Clinical relevance of lung function trajectory clusters in middle-aged and older adults

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Middle-aged and older adults exhibit eight distinct lung function trajectory clusters, which are differentially associated with all-cause mortality and incident morbidity https://bit.ly/40oFUDC

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Abstract

Background The determinants and health outcomes of lung function trajectories in adults among the general population are poorly understood. We aimed to identify and characterise clusters of lung function trajectories in adults aged ⩾45 years.

Methods Gaussian finite-mixture modelling was applied to baseline and annualised change of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio z-scores in participants of the Rotterdam Study, a prospective population-based cohort study, with repeated spirometry (n=3884; mean±SD age 64.7±8.9 years). Longitudinal outcomes were all-cause mortality, respiratory outcomes (symptoms, COPD (FEV_1/FVC <0.7 in absence of asthma), preserved ratio impaired spirometry (PRISm; FEV_1/FVC ⩾0.7 and FEV_1 or FVC <80%)), smoking cessation and weight changes. Independent risk factors, including genetics, were identified by multiple logistic regression.

Results We identified eight trajectory clusters, with the reference group having persistently normal spirometry (prevalence 42.8%). Three clusters showed higher mortality, adjusted for confounders: 1) the persistently low FEV_1 cluster (prevalence 6.8%, hazard ratio (HR) 1.71, 95% CI 1.37–2.13); 2) rapid FEV_1 decliners (prevalence 4.6%, HR 1.48, 95% CI 1.10–1.99); and 3) FVC decliners (prevalence 3.7%, HR 1.49, 95% CI 1.09–2.03). In contrast, FVC improvers (prevalence 6.7%, HR 0.61, 95% CI 0.41–0.90) and persistently high FEV_1 (prevalence 29.2%, HR 0.82, 95% CI 0.69–0.98) were protective trajectory clusters. Clusters were characterised by differences in genetic predisposition (polygenic scores of FEV_1 and FEV_1/FVC), demographics, cigarette smoking, respiratory symptoms (chronic cough, wheezing and dyspnoea), cardiovascular factors (body mass index, hypertension and heart failure) and serum C-reactive protein levels. Frailty, weight changes and the development of respiratory symptoms, COPD and PRISm were significantly associated with trajectory clusters.

Conclusions This study reveals clinically relevant lung function trajectory clusters in older adults of the general population.

Introduction

Lung function is a marker of general health and survival [1]. Achieving and maintaining normal lung function is challenged in two ways. First, early-life lung development and growth can be impaired, leading to a suboptimal maximal lung function at young adulthood. Second, age-related decline of lung function

may be further accelerated during adulthood. These phenomena probably result from early-life events (*e.g.* preterm birth, lower respiratory tract infections and allergen exposure) as well as gene–environment interactions upon exposure to noxious gases and particles (*e.g.* cigarette smoke, air pollution and occupational hazards) [2–6]. Consequently, individuals have different patterns of lung function over the life-course, referred to as the lung function trajectome [7]. It is hypothesised that individual lung function trajectories can be used to better phenotype complex respiratory diseases, such as COPD, given that different trajectories may lead to COPD and reflect different underlying mechanisms which may require differential treatment [7].

Several studies on lung function trajectories in the general population explored trajectories in childhood or young adulthood [3]. Fewer studies included follow-up data of older persons or started modelling at an older age [8–11]. Birth cohorts revealed growth failure trajectories in children [12] and studies in young adults showed the existence of rapid decline trajectories with a prevalence between 1% and 6% [4, 8, 13]. Furthermore, Lange *et al.* [10]. demonstrated that COPD in late adulthood is driven by both low peak lung function and accelerated forced expiratory volume in 1 s (FEV_1) decline. In patients with established COPD, several studies have shown substantial variability in lung function decline [14–16].

Various factors have been associated with accelerated FEV_1 and forced vital capacity (FVC) decline in the general population including smoking exposure, occupational exposures (*e.g.* aromatic solvents), air pollution (*e.g.* nitrogen dioxide exposure), socioeconomic status, physical activity level, body mass index (BMI), hypertension, and glutathione-S-transferase deficiency [3, 17–21]. Additional risk factors for FEV_1 decline include asthma [3, 17] and single-nucleotide polymorphisms in the ADAM33 gene [22].

Yet, overall, the prevalence, characteristics and clinical importance of lung function trajectories starting in middle-aged and older adults from the general population remain uncertain. This is especially relevant since older adults are expected to have the highest short-term risk of morbidity and mortality related to harmful trajectories. Additionally, the study of individual trajectories remains challenging and mainly focused on modelling FEV_1, FVC or ratio separately. Our study clustered within-person lung function trajectories in middle-aged and older adults from the general population using all three indices simultaneously, which may provide more granular trajectories and shed light on the associated factors. We aimed 1) to examine the prevalence and characteristics of such trajectory clusters; 2) to compare all-cause mortality between clusters; and 3) to compare within-trajectory health outcomes between clusters including the incidence of respiratory symptoms and diseases.

Methods

Study population

This study was embedded in the Rotterdam Study, a prospective population-based cohort study of individuals aged ⩾45 years. Detailed information on the Rotterdam Study has been published [23] and is summarised in the supplementary material. The study population of this analysis included participants with repeated spirometry at different study visits between 2002 and 2016 (supplementary figure S1). Pre-bronchodilator spirometry was performed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines by trained paramedical personnel. Participants had two or three spirometric measurements, in which baseline was defined as the participant's first study visit including spirometry.

