From

Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine
University Hospital of Munich, Ludwig-Maximilians-University

Director: Prof. Dr. med Dennis Nowak

and

Institute of Epidemiology
Helmholtz Zentrum München
- German Research Center for Environmental Health (GmbH)

Head of the research group *Lung Epidemiology*: Prof. Dr. med. Holger Schulz

---

Associations of environmental and lifestyle factors with lung function in youth and adulthood

---

Thesis

Submitted for a Doctoral degree in Human Biology at the Faculty of Medicine,
Ludwig-Maximilians-University of Munich

By

Agnes Luzak

From

Elbing

2018

With approval of the Medical Faculty of the
Ludwig-Maximilians-University of Munich

Supervisor / Examiner:	Prof. Dr. med. Dennis Nowak
Co-Examiners:	Prof. Dr. med. Jürgen Behr
	Prof. Dr. med. Markus Ege
	Prof. Dr. med. Jörg Schelling
Co-Supervisor:	Prof. Dr. med. Holger Schulz
Dean:	Prof. Dr. med. dent. Reinhard Hickel
Date of oral examination:	09.07.2018

Contents

Summary

Numerous factors influence lung function throughout the life course. Exposure to risk factors such as passive smoke or respiratory infections early in life have the potential to affect lung function already during lung development and growth. Such insults may result in respiratory impairment, a higher susceptibility to chronic lung diseases, and abnormal lung function decline in adulthood. Although the main determinants of lung function variability are sex, age, height, and ethnicity, the inter-subject variability increases in older age, indicating a complex interplay of early life, environmental, and lifestyle factors throughout life.

While many studies have identified factors that are associated with lung function, most examined only one or a few factors at specific periods of life or focused on specific lung diseases as outcomes. Research on the effects of diverse early and current factors at a certain stage or among lung-healthy populations is rare. Therefore, the purpose of this thesis was to investigate on a population-based level which factors are associated with lung function at two periods in life, in adolescence at the stage of almost finalized lung growth and adulthood during age-related lung function decline, respectively. A further aim was to determine which domains of respiratory function obtainable by spirometry, i.e. lung volume or airway function, are involved in the associations found.

Cross-sectional analyses were carried out in adolescents using data from the two German birth cohorts GINIplus and LISAplus at the 15-year follow-up and further in adults aged 45-89 years using population-based data of the KORA cohort studies. Early life events as well as current environmental and lifestyle factors were investigated in adolescents representing the stage of lung growth, while analyses at the stage of age-related lung function decline focused on environmental and lifestyle factors in adulthood.

In adolescents, emphasis was put on the analysis of aeroallergen sensitization as it is associated with a higher risk of developing allergic respiratory diseases. Although the prevalence of sensitization to aeroallergens at age 15 years was high among adolescents with asthma or allergic rhinitis, the grade of sensitization to aeroallergens i.e. no sensitization up to polysensitization was not associated with lung volume or airway function in lung-healthy adolescents or those with asthma or rhinitis.

Moreover, the associations of early life (e.g. parental atopy and education, birth weight, breastfeeding, peak weight velocity, and lower respiratory tract infections), current lifestyle and environmental factors (e.g. active smoking, serum vitamin D concentration, body mass index (BMI), and exposure to air pollution or second-hand smoke), and allergic diseases (e.g. asthma, rhinitis, and allergen sensitization) with spirometric lung function were analyzed. Besides the well-known determinants sex, height, and asthma, weight gain and pulmonary infections during infancy, as well as current BMI, indoor second-hand smoke exposure and serum vitamin D concentration were identified as prevalent factors associated with lung function in 15-year-olds. Overall, the results found for current environmental and lifestyle factors indicated associations with both lung volume and airway function, whereas weight gain and pulmonary infections in early life were consistently associated with lower airway function. However, early life events explained in median less than 5% of the variance, whereas at least

75% was captured by sex and height. Nevertheless, small effects already present during the stage of lung growth might have the potential to modify lung function in adolescence.

In adults, environmental and lifestyle factors were analyzed using questionnaire-based information on five quality of life health domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Because self-reported physical functioning was found to be associated with lung function, information on health domains was complemented by the investigation of self-reported physical activity levels. Moreover, the association between physical activity and lung function was more deeply analyzed using rarely investigated German population-based data on physical activity, obtained by accelerometers. Physical activity levels, duration pattern and associations with common chronic diseases including asthma and chronic obstructive pulmonary disease were analyzed. Furthermore, the association of time spent in moderate to vigorous physical activity (MVPA) with spirometric lung function, and additionally with measures of pulmonary gas exchange and respiratory muscle strength was examined in lung-healthy participants.

Overall, adults spent about two thirds of the day in sedentary activity, whereas the median time spent in MVPA was only 3%. About 87% of MVPA was accumulated in MVPA bouts of less than 10 minutes, indicating sporadic activity instead of exercise. MVPA was lower among older and obese subjects, while common chronic diseases were not associated with time spent in MVPA. In lung-healthy adults, the most active participants had slightly higher volumetric indices, i.e. about 150 ml higher forced vital capacity and forced expiratory volume in 1 second compared to the least active participants which would correspond to a normal age-related decline of about 6 years. In line with this finding, self-reported inactivity, i.e. no or sporadic exercise, was negatively associated with spirometric volumes. This tendency was further supported by the associations found between slightly lower spirometric volumes and reporting problems with mobility and usual activities, respectively, whereas no associations were found for the other health domains.

In summary, the results presented suggest that at the stage of lung growth in adolescence, specific early life events such as weight gain or pulmonary infections should be considered particularly in studies of airway function and, furthermore, that physical activity might be associated with lung volumes in lung-healthy adults representing the period of age-related lung function decline. Although these findings are not generalizable to other populations and the effect sizes found were small, the results nevertheless highlight the need to consider specific factors for the investigation of lung volumes and airway function at different age periods in life. Moreover, studies determining factors associated with lung function already in lung-healthy populations might help define starting points for early health interventions.

Zusammenfassung

Das ganze Leben hindurch beeinflussen zahlreiche Faktoren die Lungenfunktion. Bereits in der frühen Entwicklungs- und Wachstumsphase der Lunge können Risikofaktoren, wie Passivrauchexposition oder respiratorische Erkrankungen, Beeinträchtigungen der Lungenfunktion verursachen, welche das Risiko für chronische Lungenerkrankungen im Erwachsenenalter erhöhen und eine schnellere altersabhängige Lungenfunktionsabnahme bedingen können. Obwohl Geschlecht, Alter, Größe und Herkunft, die interindividuelle Variabilität der Lungenfunktion maßgeblich bestimmen, steigt in höherem Alter die Variabilität der Lungenfunktion an, was auf eine komplexe, lebenslange Wechselwirkung von frühkindlichen Ereignissen sowie Umwelt- und Lebensstilfaktoren schließen lässt.

Zahlreiche Studien haben Faktoren identifiziert, die mit der Lungenfunktion assoziiert sind, wobei die meisten davon lediglich einen oder nur einige Faktoren während spezifischer Lebensphasen untersucht haben oder den Fokus auf den Zusammenhang mit Lungenerkrankungen legten. Viel seltener sind hingegen Studien, die verschiedene frühe und gegenwärtige Faktoren während spezifischer Lebensphasen oder lungengesunde Populationen untersuchen. Ziel dieser Arbeit war es, auf Populationsebene zu untersuchen, welche Faktoren eine Assoziation mit spirometrischen Lungenfunktionsparametern während zweier spezifischer Lebensphasen zeigen: bei Jugendlichen in der finalen Phase des Lungenwachstums und bei Erwachsenen während der normalen altersbedingten Lungenfunktionsabnahme. Zudem wurde betrachtet welcher Bereich der Lungenfunktion, d.h. Lungenvolumen oder Atemwegsfunktion, potenzielle Zusammenhänge zeigt.

In Querschnittsanalysen wurden Daten von 15-jährigen Jugendlichen aus zwei deutschen Geburtskohorten GINIplus und LISAplus sowie von Erwachsen im Alter von 45-89 Jahren aus den deutschen Kohortenstudien KORA ausgewertet. Frühkindliche Ereignisse und gegenwärtige Umwelt- und Lebensstilfaktoren wurden bei Jugendlichen untersucht, die die Lungenwachstumsphase repräsentieren. Bei Erwachsenen, in der Phase der Lungenfunktionsabnahme, lag der Fokus auf aktuellen Umwelt- und Lebensstilfaktoren.

Bei Jugendlichen wurde zunächst spezifisch untersucht, ob die Sensibilisierung gegen Inhalationsallergene, die ein höheres Risiko für allergische respiratorische Erkrankungen birgt, bereits negativ mit Lungenfunktion assoziiert ist. Obwohl die Prävalenz von Asthma und allergischer Rhinitis bei sensibilisierten 15-Jährigen hoch war, wurde weder bei Lungengesunden, Asthmatikern, noch bei denen mit Rhinitis ein Zusammenhang zwischen dem Sensibilisierungsgrad, d.h. keine Sensibilisierung bis hin zur Polysensibilisierung, und Lungenvolumen oder Atemwegsfunktion beobachtet.

Des Weiteren wurden Assoziationen zwischen Lungenfunktion und frühen Ereignissen (z.B. Atopie und Bildung der Eltern, Geburtsgewicht, Stillen, Gewichtszunahme, und untere Atemwegsinfekte), gegenwärtigen Umwelt- und Lebensstilfaktoren (z.B. Rauchen, Serum Vitamin D Konzentration, Body-Mass-Index (BMI), Belastung durch Luftverschmutzung, und Passivrauchexposition) und allergischen Erkrankungen (z.B. Asthma, Rhinitis, und Allergen-sensibilisierung) bei 15-Jährigen untersucht. Neben den bekannten Determinanten, Geschlecht, Größe und Asthma, überwogen unter allen Faktoren die Assoziationen zwischen Lungenfunktion und folgenden Faktoren: frühe Gewichtszunahme und Lungeninfekte als frühkindliche Ereignisse sowie BMI, häusliche Passivrauchbelastung und Serum Vitamin D

Konzentration als gegenwärtige Faktoren bei 15-Jährigen. Während die gegenwärtigen Umwelt- und Lebensstilfaktoren Zusammenhänge sowohl mit Lungenvolumen als auch Atemwegsfunktion zeigten, waren die frühkindlichen Ereignisse, Gewichtszunahme und Lungeninfekte, vorwiegend mit geringerer Atemwegsfunktion assoziiert. Im Gegensatz zu Geschlecht und Größe, die rund 75% der Varianz erklärt haben, lag für frühe Ereignisse der Median bei unter 5% erklärter Varianz, wobei selbst kleine Effekte, die sich bereits während der Lungenwachstumsphase manifestieren, modulierend auf die Lungenfunktion im Jugendalter wirken können.

Bei Erwachsenen wurden Umwelt- und Lebensstilfaktoren mithilfe von Fragen zu fünf gesundheitsbezogenen Domänen der Lebensqualität (Mobilität, Für sich selbst sorgen, Allgemeine Tätigkeiten, Schmerzen/körperliche Beschwerden und Angst/Depression) analysiert. Da Assoziationen zwischen körperlichem Gesundheitszustand und Lungenfunktion berichtet wurden, wurden auch fragebogenbasierte Daten zur körperlichen Aktivität in die Analysen einbezogen. Darüber hinaus wurden bisher selten auf deutscher Populationsebene untersuchte Akzelerometerdaten zur körperlichen Aktivität ausgewertet. Betrachtet wurden die verschiedenen Aktivitätslevel und ihre Dauer sowie ihr Zusammenhang mit häufigen chronischen Erkrankungen, wie Asthma oder chronisch obstruktiver Lungenerkrankung. Bei lungengesunden Teilnehmern wurde zudem der Zusammenhang zwischen moderater bis anstrengender körperlicher Aktivität (MVPA) und spirometrisch erfasster Lungenfunktion, sowie mit der pulmonalen Gasaustauschkapazität und Atemmuskelkraft analysiert.

Rund zwei Drittel des Tages waren die Teilnehmer körperlich inaktiv, während im Schnitt nur rund 3% der Zeit in MVPA verbracht wurde. Insgesamt waren rund 87% der MVPA kürzer als 10 Minuten in Folge, was mehr auf sporadische, statt sportliche Aktivität hindeutete. Ältere und adipöse Teilnehmer verzeichneten weniger MVPA, während keine Zusammenhänge mit den untersuchten chronischen Erkrankungen beobachtet wurden. Unter den Lungengesunden hatten die aktivsten Teilnehmer im Vergleich zu den inaktivsten etwas höhere Lungenvolumina, d.h. eine um rund 150 ml höhere forcierte Vital- und Einsekundenkapazität, was einem normalen altersabhängigen Lungenfunktionsabfall von circa 6 Jahren entsprechen würde. Ergebnisse zur Aktivität basierend auf Fragebogendaten stützten dieses Ergebnis durch einen Zusammenhang zwischen Inaktivität, d.h. kein oder nur sporadischer Sport, und niedrigeren spirometrischen Volumina. Teilnehmer mit Problemen in den aktivitätsrelevanten Gesundheitsdomänen Mobilität und allgemeine Tätigkeiten zeigten die gleiche Tendenz, während für die anderen Gesundheitsdomänen keine Assoziationen beobachten wurden.

Zusammenfassend deuten diese Ergebnisse darauf hin, dass bei Jugendlichen, in der finalen Phase des Lungenwachstums, spezifische frühkindliche Ereignisse wie Gewichtszunahme und Lungeninfekte besonders in Studien zur Atemwegsfunktion berücksichtigt werden sollten. Darüber hinaus wurde gezeigt, dass bereits bei lungengesunden Erwachsenen, in der Phase der Lungenfunktionsabnahme, körperliche Aktivität mit höheren Lungenvolumina assoziiert sein kann. Obwohl diese Ergebnisse nur eingeschränkt auf andere Populationen übertragbar sind und kleine Effekte beobachtet wurden, zeigen sie dennoch auf, dass spezifische Faktoren für verschiedene Lebensphasen zur Analyse von Lungenvolumen und Atemwegsfunktion berücksichtigt werden sollten. Zudem könnten Studien bei lungengesunden Personen dazu beitragen Ansätze für frühe Interventionen zu definieren.

Abbreviations

BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
EQ-5D	EuroQol five dimensions questionnaire
$FEF_{25,50,75}$	Forced expiratory flows at 25%, 50% and 75% of exhaled FVC
$FEF_{25–75}$	Forced expiratory flow between 25% and 75% of FVC
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINIplus	German Infant study on the influence of Nutrition Intervention plus air pollution and genetics on allergy development
KORA	Cooperative Health Research in the Region of Augsburg
LISAplus	Life-style related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics
MVPA	Moderate to vigorous physical activity
PEF	Peak expiratory flow
PI_{max}	Maximal inspiratory mouth pressure
TLCO	Transfer factor of the lung for carbon monoxide
VA	Alveolar volume
WHO	World Health Organization

1 Background

Structural lung development begins *in utero* and continues for the first few years of life until a plateau in lung growth is reached at the age of 20-25 years and subsequently followed by a slow age-related lung function decline [1, 2]. Heritability contributes highly to the inter-individual variability of pulmonary function [3, 4]. Related to genetic variability, sex, age, height, and ethnicity were all shown to be key determinants of lung function [5-7]. However, various other factors were also found to be associated with lung function or chronic respiratory diseases and may therefore act as modifiers of lung function throughout the life course [1, 8-12]. Thus, a continuous interplay between genetic predisposition, early life events, environmental and lifestyle factors, and disease is suggested to influence the variability of lung function during lung growth and age-related decline [11-14]. This is indicated by an increasing coefficient of variation for lung function parameters with age, beginning in adolescence, e.g. from near 10% at 15 years of age to about 18% at age 80 years for the forced vital capacity (FVC) [7]. An overview of factors that were investigated in this thesis are displayed in Figure 1.

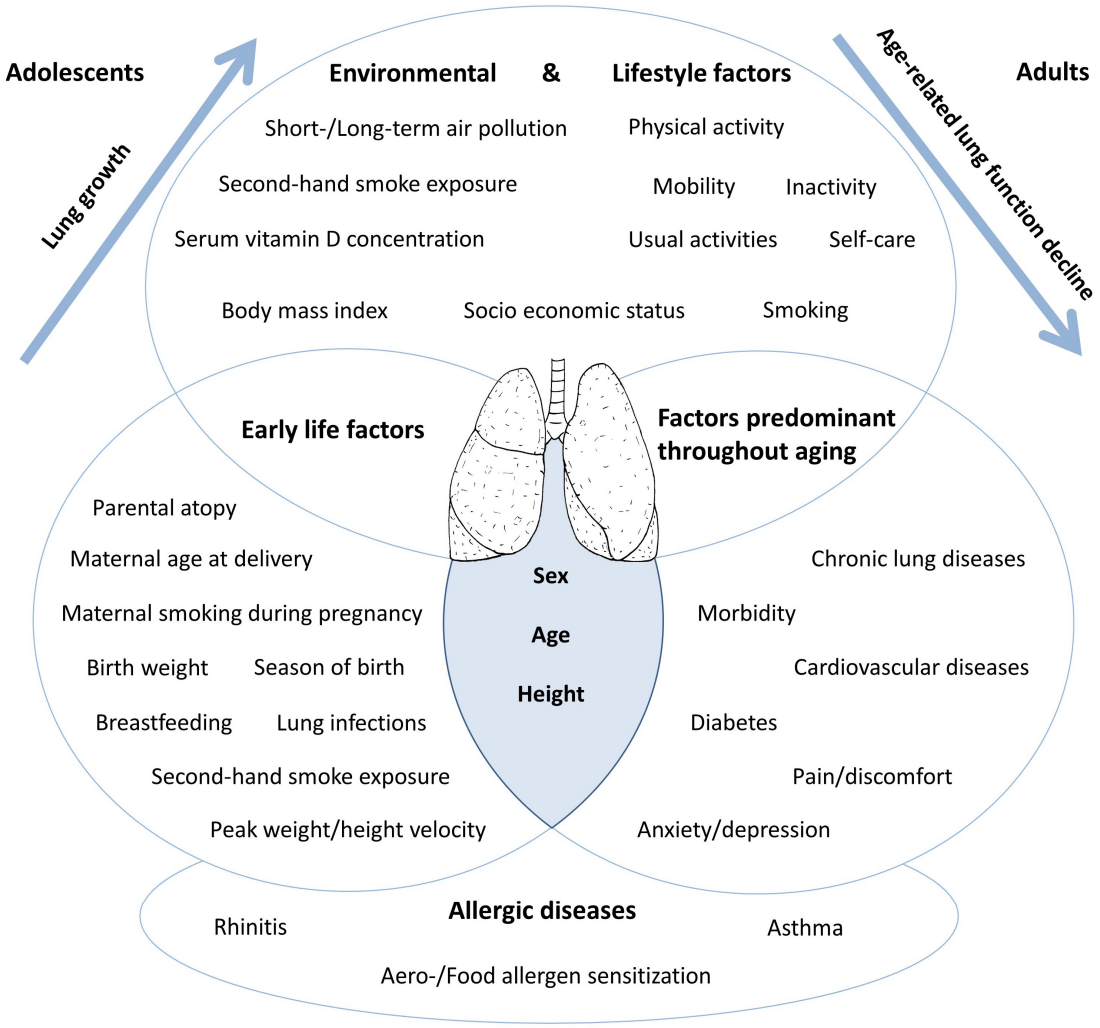


Figure 1 Overview of investigated factors that might be associated with lung function during the life course. Available data was used from the GINIplus, LISAplus, and KORA studies.

Most previous studies examined only one or a few factors at specific periods of life [8, 10, 15-25]. For example, a study among youth showed a statistically significant association between birth weight and lung function at age 8-9 years, but not at age 14-17 years [16]. Moreover, low birth weight was shown to be associated with lower lung function in adults [17, 18]. In one epidemiological study in Tunisian children aged 6-16 years the interplay of socioeconomic status and several early life and environmental factors was addressed [26]. The type of heating, e.g. electric versus gas, was shown to have the strongest relation with lung function of healthy Tunisian children along with the well-established factors – sex, age, height and weight.

Adverse influences occurring early in life may result in reduced lung growth and lung function impairment followed by a higher susceptibility to both chronic lung diseases and abnormal lung function decline in older age [1, 8, 12, 14]. Early life factors such as passive smoke exposure and respiratory infections during early childhood were found to be associated with decreased lung function in both child- and adulthood along with a higher risk of respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD) [8, 22-24]. Furthermore, air pollution showed negative effects on lung function in youth and adults, but as no clear most vulnerable time point could be determined this is suggestive of an interchanging effect based on exposure and accumulation over the life course [25, 27].

These studies suggest that the relative importance of factors might differ in certain stages of life and investigations at different age periods could add essential information on their impacts on lung health and respiratory function. Moreover, approaches that investigate the effects of diverse early and current factors at one age period are rare, but might contribute to the identification of major factors influential at specific stages of life.

With respect to the phase of age-related lung function decline in adulthood, comprehensive research into the determinants of chronic lung disease is a major research focus due to both the considerable importance for clinical practice and the increasing burden of asthma and COPD worldwide [14, 28]. Thus, the associations between lung function and environmental and lifestyle factors such as physical activity or self-rated quality of life are often investigated through comparisons of participants with chronic lung diseases and controls or, as well in clinical populations and show negative effects with less activity and disease severity [15, 29-35]. Whether these associations found in patients with respiratory diseases also apply to lung-healthy populations is less well studied. Two population-based investigations found positive associations of physical functioning with lung function, whereas the association with mental functioning remained inconclusive [36, 37]. Likewise, questionnaire-based physical activity was shown to be associated with slower lung function decline [38-41]. More evidence is needed to determine whether even those with healthy lung function at the stage of age-related lung function decline might benefit from more physical activity and whether lung-healthy participants with favorable lung function show fewer health problems.

2 Rationale and Methods

The aim of this thesis was to investigate which factors are associated with lung function, analyzing cross-sectional data at specific age stages in life and differentiating between spirometric indices for lung volume and airway function (Figure 2). The stage of lung growth was addressed using data from two German birth cohorts at the 15-year follow-up and the stage of age-related decline was investigated using population-based data of adults aged 45-89 years. This thesis is based on five publications. An overview of analyzed factors assigned to the corresponding publication is displayed in Figure 2.

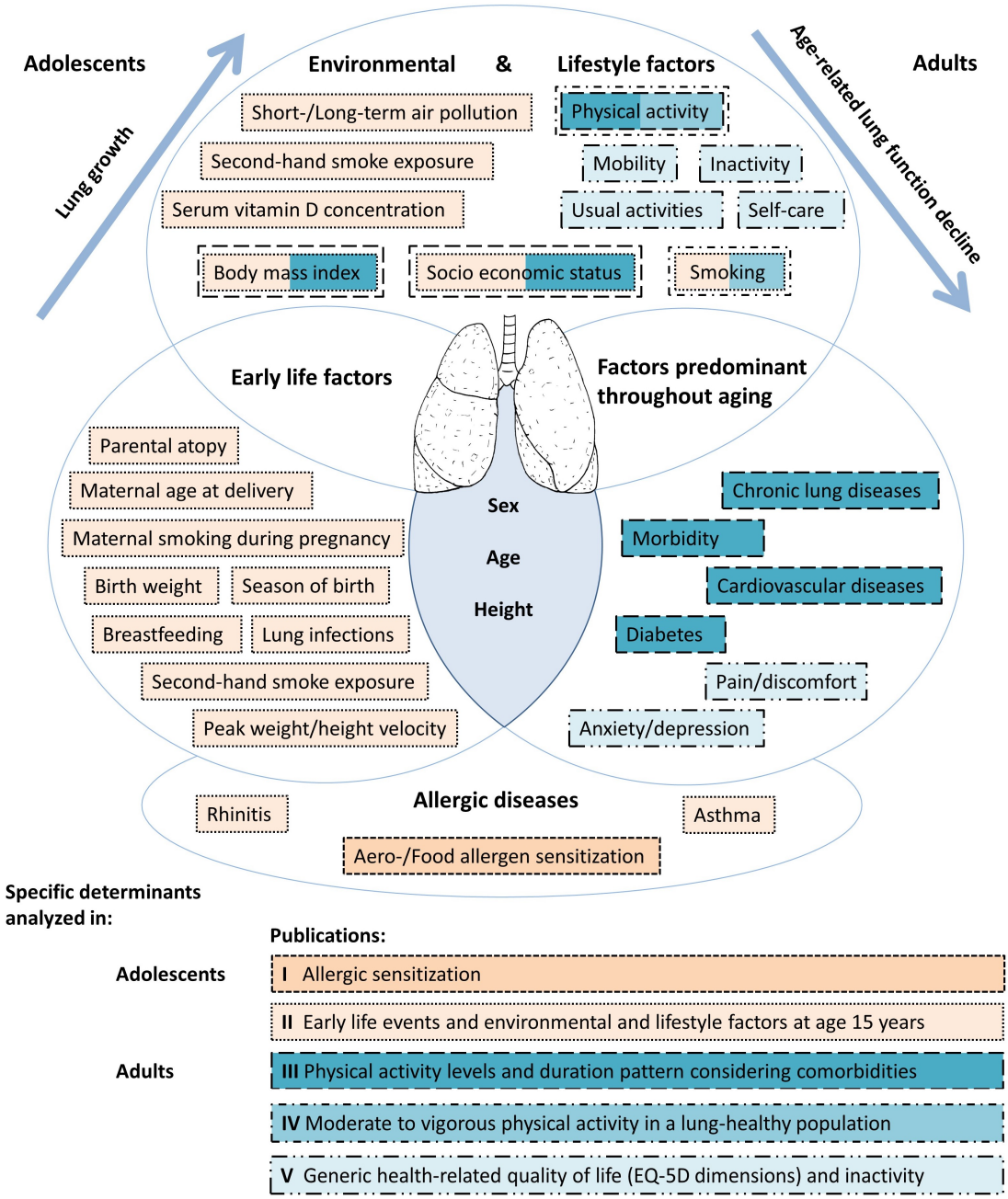


Figure 2 Overview and assignment to publications of investigated factors at the stage of lung growth in adolescents [**I** and **II**] and age-related decline in adulthood [**III-V**]. Available data was used from the GINIplus, LISAplus, and KORA studies. Shading and frame of the boxes indicate the publications [**I-V**] in which this factor was investigated as main focus.

The five publications have been published by Annals of Allergy, Asthma & Immunology [**I**], Respiratory Research [**II**], PLoS ONE [**III**], BMC Pulmonary Medicine [**IV**] and Quality of Life Research [**V**]. As first author of all five manuscripts, I was significantly involved in the definition of the research questions and study designs. Further, I was responsible for the statistical analyses, interpretation of results and manuscript preparation considering suggestions from my supervisors, co-authors and reviewers.

2.1 Specific Aims

2.1.1 Adolescents

At the stage of lung growth in adolescents, available data comprised early life (e.g. parental atopy and education, birth weight, breastfeeding, peak weight velocity, lower respiratory tract infections), current lifestyle and environmental factors (e.g. active smoking, serum vitamin D concentration, body mass index (BMI), exposure to air pollution or second-hand smoke), and allergic diseases (e.g. asthma, rhinitis, aeroallergen sensitization). Overall, 21 early life events and current factors were available to be analyzed in a comprehensive approach. Furthermore, aeroallergen sensitization was more deeply analyzed as it is associated with a higher risk of developing allergic respiratory diseases and wheezing, but whether there is a direct association between higher grade of sensitization and lower lung function remained inconclusive [42-45].

According to the research aim two main objectives were defined as follows:

- To investigate whether sensitization to common aeroallergens is associated with spirometric lung function parameters in 15-year-olds after stratification by allergic respiratory disease [Publication **I**].
- To analyze associations of diverse early life events and current environmental and lifestyle factors with spirometric measures of central and peripheral airway function and, furthermore, to investigate the relative importance of early life events compared to current factors [Publication **II**].

2.1.2 Adults

At the stage of age-related lung function decline in adults, information on five health dimensions - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression assessed via the EuroQol 5 dimensions (EQ-5D) questionnaire were used [46]. These domains were considered as surrogate for environmental and lifestyle factors potentially reflecting positive and negative influences on lung function. Further, reported problems for the health domains mobility and usual activities i.e. domains related to physical functioning, were complemented by the investigation of self-reported physical activity levels. Moreover, physical activity was more deeply investigated because of its known association with lung function in clinical cohorts [31], while there is little existing evidence on this association regarding healthy lung function variability on a population-based level. Therefore, rarely investigated German population-based data on physical activity obtained by accelerometers over a one-week period were used to determine activity levels and its associations with different lung function

domains covering lung volume and airway function, as well as pulmonary gas exchange and respiratory muscle strength.

According to the research aim three main objectives were defined as follows:

- To characterize accelerometer-based overall physical activity, activity levels and duration pattern in German adults and to investigate the associations with common chronic diseases [Publication **III**].
- To investigate the association of accelerometer-based physical activity with respiratory function measured by spirometry and, moreover, with measures of pulmonary gas exchange (TLCO/VA) and inspiratory muscle strength (PI_{max}) in lung-healthy German adults [Publication **IV**].
- To examine the associations of the health domains - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and self-reported physical inactivity with spirometric indices within the physiological variability of respiratory function of lung-healthy German adults [Publication **V**].

2.2 Methods

2.2.1 Study population

In adolescents, data from the German Infant study on the influence of Nutrition Intervention plus air pollution and genetics on allergy development (GINIplus) [47] and the study on Life-style related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics (LISAplus) [48] were used (Figure 3). Both are prospective German birth cohorts [49] with up to now each 15 years of follow-up.

In GINIplus, 5991 full-term newborns were recruited between September 1995 and July 1998 in the cities of Munich and Wesel. Newborns with a family history of allergic diseases were asked to participate in the intervention group to investigate the effect of three different types of hydrolyzed formula on allergy development (N=2252). All others participated in the observational group (N=3739). In LISAplus, 3094 full-term newborns were recruited between December 1997 and January 1999 in the area of Munich, Wesel, Leipzig and Bad Honnef. As the data of GINIplus and LISAplus were pooled for the analyses, only participants from Munich and Wesel were considered. For all analyses, lung function data of adolescents with mean age 15 years and a prevalence of females ranging from 49-51% was used.

In adults, data from the KORA (Cooperative Health Research in the Region of Augsburg) research platform that comprises several population-based cohort studies was analyzed [50] (Figure 3). Investigations on accelerometer-based physical activity were performed in middle-aged adults (48-68 years) of KORA FF4 considering common chronic diseases. For the analyses of health dimensions focusing on lung-healthy participants, data from KORA F4L and KORA Age was pooled to cover a broader age range (45-89 years). In all analyses, the prevalence of females was slightly higher (52-55%) than those for males.

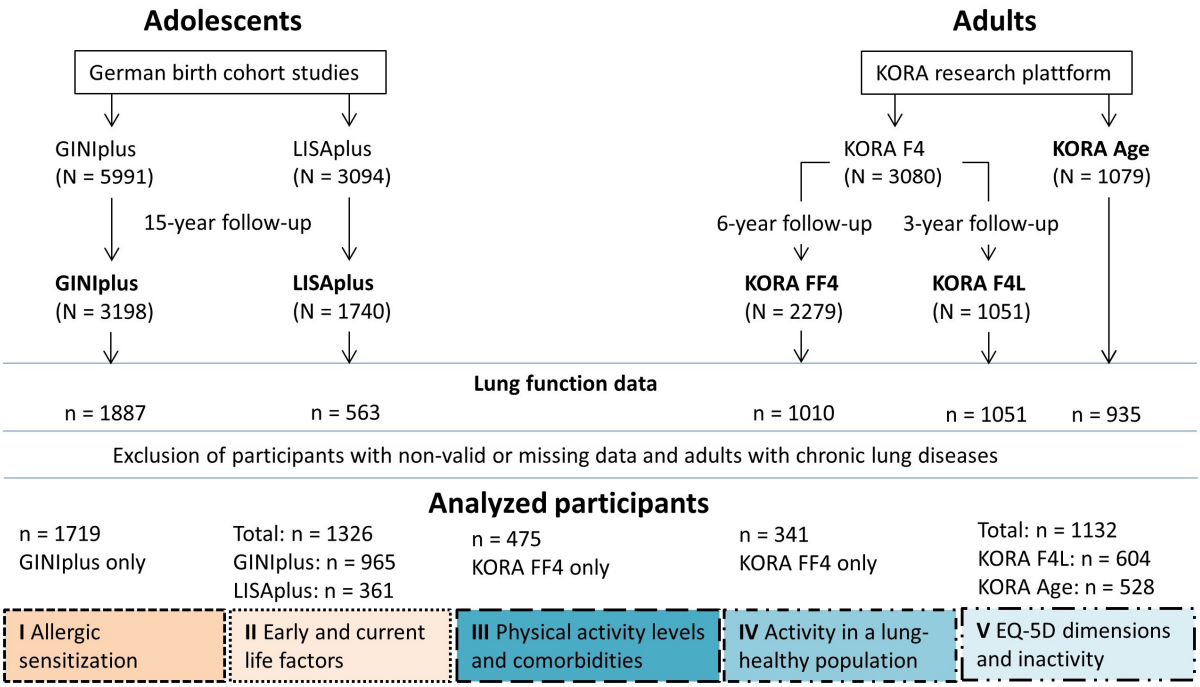


Figure 3 Analyzed study populations in publications **I** to **V**.

2.2.2 Lung function measurements

Spirometry was performed in line with the American Thoracic Society and European Respiratory Society statements [51] and similarly in all studies. During 3 to 8 spirometric maneuvers both flow-volume and volume-time curves were monitored by trained examiners and visually inspected for validity of the result afterwards. Details have been published previously [52, 53]. Spirometric parameters included the FVC, forced expiratory volume in 1 second (FEV_1), Tiffeneau-Index (FEV_1/FVC), peak expiratory flow (PEF), forced expiratory flows at 25% (FEF_{25}), 50% (FEF_{50}) and 75% (FEF_{75}) of exhaled FVC and the mid-expiratory flow between 25% and 75% of FVC ($FEF_{25–75}$). These spirometric parameters could be regarded as indicative of different domains of respiratory function [54, 55]: lung volume (FVC), airway function and lung volume (FEV_1), airflow limitation (FEV_1/FVC), flow rates for the larger conducting (PEF, FEF_{25}) and peripheral airways (FEF_{50}, FEF_{75} and $FEF_{25–75}$). Standardized z-scores for these parameters were calculated using reference equations for spirometry from the Global Lung Function Initiative [6] in order to provide comparable estimates to other studies and as well to support the findings when using absolute values.

