Association of generic health-related quality of life (EQ-5D dimensions) and inactivity with lung function in lung-healthy German adults: Results from the KORA studies F4L and Age

Running title: Association of EQ-5D and inactivity with healthy lung function

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Abstract

Purpose

Among patients with lung disease, decreased lung function is associated with lower health-related quality of life. However, whether this association is detectable within the physiological variability of respiratory function in lung-healthy populations is unknown. We analyzed the association of each EQ-5D-3L dimension (*mobility*, *self-care*, *usual activities*, *pain/discomfort*, *anxiety/depression*), and self-reported physical inactivity with spirometric indices in lung-healthy adults. Modulating effects between inactivity and EQ-5D dimensions were considered.

Methods

1132 non-smoking, apparently lung-healthy participants (48% male, aged 64±12 years) from the population-based KORA F4L and Age surveys in Southern Germany were analyzed. Associations of each EQ-5D dimension and inactivity with spirometric indices serving as outcomes (forced expiratory volume in 1s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and mid-expiratory flow) were examined by linear regression, considering possible confounders. Interactions between EQ-5D dimensions (no problems/any problems) and inactivity (four categories of time spent engaging in exercise: inactive to most active) were assessed.

Results

Amongst all participants 42% reported no problems in any EQ-5D dimension, 24% were inactive and 32% exercised >2 hours/week. After adjustment, FEV_1 was -99ml (95%CI:-166;-32) and FVC was -109ml (95%CI:-195;-24) lower among subjects with *mobility* problems. Comparable estimates were observed for *usual activities.* Inactivity was negatively associated with FVC (β-coefficient:-83ml, 95%CI:-166;0), but showed no interactions with EQ-5D.

Conclusions

Problems with *mobility* or *usual activ*ities, and inactivity were associated with slightly lower spirometric parameters in lung-healthy adults, suggesting a relationship between perceived physical functioning and volumetric lung function. Thus, prevention of inactivity appears to be reasonable even in lung-healthy adults.

Introduction

Health-related quality of life (HRQL) is reduced in patients with chronic lung diseases such as chronic obstructive pulmonary disease (COPD) [1-3]. While various factors, including impaired lung function, can lead to a decrease in HRQL with increasing disease severity, physical activity has been found to be associated with better HRQL as well as less hospital admissions in COPD [2, 4-6]. Among subjects with asthma, the forced expiratory volume in 1 second (FEV_1) differed between inactive and active participants by -5 ml/year (95% confidence interval (CI): -13; 3) [7]. Based on these findings in patients with respiratory diseases, it is possible that HRQL or being physically inactive may already be associated with lung function among apparently lung-healthy subjects or among those in transition to lung disease. Physiological variation of lung function is mainly related to age, height, gender and ethnicity in lung-healthy subjects, but is modulated by the continuous interplay between adverse and protective biological, environmental and lifestyle factors [8-11]. These factors contribute to the considerable inter-individual variability of lung function measures observed during lung development and age-related decline [9-11]. This is also indicated by the increasing variability of the coefficients of variation for lung function parameters with age, e.g. for FEV_1 and forced vital capacity (FVC) from about 11% at age 15 to nearly 18% at age 80 years [12].

While the association between lung function and HRQL is well established in patients with manifest disease [1-3], the relation between respiratory function variability and HRQL in lung-healthy subjects is less studied.

At a population level, two studies from the United Kingdom investigated the association between FEV_1 and a 36-item questionnaire on general health status (Short Form-36, SF-36) in adults aged 40-79 years and 50-74 years, respectively [13, 14]. In both studies, positive associations of self-reported physical functioning based on the SF-36 with FEV_1 were found. Subjects were more likely to report a good functional health if they were among the top 20% of the FEV_1 distribution of the study population [13].

To our knowledge, no study so far has examined the relationship between the EuroQol 5 dimensions (EQ-5D) questionnaire as a generic health-related quality of life instrument, and lung function in a lung-healthy, population-based cohort with a comprehensive set of spirometric measures.

The EQ-5D has been widely used to assess or compare health status across different populations [2, 15-19]. It covers five dimensions of health: *mobility*, *self-care*, *usual activities*, *pain/discomfort*, and *anxiety/depression.* As a short and practical preference-based measure, it offers the possibility to assess each dimension of health separately, or as an index-based utility score ranging from 0 to 1 (EQ-5D utility) with higher scores meaning better health [15]. Results from a comprehensive review revealed a range of EQ-5D utility from 0.42 to 0.93 in asthma and 0.52 to 0.84 in COPD studies, decreasing with increasing disease severity [2]. As expected, HRQL is higher in the general population; a survey among 1966 German participants reported a mean utility index of 0.94 in males and 0.92 in females (based on German reference values) [19, 20].

In the present study including a lung-healthy, non-smoking, German population derived from a population-based sample with an expected high overall HRQL, we aimed to investigate whether specific health dimensions of the EQ-5D are associated with spirometric indices, also considering possible sex differences. Since physical activity was found to be associated with better HRQL [4, 5], and further, associations between physical inactivity and decreased lung function have been reported [21, 22], we also assessed whether a direct association exists between physical inactivity and lung function, and whether inactivity has a modulating role in the association of EQ-5D dimensions with spirometric indices.

Methods

Study Population

The KORA (Cooperative Health Research in the Region of Augsburg) research platform comprises several population-based cohort studies established in 1996. Regular follow-up examinations are conducted within KORA as described previously [23, 24]. The present analysis was based on the KORA F4L survey, which is the three-year follow-up of the KORA F4 study including participants with lung function measurements, and the KORA Age survey. The KORA F4L and KORA Age studies were approved by the responsible ethics committee of the Bavarian Medical Association. Written informed consent was obtained from all participants, and all investigations were carried out in accordance with the Declaration of Helsinki.