Trajectory clustering

Z-scores of FEV_1, FVC and FEV_1/FVC were calculated using the Global Lung Initiative (GLI) reference equations [24] and represent departures from the expected lung function for a given age, sex, height and ethnicity (supplementary figure S2). Model-based clustering was applied on the baseline value (z-score) and annualised rate of decline (scaled z-score per year) of FEV_1, FVC and FEV_1/FVC to cluster individuals with a phenotypically similar lung function trajectory (supplementary table S1). Annualised rate of decline was calculated as the average decline per year using the first and last spirometry. Briefly, finite Gaussian mixture modelling was applied using an expectation-maximisation algorithm, which was initialised by complete-linkage hierarchical clustering to avoid local maxima. One to 10 clusters using spherically distributed models with equal variance per component were considered. The optimal number of clusters was selected based on maximal integrated complete-data likelihood and confirmed using bootstrap sequential likelihood ratio test (LRT) [25]. Robustness was evaluated using different initialisation and linkage methods (supplementary table S2).

Characteristics and outcomes

Detailed information on spirometry, baseline characteristics (supplementary figure S3) and outcomes are provided in the supplementary material. The longitudinal health outcomes were all-cause mortality (post-trajectory data) and the incidence of COPD, preserved ratio impaired spirometry (PRISm), respiratory symptoms, smoking cessation and weight changes (within-trajectory data). An additional cross-sectional analysis was performed to assess the association with frailty status (at the last study visit with spirometry). COPD was defined by a pre-bronchodilator FEV_1/FVC ratio <0.7 in participants without asthma. Asthma was defined by an ever physician diagnosis of asthma retrieved from medical records. PRISm was defined as FEV_1/FVC ⩾0.7 and FEV_1 or FVC <80%. Polygenic scores (PGS) of FEV_1 and FEV_1/FVC were based on Moll *et al.* [26] and calculated using the PGS Catalog [27].

Statistical analysis

An α-level of 0.05 was considered statistically significant. Normally distributed continuous variables were expressed as mean±SD. Non-normally distributed continuous variables were expressed as median and interquartile range (IQR). Mean differences were tested using Welsh's two-sample t-test and the two-sample z-test for equality of proportions, as appropriate. Logistic regression models were fitted for every cluster individually using the variables that were significantly different at baseline compared with the reference cluster. Incidences rates (new onset) were expressed per 1000 person-years and differences were tested by exact rate ratio test. Differences in all-cause mortality were evaluated by Cox proportional hazard models and adjusted for age, sex, BMI, education level, smoking status, COPD, asthma, hypertension and treated heart failure (supplementary figure S4). Proportionality was checked using Schoenfeld residuals and time-dependencies were addressed by a step function [28]. Statistical analyses were performed in R 4.1.1 (Vienna, Austria) using the "mclust", "tidyverse", "survival" and "epiR" packages [25, 29–31].

Results

Study population

The study population (n=3884) consisted of middle-aged to older adults (mean±SD age 64.7±8.9 years). Participants had two (n=2992; 77.0%) or three (n=892; 23.0%) spirometry visits over a median (IQR) period of 5.9 (4.5) years, with a maximum period of 13.3 years (supplementary tables S3 and S4). A total of 35 outliers were excluded from the analysis based on the 99.999th percentile (n=3849). Compared to individuals with only one spirometry measurement (excluded), individuals with repeated spirometry (study population) were significantly younger; had a higher education level; were less often smokers; had less often respiratory symptoms, COPD, PRISm, hypertension or heart failure; and showed lower serum C-reactive protein (CRP) levels (supplementary table S5).

Trajectory clusters

A model consisting of eight trajectory clusters was selected based on integrated completed likelihood maximisation (supplementary figure S5). Bootstrap sequential LRT confirmed that a model of eight clusters showed a significantly better model likelihood than a model of seven clusters ($p<0.001$). Trajectory clusters were labelled by their main feature in terms of FEV_1 and FVC patterns (figure 1). The prevalence and progression patterns are presented in table 1 and in supplementary figures S6 and S7. The largest trajectory cluster, comprising 42.8% of participants, exhibited persistently normal spirometry and was defined as the reference group for all comparisons. This cluster showed a median (IQR) decline of −240 (−380–−100) mL in FEV_1 and −190 (−360–−10) mL in FVC over a median period of 6.0 years (supplementary table S4).

Baseline characteristics

Baseline characteristics of the trajectory clusters are presented in table 2. In terms of general characteristics, the persistently low FEV_1 cluster showed the highest baseline age, lowest education level, most current smokers and pack-years, and fewest never-smokers. Conversely, the persistently high FEV_1 cluster was the youngest, had the most never-smokers, and the fewest current smokers and pack-years. The average BMI was highest in low-start improvers. In terms of age distribution, FVC decliners and FVC improvers consisted of a higher proportion of middle-aged individuals compared to older adults (supplementary table S6).

Respiratory symptoms (chronic cough, chronic sputum production, wheezing and dyspnoea) were present in 6–22% of participants in the reference cluster. Overall, the highest prevalence of symptoms (18–51%) was observed in the persistently low FEV_1 cluster. The persistently high FEV_1 cluster showed the lowest prevalence of wheezing (13.8%) and dyspnoea (4.9%), while FVC improvers showed the lowest prevalence of chronic cough (4.7%) and chronic sputum production (2.7%).

