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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

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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 1 s (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 Among all participants 42% reported no problems in any EQ-5D dimension, 24% were inactive and 32% exercised > 2 h/week. After adjustment, FEV_1 was − 99 ml (95% CI − 166; − 32) and FVC was − 109 ml (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: − 83 ml, 95% CI − 166; 0), but showed no interactions with EQ-5D.

Conclusions Problems with *mobility* or *usual activities*, and inactivity were associated with slightly lower spirometric parameters in lung-healthy adults, suggesting a relationship between perceived physical functioning and volumetric lung function.

Keywords Quality of life · EQ-5D · Physical activity · Spirometry · FEV_1 · FVC

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 with less hospital admissions in COPD [1, 4–6]. Among subjects with asthma, the mean decline in forced expiratory volume in 1 s (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

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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 HRQL 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 0.52–0.84 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 score of 0.94 in males and 0.92 in females [19].

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 [20, 21], we also assessed whether a direct association exists between physical inactivity and lung function, and whether the consideration of inactivity affects 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 [22, 23]. The present analysis was based on the KORA F4L survey, which is the 3-year follow-up of the KORA F4 study including participants with lung function measurements, and the KORA Age survey.

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. Of all participants with obtained spirometry ($N = 1986$), 12 participants were excluded after visual inspection of the flow-curves revealed unreproducible measurements according to international standards [24], resulting in 1974 participants with valid measurements. Further, two participants from KORA Age who did not respond to the EQ-5D questionnaire were excluded. Finally, data of 1972 participants with both, spirometry measurements and information on EQ-5D, were available. 29 (1.5%) participants did not report on all health dimensions; of those, 25 (86%) had one missing only. All the participants provided information on physical inactivity. Information on self-reported physician diagnoses of common diseases including asthma, hay fever, stroke or myocardial infarction, current medication intake up to 7 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 (1) a doctor's diagnosis of emphysema, asthma, chronic bronchitis, or COPD, or (2) the current use of pulmonary medication including inhaled sympathomimetics, anticholinergics, and steroids, or oral leukotriene antagonists, or (3) respiratory symptoms, i.e., cough or phlegm lasting more than 3 months a year, or (4) subjects with airflow limitation as indicated by a measured $FEV_1/FVC < 0.7$ [25], 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 the 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 − 0.205 to 0.999 [26] with higher values indicating better health. In addition to the results for EQ-5D dimensions which are our main focus, we report results for the EQ-5D utility. According to the observed utility score in COPD patients, we categorized the EQ-5D utility in our population into 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. [27], and those with EQ-5D utility < 0.887. The distribution of the EQ-5D utility was highly skewed (S1 Fig. A1); 539 (48%) had the best possible utility score of 0.999, followed by 386 (35%) with a utility score ≥ 0.887. Only 193 (17%) subjects had scores < 0.887, of which 31 (16%) had a utility score < 0.7. Therefore, the validity of the continuous results should be interpreted with caution, and analyses with categorized utility score were considered.

Assessment of physical activity levels was done as part of the standardized interview. The assessment method for activity was first applied and validated in the first MONICA Augsburg (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) Survey in 1984/1985 that was performed prior to the KORA studies in the region of Augsburg. 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 exercise in summer? and (2) How often do you exercise in winter? Possible answers were (a) regularly, > 2 h/week, (b) regularly, 1–2 h/week, (c) < 1 h/week, (d) not at all. A categorization matrix is displayed in Fig. 1. 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 c in combination with b), or *inactive* (c or d in both questions). Subjects engaging regularly in > 2 h of physical activity per week, i.e., those categorized as *active*, who nearly meet the WHO recommended threshold of 2.5 h of physical activity per week [28], 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 [24] 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 3–8 spirometric maneuvers per test. A detailed description has been published previously [29]. Spirometric parameters included FEV_1, FVC, FEV_1/FVC, and forced expiratory flow between 25 and 75% of exhaled FVC ($FEF_{25–75}$). The analyzed parameters point towards different domains of respiratory function [30, 31]. FVC is a measure of the maximal breathable lung volume, determined during forced exhalation. FEV_1 is dependent on both, lung volume and airway size. The ratio of both parameters (FEV_1/FVC) is indicative of airway function and a low ratio is associated with airflow limitation. $FEF_{25–75}$ measures airflow in the mid and small conducting airways. Sex, age, height, and ethnicity are important predictors of lung function and were therefore used in prediction equations from the Global Lung