Spirometric measurements were obtained from 1051 adults aged 45–65 years of the KORA F4L follow-up, examined in 2010, and from 935 participants aged 65–90 years of the KORA Age study, examined in 2009. All the participants provided information on physical inactivity. For two participants from KORA Age no information on the EQ-5D was available. 29 (1.5%) participants did not report on all health dimensions; of those, 25 (86%) had one missing only. Information on self-reported physician diagnoses of common diseases including asthma, hay fever, stroke or myocardial infarction, current medication intake up to seven days before examination, as well as sociodemographic variables, was obtained from standardized interviews and questionnaires.

Since the present study focusses on apparently lung-healthy subjects, from the participants with valid spirometry who provided information on EQ-5D and inactivity (N=1972), those reporting (i) a doctor's diagnosis of emphysema, asthma, chronic bronchitis or COPD, or (ii) the current use of pulmonary medication including inhaled sympathomimetics, anticholinergics, and steroids, or oral leukotriene antagonists, or (iii) respiratory symptoms, i.e. cough or phlegm lasting more than 3 month a year, or (IV) subjects with a measured FEV_1/FVC <0.7, were excluded from all analyses (N=692). Additionally, current smokers were excluded in order to avoid potential modification of underlying associations caused by smoking (N=140). Subjects with Parkinson's disease (N=8) were also excluded.

EQ-5D and physical inactivity

The EQ-5D-3L questionnaire was used for the assessment of HRQL. The EQ-5D-3L is a generic, preference-based HRQL instrument, which collects information on the health state of five health dimensions: *mobility*, *self-care*, *usual activities*, *pain/discomfort*, and *anxiety/depression* [15]. One of three levels of severity (no problems, some problems, and extreme problems) can be chosen for each of the five dimensions. The German time-trade-off tariff proposed by Greiner et al. was used to calculate an index-based utility score (EQ-5D utility) ranging from 0 to 1 [20] with higher values indicating better health. The utility score was used in the present study for descriptive analyses only.

Physical inactivity, defined in terms of the amount of performed exercise, was categorized according to a combination of answers derived by two questions: (1) How often do you do exercise in summer? and (2) How often do you do exercise in winter? Possible answers were (a) regularly, >2 hours/week, (b) regularly, 1-2 hours/week, (c) less than 1 hour/week, (d) not at all. Subjects were categorized as *active* (a in both questions), *moderately active* (one a in combination with b or c; or b in both questions), *slightly active* (one d in combination with a or b), or *inactive* (c or d in both questions). Subjects engaging regularly in >2 hours of physical activity per week, i.e those categorized as *active*, who nearly meet the WHO recommended threshold of 2.5 hours of physical activity per week [25], were used as the reference category to determine if less activity is associated with lower lung function.

Lung function assessment

Standardized spirometry was performed in line with the American Thoracic Society and European Respiratory Society recommendations [26] by the same study nurse in both studies. Flow-volume curves were obtained using a pneumotachograph-type spirometer (MasterScope, Jaeger, Hoechberg, Germany). Under guidance of the trained examiner, subjects performed 3 to 8 spirometric maneuvers per test. A detailed description has been published previously [27]. Spirometric parameters included FEV_1, FVC, FEV_1/FVC, and forced expiratory flow rate between 25% and 75% of exhaled FVC (FEF_{2575}). Standardized z-scores for each parameter were calculated using reference equations for spirometry from the Global Lung Function Initiative (GLI) [8].

Statistical analyses

Data from KORA F4L and KORA Age were pooled since study protocols and lung function assessment were assessed equally and were also performed in the same study center.

Population characteristics were described by means and corresponding standard deviations or percentages (%, N). Differences between males and females were assessed using chi-squared test (categorical variables) and t-test for lung function parameters. Cramér's V was calculated to assess correlations between categorical variables. The number of subjects reporting extreme problems in any health dimension was low, therefore the answers "having some problems" (range 2-48% for the five dimensions) and "having extreme problems" (range 0-2%) were combined, resulting in a dichotomous variable for each EQ-5D dimension (no problems vs. any problems). In sensitivity analyses, subjects reporting extreme problems in the investigated dimension were excluded from the analyses.

Separate adjusted linear regression models were calculated to examine the relationships between each EQ-5D health dimension or physical inactivity as exposure with each spirometric parameter serving as outcome. For EQ-5D dimensions showing a significant association with lung function, regression models were performed adjusting for both, the EQ-5D dimension of interest and physical inactivity. Further, interaction effects between the specific EQ-5D dimension and physical inactivity were tested. To account for sex differences occurring in the distribution of inactivity levels as well as anxiety/depression, and pain/discomfort, we assessed interaction effects between the analyzed exposures and sex and further report stratified analyses for females and males.

The main model was adjusted only for those variables mainly accounting for inter-individual variability of lung function (i.e. sex, age, height), and for weight as a possible confounding factor. To address other possible confounding factors we additionally adjusted the main model for the following covariates separately: (A) study (KORA F4L vs. KORA Age), (B) education level categorized as low (<10 years of school), medium (10 years of school) and high (>10 years of school), (C) doctor`s diagnosis of hay fever (ever), (D) season categorized as autumn/winter (spirometry obtained in September to February) or spring/summer (March to August), (E) a history of smoking (yes vs. no), (F) self-reported acute respiratory infections in the three weeks prior to lung function testing, and for common comorbidities: (G) hypertension, (H) diabetes, (I) cancer, (J) stroke, (K) myocardial infarction, or (L) multimorbidity, defined as the presence of at least two diseases (N=228) (G-K). Diabetes was based on self-reported physician diagnosis or use of antidiabetic agents. Subjects with self-reported hypertension, the use of antihypertensive medication, or a measured blood pressure ≥140⁄90 mmHg were defined as having hypertension.