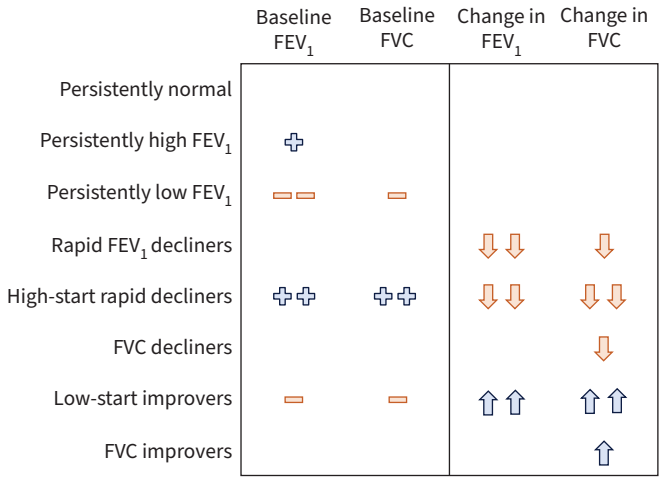

FIGURE 1 Graphical representation of lung function trajectory clusters in middle-aged and older adults. Baseline lung function in Global Lung Initiative z-scores; change in lung function calculated as annualised rate of decline (z-score per year). FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; +: higher baseline lung function; −: lower baseline lung function; ↑: attenuated decline or improvement; ↓: accelerated decline; no symbol: average z-score between −1.00 and +1.00; one symbol: average z-score between −1.65 and −1.00 or between +1.00 and +1.65; two symbols: average z-score lower than −1.65 or higher than +1.65.

Individuals with persistently low FEV_1 demonstrated the highest prevalence of COPD (64%), while the lowest prevalence of COPD (0.4%) was observed in FVC improvers followed by the persistently high FEV_1 cluster. PRISm and hypertension were most prevalent in low-start improvers and least prevalent in high-start rapid decliners. The highest prevalence of treated heart failure was observed in rapid FEV_1 decliners.

Regarding genetic predisposition and biomarkers, individuals with persistently low FEV_1 and FVC decliners demonstrated a significantly higher PGS for an impaired ratio (FEV_1/FVC). The persistently low FEV_1 cluster also showed the highest CRP levels. In contrast, those with persistently high FEV_1 had a lower PGS for impaired FEV_1 and had lower CRP values.

In a subgroup with diffusion capacity testing, the persistently low FEV_1 group exhibited significantly lower D_{LCO} values, whereas persistently high FEV_1 showed the highest D_{LCO} values. Carbon monoxide transfer coefficient values were lowest in high-start rapid decliners. Associations with diffusion data remained statistically significant after adjusting for smoking status (supplementary table S8).

Independent risk factors for persistently low FEV_1 included older age, lower education level, current smoking, higher pack-years, wheezing, dyspnoea and a higher PGS for impaired FEV_1/FVC (supplementary table S9). Risk factors for the rapid FEV_1 decliners were chronic cough and treated heart failure. A higher PGS for impaired FEV_1/FVC, current smoking and the absence of hypertension were identified as independent factors for FVC decliners. Similarly, the absence of hypertension was associated with a higher risk for being a high-start rapid decliner. Younger age was independently associated with FVC improvers, while higher BMI was associated with low-start improvers. Lastly, the persistently high FEV_1 cluster was independently associated with a lower PGS for impaired FEV_1, the absence of current smoking, wheezing and hypertension, as well as lower CRP levels.

Mortality

Participants with persistently low FEV_1, rapid FEV_1 decliners and FVC decliners were at a significantly higher risk of all-cause mortality, adjusted for age and sex, compared to the reference cluster (table 3). In contrast, FVC improvers and participants with persistently high FEV_1 showed a lower mortality hazard (table 3). These associations were driven by participants aged ⩾65 years (supplementary table S10) and remained statistically significant when additionally adjusting for BMI, education level, smoking status, COPD, asthma, hypertension and heart failure. Furthermore, there was no evidence for higher mortality in low-start improvers, despite this group having the lowest baseline FVC. The relationship between all-cause mortality and lung function trajectory clusters is plotted in figure 2.

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TABLE 1 Prevalence and progression patterns of lung function trajectory clusters