In addition to spirometry, the transfer factor of the lung for carbon monoxide divided by alveolar volume (TLCO/VA) as an index for pulmonary gas exchange and the maximal inspiratory mouth pressure (PI_{max}) as a measure of respiratory muscle strength were investigated to gain more comprehensive information on potential associations between physical activity and lung function [Publication **IV**]. In line with international recommendations, both measures were obtained under guidance of trained examiners with the performance of up to 5 maneuvers for TLCO/VA and 3 to 15 maneuvers for PI_{max} in order to obtain maximal acceptable measures [56, 57].

2.3 Adolescents – Exposures and statistical analyses

Serum Immunoglobulin E concentration was used to determine aeroallergen sensitization at age 15 years [Publication **I**]. An allergen mixture of cat, dog, mugwort, birch, timothy, rye, *Dermatophagoides pteronyssinus*, and *Cladosporium herbarum* was applied to screen for overall sensitization to aeroallergens followed by single assessment of each allergen if the screening showed a positive test result. According to the test results, participants were divided into four groups: (a) not sensitized, (b) a positive screening test, but low sensitization to the single allergens, (c) being sensitized to 1-2 single allergens, or (d) sensitization to >2 single allergens.

Multiple linear regression models considering possible confounding covariates were performed stratifying the study population into lung-healthy participants, those with rhinitis and those with asthma, respectively. Lung function parameters were applied as dependent variables investigating sensitization as the main exposure variable in the models.

Considering the sample sizes with available information in the GINIplus and LISAplus studies, factors that were shown to be associated with lung function in other studies were selected for investigation [Publication **II**]. The investigated covariates comprised early life events (e.g. maternal smoking during pregnancy, parental atopy, birth weight, breastfeeding), current environmental and lifestyle factors at age 15 years (e.g. air pollution, BMI, serum vitamin D concentration, active smoking), and allergic diseases (e.g. asthma, rhinitis, sensitization to aero- or food allergens). These data were obtained from parent-completed questionnaires at birth, yearly from 1 to 4, and at 6, 10 and 15 years of age in GINIplus. In LISAplus, data was collected at birth, 0.5, 1, 1.5, 2, 4, 6, 10 and 15 years of age. At the 15-year follow-up, a self-report questionnaire for the adolescents and blood sample collection were included in both studies.

In order to avoid overadjustment in the cross-sectional analyses at age 15 years, a best subset selection was performed for linear regression models adjusted for all covariates to determine relevant factors to be included in final models. This selection method compares a full-model to all possible subsets of variables in this model to determine a final model with preferably high precision and low bias [58]. The selection process was performed 1000 times, with two thirds of the population randomly selected to be included in the model each time. Covariates that remained in >70% of the replication models were considered for the final models and rerun in the total population. Associations found for each spirometric parameter were reported along with the sequential R^2 contribution to the explained variance for each factor [59].

2.4 Adults – Exposures and statistical analyses

Physical activity was assessed with triaxial accelerometers worn at the hip [Publication **III**]. Measured accelerations per minute were recorded over a one week period along with a wear-time diary completed by the participants. Each minute was classified into one of three activity levels (sedentary, light, or moderate to vigorous physical activity (MVPA)) [60]. Further, the duration of bouts spent in MVPA and the compliance to World Health Organization (WHO) recommendations of 150 minutes of MVPA per week spent in at least 10-minute bouts were assessed [61].

The average minutes per day per subject spent in each activity level were applied as dependent variables in separate negative binomial regression models. Stepwise (forward and backward) selection models were applied to define which covariates e.g. age, BMI, or common chronic diseases such as hypertension, diabetes or asthma were associated with any of the activity levels.

Moreover, the association of MVPA quartiles (most active to least active according to sex-specific MVPA distribution in the population), bout length and the achievement of the WHO recommendations with lung function of lung-healthy participants was analyzed by multiple linear regression models adjusted for possible confounders applying physical activity as the independent variable [Publication **IV**].

The EQ-5D-3L, representing a generic, preference-based health related quality of life instrument, was used to obtain information on the state of the five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [46]. For each of the five dimensions, the participants were asked to choose one of three levels of problem severity (no problems, some problems, and extreme problems). Furthermore, the association of self-reported levels of activity (inactive, slightly active, moderately active and active) was defined based on the reported time spent exercising during summer and winter. Subjects were categorized as inactive if they reported irregular exercise (<1 hour/week) or no exercise at all whereas subjects reporting regularly >2 hours/week of exercise were categorized as active.

Multiple linear regression models adjusted for possible confounders were calculated in lung-healthy participants to investigate the relationships between each EQ-5D health dimension or physical activity level with spirometric parameters applied as dependent variables [Publication **V**].

3 Results and Discussion

3.1 Adolescents

Being in the stage of almost finalized lung growth, 46% of 1719 adolescents were sensitized to aeroallergens. Lung function of adolescents with asthma was lower compared to lung-healthy participants and to those with rhinitis, while spirometric parameters for lung volumes and airway function between lung-healthy participants and those with rhinitis did not differ. No associations were found between spirometric lung function and increasing sensitization grade in lung-healthy participants or those with rhinitis or asthma [Publication **I**]. Considering these results, sensitization was included only as a dichotomous variable (yes/no), without further stratification into sensitization grades in the best-subset selection analyses of publication **II**. Among the 21 diverse early life events or current environmental and lifestyle factors (Figure 2), a higher peak weight velocity and early lung infections, as early life events, were associated with lower lung function parameters indicative of airway function [Publication **II**]. Of the considered current environmental and lifestyle factors at age 15 years, indoor second-hand smoke exposure, serum vitamin D concentration, and BMI were associated with both lung volume and airway function.

Sex and height, well-known lung function determinants, captured most of the explained variance in the regression models (>75%), followed by BMI (≤23.7%). Other environmental and lifestyle factors such as serum vitamin D concentration contributed little in comparison to sex and height (≤2.1%). Early life events also explained just as little variance with a median of 4.8% (range: 0.2–22.4%), but nevertheless showed consistent associations with airway function. All factors that were identified as relevant in the present study were supported by results found in other studies, most of which considered only one or a few factors at a time without reporting the relative importance of each factor [19-23]. For example, serum vitamin D concentration was positively associated with lung volume, which was also found in a study analyzing both adolescents and adults [21]. There were also factors that were not associated with lung function in the present analysis but have been shown to be associated with lung function in other studies, suggesting that the importance might vary between populations, assessment methods and certain stages in life. For example, maternal smoking during pregnancy or low socioeconomic status were shown to be associated with poor lung function in children and adolescents [23, 62], but for both factors no associations were found in the present study population. The fact that the prevalence of highly educated families was 68% in the analyzed population might have contributed to the lack of associations with factors that were found to be associated with low socioeconomic status, pointing out the need for differentiated analyses to define vulnerable subgroups.

3.2 Adults

Of 475 participants aged 48-68 years, only 14% met the WHO physical activity recommendation of at least 150 minutes of MVPA/week in bouts of at least 10 minutes. Overall, males engaged more in MVPA than females (median 35 vs. 28 minutes/day,

respectively). About 87% of MVPA was accumulated in bouts less than 10 minutes, indicating sporadic activity instead of exercise. In line with other studies, MVPA was lower among obese and older subjects [63, 64], but considered chronic diseases such as COPD, which is mainly pronounced in early disease stages in the KORA FF4 population, were not associated with time spent in MVPA [Publication **III**]. While studies in clinical cohorts have found that patients with COPD performed less physical activity compared to healthy controls [30, 31], the association of accelerometer-based physical activity with lung function in lung-healthy populations is unclear. In the present analysis of 341 lung-healthy participants representing the stage of age-related decline, positive associations of sex-specific MVPA-quartiles with FVC and FEV_1 were found in regression models adjusted for possible confounders [Publication **IV**]. Participants in the most active quartile (i.e. >47 or >50 minutes/day spent in MVPA for females and males, respectively) had an estimated 155 ml [95% confidence interval (CI): 10, 301] higher FVC and 142 ml [95% CI: 23, 260] higher FEV_1 than those in the least active quartile (i.e. <17 or <21 minutes of MVPA/day for females and males, respectively). These effect sizes would correspond to an age-related decline of about 6 years [65]. MVPA-quartiles were not associated with pulmonary gas exchange (TLCO/VA) or maximal inspiratory muscle strength, i.e. PI_{max}. Associations found with spirometric indices primarily indicative of lung volume were more pronounced among smokers, suggesting a higher benefit of being physically active for participants at a greater risk of chronic respiratory diseases. No study was found that used a directly comparable approach, but in line with the present result, a longitudinal study using questionnaire-based physical activity showed that current smokers with moderate and high activity had a decreased decline in FVC and FEV_1 compared to smokers with low activity [41].

Considering the association found between MVPA and volumetric lung function indices, five health domains, including the domains mobility and usual activities as indicators for physical functioning, and also self-reported time spent in exercise were analyzed as surrogate for environmental and lifestyle factors in lung-healthy adults [Publication **V**]. Self-reported time spent in exercise was used to increase the sample size to 1132 participants. Amongst all participants, 24% were inactive and 32% reported to exercise more than 2 hours/week. While 42% reported no problems in any EQ-5D health dimension, about half of the population reported pain/discomfort. Although the prevalence for mobility problems and problems with usual activities was much lower (17% and 13%, respectively), participants reporting problems in those domains had lower volumetric indices compared to those without problems for these domains. FEV_1 was -99 ml (95% CI: -166; -32) and FVC was -109 ml (95% CI: -195; -24) lower among subjects with mobility problems controlling for sex, age, height and weight. Similar estimates were present for usual activities. Moreover, being inactive was negatively associated with FVC (β-coefficient: -83 ml, 95% CI: -166; 0). These results are in line with two investigations from the United Kingdom showing positive associations between FEV_1 and self-reported physical functioning [36, 37], suggesting positive correlations between activity and volumetric lung function. Overall, the presented results obtained in a lung-healthy study population showed slightly lower lung function among less active participants and those with limited physical functioning, and hence add to the findings observed in previous studies in patients with lung disease [30-34].

3.3 Strengths and Limitations

A major strength of all included studies is the investigation of a broad range of standardized lung function parameters, obtained by spirometry, indicative of lung volume and airway function. Additionally, parameters for the less often investigated measures of gas exchange and respiratory muscle strength were analyzed in one study. The studies covered a wide age range, with focus on two periods in life. The period of lung growth was represented by adolescents at age 15 years, and the period of age-related lung function decline by adults from 45-89 years of age.

In adolescents, data on a broad range of early life events, environmental and lifestyle factors, and allergic diseases at age 15 years were available to be analyzed. The results showed the relative contribution of factors to the explained variance of the models differentiating into volume, airways and airflow limitation.

In adults, an approach covering environmental and lifestyle factors was performed using different health domains as well as questionnaire- and accelerometer-based information on physical activity. Evidence regarding the association between health domains or (accelerometer-based) physical activity and lung function in the general population without chronic lung diseases is rare. Therefore, the present studies meaningfully complement the evidence base for the assessed factors in lung-healthy populations at the population-level.

All included studies are cross-sectional and do not allow for drawing conclusions about causal relations or long-term effects. Furthermore, loss to follow-up in the cohorts as well as selection bias are present. Early life factors were only available for analyses of adolescents. Moreover, missing information within the study population and preselection for lung-healthy participants limited the sample size and the generalizability of the results to other populations. Effect estimates were small, partly borderline significant and with broad confidence intervals, suggesting for example for physical activity that not all, but rather only certain individuals may benefit from physical activity with respect to their lung function indices. Therefore, bearing in mind these addressed limitations, the results should be interpreted with caution.

4 Conclusion

The present cross-sectional investigations addressed the association of various factors on lung function at two periods in life; adolescence at age 15 years, in the period of lung growth, and adulthood from 45 to 89 years of age, representing the stage of age-related lung function decline. Data for adults focused on current environmental and lifestyle factors, while data on early life events as well as current environmental and lifestyle factors were available for adolescents.

In adolescents, the results identified weight gain and pulmonary infections during infancy, as well as current BMI, indoor second-hand smoke exposure and serum vitamin D concentration, asthma, sex and height as prevalent factors associated with lung function. Associations with current factors were present for both lung volume and airway function, whereas weight gain and pulmonary infections in early life were consistently associated with lower airway function only. However, early life events explained in median less than 5% of the variance, whereas at least 75% were captured by sex and height.

In lung-healthy adults, physical activity was found to be primarily associated with slightly higher volumetric indices. Both, self-reported inactivity as well as little measured time spent in MVPA, assessed by accelerometers, showed associations with lower volumetric lung function indices. The effect estimates showed a small difference between the least active and the most active group of participants of about 50 to 150 ml which would correspond to a normal age-related decline of about 2 to 6 years. This tendency was further supported by the associations found between slightly lower spirometric lung volume and reporting problems with either mobility or usual activities. The presented results suggest that being able to and indeed choosing to perform exercise may be associated with beneficial volumetric lung function even in lung-healthy adults.

Although these findings are not generalizable to other populations, they nevertheless support the inclusion of specific early life events in studies on airway function in adolescents and the consideration of physical activity, particularly for investigations on lung volumes in adults. Further, the results highlight the need for more studies considering both early and current factors at different stages in life in order to define specific associations relevant for the phases of lung growth and age-related decline, as well as to provide evidence for potential early interventions to foster lung health.

5 References

1. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. Lancet Respir Med. 2013;1(9):728-742.
2. Merkus PJ. Effects of childhood respiratory diseases on the anatomical and functional development of the respiratory system. Paediatr Respir Rev. 2003;4(1):28-39.
3. Klimentidis YC, Vazquez AI, de Los Campos G, et al. Heritability of pulmonary function estimated from pedigree and whole-genome markers. Front Genet. 2013;4:174.
4. Ingebrigtsen TS, Thomsen SF, van der Sluis S, et al. Genetic influences on pulmonary function: a large sample twin study. Lung. 2011;189(4):323-330.
5. Weiss ST. Lung function and airway diseases. Nat Genet. 2010;42(1):14-16.
6. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-1343.
7. Stanojevic S, Wade A, Stocks J, et al. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med. 2008;177(3):253-260.
8. Svanes C, Sunyer J, Plana E, et al. Early life origins of chronic obstructive pulmonary disease. Thorax. 2010;65(1):14-20.
9. Carlsen KC, Haland G, Carlsen KH. Natural history of lung function in health and diseases. Curr Opin Allergy Clin Immunol. 2009;9(2):146-150.
10. Dratva J, Zemp E, Dharmage SC, et al. Early Life Origins of Lung Ageing: Early Life Exposures and Lung Function Decline in Adulthood in Two European Cohorts Aged 28-73 Years. PLoS One. 2016;11(1):e0145127.
11. Dyer C. The interaction of ageing and lung disease. Chron Respir Dis. 2012;9(1):63-67.
12. Duijts L, Reiss IK, Brusselle G, de Jongste JC. Early origins of chronic obstructive lung diseases across the life course. Eur J Epidemiol. 2014;29(12):871-885.
13. Allinson JP, Hardy R, Donaldson GC, et al. Combined Impact of Smoking and Early-Life Exposures on Adult Lung Function Trajectories. Am J Respir Crit Care Med. 2017;196(8):1021-1030.
14. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. Lancet. 2015;385:899–909.
15. Brumpton BM, Langhammer A, Henriksen AH, et al. Physical activity and lung function decline in adults with asthma: The HUNT Study. Respirology. 2017;22(2):278-283.
16. Kotecha SJ, Watkins WJ, Henderson AJ, Kotecha S. The effect of birth weight on lung spirometry in white, school-aged children and adolescents born at term: a longitudinal population based observational cohort study. J Pediatr. 2015;166(5):1163-1167.
17. Hancox RJ, Poulton R, Greene JM, et al. Associations between birth weight, early childhood weight gain and adult lung function. Thorax. 2009;64(3):228-232.
18. Baumann S, Godtfredsen NS, Lange P, Pisinger C. The impact of birth weight on the level of lung function and lung function decline in the general adult population. The Inter99 study. Respir Med. 2015;109(10):1293-1299.
19. Cibella F, Bruno A, Cuttitta G, et al. An elevated body mass index increases lung volume but reduces airflow in Italian schoolchildren. PLoS One. 2015;10(5):e0127154.
20. den Dekker HT, Sonnenschein-van der Voort AM, de Jongste JC, et al. Early growth characteristics and the risk of reduced lung function and asthma: A meta-analysis of 25,000 children. J Allergy Clin Immunol. 2016;137(4):1026-1035.
21. Tolppanen A-M, Williams D, Henderson J, Lawlor DA. Serum 25-hydroxy-vitamin D and ionised calcium in relation to lung function and allergen skin tests. Eur J Clin Nutr. 2011;65(4):493-500.
22. Puig C, Friguls B, Gomez M, et al. Relationship between lower respiratory tract infections in the first year of life and the development of asthma and wheezing in children. Arch Bronconeumol. 2010;46(10):514-521.

23. Moshammer H, Hoek G, Luttmann-Gibson H, et al. Parental smoking and lung function in children: an international study. Am J Respir Crit Care Med. 2006;173(11):1255-1263.
24. Mannino DM, Moorman JE, Kingsley B, et al. Health effects related to environmental tobacco smoke exposure in children in the united states: Data from the third national health and nutrition examination survey. Arch Pediatr Adolesc Med. 2001;155(1):36-41.
25. Schultz ES, Litonjua AA, Melen E. Effects of Long-Term Exposure to Traffic-Related Air Pollution on Lung Function in Children. Curr Allergy Asthma Rep. 2017;17(6):41.
26. Trabelsi Y, Paries J, Harrabi I, et al. Factors affecting the development of lung function in Tunisian children. Am J Hum Biol. 2008;20(6):716-725.
27. Gotschi T, Heinrich J, Sunyer J, Kunzli N. Long-term effects of ambient air pollution on lung function: a review. Epidemiology. 2008;19(5):690-701.
28. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017;5(9):691-706.
29. Eijkemans M, Mommers M, Draaisma JMT, et al. Physical Activity and Asthma: A Systematic Review and Meta-Analysis. PLoS ONE. 2012;7(12):e50775.
30. Watz H, Pitta F, Rochester CL, et al. An official European Respiratory Society statement on physical activity in COPD. Eur Respir J. 2014;44(6):1521-1537.
31. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. Eur Respir J. 2009;33(2):262-272.
32. Wacker ME, Jörres RA, Karch A, et al. Relative impact of COPD and comorbidities on generic health-related quality of life: a pooled analysis of the COSYCONET patient cohort and control subjects from the KORA and SHIP studies. Respir Res. 2016;17(1):81.
33. Siroux V, Boudier A, Anto JM, et al. Quality-of-life and asthma-severity in general population asthmatics: results of the ECRHS II study. Allergy. 2008;63(5):547-554.
34. Stahl E, Lindberg A, Jansson SA, et al. Health-related quality of life is related to COPD disease severity. Health Qual Life Outcomes. 2005;3:56.
35. Pickard AS, Wilke C, Jung E, et al. Use of a preference-based measure of health (EQ-5D) in COPD and asthma. Respir Med. 2008;102(4):519-536.
36. Myint PK, Luben RN, Surtees PG, et al. Respiratory function and self-reported functional health: EPIC-Norfolk population study. Eur Respir J. 2005;26(3):494-502.
37. Singh-Manoux A, Dugravot A, Kauffmann F, et al. Association of lung function with physical, mental and cognitive function in early old age. Age. 2011;33(3):385-392.
38. Nystad W, Samuelsen SO, Nafstad P, Langhammer A. Association between level of physical activity and lung function among Norwegian men and women: the HUNT study. Int J Tuberc Lung Dis. 2006;10(12):1399-1405.
39. Jakes RW, Day NE, Patel B, et al. Physical Inactivity Is Associated with Lower Forced Expiratory Volume in 1 Second: European Prospective Investigation into Cancer-Norfolk Prospective Population Study. Am J Epidemiol. 2002;156(2):139-147.
40. Pelkonen M, Notkola I-L, Lakka T, et al. Delaying Decline in Pulmonary Function with Physical Activity. Am J Respir Crit Care Med. 2003;168(4):494-499.
41. Garcia-Aymerich J, Lange P, Benet M, et al. Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. Am J Respir Crit Care Med. 2007;175(5):458-463.
42. Choi SY, Sohn MH, Yum HY, et al. Correlation between inhalant allergen-specific IgE and pulmonary function in children with asthma. Pediatr Pulmonol. 2005;39(2):150-155.
43. Rajendra C, Zoratti E, Havstad S, et al. Relationships between total and allergen-specific serum IgE concentrations and lung function in young adults. Ann Allergy Asthma Immunol. 2012;108(6):429-434.
44. Simpson A, Soderstrom L, Ahlstedt S, et al. IgE antibody quantification and the probability of wheeze in preschool children. J Allergy Clin Immunol. 2005;116(4):744-749.

45. Stoltz DJ, Jackson DJ, Evans MD, et al. Specific Patterns of Allergic Sensitization in Early Childhood and Asthma & Rhinitis Risk. Clin Exp Allergy. 2013;43(2):233-241.
46. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337-343.
47. von Berg A, Krämer U, Link E, et al. Impact of early feeding on childhood eczema: development after nutritional intervention compared with the natural course - the GINIplus study up to the age of 6 years. Clin Exp Allergy. 2010;40(4):627-636.
48. Heinrich J, Bolte G, Hölscher B, et al. Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. Eur Respir J. 2002;20(3):617-623.
49. Heinrich J, Brüske I, Schnappinger M, et al. [Two German Birth Cohorts: GINIplus and LISAplus]. Bundesgesundheitsbl. 2012;55(6-7):864-874.
50. Holle R, Happich M, Löwel H, Wichmann HE. KORA--a research platform for population based health research. Gesundheitswesen. 2005;67 Suppl 1:S19-25.
51. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338.
52. Karrasch S, Flexeder C, Behr J, et al. Spirometric reference values for advanced age from a South german population. Respiration. 2013;85(3):210-219.
53. Fuertes E, Bracher J, Flexeder C, et al. Long-term air pollution exposure and lung function in 15 year-old adolescents living in an urban and rural area in Germany: The GINIplus and LISAplus cohorts. Int J Hyg Environ Health. 2015;218(7):656-665.
54. Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Eur Respir J. 1993;6(Suppl 16):5-40.
55. Simon MR, Chinchilli VM, Phillips BR, et al. FEF_{25-75} and FEV_1/FVC in Relation to Clinical and Physiologic Parameters in Asthmatic Children with Normal FEV_1 Values. J Allergy Clin Immunol. 2010;126(3):527-534.e528.
56. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26(4):720-735.
57. American Thoracic Society/European Respiratory Society. Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518-624.
58. Miller AJ. Subset Selection in Regression. 2nd Edition. Chapman & Hall/CRC: 2002.
59. Groemping U. Relative Importance for Linear Regression in R: The Package relaimpo. J Stat Softw. 2006;17(1)1–27.
60. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc. 1998;30(5):777-781.
61. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva, World Health Organization, 2010. [Assessed 13 Oct 2016]. Available from: http://www.who.int/dietphysicalactivity/factsheet_recommendations/en/.
62. Hegewald MJ, Crapo RO. Socioeconomic status and lung function. Chest. 2007;132(5):1608-1614.
63. Aresu M, Bécares L, Brage S, et al. Health Survey for England 2008 - Volume 1 Physical activity and fitness. The NHS information centre. 2009.
64. Hagstromer M, Troiano RP, Sjostrom M, Berrigan D. Levels and patterns of objectively assessed physical activity--a comparison between Sweden and the United States. Am J Epidemiol. 2010;171(10):1055-1064.
65. Tang W, Kowgier M, Loth DW, et al. Large-Scale Genome-Wide Association Studies and Meta-Analyses of Longitudinal Change in Adult Lung Function. PLoS ONE. 2014;9(7):e100776.

6 Publications comprised within this thesis

6.1 Publication I

Original title:

Relation of lung function and current inhalant allergen-specific immunoglobulin E concentrations in adolescents (GINIplus cohort)

Authors:

Agnes Luzak; Claudia Flexeder, Andrea von Berg, Dietrich Berdel, Claudia Klümper, Sibylle Koletzko, Carl-Peter Bauer, Joachim Heinrich, Dennis Nowak, and Holger Schulz

Journal:

Annals of Allergy, Asthma & Immunology

Volume:

115

Pages:

183-190

Year:

2015

DOI:

http://dx.doi.org/10.1016/j.anai.2015.06.016

Ann Allergy Asthma Immunol 115 (2015) 183–190

Contents lists available at ScienceDirect

Relation of lung function and current inhalant allergen-specific immunoglobulin E concentrations in adolescents (GINIplus cohort)

Agnes Luzak, MPH [*]; Claudia Flexeder, MSc [*]; Andrea von Berg, MD [†]; Dietrich Berdel, MD [†]; Claudia Klümper, PhD [‡]; Sibylle Koletzko, MD, PhD [§]; Carl-Peter Bauer, MD [‖]; Joachim Heinrich, PhD [*,¶]; Dennis Nowak, MD [¶,#]; and Holger Schulz, MD [*,¶]

[*] Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[†] Research Institute, Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany
[‡] IUF Leibniz Research Institute for Environmental Medicine and Medical Faculty, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany
[§] Dr von Hauner Children's Hospital, Ludwig Maximilians University of Munich, Munich, Germany
[‖] Department of Pediatrics, Technical University of Munich, Munich, Germany
[¶] Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Munich, Germany
[#] Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Munich (LMU), Munich, Germany

ARTICLE INFO

Article history:
Received for publication March 19, 2015.
Accepted for publication June 22, 2015.

ABSTRACT

Background: The prevalence of allergen sensitization reaches up to 46.6% in 14- to 17-year-old German adolescents. Polysensitization is strongly associated with a higher risk of allergic rhinitis or asthma. Whether or how sensitization also is related to lung function remains uncertain.

Objective: To assess whether sensitization to common inhalant allergens is associated with lung function in adolescents after stratification by allergic respiratory disease.

Methods: In total, 1,719 15-year-old participants of the German Infant Study on the Influence of Nutrition Intervention plus Air Pollution and Genetics on Allergy Development (GINIplus) birth cohort provided valid spirometric indices, including forced expiratory volume in 1 second, forced vital capacity (FVC), forced expiratory flow rate at 25% to 75% of the FVC, and specific immunoglobulin E (IgE) screening test to 8 inhalant allergens (ImmunoCAP). Complete information on allergic rhinitis and asthma status was available for 1,128 subjects. Associations between lung function parameters and sensitization, classified into 4 groups (no sensitization to polysensitization) were analyzed using adjusted linear regression models.

Results: Among participants, 21.1% (n = 347) had allergic rhinitis, 10.1% (n = 119) had asthma, and 46.4% (n = 798) had a positive screening test to inhalant allergens. Prevalences were consistently higher in boys. The percentage of subjects with rhinitis or asthma increased from 5.8% in non-sensitized subjects (n = 620) to 69.4% in polysensitized subjects (n = 144). Sensitization was not associated with any spirometric parameter considered in subjects with allergic rhinitis, asthma, or neither disease.

Conclusion: Although allergen-specific IgE concentrations can contribute to the identification of subjects at higher risk for allergic rhinitis and asthma, sensitization to inhalant allergens is not related to impaired spirometric lung parameters within the different allergic respiratory disease subgroups.

Reprints: Holger Schulz, MD, Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany; E-mail: schulz@helmholtz-muenchen.de.

Disclosures: Authors have nothing to disclose.

Funding: The GINIplus study was supported for the first 3 years mainly by the Federal Ministry for Education, Science, Research and Technology, the UFZ Helmholtz Zentrum Leipzig, and Helmholtz Zentrum Munich (formerly GSF). The 4-, 6-, 10-, and 15-year follow-up examinations were funded by the respective budgets of the 5 study centers (Helmholtz Zentrum Munich, Research Institute at Marien-Hospital Wesel, LMU Munich, TU Munich, and UFZ Leipzig) and for the 6- and 10-year follow-ups by the IUF Leibniz Research Institute for Environmental Medicine at the University of Düsseldorf. The 15-year follow-up examination of the GINIplus study also was supported by the Commission of the European Communities, the 7th Framework Programme, the MeDALL project, Mead Johnson, and Nestlé. This work was additionally supported by the Kompetenznetz Adipositas (Competence Network Obesity), the Federal Ministry of Education and Research (FKZ 01GI1121A), and the Comprehensive Pneumology Center Munich, a member of the German Center for Lung Research.

http://dx.doi.org/10.1016/j.anai.2015.06.016

Introduction

Allergic sensitization is a highly prevalent condition; 55.5% of 10- to 19-year-olds who participated in the Third National Health and Nutrition Examination Survey in the United States were found to be sensitized to at least 1 allergen.[1] This prevalence is similar to that reported for 14- to 17-year-old German adolescents who participated in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS; 46.6%).[2] It is well known that sensitization to inhalant or food allergens is associated with allergic respiratory diseases, such as asthma and rhinitis, in adults[3–6] and children.[1,2,7–9]

However, sensitization status alone does not independently predict the presence or absence of allergic diseases or symptoms.[10] Of children no older than 17 years included in the KiGGS study, 47.6% did not report an atopic disease, although they were found to be sensitized to at least 1 inhalant allergen. The KiGGS study also showed that allergic rhinitis was significantly more prevalent in polysensitized children compared with those sensitized to 1 or 2 allergens.[2] Asthma in children is associated with a decrease in lung function, but to what extent allergen-specific sensitization might contribute to this decrease is less apparent.[11–13] The relation of current sensitization to lung function is even less analyzed.

Previous studies that have analyzed associations between lung function and allergen-specific sensitization in children or adolescents have focused mainly on asthma characteristics and have yielded controversial results.[14–17] Choi et al[14] observed a significant negative association between forced expiratory volume in 1 second (FEV_1) and allergen-specific immunoglobulin E (IgE) concentrations against house dust mites in subjects with asthma. Although this result was not observed in the analysis of Matsui et al,[16] this latter study did find associations between the sum of allergen-specific IgE concentrations to cockroach, cat, house dust mite, and mouse and decreases in FEV_1 percent predicted and the ratio of FEV_1 to forced vital capacity (FVC). In another study, the FEV_1/FVC ratio also was associated with the sum of 6 allergen-specific IgE values, but only in girls.[15] It is difficult to fully compare these studies because of the use of different statistical methods, selection of allergens, and spirometric indices considered.[14–17] Further, these previous studies have used quantitative specific IgE concentrations to a variety of allergens or the sum of the specific IgE values. The use of a quantitative approach suggests that the allergen-specific IgE concentrations are normally distributed and that a linear inverse association exists between these concentrations and lung function parameters. However, extremely high IgE concentrations have the potential to be highly influential in the results of such an analysis, a problem that can be circumvented by analyzing associations with mono- or polysensitization status instead.

Nonetheless, these previous studies appear to generally suggest a tendency toward an inverse association between allergen-specific IgE concentrations and spirometric parameters, although associations did not reach statistical significance in many cases and differed across studies.[14–17]

The aim of the present study was to assess whether an elevated allergen-specific IgE concentration to 1 or 2 inhalant allergens is associated with a decrease in lung function assessed by spirometry in 15-year-olds, and whether this possible association is stronger in polysensitized adolescents. The impact of disease manifestation on a possible association between allergen-specific sensitization and spirometric lung function was considered for 3 groups of subjects: (1) those without allergic respiratory disease, (2) those with rhinitis but without asthma, and (3) those with asthma only or with concomitant rhinitis.

Methods

Study Population

This analysis is based on data derived from the 15-year follow-up of the German Infant Study on the Influence of Nutrition Intervention plus Air Pollution and Genetics on Allergy Development (GINIplus). A total of 5,991 healthy full-term white neonates born from September 1995 through July 1998 in Wesel and Munich were initially included in this German population-based prospective birth cohort. The intervention group was comprised of children with a familial predisposition toward allergy who were randomized at birth to 1 of 3 hydrolyzed formulas. Participating newborns with or without familial predisposition who did not receive any intervention served as the control group. Detailed inclusion criteria and the primary study design have been described previously.[18,19]

Follow-up studies with assessment of blood parameters were conducted at 6, 10, and 15 years of age. The inclusion criteria for the present analysis were a valid lung function test result and available data on allergen-specific IgE serum concentrations. Of the 3,198 subjects who participated in the 15-year follow-up, 1,719 subjects met the criteria and are included in this analysis. The GINIplus study was approved by 2 local ethics committees: the Medical Council of North-Rhine-Westphalia (Ärztekammer Nordrhein, Düsseldorf) for the study center in Wesel and the Bavarian General Medical Council (Bayerische Landesärztekammer, München) for the study center in Munich. Written informed consent was obtained from all participating families.

Lung Function Measurements

Spirometry was performed before and after bronchodilation with salbutamol in a sitting position while subjects were wearing nose clips. Flow-volume curves were obtained using a pneumotachograph-type spirometer (EasyOne Worldspirometer, ndd, Zurich, Switzerland), which was calibrated daily using a 3-L calibration pump supplied by the manufacturer. All measurements were in line with American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations.[20] To obtain optimal flow-volume curves, the subjects performed at least 3 and up to 8 trials per test under the guidance of specifically trained examiners who concurrently monitored the flow-volume and volume-time curves. Trial results were checked according to the acceptability criteria of the ATS and ERS.[20] In subjects without contraindications, a bronchodilator response with a β-agonist was performed, in line with ATS and ERS recommendations.[20] A 200-μg (2×1 puff of 100 μg) salbutamol dose was delivered into a spacer (Volumatic; GlaxoSmithKline, London, United Kingdom) by a metered-dose inhaler. The subject was subsequently asked to take 5 slow and deep breaths from the spacer with a breath-hold time of 5 to 10 seconds to allow optimal particle deposition. Fifteen minutes later, the second spirometry test was performed. According to ATS and ERS standards, a positive bronchodilation response was defined as an increase of more than 200 mL and 12% in FEV_1 or FVC after bronchodilation.[21]

Indices of the best maneuver for FEV_1, FVC, FEV_1/FVC ratio, and forced expiratory flow at 25% to 75% of the FVC ($FEF_{25\%-75\%}$) were analyzed. In addition, standardized z-scores of FEV_1, FVC, FEV_1/FVC, and $FEF_{25\%-75\%}$ were calculated using reference equations for spirometry from the Global Lung Function Initiative (GLI).[22] Of the 1,887 subjects (Munich, n = 951; Wesel, n = 936) who participated in spirometry, 65 subjects (3.4%) did not meet the acceptability criteria before bronchodilation, resulting in 1,822 valid test results.