Models in which GLI z-scores for spirometric parameters (already adjusted for sex, age and height) served as outcome were adjusted for additional variables only. Outliers were defined as greater/less than the mean plus/minus 4 times the standard deviation in lung function parameters (separately for males and females). Subjects meeting this definition for any spirometric parameter (N=2) were excluded from analyses for the relevant parameter only. All analyses were performed using the statistical software R, version 3.2.0 [30]. P-values below 0.05 were considered statistically significant.

Results

The population characteristics and lung function measurements of the 1132 analyzed apparently lung-healthy participants (male 48%, mean age 64±12 years, with mean GLI z-scores for FEV_1 and FVC of 0.71 and 0.61) are shown in Table 1. The mean EQ-5D utility score was 0.91. 42% reported no problems for all dimensions and this percentage was higher in males compared to females (46% vs. 38%, respectively). Only 2.8% reported extreme problems for any health dimension, with the highest prevalence in the health dimension *pain/discomfort* (2%). Between the different EQ-5D dimensions, the highest correlation was present between having problems with *mobility* and problems with *usual activities* (Cramér's V= 0.49).

Data on self-reported time spent in exercise revealed that 32% of the participants engaged regularly (>2 hours/week) in physical activity, while 24% were categorized as inactive, i.e. engaging in physical activity <1 hour/week or not at all.

Self-reported physical inactivity and lung function

In adjusted regression models, associations of physical inactivity with FVC and GLI z-scores for FEV_1 and FVC were found (Table 2, Table A1 in S1 Tables). Less activity was associated with lower FVC, e.g. inactive subjects had an estimated difference in FVC of -83 ml (95%CI: -166; -0.1) compared to the most active subjects. Estimates for physical inactivity were negative, although not significant, with FEV_1 (-49 ml, 95% CI: -115; 16) (Table 2), whereas significant associations were seen for the GLI z-score for FEV_1 (-0.23, 95% CI: -0.39; -0.08, p<0.01) and for FVC (-0.28, 95% CI: -0.43; -0.14; p<0.01) (Table A1 in S1 Tables). Adjustment for further covariates, such as hay fever or multimorbidity, did not substantially change the aforementioned results. No interaction effects (p>0.05) between sex and physical activity levels were present in the main model. When stratified by sex, associations remained significant in females, whereas comparable tendencies, but no significant associations, were present among males, regardless of whether absolute values or GLI z-scores were assessed (Tables A2 to A5 in S1 Tables). Inactive females had a -98 ml (95%CI: -177;-19) lower FEV_1

and a -140 ml (95% CI: - 240; -40) lower FVC compared to the most active females (S1 Table A2). No associations were observed for FEV_1/FVC or FEF_{2575}.

Associations of EQ-5D dimensions with lung function

After adjusting for sex, age, height and weight, having problems with *mobility*, and with *usual activities* were associated with lower FEV_1 and FVC (Table 2). FEV_1 was -99 ml (95% CI: -166; -32) and FVC was -109 ml (95% CI:-195; -24) lower among subjects with *mobility* problems. Subjects reporting problems with performing *usual activities* had a -97 ml (95% CI: -169; -26) lower FEV_1 and a -124 ml (95% CI: -214; -33) lower FVC, respectively. A borderline negative association was found for being *anxious/depressed* with FVC and for problems with *mobility* with FEF_{2575}, but no associations were found for the dimensions *self-care* and *pain/discomfort* or with FEV_1/FVC. Results were comparable when applying GLI z-scores instead of absolute lung function values, except for being *anxious/depressed*, which showed an association with z-scores of FEV_1 and FVC (Table A1 in S1 Tables). Further, adjustment for potential confounding covariates, e.g. hay fever or season, or the exclusion of subjects reporting extreme problems in the investigated dimension led to similar results. After adjustment for stroke, myocardial infarction, or multimorbidity the effect estimates decreased by about 6-22%, but were still statistically significant ($p<0.05$). For example, subjects who had problems with *usual activities* showed a decrease in FEV_1 by -80 ml (95% CI: -153; -8), instead of -97 ml, and FVC by -105 ml (95% CI: -197; -13), instead of -124 ml, after additional adjustment for multimorbidity. The effect estimates for subjects with *mobility problems* were -85 ml (95% CI: -153; -17), instead of -97 ml for FEV_1, and -94 ml (95% CI: -180; -7), instead of 124 ml for FVC.

EQ-5D dimensions showed no interaction effect with sex in the main regression models, except for interactions between mobility problems and sex in the FEV_1 and FEF_{2575} models. In females, associations found in the total population for *mobility* and *usual activities* with FEV_1 and FVC remained significant (*mobility*: FEV_1: β= -81 ml; FVC: β= -109 ml; *usual activities*: FEV_1: β= -86 ml; FVC: β=-106 ml) (S1 Table A2). Results for males showed similar estimates, but were significant only for the association between FEV_1 and *mobility* (*mobility*: FEV_1: β= -118 ml, p=0.04; FVC: β= -111 ml, p =0.12; *usual activities*: FEV_1: β= -119 ml, p =0.05; FVC: β= -151 ml, p=0.05) (Table A3 in S1 Tables). No associations were observed with FEV_1/FVC and FEF_{2575}. Having problems with self-care, having pain/discomfort or being anxious/depressed were not associated with any spirometric indice. Comparable results were obtained when applying GLI z-scores (Tables A4 and A5 in S1 Tables).

Effect modification between EQ-5D dimensions and physical inactivity

Physical inactivity showed weak correlations with the EQ-5D dimensions, with the highest correlations observed with *anxiety/depression* and *mobility* problems (Cramér's V 0.16 and 0.15, respectively). No interaction effects were seen in the main linear regression models. The observed associations between the EQ-5D dimensions *mobility* and *usual activities* with FEV_1 or FVC, were not affected by further adjustment for physical activity (Tables A6 and A7 in S1 Tables).

