

Early View

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Treatable traits in an English cohort: prevalence and predictors of future decline in lung function and quality of life in COPD

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Take home message

Targeting the traits of chronic bronchitis, breathlessness, underweight, sarcopaenia, depression, smoking, and poor family and social support may significantly improve health outcomes in people with COPD.

ABSTRACT

Background: “Treatable traits (TTs)” is a precision medicine approach for facilitating multidimensional assessment of every patient with chronic airway disease to determine the core traits associated with disease outcomes, where targeted treatments are applied.

Objectives: To determine the prevalence of TTs in chronic obstructive pulmonary disease (COPD) and which traits predict future decline in lung function and quality of life (QoL).

Methods: A 4 year longitudinal evaluation was conducted using data from 3,726 participants in the English Longitudinal Study of Ageing (ELSA). TTs were identified based on published recommendations. Traits that predicted decline in lung function and QoL were analysed using generalized estimating equations.

Results: Overall, 21 TTs, including pulmonary (n=5), extra-pulmonary (n=13) and behavioural/lifestyle risk-factors (n=3) were identified. In multivariate analyses, traits of chronic bronchitis ($\beta = -0.186$; 95%CI= -0.290 to -0.082), breathlessness ($\beta = -0.093$; 95%CI= -0.164 to -0.022), underweight ($\beta = -0.216$; 95%CI= -0.373 to -0.058), sarcopaenia ($\beta = -0.162$; 95%CI= -0.262 to -0.061), and current smoking ($\beta = -0.228$; 95%CI= -0.304 to -0.153), predicted decline in forced expiratory volume in 1 second (FEV₁). Of the seven traits that predicted decline in QoL, depression ($\beta = -7.19$; 95%CI= -8.81 to -5.57) and poor family and social support ($\beta = -5.12$; 95%CI= -6.65 to -3.59) were the strongest.

Conclusion: The core TTs of COPD associated with a decline in lung function and QoL were identified. Targeting these impactful traits and individualised treatment using a precision medicine approach may improve outcomes in people with COPD.

Keywords: Treatable traits; COPD; Lung function; Quality of life; English Longitudinal Study of Ageing; Multidimensional assessment

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease complicated by comorbidities and exacerbations, making its management complex. Despite the use of many evidence-based approaches to management, the burden from COPD exacerbations and symptoms continues [1]. This has led to calls for new approaches to COPD management [2-4]. ‘Treatable traits’ (TTs) is one such approach, first proposed by Agustí et al; it is a precision medicine strategy for chronic airway diseases [3]. The TTs strategy encompasses the multidimensional assessment (including a review of the clinical history, physical examination, spirometry, determination of risk factors, fractional exhaled nitric oxide [FeNO] and blood eosinophil) of every patient for identification of characteristics relating to genes, clinical and inflammatory phenotypes and psychosocial factors in that individual. A personalised management approach can then be applied according to the traits identified [2]. Traits are classified under three domains: pulmonary, extra-pulmonary and behavioural/lifestyle risk factors [3].

The strategy of TTs supports a targeted approach that is widely applicable regardless of the specific airway disease diagnosis. It is in contrast to the “one size fits all” approach to management of airway diseases. Precision medicine could be a pivotal strategy for improved outcomes for patients with chronic airway diseases [3].

Previous studies in patients with chronic airway diseases have identified that TTs such as anxiety and depression [5, 6], dysfunctional breathing [6], frequent chest infections [6], poor inhaler technique [6], smoking [7], and systemic inflammation [6, 8] were associated with a greater decline in forced expiratory volume in 1 second (FEV₁) and/or quality of life (QoL). However, which TTs matter most for optimizing the management of COPD is still unclear. Moreover, there are scarce data from longitudinal studies investigating the prevalence of TTs among patients with COPD and their associations with lung function and QoL. To address

this knowledge gap, the current analysis aimed to determine the prevalence of TTs among participants in the English Longitudinal Study of Ageing (ELSA), a population-based cohort study, and to determine which traits predict longitudinal decline in lung function and QoL.

METHODS

Study design, setting and participants

ELSA is an ongoing cohort study evaluating the health and circumstances of people aged 50 years and over, born before 1952 and living in England [9]. The participants were recruited through multistage stratified probability sampling. Data were collected through interviews and self-completed questionnaires by a team of trained researchers who followed strict protocols. For this analysis, we accessed data from ELSA, including four-year follow-up data from Wave 2 (2004–2005) and Wave 4 (2008–2009). A total of 7,666 respondents were interviewed by a nurse in Wave 2 and 8,643 in Wave 4. Of these, participants with an asthma diagnosis (Wave 2 N=703; Wave 4 N=592) and those who had no valid respiratory function measurements (Wave 2 N=775; Wave 4 N=1,019) were excluded. Of the remaining respondents (Wave 2 N=6,188; Wave 4 N=7,032), a final sample of 3,726 people who were participants in both waves was included and used for all further analyses (*Figure 1*).

Data collection/measurements

Socio-demographic characteristics: The following variables were recorded: gender, age (years), marital status (single/separated/widowed, living in a relationship), ethnicity (white, non-white) and socio-economic class based on employment (managerial and professional; intermediate; small employers; lower supervisory/technical; and semi-routine occupations), according to the National Statistics Socio-economic Classification.

Self-reported general health: Participants self-rated their health status as ‘poor’, ‘fair’, ‘good’, ‘very good’ or ‘excellent’ on a 5-point Likert-type scale.

Lung function/spirometry: At Waves 2 and 4, a trained nurse visited participants and performed spirometry (pre-bronchodilator) according to standardized criteria [10], using a portable Vitalograph Escort Spirometer (Vitalograph micro, Maids Moreton, Bucks, UK) on both occasions, which automatically accounted for ambient temperature. A 1-litre syringe was used for daily spirometer calibration [10]. This study included only those participants who were tested for lung function at baseline in 2004/05 (W2) and were followed-up in 2008/09 (W4). The Global Lung Function Initiative (GLI-2012) Spirometry Task Force reference equations [11] were used to derive the values for FEV₁% predicted and forced vital capacity (FVC) %predicted.

For the purpose of this analysis, individuals who had a fixed ratio of FEV₁/FVC <0.70 (spirometry data were not post-bronchodilator), and relevant symptoms (phlegm, dyspnoea and wheezing), but did not self-report a diagnosis of asthma, were regarded as having COPD [12]. The severity of COPD was determined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [13] and categorized into “healthy/non-COPD” (FEV₁/FVC ≥0.7), “mild” (FEV₁/FVC <0.7 and FEV₁ ≥80% predicted), “moderate” (FEV₁/FVC <0.7 and 50% ≤FEV₁ <80% predicted), “severe” (FEV₁/FVC <0.7 and 30% ≤FEV₁ <50% predicted) or “very severe” (FEV₁/FVC <0.7 and FEV₁ <30% predicted).

Quality of life: General QoL was assessed using a 19-item scale encompassing four dimensions: Control, Autonomy, Self-realization, and Pleasure (CASP) [14]. Each item was measured on a four-point Likert-type scale: never=0, not often=1, sometimes=2, and often=3. The CASP-19 total score lies between 0 and 57, higher scores suggest greater well-being.

CASP-19 is a validated tool explicitly developed for people in early old age and has been widely used in ageing surveys [14].

Treatable traits in ELSA

Potential TTs and corresponding diagnostic criteria were identified through a literature search [1-4, 15]. Data for a total of 21 TTs (pulmonary=5; extra-pulmonary=13; behavioural/lifestyle=3) could be characterized using the ELSA data set (Table 1).

Table 1: List of potential treatable traits identified from the ELSA cohort

Category	Treatable traits	Diagnostic criterion
<i>Pulmonary</i>	Airflow limitation	FEV ₁ /FVC <0.7
	Chronic bronchitis	Physician diagnosis/self-report*
	Chronic sputum production	Sputum with coughing (≥3 months/year)
	Breathlessness	mMRC Dyspnoea scale
	Frequent chest Infections	Self-report
<i>Extra-pulmonary</i>	Osteoporosis	Physician diagnosis/self-report
	Cardiovascular disease†	Physician diagnosis/self-report
	Arthritis	Physician diagnosis/self-report
	Diabetes	Physician diagnosis/self-report
	Cancer‡	Physician diagnosis/self-report
	Psychiatric problems§	Physician diagnosis/self-report
	Depression	CES-D scale
	Underweight	BMI <18.5 kg/m ²
	Obesity	BMI ≥ 30 kg/m ²
	Sarcopaenia	Handgrip strength (<27 kg for males, <16 kg for females)
	Systemic inflammation	C-reactive protein > 3 mg/litre
	Anaemia	Hb < 140 g/L in men or < 120 g/L in women
	Disability	Self-reported limitations in basic ADL and IADL
<i>Behavioural traits/ lifestyle risk factors</i>	Current smoking	Interview/self-report
	Physical inactivity¶	Interview/self-report
	Poor family and social support	Interview/self-report

*Self-reported by the participants. †Including high blood pressure (BP), angina, myocardial infarction, heart attack, high cholesterol, congestive heart failure, stroke, heart murmur or abnormal heart rhythm. ‡Including cancers of lung, breast, colorectal, lymphoma, leukaemia, and melanoma. §Including hallucinations, anxiety, emotional problems, schizophrenia, psychosis, mood swings and bipolar disorder. ¶No mild/moderate/vigorous activity per week.

FEV₁ = Forced expiratory volume in 1 second; **FVC** = Forced vital capacity; **mMRC** = Modified Medical Research Council; **CES-D** = Centre for Epidemiological Studies-Depression Scale; **BMI** = Body Mass Index; **Hb** = Haemoglobin; **ADL** = Activities of Daily Living; **IADL** = Instrumental Activities of Daily Living

Further details pertaining to the measurement of included TTs from the ELSA data set are presented in Appendix A.

Statistical analyses

The Statistical Package for Social Sciences (IBM SPSS Statistics for Windows Version 23.0. Armonk, NY: IBM Corp.) was used for data analyses. The distributions of continuous variables were assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Baseline socio-demographic and health-related characteristics were summarized using frequencies, percentages, and medians (interquartile ranges). Characteristics, including TTs, were compared between COPD and non-COPD groups using Pearson Chi-Square tests or Mann-Whitney U tests, as appropriate.

Of all cases, 62.9% had no missing values for any variable. However, 37.1% of the cases had missing value(s) for one or more variables. Little's Missing Completely at Random (MCAR) test was used to establish the nature of missing data. Missing values were imputed using a Markov chain Monte Carlo multiple imputation method based on socio-demographic and clinical characteristics. Five data sets were imputed. Each imputed data set was analysed, providing five sets of parameter estimates. Parameter estimates from each replication of analysis were averaged to provide a single estimate.