	Normal decline clusters (78.7%)			Accelerated decline clusters (11.3%)			Improving clusters (9.9%)	
	Persistently normal	Persistently high FEV_1	Persistently low FEV_1	Rapid FEV_1 decliners	High-start rapid decliners	FVC decliners	Low-start improvers	FVC improvers
Prevalence	1646 (42.8)	1122 (29.2)	263 (6.8)	176 (4.6)	116 (3.0)	144 (3.7)	124 (3.2)	258 (6.7)
Baseline lung function								
FEV_1 (L)	2.7 (2.7–2.7)	3.3 (3.2–3.3)	1.8 (1.7–1.8)	2.8 (2.7–2.9)	3.6 (3.4–3.7)	2.7 (2.6–2.8)	2.1 (2.0–2.2)	2.9 (2.8–3.0)
FVC (L)	3.5 (3.5–3.5)	4.1 (4.1–4.2)	2.8 (2.7–2.9)	3.6 (3.5–3.8)	4.6 (4.4–4.8)	3.9 (3.7–4.1)	2.7 (2.6–2.9)	3.2 (3.1–3.3)
FEV_1 (z-score)	−0.3 (−0.3–−0.3)	1.2 (1.1–1.2)	−2.1 (−2.1–−2.0)	0.0 (−0.1–0.1)	2.0 (1.8–2.1)	−0.1 (−0.2–0.0)	−1.5 (−1.6–−1.3)	0.0 (−0.1–0.1)
FVC (z-score)	−0.3 (−0.3–−0.3)	0.9 (0.9–1.0)	−1.2 (−1.3–−1.1)	−0.1 (−0.2–0.0)	1.9 (1.8–2.1)	0.7 (0.6–0.8)	−1.5 (−1.7,−1.4)	−1.0 (−1.1–−0.9)
FEV_1/FVC (z-score)	0.0 (−0.1–0.0)	0.2 (0.2–0.3)	−1.8 (−1.9–−1.7)	0.1 (0.0–0.2)	−0.1 (−0.3–0.0)	−1.2 (−1.3–−1.0)	0.0 (−0.1–0.2)	2.0 (1.9–2.1)
Annualised decline rate of lung function								
Δ in FEV_1 (mL per year)	−34 (−36–−33)	−51 (−53–−49)	−23 (−28–−18)	−130 (−136–−124)	−133 (−142–−124)	−50 (−56–−43)	+40 (+33–+48)	−30 (−35–−25)
Δ in FVC (mL per year)	−25 (−27–−23)	−45 (−47–−42)	−26 (−32–−19)	−116 (−125–−108)	−163 (−173–−153)	−119 (−128–−111)	+83 (+73–+93)	+59 (+53–+66)
Δ in FEV_1 (z-score per year)	+0.00 (−0.01–+0.00)	−0.05 (−0.05–−0.04)	+0.02 (+0.01–+0.03)	−0.22 (−0.23–−0.22)	−0.26 (−0.27–−0.24)	−0.05 (−0.06–−0.03)	+0.18 (+0.16–+0.20)	+0.00 (−0.01–+0.01)
Δ in FVC (z-score per year)	+0.02 (+0.01–+0.02)	−0.02 (−0.03–−0.02)	+0.02 (+0.01–+0.03)	−0.15 (−0.16–−0.14)	−0.24 (−0.26–−0.22)	−0.16 (−0.18–−0.15)	+0.23 (+0.21–+0.24)	+0.17 (+0.15–+0.18)
Δ in FEV_1/FVC (z-score per year)	−0.04 (−0.04–−0.03)	−0.04 (−0.04–−0.03)	+0.01 (−0.01–+0.02)	−0.15 (−0.16–−0.13)	+0.00 (−0.02–+0.01)	+0.17 (+0.15–+0.19)	−0.08 (−0.10–−0.06)	−0.35 (−0.36–−0.34)

Data are presented as n (%) or means (95% confidence intervals). The cluster labels were assigned based on the main progression pattern of FEV_1 and FVC (figure 1). FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

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TABLE 2 Baseline characteristics of lung function trajectory clusters