Discussion

Volumetric lung function indices were negatively associated with having problems with *mobility* and *usual activities* in an apparently lung-healthy study population, despite almost half of the examined subjects reporting no problems in any EQ-5D dimension. After stratification by sex, associations were more pronounced in females than in males although the prevalence of problems in *mobility* or in *usual activities* was comparable between sexes. The physical activity level did not modulate the associations observed with these EQ-5D dimensions. However, being physically inactive showed a similar tendency as EQ-5D to be associated with lower volumetric indices. About half of the population reported to have *pain/discomfort*, but no associations with lung function were present.

The frequency distribution of reporting problems in the EQ-5D dimensions was comparable to those observed in a population-based survey among 1966 German adults in 2006, which also revealed the highest prevalence for the dimension *pain/discomfort* (33.8%). Only 3.1% reported extreme problems in any of the 5 dimensions [19] compared to 2.8% in the present study population.

Being physically inactive was associated with lower FEV_1 and FVC, remaining significant among females only when performing sex-stratified analyses. This may be due to the fact that men were more often categorized as active (37.8% vs. 26.4% for men and women, respectively) and less often as inactive (22.2% vs. 25.6%, respectively). A similar pattern was also demonstrated in the German National Health survey [28]. 33.7% of the participants aged 18-79 years reported no sports activity; with lower inactivity in males than in females (33.0 % vs. 34.3%, respectively). Further, men engaged more often in regular (>2 hours/week) sports activity compared to females (29.3% vs. 21.6%) [28]. Investigations on self-reported physical activity in adults have shown that physically active subjects have higher volumetric lung function parameters and a slower lung function decline compared to inactive participants [21, 22]. Depending on the level of inactivity, FEV_1 was reduced between 20 and 170 ml [22]. The magnitude and direction of findings correspond to our results, which indicated about 100 ml lower FEV_1 in inactive subjects compared to active ones.

In our population, associations of EQ-5D with lung function were mainly seen for dimensions related to physical functioning, *mobility* and *usual activities*. Notably, the level of physical activity did not modify these associations, suggesting that regular activity and these two perceived EQ-5D dimensions may exert different pathways of functioning in lung-healthy subjects, which might also be supported by the low correlation detected between these entities. Despite the fact that a different measure, the SF-36, was applied to assess HRQL, two studies from the UK also found positive associations of self-reported physical functioning with FEV_1 and inconclusive results for the mental component in the general population [13, 14]. Thus, taken together, these and our current findings suggest that volumetric lung function indices are associated with physical functioning in lung-healthy adults.

Corresponding results were shown among subjects with COPD, where impairments of respiratory function are reflected by the increasing GOLD grades 1-4. While subjects with COPD grade 1 presented no significant effects for the mental or physical score obtained by the SF-12 in comparison to healthy controls of the KORA F4 study, subjects with higher grades of COPD showed a lower physical functioning score, but no associations with the mental component [17]. Further, in a population-based survey across 17 countries lower physical and mental scores were found in subjects with COPD in comparison to those without COPD; confirming stronger effects for the physical than for the mental score [3].

Data from the German COPD cohort COSYCONET showed a decrease in mean EQ-5D utility with increasing COPD grade, i.e. from 0.85 in COPD grade 1 to 0.74 in COPD grade 4 [29]. Our mean EQ-5D utility of 0.91 in lung-healthy subjects fits to the lower results reported for the COPD cohort. Interestingly, despite the high overall utility score of EQ-5D in our study population, associations were still detectable for problems in *mobility* or *usual activities*, and being inactive. This is further supported by a carefully extended analysis considering the findings of the COPD cohort by Wacker et al. [29]. According to the observed utility score in GOLD grade I, we categorized the EQ-5D utility in our population in three groups: (1) those with best health (0.999, used as the reference group), (2) those with a still slightly greater utility (≥0.887) than the mean of COPD grade 1 in Wacker et al. [29], and those with comparable EQ-5D utility (<0.887). In a linear regression analysis adjusting for sex, age, height and weight, subjects in the lower EQ-5D category had a -87 ml (95% CI: -160; -15) lower FEV_1 and -96 (95% CI: -187; -4) lower FVC compared to those with the best possible utility. This explorative analysis related to findings observed in early COPD extends the findings by Wacker et al. (11) and suggests a negative association of EQ-5D utility and lung function already in apparently lung-healthy adults. Nevertheless, as 48% had the best possible health utility score, categorization is limited in our study population. Therefore, we did not include this approach in our main analysis, rather, provide an appeal to further explore this first finding.

Strength and limitations

A major strength of the present study is the standardized assessment of lung function and the possibility to investigate a range of spirometric indices in an apparently lung-healthy general adult population. While HRQL is commonly investigated in lung disease, to our knowledge no evidence exists for the association between EQ-5D dimensions and lung function in the general population without chronic lung diseases.

The cross-sectional design of our analysis does not allow us to draw conclusions about long-term effects or causal relations. All information on lung diseases, stroke or myocardial infarction was assessed via self-reports and was not verified by a physician. Similarly, physical activity assessment was questionnaire-based only. We analyzed a preselected lung-healthy adult population with an age range of 45 to 89 years, of whom 20% had at least 2 chronic health conditions not directly related to lung function impairment. Further, our results should be interpreted with caution due to the small effect sizes with partially borderline significance resulting in an arguable clinical relevance. Intentionally, our study was population-based and therefore the addressed population is not comparable to a clinical cohort or narrower age ranges. However, problems in *mobility* or *usual activities* and inactivity were associated with slightly lower lung function indices after adjustment for other common chronic diseases or being inactive.