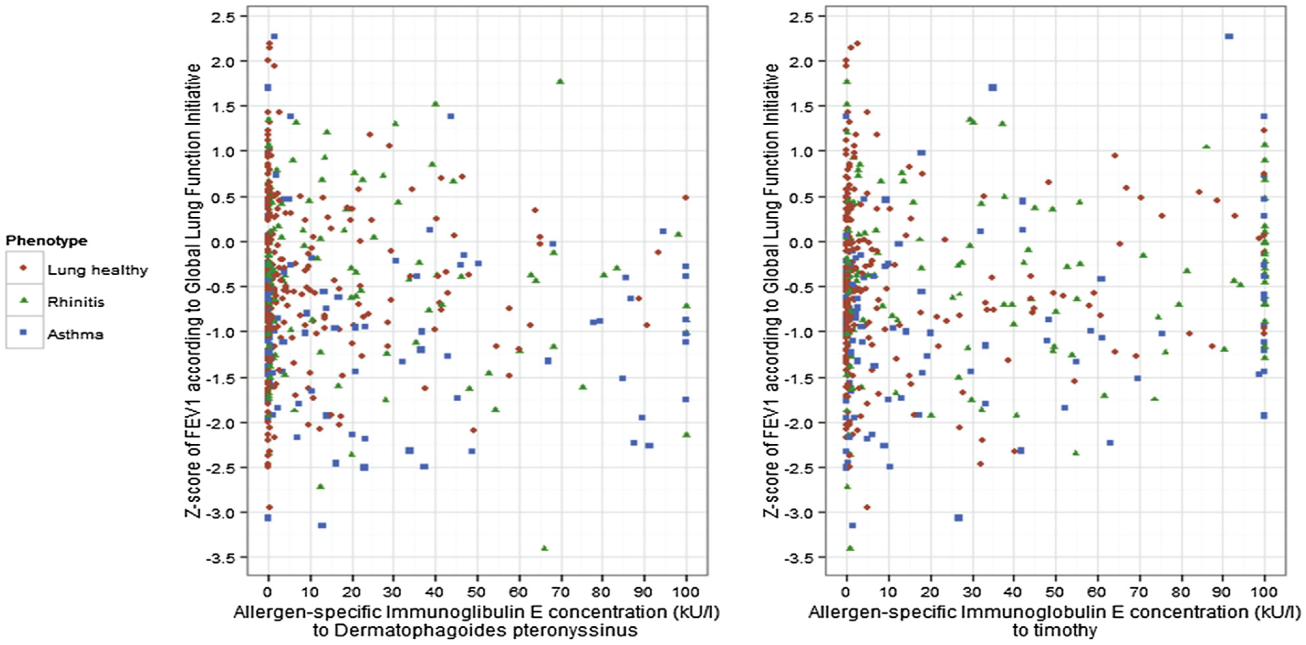


Figure 1. *Z*-scores of forced expiration volume in 1 second (FEV_1) and allergen-specific IgE concentrations of subjects allergic to *Dermatophagoides pteronyssinus* (n = 306) and timothy grass (n = 360) stratified by allergic respiratory lung disease. *Z*-score FEV_1[22] was adjusted for sex, ethnicity, age, and height.

IgE Measurements and Assessment of Sensitization Pattern

The serum level of specific IgE was determined by the ImmunoCAP Specific IgE system (Phadia GmbH, Freiburg, Germany) according to the manufacturer's instructions. Two screening tests were performed. The first covered an inhalant allergen mixture (sx1), which included cat, dog, mugwort, birch, timothy, rye, *Dermatophagoides pteronyssinus*, and *Cladosporium herbarum*. The second covered food allergens (fx5; egg white, codfish, cow milk, wheat, peanut, and soybean). For the 2 screening tests, a value higher than 0.35 kU/L was considered positive. Subjects with a positive test result for at least 1 of the screening tests underwent allergen-specific testing for all allergens contained in the respective mixture. The allergen-specific IgE concentrations were grouped on a scale from 0 to 6, with cutoff values at 0, 0.35, 0.70, 3.50, 17.50, 50, and 100 kU/L. The IgE concentration and cutoff values for having a positive test result influences the probability of having clinical symptoms that increase with increasing values.[23–25] In this study, the 3.50-kU/L (ImmunoCAP class 3) cutoff value for allergen-specific IgE concentrations was chosen to ensure a high probability of capturing clinically relevant sensitized cases.

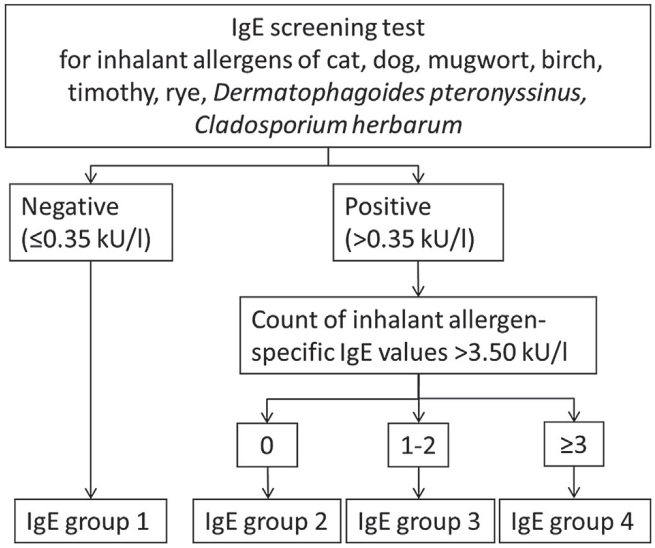


Figure 2. Group stratification according to specific IgE sensitization to inhalant allergens.

Of the 3,198 subjects who participated in the 15-year follow-up, 1,912 provided blood samples for IgE analysis, only 1 of which was excluded owing to a failed test.

The allergen-specific IgE concentrations in the present cohort were not normally distributed; data accumulated near 0 and the ImmunoCAP test range limit of 100 kU/L (Fig 1). A normal distribution could not be achieved after logarithmic transformation. As such, the application of a quantitative approach (linear regression) would have been inappropriate. Thus, a qualitative approach was applied in which the allergen-specific IgE concentrations were categorized into grades of sensitization. Figure 2 shows the stratification of subjects into 4 groups according to the measured allergen-specific IgE serum concentrations. IgE group 1 was comprised of subjects with negative screening tests (≤0.35 kU/L) for inhalant allergens. Subjects with a positive screening test (>0.35 kU/L) but no positive allergen-specific sensitization test (>3.5 kU/L) to 1 of the inhalant allergens were included in IgE group 2. Higher grades of sensitization were included in IgE groups 3 and 4: subjects with allergen-specific sensitization to 1 or 2 inhalant allergens (IgE group 3) and subjects with allergen-specific sensitization to more than 2 inhalant allergens (IgE group 4). To assess the potential relevance of additional sensitization to food allergens, another 3-level stratification was considered: non-sensitized subjects (IgE group 1), highly sensitized subjects to inhalant allergens (IgE groups 3 and 4) but without food sensitization, and those in IgE groups 3 and 4 with additional sensitization to food allergens (ie, IgE concentration >0.35 kU/L in screening test for food allergens).

Definition of Phenotypes

The presence of allergic diseases throughout childhood was assessed using parent-completed written questionnaires during the follow-ups of the study. Ultimately, yearly parental reports of

Table 1
Characteristics of study population

	Median (25th, 75th percentile) or % (n/N)		
	Boys (n = 836)	Girls (n = 883)	Total (n = 1,719)
Age (y)	15.2 (15.1, 15.4)	15.2 (15.1, 15.4)	15.2 (15.1, 15.4)
Weight (kg)	64 (57, 73)	58 (53, 63)	60 (54, 67)
Height (cm)	177 (172, 182)	167 (163, 171)	171 (166, 177)
Study center (%)			
Munich	50.72 (424/836)	50.40 (445/883)	50.55 (869/1,719)
Wesel	49.28 (412/836)	49.60 (438/883)	49.45 (850/1,719)
Study group (%)			
Control	48.68 (407/836)	49.72 (439/883)	49.21 (846/1,719)
Intervention	51.32 (429/836)	50.28 (444/883)	50.79 (873/1,719)
Parental education (%)			
Low	8.01 (67/836)	6.47 (57/881)	7.22 (124/1,717)
Medium	30.14 (252/836)	26.22 (231/881)	28.13 (483/1,717)
High	61.84 (517/836)	67.31 (593/881)	64.65 (1,110/1,717)
Exclusive breastfeeding (%)			
No	24.30 (190/782)	23.23 (194/835)	23.75 (384/1,617)
1–4 mo	28.64 (224/782)	28.14 (235/835)	28.39 (459/1,617)
>4 mo	47.06 (368/782)	48.62 (406/835)	47.87 (774/1,617)
Smoking during pregnancy, yes (%)	12.15 (92/757)	12.81 (99/773)	12.48 (191/1,530)
Rhinitis (%)	22.91 (184/803)	19.29 (163/845)	21.06 (347/1,648)
Rhinitis without asthma (%)	13.70 (74/540)	11.68 (71/608)	12.63 (145/1,148)
Asthma (%)	11.89 (66/555)	8.45 (53/627)	10.07 (119/1,182)
Positive bronchodilation (%)	5.67 (42/741)	3.36 (27/804)	4.47 (69/1,545)
Specific IgE screening test level ≥0.35 kU/L (%)			
Inhalant allergens	52.87 (442/836)	40.32 (356/883)	46.42 (798/1,719)
Food allergens	12.92 (108/836)	10.87 (96/883)	11.87 (204/1,719)

physician diagnoses of allergic diseases were available. Information on current allergic symptoms was derived from the questionnaire from the last follow-up (at 15 years of age), which asked for allergic symptoms in the past 12 months.

Asthma was defined based on the definition of the Global Allergy and Asthma European Network (GA2LEN).[26] Subjects were considered as currently having asthma if they responded positively to at least 2 of the 3 following questions: (1) Has a physician diagnosed asthma in your child? This question was asked separately for each year at 1, 2, 3, 4, 6, 10, and 15 years of age and combined into an "asthma ever" variable. (2) Has your child taken asthma medication during the past 12 months? (3) Has your child had wheezing or whistling in the chest in the past 12 months?

The International Study of Asthma and Allergies in Childhood (ISAAC) core questions served as the basis for the definition of rhinitis.[27] A child was considered as having current allergic rhinitis if a positive answer to 1 of the following questions was provided: (1) Has a physician diagnosed hay fever in your child at 11 to 15 years of age? (2) Has a physician diagnosed whole-year allergic rhinitis in your child at 11 to 15 years of age? In a sensitivity analysis, the ISAAC definition for current allergic rhinoconjunctivitis symptoms was applied, which requires 2 positive answers to the following 2 questions: (1) In the past 12 months, has your child had a clogged or itchy nose when he or she did not have a cold? (2) In the past 12 months, has your child had a clogged or itchy nose accompanied by watery eyes?[28]

All subjects who were not identified as having asthma or allergic rhinitis and who did not have a positive bronchodilation response during lung function testing (n = 29, 3.2%) were coded as being free of allergic respiratory diseases.

In summary, the population was subdivided into 3 phenotypes according to allergic respiratory disease: (1) without allergic diseases (designated as apparently "lung healthy"), (2) with allergic rhinitis (referred to as rhinitis in text) but no asthma, and (3) with asthma only or with concomitant rhinitis. Missing data for questions that were relevant for phenotype group classification led to exclusion. Ultimately, 1,128 subjects had complete and available information on allergic respiratory diseases.

Statistical Analysis

Medians and corresponding percentiles (25th, 75th) or percentages (%, n/N) were used to describe subject characteristics. The Kruskal-Wallis test was used to analyze differences in lung function among phenotypes (healthy, rhinitis, and asthma) and to assess variances in spirometric parameters according to IgE sensitization group (Fig 2) within each phenotype category. Group comparisons were performed after stratification for sex. If the Kruskal-Wallis test showed a statistically significant result, then the Wilcoxon rank-sum test, adjusting for multiple testing through the Holm correction, was applied. Adjusted linear regression models were applied to analyze associations between sensitization to inhalant allergens according to the IgE groups (Fig 2) and lung function parameters. The main model was adjusted for sex (if not already stratified), study center (Munich vs Wesel), study group (control vs intervention), and age, weight, and height assessed on the day of spirometric examination (model 1). Model 2 was further adjusted for parental education level, exclusive breastfeeding, maternal smoking during pregnancy, and intake of rhinitis medication in the past 12 months. Regression models for standardized GLI *z*-scores,[22] which are already adjusted for sex, ethnicity, age, and height, were adjusted only for additional variables of models 1 and 2. Regression analyses in subjects with asthma were adjusted for rhinitis status but not for intake of rhinitis medication. Parental education was categorized as high (>10 years), middle (10 years), or low (<10 years) according to the highest education level of the mother or father. Breastfeeding was classified as longer than 4 months, 1 to 4 months, or no exclusive breastfeeding.

Group comparisons and regression models were performed for the lung function parameters FEV_1, FVC, FEV_1/FVC ratio, and $FEF_{25\%-75\%}$ and the corresponding GLI *z*-scores. A *P* value less than .05 was considered statistically significant. All analyses were performed with the statistical software package R 3.1.0.[29]

Results

The study population was comprised of 1,719 subjects with a median age of 15.2 years (Table 1). Boys accounted for 48.6% of subjects. The prevalence of rhinitis was 21.1% (n = 347) and that of asthma was 10.1% (n = 119). The prevalences were higher in boys compared with girls for the 2 diseases (22.9% vs 19.3% for rhinitis and 11.9% vs 8.5% for asthma, respectively). Subjects with rhinitis but not asthma accounted for 12.6% (n = 145). Of the 119 subjects with asthma, 60.5% concurrently had rhinitis. Although 46.4% (n = 798) of subjects had a positive screening test to inhalant allergens, only 11.9% (n = 204) were sensitized to food allergens.

Multiple group comparisons of lung function parameters among the respiratory phenotypes showed significantly decreased lung function in boys with asthma compared with healthy boys and boys with rhinitis, except for z-score FVC, between the healthy and asthma groups ($P = .31$) and between the rhinitis and asthma groups ($P > .24$ for absolute and *z*-score FVC values; Table 2). The healthy and rhinitis groups did not differ in lung function. A similar tendency was observed in girls, but associations failed to reach statistical significance.

Sensitization According to Phenotypes

In total, data from 1,128 subjects were analyzed, and most were free of allergic respiratory disease (76.6%). Figure 3 shows the distribution of different grades of sensitization to inhalant allergens by

Table 2
Lung function parameters stratified by allergic respiratory disease

Phenotype	Boys, median (25th, 75th percentiles)			Girls, median (25th, 75th percentiles)			Total, median (25th, 75th percentiles)		
	Healthy	Rhinitis	Asthma	Healthy	Rhinitis	Asthma	Healthy	Rhinitis	Asthma
Total (N)	387	74	66	477	71	53	864	145	119
FEV_1 (L)	3.90 (3.47, 4.29)	3.84 (3.54, 4.19)	3.55[b,c] (3.09, 3.94)	3.19 (2.93, 3.44)	3.15 (2.92, 3.50)	3.12 (2.85, 3.47)	3.41 (3.06, 3.90)	3.53 (3.1, 3.93)	3.33 (2.87, 3.72)
FVC (L)	4.57 (4.04, 5.02)	4.53 (3.98, 4.76)	4.32[b] (3.74, 4.77)	3.58 (3.27, 3.92)	3.56 (3.26, 3.95)	3.68 (3.28, 3.96)	3.91 (3.43, 4.55)	3.99 (3.5, 4.56)	3.93 (3.5, 4.43)
FEV_1/FVC ratio	0.86 (0.82, 0.90)	0.87 (0.82, 0.90)	0.82[b,c] (0.77, 0.88)	0.89 (0.85, 0.93)	0.89 (0.85, 0.92)	0.86 (0.82, 0.93)	0.88 (0.83, 0.92)	0.87 (0.83, 0.92)	0.85 (0.79, 0.91)
$FEF_{25\%-75\%}$ (L/s)	4.15 (3.46, 4.85)	4.25 (3.57, 4.60)	3.30[b,c] (2.65, 4.23)	3.72 (3.22, 4.31)	3.69 (3.15, 4.32)	3.53 (2.87, 4.12)	3.90 (3.31, 4.56)	4.04 (3.39, 4.48)	3.40 (2.78, 4.16)
Z-score[a] FEV_1	−0.56 (−1.1, 0.04)	−0.33 (−0.87, 0.03)	−1.05[b,c] (−1.73, −0.39)	−0.57 (−1.15, 0.04)	−0.47 (−1.18, 0.12)	−0.87 (−1.25, −0.26)	−0.57 (−1.14, 0.04)	−0.42 (−1.07, 0.07)	−0.95 (−1.51, −0.35)
Z-score[a] FVC	−0.64 (−1.17, −0.01)	−0.57 (−1.12, 0.08)	−0.79 (−1.44, −0.22)	−0.53 (−1.1, 0.1)	−0.54 (−0.99, 0.15)	−0.54 (−0.87, −0.09)	−0.56 (−1.12, 0.06)	−0.56 (−1.06, 0.1)	−0.61 (−1.32, −0.14)
Z-score[a] FEV_1/FVC ratio	−0.03 (−0.62, 0.64)	0.04 (−0.64, 0.71)	−0.74[b,c] (−1.43, 0.28)	−0.03 (−0.71, 0.74)	−0.02 (−0.71, 0.56)	−0.41 (−1.17, 0.66)	−0.03 (−0.67, 0.69)	0.03 (−0.71, 0.57)	−0.52 (−1.25, 0.48)
Z-score[a] $FEF_{25\%-75\%}$	−0.36 (−1.07, 0.25)	−0.31 (−0.88, 0.19)	−1.26[b,c] (−1.82, −0.22)	−0.34 (−0.92, 0.40)	−0.34 (−0.95, 0.35)	−0.60 (−1.40, 0.02)	−0.35 (−0.99, 0.33)	−0.34 (−0.91, 0.30)	−0.86 (−1.62, −0.09)

Abbreviations: $FEF_{25\%-75\%}$, forced expiratory flow at 25% to 75% of forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
[a]Z-scores for lung function parameters were adjusted for sex, ethnicity, age, and height according to the Global Lung Function Initiative.[22]
[b]Significant difference by the Wilcoxon rank-sum test stratified by sex between healthy and asthmatic phenotypes.
[c]Significant difference by the Wilcoxon rank-sum test stratified by sex between rhinitis and asthmatic phenotypes.

allergic respiratory disease status: (1) no sensitization, (2) a positive screening test for inhalant allergens only, and a positive allergen-specific sensitization test to (3) at least 1 inhalant allergen (>3.5 kU/L) and (4) at least 3 inhalant allergens (Fig 2). With increasing sensitization grade, the percentage of subjects with rhinitis or asthma increased from 5.8% in IgE group 1 (total n = 620) to 69.4% in IgE group 4 (total n = 144). A positive screening test for inhalant allergens (IgE group 2, 3, or 4) was observed in 32.4% of subjects without respiratory lung disease (n = 864), in 93.8% of subjects with rhinitis (n = 145), and in 77.3% of subjects with asthma (n = 119). Of those with an increased allergen-specific IgE concentration (>3.5 kU/L) to at least 1 inhalant allergen, 55.4% of boys and 52.2% of girls in group 3 and 31.7% of boys and 29.0% of girls in group 4 were classified as having no asthma or rhinitis.

Comparison of Spirometric Parameters in IgE Groups within Phenotypes

In healthy subjects, analyses comparing all IgE groups with one another using Kruskal-Wallis tests were not significant for any lung function parameter for boys or girls. Applying linear regression model 1 (adjusted for age, height, weight, study group, and study center) and model 2 (also adjusted for parental education level, breastfeeding, maternal smoking during pregnancy, and intake of rhinitis medication; data not shown) did not show a significant difference in lung function between IgE group 1 and groups 2, 3, and 4 for healthy girls (Table 3). For healthy boys, only a significant difference between IgE groups 1 and 2 was observed for FEV_1, GLI *z*-score FEV_1, and GLI z-score FVC whereas no differences were found for IgE groups 3 and 4 compared with IgE group 1 (Table 3).

Owing to the small number of subjects with rhinitis in IgE groups 1 and 2 (<10.4%), only IgE groups 3 and 4 were included in group comparisons and linear regression models (Table 4). Nevertheless, increasing sensitization grade was not associated with any of the spirometric parameters in those with rhinitis. Sensitivity analyses applying the ISAAC definition of current allergic rhinoconjunctivitis symptoms did not yield different results. The same null findings were observed in subjects with asthma when lung function parameters in subjects without any or a low sensitization (IgE groups 1 and 2) were compared with those more highly sensitized (IgE groups 3 and 4; Table 4). Sensitization to food allergens also was not associated with lung function when analyzing subjects without sensitization (IgE group 1), those with high allergen-specific sensitization to inhalant allergens but no food sensitization (IgE groups 3 and 4), and those with concurrent sensitization to food allergens (IgE group 3 and 4 plus positive screening test for food allergens; data not shown) stratified by allergic respiratory disease.

Discussion

The present results did not show an association between lung function assessed by spirometry and increasing sensitization grade in healthy individuals or those with rhinitis or asthma. Although no associations were found for polysensitized healthy boys, low sensitized healthy boys had higher values of FEV_1, GLI *z*-score FEV_1, and GLI z-score FVC compared with non-sensitized healthy boys. However, confidence intervals were wide and results were not significant for the FEV_1/FVC ratio. Thus, this result should be interpreted with caution and might not be clinically relevant.

Previous studies that have assessed associations between lung function and allergen-specific IgE in serum in youth are highly variable for the results and methods applied.[14–17] With respect to the methods, these studies differ in which lung function parameters and allergens were considered and how the calculation of the allergen-specific IgE was conducted (analyzing individual allergen-specific IgE concentrations or summing all tested

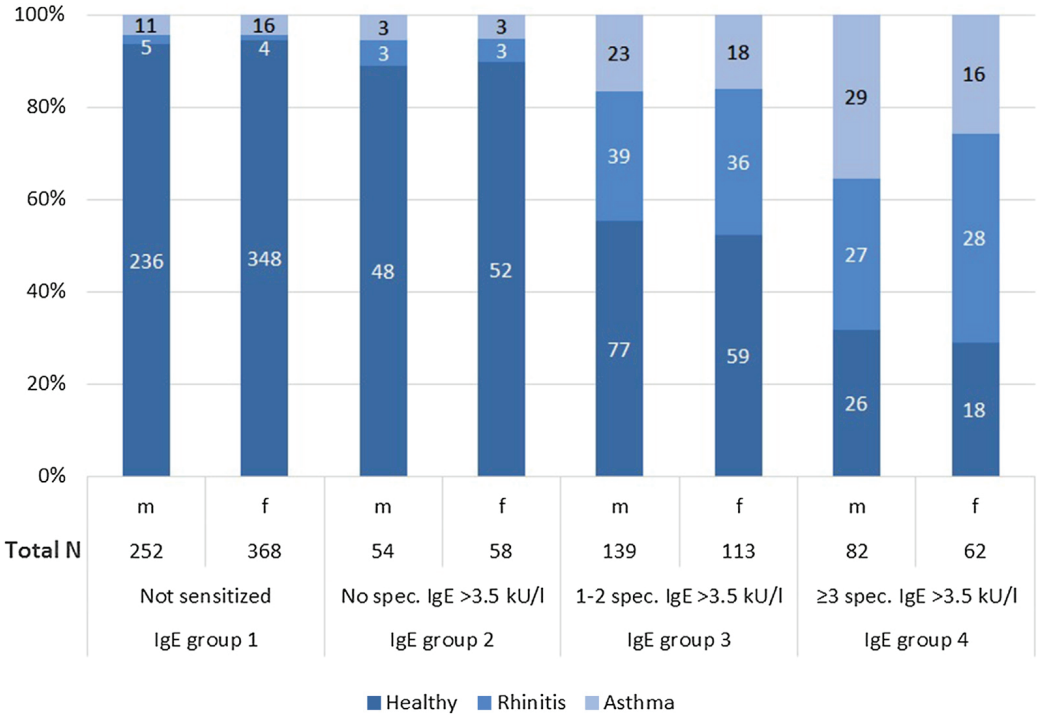


Figure 3. Distribution and prevalence of sensitization. Numbers within columns represent the number of subjects per phenotype per IgE group (Fig 2). F, female; M, male; spec. IgE, allergen-specific immunoglobulin E.

concentrations).[14–17] The number of investigated allergens in studies addressing a similar research question ranges from 1 (house dust mites[17]) to 6 (*Dermatophagoides farinae*, *Alternaria alternata*, dog, cat, timothy grass, and ragweed[15]). It also is debatable whether it is more appropriate to use the quantitatively measured specific IgE concentrations as the predictor or whether these concentrations should be categorized into groups to assess the probability of clinical symptoms. The present analytical strategy took high specific IgE values and polysensitization into account by dividing all inhalant allergen-specific IgE concentrations (cutoff 3.5 kU/L) and

Table 3
Associations between lung function and sensitization group in healthy subjects—Results of linear regression analysis[a]

Comparison	IgE group	Healthy boys, IgE group 1 vs 2, 3, 4			Healthy girls, IgE group 1 vs 2, 3, 4		
		β	95% CI	*P* value	β	95% CI	*P* value
FEV_1	2	0.18	0.04 to 0.31	.01	−0.02	−0.12 to 0.08	.67
	3	0.04	−0.07 to 0.15	.50	−0.02	−0.11 to 0.07	.66
	4	0.00	−0.18 to 0.17	.97	0.01	−0.15 to 0.17	.87
FVC	2	0.14	−0.01 to 0.29	.06	−0.06	−0.17 to 0.05	.27
	3	0.00	−0.12 to 0.12	.99	−0.08	−0.18 to 0.03	.15
	4	−0.02	−0.21 to 0.17	.84	−0.03	−0.22 to 0.15	.70
FEV_1/FVC ratio	2	0.01	−0.01 to 0.03	.23	0.01	−0.01 to 0.03	.29
	3	0.01	−0.01 to 0.02	.22	0.01	0.00 to 0.03	.10
	4	0.00	−0.02 to 0.03	.80	0.01	−0.02 to 0.04	.45
$FEF_{25\%-75\%}$	2	0.26	−0.03 to 0.54	.08	0.06	−0.17 to 0.28	.63
	3	0.15	−0.09 to 0.38	.22	0.09	−0.12 to 0.30	.40
	4	0.09	−0.28 to 0.46	.64	0.24	−0.12 to 0.61	.19
Z-score[b] FEV_1	2	0.33	0.06 to 0.59	.01	−0.01	−0.26 to 0.23	.91
	3	0.09	−0.13 to 0.31	.42	−0.03	−0.27 to 0.20	.78
	4	0.00	−0.35 to 0.34	.99	0.01	−0.40 to 0.41	.97
Z-score[b] FVC	2	0.27	0.01 to 0.53	.04	−0.09	−0.33 to 0.16	.48
	3	0.01	−0.20 to 0.23	.91	−0.15	−0.38 to 0.08	.21
	4	−0.02	−0.36 to 0.32	.90	−0.09	−0.49 to 0.31	.65
Z-score[b] FEV_1/FVC ratio	2	0.09	−0.20 to 0.39	.55	0.13	−0.15 to 0.42	.36
	3	0.13	−0.12 to 0.38	.30	0.19	−0.08 to 0.46	.17
	4	0.04	−0.34 to 0.43	.82	0.22	−0.24 to 0.68	.35
Z-score[b] $FEF_{25\%-75\%}$	2	0.23	−0.06 to 0.51	.12	0.08	−0.19 to 0.35	.55
	3	0.17	−0.07 to 0.40	.17	0.13	−0.13 to 0.38	.33
	4	0.09	−0.28 to 0.47	.62	0.26	−0.18 to 0.70	.24

Abbreviations: CI, confidence interval; $FEF_{25\%-75\%}$, forced expiratory flow at 25% to 75% of forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

[a]Results of linear regression models in healthy subjects stratified by sex and adjusted for study center, study group, age, weight, height, and specific IgE that was categorized as IgE group 1 (reference category) and IgE groups 2 to 4. The IgE groups are defined in Figure 2. A change of β by 0.1 in FEV_1 or FVC indicates a lung volume change of 100 mL (not applicable to β of z-scores).

[b]Z-scores for lung function parameters were adjusted for sex, ethnicity, age, and height according to the Global Lung Function Initiative.[22]

Table 4
Associations between lung function and sensitization group in subjects with rhinitis and asthma—Results of linear regression analysis

Comparison of	IgE group	Rhinitis—IgE groups 3 vs 4[a]			IgE group	Asthma—IgE groups 1 + 2 vs 3, 4[b]		
		β	95% CI	*P* value		β	95% CI	*P* value
FEV_1					3	0.09	−0.12 to 0.31	.39
	4	0.03	−0.10 to 0.17	.63	4	−0.09	−0.33 to 0.16	.48
FVC					3	0.22	0.01 to 0.42	.04
	4	0.03	−0.13 to 0.19	.73	4	0.11	−0.12 to 0.34	.34
FEV_1/FVC ratio					3	−0.03	−0.07 to 0.02	.29
	4	0.00	−0.02 to 0.02	.67	4	−0.05	−0.10 to 0.01	.08
$FEF_{25\%–75\%}$					3	−0.09	−0.64 to 0.46	.75
	4	0.11	−0.17 to 0.38	.44	4	−0.41	−1.03 to 0.22	.20
Z-score[c] FEV_1					3	0.04	−0.46 to 0.54	.88
	4	0.14	−0.16 to 0.44	.35	4	−0.40	−0.97 to 0.16	.16
Z-score[c] FVC					3	0.24	−0.20 to 0.68	.28
	4	0.18	−0.15 to 0.51	.29	4	−0.05	−0.54 to 0.44	.85
Z-score[c] FEV_1/FVC ratio					3	−0.38	−1.05 to 0.29	.27
	4	−0.03	−0.35 to 0.29	.86	4	−0.67	−1.43 to 0.09	.08
Z-score[c] $FEF_{25\%–75\%}$					3	−0.25	−0.88 to 0.39	.44
	4	0.13	−0.16 to 0.43	.38	4	−0.66	−1.37 to 0.05	.07

Abbreviations: CI, confidence interval; $FEF_{25\%–75\%}$, forced expiratory flow at 25% to 75% of forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
[a]Results of linear regression models were adjusted for sex, study center, study group, age, weight, and height (reference category, IgE group 3).
[b]Results of linear regression models were adjusted for sex, study center, study group, age, weight, height, and having concurrent rhinitis (reference category, combined IgE groups 1 and 2). The IgE groups are defined in Figure 2.
[c]*Z*-scores for lung function parameters were adjusted for sex, ethnicity, age, and height according to the Global Lung Function Initiative.[22]

summing up all positive concentrations (Figure 2). This high cutoff value (3.5 kU/L) was chosen to allow subjects with low and high probabilities of having symptoms to be distinguished. This approach led to a more differentiated picture of sensitization to 1 or 2 allergens vs polysensitization without emphasizing extremely high specific IgE values in the analysis. These high specific IgE values are generally limited owing to the ImmunoCAP test quantitative range limit of 100 kU/L.

Thus far, results of other analyses have suggested a tendency toward lower lung function in those highly sensitized. Rajendra et al[15] reported a negative correlation between the FEV_1/FVC ratio and the sum of allergen-specific IgE concentrations to 6 inhalant allergens in 18- to 20-year-old women with current asthma (n = 32, Pearson correlation coefficient [*r*] = −0.42, *P* = .017). Matsui et al,[16] who performed partial Pearson correlations for lung function in 12- to 20-year-old subjects with asthma and quantitative specific IgE concentrations (log_{10}), reported an inverse relation between FEV_1 percent predicted and the FEV_1/FVC ratio and the sum of specific IgE concentrations of cockroach, dust mites, cat, and mouse.

House dust mite as a single allergen has been commonly analyzed in previous studies.[14,16,17] Correlation analyses in 10-year-old children with asthma between house dust mite-specific IgE (*D pteronyssinus* and *D farinae*) and FEV_1 and $FEF_{25\%–75\%}$ percent predicted were found to be significant (FEV_1: $r = -0.37$ and −0.44, respectively, $P < .05$) in a study by Choi et al.[14] In contrast, no association was reported for FEV_1 by Silvestri et al[17] (no *P* value given, $FEF_{25\%–75\%}$ not investigated). In line with the finding reported by Silvestri et al is the study by Matsui et al[16] who found no partial Pearson correlations between FEV_1 percent predicted and quantitative specific IgE (log_{10}) for house dust mites (*D pteronyssinus* and *D farinae*) after adjusting for income, study group, sex, age, and race in 12- to 20-year-olds with asthma. For comparability with these studies, the present study applied quantitative correlation analysis and adjusted linear regression modeling (model 1) to logarithmically transformed specific IgE values of *D pteronyssinus* in subjects with asthma in this cohort. These analyses showed a slight negative correlation with the GLI *z*-score FEV_1 ($r = -0.18$, $P = .08$) and regression coefficient ($\beta = -0.04$, $P = .31$). However, applying quantitative analyses to the present data was not appropriate, because the IgE concentrations were not normally distributed (Fig 1).

Owing to the various statistical approaches used and the different selections of studied allergens included in previous studies, it is challenging to provide a general conclusion regarding a potential association between allergen-specific sensitization and lung function. The authors did not observe an association between current sensitization to inhalant allergens and absolute spirometric parameters or standardized GLI *z*-scores for spirometric indices in their analysis using linear regression models adjusted for potential confounders. Nevertheless, the positive findings from others who have applied correlation analyses need to be acknowledged.

