratio Impaired Spirometry.

Supplementary Table 4. Characteristics of participants with missing follow-up data.

Characteristic	Missing mortality data			Missing exacerbation data		
	Analyzed (*n* = 2512)	Missing (*n* = 153)	*p*[a]	Analyzed (*n* = 2222)	Missing (*n* = 443)	*p*[a]
Age	69.7 (8.2)	68.0 (7.2)	**0.009**	69.8 (8.1)	68.7 (8.1)	**0.003**
Sex			0.91			**0.03**
Male	1,219 (48.5%)	75 (49.0%)		1,058 (47.6%)	236 (53.3%)	
Female	1,293 (51.5%)	78 (51.0%)		1,164 (52.4%)	207 (46.7%)	
Race			**<0.001**			**<0.001**
Non-Hispanic White	1,869 (74.4%)	76 (49.7%)		1,698 (76.4%)	247 (55.8%)	
African American	643 (25.6%)	77 (50.3%)		524 (23.6%)	196 (44.2%)	
BMI	28.8 (6.1)	28.5 (6.2)	0.52	28.9 (6.2)	28.6 (6.0)	0.54
Current Smoker	771 (30.7%)	68 (44.4%)	**<0.001**	662 (29.8%)	177 (40.0%)	**<0.001**
Smoking Pack-Years	43.3 (22.9)	42.5 (22.6)	0.64	43.1 (22.7)	43.9 (23.7)	0.61
GOLD grade			0.61			0.81
Normal Spirometry	1,106 (44.3%)	64 (42.4%)		976 (44.2%)	194 (44.4%)	
1	280 (11.2%)	16 (10.6%)		252 (11.4%)	44 (10.1%)	
2	489 (19.6%)	32 (21.2%)		435 (19.7%)	86 (19.7%)	
3	233 (9.3%)	12 (7.9%)		200 (9.1%)	45 (10.3%)	
4	90 (3.6%)	3 (2.0%)		81 (3.7%)	12 (2.7%)	
PRISm	297 (11.9%)	24 (15.9%)		265 (12.0%)	56 (12.8%)	
Comorbidity Count	1.4 (1.2)	1.3 (1.2)	0.79	1.4 (1.2)	1.4 (1.3)	0.55
Diabetes	515 (20.5%)	36 (23.5%)	0.37	439 (19.8%)	112 (25.3%)	**0.009**
Coronary Artery Disease	474 (18.9%)	24 (15.7%)	0.33	422 (19.0%)	76 (17.2%)	0.37
Congestive Heart Failure	108 (4.3%)	7 (4.6%)	0.87	90 (4.1%)	25 (5.6%)	0.13
Cerebrovascular Disease	204 (8.1%)	19 (12.4%)	0.06	179 (8.1%)	44 (9.9%)	0.19
Kidney Disease	109 (4.3%)	12 (7.8%)	**0.04**	92 (4.1%)	29 (6.5%)	**0.03**
Liver Disease	139 (5.5%)	10 (6.5%)	0.60	107 (4.8%)	42 (9.5%)	**<0.001**
Cancer		28 (18.3%)		440 (19.8%)	87 (19.6%)	0.94
Osteoarthritis	993 (39.5%)	53 (34.6%)	0.23	893 (40.2%)	153 (34.5%)	**0.03**
Osteoporosis	381 (15.2%)	17 (11.1%)	0.17	345 (15.5%)	53 (12.0%)	0.055
Frailty Category			**0.04**			**<0.001**
Robust	872 (34.7%)	40 (26.1%)		793 (35.7%)	119 (26.9%)	
Prefrail	1,270 (50.6%)	82 (53.6%)		1,122 (50.5%)	230 (51.9%)	
Frail	370 (14.7%)	31 (20.3%)		307 (13.8%)	94 (21.2%)	

Characteristics of individuals with missing longitudinal follow-up data (exacerbations and mortality data) compared with those with follow-up data. Continuous variables reported as mean (standard deviation). Categorical variables reported as *n* (%). Abbreviations: GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: Chronic Obstructive Pulmonary Disease; PRISm: Preserved Ratio Impaired Spirometry. [a]*p*-values for continuous variables are calculated by the Wilcoxon rank sum test; for categorical variables by Pearson's chi-squared test.