Conclusion

Having problems with *mobility* or *usual activities* was associated with slightly lower lung function in lung-healthy, non-smoking, German adults. Physical activity levels did not modify the associations with EQ-5D dimensions. Associations found were more pronounced among females than in males. Other health-related EQ-5D dimensions, e.g. problems with *self-care*, having *pain/discomfort* or being *anxious/depressed,* showed no (or unstable) associations with spirometric indices. Our results suggest that, comparable to observations in subjects with chronic lung diseases, the health dimensions which are directly related to movement may be associated with volumetric lung function already in lung-healthy subjects. Lung-healthy subjects with mobility problems and those with no regular exercise might benefit from prevention programs designed to reduce inactivity, as seen for subjects with chronic lung diseases who show better health outcomes e.g. reduced lung function decline or less hospital admissions, by being physically active or becoming more active.

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Competing interests

The authors declare that they have no competing interests.

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Data availability statement

For approved reasons, access restrictions apply to the data underlying the findings. The informed consent given by KORA study participants does not cover data posting in public databases. However, data are available upon request from KORA-gen (http://epi.helmholtz-muenchen.de/kora-gen/) by means of a project agreement. Requests should be sent to kora.passt@helmholtz-muenchen.de and are subject to approval by the KORA Board.

Supplementary Material

Supplement S1: Tables A1 to A7

S1_Tables_A1_to_A7_20170612.pdf

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Table 1 Population characteristics

	Male (n=545)	Female (n=587)	Total (n=1132)
		Mean (SD) or % (N)	
Age, years	65 (12)	64 (12)	64 (12)
Height, cm*	174 (7)	161 (6)	167 (10)
Weight, kg*	87 (15)	72 (13)	79 (16)
Education*			
Low (< 10 years of school)	53.0 (289)	58.3 (342)	55.7 (631)
Medium (= 10 years of school)	18.3 (100)	26.4 (155)	22.5 (255)
High (> 10 years of school)	28.6 (156)	15.3 (90)	21.7 (246)
Smoking status*			
Never smoker	43.3 (236)	66.3 (389)	55.2 (625)
Ever smoker	56.7 (309)	33.7 (198)	44.8 (507)
Hypertension, yes	59.4 (323)	54.0 (317)	56.6 (640)
Myocardial infarction, yes*	7.2 (39)	2.9 (17)	5 (56)
Stroke, yes*	5.9 (32)	2.9 (17)	4.3 (49)
Diabetes, yes	11.6 (63)	11.3 (66)	11.4 (129)
Cancer, yes	10.8 (59)	8.7 (51)	9.7 (110)
Hay fever ever, yes	10.8 (59)	12.9 (76)	11.9 (135)
Lung function - Spirometric outcomes			
FEV_1, l*	3.61 (0.73)	2.56 (0.57)	3.07 (0.84)
FVC, l*	4.65 (0.92)	3.25 (0.72)	3.92 (1.08)
FEV_1/FVC*	0.78 (0.04)	0.79 (0.05)	0.78 (0.05)
FEF_{2575}, l/s*	3.17 (1.01)	2.34 (0.78)	2.74 (0.99)
Z-score FEV_1	0.72 (0.98)	0.70 (1.00)	0.71 (0.99)
Z-score FVC	0.62 (0.95)	0.60 (0.93)	0.61 (0.94)
Z-score FEV_1/FVC*	0.10 (0.59)	0.01 (0.65)	0.05 (0.63)
Z-score FEF_{2575}*	0.41 (0.74)	0.25 (0.82)	0.33 (0.79)
Generic health-related quality of life			
EQ-5D - Utility score (range 0.110 to 0.999)	0.91 (0.13)	0.91 (0.12)	0.91 (0.13)
No problems in any EQ-5D-dimension*	45.9 (249)	37.8 (221)	41.7 (470)
EQ-5D – Health dimensions[a]			
Problems with:			
Mobility			
no	83.1 (453)	82.6 (485)	82.9 (938)
some	16.9 (92)	17.4 (102)	17.1 (194)
extreme	-	-	-
Self-care			
no	96.5 (525)	98.3 (576)	97.4 (1101)
some	3.5 (19)	1.4 (8)	2.4 (27)
extreme	0 (0)	0.3 (2)	0.2 (2)
Usual activities			
no	87.9 (478)	85.8 (502)	86.8 (980)
some	11.9 (65)	14.0 (82)	13.0 (147)
extreme	0.2 (1)	0.2 (1)	0.2 (2)

	Male (n=545)	Female (n=587)	Total (n=1132)
		Mean (SD) or % (N)	
Having pain/discomfort*			
no	53.1 (288)	46.2 (270)	49.6 (558)
moderately	44.7 (242)	51.9 (303)	48.4 (545)
extremely	2.2 (12)	1.9 (11)	2.0 (23)
Being anxious/depressed*			
no	82.9 (450)	72.7 (426)	77.6 (876)
moderately	16.6 (90)	26.3 (154)	21.6 (244)
extremely	0.6 (3)	1.0 (6)	0.8 (9)
Physical activity*			
Inactive	22.2 (121)	25.6 (150)	23.9 (271)
Slightly active	13.4 (73)	14 (82)	13.7 (155)
Moderately active	26.6 (145)	34.1 (200)	30.5 (345)
Active	37.8 (206)	26.4 (155)	31.9 (361)

*p-value<0.05 in t-test or chi-square test (males vs. females). [a]comparisons between sexes were performed using dichotomous variables (no vs. any)

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{2575}: mean flow rate between 25 and 75% of FVC.