The present results are limited to the selected study population. To avoid misclassification, only subjects who provided complete phenotype information were included in the regression analyses. High compliance to lung function measurement and in completing questionnaires is likely to have led to some selection bias. The classification of subjects into phenotype groups was performed using questionnaire-based information that was not verified by an examination from a physician. Of subjects assigned to the rhinitis subgroup, only 9 of 145 were not sensitized to the tested inhalant allergens. For this reason, a comparison between polysensitized subjects and non-sensitized subjects was not possible.

Despite these limitations, this study has several strengths. Data on 8 common inhalant allergens and various spirometric parameters, which cover parameters indicative of airway narrowing (FEV_1, FEV_1/FVC ratio), lung volume and lung size (FVC), and flow rates ($FEF_{25\%–75\%}$), were available. When summing the quantitative values of specific IgE concentrations, high values for 1 allergen can strongly influence the summed result. Higher allergen-specific IgE values lead to a higher probability of having symptoms, but clear cutoffs are not well defined.[23,30,31] The present classification of sensitization was independent of the exact quantitative IgE values. For example, subjects in IgE group 4 were known to have at least 3 allergens with allergen-specific IgE levels higher than 3.5 kU/L and therefore could confidently be identified as polysensitized without focusing entirely on exact values or allergen combinations.

Using this qualitative approach, the authors did not identify an association between sensitization to inhalant allergens and lung function parameters in their cohort. This study population was nevertheless comparable to other epidemiologic respiratory studies in lung function and sensitization pattern.[11,12,26,32] Boys had

higher spirometric parameters than girls, were more often sensitized, and had a higher prevalence of rhinitis and asthma. Lung function parameters in subjects with asthma were lower compared with those in healthy subjects.

In conclusion, neither sensitization to 1 or 2 inhalant allergens nor polysensitization showed a relation to lung function in apparently lung-healthy adolescents, those with asthma, or those with rhinitis. These results nevertheless confirm that polysensitization contributes to the identification of subjects at higher risk for rhinitis and asthma.

Acknowledgments

The authors thank all families for their active participation in the study, the obstetric units for allowing recruitment, and the GINIplus study team for its excellent work. They thank Dr Elaine Fuertes (Institute of Epidemiology I, Helmholtz Zentrum München, Germany) for editorial assistance in the preparation of this report.

Appendix: GINIplus Study Group

J. Heinrich, I. Brüske, H. Schulz, C. Flexeder, C. Zeller, M. Standl, M. Schnappinger, M. Sußmann, E. Thiering, and C. Tiesler, Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg; D. Berdel, A. von Berg, and B. Filipiak-Pittroff, Research Institute, Department of Pediatrics, Marien-Hospital, Wesel; S. Koletzko and K. Werkstetter, Ludwig-Maximilians-University of Munich, Dr von Hauner Children's Hospital, Munich; C.P. Bauer and U. Hoffmann, Department of Pediatrics, Technische Universität München and Deutsche Rentenversicherung Bayern; and B. Hoffmann, E. Link, C. Klümper, and U. Krämer, IUF-Leibniz Institute for Environmental Research, Düsseldorf.

References

[1] Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol*. 2005;116:377–383.
[2] Langen U. Sensibilisierungsstatus bei Kindern und Jugendlichen mit Heuschnupfen und anderen atopischen Erkrankungen. *Bundesgesundheitsblatt*. 2012;55:318–328.
[3] Anto JM, Sunyer J, Basagana X, et al. Risk factors of new-onset asthma in adults: a population-based international cohort study. *Allergy*. 2010;65:1021–1030.
[4] Custovic A, Simpson A. The role of inhalant allergens in allergic airways disease. *J Investig Allergol Clin Immunol*. 2012;22:393–401.
[5] Gergen PJ, Arbes SJ Jr, Calatroni A, Mitchell HE, Zeldin DC. Total IgE levels and asthma prevalence in the US population: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol*. 2009;124:447–453.
[6] Schoefer Y, Schafer T, Meisinger C, Wichmann HE, Heinrich J. Predictivity of allergic sensitization (RAST) for the onset of allergic diseases in adults. *Allergy*. 2008;63:81–86.
[7] Schafer T, Wolke G, Ring J, Wichmann HE, Heinrich J. Allergic sensitization to cat in childhood as major predictor of incident respiratory allergy in young adults. *Allergy*. 2007;62:1282–1287.
[8] Brockow I, Zutavern A, Hoffmann U, et al. Early allergic sensitizations and their relevance to atopic diseases in children aged 6 years: results of the GINI study. *J Investig Allergol Clin Immunol*. 2009;19:180–187.
[9] Filipiak-Pittroff B, Schnopp C, Berdel D, et al. Predictive value of food sensitization and filaggrin mutations in children with eczema. *J Allergy Clin Immunol*. 2011;128:1235–1241.e5.
[10] Bousquet J, Anto JM, Bachert C, et al. Factors responsible for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens. A GA2LEN project. *Allergy*. 2006;61:671–680.
[11] Strunk RC, Weiss ST, Yates KP, Tonascia J, Zeiger RS, Szefler SJ. Mild to moderate asthma affects lung growth in children and adolescents. *J Allergy Clin Immunol*. 2006;118:1040–1047.
[12] Weiss ST, Tosteson TD, Segal MR, Tager IB, Redline S, Speizer FE. Effects of asthma on pulmonary function in children. A longitudinal population-based study. *Am Rev Respir Dis*. 1992;145:58–64.
[13] Sinisgalli S, Collins MS, Schramm CM. Clinical features cannot distinguish allergic from non-allergic asthma in children. *J Asthma*. 2012;49:51–56.
[14] Choi SY, Sohn MH, Yum HY, Kwon BC, Kim KE. Correlation between inhalant allergen-specific IgE and pulmonary function in children with asthma. *Pediatr Pulmonol*. 2005;39:150–155.
[15] Rajendra C, Zoratti E, Havstad S, et al. Relationships between total and allergen-specific serum IgE concentrations and lung function in young adults. *Ann Allergy Asthma Immunol*. 2012;108:429–434.
[16] Matsui EC, Sampson HA, Bahnson HT, et al. Allergen-specific IgE as a biomarker of exposure plus sensitization in inner-city adolescents with asthma. *Allergy*. 2010;65:1414–1422.
[17] Silvestri M, Pistorio A, Battistini E, Rossi GA. IgE in childhood asthma: relevance of demographic characteristics and polysensitisation. *Arch Dis Child*. 2010;95:979–984.
[18] Berg Av, Koletzko S, Grubl A, et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol*. 2003;111:533–540.
[19] Berg Av, Kramer U, Link E, et al. Impact of early feeding on childhood eczema: development after nutritional intervention compared with the natural course—the GINIplus study up to the age of 6 years. *Clin Exp Allergy*. 2010;40:627–636.
[20] Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319–338.
[21] Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26:948–968.
[22] Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40:1324–1343.
[23] Soderstrom L, Kober A, Ahlstedt S, et al. A further evaluation of the clinical use of specific IgE antibody testing in allergic diseases. *Allergy*. 2003;58:921–928.
[24] Johansson S. ImmunoCAP® Specific IgE test: an objective tool for research and routine allergy diagnosis. *Expert Rev Mol Diagn*. 2004;4:273–279.
[25] Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. *J Allergy Clin Immunol*. 2008;122:145–151.
[26] Lodrup Carlsen KC, Haland G, Devulapalli CS, et al. Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study. *Allergy*. 2006;61:454–460.
[27] Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8:483–491.
[28] Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368:733–743.
[29] R Core Team. *R: A language and environment for statistical computing*. Vienna: R Foundation for Statistical Computing; 2014. http://www.R-project.org/.
[30] Pastorello EA, Incorvaia C, Ortolani C, et al. Studies on the relationship between the level of specific IgE antibodies and the clinical expression of allergy: I. Definition of levels distinguishing patients with symptomatic from patients with asymptomatic allergy to common aeroallergens. *J Allergy Clin Immunol*. 1995;96:580–587.
[31] Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantification and the probability of wheeze in preschool children. *J Allergy Clin Immunol*. 2005;116:744–749.
[32] Schmitz R, Thamm M, Ellert U, Kalcklosch M, Schlaud M. Prevalence of common allergies in children and adolescents in Germany: results of the KiGGS study: first follow-up (KiGGS Wave 1). *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2014;57:771–778.

6.2 Publication II

Original title:

Which early life events or current environmental and lifestyle factors influence lung function in adolescents? – Results from the GINIplus & LISAplus studies

Authors:

Agnes Luzak, Elaine Fuertes, Claudia Flexeder, Marie Standl, Andrea von Berg, Dietrich Berdel, Sibylle Koletzko, Joachim Heinrich, Dennis Nowak, and Holger Schulz

Journal:

Respiratory Research

DOI:

10.1186/s12931-017-0619-5

Year:

2017

Luzak et al. Respiratory Research (2017) 18:138
DOI 10.1186/s12931-017-0619-5

Respiratory Research

RESEARCH Open Access

Which early life events or current environmental and lifestyle factors influence lung function in adolescents? – results from the GINIplus & LISAplus studies

Agnes Luzak[1], Elaine Fuertes[1,2,3,4], Claudia Flexeder[1], Marie Standl[1], Andrea von Berg[5], Dietrich Berdel[5], Sibylle Koletzko[6], Joachim Heinrich[1,7,8], Dennis Nowak[7,8] and Holger Schulz[1,7*]

Abstract

Background: Various factors may affect lung function at different stages in life. Since investigations that simultaneously consider several factors are rare, we examined the relative importance of early life, current environmental/lifestyle factors and allergic diseases on lung function in 15-year-olds.

Methods: Best subset selection was performed for linear regression models to investigate associations between 21 diverse early life events and current factors with spirometric parameters (forced vital capacity, forced expiratory volume in 1 s and maximal mid-expiratory flow ($FEF_{25–75}$)) in 1326 participants of the German GINIplus and LISAplus birth cohorts. To reduce model complexity, one model for each spirometric parameter was replicated 1000 times in random subpopulations ($N = 884$). Only those factors that were included in >70% of the replication models were retained in the final analysis.

Results: A higher peak weight velocity and early lung infections were the early life events prevalently associated with airflow limitation and $FEF_{25–75}$. Current environmental/lifestyle factors at age 15 years and allergic diseases that were associated with lung function were: indoor second-hand smoke exposure, vitamin D concentration, body mass index (BMI) and asthma status. Sex and height captured the majority of the explained variance (>75%), followed by BMI (≤23.7%). The variance explained by early life events was comparatively low (median: 4.8%; range: 0.2–22.4%), but these events were consistently negatively associated with airway function.

Conclusions: Although the explained variance was mainly captured by well-known factors included in lung function prediction equations, our findings indicate early life and current factors that should be considered in studies on lung health among adolescents.

Keywords: Adolescence, Spirometry, Lung function, Determinants, Epidemiology

* Correspondence: schulz@helmholtz-muenchen.de
[1]Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Epidemiology I, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany
[7]Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Max-Lebsche-Platz 31, 81377 Munich, Germany
Full list of author information is available at the end of the article

Background

Lung development begins in early gestational age and continues until early childhood, while lung growth continues until 20–25 years, at which point a plateau in lung function is reached [1, 2]. Several factors have the potential to affect lung function during this process [1–4]. Adverse events in early life may influence lung function trajectories and lead to higher susceptibility to lung diseases, such as asthma or chronic obstructive lung disease [1, 5]. Recently published results among children with asthma underline that the impairment of lung function in childhood is a predictor of reduced lung-function growth and abnormal decline over time [4]. There is an increasing focus on the influence of lung function deviations in early childhood on later life respiratory morbidity [1, 4–7]. Numerous epidemiological studies have investigated factors that might influence lung function or that are associated with allergic respiratory diseases at different stages in life (Fig. 1). However, previous studies have mainly investigated only one factor or a few factors at specific periods of life, and most are focused on early life events [7–27]. In reality, it is likely that a complex framework of several factors determines an individual's lung function throughout life [1, 2, 5]. Therefore, an approach that investigates the simultaneous effects of several factors might have the potential to identify which factors may be most influential at a certain stage of life. To date, only one epidemiological study reported on the effects of several factors (including early life events, socioeconomic status and environmental factors) on spirometric lung function between 6 and 16 years of age in Tunisian children [28]. Besides well-established factors (height, weight, sex and age), this study found that type of heating had the strongest effect on lung function in healthy Tunisian children.

In the current study, we used two large, well characterized, longitudinal German birth cohort studies to investigate associations between numerous early life events and current environmental and lifestyle factors, as well as allergic diseases, with lung function assessed by spirometry in adolescents aged 15 years. Our main purpose was to identify factors associated with spirometric measures of central and peripheral airway function in adolescents and further, to examine the relative importance of early life events compared to current environmental and lifestyle factors (Fig. 1).

Methods

Study population

We used data from two prospective German birth cohorts with each 15 years of follow-up; the German Infant study on the influence of Nutrition Intervention plus air pollution and genetics on allergy development (GINIplus) [29] and the study on Life-style related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics (LISAplus) [30]. The inclusion criteria were the same for both cohorts, German families with a full-term newborn and birth weight of at least 2500 g were considered as eligible.

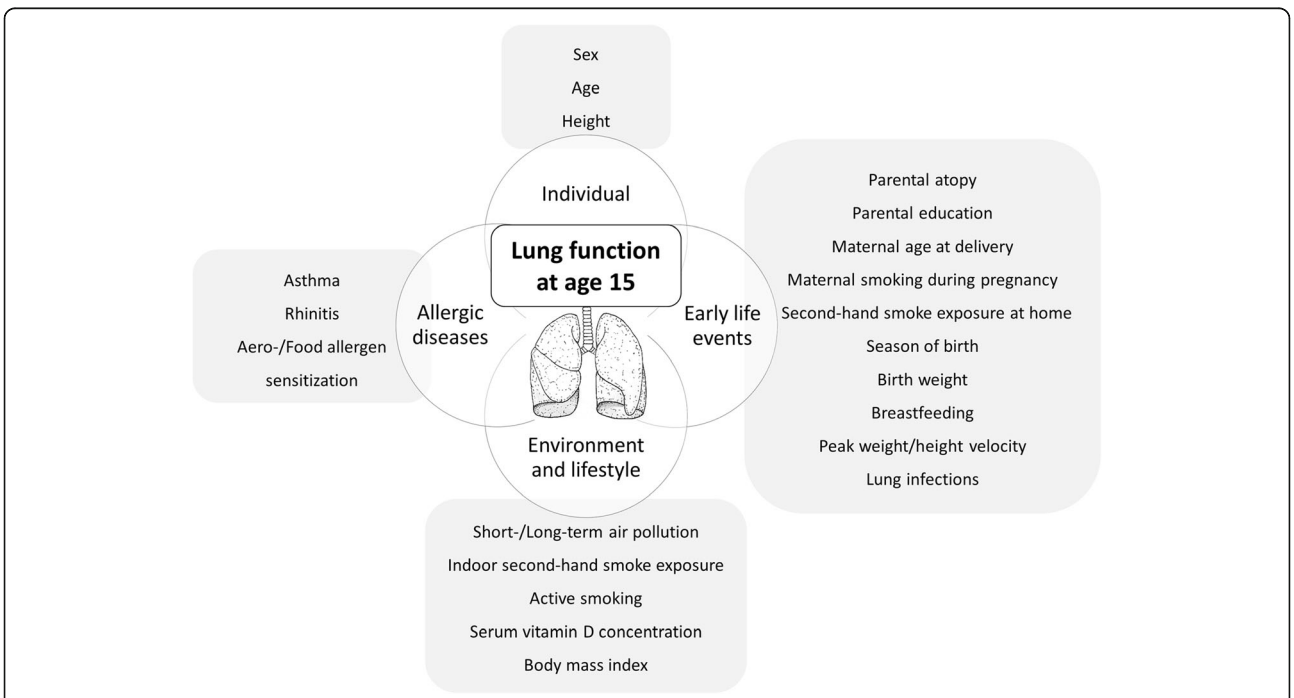


Fig. 1 Covariates investigated for association with lung function in 15-year old adolescents (definitions presented in Table 1)

In GINIplus, 5991 neonates were recruited between 1995 and 1998 in the study centers Munich and Wesel and surrounding areas. Parents who's newborns had at least one first degree family member with an atopic disease were asked to participate in the intervention study arm, which investigated the effect of three different hydrolyzed formulas on allergy development (N = 2252). All others were asked to participate in the observation study arm (N = 3739). At the 15-year follow-up, 1887 subjects participated in lung function measurements (50.4% were from the intervention arm).

In LISAplus, 3094 full-term children were recruited between 1997 and 1999 in the area of four German cities: Munich, Wesel, Leipzig and Bad Honnef. Given that air pollution concentrations (an important environmental factor considered in the analysis) were only available for Munich and Wesel in GINIplus, the population of LISAplus was restricted to these study areas, comprising 1812 subjects, of which 563 participated in lung function measurements at 15 years.

In GINIplus, parent-completed questionnaires were collected at birth, yearly from 1 to 4, and at 6, 10 and 15 years of age. In LISAplus, follow-ups were at birth, 0.5, 1, 1.5, 2, 4, 6, 10 and 15 years of age. The 15-year follow-up for both studies included a self-report questionnaire for the adolescents, lung function testing and blood sample collection. Further information about the cohorts' design is described elsewhere [29–31]. Data from the LISAplus and GINIplus birth cohorts were pooled and are presented for the complete study population considering study group and study center as potential confounders in the analyses.

Lung function measurements

Lung function measurements by spirometry were performed in line with ATS/ERS recommendations [32]. Participants were asked not to change their asthma medication prior to lung function testing. Among the analyzed participants, 83 had asthma. Of these, 89.2% reported asthma medication in the past 12 months. On the day of lung function testing, 7.2% reported the intake of short-acting beta agonists, 9.6% reported the intake of inhaled corticosteroids, and 18.1% reported the intake of both inhaled corticosteroids and beta adrenergic agonists, of which most (86.7%) consisted of long-acting beta agonists.

For the performance of spirometry assessments, the technicians were equally trained and the equipment used was the same in both study centers. Flow-volume curves were obtained using a pneumotachograph-type spirometer (EasyOne Worldspirometer, ndd, Zurich, Switzerland). Subjects performed at least three and up to eight trials per test. Trial results were visually inspected according to ATS/ERS acceptability criteria [32]. Indices of the best manoeuvre, defined as the test with the largest sum of the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC), were used in analyses. Further spirometric parameters obtained included the peak expiratory flow (PEF), the forced expiratory flow rates at 25% (FEF_{25}), 50% (FEF_{50}) and 75% (FEF_{75}) of exhaled FVC and the mean flow rate between 25% and 75% of FVC ($FEF_{25–75}$).

These parameters could be viewed as indicative of different lung regions or functions [33, 34]: lung volume (FVC), airways and lung volume (FEV_1), airflow limitation (FEV_1/FVC), flow rates for the larger conducting (PEF, FEF_{25}) and peripheral airways (FEF_{50}, FEF_{75} and $FEF_{25–75}$). We focused our analyses and results primary on four spirometric parameters (FVC, FEV_1, FEV_1/FVC and $FEF_{25–75}$) that represent lung volume and airway function. We also report if the associations for the primary parameters are supported by the results of the additional secondary parameters, which represent flow rates (PEF, FEF_{25}, FEF_{50}, FEF_{75}). Results for the secondary parameters are presented in the additional file only.

Definition of covariates

We selected factors for investigation based on a short review of the literature, including former GINIplus and LISAplus publications [8, 9, 35, 36], and after considering the number of participants with available data in our cohorts. An overview of investigated covariates is presented in Fig. 1. A detailed description was provided in Table 1. Investigated covariates were divided in early life events (e.g. parental atopy, maternal smoking during pregnancy, season of birth, birth weight), current environmental and lifestyle factors that were assessed at the 15-year follow-up (e.g. air pollution, indoor second-hand smoke exposure, BMI), and allergic diseases (e.g. asthma, rhinitis). Besides study specific variables (study group and center), sex, age and height, which are included in lung function prediction equations [37], were considered as basic covariates. The study population comprised only Caucasians, so ethnicity was not included as covariate.

Statistical analysis

Differences between sexes and between participants included and excluded in this analysis were assessed using the t-test (normally distributed) or Wilcoxon rank-sum test (non-normally distributed) for continuous variables. The chi-square test was used for categorical variables.

Associations between study specific variables, early life events, environmental and lifestyle factors, and allergic diseases, with spirometric parameters were analyzed using linear regression. In order to determine the relevant factors, best subset selection was performed using the Mallows' Cp statistic (Cp) as the model selection criterion. The Cp is based on least squares estimation

Table 1 Definition of early life events, environmental and lifestyle factors, and allergic diseases at age 15

	Definition	Assessment
Early life events		
Parental atopy	positive if the mother or father had asthma, eczema or hay fever	asked at birth; questionnaire-based
Parental education	three categories based on the highest number of education years of either parent (high: >10 years; medium: 10 years; low: <10 years)	asked at birth; questionnaire-based
Maternal age at delivery	dichotomized in ≤31 years and >31 years (mean age served as cut-off)	asked at birth; questionnaire-based
Maternal smoking during pregnancy	yes vs no	asked at birth; questionnaire-based
Early second-hand smoke exposure at home	positive if parents reported at least once that the child was exposed to second-hand smoke at home	asked up to age 4 (at 4 months, 1 year (control arm only) and yearly at 2 to 4 years in GINIplus; half-yearly from birth to 2 years and at age 4 years for past 24 months in LISAplus); questionnaire-based
Season of birth	dichotomized (December to February (winter) versus other seasons)	Birth month derived from date of birth; questionnaire-based
Birth weight	continuous, grams	asked at birth in LISAplus and at 1 year in GINIplus; questionnaire-based
Breastfeeding	exclusive breastfeeding for at least four months	asked separately for 1–6 months at 1 year in GINIplus and at 6 months in LISAplus; questionnaire-based
Peak weight and peak height velocity	maximum of the first derivative of the individual weight or height gain curves obtained between birth and two years of age (calculated using nonlinear random effects models) [9]	weight and height measurements obtained during the children's preventive medical check-ups to monitor growth
Early lower respiratory tract infections	doctor's diagnosis of pneumonia or obstructive bronchitis within the first three years of life (hereon referred to as lung infections)	asked up to age 3 (yearly in GINIplus; half-yearly up to age 2 years and up to age 3 years asked at the 4 year follow-up in LISAplus); questionnaire-based
Environmental and lifestyle factors at age 15		
Short-term air pollution exposure	continuous, the average of the daily concentrations of NO_2, $PM_{2.5}$ mass and PM_{10} mass ($\mu g/m^3$)	obtained for the seven days prior to lung function testing from monitoring sites near the centers of Munich and Wesel [8]
Long-term air pollution exposure	continuous, long-term concentrations of NO_2, $PM_{2.5}$ mass and PM_{10} mass ($\mu g/m^3$)	estimated to each participant's home address at birth, 10- and 15-years, respectively [8]
Regular indoor second-hand smoke exposure	positive if the adolescent reported indoor second-hand smoke exposure at least once a week	asked at age 15 years; one question in GINIplus, two questions for second-hand exposure: (1) at home and (2) in other locations in LISAplus (positive if regular exposure was reported in at least one question); questionnaire-based
Active smoking	yes vs no	asked at age 15 years, questionnaire-based
Vitamin D concentrations	continuous; serum 25-hydroxyvitamin D [25(OH)D] concentrations adjusted for seasonal variance using a generalized additive model (nmol/l) [36]	measured at age 15 years using Roche's vitamin D total test (E170, Roche Diagnostics, Mannheim, Germany)
Body mass index	continuous, kilogram per square meter (kg/m^2)	calculated using body height and weight obtained at lung function testing
Current allergic diseases		
Asthma	defined based on the Global Allergy and Asthma European Network (GA2LEN) definition [44]. Subjects were considered as currently having	parents were asked to provide yearly information on their child's doctor diagnosed allergic diseases throughout

Table 1 Definition of early life events, environmental and lifestyle factors, and allergic diseases at age 15 *(Continued)*

	asthma if they responded positively to at least two of the three following questions: (1) Has a doctor diagnosed asthma in your child at the age 3 to 15 years? (2) Has your child taken asthma medication during the last 12 months? (3) Has your child had wheezing or whistling in the chest in the last 12 months?	childhood; information on current allergic symptoms and asthma medication in the last 12 months was derived from the last follow-up questionnaire at age 15 years.
Current allergic rhinitis	positive if one of the following questions was positive: (1) Has a doctor diagnosed hay fever (i.e. seasonal allergic rhinitis) in your child? (2) Has a doctor diagnosed perennial allergic rhinitis in your child?	asked separately for ages 11 to 15, at the 15-year follow-up; questionnaire-based
Sensitization to food or aeroallergens	food allergen mixture including egg white, codfish, cow milk, wheat flour, peanut, and soybean and aeroallergen mixture including cat, dog, mugwort, birch, timothy, rye, *Cladosporium herbarum*, and *Dermatophagoides pteronyssinus*; for both tests, a value >0.35 kU/L was considered positive	measured by serum specific Immunoglobulin E (IgE) using the ImmunoCAP Specific IgE system (Phadia GmbH, Freiburg, Germany) at age 15 years

GINIplus: German Infant study on the influence of Nutrition Intervention plus air pollution and genetics on allergy development; LISAplus: Life-style related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics

and compares the precision and bias of a full model to models with a subset of all the independent variables, taking the number of predictors into consideration [38]. Best subset selection provides the model with the lowest Cp for all possible model sizes of the set of all potential independent variables. The model with the lowest Cp among all model sizes was chosen. Categorical variables were entered using dummy coding.

To strengthen the model selection approach, we applied a two-step process. First, we performed the selection in the total population. Second, to determine if the same variables would have been selected in a subpopulation or if any variables might have been selected by random, the model selection process was repeated 1000 times with two thirds (N = 884) of the population randomly selected for inclusion each time. The frequency of selecting a given variable in the regression models with the lowest Cp (even if the variable was not necessarily significant) was assessed and compared to the variables included in the models derived using the total population. To reduce model complexity, we focused only on variables that remained in >70% of the replication models for each particular spirometric parameter. Regression models including these selected variables (plus significant study specific variables) were rerun in the total population (N = 1326). Multicollinearity in the final models was assessed by the variance inflation factor (VIF), which is a measure of how much of the variance of an estimated regression coefficient is influenced by the correlation between independent variables. If correlations among variables exist, their relative importance, meaning the partial contribution to the total R^2 of a regression model, is influenced by the order in which the variables are entered in a model. To adjust for possible correlations, we report the relative importance of each variable as the sequential R^2 contribution [39]. The sequential R^2 is corrected for the dependence on orderings by unweighted averaging of R^2 contribution over all possible orderings. The reported results of the total sequential R^2 per variable were normalized to sum up to 100% to facilitate comparability [39].

In a sensitivity analysis, current asthmatics were excluded from the final models.

Analyses were run in the statistical program R, version 3.2.0 [40]. P-values <0.05 were considered statistically significant.

Results

Study population

Valid lung function data and information on the investigated factors (Fig. 1) was available for 1326 subjects (63% from Munich, 51% male, mean age of 15.2 years; Table 2). Due to non-random loss to follow-up over the 15-year period, participants differed from the initial cohort, e.g. higher educated parents, more breastfeeding, lower BMI (Additional file 1: Table A1).

Mean lung function parameters were higher among boys ($p < 0.05$), with the exception of FEV_1/FVC, which was higher among girls (Table 2). Of 2358 participants with valid lung function measurements at the 15-year follow-up, 43.8% were excluded due to missing information on investigated factors. Lung function did not differ between the population analyzed and the other subjects with valid spirometry (Munich and Wesel) stratified by sex, with the exception that participating males had a slightly higher FEV_1/FVC compared to non-participating males (Additional file 1: Table A2).

Variable selection

Nearly all early life events and current environmental and lifestyle factors that showed significant associations with lung function in the selection models based on the total population remained in >70% of the models (Additional file 1: Tables A3 and A4). Exceptions included parental atopy (54% in FEV_1/FVC model), parental education (52% in FEV_1 model), and regular indoor second-hand smoke exposure at age 15 (66% in FEV_1/FVC model, and slightly <70% in $FEF_{25–75}$ model), which were less often included and therefore excluded from further analyses. Linear regression results for the included variables are shown in Table 3. Results considering secondary flow rates (PEF and FEF_{25} to FEF_{75}) are shown in the additional file 1: Tables A4 and A5. The VIF was <2 for all variables in the final models, suggesting low multicollinearity.

Individual factors - sex, age and height

Sex and height at lung function testing showed stable associations with all spirometric parameters, except for the association between $FEF_{25–75}$ and sex and between FEV_1/FVC and height (Table 3). Associations for age were found with FEV_1 and FVC. Similar results were present considering further flow rates (Additional file 1: Table A5).

Early life events

Lower lung function was associated with higher peak weight velocity and early lung infections (Table 3). Peak weight velocity was negatively associated with FEV_1/FVC (β: -0.8%/IQR increase) and $FEF_{25–75}$ (β: −88 ml/s/IQR increase). An impact of peak weight velocity on mainly the peripheral airways was also supported by the negative associations found with FEF_{50} and FEF_{75} (Additional file 1: Table A5). Early lung infections were also negatively associated with airway function as associations were found for FEV_1 (β: −55 ml), FEV_1/FVC (β: −1.1%) and $FEF_{25–75}$ (β: −159 ml/s), but not for FVC. Furthermore, the larger and peripheral airways appeared to be affected by early lung infections

Table 2 Population characteristics of analyzed subjects.

	Total	Males	Females
% (*N*)	100 (1326)	51.1 (678)	48.9 (648)
		Mean (SD) or % (*n*)	
Age, years	15.2 (0.3)	15.2 (0.3)	15.2 (0.3)
Height*, cm	172 (8.2)	176 (7.4)	167 (6.0)
Study specific			
Study			
GINIplus control	38.3 (508)	38.2 (259)	38.4 (249)
GINIplus intervention	34.5 (457)	33.8 (229)	35.2 (228)
LISAplus	27.2 (361)	28.0 (190)	26.4 (171)
Study center			
Munich	63.3 (840)	63.1 (428)	63.6 (412)
Wesel	36.7 (486)	36.9 (250)	36.4 (236)
Early life events			
Parental atopy, yes	58.8 (780)	57.7 (391)	60.0 (389)
Parental education			
low (< 10 years of school)	5.2 (69)	5.8 (39)	4.6 (30)
medium (= 10 years of school)	26.7 (354)	27.0 (183)	26.4 (171)
high (> 10 years of school)	68.1 (903)	67.3 (456)	69.0 (447)
Maternal age at delivery >31 years*, yes	49.9 (662)	46.3 (314)	53.7 (348)
Maternal smoking during pregnancy, yes	12.0 (159)	11.9 (81)	12.0 (78)
Early second-hand smoke exposure at home (up to age 4), yes	32.7 (433)	32.6 (221)	32.7 (212)
Season of birth, winter	25.6 (339)	24.5 (166)	26.7 (173)
Birth weight*, g	3483 (442.0)	3541 (443.5)	3422 (432.6)
Exclusive breastfeeding >4 months, yes	60.6 (804)	58.3 (395)	63.1 (409)
Peak weight velocity*, kg/month	1.1 (0.2)	1.2 (0.2)	1.0 (0.2)
Peak height velocity*, cm/month	3.6 (0.4)	3.8 (0.4)	3.5 (0.4)
Lung infections (up to age 3)*, yes	31.2 (414)	34.8 (236)	27.5 (178)
Environmental and lifestyle factors at age 15			
Short-term air pollution			
NO_2 ($\mu g/m^3$)	20.4 (6.9)	20.5 (7.0)	20.3 (6.7)
$PM_{2.5}$ mass ($\mu g/m^3$)	14.7 (7.3)	14.4 (6.7)	15.0 (7.9)
PM_{10} mass ($\mu g/m^3$)	18.9 (7.8)	18.6 (7.2)	19.3 (8.4)
Long-term air pollution			
NO_2 ($\mu g/m^3$)	21.2 (4.8)	21.2 (5.0)	21.2 (4.6)
$PM_{2.5}$ mass ($\mu g/m^3$)	14.8 (2.1)	14.8 (2.2)	14.8 (2.1)
PM_{10} mass ($\mu g/m^3$)	22.1 (3.2)	22.0 (3.3)	22.1 (3.2)
Regular indoor second-hand smoke exposure[a], yes	20.1 (266)	19.0 (129)	21.1 (137)
Active smoking, yes	5.4 (71)	5.6 (38)	5.1 (33)
Serum vitamin D[b], nmol/l	68.4 (25.3)	67.5 (24.3)	69.3 (26.2)
Body mass index*, kg/m^2	20.7 (3.0)	20.7 (3.2)	20.8 (2.8)
Allergic diseases at age 15			
Asthma, yes	6.3 (83)	7.4 (50)	5.1 (33)
Rhinitis, yes	18.9 (251)	20.9 (142)	16.8 (109)
Sensitization to			

Table 2 Population characteristics of analyzed subjects. *(Continued)*

Aeroallergens*, yes	45.4 (602)	51.5 (349)	39.0 (253)
Food allergens, yes	11.2 (148)	12.8 (87)	9.4 (61)
Spirometric parameters at age 15			
FVC, l*	4.08 (0.77)	4.50 (0.74)	3.64 (0.51)
FEV_1, l*	3.52 (0.63)	3.83 (0.64)	3.19 (0.42)
FEV_1/FVC, %*	86.7 (6.39)	85.3 (6.43)	88.1 (6.02)
PEF, l/s*	7.15 (1.28)	7.73 (1.3)	6.54 (0.93)
FEF_{25}, l/s*	6.26 (1.17)	6.61 (1.27)	5.89 (0.92)
FEF_{50}, l/s*	4.46 (1.05)	4.71 (1.14)	4.19 (0.87)
FEF_{75}, l/s*	2.21 (0.72)	2.31 (0.78)	2.11 (0.63)
FEF_{25-75}, l/s*	3.92 (0.92)	4.12 (1.01)	3.70 (0.77)

*Significant difference (*p*-value < 0.05) between males and females (t-test, Wilcoxon rank-sum test, or chi-square test)
[a]at least once a week or more. [b]season-adjusted 25(OH)D concentration
FEV_1: forced expiratory volume in 1 s. FVC: forced vital capacity. FEF_{25}, FEF_{50}, FEF_{75}: forced expiratory flow rates at 25, 50 and 75% of exhaled FVC. FEF_{25-75}: mean flow rate between 25 and 75% of FVC. PEF: peak expiratory flow. SD: standard deviation

as inferred from the negative associations seen with all flow rates (Additional file 1: Table A5).

While clear associations indicative of airway function and not for lung volume (FVC) were observed for peak weight velocity and early lung infections, no or only unstable associations were found for parental education, parental atopy, maternal age at delivery, maternal smoking during pregnancy, early second-hand smoke exposure at home, season of birth, birth weight, exclusive breastfeeding for at least four months and peak height velocity.

Environmental and lifestyle factors at age 15

Regular indoor second-hand smoke exposure was negatively associated with FEV_1 (β: −59 ml) (Table 3), as well as PEF and FEF_{75} (Additional file 1: Table A5), which supports the notion of a potential effect on the airways. Vitamin D concentrations were positively associated with FVC (β: 65 ml/IQR increase) and FEV_1 (β: 32 ml/IQR increase), while the association with FEV_1/FVC was negative (β: -0.6%/IQR increase). BMI was positively associated with FVC (β: 222 ml/IQR increase), FEV_1 (β: 144 ml/IQR

Table 3 Coefficients (95%-confidence intervals) of regression models adjusted for covariates that remained stable in replication analyses

Spirometric parameter indicative of	Lung volume	Airways & volume	Airflow limitation	Airways
	FVC, ml	FEV_1, ml	FEV_1/FVC, %	FEF_{25-75}, ml/s
Sex, male	347 (289, 405)	220 (167, 274)	−2.2 (−2.9,-1.4)	
Age, IQR years	47 (26, 69)	30 (11, 50)		
Height, IQR cm	637 (598, 676)	517 (481, 553)		508 (438, 577)
Early life events				
Peak weight velocity, IQR kg/month			−0.8 (−1.3, −0.3)	−88 (−155, −20)
Lung infections (up to age 3), yes		−55 (−102, −7)	−1.1 (−1.8,-0.3)	−159 (−258, −60)
Environment & lifestyle at age 15				
Regular indoor second-hand smoke exposure[a], yes		−59 (−114, −5)		
Serum vitamin D[b], IQR nmol/l	65 (34, 96)	32 (3, 61)	−0.6 (−1, −0.2)	
Body mass index, IQR kg/m^2	222 (194, 250)	144 (118, 171)	−1.2 (−1.6,-0.8)	85 (31, 140)
Allergic diseases at age 15				
Asthma, yes	−118 (−216, −21)	−177 (−268, −86)	−1.8 (−3.1,-0.4)	−304 (−494, −115)
Study specific				
Study (LISAplus vs GINIplus)	68 (12, 124)			
Study center (Wesel vs Munich)	−66 (−119, −13)	−135 (−182, −88)	−1.6 (−2.3,-0.9)	−256 (−352, −161)

All associations were statistically significant (*p*-value < 0.05). Estimates for continuous variables are presented per interquartile range (IQR) increase (IQR: age (0.26 years), height (11 cm), peak weight velocity (0.28 kg/month), vitamin D (32.35 nmol/l), body mass index (3.56 kg/m^2))
[a]at least once a week or more. [b]season-adjusted 25(OH)D concentration. FEV_1: forced expiratory volume in 1 s. FVC: forced vital capacity. FEF_{25-75}: mean flow rate between 25 and 75% of FVC

increase) and $FEF_{25–75}$ (β: 85 ml/s/IQR increase) and negatively associated with FEV_1/FVC (β: -1.2%/IQR increase). Positive associations between BMI and PEF, FEF_{25} and FEF_{50} were also found (Additional file 1: Table A5).

Spirometric parameters indicative of lung volumes were positively associated with vitamin D concentrations and BMI, while regular indoor second-hand smoke exposure showed some associations with flow rates, but no clear pattern. No associations were found with short-term or long-term air pollution exposure or active smoking at age 15 (prevalence for smoking 5.4%).

Allergic diseases at age 15

Asthma was negatively associated with all lung function measures (Table 3), while no associations were found with current allergic rhinitis, or sensitization to food or aeroallergens. This was also true considering secondary parameters for airway function, except for PEF (Additional file 1: Table A5). Exclusion of subjects with asthma from the final models did not substantially modify the associations reported for early life events and environmental and lifestyle factors at age 15.

Relative importance of factors in regression models

The total R^2 was moderate in all models ($R^2 < 0.2$), except for when FVC and FEV_1 were the modelled outcomes, in which case it was higher ($R^2 = 0.68$ and $R^2 = 0.59$, respectively). As expected, the contribution to the total R^2 of each model was highest for height (61.6–75.3%) and sex (23.9–27.2%) for almost all considered indices (Table 4, Additional file 1: Table A6). Due to the varying contribution of factors to different spirometric parameters, a direct comparison of all factors and parameters is not possible. The influence of early life events was primarily detectable for airway function. The highest contribution was found for FEV_1/FVC with 22.4% and 7.2% for peak weight velocity and early lung infections, respectively. However, these two early life factors contributed less than 5% to the explained variance of the other lung function parameters of airway function (FEV_1, $FEF_{25–75}$). Among the current environmental and lifestyle factors, vitamin D concentrations (≤2.1%, maximum in FEV_1/FVC) and regular indoor second-hand smoke exposure (0.2% in FEV_1) contributed less than BMI, which contributed to almost all parameters (range 3.2% in $FEF_{25–75}$ to 23.7% in FEV_1/FVC).

Discussion

Early life events, such as peak weight velocity and early lung infections, as well as current lifestyle factors, such as BMI, indoor second-hand smoke exposure and serum vitamin D concentrations, were associated with several spirometric parameters at age 15 years. The results of our study also confirm the well-established evidence supporting a role of sex, height and asthma status on lung function.

Among the early life events, a higher peak weight velocity was associated with airflow limitation and lower peripheral flow rates. Further, early lung infections were negatively associated with all lung function parameters except lung volume, suggesting that early lung infections may lead to low, long-term airflow limitation. A study by Svanes et al. reported an association of early childhood disadvantage factors, e.g. respiratory infections, maternal smoking and others, with lower lung function in adults and also a larger decline in lung function over time [6]. Early structural and functional changes on the developing or growing lung might lead to an impaired lung function and a higher susceptibility to lung diseases, but possible underlying mechanisms are not fully understood yet [1, 5, 6].

Regular indoor second-hand smoke exposure at age 15 years was associated with somewhat poorer airway function. The relative contribution of indoor second-hand smoke exposure was relatively low and no clear pattern with the lung function parameters could be determined. Higher vitamin D concentrations were primarily associated with volumetric indices, and with some airflow limitation, but with relatively small effects (<2.5% of R^2). After height and sex, BMI contributed the most to the explained variance for nearly all spirometric parameters. BMI was positively associated with all lung function parameters indicative of lung volume and airway function, but also with airflow limitation. Similar associations have been reported in other studies among youth [15, 21].

Except for BMI, the relative importance of early life events and environmental and lifestyle factors was relatively low, in comparison to the contribution of sex and height. Nevertheless, early life events were primarily negatively associated with parameters indicative of airway function, while no associations were found for lung volume. This suggests that early life factors should be considered in studies focusing on airway function. Regular indoor second-hand smoke exposure at age 15, an environmental and lifestyle factor, showed the same tendency. On the contrary, positive associations were detected for vitamin D concentration with volumetric parameters and for BMI with both, volumes and airway function. Given the associations between higher weight gain in the first 2 years of life and current BMI with the spirometric indices, it appears that body weight at several points in life is important for lung function.

Associations of lung function with peak weight velocity [26, 27], lower respiratory infections [10, 14, 41], BMI [15, 21], vitamin D concentrations [16, 17] and second-hand smoke exposure [18, 20] have been also

Table 4 Relative importance of variables in final regression models (averaged R^2 contribution)

Spirometric parameter indicative of	Lung volume	Airways & volume	Airflow limitation	Airways
	FVC	FEV_1	FEV_1/FVC	FEF_{25-75}
Total R^2 of the model	0.68	0.59	0.12	0.18
Sex	26.1	23.9	27.2	
Age	1.1	1.0		
Height	61.6	65.2		75.3
Early life events				
Peak weight velocity			22.4	4.8
Lung infections (up to age 3)		0.2	7.2	3.8
Environment & lifestyle at age 15				
Regular indoor second-hand smoke exposure[1]		0.2		
Serum vitamin D[2]	0.5	0.3	2.1	
Body mass index	10.2	7.3	23.7	3.2
Allergic diseases at age 15				
Asthma	0.2	0.9	5.0	4.8
Study specific				
Study (LISAplus vs GINIplus)	0.2			
Study center (Wesel vs Munich)	0.2	1.0	12.4	8.2

< 1%	< 3%	< 5%	< 10%	< 15%	≥ 15%

Relative importance of variables in regression models adjusted for covariates that remained stable in replication analyses are displayed as normalized percent of R^2 contribution averaged (unweighted) over variable orderings.
[1]at least once a week or more. [2]season-adjusted 25(OH)D concentration. FEV_1: forced expiratory volume in 1 s. FVC: forced vital capacity. FEF_{25-75}: mean flow rate between 25 and 75% of FVC

found in other studies. Only one previous study investigated associations between several early life events and current lifestyle factors with lung function [28]. This cross-sectional study investigated Tunisian children with an age range of 6–16 years (92 participants were 14–16 years old and would be comparable to our population). Similar to our results, associations between lung function with sex, height and weight were found. Strong associations with age were also reported [28], whereas the more narrow age distribution in our analysis was only associated with some spirometric parameters. As in our study, no associations between normal birth weight and lung function were observed in this previous publication [28]. Kotecha et al. reported an association between birth weight and lung function at age 8–9 years, but not at age 14–17 years, suggesting that the importance of early factors on lung function might differ by age [13].

As a complex framework of factors influences lung function [1, 2], we considered several early life and current environmental and lifestyle factors in adolescence to identify factors associated with lung function and their relative importance at age 15. Correlations, interactions or modulating effects between some investigated factors are very likely and study specific population characteristics might influence the impact and contribution of single factors. Study center was shown to be associated with lung function in our cohort but might partially stand as a surrogate for other factors not captured by our data. For example, there might be differences in lifestyle and environmental factors between the included rural (Wesel) and urban (Munich) areas.

Due to loss to follow-up, the prevalence of low education (<10 years of school) among the participants' parents was only 5.2%, which may partially explain why socioeconomic status did not remain in the main models. In contrast to our results, a review covering different countries and age ranges showed that low socioeconomic status was associated with reduced lung

function [42]. The underrepresentation of less educated families in our study might have also led to a lack of association with some factors that are correlated with socioeconomic status, such as maternal smoking during pregnancy (prevalence 12%), which otherwise, has been shown to have a negative effect in previous studies [18, 20]. Furthermore, results of a study among schoolchildren in Canada suggested a modifying effect of socioeconomic status on the association of air pollution and traffic exposure with respiratory symptoms and lung function [43]. In this study, a tendency for a higher risk of respiratory symptoms and lower lung function associated with traffic or air pollution exposure was seen in less educated households, although most associations were not statistically significant [43].

Strengths and limitations

A major strength of this study is the investigation of a full range of standardized measured and visually inspected spirometric lung function parameters indicative of lung volume, as well as less often investigated lung function measures of larger conducting and peripheral airways, in two prospective birth cohorts. Furthermore, information on a broad range of early life events, environmental and lifestyle factors, and allergic diseases at age 15 was available for 1326 German adolescents, enabling this rarely applied comprehensive approach. Further factors that were available only in a subset of our population (986 subjects (74%)) e.g. having <2 or ≥2 siblings at age 15 (one variable for older, another for younger siblings), using gas for cooking and having mold at home, both asked in the first year of life, and daycare center attendance during the first three years of life would not have been included in the final models (based on best subset selection in this reduced population). This result and the limited data availability for these factors led to their exclusion from the main analysis. The inclusion of physical activity assessed by accelerometry would also have diminished our sample size to 721 subjects (54%) and was not shown to be associated with lung function in our cohort [35].

A major limitation of this study is selective loss to follow-up. For example, participants included in the analysis had higher parental education, more breastfeeding and less maternal smoking during pregnancy (Additional file 1: Table A1). Our results might therefore not be generalizable to all German adolescents. It is possible that covariates that were not associated with lung function in our population could play a role in others, pointing out a need for replication in other, larger studies. Further, study center (Munich/Wesel) was associated with lung function in our study population, which might suggest regional environmental and lifestyle differences not captured by the considered factors.

Our use of the Cp statistic as a selection criterion for automatic model selection might have resulted in the selection of a group of variables that would not have been selected using a different selection criterion (e.g. adjusted R^2). To reduce model complexity, we chose to use the Cp statistic because it penalizes the number of included variables. Further, we replicated our analysis (N = 1000) in randomly chosen subpopulations to reduce potential selection bias attributable to influential cases.

Conclusions

In addition to well-known measures included in lung function prediction equations (sex and height), as well as current asthma and BMI, our study showed that among a variety of factors considered in our analysis, weight gain and pulmonary infections during infancy were prevalent factors associated with lung function in 15-year-olds. While the early life factors were primarily associated with airway function, factors at age 15 showed associations with airway function as well as lung volume. Although our findings require replication in independent studies, they nevertheless highlight the need to include specific early life events and current lifestyle factors in studies on lung health among adolescents and suggest that effective health promotion should exist at all ages.

Additional files

Additional file 1: Table A1. Population characteristics of analyzed participants in comparison to the initial study population for the Munich and Wesel study centers. **Table A2.** Characteristics of lung function parameters of analyzed participants in comparison to all other subjects with valid lung function measurements at age 15 in the Munich and Wesel study centers .**Table A3.** Coefficients (95% confidence intervals) of regression models with the lowest Mallows' Cp, determined by best subset selection in the total population. **Table A4.** Distribution of the frequency of inclusion of each factor in 1000 replication analyses (%). **Table A5.** Coefficients (95% confidence intervals) of regression models of flow rates adjusted for covariates that remained stable in replication analyses. **Table A6.** Relative importance of variables in final regression models of flow rates (averaged R2 contribution). (PDF 548 kb)

Abbreviations

BMI: Body mass index (kg/m^2); FEF_{25}: Forced expiratory flow rate at 25% of exhaled FVC; FEF_{25-75}: Mean flow rate between 25 and 75% of FVC; FEF_{50}: Forced expiratory flow rate at 50% of exhaled FVC; FEF_{75}: Forced expiratory flow rate at 75% of exhaled FVC; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; GINIplus: German Infant study on the influence of Nutrition Intervention plus air pollution and genetics on allergy development; LISAplus: Life-style related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics; NO_2: Nitrogen dioxide; PEF: Peak expiratory flow; PM_{10}: Particulate matter with diameters <10 μm; $PM_{2.5}$: Particulate matter with diameters <2.5 μm; SD: Standard deviation. VIF: variance inflation factor

Acknowledgements

The authors thank all the families for their active participation in the GINIplus study and the LISAplus study. Furthermore, we thank all members of the GINIplus Study Group and the LISAplus Study Group for their excellent work. The GINIplus Study Group consists of the following: Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of

Epidemiology I, Neuherberg (Heinrich J, Brüske I, Schulz H, Standl M, Schnappinger M, Ferland M, Thiering E, Tiesler C, Flexeder C, Zeller C); Marien-Hospital Wesel, Research Institute, Department of Pediatrics, Wesel (Berdel D, von Berg A, Filipiak-Pittroff B); Ludwig-Maximilians-University of Munich, Dr. von Hauner Children's Hospital, Munich (Koletzko S); Child and Adolescent Medicine, University Hospital rechts der Isar of the Technical University Munich (Bauer CP, Hoffmann U); IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf (Schikowski T, Hoffmann B, Link E, Klümper C, Krämer U, Sugiri D).
The LISAplus Study Group consists of the following: Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Epidemiology I, Munich (Heinrich J, Brüske I, Schulz H, Standl M, Schnappinger M, Ferland M, Thiering E, Tiesler C, Flexeder C, Zeller C); Municipal Hospital 'St Georg', Department of Pediatrics, Leipzig (Borte M, Diez U, Dorn C, Braun E); Marien-Hospital Wesel, Research Institute, Department of Pediatrics, Wesel (von Berg A, Berdel D, Stiers G, Maas B); Pediatric Practice, Bad Honnef (Schaaf B); Helmholtz Centre of Environmental Research – UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (Lehmann I, Bauer M, Herberth G, Müller J, Röder S, Nowak M, Schilde M); Technical University Munich, Department of Pediatrics, Munich (Bauer CP, Hoffmann U, Paschke M, Marra S); Technical University Munich, Center of Allergy and Environment Munich (ZAUM), Munich (Ollert M, Grosch J).

Funding
The GINIplus study was mainly supported for the first 3 years by the Federal Ministry for Education, Science, Research and Technology (interventional arm) and Helmholtz Zentrum Munich (former GSF) (observational arm). The 4 year, 6 year, 10 year and 15 year follow-up examinations of the GINIplus study were covered from the respective budgets of the 5 study centers (Helmholtz Zentrum Munich (former GSF), Research Institute at Marien-Hospital Wesel, LMU Munich, TU Munich, and from 6 years onwards also from IUF - Leibniz Research-Institute for Environmental Medicine at the University of Düsseldorf) and a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). Further, the 15 year follow-up examination of the GINIplus study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project, and as well by the companies Mead Johnson and Nestlé. The LISAplus study was mainly supported by grants from the Federal Ministry for Education, Science, Research and Technology and in addition from Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research - UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef for the first 2 years. The 4 year, 6 year, 10 year and 15 year follow-up examinations of the LISAplus study were covered from the respective budgets of the involved partners (Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research - UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef, IUF – Leibniz-Research Institute for Environmental Medicine at the University of Düsseldorf) and in addition by a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). Further, the 15 year follow-up examination of the LISAplus study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project. This work was additionally supported by the Comprehensive Pneumology Center Munich (CPC-M), a member of the German Center for Lung Research.

Availability of data and materials
The authors confirm that, for approved reasons, restrictions apply to the availability of the data underlying the findings. The informed consent given by the GINIplus and LISAplus study participants does not cover providing individual data in public databases. Interested researchers may request a de-identified dataset from the corresponding author Holger Schulz (schulz@helmholtz-muenchen.de).

Authors' contributions
AL, DN and HS were involved in the conception and design of the study. CF, EF, MS, AvB, DB, SK, JH and HS contributed with data acquisition and data coding and AL with statistical analyses. AL, DN and HS contributed to the interpretation of the findings. AL drafted the manuscript and all authors revised it critically for important intellectual content and approved the final version.

Ethics approval and consent to participate
The study protocols were approved by the local ethics committees (Bavarian General Medical Council, University of Leipzig, Medical Council of North-Rhine-Westphalia) and written consent was obtained from all participating families.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

Author details
[1]Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Epidemiology I, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany. [2]ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Doctor Aiguader 88, 08003 Barcelona, Spain. [3]Universitat Pompeu Fabra (UPF), Plaça de la Mercè 10, 08002 Barcelona, Spain. [4]CIBER Epidemiología y Salud Pública (CIBERESP), Av. Monforte de Lemos, 3-5. Pabellón 11, 28029 Madrid, Spain. [5]Department of Pediatrics, Research Institute, Marien-Hospital Wesel, Pastor-Janßen-Str. 8-38, 46483 Wesel, Germany. [6]Dr von Hauner Children's Hospital, Ludwig-Maximilians-University of Munich, Lindwurmstr. 4, 80337 Munich, Germany. [7]Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Max-Lebsche-Platz 31, 81377 Munich, Germany. [8]Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Munich (LMU), Ziemssenstr. 1, 80336 Munich, Germany.

Received: 4 November 2016 Accepted: 3 July 2017
Published online: 12 July 2017

References
1. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. Lancet Respir Med. 2013;1:728–42.
2. Merkus PJ. Effects of childhood respiratory diseases on the anatomical and functional development of the respiratory system. Paediatr Respir Rev. 2003;4:28–39.
3. Carlsen KC, Haland G, Carlsen KH. Natural history of lung function in health and diseases. Curr Opin Allergy Clin Immunol. 2009;9:146–50.
4. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, et al. Patterns of growth and decline in lung function in persistent childhood asthma. N Engl J Med. 2016;374:1842–52.
5. Duijts L, Reiss IK, Brusselle G, de Jongste JC. Early origins of chronic obstructive lung diseases across the life course. Eur J Epidemiol. 2014;29:871–85.
6. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, et al. Early life origins of chronic obstructive pulmonary disease. Thorax. 2010;65:14–20.
7. Dratva J, Zemp E, Dharmage SC, Accordini S, Burdet L, Gislason T, et al. Early life origins of lung ageing: early life exposures and lung function decline in adulthood in two European cohorts aged 28-73 years. PLoS One. 2016;11:e0145127.
8. Fuertes E, Bracher J, Flexeder C, Markevych I, Klümper C, Hoffmann B, et al. Long-term air pollution exposure and lung function in 15 year-old adolescents living in an urban and rural area in Germany: the GINIplus and LISAplus cohorts. Int J Hyg Environ Health. 2015;218:656–65.
9. Flexeder C, Thiering E, von Berg A, Berdel D, Hoffmann B, Koletzko S, et al. Peak weight velocity in infancy is negatively associated with lung function in adolescence. Pediatr Pulmonol. 2016;51:147–56.
10. Bonnelykke K, Vissing NH, Sevelsted A, Johnston SL, Bisgaard H. Association between respiratory infections in early life and later asthma is independent of virus type. J Allergy Clin Immunol. 2015;136:81-86.e4.
11. Jaakkola JJ, Nafstad P, Magnus P. Environmental tobacco smoke, parental atopy, and childhood asthma. Environ Health Perspect. 2001;109:579–82.
12. Soto-Ramirez N, Alexander M, Karmaus W, Yousefi M, Zhang H, Kurukulaaratchy RJ, et al. Breastfeeding is associated with increased lung function at 18 years of age: a cohort study. Eur Respir J. 2012;39:985–91.

13. Kotecha SJ, Watkins WJ, Henderson AJ, Kotecha S. The effect of birth weight on lung spirometry in white, school-aged children and adolescents born at term: a longitudinal population based observational cohort study. J Pediatr. 2015;166:1163–7.
14. Puig C, Friguls B, Gomez M, Garcia-Algar O, Sunyer J, Vall O. Relationship between lower respiratory tract infections in the first year of life and the development of asthma and wheezing in children. Arch Bronconeumol. 2010;46(10):514–21.
15. Cibella F, Bruno A, Cuttitta G, Bucchieri S, Melis MR, De Cantis S, et al. An elevated body mass index increases lung volume but reduces airflow in Italian schoolchildren. PLoS One. 2015;10:e0127154.
16. Niruban SJ, Alagiakrishnan K, Beach J, Senthilselvan A. Association between vitamin D and respiratory outcomes in Canadian adolescents and adults. J Asthma. 2015;52:653–61.
17. Yao TC, Tu YL, Chang SW, Tsai HJ, Gu PW, Ning HC, et al. Serum 25-hydroxyvitamin D levels in relation to lung function and exhaled nitric oxide in children. J Pediatr. 2014;165:1098–103. e1
18. Moshammer H, Hoek G, Luttmann-Gibson H, Neuberger MA, Antova T, Gehring U, et al. Parental smoking and lung function in children: an international study. Am J Respir Crit Care Med. 2006;173:1255–63.
19. Gehring U, Gruzieva O, Agius RM, Beelen R, Custovic A, Cyrys J, et al. Air pollution exposure and lung function in children: the ESCAPE project. Environ Health Perspect. 2013;121:1357–64.
20. Cook DG, Strachan DP, Carey IM. Health effects of passive smoking. 9. Parental smoking and spirometric indices in children. Thorax. 1998;53:884–93.
21. He QQ, Wong TW, Du L, Jiang ZQ, Qiu H, Gao Y, et al. Respiratory health in overweight and obese Chinese children. Pediatr Pulmonol. 2009;44:997–1002.
22. Slachtova H, Gehring U, Hoek G, Tomaskova H, Luttmann-Gibson H, Moshammer H, et al. Parental education and lung function of children in the PATY study. Eur J Epidemiol. 2011;26:45–54.
23. Brockow I, Zutavern A, Hoffmann U, Grubl A, von Berg A, Koletzko S, et al. Early allergic sensitizations and their relevance to atopic diseases in children aged 6 years: results of the GINI study. J Investig Allergol Clin Immunol. 2009;19(3):180–7.
24. Corbo GM, Agabiti N, Forastiere F, Dell'Orco V, Pistelli R, Kriebel D, et al. Lung function in children and adolescents with occasional exposure to environmental tobacco smoke. Am J Respir Crit Care Med. 1996;154:695–700.
25. Gold DR, Wang X, Wypij D, Speizer FE, Ware JH, Dockery DW. Effects of cigarette smoking on lung function in adolescent boys and girls. N Engl J Med. 1996;335:931–7.
26. van der Gugten AC, Koopman M, Evelein AM, Verheij TJ, Uiterwaal CS, van der Ent CK. Rapid early weight gain is associated with wheeze and reduced lung function in childhood. Eur Respir J. 2012;39:403–10.
27. den Dekker HT. Sonnenschein-van der Voort AM, de Jongste JC, Anessi-Maesano I, Arshad SH, Barros H, et al. Early growth characteristics and the risk of reduced lung function and asthma: a meta-analysis of 25,000 children. J Allergy Clin Immunol. 2016;137:1026–35.
28. Trabelsi Y, Paries J, Harrabi I, Zbidi A, Tabka Z, Richalet JP, et al. Factors affecting the development of lung function in Tunisian children. Am J Hum Biol. 2008;20:716–25.
29. von Berg A, Krämer U, Link E, Bollrath C, Heinrich J, Brockow I, et al. Impact of early feeding on childhood eczema: development after nutritional intervention compared with the natural course - the GINIplus study up to the age of 6 years. Clin Exp Allergy. 2010;40:627–36.
30. Heinrich J, Bolte G, Hölscher B, Douwes J, Lehmann I, Fahlbusch B, et al. Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. Eur Respir J. 2002;20:617–23.
31. Heinrich J, Brüske I, Schnappinger M, Standl M, Flexeder C, Thiering E, et al. Die zwei deutschen Geburtskohorten GINIplus and LISAplus. Bundesgesundheitsblatt. 2012;55:864–74.
32. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
33. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. Eur Respir J. 1993;6:5–40.
34. McNulty W, Usmani OS. Techniques of assessing small airways dysfunction. European Clinical Respiratory Journal. 2014;1: doi:10.3402/ecrj.v1.25898.
35. Smith MP, von Berg A, Berdel D, Bauer CP, Hoffmann B, Koletzko S, et al. Physical activity is not associated with spirometric indices in lung-healthy German youth. Eur Respir J. 2016;48:428–40.
36. Flexeder C, Thiering E, Koletzko S, Berdel D, Lehmann I, von Berg A, et al. Higher serum 25(OH)D concentrations are associated with improved FEV1 and FVC in adolescence. Eur Respir J. 2017;49:1601804.
37. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40:1324–43.
38. Miller AJ. Subset Selection in Regression. 2nd Edition. Boca Raton: Chapman & Hall/CRC; 2002.
39. Groemping U. Relative Importance for Linear Regression in R: The Package relaimpo. J Stat Softw. 2006;17(1)1–27.
40. R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2015. URL http://www.R-project.org/. Accessed 8 Aug 2016.
41. Chan JY, Stern DA, Guerra S, Wright AL, Morgan WJ, Martinez FD. Pneumonia in childhood and impaired lung function in adults: a longitudinal study. Pediatrics. 2015;135:607–16.
42. Hegewald MJ, Crapo RO. Socioeconomic status and lung function. Chest. 2007;132:1608–14.
43. Cakmak S, Hebbern C, Cakmak JD, Vanos J. The modifying effect of socioeconomic status on the relationship between traffic, air pollution and respiratory health in elementary schoolchildren. J Environ Manag. 2016;177:1–8.
44. Lodrup Carlsen KC, Haland G, Devulapalli CS, Munthe-Kaas M, Pettersen M, Granum B, et al. Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study. Allergy. 2006;61:454–60.

Additional file – Tables A1 to A6

Table A1 Population characteristics of analyzed participants in comparison to the initial study population for the Munich and Wesel study centers

	Study population analyzed (N=1326)	Study population excluded (N=6477)[A]	p-value*
	Mean (SD) or n/N (%)		
Sex			
male	678/1326 (51)	3267/6316 (52)	0.72
female	648/1326 (49)	3049/6316 (48)	
Age at lung function measurement, years	15.2 (0.3)	15.3 (0.3)	< 0.01
Height at lung function measurement, cm	171.5 (8.2)	171.6 (8.5)	0.86
Study specific			
Study			
GINIplus control	508/1326 (38)	3231/6477 (50)	< 0.01
GINIplus intervention	457/1326 (34)	1795/6477 (28)	
LISAplus	361/1326 (27)	1451/6477 (22)	
Study center			
Munich	840/1326 (63)	3573/6477 (55)	< 0.01
Wesel	486/1326 (37)	2904/6477 (45)	
Early life events			
Parental atopy, yes	780/1326 (59)	3194/6276 (51)	< 0.01
Parental education			
low (< 10 years of school)	69/1326 (5)	827/6413 (13)	< 0.01
medium (= 10 years of school)	354/1326 (27)	1775/6413 (28)	
high (> 10 years of school)	903/1326 (68)	3811/6413 (59)	
Maternal age at delivery >31 years, yes	662/1326 (50)	2897/6461 (45)	< 0.01
Maternal smoking during pregnancy, yes	159/1326 (12)	1069/5657 (19)	< 0.01
Early second-hand smoke exposure at home (up to age 4), yes	433/1326 (33)	2117/4448 (48)	< 0.01
Season of birth, winter	339/1326 (26)	1702/6477 (26)	0.61
Birth weight, g	3482.7 (442.0)	3463.7 (461.3)	0.17
Exclusive breastfeeding > 4 months, yes	804/1326 (61)	2498/4957 (50)	< 0.01
Peak weight velocity, kg/month	1.06 (0.22)	1.09 (0.23)	< 0.01
Peak height velocity, cm/month	3.62 (0.42)	3.67 (0.42)	< 0.01
Lung infections (up to age 3), yes	414/1326 (31)	1371/4230 (32)	0.44

	Study population analyzed (N=1326)	Study population excluded (N=6477)[A]	p-value*
	Mean (SD) or n/N (%)		
Environmental and lifestyle factors at age 15			
Short-term air pollution at lung function measurement			
NO_2 ($\mu g/m^3$)	20.4 (6.9)	20.4 (6.7)	0.83
$PM_{2.5}$ mass ($\mu g/m^3$)	14.6 (7.3)	15.7 (7.2)	< 0.01
PM_{10} mass ($\mu g/m^3$)	18.9 (7.8)	20.1 (7.8)	< 0.01
Long-term air pollution at participant's home address			
NO_2 ($\mu g/m^3$)	21.2 (4.8)	22.0 (4.4)	< 0.01
$PM_{2.5}$ mass ($\mu g/m^3$)	14.8 (2.1)	15.5 (2.2)	< 0.01
PM_{10} mass ($\mu g/m^3$)	22.1 (3.2)	22.9 (3.3)	< 0.01
Regular indoor second-hand smoke exposure[1], yes	266/1326 (20)	438/2242 (20)	0.74
Active smoking, yes	71/1326 (5)	165/2246 (7)	0.02
Serum vitamin D concentration[2], nmol/l	68.4 (25.3)	66.3 (24.1)	0.07
Body mass index, kg/m^2	20.7 (3)	21.2 (3.5)	< 0.01
Allergic diseases at age 15			
Asthma, yes	83/1326 (6)	145/2938 (5)	0.09
Rhinitis, yes	251/1326 (19)	491/2839 (17)	0.21
Sensitization to			
Aeroallergens, yes	602/1326 (45)	560/1199 (47)	0.54
Food allergens, yes	148/1326 (11)	144/1199 (12)	0.55

[A]Only participants from the Munich and Wesel study centers.*t-test, Wilcoxon rank-sum test or Pearson's chi-square test. [1]at least once a week or more. [2]season-adjusted 25(OH)D concentration.

Table A2 Characteristics of lung function parameters of analyzed participants in comparison to all other subjects with valid lung function measurements at age 15 in the Munich and Wesel study centers

	Males		Females	
	Study population analyzed (N=678)	**Study population excluded (N=470)[A]**	**Study population analyzed (N=648)**	**Study population excluded (N=562)[A]**
Spirometric parameter	**Mean (SD)**		**Mean (SD)**	
FVC, l	4.50 (0.74)	4.53 (0.77)	3.64 (0.51)	3.65 (0.49)
FEV_1, l	3.83 (0.64)	3.82 (0.67)	3.19 (0.42)	3.22 (0.42)
FEV_1/FVC, %	85.33 (6.43)*	84.46 (6.37)	88.12 (6.02)	88.39 (5.99)
FEF_{25-75}, l/s	4.12 (1.01)	4.03 (1.04)	3.70 (0.77)	3.77 (0.82)
PEF, l/s	7.73 (1.3)	7.64 (1.34)	6.54 (0.93)	6.55 (0.98)
FEF_{25}, l/s	6.61 (1.27)	6.46 (1.32)	5.89 (0.92)	5.92 (0.99)
FEF_{50}, l/s	4.71 (1.14)	4.58 (1.14)	4.19 (0.87)	4.29 (0.94)
FEF_{75}, l/s	2.31 (0.78)	2.26 (0.80)	2.11 (0.63)	2.15 (0.64)

*Significant difference in lung function parameter between participants analyzed and those excluded, stratified by sex (t-test, $p<0.05$). [A]Participants with valid lung function measurements at age 15 from the Munich and Wesel study centers.

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25}, FEF_{50}, FEF_{75}: forced expiratory flow rates at 25, 50 and 75% of exhaled FVC. FEF_{25-75}: mean flow rate between 25 and 75% of FVC. PEF: peak expiratory flow. SD: standard deviation.