To assess the TTs that predicted longitudinal changes in lung function (FEV₁ in litres and %predicted) and QoL in the COPD and non-COPD groups, generalized estimating equations (GEE) were used, while controlling for potential confounders. We used two models for adjusting the potential confounders. The first model (M1) included socio-demographic variables and TTs that had $p < 0.1$ from univariate analyses and the second model (M2)

included socio-demographic variables and TTs that had $p < 0.1$ from the multivariate analyses. Quasi Likelihood under Independence or Corrected Quasi Likelihood under Independence Model Criteria was compared between models to determine the best-working correlation structure. The GEE results were based on an independent correlation matrix for unadjusted analyses and upon an unstructured correlation matrix for the adjusted analyses (Models 1 & 2). All regression coefficients (β) were reported along with 95% confidence intervals (CIs) and p-values. A two-sided p-value < 0.05 was considered statistically significant.

Complete case analyses were conducted within the GEE and presented as the primary analyses. Sensitivity analysis was performed using data obtained after multiple imputations to ensure robustness of the primary analysis. Furthermore, an additional sensitivity analysis was conducted for the non-COPD/control participants after excluding patients with airflow limitation and chronic bronchitis.

RESULTS

Of the 3,726 participants at baseline (Wave 2), 10.9% had COPD (median age 67 years).

Participants with COPD, compared to those without, were older, more likely to be single/separated/widowed, semi-routine employees, current smokers and had fair or poor self-reported health status, limited physical activity, more severe dyspnoea, and worse lung function (Table 2).

Table 2: Baseline socio-demographic and clinical characteristics of the cohort

Variable		COPD N = 406 (%)	Non-COPD N = 3,320 (%)	P-value
Gender	Male	186 (45.8)	1,526 (46.0)	0.954
Age (years) median [IQR]		67.0 [59–73]	63.0 [57–70]	<0.001
Marital status	Single/separated/widowed	153 (37.7)	938 (28.3)	<0.001
	Living in a relationship	253 (62.3)	2,382 (71.7)	
Ethnicity	White	395 (97.3)	3,272 (98.6)	0.054
Socio-economic class	Managerial and professional	108 (26.6)	1,209 (36.4)	<0.001
	Intermediate	53 (13.1)	467 (14.1)	
	Small employers and own-account workers	44 (10.8)	388 (11.7)	
	Lower supervisory and technical	50 (12.3)	329 (9.9)	
	Semi-routine occupations	144 (35.5)	899 (27.1)	
	Others	7 (1.7)	28 (0.8)	
Self-reported health	Excellent	36 (8.9)	577 (17.4)	<0.001
	Very good	99 (24.4)	1,140 (34.3)	
	Good	144 (35.5)	1,071 (32.3)	
	Fair	93 (22.9)	438 (13.2)	
	Poor	34 (8.4)	94 (2.8)	
Physical activity	None	25 (6.2)	118 (3.6)	<0.001
	Mild	64 (15.8)	373 (11.2)	
	Moderate	236 (58.1)	1,684 (50.7)	
	Vigorous	81 (20.0)	1,145 (34.5)	
Dyspnoea	Grade 0	172 (42.4)	2,519 (75.9)	<0.001
	Grade 1	151 (37.2)	549 (16.5)	
	Grade 2	34 (8.4)	90 (2.7)	
	Grade 3	49 (12.1)	162 (4.9)	
Smoking status	Never smoker	100 (24.6)	1,346 (40.5)	<0.001
	Former smoker	160 (39.4)	1,518 (45.7)	
	Current smoker	146 (36.0)	456 (13.7)	
Spirometry measurements	FEV ₁ (litres), median [IQR]	1.7 [1.1–2.3]	2.5 [2.0–3.1]	<0.001
	FVC (litres), median [IQR]	3.1 [2.3–3.8]	3.2 [2.6–4.0]	0.001
	PEF (litres per minute), median [IQR]	286.5 [202.8–378.8]	385 [307.0–493.0]	<0.001
	FEV ₁ % predicted, median [IQR]	70.2 [49.5–84.6]	94.0 [83.5–104.8]	<0.001
	FVC% predicted, median [IQR]	92.2 [78.0–107.2]	94.4 [83.6–106.0]	0.056

*Percentages are given with respect to total sample size in the respective column. **IQR** = Interquartile range [25%le-75%le]; **FEV₁** = Forced expiratory volume in 1 second; **FVC** = Forced vital capacity; **PEF** = Peak expiratory flow

Prevalence of treatable traits

All TTs had a higher prevalence among COPD participants in comparison to non-COPD participants (Table 3). The following pulmonary TTs were significantly more prevalent among people with COPD: airflow limitation, breathlessness, chronic bronchitis, chronic sputum production, and frequent chest infections. However, the COPD cohort also had a significantly higher prevalence of non-pulmonary traits including osteoporosis, arthritis, depression, sarcopaenia, systemic inflammation, disability, current smoking status, physical inactivity, and poor family and social support (Table 3).

Table 3: Prevalence of various treatable traits at baseline by GOLD severity status

Treatable traits		COPD					Non-COPD (N = 3,320)	COPD (overall) vs Non-COPD P-value
		Mild N = 129	Moderate N = 172	Severe N = 74	Very severe N = 31	Overall N = 406		
Pulmonary	Airflow limitation	129 (100)	172 (100)	74 (100)	31 (100)	406 (100)	462 (13.9)	<0.001
	Breathlessness	61 (47.3)	102 (59.3)	50 (67.6)	16 (51.6)	229 (56.4)	789 (23.8)	<0.001
	Chronic bronchitis	4 (3.1)	26 (15.1)	9 (12.2)	4 (12.9)	43 (10.6)	49 (1.5)	<0.001
	Chronic sputum production	29 (22.5)	59 (34.3)	22 (29.7)	10 (32.2)	120 (29.6)	221 (6.7)	<0.001
	Frequent chest infections	10 (7.8)	24 (14.0)	10 (13.5)	2 (6.5)	46 (11.3)	237 (7.1)	0.003
Extra-pulmonary	Osteoporosis	6 (4.7)	13 (7.6)	9 (12.2)	2 (6.5)	30 (7.4)	149 (4.5)	0.010
	Cardiovascular disease	23 (17.8)	43 (25)	18 (24.3)	8 (25.8)	92 (22.7)	742 (22.3)	0.747
	Arthritis	52 (40.3)	76 (44.2)	30 (40.5)	10 (32.3)	168 (41.4)	1130 (34)	0.003
	Diabetes	5 (3.9)	14 (8.1)	6 (8.1)	1 (3.2)	26 (6.4)	211 (6.4)	0.970
	Cancer	8 (6.2)	15 (8.7)	5 (6.8)	1 (3.2)	29 (7.1)	225 (6.8)	0.783
	Psychiatric problems	11 (8.5)	8 (4.7)	2 (2.7)	0 (0.0)	21 (5.2)	167 (5.0)	0.902
	Depression	26 (20.2)	51 (29.7)	19 (25.7)	8 (25.8)	104 (25.6)	576 (17.3)	<0.001
	Underweight	1 (0.8)	2 (1.2)	1 (1.4)	1 (3.2)	5 (1.2)	26 (0.8)	0.202
	Obesity	36 (27.9)	45 (26.2)	26 (35.1)	8 (25.8)	115 (28.3)	912 (27.5)	0.765
	Sarcopaenia	6 (4.7)	14 (8.1)	6 (8.1)	2 (6.5)	29 (7.1)	157 (4.7)	0.035
	Systemic inflammation	44 (34.1)	79 (45.9)	35 (47.3)	11 (35.5)	168 (41.4)	985 (29.7)	<0.001
	Anaemia	8 (6.2)	16 (9.3)	5 (6.8)	2 (6.5)	31 (7.6)	223 (6.7)	0.473
	Disability	77 (59.7)	131 (76.2)	58 (78.4)	22 (71.0)	288 (70.9)	1,674 (50.4)	<0.001
Behavioural/ lifestyle	Current smoking	33 (25.6)	73 (42.4)	27 (36.5)	13 (41.9)	146 (36.0)	458 (13.8)	<0.001
	Physical inactivity	3 (2.3)	12 (7.0)	10 (13.5)	0 (0.0)	25 (6.2)	118 (3.6)	0.010
	Poor family and social support	27 (20.9)	37 (21.5)	14 (18.9)	8 (25.8)	86 (21.2)	574 (17.3)	0.039

Note: Percentages are given with respect to total sample size in each column

Treatable traits and lung function

The association between individual TTs and FEV₁ is shown in Table 4. Among individuals with COPD, univariate analyses showed that eight traits: chronic bronchitis, breathlessness, osteoporosis, depression, underweight, sarcopaenia, disability, and physical inactivity were associated with a statistically and clinically significant decline in FEV₁ (range = -149 to -682 mL). In multivariate analyses, chronic bronchitis, breathlessness, underweight, sarcopaenia and current smoking were associated with a statistically and clinically significant decline in FEV₁ (range = -93 to -228 mL, Table 4). Results from the sensitivity analyses were quite similar (Supplementary Table S1A). The associations between individual TTs and FEV₁% predicted are shown in Supplementary Tables S2A, S2B and S2C.

Among individuals without COPD, univariate analyses showed that 15 traits: airflow limitation, chronic bronchitis, breathlessness, osteoporosis, cardiovascular disease, arthritis, diabetes, cancer, depression, obesity, sarcopaenia, systemic inflammation, disability, current smoking and physical inactivity were associated with a statistically and clinically significant decline in FEV₁ (range = -111 to -555 mL). In multivariate analyses, eight traits: breathlessness, diabetes, obesity, sarcopaenia, systemic inflammation, disability, current smoking and physical inactivity were significantly associated with decline in FEV₁ (range = -36 to -202 mL, Table 4). Results from the sensitivity analyses were similar, except for traits of chronic bronchitis and frequent chest infections, which showed an association with a decline in FEV₁ in the multivariate analyses (Supplementary Table S1A). Additional sensitivity analyses executed for non-COPD/control participants showed similar results (as presented in Table 4), except for the trait of disability, which did not show an association with a decline in FEV₁ in the multivariate analyses (Supplementary Table S1B).