Table 2 Results of multiple linear regression analyses

	FEV_1, ml		FVC, ml		FEV_1/FVC, %		FEF_{2575}, ml/s	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
EQ-5D								
Problems with								
Mobility								
no	ref.		ref.		ref.		ref.	
some	**-99 (-166; -32)**	**<0.01**	**-109 (-195; -24)**	**0.01**	-0.33 (-1.05; 0.40)	0.37	**-123 (-246; -1)**	**0.05**
Self-care								
no	ref.		ref.		ref.		ref.	
some/extreme	-9 (-162; 143)	0.90	-19 (-212; 174)	0.85	-0.74 (-2.40; 0.92)	0.38	45 (-231; 321)	0.75
Usual activities								
no	ref.		ref.		ref.		ref.	
some/extreme	**-97 (-169; -26)**	**0.01**	**-124 (-214; -33)**	**0.01**	-0.26 (-1.03; 0.51)	0.51	-106 (-236; 23)	0.11
Having pain/discomfort								
no	ref.		ref.		ref.		ref.	
moderately/extremely	-5 (-54; 45)	0.85	-10 (-73; 53)	0.75	0.02 (-0.51; 0.55)	0.94	6 (-84; 96)	0.89
Being anxious/depressed								
no	ref.		ref.		ref.		ref.	
moderately/extremely	-49 (-107; 8)	0.09	-72 (-145; 1)	0.05	0.13 (-0.48; 0.75)	0.67	-19 (-124; 85)	0.71
Physical activity								
Active	ref.		ref.		ref.		ref.	
Moderately active	-51 (-111; 10)	0.10	**-81 (-158; -5)**	**0.04**	0.30 (-0.35; 0.95)	0.36	-2 (-111; 108)	0.98
Slightly active	-58 (-135; 19)	0.14	**-111 (-209; -14)**	**0.02**	0.73 (-0.09; 1.55)	0.08	23 (-117; 163)	0.75
Inactive	-49 (-115; 16)	0.14	**-83 (-166; 0)**	**0.05**	0.23 (-0.47; 0.93)	0.51	-8 (-127; 110)	0.89

The linear regression model included one EQ-5D dimension variable or physical activity and sex, age, height, and weight.

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{2575}: mean flow rate between 25 and 75% of FVC.

Supplement S1 Tables A1 to A7

Table A1 Results of multiple linear regression models applying GLI z-scores – Total population

	Z-score FEV_1		Z-score FVC		Z-score FEV_1/FVC		Z-score FEF_{2575}	
EQ-5D	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Problems with								
Mobility								
no	ref.		ref.		ref.		ref.	
some	**-0.23 (-0.38; -0.08)**	**<0.01**	**-0.27 (-0.41; -0.12)**	**<0.01**	0.06 (-0.04; 0.16)	0.24	-0.05 (-0.18; 0.07)	0.39
Self-care								
no	ref.		ref.		ref.		ref.	
some/extreme	0.01 (-0.35; 0.37)	0.98	-0.09 (-0.42; 0.25)	0.62	0.04 (-0.19; 0.28)	0.72	0.14 (-0.15; 0.43)	0.34
Usual activities								
no	ref.		ref.		ref.		ref.	
some/extreme	**-0.27 (-0.43; -0.10)**	**<0.01**	**-0.30 (-0.46; -0.14)**	**<0.01**	0.02 (-0.09; 0.13)	0.68	-0.11 (-0.24; 0.03)	0.13
Having pain/discomfort								
no	ref.		ref.		ref.		ref.	
moderately/extremely	-0.04 (-0.16; 0.07)	0.47	-0.09 (-0.2; 0.01)	0.09	0.07 (-0.01; 0.14)	0.07	0.03 (-0.06; 0.13)	0.48
Being anxious/depressed								
no	ref.		ref.		ref.		ref.	
moderately/extremely	**-0.14 (-0.28; 0)**	**0.04**	**-0.16 (-0.29; -0.03)**	**0.02**	0.02 (-0.06; 0.11)	0.59	-0.02 (-0.13; 0.09)	0.70
Physical activity								
Active	ref.		ref.		ref.		ref.	
Moderately active	-0.15 (-0.29; 0)	0.05	**-0.16 (-0.30; -0.03)**	**0.02**	0.01 (-0.08; 0.10)	0.80	-0.04 (-0.16; 0.07)	0.48
Slightly active	-0.17 (-0.35; 0.01)	0.07	**-0.24 (-0.41; -0.07)**	**0.01**	0.11 (-0.01; 0.23)	0.06	-0.02 (-0.17; 0.13)	0.78
Inactive	**-0.23 (-0.39; -0.08)**	**<0.01**	**-0.28 (-0.43; -0.14)**	**<0.01**	0.05 (-0.05; 0.15)	0.29	-0.08 (-0.21; 0.04)	0.19

Regression models for standardized Global Lung Function Initiative z-scores that are already adjusted for ethnicity, sex, age, and height were adjusted only for weight and one EQ-5D dimension or physical activity variable at a time.

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{2575}: mean flow rate between 25 and 75% of FVC.

Table A2 Results of multiple linear regression models – Females

	FEV_1, ml		FVC, ml		FEV_1/FVC, %		FEF_{2575}, ml/s	
EQ-5D	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Problems with								
Mobility								
no	ref.		ref.		ref.		ref.	
some	-81 (-160; -2)	0.04	-109 (-210; -9)	0.03	0.14 (-0.90; 1.18)	0.79	-61 (-210; 89)	0.43
Self-care								
no	ref.		ref.		ref.		ref.	
some/extreme	41 (-176; 258)	0.71	34 (-242; 310)	0.81	-0.06 (-2.90; 2.78)	0.97	213 (-197; 623)	0.31
Usual activities								
no	ref.		ref.		ref.		ref.	
some/extreme	-86 (-167; -5)	0.04	-106 (-209; -3)	0.04	-0.34 (-1.40; 0.73)	0.54	-101 (-254; 53)	0.20
Having pain/discomfort								
no	ref.		ref.		ref.		ref.	
moderately/extremely	-4 (-63; 54)	0.89	-13 (-87; 61)	0.73	0.23 (-0.54; 0.99)	0.56	0 (-110; 111)	0.99
Being anxious/depressed								
no	ref.		ref.		ref.		ref.	
moderately/extremely	-41 (-103; 22)	0.20	-58 (-137; 22)	0.15	0.13 (-0.69; 0.95)	0.75	-14 (-132; 104)	0.81
Physical activity								
Active	ref.		ref.		ref.		ref.	
Moderately active	-45 (-117; 27)	0.22	-62 (-153; 29)	0.18	0.18 (-0.76; 1.13)	0.7	9 (-127; 145)	0.90
Slightly active	-84 (-176; 8)	0.07	-126 (-242; -9)	0.04	0.55 (-0.66; 1.76)	0.37	-37 (-211; 138)	0.68
Inactive	-98 (-177; -19)	0.02	-140 (-240; -40)	0.01	0.21 (-0.83; 1.25)	0.69	-33 (-183; 117)	0.67

The model was adjusted for age, height, weight and one EQ-5D dimension or physical activity variable at a time.