Table A3 Coefficients (95% confidence intervals) of regression models with the lowest Mallows' Cp, determined by best subset selection in the total population

Spirometric parameter indicative of	**Lung volume**	**Airways & volume**	**Airflow limitation**	**Airways**	**Function of larger conducting airways**		**peripheral airways**	
	FVC, ml	FEV_1, ml	FEV_1/FVC, %	FEF_{25-75}, ml/s	PEF, ml/s	FEF_{25}, ml/s	FEF_{50}, ml/s	FEF_{75}, ml/s
Sex, male	**349 (291, 406)**	**217 (164, 270)**	**-2 (-2.8, -1.1)**	**118 (1, 234)**	**607 (473, 740)**	**274 (140, 409)**	**229 (99, 360)**	
Age, IQR years	**49 (27, 70)**	**34 (14, 54)**		31 (-10, 71)	45 (-4, 93)	**72 (22, 123)**	42 (-4, 88)	
Height, IQR cm	**646 (606, 687)**	**519 (483, 555)**	-0.4 (-1, 0.1)	**467 (389, 545)**	**709 (619, 799)**	**560 (469, 651)**	**482 (394, 571)**	**330 (274, 385)**
Early life events								
Parental atopy, yes			**-0.7 (-1.4, -0.1)**	-77 (-172, 18)	**-124 (-238, -10)**			-67 (-142, 9)
Parental education[#]								
high		**-51 (-100, -2)**		-90 (-193, 12)	**-154 (-282, -25)**	-118 (-243, 7)	-114 (-229, 2)	
low					-193 (-454, 67)			
Early second-hand smoke exposure at home (up to age 4), yes						**133 (7, 258)**		
Season of birth, winter	46 (-8, 100)							
Birth weight, IQR g	-33 (-66, 1)							
Peak weight velocity, IQR kg/month			**-0.7 (-1.2, -0.2)**	**-110 (-180, -40)**			**-120 (-200, -41)**	**-89 (-143, -35)**
Lung infections (up to age 3), yes		**-54 (-101, -6)**	**-1.0 (-1.7, -0.3)**	**-161 (-260, -62)**	**-131 (-249, -12)**	**-143 (-263, -23)**	**-169 (-281, -57)**	**-117 (-196, -38)**
Environment & lifestyle at age 15								
Long term air pollution								
NO_2, IQR µg/m^3			-0.4 (-0.9, 0.1)					-43 (-98, 12)
$PM_{2.5}$ mass, IQR µg/m^3	86 (-29, 201)							
Regular indoor second-hand smoke exposure[1], yes		**-65 (-120, -10)**	**-0.8 (-1.6, 0)**	**-132 (-246, -17)**	**-177 (-315, -40)**	-137 (-278, 5)	-124 (-254, 6)	**-126 (-217, -35)**

Spirometric parameter indicative of	**Lung volume**	**Airways & volume**	**Airflow limitation**	**Airways**	**Function of larger conducting airways**		**peripheral airways**	
	FVC, ml	FEV_1, ml	FEV_1/FVC, %	FEF_{25-75}, ml/s	PEF, ml/s	FEF_{25}, ml/s	FEF_{50}, ml/s	FEF_{75}, ml/s
Serum vitamin D concentration[2], IQR nmol/L	**63 (32, 94)**	**31 (3, 60)**	**-0.6 (-1, -0.2)**					
Body mass index, IQR kg/m^2	**226 (197, 254)**	**142 (116, 169)**	**-1.2 (-1.6, -0.8)**	**93 (38, 149)**	**261 (195, 327)**	**227 (161, 294)**	**149 (86, 211)**	
Allergic diseases at age 15								
Asthma, yes	**-119 (-216, -22)**	**-178 (-269, -88)**	**-2 (-3.4, -0.6)**	**-346 (-538, -154)**	-198 (-434, 38)	**-398 (-627, -168)**	**-405 (-620, -190)**	**-193 (-346, -40)**
Rhinitis, yes					119 (-28, 265)			
Aeroallergen sensitization, yes			0.6 (-0.1, 1.3)	78 (-17, 172)				70 (-5, 144)
Study specific								
Study group[#]								
GINIplus (intervention)	49 (-7, 105)							
LISAplus	**97 (34, 160)**	45 (-6, 97)				121 (-9, 252)		
Study center, Wesel	**-145 (-276, -15)**	**-138 (-188, -87)**	**-1.3 (-2.1, -0.6)**	**-266 (-368, -164)**	**-325 (-446, -204)**	**-334 (-462, -206)**	**-282 (-396, -168)**	**-179 (-263, -95)**

Significant associations are shown in bold ($p<0.05$). Estimates for continuous variables are presented per interquartile range (IQR) increase (IQR: age (0.26 years), height (11 cm), birth weight (587.5 g), peak weight velocity (0.28 kg/month), long term NO_2 (6.64 µg/m^3), long term PM 2.5 mass (4.00 µg/m^3), vitamin D concentration (32.35 nmol/l), body mass index (3.56 kg/m^2).

[#]Factor entered using dummy coding. [1]at least once a week or more. [2]season-adjusted 25(OH)D concentration.

FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25}, FEF_{50}, FEF_{75}: forced expiratory flow rates at 25, 50 and 75% of exhaled FVC. FEF_{25-75}: mean flow rate between 25 and 75% of FVC. PEF: peak expiratory flow.

Table A4 Distribution of the frequency of inclusion of each factor in 1000 replication analyses (%)

Spirometric parameter	FVC	FEV_1	FEV_1/FVC	FEF_{25-75}	PEF	FEF_{25}	FEF_{50}	FEF_{75}
Sex, male	100	100	100	62	100	100	98	2
Age, years	100	98	14	35	51	90	54	23
Height, cm	100	100	42	100	100	100	100	100
Early life events								
Parental atopy, yes	10	26	54	38	72	11	31	36
Parental education[#]								
high	12	52	20	50	57	52	49	34
low	15	10	3	3	31	8	8	3
Maternal age at delivery >31 years, yes	7	3	20	17	12	8	13	16
Maternal smoking during pregnancy, yes	29	23	3	1	5	6	3	1
Early second-hand smoke exposure at home (up to age 4), yes	16	10	2	1	31	66	2	1
Season of birth, winter	43	18	1	2	10	9	2	10
Birth weight, g	44	8	5	4	18	11	20	10
Exclusive breastfeeding > 4 months, no	3	2	2	3	19	4	6	2
Peak weight velocity, kg/month	3	22	93	92	1	25	95	97
Peak height velocity, cm/month	23	18	3	4	12	3	4	11
Lung infections (up to age 3), yes	6	73	94	98	74	80	95	95
Environment & lifestyle at age 15								
Short-term air pollution								
NO_2 ($\mu g/m^3$)	2	4	17	24	7	4	41	13
$PM_{2.5}$ mass ($\mu g/m^3$)	4	4	11	9	4	3	12	3
PM_{10} mass ($\mu g/m^3$)	9	1	39	12	3	2	17	10

Spirometric parameter	FVC	FEV_1	FEV_1/FVC	FEF_{25-75}	PEF	FEF_{25}	FEF_{50}	FEF_{75}
Long-term air pollution								
NO_2 ($\mu g/m^3$)	6	19	31	27	19	6	28	24
$PM_{2.5}$ mass ($\mu g/m^3$)	36	31	24	10	21	8	10	9
PM_{10} mass ($\mu g/m^3$)	8	4	8	9	16	3	13	20
Regular indoor second-hand smoke exposure[1], yes	21	80	66	70	86	54	51	95
Active smoking, yes	9	12	7	7	21	8	6	9
Serum vitamin D concentration [2], nmol/l	100	74	85	1	16	2	4	32
Body mass index, kg/m^2	100	100	100	97	100	100	100	8
Allergic diseases at age 15								
Asthma, yes	79	99	84	97	39	97	99	79
Rhinitis, yes	7	5	6	8	31	3	10	5
Sensitization to								
Aeroallergens, yes	1	11	41	44	4	2	32	45
Food allergens, yes	3	2	4	4	3	8	5	2
Study specific								
Study group[#]								
GINIplus (intervention)	53	17	7	6	13	6	3	4
LISAplus	90	54	16	3	4	53	7	10
Study center, Wesel	82	99	63	86	99	99	83	78

Factors that were included in >70% of replication analyses are shaded in gray.

[#]Factor entered using dummy coding. [1]at least once a week or more. [2]season-adjusted 25(OH)D concentration. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25}, FEF_{50}, FEF_{75}: forced expiratory flow rates at 25, 50 and 75% of exhaled FVC. FEF_{25-75}: mean flow rate between 25 and 75% of FVC. PEF: peak expiratory flow.

Table A5 Coefficients (95% confidence intervals) of regression models of flow rates adjusted for covariates that remained stable in replication analyses

Spirometric parameter indicative of airway function of	**larger conducting airways**		**peripheral airways**	
	PEF, ml/s	FEF_{25}, ml/s	FEF_{50}, ml/s	FEF_{75}, ml/s
Sex, male	602 (470, 735)	285 (150, 420)	227 (97, 358)	
Age, IQR years		63 (14, 112)		
Height, IQR cm	713 (623, 803)	555 (464, 646)	488 (399, 576)	328 (272, 383)
Early life events				
Parental atopy, yes	-123 (-236, -11)			
Peak weight velocity, IQR kg/month			-122 (-202, -43)	-82 (-136, -28)
Lung infections (up to age 3), yes	-140 (-258, -23)	-150 (-270, -29)	-171 (-283, -58)	-118 (-198, -39)
Environment & lifestyle at age 15				
Regular indoor second-hand smoke exposure [1], yes	-164 (-301, -27)			-130 (-220, -39)
Serum vitamin D concentration[2], IQR nmol/l				
Body mass index, IQR kg/m^2	265 (200, 331)	231 (165, 297)	149 (87, 212)	
Allergic diseases at age 15				
Asthma, yes		-391 (-621,-161)	-392 (-607,-177)	-171 (-323, -20)
Study specific				
Study center (Wesel vs Munich)	-314 (-430,-198)	-303 (-419,-186)	-266 (-375,-157)	-201 (-277,-125)

All associations were statistically significant ($p<0.05$). Estimates for continuous variables are presented per interquartile range (IQR) increase (IQR: age (0.26 years), height (11 cm), peak weight velocity (0.28 kg/month), vitamin D (32.35 nmol/l), body mass index (3.56 kg/m^2)).

[1]at least once a week or more. [2]season-adjusted 25(OH)D concentration.

FEF_{25}, FEF_{50}, FEF_{75}: forced expiratory flow rates at 25, 50 and 75% of exhaled forced vital capacity. PEF: peak expiratory flow.

Table A6 Relative importance of variables in final regression models of flow rates (averaged R^2 contribution)

Spirometric parameter indicative of airway function of	**larger conducting airways**		**peripheral airways**	
	PEF	FEF_{25}	FEF_{50}	FEF_{75}
Total R^2 of the model	0.38	0.24	0.18	0.13
Sex	32.9	21.8	18.2	
Age		2.6		
Height	55.0	54.8	55.5	68.3
Early life events				
Parental atopy	0.7			
Peak weight velocity			4.0	4.1
Lung infections (up to age 3)	0.4	1.3	3.3	5.1
Environment & lifestyle at age 15				
Regular indoor second-hand smoke exposure[1]	0.6			5.1
Serum vitamin D concentration[2]				
Body mass index	8.2	12.1	6.9	
Allergic diseases at age 15				
Asthma		3.0	5.5	3.9
Study specific				
Study center (Wesel vs Munich)	2.1	4.4	6.7	13.5

< 1%	< 3%	< 5%	< 10%	< 15%	≥ 15%

Relative importance of variables in regression models adjusted for covariates that remained stable in replication analyses are displayed as normalized percent of R^2contribution averaged (unweighted) over variable orderings.

[1]at least once a week or more. [2]season-adjusted 25(OH)D concentration.

FEF_{25}, FEF_{50}, FEF_{75}: forced expiratory flow rates at 25, 50 and 75% of exhaled forced vital capacity. PEF: peak expiratory flow.

6.3 Publication III

Original title:

Physical activity levels, duration pattern and adherence to WHO recommendations in German adults

Authors:

Agnes Luzak, Margit Heier, Barbara Thorand, Michael Laxy, Dennis Nowak, Annette Peters, and Holger Schulz; for the KORA-Study Group

Journal:

PLoS ONE

DOI:

10.1371/journal.pone.0172503

Year:

2017

PLOS ONE

RESEARCH ARTICLE

Physical activity levels, duration pattern and adherence to WHO recommendations in German adults

Agnes Luzak[1], Margit Heier[2,3], Barbara Thorand[2], Michael Laxy[4], Dennis Nowak[5,6], Annette Peters[2], Holger Schulz[1,6]*, for the KORA-Study Group[¶]

1 Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany, **2** Institute of Epidemiology II, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany, **3** MONICA/KORA Myocardial Infarction Registry, Central Hospital of Augsburg, Augsburg, Germany, **4** Institute of Health Economics and Health Care Management, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany, **5** Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Munich (LMU), Munich, Germany, **6** Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Munich, Germany

¶ Members of the KORA-Study Group are listed in the Acknowledgments.
* schulz@helmholtz-muenchen.de

Citation: Luzak A, Heier M, Thorand B, Laxy M, Nowak D, Peters A, et al. (2017) Physical activity levels, duration pattern and adherence to WHO recommendations in German adults. PLoS ONE 12(2): e0172503. doi:10.1371/journal.pone.0172503

Editor: Alejandro Lucía, Universidad Europea de Madrid, SPAIN

Received: September 27, 2016

Accepted: February 6, 2017

Published: February 28, 2017

Data Availability Statement: The authors confirm that, for approved reasons, access restrictions apply to the data underlying the findings. Data are subject to ethical and national data protection laws and are available only through an individual project agreement with KORA. Applications for access to the data sets can be found at the following link: https://www.helmholtz-muenchen.de/en/kora/for-scientists/cooperation-with-kora/index.html. Requests should be sent to kora.passt@helmholtz-muenchen.de and are subject to approval by the KORA Board.

Abstract

Background

Intensity and duration of physical activity are associated with the achievement of health benefits. Our aim was to characterize physical activity behavior in terms of intensity, duration pattern, and adherence to the WHO physical activity recommendations in a population-based sample of adults from southern Germany. Further, we investigated associations between physical activity and sex, age, and body mass index (BMI), considering also common chronic diseases.

Methods

We analyzed 475 subjects (47% males, mean age 58 years, range 48–68 years) who wore ActiGraph accelerometers for up to seven days. Measured accelerations per minute obtained from the vertical axis (uniaxial) and the vector magnitude of all three axes (triaxial) were classified as sedentary, light or moderate-to-vigorous physical activity (MVPA) according to predefined acceleration count cut-offs. The average minutes/day spent in each activity level per subject served as outcome. Associations of sex, age, BMI, and seven chronic diseases or health limitations, with the activity levels were analyzed by negative binomial regression.

Results

Most of the wear time was spent in sedentarism (median 61%/day), whereas the median time spent in MVPA was only 3%, with men achieving more MVPA than women (35 vs. 28 minutes/day, $p<0.05$). Almost two thirds of MVPA was achieved in short bouts of less than 5

Funding: The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. This work was further supported by the Comprehensive Pneumology Center Munich (CPC-M) as member of the German Center for Lung Research and by the Competence Network Asthma and COPD (ASCONET), network COSYCONET (subproject 2, BMBF FKZ 01GI0882) funded by the German Federal Ministry of Education and Research (BMBF). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors declare that they have no competing interests besides the research grants from the German Federal Ministry of Education and Research (BMBF) for the Competence Network Asthma and COPD (ASCONET), network COSYCONET (subproject 2, BMBF FKZ 01GI0882).

minutes, and 35% of the subjects did not achieve a single 10-minute bout. Hence, only 14% adhered to the WHO recommendation of 2.5 hours of MVPA/week in at least 10-minute bouts. Females, older subjects and obese subjects spent less time in MVPA ($p<0.05$), but no clear association with hypertension, asthma, diabetes, chronic obstructive pulmonary disease, anxiety/depression, pain or walking difficulties was observed in regression analyses with MVPA as outcome.

Conclusions

Activity behavior among middle-aged German adults was highly insufficient, indicating a further need for physical activity promotion in order to gain health benefits.

Background

Being physically active is linked to several health benefits, including the improvement of functional ability, cardiorespiratory fitness, metabolic health, and the prevention of premature death [1–4]. Although every bit of physical activity (PA) counts towards health benefits, the frequency, intensity and duration have great impact on these benefits [1–3]. Existing evidence supports a dose-response relationship of PA and reduced risk of chronic conditions like type 2 diabetes, cardiovascular disease, or stroke [3]. Therefore, the World Health Organization (WHO) recommends that adults without mobility-related chronic diseases should accumulate at least 2.5 hours of moderate-intensity PA per week spent in bouts of at least 10 minutes [1].

In order to improve adherence and to establish PA promotion, it is important to collect evidence on the pattern of PA behavior, however assessing PA is challenging [5–7]. Various approaches exist that rely either on self-reports or objective motion sensors [5, 6]. A systematic review comparing self-reported and objectively measured activity in adults found that correlations were generally low-to-moderate [6]. This is illustrated by the results of the fitness health survey for England in 2008 in which, based on self-report, 39% of men and 29% of women aged >16 years achieved at least moderate activity for a minimum of 30 minutes at five or more days a week; while, based on accelerometer data, only 6% of men and 4% of women met this threshold in at least 10 minute bouts [8]. Self-report tends to overestimate the time spent physically active at high intensity levels, whereas activity gained through lifestyle activities, e.g. during house work or active transportation, might be underestimated [6, 9]. Accelerometry provides the possibility to measure PA in a more standardized manner regardless of the current fitness level that might influence the subjectively perceived and reported intensity of PA [6, 9, 10]. Therefore, the number of studies that investigate objectively measured PA is increasing [11]. However, to date few population-based studies that objectively investigate the adherence to PA recommendations for moderate to vigorous activity (MVPA) in adults exist [8, 9, 12–14]. In the United States, data from the National Health and Nutrition Examination Survey (NHANES) revealed that if at least 30 minutes of MVPA on 5 out of 7 days, in bouts of at least 8–10 minutes, was considered as the recommended threshold, the adherence was less than 5% among adults [9]. Further, European data for adults from England, Norway, Sweden and Portugal revealed a generally low achievement of PA recommendations (1% to 20%) [8, 12–14].

Large scale, population-based data on PA in German adults was provided from the health monitoring system at the Robert Koch Institute based only on self-reports. Among 7671 participants, aged 18–79 years, 20% reported to achieve the WHO threshold of at least 2.5 hours of MVPA/week [15]. Furthermore, investigations of objectively measured PA in Germany

were performed in 168 participants aged 65–89 years. Of those, 12% reached 2.5 hours of MVPA/week in bouts lasting at least 10 minutes [16]. To our knowledge further data on PA from population-based studies assessing PA with accelerometers in German adults are missing.

The aim of the present study was to determine the PA levels and PA duration pattern assessed by accelerometry in a German adult cohort aged 48–68 years. Duration patterns of interest were the time spent in MVPA assessed in various bouts and the adherence to the WHO PA recommendations for adults categorized by sex and age. A further goal was to analyze the associations of sex, age, and BMI with activity levels serving as outcome. Since evidence indicates that subjects with chronic health issues engage less in PA [16, 17], we further addressed, if common chronic diseases or health limitations such as hypertension, asthma or physical complaints were associated with PA in a population-based sample of German adults.

Methods

Study population

The present analysis was based on a follow-up study of the KORA (Cooperative Health Research in the Region of Augsburg) S4 cohort comprising 4261 adults examined in 1999–2001. The primary study design has been described previously [18]. Between June 2013 and September 2014, 2279 subjects (age range 38 to 88 years) participated in the KORA FF4 follow-up of whom 1043 were designated to participate in the "Lung health & physical activity" section, which involved spirometric lung function measurements and PA assessment by accelerometry (Fig 1). The study was approved by the responsible ethics committee of the Bavarian Medical Association. The investigations were carried out in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants.

Baseline information on sociodemographic variables, self-reported physician diagnosis of common chronic diseases such as asthma or diabetes, and medication use was obtained during a standardized interview, also including questionnaires such as the EuroQol—5 Dimensions (EQ-5D) questionnaire and the shortened medical outcome survey (SF-12) which are assessment tools for health status and health-related quality of life. Further, participants underwent a standardized medical examination. Height and weight were assessed while subjects were wearing light clothes without shoes. After a rest of at least 5 minutes in a sitting position, blood pressure was measured three times on the right arm and determined by the mean of the second and third measurement.

In the present analysis, diabetes was defined based on self-reported physician diagnosis or use of antidiabetic agents. Hypertension was defined as blood pressure greater or equal to 140/90 mmHg or if the subject reported the use of antihypertensive medication given that the subject was aware of being hypertensive. Subjects who reported a doctor's diagnosis of chronic bronchitis or chronic obstructive pulmonary disease (COPD) were classified as having COPD. Information on mobility, pain/physical complaints and anxiety/depression was derived from the EQ-5D, and on overall health from the SF-12 questionnaire.

Physical activity assessment

The subjects received the accelerometer, instructions on its use, and a diary sheet at the study center. Participants were asked to start wearing the monitor on the following morning immediately after getting out of bed, and to complete a daily diary (S1 Methods) which included the time of getting up, going to work, getting back from work, start and end of specific sport episodes, type of sport performed, and going to sleep. Non-wear time was also included along with an explanation e. g. taking a shower or swimming. The measurement of PA was obtained

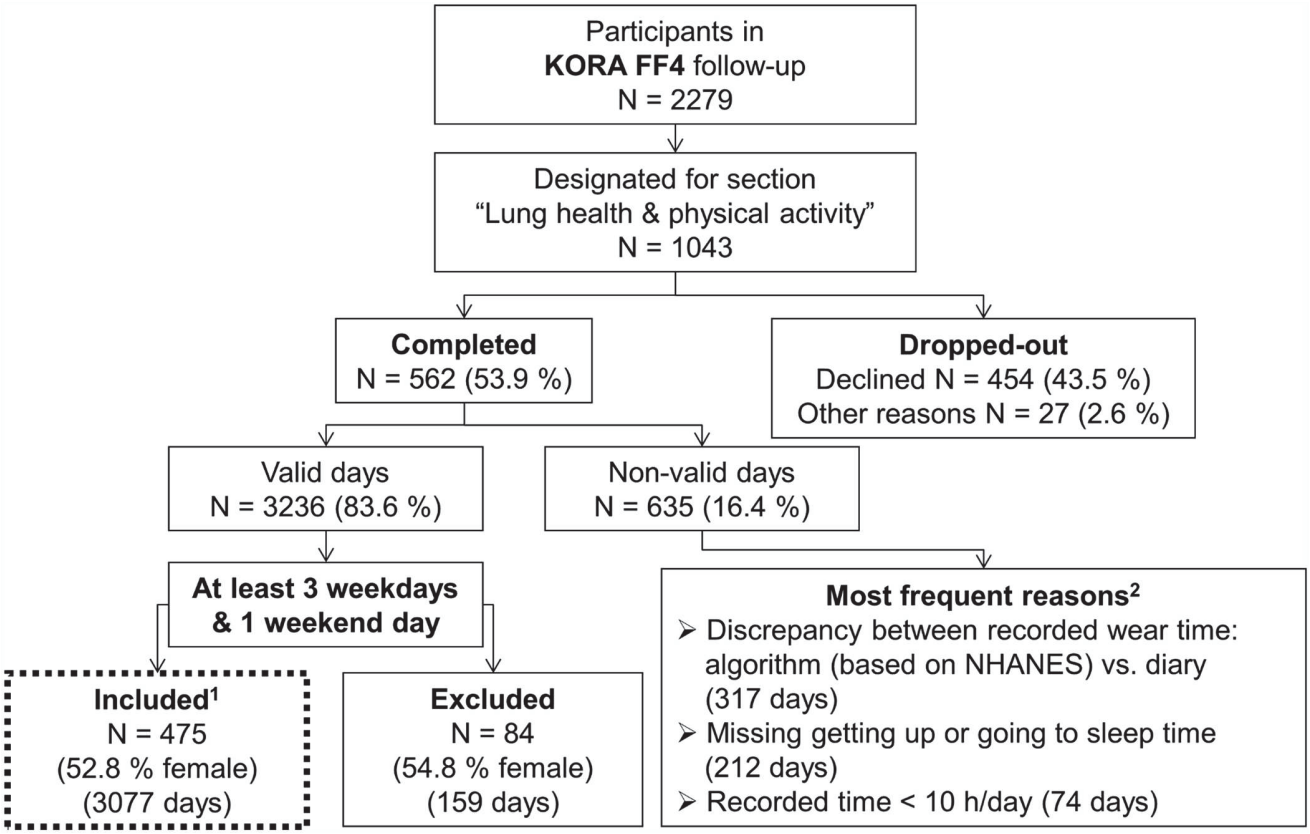


Fig 1. Participant recruitment and data handling. [1]After exclusion of 3 outliers. [2]Multiple reasons possible (detailed description in S1 Methods). NHANES algorithm: National Health and Nutrition Examination Survey algorithm [19].

doi:10.1371/journal.pone.0172503.g001

from ActiGraph GT3X (Pensacola, Florida) accelerometers with the use of the ActiLife software (version 6.11.2, firmware 4.4.0). The accelerometer was attached to an elastic belt and worn over a one week period at the hip on the side of the dominant hand.

Measured accelerations primarily sampled at 30 Hz and stored at 1 Hz were resampled in one minute epochs for further data analysis. As recommended by ActiGraph, data filtering was set to default ('normal'). 1-minute epochs were chosen to allow for comparisons with other population-based studies [8, 9, 12–14] and for applicability of available activity level calibration studies that were performed based on accelerometer counts and oxygen consumption per minute [20, 21]. Since it is debated whether the triaxial assessment of PA might be able to capture more complex movement than uniaxial and therefore might derive a better estimation of PA, we used both information for our analysis [22, 23].

According to the recorded acceleration value per minute, each minute was classified into one of three activity levels (sedentary, light, MVPA) using two approaches: the uniaxial count cut-offs of the vertical axis were based on the commonly used Freedson et al. [20] cut-offs and the triaxial vector magnitude cut-offs referred to Sasaki et al. [21]. In our analysis the uniaxial cut-offs for sedentary, light and MVPA were set to $\leq$100, $>$100, and $\geq$1952 counts/minute and the triaxial cut-offs to $<$200, $\leq$2690, and $>$2690 counts/minute, respectively. Further, the minutes per person obtained in each single activity level were summed and divided by the number of recorded days; resulting in the average minutes per day per subject spent in sedentary, light, or MVPA. Several steps were applied to assure high quality data, which are

described in detail in the additional file–S1 Methods. Days were excluded if the difference between the non-wear time algorithm, which was based on the NHANES algorithm [19], and the diary non-wear time was >120 minutes (if the accelerometer indicated a non-wear time) or >60 minutes (if the non-wear time was reported in the diary). Further reasons for exclusion were missing information on time spent awake, no reported non-wear time over the whole reporting period, and an incorrect handling of the accelerometer. MVPA for non-wear time <2 hours during sport was imputed using the percent of time spent in MVPA during PA of each subject or, if not available, through sex specific averages [24]. Through imputation, a mean of 3 minutes of MVPA/day (about 11%) was added to the recorded MVPA of 56 subjects. Valid days were required to have at least 10 hours of recording time, or >7 hours if the subjects reported day length was <10 hours. To account for differences in PA between weekdays and weekends that were shown in previous studies [25, 26], subjects were included in the analysis only if they had at least 3 valid weekdays and 1 valid weekend day.

Statistical analyses

Pearson's Chi-square test, Fishers exact test (if cell count <5), and Wilcoxon rank-sum test (adjusting for multiple testing using the Holm correction, if necessary) were used to assess sex specific differences, group differences in the analyzed study population, and differences between subjects designated to participate in the "Lung health & physical activity" section and those who participated in the PA assessment. Time counts of all three activity levels were averaged over the reporting period for each subject and described by median and the 25^{th} and 75^{th} percentiles.

Among the study population, age, ranging from 48 to 68 years, was grouped into three age tertiles (low: <55 years; intermediate: 55–61, and advanced: >61 years). BMI (kg/m^2) was calculated using values of height and weight obtained by physical examination in the study center. Subjects were categorized as normal weight (BMI 18–25 kg/m^2), overweight (BMI ≥25 kg/m^2), and obese (BMI ≥30 kg/m^2) [27].

Mean minutes of MVPA/subject showed a skewed distribution, with a great variance. Negative binomial regression, which accounts for overdispersion, was applied to investigate the associations between time spent in each PA level (sedentary, light, or MVPA) with sex, age and BMI.

Sedentary, light and MVPA served as outcome in all analyses. Each outcome was expressed in minutes averaged over the recording period for each subject and rounded to the nearest integer. For each outcome, a basic model was applied, which was adjusted for sex, age and BMI. Stepwise selection (combined forward and backward selection), using the lowest Akaike information criterion (AIC) as stopping rule, was performed to determine a model for each activity level considering several covariates. Besides sex, age and BMI, the following covariates were assessed: (1) season, categorized as winter (start of measurement: December to February), spring (March to May), summer (June to August), and autumn (September to November), (2) education, categorized as low (<10 years of school), middle (10 years of school) and high (>10 years of school), (3) hypertension, (4) diabetes, (5) asthma, (6) COPD, (7) difficulties with walking, (8) pain or physical complaints, and (9) anxiety or depression. All models with sedentary and light activity as outcome were additionally adjusted for average wear time/day. Our study population comprised Caucasians only, so ethnicity was not considered as a covariate.

A potential interaction effect of sex was tested in the final models. Sensitivity analyses were performed through exclusion of subjects reporting fair/poor overall health (N = 49) and exclusion of subjects who reported myocardial infarction (N = 14) and/or stroke (N = 8), to avoid possible bias towards a lower PA due to these diseases. All analyses were performed with

uniaxial cut-offs. To assess the impact of uni- vs. triaxial motion monitoring and to ensure better comparability to other studies, we replicated all aforementioned analyses using triaxial cut-offs.

Adherence to the WHO PA recommendation was defined as achieving at least 2.5 hours of MVPA/week in bouts of at least 10 minutes. Therefore, hours of MVPA/day spent in bouts of at least 10 minutes were averaged across the recording period for each subject and multiplied by seven.

For all analyses the statistical program R, version 3.2.0 [28], was used and p-values below 0.05 were considered statistically significant.

Results

Of 562 subjects who provided accelerometer data, 478 had valid data that passed the quality control (Fig 1, S1 Methods). Three subjects were excluded from the analyses; one male due to extremely high total measured uniaxial MVPA values (averaged 223 minutes/day compared to the median 35 minutes/day in all males), one female due to extremely high MVPA values in the triaxial measurement (averaged 252 minutes/day compared to the median 43 minutes/day in all females) and a second male due to severe obesity (BMI of 62 kg/m^2). The final study population comprised of 475 subjects with a mean age of 58 years (Table 1). At least 6 valid days were recorded by 89% of the subjects while 2% had 4 valid days. Males accounted for 47% of the subjects. The prevalence of overweight and obesity was 80% in males and 63% in females, respectively, and differed significantly between sexes. Subjectively reported overall health was good to excellent in 90% of subjects. 53% reported at least one chronic morbidity when considering hypertension, diabetes, asthma, COPD, walking difficulties, pain/physical complaints or anxiety/depression. In comparison to all other participants designated to the "Lung health & physical activity" section of the KORA FF4 follow up (N = 481) participants in PA (N = 562) reported more often a very good overall health. All other population characteristics did not differ (Table A in S1 Tables).

Activity levels

The overall median recorded wear time averaged per subject was about 15 h/day (Fig 2). The daily median time spent sedentary was higher in males than in females (586 vs. 529 minutes, respectively, $p<0.05$), whereas females engaged in more light activity (303 vs. 343 minutes, respectively, $p<0.05$) (Fig 2, Table B in S1 Tables). The daily median time spent in MVPA was 35 minutes (25-75th percentile: 21–49 minutes) for males and 28 minutes for females (25-75th percentile: 17–47 minutes) ($p<0.05$). In the total population, of the daily recorded time, a median of 61% (25-75th percentile: 54–67%) was spent in sedentary behavior, whereas the median time spent in light and MVPA was 35% (25-75th percentile: 30–42%) and 3% (25-75th percentile: 2–5%), respectively.

Age comparisons revealed that subjects aged <55 years spent more minutes in MVPA/day than those aged >61 years, irrespective of sex (median: 35 and 26 minutes in males, and 31 and 21 minutes in females, respectively, $p<0.05$). Normal and overweight men and women spent more time in MVPA/day compared to obese subjects (median: 44, 36 and 28 minutes in males, and 34, 28, and 20 minutes in females, respectively ($p<0.05$); Table C in S1 Tables).

Investigation of covariates

Whilst in sedentary and light activity no associations were seen with age and BMI in the basic models, negative associations were present between MVPA and the highest age tertile (ratio 0.75; 95% confidence interval (CI) 0.65, 0.87)) as well as obesity (ratio 0.67; CI: 0.57, 0.78)

Table 1. Characteristics of the study population (% (N)).

	Males	Females	Total
	47.2% (224)	**52.8% (251)**	**100% (475)**
Age, years (mean: 58; range: 48–68)			
<55	34.8 (78)	30.7 (77)	32.6 (155)
55–61	31.7 (71)	38.6 (97)	35.4 (168)
>61	33.5 (75)	30.7 (77)	32.0 (152)
Working, yes*	75.9 (170)	64.9 (163)	70.1 (333)
Education			
Low (<10 years of school)	46.0 (103)	45.8 (115)	45.9 (218)
Medium (= 10 years of school)	25.0 (56)	32.7 (82)	29.1 (138)
High (>10 years of school)	29.0 (65)	21.5 (54)	25.1 (119)
Body mass index, kg/m^2*			
Normal (<25)	19.6 (44)	37.1 (93)	28.8 (137)
Overweight (≥25, <30)	50.9 (114)	35.5 (89)	42.7 (203)
Obese (≥30)	29.5 (66)	27.5 (69)	28.4 (135)
Overall health (reported)			
Excellent/very good	32.1 (72)	25.1 (63)	28.4 (135)
Good	60.3 (135)	62.2 (156)	61.3 (291)
Fair/poor	7.6 (17)	12.7 (32)	10.3 (49)
Hypertension, yes*	39.3 (88)	29.1 (73)	33.9 (161)
Diabetes, yes	6.2 (14)	7.2 (18)	6.7 (32)
Asthma ever, yes	8.0 (18)	11.6 (29)	9.9 (47)
COPD, yes	7.1 (16)	10.4 (26)	8.8 (42)
Difficulties in walking			
Not at all/slight	95.1 (213)	93.2 (232)	94.1 (445)
Moderate/hard	4.9 (11)	6.8 (17)	5.9 (28)
Pain or physical complaints*			
Not at all/slight	90.2 (202)	81.3 (204)	85.5 (406)
Moderate/hard	9.8 (22)	18.7 (47)	14.5 (69)
Feeling anxious/depressed*			
Not at all/slight	96.9 (216)	90.0 (226)	93.2 (442)
Moderate/strong	3.1 (7)	10.0 (25)	6.8 (32)

*p<0.05 in Chi-square test (males vs. females).