Table 4: Treatable traits associated with FEV₁ (litres) decline

Treatable traits	COPD			Non-COPD		
	Unadjusted	Model 1 [*]	Model 2 [†]	Unadjusted	Model 1 [‡]	Model 2 [§]
	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI
Airflow limitation	3.046, 2.825 to 3.268	2.957, 2.736 to 3.178	2.976, 2.760 to 3.193^{††}	1.821, 1.645 to 1.997	2.046, 1.823 to 2.268	2.018, 1.798 to 2.238^{††}
Chronic bronchitis	-0.243, -0.387 to -0.100	-0.172, -0.273 to -0.070	-0.186, -0.290 to -0.082^{††}	-0.257, -0.412 to -0.103	-0.097, -0.213 to 0.019	---
Chronic sputum production	-0.031, -0.144 to 0.082	---	---	-0.046, -0.125 to 0.032	---	---
Breathlessness	-0.304, -0.416 to -0.192	-0.076, -0.147 to -0.005	-0.093, -0.164 to -0.022^{**}	-0.360, -0.406 to -0.314	-0.112, -0.146 to -0.078	-0.112, -0.144 to -0.080^{††}
Frequent chest Infections	-0.043, -0.188 to 0.103	---	---	-0.063, -0.131 to 0.006	-0.031, -0.082 to 0.020	---
Osteoporosis	-0.383, -0.540 to -0.226	-0.056, -0.182 to 0.069	---	-0.492, -0.571 to -0.413	-0.039, -0.037 to 0.115	---
Cardiovascular disease	-0.024, -0.129 to 0.080	---	---	-0.111, -0.155 to -0.068	0.012, -0.018 to 0.042	---
Arthritis	-0.072, -0.180 to 0.035	---	---	-0.248, -0.295 to -0.200	0.046, 0.014 to 0.079	0.039, 0.007 to 0.071^{**}
Diabetes	-0.135, -0.306 to 0.036	---	---	-0.141, -0.228 to -0.053	-0.078, -0.142 to -0.015	-0.082, -0.144 to -0.020^{††}
Cancer	0.062, -0.153 to 0.276	---	---	-0.165, -0.245 to -0.084	-0.006, -0.067 to 0.055	---
Psychiatric problems	0.196, -0.028 to 0.420	-0.066, -0.240 to 0.107	---	0.102, -0.010 to 0.214	0.011, -0.057 to 0.078	---
Depression	-0.149, -0.263 to -0.036	0.007, -0.066 to 0.080	---	-0.232, -0.285 to -0.178	-0.019, -0.052 to 0.015	---
Underweight	-0.682, -0.947 to -0.417	-0.207, -0.370 to -0.043	-0.216, -0.373 to -0.058^{††}	-0.174, -0.470 to 0.123	---	---
Obesity	-0.051, -0.162 to 0.060	---	---	-0.140, -0.190 to -0.091	-0.110, -0.145 to -0.074	-0.104, -0.139 to -0.069^{††}
Sarcopaenia	-0.402, -0.537 to -0.267	-0.137, -0.240 to -0.034	-0.162, -0.262 to -0.061^{††}	-0.555, -0.634 to -0.476	-0.120, -0.177 to -0.063	-0.114, -0.167 to -0.060^{††}
Systemic inflammation	-0.061, -0.171 to 0.050	---	---	-0.272, -0.323 to -0.221	-0.076, -0.108 to -0.044	-0.081, -0.112 to -0.050^{††}
Anaemia	-0.001, -0.167 to 0.170	---	---	0.049, -0.037 to 0.135	---	---
Disability	-0.244, -0.344 to -0.143	-0.038, -0.100 to 0.024	---	-0.277, -0.318 to -0.235	-0.031, -0.062 to -0.001	-0.036, -0.064 to -0.009^{**}
Current smoking	-0.092, -0.201 to 0.017	-0.218, -0.294 to -0.142	-0.228, -0.304 to -0.153^{††}	-0.213, -0.280 to -0.145	-0.192, -0.246 to -0.138	-0.202, -0.254 to -0.150^{††}
Physical inactivity	-0.273, -0.448 to -0.097	-0.085, -0.197 to 0.026	---	-0.344, -0.440 to -0.248	-0.108, -0.185 to -0.030	-0.096, -0.169 to -0.023^{**}
Poor family and social support	0.093, -0.034 to 0.220	---	---	0.024, -0.036 to 0.085	---	---

*Adjusted for sex, age, marital status, socioeconomic class and treatable traits (p <0.1) from the univariate analyses; [†]Adjusted for sex, age and treatable traits (p <0.1) from the multivariate analyses; [‡]Adjusted for sex, age, marital status, ethnicity, socioeconomic class and treatable traits (p <0.1) from the univariate analyses; [§]Adjusted for sex, age, marital status, ethnicity, socioeconomic class and treatable traits (p <0.1) from the multivariate analyses. ** = p<0.05; ^{††} = p<0.01; ^{†††} = p<0.001

Treatable traits and quality of life

The association between individual TTs and QoL decline is shown in Table 5. Among individuals with COPD, univariate analyses showed that 13 traits: chronic bronchitis, chronic sputum production, breathlessness, cardiovascular disease, arthritis, diabetes, depression, sarcopaenia, anaemia, disability, current smoking, physical inactivity, and poor family and social support were significantly associated with a decline in QoL (range = -1.44 to -7.88). In the multivariate model, seven traits – chronic bronchitis, cardiovascular disease, arthritis, depression, anaemia, disability, and poor family and social support were significantly associated with a decline in QoL (range = -1.52 to -7.19 , *Figure 2*). Among these, traits of depression and poor family and social support had the strongest associations with a decline in QoL (Table 5). Results from the sensitivity analyses were similar except that chronic bronchitis and anaemia were not associated with a decline in QoL in the multivariate analyses. Nevertheless, chronic sputum production, breathlessness and current smoking showed associations with a decline in QoL in multivariate analyses (Supplementary Table S3A).

Among individuals without COPD, 13 traits: chronic sputum production, breathlessness, osteoporosis, cardiovascular disease, arthritis, depression, obesity, sarcopaenia, anaemia, disability, current smoking, physical inactivity, and poor family and social support were significantly associated with a decline in QoL in multivariate analyses (range = -0.51 to -5.82 , Table 5). Results from the sensitivity analyses were similar, except for anaemia, which was not associated with a decline in QoL in multivariate analyses. Nevertheless, diabetes showed associations with a decline in QoL in multivariate analyses (Supplementary Table S3A). Additional sensitivity analyses executed for non-COPD/control subjects showed quite similar

results (as presented in Table 5), except for traits of obesity and sarcopaenia, which did not show an association with a decline in QoL in the multivariate analyses (Supplementary Table S3B).

Table 5: Treatable traits associated with decline in quality of life

Treatable traits	COPD			Non-COPD		
	Unadjusted	Model 1*	Model 2†	Unadjusted	Model 1‡	Model 2§
	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI
Airflow limitation	-3.63, -8.17 to 0.91	---	---	-4.02, -5.77 to -2.28	-0.366, -1.95 to 1.21	---
Chronic bronchitis	-3.28, -5.46 to -1.09	-2.81, -4.67 to -0.95	-2.87, -4.65 to -1.08^{††}	-4.09, -6.24 to -1.95	-0.68, -2.39 to 1.03	---
Chronic sputum production	-2.10, -3.49 to -0.72	-0.96, -2.35 to 0.43	---	-3.96, -4.93 to -2.99	-0.88, -1.79 to 0.03	-0.96, -1.86 to -0.06^{**}
Breathlessness	-3.64, -4.91 to -2.38	-0.76, -2.03 to 0.50	---	-4.53, -5.11 to -3.95	-1.76, -2.30 to -1.22	-1.76, -2.29 to -1.23^{††}
Frequent chest infections	-2.10, -4.43 to 0.23	-1.25, -3.13 to 0.63	---	-0.71, -1.53 to 0.10	-0.19, -0.94 to 0.55	---
Osteoporosis	-0.83, -2.86 to 1.20	---	---	-2.85, -3.95 to -1.74	-1.58, -2.63 to -0.52	-1.57, -2.62 to -0.52^{††}
Cardiovascular disease	-2.62, -3.93 to -1.31	-1.34, -2.60 to -0.08	-1.69, -2.90 to -0.48^{††}	-2.03, -2.51 to -1.56	-1.16, -1.57 to -0.76	-1.17, -1.57 to -0.77^{††}
Arthritis	-3.52, -4.80 to -2.23	-1.41, -2.67 to -0.15	-1.52, -2.76 to -0.28^{**}	-3.05, -3.55 to -2.56	-1.28, -1.71 to -0.84	-1.28, -1.72 to -0.85^{††}
Diabetes	-3.56, -5.42 to -1.69	-1.40, -3.17 to 0.37	---	-2.56, -3.50 to -1.62	-0.81, -1.64 to 0.03	-0.81, -1.64 to 0.02
Cancer	-1.40, -4.26 to 1.47	---	---	-0.22, -1.21 to 0.77	---	---
Psychiatric problems	-0.68, -3.23 to 1.88	---	---	-0.15, -1.12 to 0.83	---	---
Depression	-7.88, -9.38 to -6.38	-7.08, -8.73 to -5.44	-7.19, -8.81 to -5.57^{††}	-8.70, -9.38 to -8.01	-5.87, -6.54 to -5.20	-5.82, -6.48 to -5.15^{††}
Underweight	-0.71, -3.51 to 2.10	---	---	0.62, -3.49 to 4.74	---	---
Obesity	-0.27, -1.70 to 1.16	---	---	-1.95, -2.51 to -1.40	-0.58, -1.09 to -0.07	-0.51, -1.01 to -0.02^{**}
Sarcopaenia	-3.35, -5.16 to -1.54	-1.32, -3.49 to 0.84	---	-4.24, -5.24 to -3.24	-1.32, -2.26 to -0.38	-1.34, -2.28 to -0.41^{††}
Systemic inflammation	-0.93, -2.43 to 0.57	---	---	-1.13, -1.69 to -0.57	0.11, -0.34 to 0.56	---
Anaemia	-3.15, -5.55 to -0.75	-2.61, -4.42 to -0.79	-3.28, -5.06 to -1.49^{††}	-1.42, -2.27 to -0.57	-0.88, -1.56 to -0.20	-0.90, -1.57 to -0.23^{††}
Disability	-3.81, -4.95 to -2.67	-2.30, -3.59 to -1.01	-2.83, -4.06 to -1.60^{††}	-4.15, -4.62 to -3.68	-0.82, -1.25 to -0.39	-0.80, -1.22 to -0.37^{††}
Current smoking	-1.44, -2.82 to -0.05	-1.31, -2.66 to 0.04	-1.12, -2.40 to 0.17	-2.69, -3.52 to -1.85	-1.92, -2.70 to -1.14	-1.90, -2.67 to -1.13^{††}
Physical inactivity	-3.47, -5.48 to -1.46	1.35, -0.68 to 3.37	---	-4.90, -6.14 to -3.67	-1.43, -2.55 to -0.32	-1.41, -2.50 to -0.31^{**}
Poor family and social support	-5.44, -7.05 to -3.83	-5.25, -6.82 to -3.68	-5.12, -6.65 to -3.59^{††}	-5.58, -6.29 to -4.88	-3.59, -4.22 to -2.96	-3.57, -4.19 to -2.95^{††}

*Adjusted for age, marital status, socioeconomic class and treatable traits (p <0.1) from the univariate analyses; †Adjusted for socioeconomic class and treatable traits (p <0.1) from the multivariate analyses; ‡Adjusted for age, marital status, socioeconomic class and treatable traits (p <0.1) from the univariate analyses; §Adjusted for age, socioeconomic class and treatable traits (p <0.1) from the multivariate analyses. ** = p<0.05; †† = p<0.01; ††† = p<0.001

DISCUSSION

This longitudinal study assessed the prevalence of a large number of TTs and identified the traits that independently predicted decline in lung function and QoL among older people with or without COPD. All TTs had a higher prevalence among individuals with COPD, demonstrating the additional burden experienced by people with COPD compared to their counterparts. Importantly, we identified core TTs in COPD and non-COPD groups that independently predicted decline in lung function and QoL.

The current analysis highlights the fact that the declines in different outcomes, whether QoL or lung function, are associated with different traits. From 21 identified traits, five including chronic bronchitis, breathlessness, underweight, sarcopaenia and current smoking were associated with decline in lung function. For QoL there were seven traits including chronic bronchitis, cardiovascular disease, arthritis, depression, anaemia, disability, and poor family and social support that independently predicted decline (*Figure 2*) among individuals with COPD.

These findings are particularly important when making clinical decisions and in the design of interventions for TTs. This work advances knowledge of a precision medicine approach in COPD management and provides novel insights into the design of future trials targeting TTs and their implementation in clinical practice. Future studies should also investigate the impact of these traits on exacerbations, disease modification, healthcare utilisation and survival.

Our analyses showed that traits of chronic bronchitis, breathlessness, underweight, sarcopaenia, and current smoking were associated with a decline in lung function among people with COPD. Various pharmacological and non-pharmacological strategies can be used for managing these traits. For instance, roflumilast [16], mucolytics (e.g. N-acetylcysteine, erdosteine) [17] and macrolides [18] have proven to be effective in reducing exacerbations among patients with

COPD who have chronic bronchitis. Similarly, breathing retraining may improve lung function and breathlessness in patients with COPD [19]. Healthy dietary patterns, increasing consumption of fruits and vegetables along with vitamin D, vitamin E, n-3 polyunsaturated fatty acids (PUFAs), essential amino acids, L-carnitine and whey protein, particularly when used in combination with a pulmonary rehabilitation program improves/maintains lung function among individuals with COPD, and should be a treatment priority in underweight individuals [20].

Furthermore, respiratory muscle training or resistance training may improve lung function and dyspnoea in patients with COPD who have sarcopaenia [21, 22]. Smoking cessation plays a vital role in decreasing the decline in lung function associated with smoking [23]. Smoking cessation not only leads to a decreased risk of developing CVD and several types of cancer, but also increases the life expectancy of an individual [24]. A comprehensive and multidisciplinary approach is necessary for identifying the needs of people with COPD and this may have a positive effect on lung function and other health outcomes.

COPD can cause severe impairments on QoL resulting in long-term and distressing burden. Thus, improving general QoL is crucial from a patient's perspective [25]. Unfortunately this goal has largely not been achieved despite advances in pharmacotherapy [26]. There is little agreement regarding the factors responsible for excessive decline in QoL. Our analyses showed that seven traits were associated with excessive decline in general QoL; among the strongest predictors were depression and poor family and social support. Unfortunately, in the absence of a multidimensional assessment, depression remains the most common, yet least recognised and undertreated comorbidity in COPD, with a prevalence of 17–44% [27]. This negatively affects the evolution of the respiratory disease and the patient's general QoL. Our results confirm the negative association between depression and QoL and emphasise the need to recognise

depression as a core trait in COPD. Appropriate strategies must be developed and implemented for diagnosing and managing depression which may in turn improve QoL among people with and without COPD.

Poor family and social support in people with and without COPD predicted excessive decline in QoL. Strong social networks along with social support have a pivotal role in maintaining good health and QoL [28]. Studies have shown that social support improves health, motivates an individual to adhere to treatment, reduces depression, anxiety, hospitalisation and mortality, increases life span, functional capacity and willingness to take part in self-care activities [29, 30]. Strategies such as support groups, family therapy and multidisciplinary teams, including social workers, may be beneficial in patients with and without COPD.

Many of the predictors of lung function and QoL changes were significant and pointing in the same direction in both COPD and non-COPD groups. However, the associations were stronger in the COPD group. These findings indicate the importance of multi-dimensional assessment not only among people with COPD, but also among older patients with other chronic diseases.

This study has several strengths. To the best of our knowledge, it is the first comprehensive longitudinal study of TTs and their associations with health status among individuals with COPD, encompassing 21 TTs. The data were obtained from a large population based prospective cohort, allowing minimum selection bias, thus increasing the generalisability of the findings.

However, there were also some limitations. Data pertaining to exacerbations were not captured in the ELSA cohort. Thus, we were unable to evaluate exacerbations as a pertinent outcome of COPD, along with lung function and QoL. Lung function data were based on pre-bronchodilator spirometry, thus some with reversible airway obstruction or mixed airway disorder were possibly

included in the COPD cohort. The number of traits assessed was restricted by the information available from the ELSA data set, thus not all traits in COPD reported in the literature could be assessed. We did not have medication data and could not adjust for the effects of treatments on outcomes. QoL was assessed using a generic scale, not specific to COPD. However, this allowed exploration of the associations of traits in a non-COPD sample. Finally, the validity of physician or participant self-reports were not established. Nevertheless, the repeated, structured questionnaires were designed for reducing the inaccuracy and to deal with uncertainty in participant recall.

CONCLUSIONS

Our study provided information regarding TTs contributing to decline in lung function and general QoL among individuals with COPD. Targeting the pulmonary traits of chronic bronchitis and breathlessness, extra-pulmonary traits of underweight, sarcopaenia, and depression and behavioural/life-style traits of smoking, and poor family and social support may significantly improve health outcomes in people with COPD. Future studies should investigate holistic interventions targeting those core traits using a precision medicine approach and their short and long-term effects on health outcomes in COPD.

Declarations

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Author's contributions: JG, MJA, VM and MRS conceived the research idea. Statistical analyses were conducted by MRS and EP. The findings were interpreted, and the first draft written by MRS. All authors contributed to drafting and revising the manuscript, and approved the final version for publication.

Conflict of interests: MJA and JG hold investigator initiated grants from GSK, Pfizer and Boehringer-Ingelheim for unrelated research. VM has received research funding from AstraZeneca, Cyclopharm, GSK, NHMRC, and Ramaciotti; speaker's honoraria from AstraZeneca and GSK; and provided consultancy for AstraZeneca, GSK, and Menarini. MJA has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi. He has also received a speaker's fee from GSK. The other authors declare no conflicts of interest.

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Patient consent for publication: Not required

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University Human Research Ethics Committee (MUHREC-22030) for the secondary analyses of the data.

Data availability statement: The raw data on which conclusions of this manuscript rely are available upon reasonable requests. The overall data results are available as part of the manuscript and supplementary tables, but if individual data points are needed, this could be provided in response to a reasonable request.

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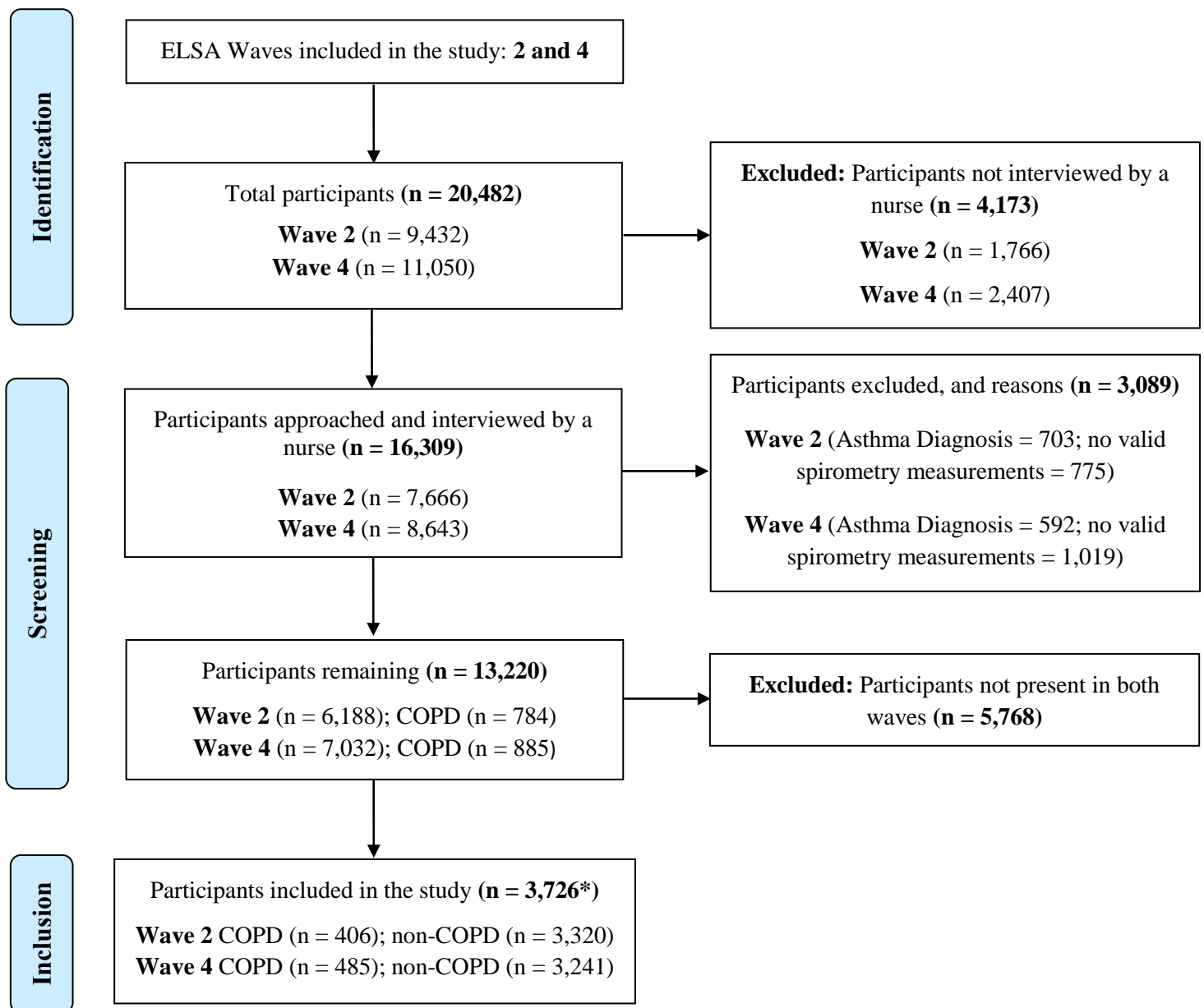


Figure 1: Schematic diagram explaining the flow of study participants

* Out of the 7,452 remaining participants, 3,726 were common in both waves thus yielding a final sample of 3,726 participants with 4-year follow-up.

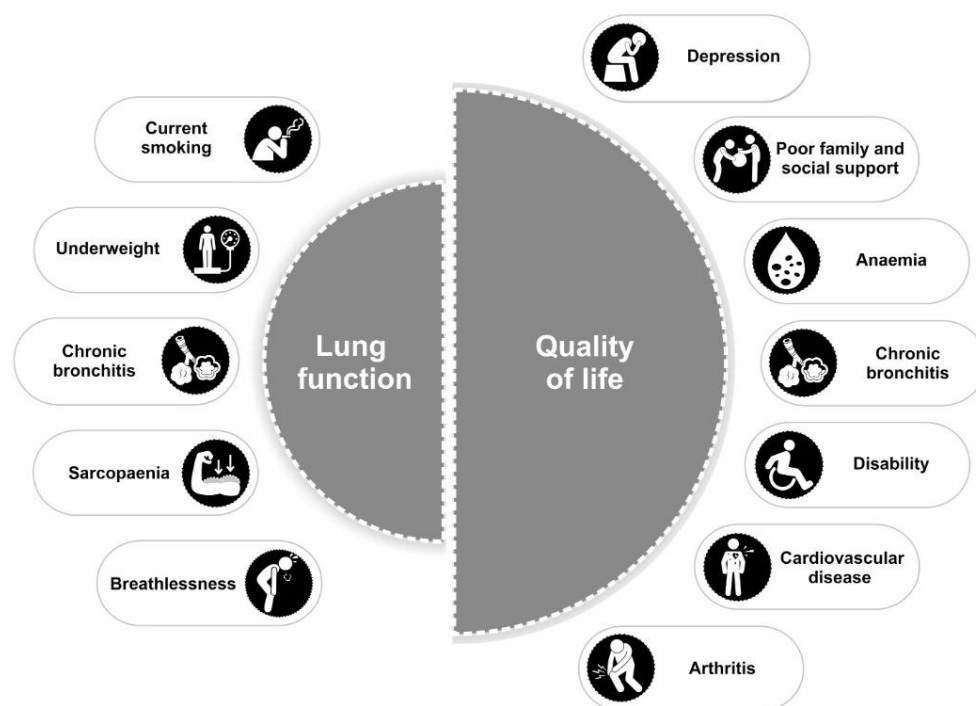


Figure 2: Treatable traits associated with decline in lung function and quality of life

Details of included treatable traits from the ELSA data set

Dyspnoea/breathlessness: The severity of breathlessness was determined using a modified Medical Research Council (mMRC) dyspnoea scale [1]. The full MRC scale comprises five grades. However, ELSA used only three grades i.e., Grade 1 “*short of breath when hurrying or walking up a slight hill*”; Grade 2 “*walks slower than contemporaries on level ground because of breathlessness*”; Grade 3 “*has to stop for breath when walking at own pace on level ground*”. Grade 0 was allocated to those who did not report dyspnoea.

Chronic sputum production: Chronic sputum production was measured as a dichotomous variable (yes/no). Self-report of “*brings phlegm from chest up on most days for as much as 3 months/year*” was regarded as an affirmative response.

Chronic bronchitis: Chronic bronchitis was measured as a dichotomous variable (yes/no). The response was considered “yes” when the participant self-reported that he/she “*had chronic bronchitis or taking medication for it*”.

Frequent chest infections: Frequent chest infection/s was measured as a dichotomous variable (yes/no). Self-report of “*had any chest infection/s in last 3 weeks*” was regarded as an affirmative response.

Osteoporosis: This was measured as a dichotomous variable (yes/no). The response was considered “yes” when the participant self-reported that he/she “*had osteoporosis or taking medication for it*”.

Cardiovascular disease: The participants were considered to have CVD (yes/no) in the presence of one or more of the following; high BP (140/90 mmHg or higher), history of angina, myocardial infarction, heart attack, high cholesterol, congestive heart failure, stroke, heart murmur or abnormal heart rhythm.

Comorbidities/significant medical history: Each comorbidity was measured as a dichotomous variable (yes/no). Participants self-reported the presence of “*chronic disease/s or reported taking medications for it/them*”, including diabetes, cancer, arthritis, and psychiatric problems.

Depression: A brief version of the Center for Epidemiological Studies-Depression (CES-D) scale was used for determining the depressive symptoms [2]. The scale comprises eight questions about the depressive symptoms experienced a week before the interview. A dichotomous variable (yes/no) was derived and a validated cut-off point of ≥ 3 depressive symptoms was termed as depression [3].

Body mass index: Anthropometric data (weight, height) were measured by the nurse. The bodyweight of study participants was determined through Tanita electronic scales, in the absence of shoes and light clothing. A Stadiometer with the Frankfort plane lying in the horizontal direction was used to measure the height. The formulae: [weight (kilograms)/height (metres) squared] was used for calculating body mass index (BMI). Respondents were classified as “underweight ($<18.5 \text{ kg/m}^2$)” or “obese ($\geq 30 \text{ kg/m}^2$)” based on their BMI [4].

Sarcopaenia: The handgrip strength (dominant/non-dominant hand) was determined through a Smedley handheld dynamometer (Stoelting, Illinois, USA). Individuals held the dynamometer perpendicular to their bodies and applied maximum force for a few seconds upon instruction. Participants were not included in the test in the presence of severe pain, swelling/inflammation or a recent injury or hand surgery in the past six months. Sarcopaenia was defined as handgrip $<27 \text{ kg}$ for males and $<16 \text{ kg}$ for females.

Systemic inflammation: C-reactive protein (CRP) was used as a biomarker of systemic inflammation, assessed in serum through the N-Latex high-sensitivity CRP mono-

immunoassay (Dade Behring, Illinois, USA) on a Behring Nephelometer II analyser, with a detection limit of 0.17 mg/L and a coefficient of variation <6% [5]. A CRP level of >3 mg/L was considered a mark of inflammation.

Anaemia: The blood samples were obtained to measure the biomarkers and stored at -80°C until the completion of analysis. Men with haemoglobin (Hb) < 140 g/L and women with Hb < 120 g/L were termed to have anaemia.

Disability: Self-reported limitations in the basic Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) were measured [6]. ADL comprises six activities i.e., getting in or out of bed, eating, dressing, using the toilet, moving around the room, bathing or showering. IADL comprises seven activities: preparation of hot meals, use of Google Maps to get around in a strange place, doing work around the house or garden, taking medications, shopping for household items, managing money and making calls on the telephone. A limitation in one or more of these activities was defined as a disability.

Smoking status: Smoking status was determined through interview and participants were classified as former smokers, current smokers or never smokers.

Physical activity: Individuals were inquired about their participation in physical activities at three levels: mild (e.g., home repairs, laundry, etc.), moderate (e.g., gardening, cleaning the car, moderate pace walking, etc.) and vigorous (e.g., running or jogging, aerobics or gym workouts, swimming or cycling, etc.). The options included: hardly ever/never, one to three times per month, once per week, more than once per week. Physical activity was further classified into four groups: none (no mild/moderate/vigorous activity per week); mild (no moderate/vigorous activity per week), moderate activity at least once per week; and vigorous activity at least once per week.

Family and social support: Social support (used as a dichotomous variable (yes/no)) received from partner/children/friends/relatives was determined through self-reported measurements. Participants who self-reported 'a lot' for three questions (*"How much respondent feels their spouse/partner understands their feelings"*; *"How much respondent can rely on spouse/partner if they have a serious problem"*; *"How much respondent can open up to their spouse/partner if they need to talk"*) or 'a lot' for two questions and 'some' for one, were regarded as having positive social support. Subsequently, four network types (partner/children/friends/relatives) were combined. High positive social support was termed as being supported in a minimum of one network type, whereas, low social support was termed as having no support from any type of network.

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Table S1A: Treatable traits associated with FEV₁ (litres) – multiple imputations – sensitivity analysis

Treatable traits	COPD			Non-COPD		
	Unadjusted	Model 1*	Model 2†	Unadjusted	Model 1‡	Model 2§
	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI
Airflow limitation	3.046, 2.825 to 3.268	2.979, 2.769 to 3.190	2.991, 2.783 to 3.198‡‡	1.821, 1.645 to 1.997	2.041, 1.853 to 2.229	2.041, 1.853 to 2.229‡‡
Chronic bronchitis	-0.243, -0.387 to -0.100	-0.164, -0.259 to -0.068	-0.0178, -0.276 to -0.81‡‡	-0.257, -0.412 to -0.103	-0.109, -0.210 to -0.008	-0.109, -0.210 to -0.009**
Chronic sputum production	-0.031, -0.144 to 0.082	---	---	-0.047, -0.126 to 0.032	---	---
Breathlessness	-0.264, -0.373 to -0.154	-0.080, -0.147 to -0.014	-0.094, -0.161 to -0.027††	-0.353, -0.400 to -0.306	-0.095, -0.122 to -0.068	-0.095, -0.121 to -0.069‡‡
Frequent chest Infections	-0.043, -0.188 to 0.103	---	---	-0.063, -0.131 to 0.006	-0.047, -0.086 to -0.008	-0.047, -0.086 to -0.008**
Osteoporosis	-0.383, -0.540 to -0.226	-0.053, -0.168 to 0.061	---	-0.492, -0.571 to -0.413	-0.005, -0.062 to 0.052	---
Cardiovascular disease	-0.026, -0.128 to 0.077	---	---	-0.107, -0.150 to -0.064	0.002, -0.022 to 0.026	---
Arthritis	-0.072, -0.180 to 0.035	---	---	-0.247, -0.294 to -0.200	0.035, 0.007 to 0.062	0.035, 0.007 to 0.062**
Diabetes	-0.135, -0.306 to 0.036	---	---	-0.141, -0.228 to -0.053	-0.073, -0.126 to -0.021	-0.073, -0.126 to -0.021††
Cancer	0.062, -0.153 to 0.276	---	---	-0.165, -0.245 to -0.084	0.005, -0.048 to 0.039	---
Psychiatric problems	0.196, -0.028 to 0.420	-0.091, -0.254 to 0.073	---	0.102, -0.010 to 0.214	0.011, -0.044 to 0.065	---
Depression	-0.150, -0.263 to -0.036	0.013, -0.083 to 0.057	---	-0.231, -0.285 to -0.178	-0.000, -0.027 to 0.028	---
Underweight	-0.667, -0.944 to -0.389	-0.152, -0.331 to 0.026	-0.175, -0.341 to -0.008**	-0.171, -0.437 to 0.094	---	---
Obesity	-0.052, -0.163 to 0.059	---	---	-0.140, -0.190 to -0.091	-0.119, -0.151 to -0.087	-0.119, -0.150 to -0.087‡‡
Sarcopaenia	-0.400, -0.535 to -0.265	-0.134, -0.229 to -0.039	-0.160, -0.253 to -0.068††	-0.556, -0.634 to -0.478	-0.101, -0.144 to -0.057	-0.100, -0.144 to -0.057‡‡
Systemic inflammation	-0.088, -0.218 to 0.042	---	---	-0.268, -0.314 to -0.223	-0.071, -0.101 to -0.042	-0.071, -0.101 to -0.042‡‡
Anaemia	-0.003, -0.178 to 0.172	---	---	0.049, -0.034 to 0.133	---	---
Disability	-0.244, -0.344 to -0.143	-0.035, -0.095 to 0.026	---	-0.277, -0.318 to -0.235	-0.037, -0.060 to -0.014	-0.037, -0.060 to -0.014††
Current smoking	-0.092, -0.201 to 0.017	-0.227, -0.301 to -0.153	-0.237, -0.311 to -0.163‡‡	-0.213, -0.280 to -0.145	-0.186, -0.230 to -0.142	-0.186, -0.230 to -0.142‡‡
Physical inactivity	-0.273, -0.448 to -0.097	-0.074, -0.177 to 0.030	---	-0.344, -0.440 to -0.248	-0.086, -0.140 to -0.031	-0.086, -0.140 to -0.031††
Poor family and social support	0.078, -0.046 to 0.203	---	---	0.019, -0.042 to 0.079	---	---

* Adjusted for sex, age, marital status, socioeconomic class and treatable traits (p <0.1) from the univariate analysis; † Adjusted for sex, age and treatable traits (p <0.1) from the multivariate analysis; ‡ Adjusted for sex, age, marital status, ethnicity, socioeconomic class and treatable traits (p <0.1) from the univariate analysis; § Adjusted for sex, age, marital status, ethnicity, socioeconomic class and treatable traits (p <0.1) from the multivariate analysis. ** = p<0.05; †† = p<0.01; ‡‡ = p<0.001

Table S1B: Treatable traits associated with FEV₁ (litres) – excluding patients with airflow limitation and chronic bronchitis – sensitivity analysis for the non-COPD/control group

Treatable traits	COPD			Non-COPD		
	Unadjusted	Model 1*	Model 2†	Unadjusted	Model 1‡	Model 2§
	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI
Airflow limitation	3.046, 2.825 to 3.268	2.957, 2.736 to 3.178	2.976, 2.760 to 3.193^{‡‡}	---	---	---
Chronic bronchitis	-0.243, -0.387 to -0.100	-0.172, -0.273 to -0.070	-0.186, -0.290 to -0.082^{‡‡}	---	---	---
Chronic sputum production	-0.031, -0.144 to 0.082	---	---	-0.082, -0.165 to 0.001	-0.042, -0.096 to 0.011	---
Breathlessness	-0.304, -0.416 to -0.192	-0.076, -0.147 to -0.005	-0.093, -0.164 to -0.022^{**}	-0.434, -0.481 to -0.386	-0.088, -0.121 to -0.056	-0.093, -0.125 to -0.061^{‡‡}
Frequent chest Infections	-0.043, -0.188 to 0.103	---	---	-0.060, -0.133 to 0.012	---	---
Osteoporosis	-0.383, -0.540 to -0.226	-0.056, -0.182 to 0.069	---	-0.511, -0.591 to -0.430	0.059, -0.018 to 0.137	---
Cardiovascular disease	-0.024, -0.129 to 0.080	---	---	-0.128, -0.174 to -0.083	0.014, -0.016 to 0.045	---
Arthritis	-0.072, -0.180 to 0.035	---	---	-0.262, -0.311 to -0.213	0.033, 0.001 to 0.065	0.029, 0.003 to 0.061
Diabetes	-0.135, -0.306 to 0.036	---	---	-0.142, -0.234 to -0.051	-0.081, -0.151 to -0.011	-0.081, -0.150 to -0.012^{**}
Cancer	0.062, -0.153 to 0.276	---	---	-0.170, -0.254 to -0.086	-0.032, -0.090 to 0.027	---
Psychiatric problems	0.196, -0.028 to 0.420	-0.066, -0.240 to 0.107	---	0.090, -0.034 to 0.215	---	---
Depression	-0.149, -0.263 to -0.036	0.007, -0.066 to 0.080	---	-0.253, -0.307 to -0.198	-0.027, -0.057 to 0.004	-0.024, -0.053 to 0.005
Underweight	-0.682, -0.947 to -0.417	-0.207, -0.370 to -0.043	-0.216, -0.373 to -0.058^{††}	-0.295, -0.562 to 0.028	-0.047, -0.221 to 0.128	---
Obesity	-0.051, -0.162 to 0.060	---	---	-0.192, -0.244 to -0.141	-0.101, -0.135 to -0.066	-0.098, -0.131 to -0.066^{‡‡}
Sarcopaenia	-0.402, -0.537 to -0.267	-0.137, -0.240 to -0.034	-0.162, -0.262 to -0.061^{††}	-0.546, -0.626 to -0.465	-0.119, -0.173 to -0.064	-0.103, -0.153 to -0.052^{‡‡}
Systemic inflammation	-0.061, -0.171 to 0.050	---	---	-0.287, -0.340 to -0.243	-0.080, -0.111 to -0.050	-0.082, -0.112 to -0.053^{‡‡}
Anaemia	-0.001, -0.167 to 0.170	---	---	0.050, -0.043 to 0.144	---	---
Disability	-0.244, -0.344 to -0.143	-0.038, -0.100 to 0.024	---	-0.291, -0.334 to -0.248	-0.002, -0.028 to 0.025	---
Current smoking	-0.092, -0.201 to 0.017	-0.218, -0.294 to -0.142	-0.228, -0.304 to -0.153^{‡‡}	-0.142, -0.218 to -0.067	-0.179, -0.238 to -0.119	-0.192, -0.247 to -0.136^{‡‡}
Physical inactivity	-0.273, -0.448 to -0.097	-0.085, -0.197 to 0.026	---	-0.323, -0.427 to -0.219	-0.093, -0.169 to -0.018	-0.085, -0.154 to -0.015^{**}
Poor family and social support	0.093, -0.034 to 0.220	---	---	0.020, -0.044 to 0.084	---	---

*Adjusted for sex, age, marital status, socioeconomic class and treatable traits (p <0.1) from the univariate analyses; †Adjusted for sex, age and treatable traits (p <0.1) from the multivariate analyses; ‡Adjusted for sex, age, marital status, ethnicity, socioeconomic class and treatable traits (p <0.1) from the univariate analyses; §Adjusted for sex, age, marital status, ethnicity, socioeconomic class and treatable traits (p <0.1) from the multivariate analyses. ** = p<0.05; †† = p<0.01; ‡‡ = p<0.001

Table S2A: Treatable traits associated with FEV₁% predicted – Complete case analysis

Treatable traits	COPD			Non-COPD		
	Unadjusted	Model 1*	Model 2†	Unadjusted	Model 1‡	Model 2§
	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI
Airflow limitation	114.17, 107.80 to 120.55	110.38, 103.59 to 117.18	110.88, 104.44 to 117.31‡‡	70.02, 64.58– 75.46	74.39, 67.40 to 81.39	73.23, 66.33 to 80.14‡‡
Chronic bronchitis	-12.69, -17.02 to -8.37	-6.40, -9.95 to -2.85	-6.73, -10.09 to -3.36‡‡	-10.58, -14.80 to -6.36	-4.63, -8.48 to -0.79	-4.25, -8.01 to -0.50**
Chronic sputum production	-4.24, -7.79 to -0.69	-2.22, -4.78 to 0.34	-1.83, -4.35 to 0.69	-1.34, -3.40 to 0.72	---	---
Breathlessness	-4.37, -7.81 to -0.92	-1.63, -4.15 to 0.89	---	-4.82, -6.01 to -3.64	-4.23, -5.48 to -2.98	-4.40, -5.59 to -3.20‡‡
Frequent chest infections	-2.51, -6.96 to 1.95	---	---	-2.34, -4.16 to -0.52	-0.83, -2.65 to 0.99	---
Osteoporosis	-5.20, -10.83 to 0.44	-1.90, -6.73 to 2.93	---	-2.28, -4.83 to 0.27	1.11, -1.85 to 4.06	---
Cardiovascular disease	-0.80, -4.13 to 2.53	---	---	-1.23, -2.29 to -0.16	0.32, -0.79 to 1.44	---
Arthritis	1.88, -1.47 to 5.23	---	---	0.08, -1.06 to 1.23	---	---
Diabetes	-4.58, -9.66 to 0.51	-5.72, -9.89 to -1.56	-5.84, -9.89 to -1.80††	-5.17, -7.25 to -3.09	-3.30, -5.35 to -1.25	-3.38, -5.36 to -1.39††
Cancer	2.77, -3.90 to 9.44	---	---	-2.31, -4.51 to -0.12	0.44, -1.92 to 2.79	---
Psychiatric problems	4.44, -2.86 to 11.74	---	---	1.09, -1.48 to 3.67	---	---
Depression	-1.38, -5.05 to 2.29	---	---	-2.80, -4.12 to -1.49	-1.11, -2.40 to 0.18	-1.10, -2.35 to 0.15
Underweight	-25.25, -35.33 to -15.18	-5.92, -12.43 to 0.59	-6.87, -12.72 to -1.01**	3.71, -5.96 to 13.37	---	---
Obesity	-0.20, -3.76 to 3.36	---	---	-2.89, -4.10 to -1.68	-2.13, -3.44 to -0.82	-2.14, -3.44 to -0.85††
Sarcopaenia	-7.30, -11.82 to -2.78	-4.84, -8.63 to -1.06	-5.98, -9.63 to -2.34††	-5.65, -8.14 to -3.16	-2.93, -5.38 to -0.48	-2.96, -5.30 to -0.62**
Systemic inflammation	-2.24, -5.82 to 1.34	---	---	-5.67, -6.99 to -4.35	-2.98, -4.20 to -1.76	-3.24, -4.40 to -2.08‡‡
Anaemia	-2.41, -7.48 to 2.66	---	---	-1.85, -3.88 to 0.17	-1.52, -3.28 to 0.25	-1.40, -3.12 to 0.33
Disability	-4.69, -7.93 to -1.46	-1.20, -3.48 to 1.09	---	-3.05, -4.12 to -1.99	-0.60, -1.67 to 0.48	---
Current smoking	-8.76, -12.05 to -5.46	-7.77, -10.27 to -5.27	-7.94, -10.41 to -5.46‡‡	-10.82, -12.49 to -9.15	-6.94, -8.75 to -5.12	-7.35, -9.07 to -5.62‡‡
Physical inactivity	-7.80, -13.36 to -2.25	-3.08, -7.33 to 1.18	-4.60, -9.94 to 0.74	-7.64, -10.43 to -4.86	-2.95, -5.78 to 0.12	-2.78, -5.47 to -0.08**
Poor family and social support	3.03, -1.22 to 7.28	---	---	-0.39, -1.76 to 0.98	---	---

*Adjusted for marital status and treatable traits (p <0.1) from the univariate analyses; †Adjusted for treatable traits (p <0.1) from the multivariate analyses; ‡Adjusted for age, marital status, ethnicity, socioeconomic class and treatable traits (p <0.1) from the univariate analyses; §Adjusted for marital status, ethnicity, age and treatable traits (p <0.1) from the multivariate analyses. ** = p<0.05; †† = p<0.01; ‡‡ = p<0.001

Table S2B: Treatable traits associated with FEV₁% predicted – multiple imputations – sensitivity analysis

Treatable traits	COPD			Non-COPD		
	Unadjusted	Model 1*	Model 2†	Unadjusted	Model 1‡	Model 2§
	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI
Airflow limitation	114.17, 107.80 to 120.55	110.87, 104.35 to 117.39	111.24, 104.86 to 117.62‡‡	70.02, 64.58 to 75.46	74.31, -68.49 to 80.12	74.15, 68.34 to 79.97‡‡
Chronic bronchitis	-12.69, -17.02 to -8.37	-6.09, -9.43 to -2.76	-7.32, -10.64 to -3.99 ‡‡	-10.58, -14.80 to -6.36	-5.69, -9.15 to -2.22	-5.82, -9.29 to -2.35††
Chronic sputum production	-4.23, -7.78 to -0.68	-1.55, -4.06 to 0.95	---	-1.38, -3.46 to 0.70	---	---
Breathlessness	-3.66, -7.04 to -0.27	-1.89, -4.32 to 0.53	---	-4.82, -6.03 to -3.62	-3.60, -4.61 to -2.59	-3.66, -4.66 to -2.66‡‡
Frequent chest infections	-2.51, -6.96 to 1.95	---	---	-2.34, -4.16 to -0.52	-1.57, -3.01 to -0.13	-1.67, -3.11 to 0.23**
Osteoporosis	-5.20, -10.83 to 0.44	-1.78, -6.41 to 2.84	---	-2.28, -4.83 to 0.27	-1.01, -3.27 to 1.24	---
Cardiovascular disease	-0.68, -3.89 to 2.53	---	---	-1.16, -2.20 to -0.13	-0.15, -1.04 to 0.73	---
Arthritis	1.88, -1.47 to 5.23	---	---	0.09, -1.04 to 1.24	---	---
Diabetes	-4.58, -9.66 to 0.51	-5.46, -9.49 to -1.42	-5.69, -9.67 to -1.70 ††	-5.17, -7.25 to -3.09	-3.62, -5.35 to -1.88	-3.69, -5.42 to -1.95‡‡
Cancer	2.77, -3.90 to 9.44	---	---	-2.31, -4.51 to -0.12	-0.16, -1.88 to 1.56	---
Psychiatric problems	4.44, -2.86 to 11.74	---	---	1.09, -1.48 to 3.67	---	---
Depression	-1.42, -5.09 to 2.25	---	---	-2.81, -4.13 to -1.50	-0.25, -1.30 to 0.79	---
Underweight	-24.43, -35.99 to -12.88	-5.31, -12.30 to 1.69	---	1.97, -8.53 to 12.46	---	---
Obesity	-0.22, -3.79 to 3.35	---	---	-2.92, -4.14 to -1.71	-2.65, -3.80 to -1.50	-2.80, -3.94 to -1.66‡‡
Sarcopaenia	-7.15, -11.62 to -2.68	-4.99, -8.66 to -1.31	-6.16, -9.81 to -2.51††	-5.76, -8.24 to -3.29	-2.97, -4.89 to -1.05	-2.93, -4.79 to -1.06††
Systemic inflammation	-2.92, -6.78 to 0.93	---	---	-5.58, -6.78 to -4.37	-2.76, -3.88 to -1.64	-2.79, -3.91 to -1.66‡‡
Anaemia	-2.80, -8.46 to 2.87	---	---	-1.59, -3.41 to 0.22	-0.54, -1.95 to 0.86	---
Disability	-4.69, -7.93 to -1.46	-1.29, -3.55 to 0.97	---	-3.05, -4.12 to -1.99	-0.99, -1.83 to -0.15	-1.09, -1.91 to -0.26**
Current smoking	-8.76, -12.05 to -5.46	-8.25, -10.71 to -5.79	-8.53, -11.00 to -6.06 ‡‡	-10.82, -12.49 to -9.15	-6.54, -8.01 to -5.06	-6.90, -8.34 to -5.46‡‡
Physical inactivity	-7.80, -13.36 to -2.25	-3.15, -7.27 to 0.97	---	-7.64, -10.43 to -4.86	-2.89, -4.93 to -0.86	-2.90, -4.93 to -0.86††
Poor family and social support	2.50, -1.60 to 6.61	---	---	-0.42, -1.77 to 0.93	---	---

* Adjusted for marital status and treatable traits (p <0.1) from the univariate analysis; † Adjusted for treatable traits (p <0.1) from the multivariate analysis; ‡ Adjusted for age, marital status, ethnicity, socioeconomic class and treatable traits (p <0.1) from the univariate analysis; § Adjusted for marital status, ethnicity and treatable traits (p <0.1) from the multivariate analysis. ** = p<0.05; †† = p<0.01; ‡‡ = p<0.001

Table S2C: Treatable traits associated with FEV₁% predicted – excluding patients with airflow limitation and chronic bronchitis – sensitivity analysis for the non-COPD/control group

Treatable traits	COPD			Non-COPD		
	Unadjusted	Model 1*	Model 2†	Unadjusted	Model 1‡	Model 2§
	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI
Airflow limitation	114.17, 107.80 to 120.55	110.38, 103.59 to 117.18	110.88, 104.44 to 117.31‡‡	---	---	---
Chronic bronchitis	-12.69, -17.02 to -8.37	-6.40, -9.95 to -2.85	-6.73, -10.09 to -3.36‡‡	---	---	---
Chronic sputum production	-4.24, -7.79 to -0.69	-2.22, -4.78 to 0.34	-1.83, -4.35 to 0.69	-2.55, -4.67 to 0.43	-1.07, -3.08 to 0.94	---
Breathlessness	-4.37, -7.81 to -0.92	-1.63, -4.15 to 0.89	---	-7.03, -8.20 to -5.86	-3.67, -4.87 to -2.47	-3.94, -5.07 to -2.80‡‡
Frequent chest infections	-2.51, -6.96 to 1.95	---	---	-1.91, -3.70 to -0.13	-0.24, -2.16 to 1.67	---
Osteoporosis	-5.20, -10.83 to 0.44	-1.90, -6.73 to 2.93	---	-2.22, -4.80 to 0.36	1.82, -1.14 to 4.77	---
Cardiovascular disease	-0.80, -4.13 to 2.53	---	---	-1.80, -2.81 to -0.79	0.51, -0.60 to 1.63	---
Arthritis	1.88, -1.47 to 5.23	---	---	0.39, -1.51 to 0.73	---	---
Diabetes	-4.58, -9.66 to 0.51	-5.72, -9.89 to -1.56	-5.84, -9.89 to -1.80††	-5.28, -7.31 to -3.24	-2.98, -5.21 to -0.75	-3.17, -5.32 to -1.01††
Cancer	2.77, -3.90 to 9.44	---	---	-2.62, -4.80 to -0.44	0.47, -2.89 to 1.95	---
Psychiatric problems	4.44, -2.86 to 11.74	---	---	0.45, -2.19 to 3.09	---	---
Depression	-1.38, -5.05 to 2.29	---	---	-2.58, -4.84 to -2.32	-1.30, -2.53 to -0.08	-1.29, -2.43 to -0.15 **
Underweight	-25.25, -35.33 to -15.18	-5.92, -12.43 to 0.59	-6.87, -12.72 to -1.01**	-0.52, -7.61 to 6.57	---	---
Obesity	-0.20, -3.76 to 3.36	---	---	-4.47, -5.65 to -3.29	-2.01, -3.38 to -0.64	-1.84, -3.11 to -0.57††
Sarcopaenia	-7.30, -11.82 to -2.78	-4.84, -8.63 to -1.06	-5.98, -9.63 to -2.34††	-5.11, -7.55 to -2.66	-2.59, -4.96 to -0.22	-2.20, -4.37 to -0.03 **
Systemic inflammation	-2.24, -5.82 to 1.34	---	---	-5.75, -7.03 to -4.46	-3.07, -4.24 to -1.90	-3.29, -4.38 to -2.19‡‡
Anaemia	-2.41, -7.48 to 2.66	---	---	-1.82, -3.86 to 0.23	-1.36, -3.10 to 0.39	---
Disability	-4.69, -7.93 to -1.46	-1.20, -3.48 to 1.09	---	-3.61, -4.64 to -2.58	-0.01, -0.99 to 1.03	---
Current smoking	-8.76, -12.05 to -5.46	-7.77, -10.27 to -5.27	-7.94, -10.41 to -5.46‡‡	-8.41, -10.10 to -6.71	-6.88, -8.88 to -4.88	-6.90, -8.72 to -5.09‡‡
Physical inactivity	-7.80, -13.36 to -2.25	-3.08, -7.33 to 1.18	-4.60, -9.94 to 0.74	-7.20, -10.06 to -4.35	-2.60, -5.43 to 0.22	-2.27, -4.88 to 0.33
Poor family and social support	3.03, -1.22 to 7.28	---	---	-0.16, -1.44 to 1.12	---	---

*Adjusted for marital status and treatable traits (p <0.1) from the univariate analyses; †Adjusted for treatable traits (p <0.1) from the multivariate analyses; ‡Adjusted for marital status, ethnicity, socioeconomic class and treatable traits (p <0.1) from the univariate analyses; §Adjusted for marital status and treatable traits (p <0.1) from the multivariate analyses. ** = p<0.05; †† = p<0.01; ‡‡ = p<0.001

Table S3A: Treatable traits associated with quality of life – multiple imputations – sensitivity analysis

Treatable traits	COPD			Non-COPD		
	Unadjusted	Model 1*	Model 2†	Unadjusted	Model 1‡	Model 2§
	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI
Airflow limitation	-3.30, -7.35 to 1.29	---	---	-4.01, -5.83 to -2.18	-1.16, -2.75 to 0.43	---
Chronic bronchitis	-3.23, -5.27 to -1.19	-1.25, -2.84 to 0.34	---	-3.98, -5.90 to -2.06	-0.54, -2.03 to 0.95	---
Chronic sputum production	-2.11, -3.48 to -0.73	-1.02, -2.16 to 0.13	-1.43, -2.57 to -0.30**	-4.07, -5.06 to -3.08	-1.34, -2.16 to -0.53	-1.43, -2.24 to -0.63
Breathlessness	-3.34, -4.64 to -2.04	-1.46, -2.51 to -0.41	-1.77, -2.84 to -0.70††	-4.54, -5.25 to -3.83	-1.69, -2.32 to -1.07	-1.73, -2.31 to -1.14
Frequent chest infections	-2.06, -4.14 to 0.03	-0.95, -2.54 to 0.64	---	-0.70, -1.55 to 0.16	---	---
Osteoporosis	-1.67, -4.38 to 1.03	---	---	-2.88, -3.96 to -1.80	-1.17, -2.03 to -0.32	-1.17, -2.04 to -0.31
Cardiovascular disease	-2.30, -3.63 to -0.98	-1.22, -2.41 to -0.02	-1.54, -2.65 to -0.43††	-2.04, -2.48 to -1.60	-1.35, -1.70 to -1.00	-1.38, -1.73 to -1.03
Arthritis	-3.51, -4.84 to -2.18	-1.36, -2.59 to -0.13	-1.45, -2.68 to -0.22**	-3.17, -3.68 to -2.66	-1.47, -1.87 to -1.07	-1.47, -1.88 to -1.06
Diabetes	-2.76, -4.72 to -0.80	-1.06, -2.71 to 0.59	---	-2.44, -3.33 to -1.54	-0.81, -1.52 to -0.10	-0.89, -1.61 to -0.16
Cancer	-0.58, -3.40 to 2.25	---	---	-0.30, -1.28 to 0.69	---	---
Psychiatric problems	0.20, -2.48 to 2.88	---	---	0.22, -0.77 to 1.22	---	---
Depression	-8.11, -9.62 to -6.61	-6.31, -7.67 to -4.95	-6.51, -7.90 to -5.12‡‡	-8.73, -9.36 to -8.10	-5.69, -6.26 to -5.13	-5.69, -6.25 to -5.12
Underweight	-1.77, -6.80 to 3.26	---	---	-0.24, -3.59 to 3.10	---	---
Obesity	-0.22, -1.69 to 1.25	---	---	-1.89, -2.46 to -1.32	-0.65, -1.22 to -0.09	-0.61, -1.13 to -0.09
Sarcopaenia	-3.00, -4.75 to -1.25	-0.74, -2.46 to 0.98	---	-4.46, -5.45 to -3.48	-1.39, -2.30 to -0.48	-1.43, -2.35 to -0.52
Systemic inflammation	-0.70, -1.93 to 0.52	---	---	-1.20, -1.75 to -0.64	0.16, -0.35 to 0.67	---
Anaemia	-2.83, -4.64 to -1.02	-1.23, -2.83 to 0.38	---	-1.52, -2.51 to -0.52	-0.68, -1.54 to 0.19	---
Disability	-3.61, -4.70 to -2.51	-1.30, -2.35 to -0.26	-1.40, -2.41 to -0.39††	-4.10, -4.57 to -3.62	-0.85, -1.24 to -0.46	-0.84, -1.23 to -0.45
Current smoking	-1.39, -2.71 to -0.06	-1.43, -2.54 to -0.32	-1.63, -2.73 to -0.54††	-2.69, -3.45 to -1.93	-2.02, -2.64 to -1.40	-1.93, -2.55 to -1.32
Physical inactivity	-4.25, -6.43 to -2.07	-0.85, -2.85 to 1.14	---	-4.87, -6.00 to -3.74	-1.75, -2.68 to -0.82	-1.76, -2.69 to -0.83
Poor family and social support	-5.52, -7.42 to -3.61	-4.73, -6.38 to -3.09	-4.70, -6.34 to -3.06‡‡	-5.68, -6.37 to -5.00	-4.03, -4.56 to -3.50	-4.00, -4.54 to -3.47

* Adjusted for age, marital status, socioeconomic class and treatable traits ($p < 0.1$) from the univariate analysis; † Adjusted for age and treatable traits ($p < 0.1$) from the multivariate analysis; ‡ Adjusted for age, marital status, ethnicity, socioeconomic class and treatable traits ($p < 0.1$) from the univariate analysis; § Adjusted for age, socioeconomic class and treatable traits ($p < 0.1$) from the multivariate analysis. ** = $p < 0.05$; †† = $p < 0.01$; ‡‡ = $p < 0.001$

Table S3B: Treatable traits associated with quality of life – excluding patients with airflow limitation and chronic bronchitis – sensitivity analysis for the non-COPD/control group

Treatable traits	COPD			Non-COPD		
	Unadjusted	Model 1*	Model 2†	Unadjusted	Model 1‡	Model 2§
	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI	β , 95%CI
Airflow limitation	-3.63, -8.17 to 0.91	---	---	---	---	---
Chronic bronchitis	-3.28, -5.46 to -1.09	-2.81, -4.67 to -0.95	-2.87, -4.65 to -1.08^{††}	---	---	---
Chronic sputum production	-2.10, -3.49 to -0.72	-0.96, -2.35 to 0.43	---	-3.67, -4.69 to -2.65	-0.96, -1.91 to 0.02	-1.00, -1.96 to -0.05^{**}
Breathlessness	-3.64, -4.91 to -2.38	-0.76, -2.03 to 0.50	---	-4.50, -5.11 to -3.89	-1.86, -2.44 to -1.28	-1.82, -2.40 to -1.25^{‡‡}
Frequent chest infections	-2.10, -4.43 to 0.23	-1.25, -3.13 to 0.63	---	-0.77, -1.67 to 0.13	-0.33, -1.16 to 0.51	---
Osteoporosis	-0.83, -2.86 to 1.20	---	---	-2.46, -3.59 to -1.32	-1.68, -2.81 to -0.55	-1.67, -2.79 to -0.55^{††}
Cardiovascular disease	-2.62, -3.93 to -1.31	-1.34, -2.60 to -0.08	-1.69, -2.90 to -0.48^{††}	-2.08, -2.60 to -1.57	-1.08, -1.53 to -0.63	-1.08, -1.53 to -0.63^{‡‡}
Arthritis	-3.52, -4.80 to -2.23	-1.41, -2.67 to -0.15	-1.52, -2.76 to -0.28^{**}	-3.16, -3.70 to -2.63	-1.44, -1.92 to -0.97	-1.43, -1.90 to -0.95^{‡‡}
Diabetes	-3.56, -5.42 to -1.69	-1.40, -3.17 to 0.37	---	-2.83, -3.86 to -1.80	-0.91, -1.83 to 0.01	-0.91, -1.83 to 0.01
Cancer	-1.40, -4.26 to 1.47	---	---	-0.39, -1.45 to 0.68	---	---
Psychiatric problems	-0.68, -3.23 to 1.88	---	---	-0.24, -1.33 to 0.85	---	---
Depression	-7.88, -9.38 to -6.38	-7.08, -8.73 to -5.44	-7.19, -8.81 to -5.57^{††}	-8.63, -9.36 to -7.90	-5.96, -6.67 to -5.25	-5.89, -6.59 to -5.18^{‡‡}
Underweight	-0.71, -3.51 to 2.10	---	---	0.32, -3.88 to 4.51	---	---
Obesity	-0.27, -1.70 to 1.16	---	---	-1.90, -2.49 to -1.31	-0.54, -1.09 to -0.00	-0.44, -0.97 to 0.09
Sarcopaenia	-3.35, -5.16 to -1.54	-1.32, -3.49 to 0.84	---	-3.87, -4.95 to -2.80	-0.97, -2.03 to -0.08	-0.97, -2.02 to 0.09
Systemic inflammation	-0.93, -2.43 to 0.57	---	---	-1.03, -1.66 to -0.41	0.22, -0.28 to 0.72	---
Anaemia	-3.15, -5.55 to -0.75	-2.61, -4.42 to -0.79	-3.28, -5.06 to -1.49^{††}	-1.43, -2.40 to -0.46	-1.11, -1.87 to -0.35	-1.10, -1.85 to -0.35^{††}
Disability	-3.81, -4.95 to -2.67	-2.30, -3.59 to -1.01	-2.83, -4.06 to -1.60^{††}	-4.08, -4.59 to -3.58	-0.83, -1.30 to -0.36	-0.79, -1.26 to -0.33^{††}
Current smoking	-1.44, -2.82 to -0.05	-1.31, -2.66 to 0.04	-1.12, -2.40 to 0.17	-2.87, -3.82 to -1.93	-2.36, -3.27 to -1.44	-2.31, -3.22 to -1.40^{‡‡}
Physical inactivity	-3.47, -5.48 to -1.46	1.35, -0.68 to 3.37	---	-4.53, -5.87 to -3.19	-1.18, -2.32 to -0.05	-1.18, -2.29 to -0.07^{**}
Poor family and social support	-5.44, -7.05 to -3.83	-5.25, -6.82 to -3.68	-5.12, -6.65 to -3.59^{††}	-5.72, -6.49 to -4.94	-3.70, -4.40 to -2.99	-3.65, -4.35 to -2.95^{‡‡}

*Adjusted for age, marital status, socioeconomic class and treatable traits (p <0.1) from the univariate analyses; †Adjusted for socioeconomic class and treatable traits (p <0.1) from the multivariate analyses; ‡Adjusted for age, marital status, socioeconomic class and treatable traits (p <0.1) from the univariate analyses; §Adjusted for age, socioeconomic class and treatable traits (p <0.1) from the multivariate analyses. ** = p<0.05; †† = p<0.01; ‡‡ = p<0.001