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{2575}: mean flow rate between 25 and 75% of FVC.

Table A3 Results of multiple linear regression models – Males

EQ-5D	FEV_1, ml β (95% CI)	p	FVC, ml β (95% CI)	p	FEV_1/FVC, % β (95% CI)	p	FEF_{2575}, ml/s β (95% CI)	p
Problems with								
Mobility								
no	ref.		ref.		ref.		ref.	
some	-118 (-227; -8)	0.04	-111 (-250; 27)	0.12	-0.82 (-1.82; 0.19)	0.11	-184 (-378; 11)	0.07
Self-care								
no	ref.		ref.		ref.		ref.	
some/extreme	-5 (-219; 209)	0.96	-13 (-284; 257)	0.92	-1.02 (-3.03; 0.98)	0.32	-2 (-382; 378)	0.99
Usual activities								
no	ref.		ref.		ref.		ref.	
some/extreme	-119 (-240; 2)	0.05	-151 (-304; 1)	0.05	-0.24 (-1.35; 0.88)	0.68	-130 (-345; 84)	0.23
Having pain/discomfort								
no	ref.		ref.		ref.		ref.	
moderately/extreme	-12 (-92; 69)	0.78	-13 (-115; 88)	0.80	-0.25 (-0.98; 0.49)	0.51	3 (-139; 146)	0.96
Being anxious/depressed								
no	ref.		ref.		ref.		ref.	
Moderately/extreme	-56 (-160; 47)	0.28	-86 (-216; 44)	0.19	0.14 (-0.81; 1.08)	0.77	-23 (-206; 161)	0.81
Physical activity								
Active	ref.		ref.		ref.		ref.	
Moderately active	-65 (-163; 32)	0.19	-112 (-235; 12)	0.08	0.41 (-0.48; 1.31)	0.36	-21 (-195; 153)	0.82
Slightly active	-47 (-170; 76)	0.46	-111 (-267; 44)	0.16	0.87 (-0.26; 1.99)	0.13	64 (-155; 283)	0.57
Inactive	-36 (-141; 70)	0.51	-61 (-194; 72)	0.37	0.10 (-0.87; 1.06)	0.84	-40 (-228; 147)	0.67

The model was adjusted for age, height, weight and one EQ-5D dimension or physical activity variable at a time.

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{2575}: mean flow rate between 25 and 75% of FVC.

Table A4 Results of multiple linear regression models applying GLI z-scores – Females

	Z-score FEV_1		Z-score FVC		Z-score FEV_1/FVC		Z-score FEF_{2575}	
EQ-5D	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Problems with								
Mobility								
no	ref.		ref.		ref.		ref.	
some	-0.20 (-0.42; 0.01)	0.07	-0.28 (-0.48; -0.08)	0.01	0.14 (0; 0.28)	0.05	0.01 (-0.17; 0.18)	0.95
Self-care								
no	ref.		ref.		ref.		ref.	
some/extreme	0.04 (-0.57; 0.66)	0.89	-0.11 (-0.68; 0.47)	0.71	0.14 (-0.27; 0.55)	0.50	0.29 (-0.22; 0.80)	0.27
Usual activities								
no	ref.		ref.		ref.		ref.	
some/extreme	-0.23 (-0.46; 0)	0.05	-0.26 (-0.47; -0.05)	0.02	0.04 (-0.12; 0.19)	0.65	-0.08 (-0.27; 0.11)	0.42
Having pain/discomfort								
no	ref.		ref.		ref.		ref.	
moderately/extremely	-0.02 (-0.18; 0.14)	0.82	-0.10 (-0.25; 0.05)	0.21	0.11 (0.01; 0.22)	0.04	0.06 (-0.07; 0.20)	0.36
Being anxious/depressed								
no	ref.		ref.		ref.		ref.	
moderately/extremely	-0.12 (-0.30; 0.06)	0.20	-0.12 (-0.29; 0.04)	0.14	0.02 (-0.10; 0.14)	0.70	-0.01 (-0.16; 0.14)	0.93
Physical activity								
Active	ref.		ref.		ref.		ref.	
Moderately active	-0.09 (-0.30; 0.11)	0.37	-0.10 (-0.29; 0.09)	0.32	0.01 (-0.13; 0.15)	0.89	0 (-0.17; 0.17)	0.99
Slightly active	-0.19 (-0.45; 0.07)	0.16	-0.25 (-0.49; -0.01)	0.05	0.11 (-0.07; 0.28)	0.23	-0.03 (-0.25; 0.19)	0.82
Inactive	-0.25 (-0.48; -0.03)	0.03	-0.33 (-0.53; -0.12)	<0.01	0.11 (-0.04; 0.26)	0.15	-0.03 (-0.21; 0.16)	0.77

Regression models for standardized Global Lung Function Initiative z-scores that are already adjusted for ethnicity, sex, age, and height were adjusted only for weight and one EQ-5D dimension or physical activity variable at a time.

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{2575}: mean flow rate between 25 and 75% of FVC.