	Normal decline clusters			Accelerated decline clusters			Improving clusters	
	Persistently normal	Persistently high FEV_1	Persistently low FEV_1	Rapid FEV_1 decliners	High-start rapid decliners	FVC decliners	Low-start improvers	FVC improvers
Participants	1646	1122	263	176	116	144	124	258
General characteristics								
Age (years)	65.2±8.9	**64.3±8.5**	**68.1±8.3**$^{+}$	65.7±9.7	63.7±8.2	63.7±9.9	65.2±8.7	**60.6±9.5**$^{+}$
Female	902 (54.8)	644 (57.4)	142 (54.0)	88 (50.0%)	70 (60.3%)	91 (63.2%)	76 (61.3%)	147 (57.0%)
BMI ($kg·m^{-2}$)	27.8±4.2	**27.2±3.8**	27.5±4.3	28.5±4.7	**26.9±4.1**	**27.0±4.0**	**29.0±4.9**$^{+}$	28.4±4.7
Primary/lower education	762 (46.3)	481 (42.9)	**153 (58.2)**$^{+}$	74 (42.0%)	51 (44.0%)	73 (50.7%)	49 (39.5%)	132 (51.2%)
Higher/intermediate education	871 (52.9)	618 (55.1)	**107 (40.7)**	99 (56.3%)	63 (54.3%)	68 (47.2%)	71 (57.3%)	126 (48.8%)
Current smoker	214 (13.0)	**90 (8.0)**$^{+}$	**66 (25.3)**$^{+}$	30 (17.0%)	18 (15.5%)	**30 (20.8%)**$^{+}$	18 (14.5%)	46 (17.8%)
Former smoker	923 (56.1)	618 (55.2)	146 (55.9)	98 (55.7%)	61 (52.6%)	**64 (44.4%)**	74 (59.7%)	**126 (48.8%)**
Never-smoker	508 (30.9)	**411 (36.7)**	**49 (18.8)**	48 (27.3%)	37 (31.9%)	50 (34.7%)	32 (25.8%)	86 (33.3%)
Smoking (pack-years)	6.0 (0.0–25.0)	**2.1 (0.0–14.4)**$^{+}$	**26.4 (4.0–46.4)**$^{+}$	7.7 (0.0–29.0)	5.1 (0.0–20.0)	2.4 (0.0–20.1)	10.1 (0.0–31.5)	4.5 (0.0–20.2)
Respiratory symptoms								
Chronic cough	151 (9.3)	**73 (6.6)**	**53 (20.4)**	**27 (15.4%)**$^{+}$	10 (8.7%)	14 (9.8%)	10 (8.1%)	**12 (4.7%)**
Chronic sputum production	100 (6.2)	**47 (4.2)**	**47 (18.1)**	11 (6.3%)	10 (8.7%)	11 (7.7%)	9 (7.3%)	**7 (2.7%)**
Wheezing	356 (21.9)	**153 (13.8)**$^{+}$	**133 (51.2)**$^{+}$	42 (24.0%)	24 (20.9%)	31 (21.7%)	29 (23.4%)	58 (22.6%)
Dyspnoea	125 (7.7)	**54 (4.9)**	**57 (21.9)**$^{+}$	18 (10.3%)	7 (6.1%)	14 (9.8%)	10 (8.1%)	21 (8.2%)
Respiratory diseases								
COPD	82 (5.0)	**13 (1.2)**	**168 (63.9)**	8 (4.5%)	7 (6.0%)	**27 (18.8%)**	**14 (11.3%)**	**1 (0.4%)**
Asthma	130 (7.9)	**53 (4.7)**	27 (10.3)	17 (9.7%)	6 (5.2%)	13 (9.0%)	9 (7.3%)	13 (5.0%)
PRISm	92 (5.6)	**0 (0.0)**	**38 (14.4)**	5 (2.8%)	**0 (0.0%)**	**2 (1.4%)**	**76 (61.3%)**	**77 (29.8%)**
Cardiovascular diseases								
Hypertension	1111 (67.5)	**661 (59.1)**$^{+}$	**199 (76.0)**	126 (71.6%)	**63 (54.3)**$^{+}$	**83 (57.6)**$^{+}$	**96 (78.0%)**	157 (61.3%)
Heart failure (treated)	63 (3.8)	**27 (2.4)**	18 (6.9)	**16 (9.1%)**$^{+}$	4 (3.5%)	2 (1.4%)	9 (7.3%)	15 (5.8%)
Genetics and biomarkers								
PGS for low FEV_1 (z-score)	0.02±0.98	**−0.15±1.00**$^{+}$	**0.20±0.99**	0.13±0.98	−0.11±1.07	0.11±0.97	−0.12±1.00	0.07±0.99
PGS for low FEV_1/FVC (z-score)	−0.03±1.01	−0.09±1.01	**0.17±1.01**$^{+}$	0.09±0.98	−0.06±1.03	**0.19±0.99**$^{+}$	−0.16±0.99	−0.03±0.92
Serum CRP ($mg·L^{-1}$)$^{\#}$	1.2 (0.5–2.7)	**0.8 (0.4–1.9)**$^{+}$	**1.8 (0.7–3.4)**	1.5 (0.6–2.7)	**0.8 (0.3–2.3)**	1.1 (0.6–3.1)	**1.7 (0.6–3.3)**	1.1 (0.5–2.3)
Lung diffusion test¶								
D_{LCO} (% predicted)	103±17	**108±14**	**93±27**	103±16	104±10	100±16	102±19	104±15
K_{CO} (% predicted)	112±16	**106±14**	**102±23**	114±18	**99±10**	**102±14**	115±17	115±19
V_a (% predicted)	100±12	**110±15**	99±18	99±12	**111±7**	106±17	98±19	99±13

Data are presented as n, mean±SD, n (%) or median (interquartile range). Bold type shows significant mean differences ($p<0.05$) compared to the reference cluster (persistently normal). Mean differences and missing data are reported in supplementary table S7. Lung function tests and derived variables (COPD and preserved ratio impaired spirometry (PRISm)) were not considered in the logit models due to its direct use in the trajectory clustering. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; PGS: polygenic score; CRP: C-reactive protein; D_{LCO}: diffusion capacity of the lung for carbon monoxide ($mmol·min^{-1}·kPa^{-1}$); K_{CO}: carbon monoxide transfer coefficient ($mmol·min^{-1}·kPa^{-1}·L^{-1}$); V_a: alveolar volume. $^{\#}$: CRP was measured at cohort inception, a mean±SD 5.7±5.6 years before baseline spirometry; ¶: diffusion tests were performed in a subset at baseline (n=609) and corrected for haemoglobin concentration; $^{+}$: baseline characteristics that were significantly different compared to the reference cluster (univariate) found to be independent upon testing for independence using multivariable logistic regression (supplementary table S9).

TABLE 3 All-cause mortality of trajectory clusters

	Model 1[#]			Model 2[¶]		
	At risk	Deceased	HR (95% CI)	At risk	Deceased	HR (95% CI)
Persistently normal	1630	389	Reference	1605	384	Reference
Persistently high FEV_1	1110	198	**0.81 (0.69–0.97)**	1079	194	**0.82 (0.69–0.98)**
Persistently low FEV_1	263	129	**1.87 (1.53–2.28)**	260	128	**1.71 (1.37–2.13)**
Rapid FEV_1 decliners	176	53	**1.62 (1.21–2.16)**	173	51	**1.48 (1.10–1.99)**
High-start rapid decliners	115	22	0.93 (0.61–1.43)	111	21	1.03 (0.66–1.61)
FVC decliners	143	48	**1.46 (1.08–1.98)**	139	46	**1.49 (1.09–2.03)**
Low-start improvers	124	20	0.90 (0.57–1.41)	118	19	0.84 (0.53–1.34)
FVC improvers	258	26	**0.65 (0.44–0.98)**	256	26	**0.61 (0.41–0.90)**

Data are presented as n, unless otherwise stated. In case of violation of the proportional hazards assumption, a step function (time=5 years) was applied and age, sex and smoking status were interacted with time period to obtain proportional hazards. Survival follow-up was censored on 20 October 2022. Bold type shows significant differences ($p<0.05$) compared to the reference cluster (persistently normal). HR: hazard ratio; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: Cox proportional hazards model adjusted for age and sex; [¶]: Cox proportional hazards model adjusted for age, sex, body mass index, education level, smoking status, COPD, asthma, hypertension and treated heart failure.

Morbidity

Participants with persistently low FEV_1 demonstrated a significantly higher incidence rate of new onset chronic cough, wheezing and dyspnoea. Additionally, this cluster was associated with a higher incidence of clinically relevant weight loss and chronic sputum production, and had the highest prevalence of frailty at the last spirometry visit (table 4).

All declining clusters (rapid FEV_1 decliners, high-start rapid decliners and FVC decliners) showed a higher incidence of weight gain. Rapid FEV_1 decliners additionally showed the highest incidence of COPD, chronic cough and sputum production, and were at a higher risk for incident wheezing and PRISm. FVC decliners also demonstrated a higher incidence of PRISm, whereas they had the lowest incidence of COPD.

Low-start improvers showed the highest incidence of weight loss and, together with FVC improvers, a higher incidence of PRISm resolving to normal spirometry.

Persistently high FEV_1 was protective against incident wheezing, COPD and PRISm, and showed a lower prevalence of frail individuals at the last spirometry visit. None of the clusters showed a significant association with the incidence of smoking cessation, although the percentage of quitters was borderline significantly higher in the persistently high FEV_1 cluster (+12.4 percentage points, 95% CI −0.5–+25.3 percentage points).

Discussion

Eight distinct lung function trajectory clusters were identified in middle-aged and older adults based on longitudinal patterns of FEV_1, FVC and FEV_1/FVC. Our findings show that the progression of lung function over time is heterogeneous and informative for respiratory and overall health beyond disease labels in older adults from the general population. Independent risk factors included genetic predisposition for impaired FEV_1 and FEV_1/FVC, demographics (age and education level), cigarette smoking, respiratory symptoms (chronic cough, wheezing and dyspnoea), cardiovascular factors (BMI, hypertension and heart failure) and inflammation markers (CRP). Secondly, three lung function trajectory clusters were at a higher mortality risk: 1) individuals with persistently low FEV_1; 2) rapid FEV_1 decliners; and 3) FVC decliners. Two trajectory clusters were protective for mortality: 1) FVC improvers and 2) individuals with persistently high FEV_1. Thirdly, trajectory clusters were differentially associated with frailty, weight changes, and the development of respiratory symptoms, COPD and PRISm over time. Overall, our results suggest that in a general population of older adults, two spirometric measurements over a period of 5 years may describe clinically relevant short-term lung function trajectories.

A novel phenotype of FVC improvers was observed in ∼7% of middle-aged and older adults. Participants in this cluster demonstrated a median improvement of +345 mL FVC over 5.8 years. Promisingly, this trajectory cluster showed lower all-cause mortality than the reference cluster. In line with the overall