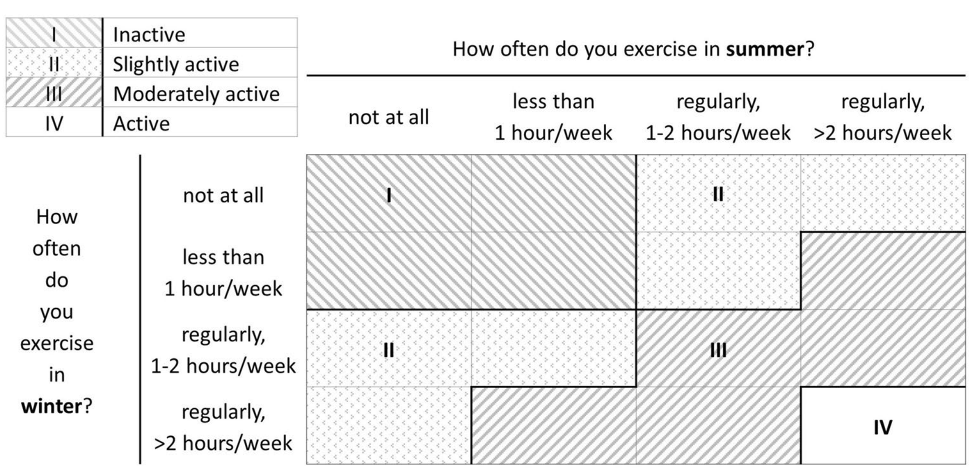

Fig. 1 Categorization of activity levels. Participants were categorized into activity levels I–IV based on the duration of reported exercise in summer and winter

Function Initiative (GLI) to provide standardized references across different populations [8]. Compared to adjustment in multiple linear regression models, standardized GLI z-scores comprise a more complex and refined adjustment for sex, age, height, and ethnicity accounting for non-linear relationships. Thus, we report results for standardized z-scores for each parameter to provide information which is comparable to other investigations as z-scores are standardized to a mean of 0 and a standard deviation of 1 and further, to support our results found when using absolute values.

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 Pearson's 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). As sensitivity analysis, subjects reporting extreme problems in the investigated dimension were excluded from the analyses.

To avoid overadjustment, separate adjusted linear regression models were calculated to examine the relationships between each EQ-5D health dimension and 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. Interaction effects between the EQ-5D dimensions and physical inactivity were tested for each EQ-5D dimension separately by inclusion of an interaction term with activity levels in linear regression models adjusted for sex, age, height, and weight. 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 3 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 including adjustment for sex, age, height, and ethnicity) served as outcome were adjusted for additional variables only. All participants were Caucasian, therefore ethnicity was not considered in models with absolute values. Outliers were defined as greater/less than the mean plus/minus four 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) are shown in Table 1. Analyzed participants had mean GLI z-scores for FEV_1 and FVC of 0.71 and 0.61, respectively. 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, $p<0.01$). 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, $p<0.01$ in chi-squared test).

Applying continuous EQ-5D utility in regression models adjusting for sex, age, height, and weight suggests an association between better lung function and higher EQ-5D utility (S1 Fig. A1, S2 Table A1). Further, subjects in the lowest EQ-5D category had a − 87 ml (95% CI − 160; − 15) lower