Table A5 Results of multiple linear regression models applying GLI z-scores – Males

	Z-score FEV_1		Z-score FVC		Z-score FEV_1/FVC		Z-score FEF_{2575}	
EQ-5D	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Problems with								
Mobility								
no	ref.		ref.		ref.		ref.	
some	-0.23 (-0.44; -0.01)	0.04	-0.22 (-0.43; -0.02)	0.03	-0.02 (-0.15; 0.12)	0.80	-0.08 (-0.25; 0.09)	0.34
Self-care								
no	ref.		ref.		ref.		ref.	
some/extreme	-0.05 (-0.49; 0.38)	0.82	-0.11 (-0.53; 0.30)	0.60	-0.01 (-0.29; 0.26)	0.93	0.03 (-0.31; 0.38)	0.84
Usual activities								
no	ref.		ref.		ref.		ref.	
some/extreme	-0.26 (-0.51; -0.02)	0.04	-0.29 (-0.53; -0.06)	0.01	0.01 (-0.14; 0.17)	0.86	-0.10 (-0.29; 0.10)	0.33
Having pain/discomfort								
no	ref.		ref.		ref.		ref.	
moderately/extremely	-0.02 (-0.18; 0.14)	0.79	-0.04 (-0.20; 0.11)	0.57	0.03 (-0.07; 0.13)	0.59	0.04 (-0.09; 0.17)	0.54
Being anxious/depressed								
no	ref.		ref.		ref.		ref.	
moderately/extremely	-0.10 (-0.31; 0.12)	0.37	-0.13 (-0.33; 0.07)	0.21	0.04 (-0.09; 0.17)	0.55	0.02 (-0.14; 0.19)	0.80
Physical activity								
Active	ref.		ref.		ref.		ref.	
Moderately active	-0.15 (-0.35; 0.05)	0.14	-0.18 (-0.38; 0.01)	0.06	0.04 (-0.09; 0.16)	0.58	-0.03 (-0.19; 0.13)	0.71
Slightly active	-0.10 (-0.35; 0.16)	0.46	-0.18 (-0.42; 0.07)	0.15	0.13 (-0.03; 0.29)	0.11	0.04 (-0.16; 0.24)	0.71
Inactive	-0.12 (-0.33; 0.10)	0.29	-0.14 (-0.35; 0.07)	0.19	0.01 (-0.13; 0.14)	0.94	-0.07 (-0.24; 0.10)	0.43

Regression models for standardized Global Lung Function Initiative z-scores that are already adjusted for sex, age, and height were adjusted only for weight and one EQ-5D dimension or physical activity variable at a time.

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{2575}: mean flow rate between 25 and 75% of FVC.

Table A6 Results of multiple linear regression models with further adjustment for problems with mobility and physical activity

	Models adjusted for both, *mobility* and physical inactivity					
	Total population[a]		Males[b]		Females[b]	
FEV_1, ml	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
EQ-5D						
Problems with						
Mobility						
no	ref.		ref.		ref.	
some	**-96 (-164; -18)**	**0.01**	**-114 (-225; -3)**	**0.04**	-74 (-154; 5)	0.07
Physical activity						
Active	ref.		ref.		ref.	
Moderately active	-46 (-107; 14)	0.13	-56 (-154; 42)	0.26	-43 (-115; 28)	0.24
Slightly active	-58 (-135; 19)	0.14	-49 (-172; 73)	0.43	-82 (-174; 10)	0.08
Inactive	-41 (-106; 25)	0.23	-24 (-130; 82)	0.66	**-92 (-171;-13)**	**0.02**
FVC, ml						
Problems with						
Mobility						
no	ref.		ref.		ref.	
some	**-104 (-189; -18)**	**0.02**	-105 (-245; 35)	0.14	-100 (-200; 1)	0.05
Physical activity						
Active	ref.		ref.		ref.	
Moderately active	-77 (-153; 0)	0.05	-103 (-227; 20)	0.10	-60 (-151; 31)	0.20
Slightly active	**-111 (-208, -14)**	**0.03**	-114 (-269; 42)	0.15	**-123 (-239; -7)**	**0.04**
Inactive	-74 (-157; 9)	0.08	-50 (-183; 84)	0.47	**-133 (-233; -32)**	**0.01**

[a]Model was adjusted for sex, age, height, weight, *mobility* and physical activity.

[b]Model was adjusted for age, height, weight, *mobility* and physical activity.

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity.

Table A7 Results of multiple linear regression models with further adjustment for problems with usual activity and physical activity

	Models adjusted for both, *usual activity* and physical inactivity					
	Total population[a]		Males[b]		Females[b]	
FEV_1, ml	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
EQ-5D						
Problems with						
Usual activities						
no	ref.		ref.		ref.	
some/extreme	**-91 (-163; -20)**	**0.01**	-114 (-236; 8)	0.07	-79 (-160; 2)	0.06
Physical activity						
Active	ref.		ref.		ref.	
Moderately active	-43 (-103; 18)	0.17	-56 (-155; 42)	0.26	-38 (-110; 34)	0.30
Slightly active	-50 (-127; 28)	0.21	-39 (-163; 84)	0.53	-74 (-166; 18)	0.12
Inactive	-39 (-104; 27)	0.25	-25 (-131; 81)	0.64	**-86 (-165; -7)**	**0.03**
FVC, ml						
Problems with						
Usual activities						
no	ref.		ref.		ref.	
some/extreme	**-113 (-203; -22)**	**0.02**	-141 (-295; 12)	0.07	-95 (-198; 8)	0.07
Physical activity						
Active	ref.		ref.		ref.	
Moderately active	-70 (-147; 6)	0.07	-101 (-225; 23)	0.11	-52 (-143; 40)	0.27
Slightly active	**-100 (-197; -3)**	**0.04**	-102 (-257; 54)	0.20	-112 (-228; 5)	0.06
Inactive	-69 (-152; 14)	0.10	-48 (-181; 86)	0.49	**-124 (-225; -24)**	**0.02**

[a]Model was adjusted for sex, age, height, weight, *usual activity* and physical activity.

[b]Model was adjusted for age, height, weight, *usual activity* and physical activity.

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity.