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Early View

Original article

REINVENT: International Survey on REstrictive thoracic diseases IN long term home noninvasive VENTilation

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Please cite this article as: Pierucci P, Crimi C, Carlucci A, *et al*. REINVENT: International Survey on REstrictive thoracic diseases IN long term home noninvasive VENTilation. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00911-2020).

TITLE PAGE

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REINVENT: International Survey on REstrictive thoracic diseases IN long term home noninvasive VENTilation

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Key words: Noninvasive ventilation, chronic respiratory failure, restrictive thoracic disease, neuromuscular disease, chest wall disorders, international survey.

Abstract:

Background and aim: Little is known about the current use of long-term home non-invasive ventilation (LTHNIV) in restrictive thoracic diseases (RTD), including chest wall and neuromuscular disorders (CWD, NMD). This study aimed to capture the pattern of LTHNIV in RTD patients via a web-based international survey.

Methods: The survey involved ERS Assembly 2.02 (NIV dedicated group) October-December 2019.

Results: 166/748 (22.2%) members from 41 countries responded; 80% were physicians, of whom 43% worked in a respiratory intermediate intensive care unit (RIICU). The NMD:CWD ratio was 5:1, Amyotrophic lateral sclerosis (ALS) being the most frequent indication within NMD (78%). The main reason to initiate LTHNIV was diurnal hypercapnia (71%). Quality of life/sleep was the most important goal to achieve. In 25% of cases, clinicians based their choice of the ventilator on patients’ feedback. Among NIV-modes, pressure support ventilation spontaneous-timed (PSV-ST) was the most frequently prescribed for day and night-time. Mouthpieces were the preferred daytime NIV interface, whereas oro-nasal masks the first choice overnight. Heated humidification was frequently added to LTHNIV (72%). Single-limb circuits with intentional leaks (79%) were the most frequently prescribed. Follow-up was most often provided in an outpatient setting.

Conclusions: This ERS survey illustrates physicians' practices of LTHNIV in RTD patients. NMD and, specifically, ALS were the main indications for LTHNIV. NIV was started mostly because of diurnal hypoventilation with a primary goal of patient-centred benefits. Bi-level PSV-ST and oro-nasal masks were more likely to be chosen for providing NIV. LTHNIV efficacy was assessed mainly in an outpatient setting.

Short title: REINVENT international survey of NIV in RTD

Introduction

In the mid 1980's, non-invasive ventilation (NIV) became the reference treatment for chronic respiratory failure (CRF). This allowed a drastic decrease in invasive ventilation (tracheostomy), while improving survival, quality of sleep and quality of life (QoL) in patients with both obstructive and restrictive thoracic disorders (RTD)[1-4]. Over the last decades, the management of home NIV has changed dramatically. [5-7]

Published data support the use of NIV in RTD patients and have shown its clinical and physiological benefits. Long term NIV increases the likelihood of prolonged survival and thus most often allows avoiding tracheostomy and home invasive mechanical ventilation. Except for a few RCT in Amyotrophic lateral sclerosis (ALS)[8], the positive impact of NIV in RTD is based mainly on observational uncontrolled studies. Survey-based findings represent a valuable alternative source of data. They can reliably describe the practices of clinicians in different domains of medicine, such as home non-invasive ventilation.

In 2005, the Eurovent survey provided a comprehensive picture of practices regarding home mechanical ventilation (HMV) in patients with CRF across 16 European countries. [9] For the first time, it identified patterns of use and settings of HMV across Europe. This study helped many physicians to confront their clinical practice to the information gathered.

Since the Eurovent survey, there has been no follow-up study of the use of NIV in patients affected by RTD across Europe. Indeed, there is an evident gap in the literature on this topic. Updating information on settings, interfaces and modalities of NIV use in Europe (i.e. mouthpiece ventilation) is necessary and warranted.[10-14] To the best of our knowledge, only a few studies in the literature tried to assess settings and current NIV practices in RTD [7, 15-19].

We therefore performed an international survey to collect NIV users' experience and report the current clinical real-world practices for REstrictive disorders IN long term home noninvasive VENTilation: REINVENT.

Material and methods

Survey development

This web-based survey was developed using Survey-Monkey, an online platform with a cloud-based survey development application.

The ideated survey was then conducted to explore physicians' clinical management of long-term NIV in the treatment of CRF due to RTD. For the purpose of the survey, "long-term home, non-invasive ventilation" (LTHNIV) included only patients with RTD as defined hereafter Respiratory diseases included were: chest-wall deformity (CWD), neuromuscular diseases (NMD), spinal cord injury, phrenic nerve paralysis, fibrothorax-post TB, and thoracoplasty. We excluded patients with obesity hypoventilation syndrome (OHS) or parenchymal restrictive lung diseases (RLD). A list of illnesses included was provided on the first page of the survey with a brief explanation of the aim of our research.

The survey was developed based on previous work, exploring physicians' perceptions as to use of NIV [20-22]. The survey instrument was designed after a thorough literature review to generate relevant survey items. A panel of ERS experts on NIV, part of the Steering Committee of the project, reviewed the survey items for content validity, relevance, and ability to discriminate among respondents. The ERS management group then revised the survey by adding further details based on previous proposed survey studies. The final survey questionnaire included various formats such as Likert scales, ranking, and yes/no, but did not allow for open-ended questions.

The survey consisted of three parts. The first part included general questions about the participants' professional status, general characteristics, experience with LTHNIV in the treatment of RTD and the type of RTD most often encountered in their hospital practice. The second part was mainly centred on reasons for NIV initiation, clinical benefits expected, and characteristics of ventilators used: pre-set modes, circuits, interfaces, and humidification. Ventilation pre-set modes were defined as follows: mouthpiece ventilation (MPV), spontaneous pressure support ventilation (S-PSV), spontaneous-timed PSV (ST-PSV), PSV with target volume (TV-PSV), pressure controlled ventilation (PCV), continuous positive airway pressure (CPAP), volume controlled ventilation (VCV). The third and last part was referred to as “timing and type of follow-up”. The full survey is in the supplement material.

Survey testing

We administered the survey to 10 respondents, including pulmonologists and critical care physicians, to test the comprehensiveness, clarity, and validity. We estimated interrater reliability using Cohen's kappa test with a threshold value above 0.4 (i.e. moderate agreement).

Survey administration

To identify clinicians interested and involved in NIV practices, we contacted the members of ERS assembly 2, Group 2.02. This group is a heterogeneous, multidisciplinary and multi-professional group, incorporating physicians with different educational backgrounds, such as pulmonology, anaesthesiology, internal medicine, intensive care medicine and emergency medicine, as well as allied healthcare professions (nurses and physiotherapists). These professional figures participate together in this group based on their common interests and expertise in NIV practice.

Email notifications with a link to a web-based questionnaire were sent in September 2019 to all the 748 members of ERS Assembly 2, Group 2.02. Reminders were sent every four weeks. The survey was closed in December 2019.

Data entry and analysis

We reported descriptive statistics, including proportions, means, and standard deviation (SD) or median and interquartile range (IQR), when appropriate.

The respondents were grouped based on the type of ward in which they principally worked: 1) critical care (emergency department, ICU, pulmonary ward + high dependency unit), and 2) general (pulmonary ward & general ward vs. rehab, private practice, outpatient clinic) to allow comparisons. Contingency tables were computed, and proportions were compared using the chi-squared test. Analyses were performed with SPSS version 24. A p value <0.05 was considered significant.

Results

Survey response rate

Out of the 748 ERS Assembly 2.02 members, 166 health care professionals responded to the survey, i.e. a response rate of 22.1%. Respondents belonged to 41 different countries: 19 European and 22 non-European countries. The full list is included in an e-table (on-line supplement).

Respondents' characteristics

The majority of responders worked in university teaching hospitals (64.8%), followed by community hospitals (22.4%), rehabilitation centers (6.7%), private hospitals/clinics (4.2%), and outpatient clinics (1.8%). They worked mainly in respiratory wards with a dedicated respiratory intermediate intensive care unit (RIICU) (43%). Distribution of other facilities is shown in Table 1. Responders belonged to different health care professions: physicians, physiotherapists, nurses, and others. The most represented were physicians (80%). They were generally very experienced in NIV, most of them having more than 10 years of experience (61%). Fifteen percent of respondents reported more than 50 ventilator prescriptions per year.

Indication for LTHNIV

The NMD was the most important indication for 80.9% of the respondents, with ALS representing 78% of these cases, followed by Duchenne Muscular Dystrophy (DMD, 11%), CWD 14.5% and others (4.6%).

The most important reasons for initiating LTHNIV reported by respondents are shown in figure 1. Respondents ranked the most significant treatment targets to achieve using LTHNIV, as shown in figure 2.

Instruments and Settings

Ventilators and settings

Participants were more likely to choose a specific ventilator based on the following characteristics of devices: good feedback from patients (25%), presence of both pressure and volume ventilation options, and transportability (20%). (Figure 3).

The majority of interviewees used MPV during daytime only (65%), followed by S-PSV (17%), and ST-PSV (9%). MPV was more frequently used in general respiratory wards (rehabilitation and acute wards) than in critical care wards (ICU, RICU, ED) (p=0.015). Respondents reported that TV-PSV (29%) was the preferred mode of ventilation during night-time, followed by PCV (20%), ST-PSV (19%), CPAP (18%), and VCV (10%). However, if one mode was chosen for both day and night-time ventilation, then ST-PSV was the most frequently used (36%), followed by TV- PSV (25%), PCV (16%), and VCV (15%). All modalities used between day and night time are detailed in figure 4.

Clinicians were more likely to use a single-limb circuits with intentional leaks or exhalation ports (79%), followed by expiration valves (13%) and double-limb circuits (8%).

Interfaces preferred by all responders during the day and night-time ventilation are shown in figure 5.

No further significant results were found from other comparisons among groups considered. Clinicians working both in general respiratory wards and critical care wards reported similar preferences in terms of modes of ventilation, interfaces and circuits' configuration.

Most prescribers added humidification to NIV. A heated humidifier was the first choice (72%) followed by heat and moisture exchangers (HME) (20%). No humidification was prescribed in only 8% of cases.

Patients' follow-up

The vast majority of responders initiated patients to NIV as inpatients (67%). During the hospital stay, an educational program was provided for new patients via either educational material combined with practical sessions for patient and caregiver (40%) or only practical sessions for patient and caregiver (33%). Lack of educational programs was reported by 27% of respondents. The prescriber was usually also involved in long term patient follow-up (95%). Follow-up was performed during outpatient visits in 65% of cases, as inpatients in 18% and at home in 12%. The remaining 5% of responders described a combined schedule of outpatient visit and telemedicine or ventilator tele-monitoring. The different types of follow-up provided are reported in figure 6. Finally, on top of follow up visits described, in 65% of cases, a home care program with control visits was provided through either a physician (11%), a nurse (14%), a physiotherapist (11%), or a home care provider (19%). The remaining responders (10%) provided a home care program combining at home follow-up visit by health care practitioners (i.e. physician, nurse, physiotherapist) and telemedicine or tele-monitoring. Conversely, in 35% of cases, the option of a home care program was not available for RTD patients on LTHNIV.

Discussion

The REINVENT survey study explored the clinicians' perspectives as to use of LTHNIV for RTD among professionals of different countries and members of the ERS assembly group on non-invasive respiratory support. Fifteen years after EUROVENT, this study describes the type of RTD patients requiring NIV, settings, modes, and interfaces used. Survey response rate was 22.2%, which is in line with reported response rates of internet-based surveys [23]. Responders were mainly physicians (80%) involved in the care of NMD patients, primarily in teaching hospitals (64.8%) and community hospitals (22,4%). This is in line with what was previously reported in EUROVENT [9]. The vast majority of responders (61%) had extensive experience in LTHNIV (>10 years). Therefore this study provides an indicative picture of experienced physicians working in the field of RTD.

The most important reasons for LTHNIV initiation were diurnal hypercapnia, hospitalizations for respiratory failure, muscle weakness symptoms, and nocturnal hypercapnia. Interestingly, having an FVC lower than 80% of predicted, which is recommended for NIV initiation in current ALS treatment guidelines, was not in the top three answers [24]. Targets of LTHNIV treatment were more often related to QoL and quality of sleep than to increasing survival. Most probably, a lesser importance is given to survival in RTD patients and, in particular, in ALS patients, given their prognosis, which seems to be only partially influenced by LTHNIV [25-27]. More importance is given to the quality of patient's experience during LTHNIV used during day and night-time [28]. Indeed, less evidence is present in the literature for LTHNIV in RTD use compared to other respiratory diseases such as COPD, where LTHNIV management has only recently been defined [29].

Interestingly, prescribers took into high consideration feedbacks from other patients already using the same machines. Indeed, these feedbacks were used in 25% of cases to drive the choice of the ventilator. Secondly, the presence of both pressure and volume modes was important: many prescribers chose hybrid modes with pressure and volume settings in RTD patients. Thirdly, transportability and battery autonomy or presence of an external battery were on the top of the list of aspects to consider when choosing a ventilator. Given the weakness and total dependence of NMD patients, these items play a vital role in patient autonomy. Patients may feel safe despite depending on the ventilator, and they may continue to enjoy a good quality of life moving around with their caregivers and outside their homes.

Ventilation modes with combined pressure and volume settings (hybrid modes: TV- PSV), are often chosen by the prescribers to be preferably used overnight. These results are interesting and deserve to be reviewed in depth. Indeed, hybrid modes are relatively new setting modalities in the LTHNIV scenario, and therefore their potential is yet to be explored [30]. These modes combine pressure and volume modes by delivering a targeted volume via a predefined pressure range (minimal and maximal IPAP) set on the ventilator[31]. There is no support in the literature for the use of these modes in long term NIV. Therefore the question is why opt for them when simple bi-level PSV/ST modality is widely used by prescribers and accepted by the patients. To date, only a few studies have explored the use of these hybrid modes in patients with OHS and chronic respiratory failure [32-34]. Although, intuitively in patients with RTD, hybrid modes could present several advantages, there is no evidence as

yet in the literature as to their real effectiveness. For instance, their response in presence of leaks may be unpredictable in NMD patients. Since many ventilators already provide these modes, and prescribers use them for the treatment of RTD patients as confirmed in this survey, studies are warranted to explore their benefit (or absence of) in more detail in this population. However, it is important to highlight that despite the larger use of hybrid modes, PSV-ST was the preferred mode for both day and night-time ventilation. This confirms the large knowledge and practicability of this mode among prescribers surveyed.

The extensive use of CPAP/auto-CPAP at night in RTD patients highlighted by this survey deserves a comment. These modalities are not a ventilation mode, and they are not indicated in RTD albeit in the presence of sleep-related disordered breathing (SDB). SDB may be one of the presenting symptoms in NMD patients. When using CPAP/auto-CPAP in NMD, a close follow up is warranted to switch to bi-level support when required, and provide adequate respiratory support.

The most frequently used circuit is a single-limb tubing with an intentional leak port. This is in line with recent evidence describing this option as easier to use, and allowing a sufficient CO_2 exhalation compared to single or double limb circuits with expiratory valves [35]

In this survey, in NMD (mostly ALS), mouthpiece ventilation is the most frequently used mode of daytime ventilation. Although nasal masks and nasal pillows are used less than mouthpieces during daytime ventilation only, when patients require prolonged ventilation during the day and night time, they become the first choice. Oro-nasal interfaces are used preferably for nocturnal ventilation only, probably to avoid excessive mouth leaks [18].

Humidification seems to be very important for prescribers who prefer active humidification (72% of cases) to HME (20% of cases). Indeed, bronchial secretions may become very thick during prolonged ventilation; therefore, heated humidification plays a role in improving the rheology of secretions and overall quality of ventilation [36].

Follow-up was mainly provided by physicians via outpatient visits or via a home care provider. At the time of the survey a very large number of prescribers did not provide any home care program. The picture has changed over the last months[37]. Indeed, a few RCTs have recently highlighted that initiation of mechanical ventilation at home is cost effective, improves HRQL and is not inferior to hospital initiation also for patients with RTD [38-42]. This survey was launched and concluded right before the COVID-19 pandemic, which had a profound impact on our way of managing LTHNIV patients. Social distancing has promoted the use of tele-monitoring, telecommunication and tele-visiting within many specialties and many patients. The scenario ahead of us will probably be very different: it may be preferable for these vulnerable patients to be managed by remote monitoring. A further upgrade to improve control and to modify ventilator settings remotely will probably be provided.

This study has a few limitations. First, although the survey was conducted among members of the ERS assembly for NIV, specifically dedicated to non-invasive respiratory support, results may not be representative of physicians' clinical experience and perceptions with long term

NIV treatment of patients with RTD across Europe. Secondly, the 22% response rate could be considered as relatively low. It is however in line with reported response rates for electronic surveys. Also, some RTDs are rare diseases sometimes managed only in few dedicated and specialized centres: this could have further affected the overall response rate. Thirdly, there may be a selection bias in this survey, with almost 2/3 of responders working in university teaching hospitals: this may impact on severity of cases, and choice of devices and settings.

The major strengths of our study are that it was the first study since Eurovent that focused on LTHNIV in RTD. Secondly, respondents could not skip sessions or answers: therefore full data collection of respondents' opinions was guaranteed. Lastly, we gathered quality responses from health-care professionals who are experts in this field.

In conclusion, the present REINVENT survey has provided a global picture of LTHNIV in patients with RTD and, in particular, with rare NMD who require long term ventilation. Compared to the previous EUROVENT survey, it showed different reasons to initiate LTHNIV and goals to be achieved. Patterns of ventilation and modes used have considerably changed, highlighting the increase in use of combined modes in LTHNIV. Follow-up of these patients before the COVID-19 pandemic was mainly via out-patient visits or home care programs with an in-person appointment. We expect that after the COVID 19 global pandemic, common practices will change significantly via the use of tele-monitoring and telehealth techniques. Further studies are needed to evaluate what has changed among the clinical practice of LTHNIV in these patients affected by rare NMD.

Acknowledgements

Authorship: PP, CC, AC, RS made substantial contribution to the conception and design of the work, GEC for the acquisition, PP, CC and AN, for the analysis, JPJ, ML, PJW, WW for interpretation of data for the work. PP, CC, AC, GEC, AN, RS, contributed to drafting the article and JPJ, ML, PJW, WW in revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding: no funding support was granted for this study.

PP would like to thank Prof S. Nava for his great contribution in starting the project and helping to join all authors' forces together.

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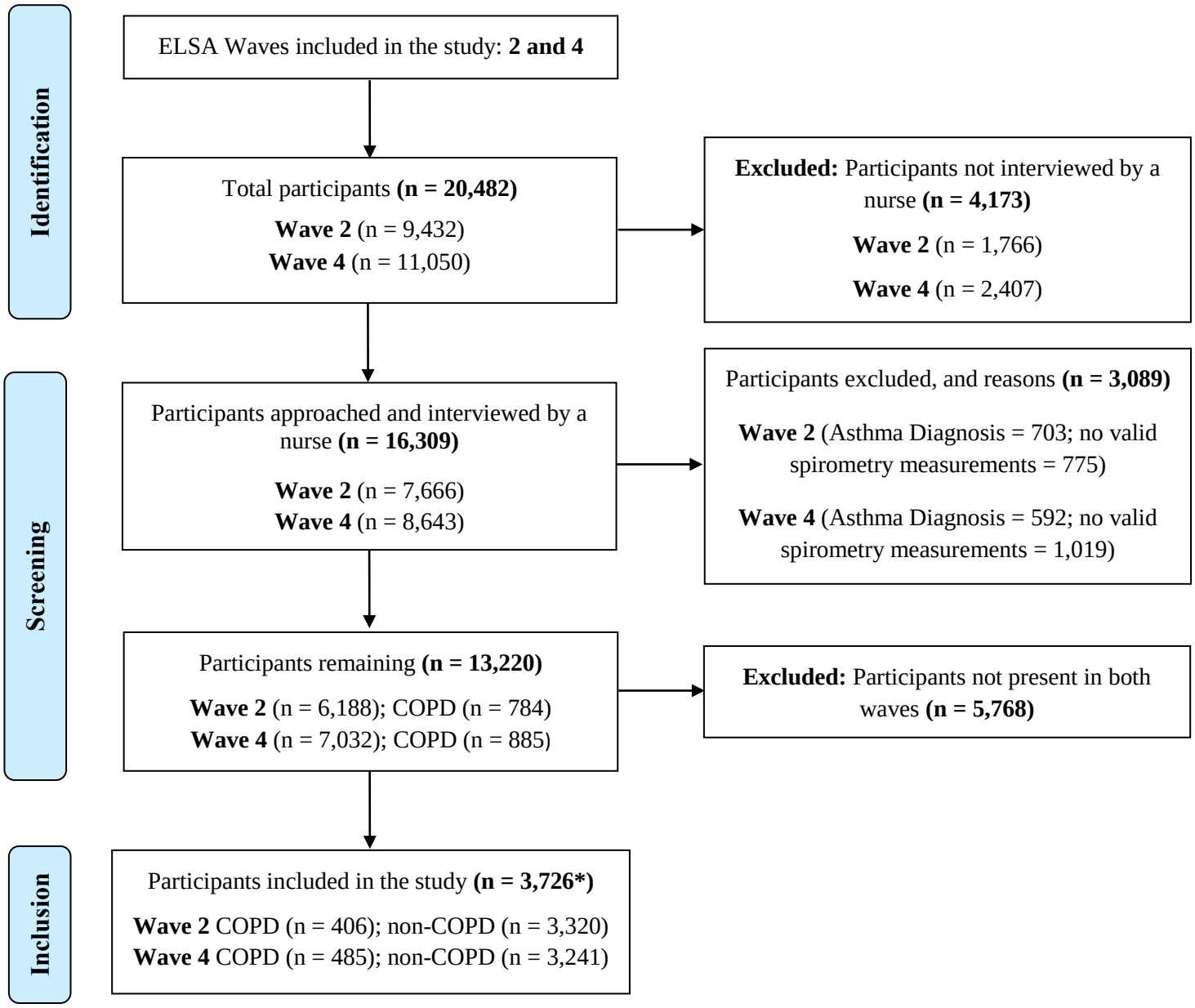

Figure 1: **Schematic diagram explaining the flow of study participants**

***** 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 $\geq$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 kg/m^2)" or "obese ($\geq$ 30 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 kg for males and <16 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 FEV_1 (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 FEV_1 (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 FEV_1% 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 FEV_1% 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 FEV_1% 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

Supplement E- Table. Survey Response rate

Countries	N	%
Italy	33	19.88%
United Kingdom	19	11.45%
Spain	16	9.64%
Germany	11	6.63%
Portugal	10	6.02%
Netherlands	8	4.82%
France	7	4.22%
Poland	6	3.61%
Switzerland	5	3.01%
Australia	4	2.41%
Canada	3	1.81%
Greece	3	1.81%
Malaysia	3	1.81%
Turkey	3	1.81%
Austria	2	1.20%
Chile	2	1.20%
Croatia	2	1.20%
Estonia	2	1.20%
Ireland	2	1.20%
Pakistan	2	1.20%
Romania	2	1.20%
Russia	2	1.20%
Albania	1	0.60%
Argentina	1	0.60%
Czech Republic	1	0.60%
Finland	1	0.60%
Hungary	1	0.60%
Kazakhstan	1	0.60%
Kuwait	1	0.60%
Lithuania	1	0.60%
Mexico	1	0.60%
Norway	1	0.60%
People 's Republic of China	1	0.60%
Peru	1	0.60%
Serbia	1	0.60%
Singapore	1	0.60%
Slovenia	1	0.60%
Sri Lanka	1	0.60%
Sweden	1	0.60%
Tunisia	1	0.60%
Venezuela	1	0.60%
Total	166	100.00%

Table Legend: The highest response rates/country (≥ than 10 responses per country) came from Italy, UK, Spain, Germany, and Portugal. Intermediate response rates/country (between 5 and 10

answers) were provided by France, The Netherlands, Poland, and Switzerland. The remaining countries involved provide low response rates/country (<5 responses).