Table 1 Population characteristics

	Males ($n=545$) Mean (SD) or % (N)	Females ($n=587$)	Total ($n=1132$)
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)	5.0 (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)
$FEF_{25–75}$(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 $FEF_{25–75}$*	0.41 (0.74)	0.25 (0.82)	0.33 (0.79)
Generic health-related quality of life			
EQ-5D—utility score	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]			
Mobility			
No problems in walking about	83.1 (453)	82.6 (485)	82.9 (938)
Some problems in walking about	16.9 (92)	17.4 (102)	17.1 (194)
Confined to bed	–	–	–
Self-care			
No problems with self-care	96.5 (525)	98.3 (576)	97.4 (1101)
Some problems washing or dressing	3.5 (19)	1.4 (8)	2.4 (27)
Unable to wash or dress him/herself	0 (0)	0.3 (2)	0.2 (2)
Usual activities			
No problems with performing usual activities	87.9 (478)	85.8 (502)	86.8 (980)
Some problems with performing usual activities	11.9 (65)	14.0 (82)	13.0 (147)
Unable to perform usual activities	0.2 (1)	0.2 (1)	0.2 (2)
Pain/discomfort*			
No	53.1 (288)	46.2 (270)	49.6 (558)
Moderate	44.7 (242)	51.9 (303)	48.4 (545)
Extreme	2.2 (12)	1.9 (11)	2.0 (23)
Anxiety/depression*			
No	82.9 (450)	72.7 (426)	77.6 (876)
Moderate	16.6 (90)	26.3 (154)	21.6 (244)
Extreme	0.6 (3)	1.0 (6)	0.8 (9)

Table 1 (continued)

	Males ($n=545$) Mean (SD) or % (N)	Females ($n=587$)	Total ($n=1132$)
Physical activity*			
Inactive	22.2 (121)	25.6 (150)	23.9 (271)
Slightly active	13.4 (73)	14.0 (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)

SD standard deviation, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, FEF_{25-75} forced expiratory flow between 25 and 75% of FVC

*p-Value <0.05 in t-test or chi-squared test (males vs. females)

[a]Comparisons between sexes were performed using dichotomous variables (no vs. any)

FEV_1 and − 96 (95% CI − 187; − 4) lower FVC compared to those within the category with the best possible utility.

Data on self-reported time spent in exercise revealed that 32% of the participants engaged regularly (> 2 h/week) in physical activity, while 24% were categorized as inactive, i.e., engaging in physical activity < 1 h/week or not at all ($p<0.01$).

Self-reported physical inactivity and lung function

In regression models adjusted for sex, age, height, and weight, associations of physical inactivity with FVC and GLI z-scores for FEV_1 and FVC were found (Table 2, S2 Table A2). Less activity was associated with lower FVC, e.g., inactive subjects had an estimated difference in FVC of − 83 ml (95% CI − 166; 0) 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) and for FVC (− 0.28, 95% CI − 0.43; − 0.14) (S2 Table A2). For FVC, slightly active participants had an estimated decrease of − 111 ml (95% CI − 209; − 14) compared to active participants, which was 28 ml higher than for inactive participants. However, this did not hold true for the model based on the z-score for FVC with a lower decrease in the slightly active group (− 0.24, 95% CI − 0.41; − 0.07) than in the inactive group. Adjustment for further covariates, such as hay fever or multimorbidity, did not substantially change the aforementioned results, i.e., effect estimates changed by a maximum of 8 ml, e.g., in models for FVC after additional adjustment for stroke ($p=0.08$) (S2 Table A3). 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 (S2 Tables A4–A7). 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 (S2 Table A4). No associations were observed for FEV_1/FVC or FEF_{25-75}.

Associations of EQ-5D dimensions with lung function

After adjusting for sex, age, height, and weight in regression models, 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 negative association was found for being *anxious/depressed* with FVC ($p=0.05$) and for problems with *mobility* with FEF_{25-75} ($p=0.048$), 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 for FEV_1 and FVC (S2 Table A2). 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 (S2 Tables A3 and A8). 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 − 99 ml for

Table 2 Results of multiple linear regression analyses

	FEV_1 (ml)		FVC (ml)		FEV_1/FVC (%)		$FEF_{25–75}$ (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)**	**0.048**
Self-care								
No	Ref.		Ref.		Ref.		Ref.	
Some/unable to	−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/unable to	**−97 (−169; −26)**	**0.01**	**−124 (−214; −33)**	**0.01**	−0.26 (−1.03; 0.51)	0.51	−106 (−236; 23)	0.11
Pain/discomfort								
No	Ref.		Ref.		Ref.		Ref.	
Moderate/extreme	−5 (−54; 45)	0.85	−10 (−73; 53)	0.75	0.02 (−0.51; 0.55)	0.94	6 (−84; 96)	0.89
Anxiety/depression								
No	Ref.		Ref.		Ref.		Ref.	
Moderate/extreme	−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)**	**0.049**	0.23 (−0.47; 0.93)	0.51	−8 (−127; 110)	0.89

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

Statistically significant associations ($p < 0.05$) are highlighted in bold

CI confidence interval, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *$FEF_{25–75}$* forced expiratory flow between 25 and 75% of FVC

FEV_1, and −94 ml (95% CI −180; −7), instead of −109 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 $FEF_{25–75}$ models. In females, associations found in the total population for *mobility* and *usual activities* with FEV_1 and FVC remained significant (*mobility*: FEV_1: $\beta = -81$ ml, $p = 0.04$; FVC: $\beta = -109$ ml, $p = 0.03$; *usual activities*: FEV_1: $\beta = -86$ ml, $p = 0.04$; FVC: $\beta = -106$ ml, $p = 0.04$) (S2 Table A4). Results for males showed similar estimates, but were significant only for the association between FEV_1 and *mobility* (*mobility*: FEV_1: $\beta = -118$ ml, $p = 0.04$; FVC: $\beta = -111$ ml, $p = 0.12$; *usual activities*: FEV_1: $\beta = -119$ ml, $p = 0.05$; FVC: $\beta = -151$ ml, $p = 0.05$) (S2 Table A5). No associations were observed with FEV_1/FVC and $FEF_{25–75}$. Having problems with *self-care*, having *pain/discomfort*, or being *anxious/depressed* were not associated with any spirometric indices. Comparable results were obtained when applying GLI z-scores (S2 Tables A6 and A7).

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, $p < 0.01$). No interaction effects, i.e., only interaction terms with $p > 0.05$, were present between each EQ-5D dimension and physical activity levels in linear regression models adjusted for sex, age, height, and weight. 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 (S2 Tables A9 and A10).

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 five 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 a German Health survey [32]. 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, males engaged more often in regular (≥ 2 h/week) sports activity compared to females (29.3 vs. 21.6%) [32]. 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 [20, 21]. Depending on the level of inactivity, FEV_1 was reduced between 20 and 170 ml [21]. The magnitude and direction of findings correspond to our results, which indicated about 100 ml lower FVC 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 [27]. 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. Applying the EQ-5D utility showed a similar negative trend with lower lung function as shown by Wacker et al. among COPD patients [27], and suggests a negative association of EQ-5D utility and lung function already in apparently lung-healthy adults.

Strengths 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, i.e., we cannot determine causal pathways between EQ-5D dimensions and activity levels, e.g., if inactivity is caused by worse quality of life or vice versa. Thus, we can only assess if inactivity influences the association between

EQ-5D dimensions and lung function. 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 45–89 years, of whom 20% had at least 2 chronic health conditions not directly related to lung function impairment. Although we applied information on doctor's diagnoses of lung diseases, lung medication intake, and a $FEV_1/FVC < 0.07$ as exclusion criteria, we still might have missed some participants with undiagnosed asthma. Post-bronchodilation data were not available to detect subjects with reversible airway limitation. Further, our results should be interpreted with caution due to the small effect estimates of about 80–120 ml for volumetric indices with significance levels near 0.05 resulting in an arguable clinical relevance. We did not adjust for multiple testing as the spirometric indices as well as the EQ-5D dimensions were correlated. Across the sensitivity analyses the same trend was evident, while not all results remained statistically significant. Thus, further studies are needed to support our findings of the association between physical functioning and lung function in healthy lungs. 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.

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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.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval 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. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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