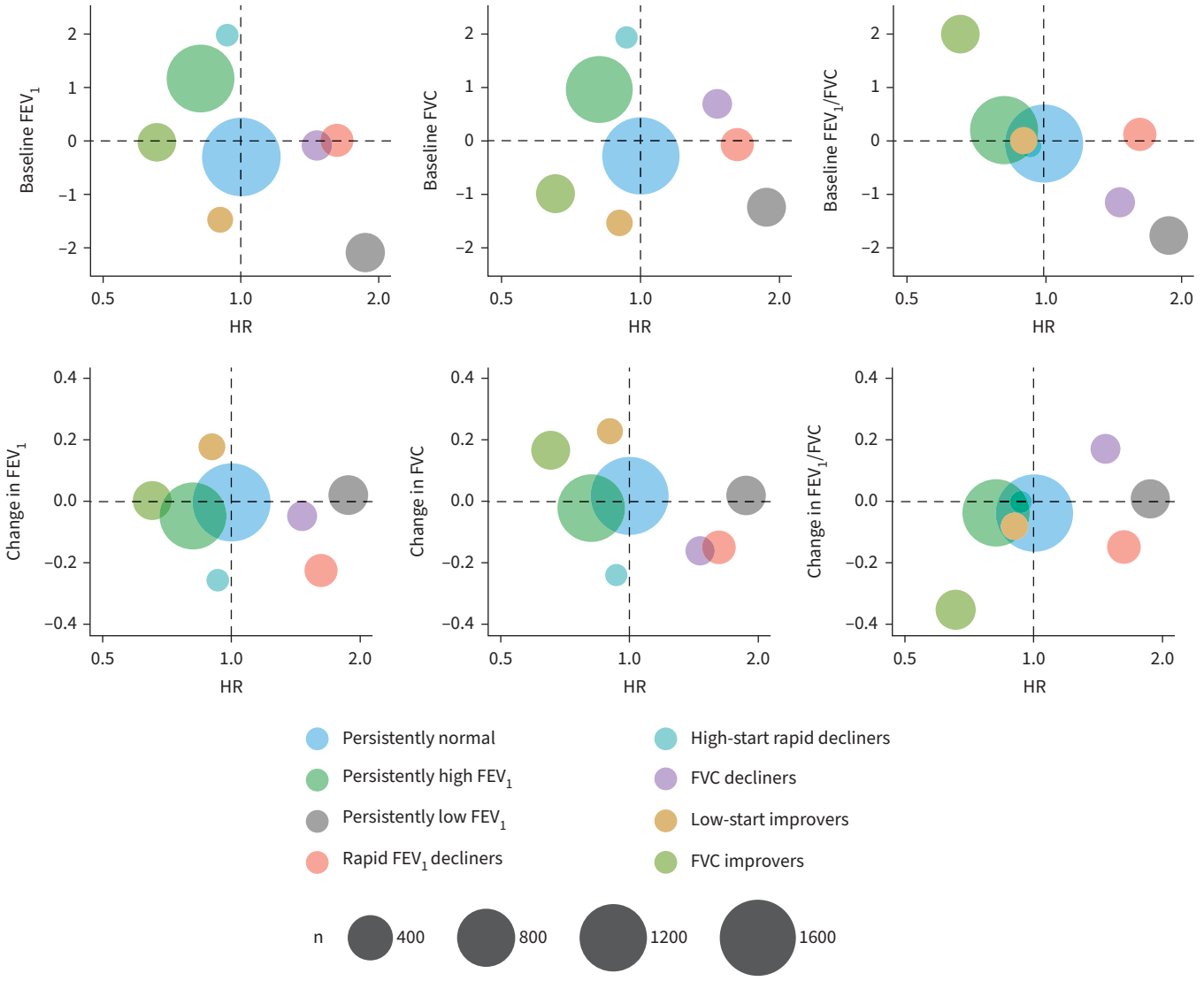

FIGURE 2 Lung function trajectory clusters and all-cause mortality. Baseline lung function expressed in Global Lung Initiative z-scores and change calculated as an annualised rate of decline (z-score per year). Cox proportional hazards model was adjusted for age and sex (model 1). FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; HR hazard ratio.

importance of FVC on survival [32], these results show that resilience toward FVC decline is a protective factor for overall health in middle-aged and older adults.

Approximately 3% of the study population exhibited low baseline spirometry levels followed by improvements in both FEV_1 and FVC (low-start improvers). Even though this cluster had the lowest baseline FVC values, it did not show higher mortality, nor an increased development of symptoms or diseases, in sheer contrast to those with persistently low FEV_1, who had similar low baseline spirometric values. ~60% of low-start improvers had PRISm at baseline, which was generally followed by a reversal to normal spirometry in subsequent years. This PRISm-to-normal phenotype has been described previously in both young and older adults [33, 34].

Low FVC at baseline may be the result of a myriad factors, including an early-life trajectory of reduced lung growth and development [11] or air trapping [35] (*e.g.* due to small airway disease). Low-start improvers showed the largest incidence of weight loss and a significantly lower prevalence of frailty (−11.0 percentage points, 95% CI −17.0–−4.7 percentage points) compared to individuals with persistently low FEV_1, indicating potential opportunities for improving lung health. This is consistent with previous studies showing beneficial effects of weight loss in obese individuals [17, 21]. Other mechanisms

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TABLE 4 Within-trajectory morbidity outcomes

	Normal decline clusters			Accelerated decline clusters			Improving clusters	
	Persistently normal	Persistently high FEV_1	Persistently low FEV_1	Rapid FEV_1 decliners	High-start rapid decliners	FVC decliners	Low-start Improvers	FVC improvers
Participants	1646	1122	**263**	**176**	144	124	258	
Respiratory outcomes								
Chronic cough	12 (10–14)	10 (8–12)	**20 (13–28)**	**25 (15–38)**	7 (2–17)	12 (6–22)	13 (6–25)	12 (8–19)
Chronic sputum production	9 (7–11)	7 (5–9)	**17 (11–24)**	**18 (10–29)**	7 (2–17)	6 (2–14)	10 (4–21)	8 (4–14)
Wheezing	18 (16–21)	**11 (9–14)**	**37 (26–52)**	**37 (24–54)**	15 (7–29)	18 (10–31)	23 (12–39)	13 (7–21)
Dyspnoea	6 (5–8)	5 (4–7)	**21 (14–30)**	9 (4–18)	5 (1–14)	8 (3–17)	10 (4–21)	5 (2–11)
COPD	23 (20–26)	**13 (11–16)**	**37 (24–53)**	**63 (48–81)**	22 (13–36)	**4 (1–12)**	30 (19–47)	18 (12–26)
PRISm	8 (7–10)	**0 (0–1)**	12 (8–19)	**36 (25–50)**	6 (2–15)	**17 (10–28)**	0 (0–15)	3 (1–8)
PRISm to normal	34 (21–51)	NA	10 (2–30)	0 (0–152)	NA	0 (0–296)	**92 (67–124)**	**107 (80–139)**
PRISm to COPD	30 (19–47)	NA	54 (31–88)	123 (25–360)	NA	0 (0–296)	41 (25–63)	16 (7–31)
Smoking cessation	48 (38–61)	66 (48–90)	54 (34–80)	51 (23–97)	60 (24–123)	59 (29–105)	49 (16–115)	46 (25–79)
Frailty[#] and weight changes								
Frail	91 (5.7)	**40 (3.7)**	**35 (13.9)**	11 (6.4)	2 (1.8)	9 (6.3)	4 (3.3)	8 (3.1)
Pre-frail	837 (52.4)	543 (50.1)	**161 (64.1)**	98 (56.6)	58 (50.9)	76 (53.5)	70 (57.9)	125 (49.2)
Robust	670 (41.9)	**500 (46.2)**	**55 (21.9)**	64 (37.0)	54 (47.4)	57 (40.1)	47 (38.8)	121 (47.6)
Weight gain (>5%)	16 (14–19)	19 (16–22)	20 (15–28)	**35 (24–48)**	**42 (29–59)**	**34 (23–48)**	14 (7–25)	22 (16–31)
Weight loss (>5%)	32 (29–36)	28 (25–32)	**51 (41–62)**	30 (20–42)	20 (12–33)	34 (23–48)	**59 (43–79)**	38 (29–49)

Data are presented as n, incidence rate per 1000 person-years (95% confidence interval) or n (%). Incidence rates were calculated between first and last study visit (within-trajectory data) and excluded individuals with baseline symptoms/disease. Frailty prevalence was calculated at the last spirometry visit. Bold type shows significant differences ($p<0.05$) compared to the reference cluster (persistently normal). Incidence rate ratios and missing data are reported in supplementary table S11. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PRISm: preserved ratio impaired spirometry; NA: not applicable. [#]: frail: ⩾3 Fried phenotype criteria; nonfrail: robust and pre-frail; pre-frail: 1 or 2 Fried phenotype criteria; robust: no Fried phenotype criteria.

explaining lung function improvements may include incident bronchodilator use, reversal of air trapping, improving health status, increased physical activity and heart failure control. Smoking cessation was not associated with improving clusters over a relatively short-term period, yet previous studies showed that its effects are more apparent as long-term attenuation of lung function decline in sustained quitters [36].

Furthermore, we identified two trajectory clusters leading to both a low FEV_1/FVC ratio and low FVC in older adults: one consisting of individuals with persistently low FEV_1 (∼7%) who also showed lower FVC values, and rapid FEV_1 decliners (∼5%) who concomitantly showed accelerated FVC decline, albeit to a lesser extent. Such mixed spirometry patterns were also observed recently in a younger age range (7–53 years) of the general population [11]. Both trajectory clusters were associated with higher mortality and showed the highest incidence of respiratory symptoms, COPD and PRISm. Persistently low FEV_1 was also associated with frailty suggesting poor resilience among these persons. Most notably, this cluster was significantly more genetically predisposed to impaired FEV_1/FVC while this was not the case in rapid FEV_1 decliners. This supports that the genetic variants included in the FEV_1/FVC PGS [26] (∼1.2 million) are associated with COPD age of onset [37] and that these variants might be more informative for incident airflow obstruction before the age of 65 years. Risk factors for rapid FEV_1 decline included chronic cough, in line with previous literature [38], and heart failure. Rapid FEV_1 decline is a known risk factor for incident heart failure [39], yet our study adds that this acceleration may persist in individuals with prevalent heart failure.

Additionally, our study provides evidence for a trajectory of FVC decline (∼4%), which was associated with higher mortality and PRISm development. Interestingly, we also observed a cluster of high-start rapid decliners (∼3%). This latter group did not show increased morbidity over time, nor higher mortality. This may indicate that their supranormal decline did not persist in the long term and did not compromise their functional capacities due to their protective baseline values. Smoking, genetic predisposition for low FEV_1/FVC and the absence of (treated) hypertension were independent risk factors for FVC decline in older adults of the general population.

Together, ∼11% of this population demonstrated rapid FEV_1 and/or FVC decline, exceeding the proportion of rapid decliners identified in other studies [8, 11, 13, 40]. This may be explained by the fact that our study clustered (short-term) individual trajectories and did not investigate life-long trajectories, therefore also capturing more extreme trajectories. Indeed, rapid decline which persists over several decades may be relatively rare due to incompatibility with life and is therefore harder to observe due to loss-to-follow-up [1].

Study strengths include 1) generalisability of our findings, as no exclusion criteria were defined; 2) longitudinal morbidity and mortality data in a large cohort of middle-aged and older adults; and 3) the data-driven way of phenotyping participants based on the progression of FEV_1, FVC and FEV_1/FVC simultaneously, which led to a comprehensive set of distinct trajectory clusters.

Limitations of our study include 1) selection bias due to the repeated spirometry inclusion criterion, initial cohort response and attrition before the first research visit including spirometry; 2) the use of pre-bronchodilator spirometry; and 3) the lack of post-trajectory morbidity data. Furthermore, as spirometry is effort-dependent, an underestimation of FVC due to poor effort cannot be ruled out. Future studies should investigate whether case-finding by repeated spirometry is justified in this population and disentangle the mechanisms which drive improving trajectory clusters.

To conclude, we demonstrated that middle-aged and older adults show distinct clusters of lung function trajectories, which appear to be clinically relevant.

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Author contributions: X. Bertels designed and planned this analysis guided by L. Lahousse. Methodological advice was provided by L. Lahousse, J.C. Ross, M.H. Cho and R. Faner. Formal analysis and drafting of manuscript was performed by X. Bertels. Critical revision and expert feedback were received from J.C. Ross, M.H. Cho, R. Faner, M.A. Ikram, G.G. Brusselle and L. Lahousse.

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