Supplementary Table 5. Odds of respiratory exacerbations by frailty and spirometric category.

(A) Adjusted models

	All subjects					Normal Spirometry					GOLD 2–4				
	Robust (*n* = 787)	Prefrail (*n* = 1119)		Frail (*n* = 303)		Robust (*n* = 407)	Prefrail (*n* = 489)		Frail (*n* = 80)		Robust (*n* = 198)	Prefrail (*n* = 358)		Frail (*n* = 160)	
	OR/IRR	OR/IRR	*p*	OR/IRR	*p*	OR/IRR	OR/IRR	*p*	OR/IRR	*p*	OR/IRR	OR/IRR	*p*	OR/IRR	*p*
Exacerbation Rate	1	**1.8 (1.4–2.3)**	**<0.001**	**3.4 (2.4–4.8)**	**<0.001**	1	**2.0 (1.2–3.2)**	**0.006**	**4.2 (1.8–9.6)**	**<0.001**	**1**	**2.6 (1.8–3.7)**	**<0.001**	**3.9 (2.5–6.2)**	**<0.001**
Severe Exacerbations	1	**1.6 (1.1–2.2)**	**0.005**	**2.8 (1.8–4.2)**	**<0.001**	1	1.6 (0.9–3.0)	0.10	**3.4 (1.5–7.7)**	**0.004**	**1**	**1.9 (1.1–3.1)**	**0.02**	**2.7 (1.5–5.1)**	**0.002**
Frequent Exacerbations	1	**2.6 (1.7–4.1)**	**<0.001**	**5.5 (3.2–9.3)**	**<0.001**	1	**3.2 (1.4–7.1)**	**0.004**	**9.1 (3.0–27.9)**	**<0.001**	**1**	**4.3 (2.0–9.4)**	**<0.001**	**9.8 (4.1–23.5)**	**<0.001**

	GOLD 1					PRISm				
	Robust (*n* = 104)	Prefrail (*n* = 127)		Frail (*n* = 21)		Robust (*n* = 78)	Prefrail (*n* = 145)		Frail (*n* = 42)	
	OR/IRR	OR/IRR	*p*	OR/IRR	*p*	OR/IRR	OR/IRR	*p*	OR/IRR	*p*
Exacerbation Rate	1	1.2 (0.6–2.4)	0.68	2.6 (0.7–9.1)	0.15	1	1.1 (0.5–2.4)	0.90	2.5 (.99–6.1)	0.051
Severe Exacerbations	1	1.1 (0.5–2.5)	0.83	1.9 (0.6–6.7)	0.31	1	1.3 (0.5–3.7)	0.56	**3.2 (1.01–10.3)**	**0.047**
Frequent Exacerbations	1	1.5 (0.5–4.6)	0.47	–	–	1	0.8 (0.3–2.7)	0.78	1.9 (0.5–7.4)	0.38

(B) Unadjusted models

	All subjects					Normal Spirometry					GOLD 2–4				
	Robust	Prefrail		Frail		Robust	Prefrail		Frail		Robust	Prefrail		Frail	
	OR/IRR	OR/IRR	*p*	OR/IRR	*p*	OR/IRR	OR/IRR	*p*	OR/IRR	*p*	OR/IRR	OR/IRR	*p*	OR/IRR	*p*
Exacerbation Rate	1	**2.1 (1.6–2.7)**	**<0.001**	**5 (3.6–6.9)**	**<0.001**	1	**2.1 (1.3–3.3)**	**0.003**	**4.3 (1.9–9.7)**	**<0.001**	1	**2.5 (1.7–3.6)**	**<0.001**	**4.8 (3.2–7.2)**	**<0.001**
Severe Exacerbations	1	**1.8 (1.3–2.5)**	**<0.001**	**4.2 (2.9–6)**	**<0.001**	1	1.7 (1–3.1)	0.07	**3.8 (1.8–8.3)**	**<0.001**	1	**2.0 (1.2–3.3)**	**0.005**	**3.4 (2.0–5.8)**	**<0.001**
Frequent Exacerbations	1	**2.9 (1.9–4.5)**	**<0.001**	**8.1 (5.1–12.9)**	**<0.001**	1	**3.3 (1.5–7.2)**	**0.003**	**6.3 (2.4–16.9)**	**<0.001**	1	**4.5 (2.1–9.6)**	**<0.001**	**11.1 (5.1–24.3)**	**<0.001**

	GOLD 1					PRISm				
	Robust	Prefrail		Frail		Robust	Prefrail		Frail	
	OR/IRR	OR/IRR	*p*	OR/IRR	*p*	OR/IRR	OR/IRR	*p*	OR/IRR	*p*
Exacerbation Rate	1	1.1 (0.5–2.2)	0.87	3.0 (0.9–10.4)	0.08	1	1.2 (0.5–2.6)	0.73	2.5 (1.0–6.1)	0.06
Severe Exacerbations	1	1.0 (0.5–2.2)	0.98	2.2 (0.7–7.0)	0.19	1	1.6 (0.6–4.2)	0.35	**3.3 (1.1–10)**	**0.04**
Frequent Exacerbations	1	1.2 (0.4–3.6)	0.69	-	-	1	1 (0.3–3.0)	0.95	2.0 (0.5–7.2)	0.31

Odds ratio of frailty (vs robustness) and prefrailty (vs robustness) on exacerbations for all subjects and for subgroups of participants by spirometric category. Abbreviations: OR: odds ratio; IRR: incident rate ratio; GOLD: Global Initiative for Chronic Obstructive Lung Disease; PRISm: Preserved Ratio Impaired Spirometry. N is # of individuals within each category who had over 180 days of follow-up exacerbation data *and* spirometry collected. Reported as OR/IRR (95% confidence interval). (**A)** Models adjusted for age, sex, current smoking status, and forced expiratory volume in 1 second (FEV1) %predicted. OR for frailty not calculated for frequent exacerbations in GOLD 1 subgroup due to low cell count (<5). (**B)** Results from unadjusted model.

Supplementary Table 6. Crude and adjusted all-cause mortality.

(A) Crude event counts and log-rank *p*-values for all-cause mortality by spirometric category

	All subjects				Normal Spirometry				GOLD 1				GOLD 2–4				PRISm			
	Rob	Pre	Frail	p^a	Rob	Pre	Frail	*p*	Rob	Pre	Frail	*p*	Rob	Pre	Frail	*p*	Rob	Pre	Frail	*p*
# Events	18	70	58	**<0.001**	4	20	8	**<0.001**	2	8	3	**0.049**	9	37	42	**<0.001**	3	5	4	0.2
n	872	1270	370		449	556	101		111	143	26		215	406	191		90	160	47	

(B) Unadjusted and adjusted hazard ratios of frailty and prefrailty for all-cause mortality

	All subjects				GOLD 2–4				GOLD 0			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI)	p^b	AHR (95% CI)	*p*	HR (95% CI)	*p*	AHR (95% CI)	*p*	HR (95% CI)	*p*	AHR (95% CI)	*p*
Prefrailty	**3.0 (1.8–5.1)**	**<0.001**	**2.5 (1.5–4.2)**	**<0.001**	**2.5 (1.2–5.2)**	**0.014**	**2.1 (1.02–4.4)**	**0.045**	**5.0 (1.7–14.5)**	**0.003**	**4.2 (1.4–12.6)**	**0.01**
Frailty	**9.9 (5.8–16.8)**	**<0.001**	**4.5 (2.4–8.5)**	**<0.001**	**7.1 (3.5–14.7)**	**<0.001**	**4.0 (1.7–9.3)**	**0.001**	**15.4 (4.6–51.6)**	**<0.001**	**7.9 (1.9–32.5)**	**0.004**

(**A**) Crude event counts and log-rank *p*-values for all-cause mortality by spirometric category. Abbreviations: Rob: robust; Pre: prefrail; GOLD: Global Initiative for Chronic Obstructive Lung Disease. PRISm: Preserved Ratio Impaired Spirometry. [a]log-rank *p*-value for frailty category (frail, prefrail, or robust) vs all-cause mortality. (**B**) Unadjusted and adjusted hazard ratios of frailty and prefrailty for all-cause mortality. Unadjusted Hazard Ratios (HR) adjusted Hazard Ratios (AHR), 95% confidence intervals (95% CI) and [b]*p*-values from Cox models are reported overall and for the largest spirometric subgroups. For both frailty and prefrailty, robust groups were the comparator. Adjusted Cox models adjusted for age, sex, body mass index, smoking pack-years, forced expiratory volume in one second (FEV1) % predicted, diabetes, and heart disease (presence of any of: coronary artery disease, myocardial infarction, angina, angioplasty, coronary artery bypass graft surgery, or congestive heart failure).

Supplementary Table 7. Characteristics of participants with missing DNA methylation data.

Characteristic	Missing DNA Methylation data (Either Phase)			Missing DNA Methylation data (Phase 1)			Missing DNA Methylation data (Phase 2)		
	Analyzed (*n* = 2104)	Missing (*n* = 561)	p^a	Present (*n* = 2247)	Missing (*n* = 418)	p^a	Present (*n* = 2376)	Missing (*n* = 289)	p^a
Age	69.4 (8.1)	70.3 (8.1)	**0.02**	69.4 (8.1)	70.6 (8.0)	**0.004**	69.6 (8.1)	69.3 (8.1)	0.51
Sex			0.61			0.83			0.93
Male	1,027 (48.8%)	267 (47.6%)		1,089 (48.5%)	205 (49.0%)		1,153 (48.5%)	141 (48.8%)	
Female	1,077 (51.2%)	294 (52.4%)		1,158 (51.5%)	213 (51.0%)		1,223 (51.5%)	148 (51.2%)	
Race			**0.01**			**0.02**			**<0.001**
Non-Hispanic White	1,559 (74.1%)	386 (68.8%)		1,659 (73.8%)	286 (68.4%)		1,761 (74.1%)	184 (63.7%)	
African American	545 (25.9%)	175 (31.2%)		588 (26.2%)	132 (31.6%)		615 (25.9%)	105 (36.3%)	
BMI	28.9 (6.2)	28.6 (6.1)	0.24	28.9 (6.2)	28.5 (5.7)	0.32	28.8 (6.1)	28.6 (6.4)	0.21
Current Smoker	672 (32.0%)	167 (29.8%)	0.32	719 (32.0%)	120 (28.7%)	0.18	745 (31.4%)	94 (32.5%)	0.69
Smoking Pack-Years	43.0 (22.7)	44.0 (23.5)	0.52	43.0 (22.8)	44.2 (23.1)	0.38	43.0 (22.6)	45.2 (24.6)	0.27
GOLD grade			**0.03**			**0.006**			0.20
Normal Spirometry	907 (43.4%)	263 (47.2%)		973 (43.6%)	197 (47.5%)		1,047 (44.4%)	123 (42.9%)	
1	236 (11.3%)	60 (10.8%)		250 (11.2%)	46 (11.1%)		268 (11.4%)	28 (9.8%)	
2	429 (20.5%)	92 (16.5%)		459 (20.6%)	62 (14.9%)		464 (19.7%)	57 (19.9%)	
3	188 (9.0%)	57 (10.2%)		205 (9.2%)	40 (9.6%)		214 (9.1%)	31 (10.8%)	
4	65 (3.1%)	28 (5.0%)		68 (3.0%)	25 (6.0%)		76 (3.2%)	17 (5.9%)	
PRISm	264 (12.6%)	57 (10.2%)		276 (12.4%)	45 (10.8%)		290 (12.3%)	31 (10.8%)	
Comorbidity Count	1.3(1.2)	1.5(1.3)	**0.05**	1.3(1.2)	1.4(1.3)	0.21	1.4(1.2)	1.4(1.3)	0.27
Diabetes	430 (20.4%)	121 (21.6%)	0.56	462 (20.6%)	89 (21.3%)	0.74	484 (20.4%)	67 (23.2%)	0.27
Coronary Artery Disease	378 (18.0%)	120 (21.4%)	0.06	406 (18.1%)	92 (22.0%)	0.06	433 (18.2%)	65 (22.5%)	0.08

Congestive Heart Failure	89 (4.2%)	26 (4.6%)	0.68	97 (4.3%)	18 (4.3%)	0.99	99 (4.2%)	16 (5.5%)	0.28
Cerebrovascular Disease	164 (7.8%)	59 (10.5%)	**0.04**	179 (8.0%)	44 (10.5%)	0.08	190 (8.0%)	33 (11.4%)	**0.05**
Kidney Disease	95 (4.5%)	26 (4.6%)	0.90	104 (4.6%)	17 (4.1%)	0.61	108 (4.5%)	13 (4.5%)	0.97
Liver Disease	102 (4.8%)	47 (8.4%)	**0.001**	111 (4.9%)	38 (9.1%)	**<0.001**	125 (5.3%)	24 (8.3%)	**0.03**
Cancer	405 (19.2%)	122 (21.7%)	0.19	444 (19.8%)	83 (19.9%)	0.96	465 (19.6%)	62 (21.5%)	0.45
Osteoarthritis	830 (39.4%)	216 (38.5%)	0.68	894 (39.8%)	152 (36.4%)	0.19	940 (39.6%)	106 (36.7%)	0.34
Osteoporosis	313 (14.9%)	85 (15.2%)	0.87	329 (14.6%)	69 (16.5%)	0.33	365 (15.4%)	33 (11.4%)	0.08
Frailty Category			0.10			0.37			**0.004**
Robust	738 (35.1%)	174 (31.0%)		781 (34.8%)	131 (31.3%)		835 (35.1%)	77 (26.6%)	
Prefrail	1,062 (50.5%)	290 (51.7%)		1,128 (50.2%)	224 (53.6%)		1,198 (50.4%)	154 (53.3%)	
Frail	304 (14.4%)	97 (17.3%)		338 (15.0%)	63 (15.1%)		343 (14.4%)	58 (20.1%)	

Characteristics of individuals with missing methylation data at baseline (Phase 1) or 5-year follow-up (Phase 2) compared with those with methylation data. Continuous variables reported as mean (standard deviation). Categorical variables reported as *n* (%). Abbreviations: GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: Chronic Obstructive Pulmonary Disease; PRISm: Preserved Ratio Impaired Spirometry. [a]*p*-values for continuous variables are calculated by the Wilcoxon rank sum test; for categorical variables by Pearson's chi-squared test. While complete case analysis was performed (only individuals with methylation data at both Phase 1 and Phase 2 were included in analysis – left hand columns), participant characteristics based on methylation missingness by Phase are also reported for completeness (right hand columns).

Supplementary Table 8. DunedinPACE of Epigenetic Aging (Phases 1 and 2) by frailty status at phase 3 (stratified by smoking status).

		Frailty Status at Phase 3							
		Robust	**Prefrail**	**Frail**	***p***	**Robust**	**Prefrail**	**Frail**	***p***
Phase 1	**Smoking Status (at Phase 1)**	Former (Phase 1)				Current (Phase 1)			
	n	431	576	159		307	486	145	
	Mean Age (SD)	60 (7)	62 (8)	66 (8)		54 (7)	55 (7)	55 (7)	
	DunedinPACE	1.01 (0.12)	1.05 (0.12)	1.10 (0.11)	**<0.001**	1.10 (0.12)	1.14 (0.12)	1.17 (0.13)	**<0.001**
Phase 2	**Smoking Status (at Phase 2)**	Former (Phase 2)				Current (Phase 2)			
	n	497	660	187		241	402	117	
	Mean Age (SD)	65 (7)	67 (8)	70 (9)		60 (7)	60 (7)	61 (7)	
	DunedinPACE	1.02 (0.11)	1.07 (0.12)	1.12 (0.12)	**<0.001**	1.12 (0.11)	1.14 (0.12)	1.18 (0.13)	**<0.001**

The DunedinPACE of epigenetic aging (units represent biological years aged per chronological year aged) as measured by methylation data collected at baseline (Phase 1) and at 5-year follow up (Phase 2) stratified by smoking status at time of blood draw. DunedinPACE is reported as mean (standard deviation). This is reported by frailty status at 10-year (Phase 3) follow-up. *p*-values were calculated by Kruskal-Wallis rank sum test across the frailty categories. For reference, mean age (standard deviation) at each Phase is also reported across smoking status category and frailty category.

Supplementary Table 9. Odds of frailty at phase 3 by DunedinPACE of Aging (Phases 1 and 2) (stratified by smoking status).

		Prefrailty		Frailty	
Phase	**Smoking Status**	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
1	Current	1.99 (1.51–2.60)	**<0.001**	2.58 (1.85–3.60)	**<0.001**
	Former	1.91 (1.49–2.45)	**<0.001**	3.22 (2.43–4.27)	**<0.001**
	Overall	1.90 (1.60–2.25)	**<0.001**	2.78 (2.26–3.40)	**<0.001**
2	Current	1.38 (1.01–1.90)	**0.045**	2.56 (1.75–3.76)	**<0.001**
	Former	2.25 (1.79–2.84)	**<0.001**	3.70 (2.86–4.79)	**<0.001**
	Overall	1.91 (1.60–2.28)	**<0.001**	3.05 (2.49–3.73)	**<0.001**

OR (odds ratio) and 95% CI (95% Confidence Interval) of blood DunedinPACE (epigenetic pace of aging – one unit represents one biological year aged per chronological year aged) on the outcome of subsequent prefrailty and frailty (compared to robustness) is calculated. The odds of DunedinPACE from Phase 1 (baseline) blood draw and from Phase 2 (5-year) blood draw on Phase 3 (10-year) frailty and prefrailty are reported. Results are stratified by smoking status at the time of blood draw.

Supplementary Table 10. Odds of respiratory exacerbations by number of frailty components.

Outcome	**# Frailty components**	**Unadjusted**		**Adjusted**	
		OR/IRR (95% CI)	***p***	**OR/IRR (95% CI)**	***p***
Exacerbation Rate	0	–	–	–	–
	1	**1.8 (1.4–2.4)**	**<0.001**	**1.7 (1.3–2.2)**	**<0.001**
	2	**2.6 (1.9–3.6)**	**<0.001**	**2.0 (1.5–2.8)**	**<0.001**
	3	**4.2 (2.8–6.3)**	**<0.001**	**3.2 (2.1–4.7)**	**<0.001**
	4	**5.5 (3.2–9.3)**	**<0.001**	**3.2 (1.9–5.3)**	**<0.001**
	5	**8.9 (3.5–22.5)**	**<0.001**	**5.3 (2.1–12.9)**	**<0.001**
Severe Exacerbations	0	–	–	–	–
	1	**1.5 (1.1–2.1)**	**0.02**	**1.5 (1.0–2.1)**	**0.04**
	2	**2.5 (1.7–3.6)**	**<0.001**	**2 (1.3–2.9)**	**<0.001**
	3	**3.4 (2.2–5.2)**	**<0.001**	**2.3 (1.5–3.7)**	**<0.001**
	4	**4.9 (2.9–8.1)**	**<0.001**	**2.5 (1.4–4.3)**	**0.002**
	5	**8.6 (3.8–19.6)**	**<0.001**	**4.3 (1.7–10.4)**	**0.001**
Frequent Exacerbations	0	–	–	–	–
	1	**2.5 (1.6–3.9)**	**<0.001**	**2.4 (1.5–3.9)**	**<0.001**
	2	**3.9 (2.4–6.5)**	**<0.001**	**3.2 (1.9–5.3)**	**<0.001**
	3	**6.6 (3.9–11.3)**	**<0.001**	**4.9 (2.8–8.6)**	**<0.001**
	4	**10.0 (5.5–18.1)**	**<0.001**	**5.2 (2.7–10.0)**	**<0.001**
	5	**12.6 (5–31.5)**	**<0.001**	**6.6 (2.4–18.0)**	**<0.001**

Crude and adjusted odds ratios (OR) and 95% confidence interval (95% CI) of the number of frailty components (0–5, treated categorically using 0 as comparator) on odds of severe and frequent exacerbations, and crude and adjusted incident rate ratio (IRR) of the number of frailty components on exacerbation rate. Covariates in adjusted models: age, sex, smoking status, and forced expiratory volume in 1 second (FEV1) %predicted (exacerbation rate models also included an offset term for the log(follow-up time)). (See Supplementary Figure 4 for raw exacerbation counts).

Supplementary Table 11. Sex-stratified analysis of frailty category on respiratory exacerbations and mortality.

	Prefrailty				Frailty			
	Men		Women		Men		Women	
	OR/IRR/AHR	*p*	OR/IRR/AHR	*p*	OR/IRR/AHR	*p*	OR/IRR/AHR	*p*
Exacerbation Rate	1.3 (0.9–1.9)	0.24	**2.5 (1.8–3.5)**	**<0.001**	**2.3 (1.3–4.1)**	**0.003**	**4.7 (3.1–7.2)**	**<0.001**
Severe Exacerbations	1.3 (0.8–2.0)	0.32	**1.9 (1.2–3.1)**	**0.004**	**2.2 (1.2–4.1)**	**0.01**	**3.4 (1.9–6.0)**	**<0.001**
Frequent Exacerbations	**1.9 (1.0–3.3)**	**0.04**	**4.0 (2.0–8.0)**	**<0.001**	**3.6 (1.7–7.6)**	**<0.001**	**8.9 (4.1–19.6)**	**<0.001**
Mortality	**2.4 (1.3–4.6)**	**0.01**	**2.5 (1.0–6.2)**	**0.05**	**4.3 (2.0–9.2)**	**<0.001**	**5.0 (1.7–14.5)**	**0.003**

Odds ratio (OR - severe exacerbations and frequent exacerbations), incident rate ratio (IRR - exacerbation rate), and adjusted hazard ratio (AHR; mortality from Cox proportional hazard model) are reported as OR/IRR/AHR (95% confidence interval).

Supplementary Table 12. Frailty category vs. Odds of respiratory exacerbations stratified by time of Phase 3 visit relative to the Covid-19 pandemic (Sensitivity Analysis).

	Pre-Pandemic (*n* = 1596)					Post-Pandemic (*n* = 626)				
	Robust (*n* = 588)	Prefrail (*n* = 790)	Frail (*n* = 218)	Prefrailty OR/IRR	Frailty IRR/OR	Robust (*n* = 205)	Prefrail (*n* = 332)	Frail (*n* = 89)	Prefrailty OR/IRR	Frailty OR/IRR
Annual exacerbation rate	0.14 (0.45)	0.28 (0.71)	**0.64**[a] (1.15)	**1.8 (1.4–2.4)**	**3.0 (2.1–4.4)**	.14 (.61)	.28 (.86)	**.76**[a] (2.0)	1.8 (0.97–3.5)	**4.8 (1.9–11.9)**
Severe exacerbations	9.2% (54)	15.6% (123)	**29.8%**[a] (65)	**1.6 (1.1–2.2)**	**2.6 (1.7–4.2)**	3.9% (8)	8.1% (27)	**17%**[a] (15)	2.0 (0.9–4.7)	**4.5 (1.6–12.5)**
Frequent exacerbations	2.9% (17)	9.5% (75)	**22.9%**[a] (50)	**3.1 (1.8–5.4)**	**6.5 (3.4–12.3)**	4.9% (10)	9.0% (30)	**20%**[a] (18)	1.7 (0.8–3.6)	**3.6 (1.4–9.3)**

Annual exacerbation rate reported as mean (standard deviation). Frequencies reported as % (n). For exacerbation rate, the incident rate ratio (IRR) (95% CI) is reported. For severe and frequent exacerbations, the odds ratio (OR) (95% CI) is reported. Frailty and prefrailty OR/IRR are compared to robust group. [a]*p*-value < 0.05 across frailty category by Kruskal-Wallis rank sum test for exacerbation rate or Pearson's chi-squared test for severe and frequent exacerbations.