COPD: Chronic obstructive pulmonary disease.

doi:10.1371/journal.pone.0172503.t001

(Table 2). Exclusion of subjects with myocardial infarction and/or stroke (N = 21) did not substantially alter the results. Models with the lowest AIC after stepwise selection (combined forward and backward selection) considering sex, age, BMI, seven chronic morbidities or health limitations, season and education as covariates are shown in Table 2. Associations of sex, the highest age tertile and obesity with MVPA remained significant.

In our cohort, no or only unstable associations of morbidity with PA levels could be determined. Pain or physical complaints were negatively associated with MVPA in the best fit model obtained by stepwise selection, but were not significant after exclusion of subjects with myocardial infarction and those with stroke ($p<0.1$). Results were only slightly altered after exclusion of subjects who reported fair/poor overall health. Due to an interaction effect between sex and diabetes, we stratified the models of sedentary and light activity by sex. After stratification, diabetes showed a negative association with light activity and a positive

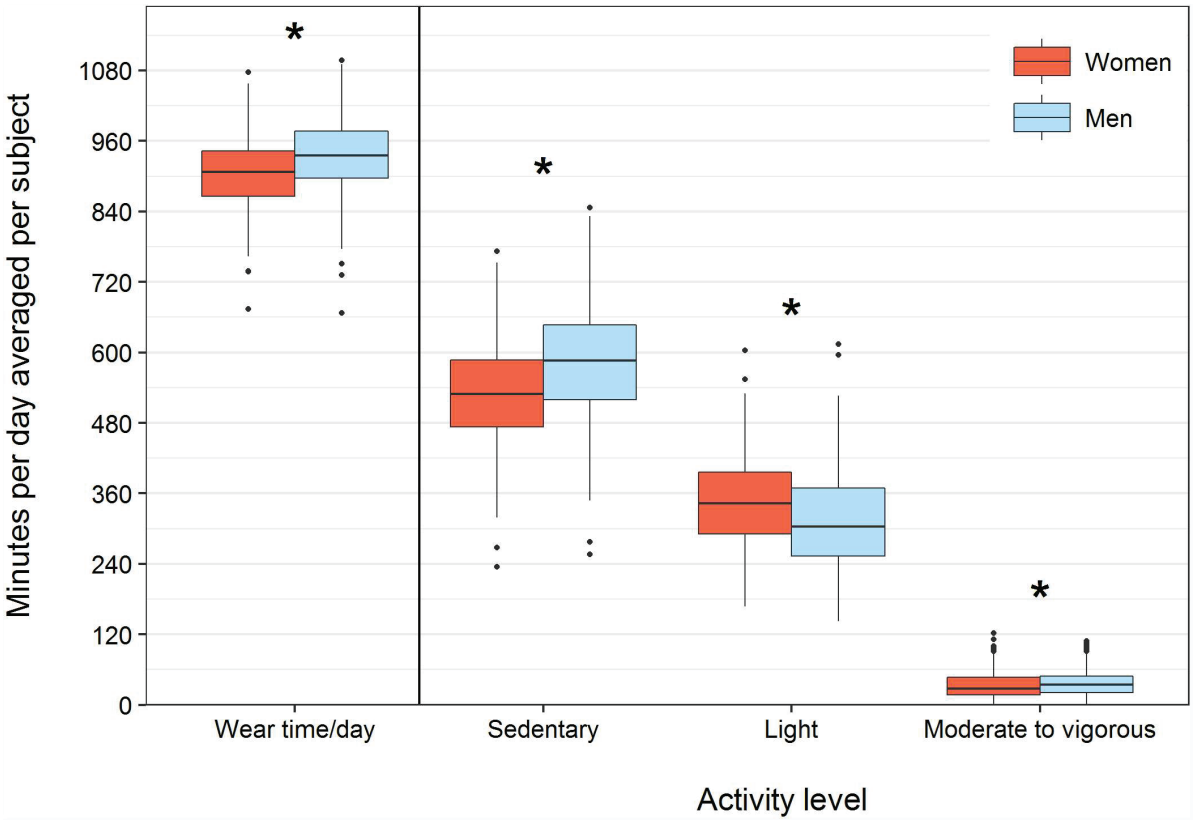


Fig 2. Total wear time and time spent in sedentary, light and moderate to vigorous (MVPA) activity in minutes/day averaged per subject. *p<0.05 in Wilcoxon rank-sum test (males vs. females).

doi:10.1371/journal.pone.0172503.g002

association with time spent sedentary in females only ($p<0.05$; Table 2). Further, an unstable interaction effect was found between sex and the highest age tertile (>61 years), suggesting a positive association of advanced age with sedentary and a negative association with light activity in men, while no association was shown in females (data not shown).

Duration pattern of time spent in MVPA

The majority of time spent in MVPA was accumulated in short bouts i.e. less than 5 minutes (Fig 3, Table D in S1 Tables). Overall, the median time spent in bouts of at least 1 minute was 3.52 hours/week, 1.11 hours in bouts of at least 5 minutes and only 0.45 hours in bouts of at least 10 minutes. The median decrease of time spent in MVPA per subject lasting at least 1 minute was 66% when the bout was raised to at least 5 minutes and 86% when the bout was further raised to at least 10 minutes. MVPA bouts of at least 10 minutes did not differ between age tertiles for either sex.

We found that 168 subjects in our population did not achieve a single episode of MVPA lasting at least 10 minutes. While 26% of normal weight subjects did not reach at least one episode of MVPA spent in at least 10 minutes, this amount was almost double in obese subjects (45%) (Table E in S1 Tables). The highest proportion of subjects who did not meet this 10 minute threshold was found among those with difficulties in walking or pain/physical complaints.

Table 2. Count ratios (95% confidence intervals) of uniaxial average minutes/day of moderate-to-vigorous physical activity (MVPA), sedentary or light activity estimated by negative binomial regression.

Outcome		Sedentary		Light		MVPA	
Variables	**Model**	**Basic[1]**	**Stepwise[1]**	**Basic[1]**	**Stepwise[1]**	**Basic**	**Stepwise**
Sex	Female	-	-	-	-	-	-
	Male	**1.06 (1.03; 1.10)**	**1.06 (1.03; 1.09)**	**0.88 (0.84; 0.92)**	**0.89 (0.85; 0.93)**	**1.24 (1.10; 1.39)**	**1.23 (1.09; 1.38)**
Age, years	<55	-	-	-	-	-	-
	55–61	0.97 (0.94; 1.01)	**0.97 (0.93; 1.00)**	1.05 (1.00; 1.11)	**1.06 (1.00; 1.11)**	0.99 (0.86; 1.13)	0.99 (0.86; 1.14)
	>61	1.04 (1.00; 1.07)	**1.04 (1.00; 1.08)**	0.97 (0.91; 1.02)	0.96 (0.91; 1.01)	**0.75 (0.65; 0.87)**	**0.76 (0.65; 0.87)**
BMI (kg/m^2)	Normal (<25)	-	-	-	-	-	-
	Overweight (≥25, <30)	0.99 (0.96; 1.03)	1.00 (0.97; 1.04)	1.02 (0.97; 1.08)	x	**0.85 (0.74; 0.98)**	0.87 (0.76; 1.00)
	Obese (≥30)	1.03 (0.99; 1.07)	1.04 (1.00; 1.08)	0.99 (0.94; 1.05)	x	**0.67 (0.57; 0.78)**	**0.71 (0.60; 0.83)**
Education	Low (<10 years of school)	-	-	-	-	-	-
	Medium (= 10 years of school)	-	**1.05 (1.01; 1.08)**	-	**0.93 (0.88; 0.98)**	-	x
	High (>10 years of school)	-	**1.09 (1.06; 1.13)**	-	**0.87 (0.82; 0.92)**	-	x
Pain/physical complaints	Not at all/slight	-	-	-	-	-	-
	Moderate/hard	-	x	-	x	-	**0.83 (0.70; 0.98)**
Hypertension	No	-	-	-	-	-	-
	Yes	-	x	-	x	-	0.91 (0.80; 1.04)
Diabetes	No	-	-	-	-	-	-
	Yes	-	**1.07 (1.01; 1.13)**	-	**0.89 (0.82; 0.97)**	-	x
			[stratified by sex: **1.12 (1.04; 1.21)** females; 0.99 (0.91;1.08) males]		[stratified by sex: **0.80 (0.72; 0.88)** females; 1.00 (0.87;1.16) males]		

Significant associations (p<0.05) are shown in bold. Basic model was adjusted for sex, age, and body mass index (BMI). Besides sex, age, and BMI, considered variables in the stepwise selection model (combined forward and backward selection) were: season, education, hypertension, diabetes, asthma, chronic obstructive pulmonary disease (COPD), difficulties with walking, pain or physical complaints, and anxiety/depression. Models with the lowest Akaike information criterion (AIC) are shown.

[1]Model additionally adjusted for average recorded wear time/day.

[x]Covariate did not remain in main model.

doi:10.1371/journal.pone.0172503.t002

Adherence to WHO physical activity recommendation

As recommended by the WHO adults should accumulate a minimum of 2.5 hours of at least moderate intensity PA/week spent in bouts of 10 minutes or greater. In our population, only 14% met this recommendation; 36 men and 30 women, respectively. While 15% of subjects aged <55 years adhered to the WHO recommendation, 11% reached this threshold in the advanced age category (>61 years). The highest prevalence of adherence was found within the

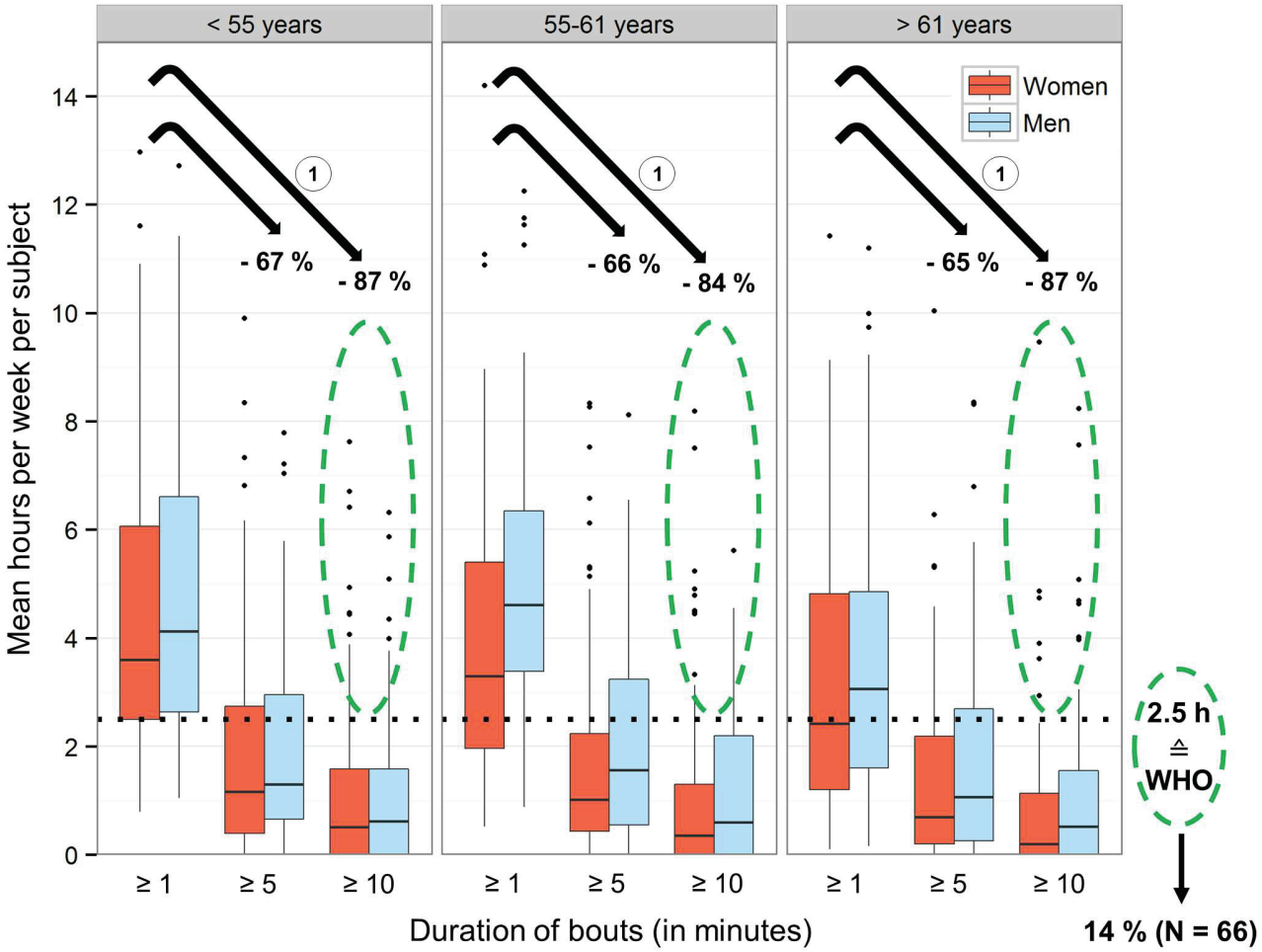


Fig 3. Time spent in moderate to vigorous activity (MVPA) in at least 1, 5, and 10 minute bouts categorized by age and adherence to WHO physical activity recommendations. Hours/day spent in MVPA are averaged over the recording period of each subject and multiplied by seven. MVPA cut-off set at 1952 counts/minute (uniaxial). Green dashed circles: Subjects who met the WHO physical activity recommendation of $\geq$ 2.5 hours of MVPA/week in at least 10 minute bouts. [1] Median percent decrease in time spent in MVPA after excluding bouts shorter than 5 and 10 minutes, respectively.

doi:10.1371/journal.pone.0172503.g003

middle aged group with 55 to 61 years (16%). Among subjects adhering to the WHO recommendation the prevalence of having hypertension, diabetes, asthma, COPD, walking difficulties, pain/physical complaints or anxiety/depression ranged from 3% (walking difficulties) up to 24% (hypertension) (Table E in S1 Tables), while 50% presented none of these morbidities.

Comparison of triaxial to uniaxial results

When applying triaxial cut-offs, subjects were less inactive and spent more time in light activity or MVPA compared to uniaxial cut-offs (median 469 vs. 552 minutes sedentary, 397 vs. 324 minutes light, and 46 vs. 30 minutes MVPA, respectively), whereas group comparisons considering sex, age and BMI showed similar trends. Males, younger subjects and subjects with a lower BMI spent more time in MVPA (Tables B and C in S1 Tables). As observed for uniaxial data, the strongest associations in regression analyses were also present between MVPA and advanced age (ratio 0.77; CI: 0.67, 0.87) or obesity (ratio 0.79; CI: 0.69, 0.91) (Table F in

S1 Tables). Obesity was negatively associated with light activity (ratio 0.91; CI: 0.86, 0.96) and positively with sedentary behavior (ratio 1.11; CI: 1.05, 1.16). Considering 1 minute, 5 minute and 10 minute bouts of time spent in MVPA showed a similar pattern as with uniaxial cut-offs (S1 Fig). In line with increased time spent in MVPA observed by triaxial assessment the number of subjects meeting the WHO recommendation increased from 66 to 81. Comparable to uniaxial, the adherence was 17.1% (41 males and 40 females) (Table D in S1 Tables), with 18% of subjects aged <55 years, 19% aged 55–61 years and 14% aged >61 meeting the threshold. Among subjects not achieving at least one episode of time spent in MVPA in a 10 minute bout, the highest prevalence of the investigated morbidities was still present among subjects with difficulties in walking (Table G in S1 Tables).

Discussion

The time spent in MVPA was generally low among adults aged 48–68 years from southern Germany, while men engaged more in MVPA than women. MVPA was significantly lower among obese subjects and those aged >61 years. Only a median of 14% of MVPA was accumulated in bouts of at least 10 minutes, which would count towards meeting the WHO PA recommendations. This is why only 66 subjects (14%) met the threshold of at least 2.5 hours of MVPA/week in bouts of at least 10 minutes.

The low prevalence of adherence to the WHO PA recommendation is comparable to other European studies. In Norway, 20% of the study population (N = 3267), aged 20–85 years, accumulated at least 30 minutes of daily MVPA in bouts of 8–10 minutes [12]. Of 1114 Swedish participants (age range 18–79 years), 52% accumulated at least 30 minutes/day of MVPA, but only 1% reached 30 minutes/day in ≥ 3 periods of 10 minute bouts [13]. In Portugal, 7–9% participants aged 40–64 years and 3% aged 65 years or older, accumulated at least 30 minutes MVPA/day in periods of at least 10 minutes [14]. Similar to our study, all three studies used ActiGraph accelerometers, which is a commonly used device for objective PA assessment [11], but varied slightly in terms of cut-offs (1952 to 2020 counts/minute for MVPA), number of measured days (4 to 7) as well as application of international PA recommendations (e.g. allowing 1–2 minutes of non-movement throughout the 10 minute bout) and population characteristics such as age. Nevertheless, in general the adherence to the WHO PA recommendation among all studies was widely below 50%.

In our analysis, in both, men and women, the majority of wear time was spent sedentary, being higher in males than in females. A meta-analysis has recently reported that the risk for all-cause mortality is increased for subjects with high amounts of sedentary behavior, assessed as sitting time, but that this effect seems to be mitigated through PA [29]. Subjects in the highest quartile of PA and sitting time for >8h showed a lower mortality risk than those in the least active quartile and <4h sitting time. The highly active subjects achieved about 60–75 minutes moderate PA/day which was even higher than the recommended WHO threshold [29]. In contrast, not meeting the WHO PA recommendations was found to account for about 6% of the burden of coronary heart disease, 7% of type 2 diabetes, and 10% of colon cancers worldwide, which would be addressed by increasing PA [30].

German large scale population-based data, based on self-reports, reported an adherence to WHO PA recommendation of 18%, both in the 50–59 years and the 60–69 years age groups [15]. This prevalence was only slightly higher than the prevalence found in our cohort (14% uniaxial and 17% triaxial). However, despite the similar trend, no direct comparisons are possible, as the correlation between self-reported and directly measured PA was found to be only low-to-moderate [6].

Our data showed that the median number of daily minutes of MVPA decreased across age and BMI categories, and further, that males achieved more minutes of MVPA, which is in line with other studies [8, 9, 13, 14]. A similar pattern was shown in the health survey for England in 2008, where participants in the normal weight category spent on average fewer minutes in sedentary time and more time in MVPA than those who were in the overweight or obese category, showing also a declining gradient of averaged minutes spent in MVPA with age [8]. In contrast, we found that within all three age tertiles (<55, 55–61 and >61 years) the median decrease of averaged hours spent in MVPA/week per subject was around 66% when raising the consecutive MVPA counts to 5 minutes, and around 87% when raising this threshold to at least 10 minutes. While the highest amount of subjects not achieving a single MVPA bout of at least 10 minutes was seen among subjects reporting difficulties in walking (61%) and pain or physical complaints (58%), the majority of subjects reporting any other investigated morbidity reached at least one 10 minute bout of MVPA. A study investigating German adults aged between 65–89 years reported a similar tendency, showing a stronger association between disability and PA than between multimorbidity and PA [16].

No stable association of hypertension, asthma, diabetes, COPD, walking difficulties, pain/physical complaints, or anxiety/depression with time spent in MVPA was found. This result should be interpreted with caution due to the low prevalence of morbidities such as COPD (9%) or diabetes (7%) and probably mainly mild disease stages in our study population. Despite the possibility that more active subjects participated in the PA assessment, our results indicate that there is an urgent need to improve PA among adults in southern Germany, given that subjects spent a median of 61% of the time sedentary, and in contrast only 3% in MVPA/day. Furthermore, only 14% met the WHO PA recommendation.

The present results, including subjects aged 48–68 years resident in the region of Augsburg in southern Germany, are limited to the selected study population which had a relatively low response of 54%, likely leading to a potential risk of selection bias. Further, our results are based on cross-sectional data, which does not allow generalizations about long term PA behavior. Within our study population, the prevalence of morbidities was low and probably at early stages. Furthermore, these were assessed by questionnaires only and were not verified by an examination from a physician. The assessment of pain or physical complaints, and walking difficulties was based on self-report without precise definition of the cause.

Despite these limitations, this study has several strengths revealing new insights into PA levels and duration pattern of German adults assessed by accelerometry. Data on objectively measured PA among German adults is rare. Despite the inability to measure all PA engagement equally well, the advantage of the use of accelerometers is the ability to analyze the intensity and duration of consecutive minutes of PA, while minimizing the risk of reporting bias occurring in self-reports [5, 6, 9, 10].

There is a lot of methodological diversity among studies investigating PA with accelerometers [22]. This is partly due to the use of different devices, the investigation of uni- or triaxial movement measures as well as the chosen cut-points [11, 21–23]. Thus we provided data based on different approaches to illustrate the potential impact on the measured PA of adults in our study and to provide data for comparability with other studies published.

Conclusions

In conclusion, the prevalence of being physically active was found to be generally low among adults from southern Germany. Overall, time spent in MVPA was accumulated mainly in very short bouts and one third of the population did not achieve a single 10 minute bout of MVPA contributing towards the WHO PA recommendation. Furthermore, only one in eight subjects

achieved the WHO threshold, indicating a further need for PA promotion in Germany, particularly among older and obese subjects.

Supporting information

S1 Fig. Time spent in moderate to vigorous activity (MVPA) (triaxial cut-offs) in at least 1, 5, and 10 minute bouts categorized by age and adherence to WHO physical activity recommendations.
(PDF)

S1 Methods. Detailed description of diary, quality control and data imputation.
(PDF)

S1 Tables. Tables A-G.
(PDF)

Acknowledgments

The authors thank all attendees for their active participation in the KORA study.

The KORA-Study Group consists of A. Peters (speaker), H. Schulz, R. Holle, R. Leidl, C. Meisinger, K. Strauch, and their co-workers, who are responsible for the design and conduct of the KORA studies.

Author Contributions

Conceptualization: AL DN HS.

Data curation: AL MH BT ML AP HS.

Formal analysis: AL HS.

Funding acquisition: AP HS.

Investigation: MH BT ML AP HS.

Methodology: AL HS.

Project administration: AP HS MH.

Resources: MH BT AP HS.

Supervision: DN HS.

Validation: AL HS MH AP.

Visualization: AL.

Writing – original draft: AL.

Writing – review & editing: AL MH BT ML DN AP HS.

References

1. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva, World Health Organization, 2010. http://www.who.int/dietphysicalactivity/factsheet_recommendations/en/.
2. Aadahl M, Kjaer M, Jorgensen T. Associations between overall physical activity level and cardiovascular risk factors in an adult population. Eur J Epidemiol. 2007; 22(6):369–78. Epub 2007/03/03. doi: 10.1007/s10654-006-9100-3 PMID: 17333472

3. Warburton DER, Charlesworth S, Ivey A, Nettlefold L, Bredin SSD. A systematic review of the evidence for Canada's Physical Activity Guidelines for Adults. Int J Behav Nutr Phys Act. 2010; 7:39-. doi: 10.1186/1479-5868-7-39 PMID: 20459783
4. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008; 15(3):239–46. Epub 2008/06/06. doi: 10.1097/HJR.0b013e3282f55e09 PMID: 18525377
5. Warren JM, Ekelund U, Besson H, Mezzani A, Geladas N, Vanhees L. Assessment of physical activity—a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil. 2010; 17(2):127–39. Epub 2010/03/11. doi: 10.1097/HJR.0b013e32832ed875 PMID: 20215971
6. Prince SA, Adamo KB, Hamel ME, Hardt J, Gorber SC, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act. 2008; 5:56. doi: 10.1186/1479-5868-5-56 PMID: 18990237
7. Cavill N, Foster C, Oja P, Martin BW. An evidence-based approach to physical activity promotion and policy development in Europe: contrasting case studies. Promot Educ. 2006; 13(2):104–11. Epub 2006/10/05. PMID: 17017287
8. Aresu M, Bécares L, Brage S, Chaudhury M, Doyle-Francis M, Esliger D, et al. Health Survey for England 2008—Volume 1 Physical activity and fitness. 2009. 385 p.
9. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc. 2008; 40(1):181–8. Epub 2007/12/20. doi: 10.1249/mss.0b013e31815a51b3 PMID: 18091006
10. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. Br J Sports Med. 2003; 37(3):197–206; discussion Epub 2003/06/05. doi: 10.1136/bjsm.37.3.197 PMID: 12782543
11. Wijndaele K, Westgate K, Stephens SK, Blair SN, Bull FC, Chastin SF, et al. Utilization and Harmonization of Adult Accelerometry Data: Review and Expert Consensus. Med Sci Sports Exerc. 2015; 47(10):2129–39. Epub 2015/03/19. doi: 10.1249/MSS.0000000000000661 PMID: 25785929
12. Hansen BH, Kolle E, Dyrstad SM, Holme I, Anderssen SA. Accelerometer-determined physical activity in adults and older people. Med Sci Sports Exerc. 2012; 44(2):266–72. Epub 2011/07/29. doi: 10.1249/MSS.0b013e31822cb354 PMID: 21796052
13. Hagstromer M, Oja P, Sjostrom M. Physical activity and inactivity in an adult population assessed by accelerometry. Med Sci Sports Exerc. 2007; 39(9):1502–8. Epub 2007/09/07. doi: 10.1249/mss.0b013e3180a76de5 PMID: 17805081
14. Baptista F, Santos DA, Silva AM, Mota J, Santos R, Vale S, et al. Prevalence of the Portuguese population attaining sufficient physical activity. Med Sci Sports Exerc. 2012; 44(3):466–73. Epub 2011/08/17. doi: 10.1249/MSS.0b013e318230e441 PMID: 21844823
15. Krug S JS, Mensink GBM, Müters S, Finger JD, Lampert T. English version of "Körperliche Aktivität. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1)" Bundesgesundheitsblatt. 2013; 56:765–771.
16. Ortlieb S, Gorzelniak L, Nowak D, Strobl R, Grill E, Thorand B, et al. Associations between multiple accelerometry-assessed physical activity parameters and selected health outcomes in elderly people–results from the KORA-age study. PLoS One. 2014; 9(11):e111206. doi: 10.1371/journal.pone.0111206 PMID: 25372399
17. Vorrink SN, Kort HS, Troosters T, Lammers JW. Level of daily physical activity in individuals with COPD compared with healthy controls. Respir Res. 2011; 12:33. Epub 2011/03/24. doi: 10.1186/1465-9921-12-33 PMID: 21426563
18. Holle R, Happich M, Lowel H, Wichmann HE. KORA–a research platform for population based health research. Gesundheitswesen. 2005; 67 Suppl 1:S19–25. Epub 2005/07/21.
19. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. Med Sci Sports Exerc. 2011; 43(2):357–64. Epub 2010/06/29. doi: 10.1249/MSS.0b013e3181ed61a3 PMID: 20581716
20. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc. 1998; 30(5):777–81. Epub 1998/05/20. PMID: 9588623
21. Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph activity monitors. J Sci Med Sport. 2011; 14(5):411–6. doi: 10.1016/j.jsams.2011.04.003 PMID: 21616714
22. Matthew CE. Calibration of accelerometer output for adults. Med Sci Sports Exerc. 2005; 37(11 Suppl):S512–22. Epub 2005/11/19. PMID: 16294114

23. Vanhelst J, Béghin L, Duhamel A, Bergman P, Sjöström M, Gottrand F. Comparison of uniaxial and triaxial accelerometry in the assessment of physical activity among adolescents under free-living conditions: the HELENA study. BMC Med Res Methodol. 2012; 12(1):1–6.

24. Smith MP, Berdel D, Nowak D, Heinrich J, Schulz H. Physical Activity Levels and Domains Assessed by Accelerometry in German Adolescents from GINIplus and LISAplus. PLoS One. 2016; 11(3): e0152217. doi: 10.1371/journal.pone.0152217 PMID: 27010227

25. Evenson KR, Wen F, Metzger JS, Herring AH. Physical activity and sedentary behavior patterns using accelerometry from a national sample of United States adults. Int J Behav Nutr Phys Act. 2015; 12:20. doi: 10.1186/s12966-015-0183-7 PMID: 25889192

26. Kruger J, Ham SA, Kohl HW III. Characteristics of a "Weekend Warrior": Results from Two National Surveys. Med Sci Sports Exerc. 2007; 39(5).

27. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014; 384(9945):766–81. Epub 2014/06/02. doi: 10.1016/S0140-6736(14)60460-8 PMID: 24880830

28. R Core Team. R. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. (2015). URL http://www.R-project.org/.

29. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet. 2016. Epub 2016/08/01.

30. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Impact of Physical Inactivity on the World's Major Non-Communicable Diseases. Lancet. 2012; 380(9838):219–29.

S1 Methods: Detailed description of diary, quality control and data imputation.

Diary

Participants were asked to fill out a detailed course of the day diary for seven consecutive days. For a better understanding, a one day example was provided. The diary was provided in German language to the participants and was translated to English for publication only.

Course of the day	Example
Date	**13.04.2012**
Getting up: Sensor from wrist to hip (time)	6:15
How well did you sleep? (1: Very good to 6: Poor)	3
How do you get to work? (e. g. by car, bus)	Car
Time you leave the house - to work	7:30
Starting time of work	8:00
End time of work	18:00
Arrival time at home	18:45
Have you taken a nap? (if yes, time from … to)	13:00 - 13:45
Type of physical activity e.g. soccer, basketball, hiking, cycling Was this activity performed as member of a sports club or gym? Start …… Finish ……..	Soccer Yes 19:30 21:15
Going to bed time	23:30
How did you feel today? →	2
	
Time and reason for removing the accelerometer	
	Example
Time and duration	6:20 - 6:40
Reason	Showering
Time and duration	19:45 - 21:00
Reason	Swimming

Quality control

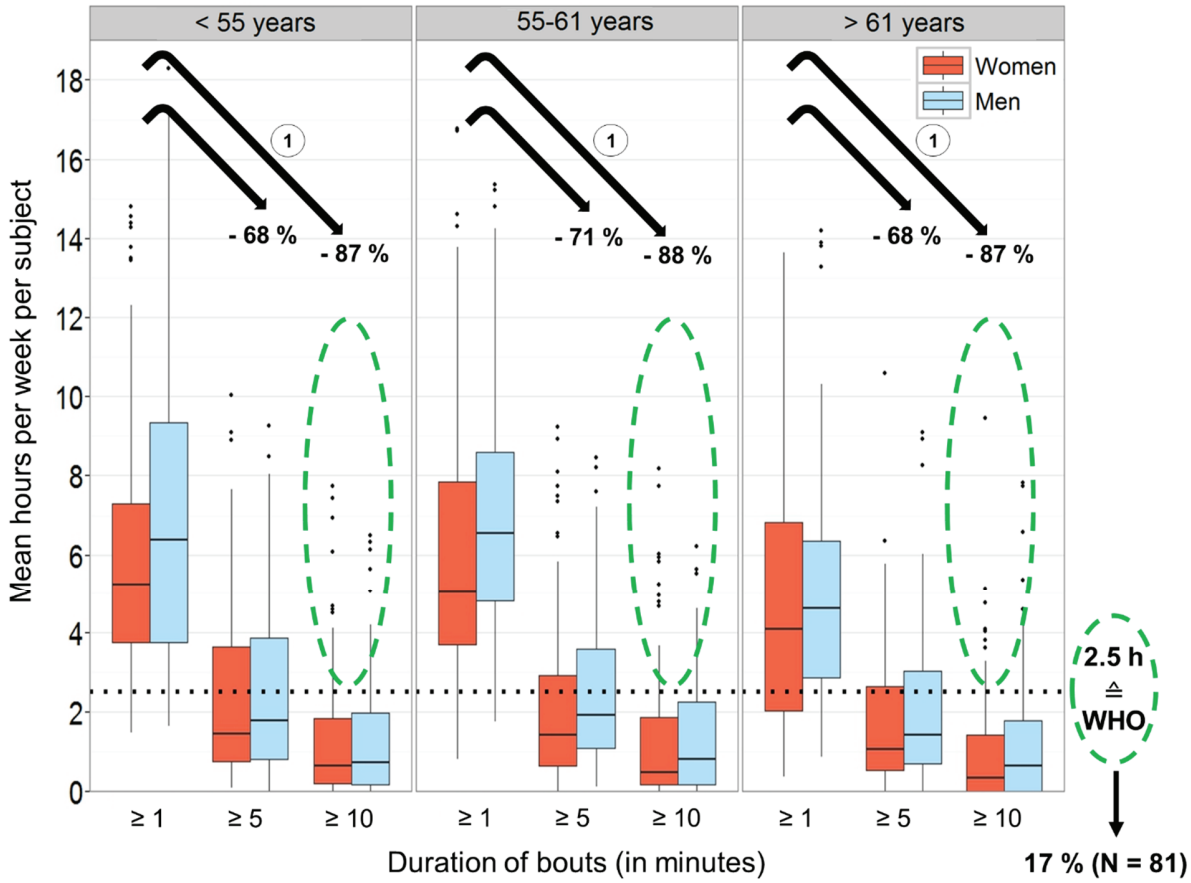
We performed several steps to assure the best possible data quality. The number of non-valid days was 635 (16.4%). Wearing days were excluded if one or more of the below described exclusion criteria were met. Days were excluded if:

- differences occurred by comparison of the wear time between the diary report and the accelerometric data. Therefore, an algorithm based on the algorithm derived from the National Health and Nutrition Examination Survey (http://riskfactor.cancer.gov/tools/nhanes_pam) was applied. Non-wear time periods were defined as at least 60-minute time intervals of consecutive zero counts, allowing up to two consecutive minutes with nonzero counts less than or equal to 100 counts. Differences between this non-wear time algorithm and the reported wear time were calculated in minutes for each event. Because of the uncertainty of misclassification of wear periods as non-wear time and the other way round, we based our limits for exclusion of time intervals near the 3th and 97th percentile of the difference distribution. The limits were set to > |- 120| min difference between algorithm and diary, if algorithm reported non-wear time, and > 60 minutes, if the subject reported non-wear time, but the accelerometer showed counts of wear time → 317 days
- time of getting up or going to sleep could not be assessed or were missing > 4 times throughout the measuring period → 212 days
- the wear time was < 10 hours according to the diary (exception: if the total time spent awake was only between 8 to 10 hours than this day was excluded if the reported wear time in the diary was < 7 hours) → 74 days
- non wear-time was not at all reported through the whole wear time period, despite the fact that the accelerometer is not waterproof → 71 days
- reported sport activities without wearing the accelerometer lasted > 2 hours, e.g. during a competition or skiing → 43 days
- the sensor was defective or worn incorrectly (upside down or on hand instead of hip) → 13 days
- the subject reported to be sick (excluding headache or cold) on 2 or more days in a row (exclusion of days from the second day on) → 13 days
- the subject reported to be sick on most of the reporting days → 10 days
- the subject reported to be on a trip – meaning non-regular hole day activity - on 2 or more days in a row (exclusion of days from the second day on) → 1 day

Imputation of non-wear time periods during sport

To account for MVPA obtained through sport activities lasting < 2 hours when the accelerometer was not worn, e.g. during swimming or material arts, we imputed non-wear time MVPA. If the reported non-wear time period lasted between 30 and 120 minutes, we subtracted 15 minutes before imputation accounting for preparing for PA, e.g. changing clothes. The efficiency (e.g. % of time spent in MVPA during PA) of each subject as well as sex specific averages were calculated. If the subject had a period of reported PA while wearing the accelerometer, MVPA of non-wear time sport was imputed through multiplication of time spent in PA without wearing the accelerometer by his or her efficiency and added to the subjects total MVPA on this particular day. If no PA activities were reported where the accelerometer was worn, sex specific efficiency averages were used for imputation.

S1 Fig. Time spent in moderate to vigorous activity (MVPA) (triaxial cut-offs) in at least 1, 5, and 10 minute bouts categorized by age and adherence to WHO physical activity recommendations.



Hours/day spent in MVPA are averaged over the recording period of each subject and multiplied by seven. MVPA cut-off set at 2690 counts/minute (triaxial). - - - Subjects who met the WHO physical activity recommendation of ≥ 2.5 hours of MVPA/week in at least 10 minute bouts.

① Median percent decrease in time spent in MVPA after excluding bouts shorter than 5 and 10 minutes, respectively.

S1 Tables: Tables A-G.

Table A. Comparison of subjects participating in accelerometry compared to all other participants designated to participate in the "Lung health & physical activity" section of the KORA FF4 follow-up (n/N (%)).

Participating in accelerometry	**Yes** (N=562)	**No** (N=481)
Sex, male	264/562 (47)	224/481 (47)
Age, years		
< 55	189/562 (34)	145/481 (30)
55-61	201/562 (36)	159/481 (33)
> 61	172/562 (31)	177/481 (37)
Working, yes	400/561 (71)	317/481 (66)
Education		
Low (< 10 years of school)	261/561 (47)	238/479 (50)
Medium (= 10 years of school)	153/561 (27)	117/479 (24)
High (> 10 years of school)	147/561 (26)	124/479 (26)
Body mass index, kg/m^2		
Normal (< 25)	156/562 (28)	154/481 (32)
Overweight (< 30)	245/562 (44)	181/481 (38)
Obese (≥ 30)	161/562 (29)	146/481 (30)
Overall health (reported)*		
Excellent/very good	155/562 (28)	102/479 (21)
Good	346/562 (62)	304/479 (63)
Fair/poor	61/562 (11)	73/479 (15)
Hypertension, yes	185/561 (33)	184/481 (38)
Diabetes, yes	37/561 (7)	37/481 (8)
Asthma ever, yes	54/562 (10)	47/481 (10)
COPD, yes	48/562 (9)	34/480 (7)
Myocardial infarction, yes	17/561 (3)	14/481 (3)
Stroke, yes	12/562 (2)	11/477 (2)
Difficulties in walking		
Not at all/slight	523/559 (94)	439/479 (92)
Moderate/hard	36/559 (6)	40/479 (8)
Pain or physical complaints		
Not at all/slight	476/562 (85)	388/479 (81)
Moderate/hard	86/562 (15)	91/479 (19)

Participating in accelerometry	**Yes** (N=562)	**No** (N=481)
Feeling anxious/depressed		
Not at all/slight	519/560 (93)	439/478 (92)
Moderate/strong	41/560 (7)	39/478 (8)

*p < 0.05 in Chi-square test. COPD: Chronic obstructive pulmonary disease.

Table B. Median time spent in the three activity levels – sedentary, light and moderate to vigorous (MVPA) stratified by sex.

	Uniaxial		**Triaxial**	
	Males	Females	Males	Females
	47.2 % (224)	52.8 % (251)	47.2 % (224)	52.8 % (251)
Median (25^{th}, 75^{th} percentile) of minutes per day averaged per subject				
Sedentary	586 (520, 646)*	529 (473, 587)	504 (434, 577)*	435 (376, 498)
Light	303 (253, 369)*	343 (291, 396)	370 (308, 437)*	416 (362, 471)
MVPA	35 (21, 49)*	28 (17, 47)	49 (33, 71)*	43 (28, 62)
Median % (25^{th}, 75^{th} percentile) of recorded time spent in each level per day averaged per subject				
Sedentary	63 (56, 69)*	58 (52, 65)	54 (47, 62)*	48 (42, 55)
Light	32 (27, 40)*	38 (33, 44)	40 (34, 48)*	46 (40, 52)
MVPA	4 (2, 5)*	3 (2, 5)	5 (4, 8)	5 (3, 7)

*$p < 0.05$ in Wilcoxon rank-sum test (males vs. females).

Table C. Median time spent in moderate to vigorous activity stratified either by age tertile or body mass index (BMI) for males and females.

		Uniaxial		**Triaxial**	
		Males	Females	Males	Females
Median (25th, 75th percentile) of minutes per day averaged per subject					
Age, years	< 55	35 (24, 57)[1]	31 (21, 52)[1]	57 (32, 80)[1]	45 (32, 65)[1]
	55 - 61	40 (29, 54)[2]	28 (17, 46)	56 (41, 74)[2]	43 (32, 67)
	> 61	26 (15, 43)	21 (10, 42)	39 (26, 55)	38 (17, 58)
BMI, kg/m^2	Normal (< 25)	44 (30, 59)[3]	34 (20, 54)[3]	55 (39, 79)	50 (30, 72)[3]
	Overweight (≥ 25)	36 (21, 51)[4]	28 (18, 40)[4]	49 (32, 70)	40 (32, 58)
	Obese (≥ 30)	28 (17, 41)	20 (11, 33)	43 (32, 63)	35 (21, 57)

Significant difference ($p < 0.05$) by pairwise Wilcoxon rank-sum test stratified by sex between the categories:

[1] age < 55 and age > 61

[2] age 55-61 and age > 61

[3] normal and obese

[4] overweight and obese

Table D. Bout-length of median hours/week spent in moderate to vigorous activity stratified by sex and age.

		Uniaxial		Triaxial	
		Males	Females	Males	Females
Median hours (25th, 75th percentile) of MVPA/week					
A	≥ 1 min bouts	4.00 (2.43, 5.68)*	3.22 (1.92, 5.4)	5.76 (3.78, 8.12)*	5.02 (3.22, 7.21)
	≥ 5 min bouts	1.27 (0.53, 2.95)	0.99 (0.35, 2.45)	1.75 (0.83, 3.42)	1.38 (0.64, 2.98)
	≥ 10 min bouts	0.59 (0, 1.75)	0.35 (0, 1.36)	0.70 (0.17, 2.01)	0.52 (0, 1.76)
Median % (25th, 75th percentile) of MVPA/week spent in ≥ 5 and ≥ 10 minute bouts of total MVPA/week					
B	**≥ 5 min bouts**				
	Age, years				
	< 55	32 (20, 49)	39 (17, 55)	32 (21, 42)	32 (19, 46)
	55 - 61	30 (19, 55)	34 (17, 54)	29 (20, 50)	28 (17, 46)
	> 61	37 (15, 59)	34 (12, 54)	33 (15, 49)	32 (16, 51)
	≥ 10 min bouts				
	Age, years				
	< 55	13 (0, 33)	12 (0, 38)	14 (2, 25)	13 (4, 37)
	55 - 61	15 (0, 34)	17 (0, 31)	11 (4, 29)	12 (4, 28)
	> 61	17 (0, 37)	9 (0, 32)	16 (0, 30)	10 (0, 32)
% (n) reached WHO recommendation					
		16.1 (36)	12.0 (30)	18.3 (41)	15.9 (40)

*$p < 0.05$ (pairwise) Wilcoxon rank-sum test between (A) males and females, and (B) age categories stratified by sex.

Table E. Achieved bout-length applying uniaxial cut-offs.

% (N) achieved bout of MVPA	< 10 minutes[1] (N=168)	≥ 10 minutes[2] (N=241)	≥ 10 minutes + adherence to WHO[3] (N=66)
Sex			
Male	32.1 (72)	51.8 (116)	16.1 (36)
Female	38.2 (96)	49.8 (125)	12.0 (30)
Age, years (range: 48 - 68)			
< 55	32.9 (51)	52.3 (81)	14.8 (23)
55-61	31.5 (53)	52.4 (88)	16.1 (27)
> 61	42.1 (64)	47.4 (72)	10.5 (16)
Body mass index, kg/m^2 *			
Normal (< 25)	25.5 (35)	50.4 (69)	24.1 (33)
Overweight (≥ 25)	35.5 (72)	53.7 (109)	10.8 (22)
Obese (≥ 30)	45.2 (61)	46.7 (63)	8.1 (11)
Education*			
Low (< 10 years of school)	45.4 (99)	45.9 (100)	8.7 (19)
Medium (= 10 years of school)	32.6 (45)	48.6 (67)	18.8 (26)
High (> 10 years of school)	20.2 (24)	62.2 (74)	17.6 (21)
Hypertension*			
No	30.3 (95)	53.8 (169)	15.9 (50)
Yes	45.3 (73)	44.7 (72)	9.9 (16)
Diabetes			
No	34.5 (153)	51.5 (228)	14.0 (62)
Yes	46.9 (15)	40.6 (13)	12.5 (4)
Asthma			
No	34.1 (146)	51.4 (220)	14.5 (62)
Yes	46.8 (22)	44.7 (21)	8.5 (4)
COPD			
No	34.6 (150)	51.5 (223)	13.9 (60)
Yes	42.9 (18)	42.9 (18)	14.3 (6)
Difficulties in walking*			
Not at all/slight	33.7 (150)	52.1 (232)	14.2 (63)
Moderate/hard	60.7 (17)	32.1 (9)	7.1 (2)
Pain or physical complaints*			
Not at all/slight	31.5 (128)	53.2 (216)	15.3 (62)
Moderate/hard	58.0 (40)	36.2 (25)	5.8 (4)
Feeling anxious/depressed			
Not at all/slight	34.6 (153)	52.0 (230)	13.3 (59)
Moderate/strong	43.8 (14)	34.4 (11)	21.9 (7)

[1]subjects who did not achieve moderate to vigorous activity (MVPA) in bouts of at least 10 minutes. [2]subjects who achieved bouts of at least 10 minutes, but less than 2.5 hours per week. [3]subjects who met the WHO recommendation of 2.5 hours a week in bouts of at least 10 minutes. *$p < 0.05$ Chi-square test or Fisher's Exact Test (if cell counts < 5). COPD: Chronic obstructive pulmonary disease.

Table F. Count ratios (95% confidence intervals) of triaxial average minutes per day of moderate-to-vigorous physical activity (MVPA), sedentary or light activity estimated by negative binomial regression.

Outcome		**Sedentary**		**Light**		**MVPA**	
Variables \ Model		Basic[1]	Stepwise[1]	Basic[1]	Stepwise[1]	Basic	Stepwise
Sex	Female	-	-	-	-	-	-
	Male	**1.09 (1.05; 1.13)**	**1.09 (1.05; 1.13)**	**0.89 (0.85; 0.92)**	**0.89 (0.85; 0.92)**	**1.18 (1.06; 1.31)**	**1.18 (1.06; 1.31)**
Age	< 55	-	-	-	-	-	-
	55-61	0.96 (0.92; 1.00)	**0.95 (0.91; 0.99)**	1.05 (1.00; 1.10)	**1.05 (1.01; 1.10)**	1.01 (0.89; 1.15)	1.02 (0.90; 1.15)
	> 61	1.03 (0.98; 1.08)	1.04 (0.99; 1.08)	0.99 (0.94; 1.04)	0.99 (0.94; 1.04)	**0.77 (0.67; 0.87)**	**0.76 (0.67; 0.87)**
BMI	Normal	-	-	-	-	-	-
	Overweight	1.04 (0.99; 1.08)	**1.05 (1.00; 1.09)**	0.97 (0.93; 1.02)	0.96 (0.92; 1.01)	**0.88 (0.78; 1.00)**	**0.88 (0.77; 0.99)**
	Obese	**1.11 (1.05; 1.16)**	**1.12 (1.07; 1.18)**	**0.91 (0.86; 0.96)**	**0.90 (0.85; 0.95)**	**0.79 (0.69; 0.91)**	**0.78 (0.68; 0.90)**
Education	Low	-	-	-	-	-	-
	Medium	-	**1.07 (1.02; 1.11)**	-	**0.93 (0.89; 0.98)**	-	0.97 (0.86; 1.10)
	High	-	**1.12 (1.07; 1.17)**	-	**0.90 (0.86; 0.94)**	-	**0.85 (0.75; 0.97)**
Pain/physical complaints	Not at all/slight	-	-	-	-	-	-
	Moderate/hard	-	[x]	-	[x]	-	0.87 (0.75; 1.01)
Diabetes	No	-	-	-	-	-	[-]
	Yes	-	**1.10 (1.02; 1.18)** [stratified by sex: **1.18 (1.07; 1.30)** females; 0.99 (0.89; 1.11) males]	-	**0.90 (0.83; 0.97)** [stratified by sex: **0.81 (0.74; 0.89)** females; 1.02 (0.90; 1.16) males]	-	[x]

Significant associations ($p < 0.05$) are shown in bold. Basic model was adjusted for sex, age, and body mass index (BMI). Besides sex, age, and BMI considered variables in the stepwise selection model were: season, education, hypertension, diabetes, asthma, chronic obstructive pulmonary disease (COPD), difficulties with walking, pain or physical complaints, and anxiety/depression. Models with the lowest Akaike information criterion (AIC) are shown. [1]Model additionally adjusted for average recorded wear time/day. [x]Covariate did not remain in main model.

Table G. Achieved bout-length applying triaxial cut-offs.

% (N) achieved bout of MVPA	< 10 minutes[1] (N=116)	≥ 10 minutes[2] (N=278)	≥ 10 minutes + adherence to WHO[3] (N=81)
Sex			
Male	23.2 (52)	58.5 (131)	18.3 (41)
Female	25.5 (64)	58.6 (147)	15.9 (40)
Age, years (range: 48 - 68)			
< 55	23.9 (37)	58.1 (90)	18.1 (28)
55-61	19.6 (33)	61.3 (103)	19.0 (32)
> 61	30.3 (46)	55.9 (85)	13.8 (21)
Body mass index, kg/m^2 *			
Normal (< 25)	17.5 (24)	54.7 (75)	27.7 (38)
Overweight (≥ 25)	26.6 (54)	59.6 (121)	13.8 (28)
Obese (≥ 30)	28.1 (38)	60.7 (82)	11.1 (15)
Education*			
Low (< 10 years of school)	29.8 (65)	57.3 (125)	12.8 (28)
Medium (= 10 years of school)	24.6 (34)	53.6 (74)	21.7 (30)
High (> 10 years of school)	14.3 (17)	66.4 (79)	19.3 (23)
Hypertension,			
No	22.3 (70)	58.3 (183)	19.4 (61)
Yes	28.6 (46)	59.0 (95)	12.4 (20)
Diabetes,			
No	23.3 (103)	59.6 (264)	17.2 (76)
Yes	40.6 (13)	43.8 (14)	15.6 (5)
Asthma,			
No	23.4 (100)	59.1 (253)	17.5 (75)
Yes	34.0 (16)	53.2 (25)	12.8 (6)
COPD,			
No	23.6 (102)	59.4 (257)	17.1 (74)
Yes	33.3 (14)	50.0 (21)	16.7 (7)
Difficulties in walking*			
Not at all/slight	22.9 (102)	59.6 (265)	17.5 (78)
Moderate/hard	50.0 (14)	42.9 (12)	7.1 (2)
Pain or physical complaints*			
Not at all/slight	22.4 (91)	58.6 (238)	19.0 (77)
Moderate/hard	36.2 (25)	58.0 (40)	5.8 (4)
Feeling anxious/depressed			
Not at all/slight	24.2 (107)	59 (261)	16.7 (74)
Moderate/strong	25.0 (8)	53.1 (17)	21.9 (7)

[1]subjects who did not achieve moderate to vigorous activity (MVPA) in bouts of at least 10 minutes. [2]subjects who achieved bouts of at least 10 minutes, but less than 2.5 hours per week. [3]subjects who met the WHO recommendation of 2.5 hours a week in bouts of at least 10 minutes. *$p < 0.05$ Chi-square test or Fisher's Exact Test (if cell counts < 5). COPD: Chronic obstructive pulmonary disease.

6.4 Publication IV

Original title:

Association of physical activity with lung function in lung-healthy German adults: results from the KORA FF4 study

Authors:

Agnes Luzak, Stefan Karrasch, Barbara Thorand, Dennis Nowak, Rolf Holle, Annette Peters, and Holger Schulz

Journal:

BMC Pulmonary Medicine

DOI:

10.1186/s12890-017-0562-8

Year:

2017

Luzak et al. BMC Pulmonary Medicine (2017) 17:215
DOI 10.1186/s12890-017-0562-8

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Association of physical activity with lung function in lung-healthy German adults: results from the KORA FF4 study

Agnes Luzak[1], Stefan Karrasch[1,2,4], Barbara Thorand[3], Dennis Nowak[2,4], Rolf Holle[5], Annette Peters[3] and Holger Schulz[1,4*]

Abstract

Background: In lung disease, physical activity (PA) yields beneficial health effects, but its association with the function of healthy lungs has rarely been studied. We investigated the association of accelerometer-based PA with spirometric indices, maximal inspiratory mouth pressure (PI_{max}) and lung diffusion capacity in lung-healthy adults.

Methods: In total, 341 apparently lung-healthy participants from the population-based KORA (Cooperative Health Research in the Region of Augsburg) FF4 cohort study (45% male, aged 48-68 years, 47% never smokers) completed lung function testing and wore ActiGraph accelerometers over a one week period at the hip. In adjusted regression analyses, moderate to vigorous PA (MVPA) was characterized as: sex-specific activity quartiles, achieving ≥ 10 consecutive minutes (yes vs. no), and meeting the WHO PA recommendations (yes vs. no).

Results: Positive associations of MVPA-quartiles with forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and corresponding Global Lung Function Initiative z-scores were found. Subjects in the most active quartile (> 47 or > 50 min/day for females and males, respectively) had 142 ml [95% CI: 23, 260] higher FEV_1 and 155 ml [95% CI: 10, 301] higher FVC than those in the least active quartile (< 17 or < 21 min/day for females and males, respectively); however these associations were stronger among ex−/current smokers. Achieving at least once 10 consecutive minutes of MVPA was only associated with higher PI_{max} [β-estimate: 0.57 kPa; 95% CI: 0.04, 1.10], remaining significant among never smokers. No associations were found with diffusion capacity or for reaching the WHO-recommended 150 min of MVPA/week in 10-min bouts.

Conclusions: Although the effects were small, active subjects showed higher spirometric results. The observed associations were more pronounced among ever smokers suggesting a higher benefit of PA for subjects being at a higher risk for chronic lung diseases.

Keywords: Lung function, Spirometry, Activity behavior, Accelerometer

Background

Physical activity (PA) reduces the risk of premature mortality and chronic diseases like cardiovascular disease or diabetes mellitus [1]. Benefits of activity apply also to persons with chronic lung diseases such as asthma or chronic obstructive pulmonary disease (COPD), who are therefore encouraged to engage in regular PA [2, 3]. Studies have shown that higher PA was associated with a lower risk of hospital admissions and all-cause mortality in COPD patients [3, 4]. Furthermore, the diffusion capacity of the lung for carbon monoxide was shown to be a predictor of a decline in 6-min-walking distance in COPD patients [5]. Moreover, exercise training in COPD patients was associated with improved ventilatory muscle function and showed positive effects on the forced vital capacity (FVC) [6, 7]. Due to the positive health effects of PA in patients with chronic lung

* Correspondence: schulz@helmholtz-muenchen.de
[1]Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany
[4]Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Max-Lebsche-Platz 31, 81377 Munich, Germany
Full list of author information is available at the end of the article

diseases, PA has been incorporated into pulmonary rehabilitation programs [8].

In population-based studies, PA was shown to be associated with slower age-related decline of the forced expiratory volume in 1 s (FEV_1) in adults [9, 10]. Results from a longitudinal study among middle-aged men showed that those with higher levels of PA experienced slower lung function decline over 25 years [11]. However, all these studies assessed PA by questionnaires, which was found to correlate only low-to-moderately with activity objectively assessed by motion sensors in adults [12, 13].

Only a few studies have investigated the association of accelerometer-based PA with lung function. Moreover, the association between PA and lung function in lung-healthy persons is unclear. In lung-healthy adolescents, no associations were found between accelerometer-based PA and a broad range of spirometric parameters [14]. In adults, results of a study among 62 smokers showed that lung function between inactive participants, defined as those who engaged in less than 150 min/week of moderate to vigorous PA (MVPA), and active ones did not differ [15]. Thus, the evidence is inconclusive.

Furthermore, studies among athletes suggest that endurance exercise is associated with higher FVC and improved lung diffusion capacity [16, 17]. A study among 25 healthy men showed an improvement of maximal inspiratory pressure after 5 weeks of inspiratory muscle training [18], as observed in COPD patients after exercise training [6], whereas the increase in respiratory muscle endurance of marathon runners was described as a consequence of differences in breathing pattern developed during running rather than respiratory muscle strength [19].

Considering the limited evidence on the association between PA and lung function in lung-healthy populations, our aim was to investigate the association of accelerometer-based PA with lung function in apparently lung-healthy German adults from a population-based sample. Therefore, we addressed different aspects of lung function i.e. lung volume, airflow limitation, pulmonary gas exchange (TLCO/VA) and inspiratory muscle strength (PI_{max}).

Methods

Study population

The present analysis was based on a follow-up study of the KORA S4 (KORA: Cooperative Health Research in the Region of Augsburg) cohort comprising 4261 adults (51.0% female) examined in 1999 – 2001. A description of the primary study design has been published previously [20].

The selection of the study population is displayed in detail in Fig. 1. In the KORA FF4 follow-up study 2279 participants (51.6% female) aged 38-88 years were examined between June 2013 and September 2014. Covering only the age range 48-68 years, 1043 of these participants were selected for the "Lung health & physical activity" study, which comprised spirometry, assessment of

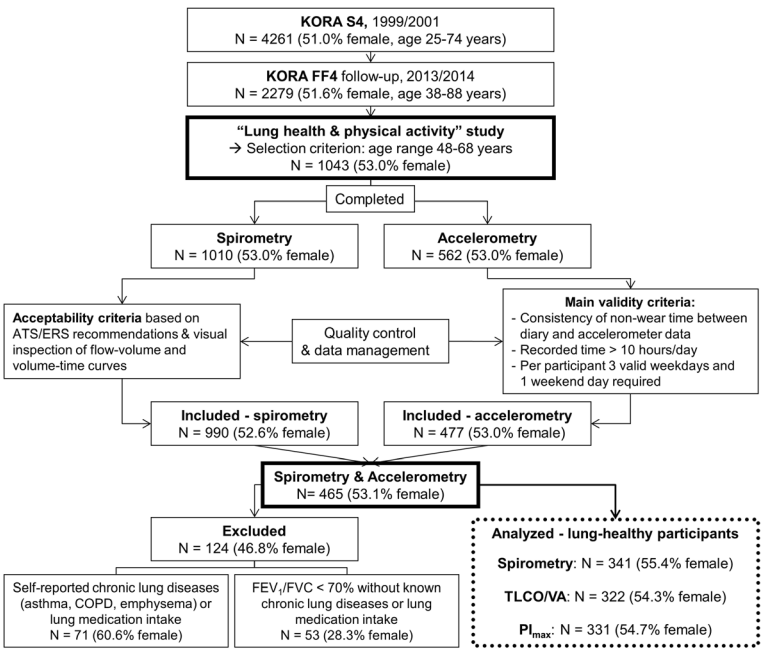


Fig. 1 Selection of participants. KORA: Cooperative Health Research in the Region of Augsburg. ATS: American Thoracic Society. ERS: European Respiratory Society. COPD: chronic obstructive pulmonary disease. FEV_1: forced expiratory volume in 1 s. FVC: forced vital capacity. TLCO/VA: transfer factor of the lung for carbon monoxide adjusted for hemoglobin and divided by alveolar volume. PI_{max}: maximum inspiratory mouth pressure

inspiratory muscle strength (PI_{max}), measures of pulmonary gas exchange, and accelerometer-based assessment of habitual PA over one week. Information on sociodemographic variables, and current medication intake seven days before examination was obtained from standardized interviews and questionnaires. For the assessment of common diseases such as stroke or myocardial infarction, subjects were asked for each disease separately if a doctor has ever diagnosed this particular disease. Further, information on mobility and pain/discomfort was obtained from the EuroQol five dimensions questionnaire (EQ-5D 5 L) [21].

Of 1010 subjects who participated in spirometry, spirometric data of 990 participants were considered as valid based on international recommendations [22]. In accelerometry, two males with values greater than the mean plus seven times the standard deviation for weight and MVPA, respectively, were excluded during data management after quality control, resulting in 477 subjects with valid accelerometric data out of 562 who initially participated. For the selection of lung-healthy subjects, 465 subjects who had both, valid spirometry and accelerometry were considered. Subjects who reported a doctor's diagnosis of asthma, emphysema, chronic bronchitis or COPD, or used pulmonary medication including antileukotrienes, inhaled sympathomimetics, anticholinergics, and/or steroids were excluded from this analysis ($N = 71$). Furthermore, subjects with $FEV_1/FVC < 0.7$ (indication of airflow limitation) were excluded ($N = 53$) [23]. Finally, 341 apparently lung-healthy subjects were available for the present analysis. Among these, PI_{max} results were available for 331 subjects (54.7% female) and results for the transfer factor of the lung for carbon monoxide divided by alveolar volume (TLCO/VA) for 322 subjects (54.3% female).

Physical activity assessment

A detailed description of the procedure, data handling, quality control and inclusion criteria has been reported previously [24]. In brief, participants were asked to wear an ActiGraph GT3X accelerometer (Pensacola, Florida) over a one week period at the hip from getting up until going to bed time and to complete a daily diary which included the time of getting up, going to sleep, and reasons for and duration of non-wear time. Non-wear time according to the accelerometer data was assessed based on the algorithm derived from the National Health and Nutrition Examination Survey [25]. Days were considered as not valid, if the difference between the non-wear time algorithm applied to the accelerometer data and the diary non-wear time was greater than 60 min (if the non-wear time was reported in the diary) or greater than 120 min (if the accelerometer indicated a non-wear time). Subjects were excluded in case of no reported non-wear time over the whole 7 day reporting period although the accelerometer should have been removed during water activities e.g. showering. Further exclusion criteria for single days were missing information on time spent awake, day length < 10 h/day, non-wear time during sport activities lasting > 2 h, or incorrect handling of the accelerometer e.g. hand instead of hip. Further details of all exclusion criteria have been previously published [24]. Subjects were only included in the analysis if they had at least 3 valid weekdays and 1 valid weekend day. 89% of the subjects included in our analysis recorded at least 6 days, 9% had 5 days and 2% provided 4 days only. Measured accelerations of the vertical axis were stored at 1 Hz and converted into 1-min epochs classifying a moderate to vigorous PA (MVPA) level as ≥ 1952 counts per minute, as proposed by Freedson et al. [26]. Non-wear time during sport was imputed as described here [14, 24].

Since the relationship between MVPA and lung function measures adjusted for sex, age, and height was non-linear, MVPA was divided into sex-specific quartiles. In addition, two further binary PA variables were built based on the World Health Organization (WHO) recommendation stating that adults should accumulate at least 150 min of MVPA/week in bouts of at least 10 min [27].

PA was quantified as exposure in three ways: (1) sex-specific MVPA quartiles; (2) achieving at least one 10-min bout of MVPA over the whole measurement period (yes vs. no); (3) reaching the WHO threshold of 150 min MVPA/week in at least 10-min bouts (yes vs. no). Cut-offs for sex-specific MVPA quartiles were set as follows: cut-off for males: 1st ≤ 21.6 min/day, 2nd > 21.6-35.2 min/day, 3rd > 35.2-49.9 min/day, 4th > 49.9 min/day; and cut-offs for females: 1st ≤ 17.2 min/day, 2nd > 17.2-28.3 min/day, 3rd > 28.3-46.7 min/day, 4th > 46.7 min/day, respectively.

Lung function assessment

Lung function assessment was performed in line with the American Thoracic Society (ATS) and European Respiratory Society (ERS) statements [22, 28, 29].

Flow-volume curves were obtained using a pneumotachograph-type spirometer (MasterScope, Jaeger, Hoechberg, Germany). Subjects were guided to perform at least 3 and up to 8 spirometric maneuvers per test in order to obtain acceptable and reproducible values. During the maneuvers both flow-volume and volume-time curves were monitored online by a trained examiner. After each test, the curves were visually inspected, artifacts e.g. coughing were excluded and the results were selected and evaluated according to the ATS/ERS recommendations [22], including a good start with extrapolated volume < 0.5% of FVC or 0.15 l, an exhalation of ≥ 6 s or a plateau in volume-time curve. Spirometric parameters included FEV_1, FVC, FEV_1/FVC, and forced expiratory flow between 25% and

75% of exhaled FVC (FEF_{25-75}). Standardized z-scores were calculated using reference equations for spirometry from the Global Lung Function Initiative (GLI) [30]. TLCO was determined using the single-breath technique. Subjects were asked to perform a maximum of 5 trials in order to achieve acceptable and reproducible values with an inspired volume > 85% of the largest vital capacity in <4 s, and an effective breath hold time within 8 to 12 s according to ATS/ERS recommendations [28]. TLCO results were adjusted for hemoglobin obtained from blood samples collected on the day of the physical examination in the study center [28]. For determination of PI_{max}, subjects were instructed to exhale to residual volume followed by a maximal voluntary inspiration against an obstructed mouth piece with a small leak to prevent glottic closure using a flanged mouth piece [29]. The highest peak inspiratory pressure achieved during a minimum of 3 and a maximum of 15 maneuvers was used for analysis (MasterScreen PFT, Jaeger, Hoechberg, Germany).

Statistical analyses

Sex-specific differences were assessed using Pearson's Chi-squared test (categorical variables), the t-test (normal distribution), and Wilcoxon rank-sum test (skewed distribution). Mean and corresponding standard deviation or percentages (%, N) were used to describe subject characteristics and categorized PA. Due to a non-normal distribution, median and 1st and 3rd quartiles were reported for continuous MVPA.

Adjusted linear regression models were applied to analyze associations between PA and lung function parameters. Since spirometric parameters (FEV_1, FVC, and FEF_{25-75}) were correlated ($r = 0.61$ to 0.98), the results of regression analyses were not adjusted for multiple testing. For each spirometric parameter, the mean plus/minus 4 times the standard deviation was calculated for each sex to determine sex-specific outliers. According to this definition one subject was excluded in the analyses using z-scores for FEV_1 and FVC and another in FEF_{25-75} models. The main model was adjusted for sex, age, height, weight, smoking status categorized as *never*, *ex-*, or *current* smokers, education level categorized as low (<10 years of school, i. e. "Hauptschule" in Germany), middle (10 years of school, i.e. "Realschule") and high (>10 years of school, i.e. "Gymnasium"), and a doctor's diagnosis of hay fever (ever). Regression models for standardized GLI z-scores [30] that are already adjusted for ethnicity, sex, age, and height, were adjusted only for additional variables. Covariates remained in the model independent of statistical significance. As the mean body mass index (BMI) was 27.7 kg/m^2 we included a sensitivity analysis, replacing weight with BMI in the main analysis.

To assess if the association might be modified through other covariates potentially associated with lung function, sensitivity analyses were done. Since smoking behavior has an impact on lung function and might modify potential associations, we calculated the main regression model with stratification into never and ex–/current smokers. In further analyses, the main model was additionally adjusted for moderate to extreme problems in walking about and/or pain or discomfort, season categorized as winter (start of measurement: December to February), spring (March to May), summer (June to August), and autumn (September to November), or for self-reported acute respiratory infections in the last three weeks prior to lung function testing. All participants were Caucasian therefore ethnicity was not included as a covariate. Interaction effects between MVPA and sex were tested in the main model. In case of significant interaction effects ($p < 0.05$), stratified results were reported additionally.

To eliminate a possible impact of myocardial infarction and/or stroke ($N = 15$), subjects with a history of these events were excluded from the main model as a further sensitivity analysis.

The statistical program R, version 3.3.3 [31], was used for all analyses and p-values below 0.05 were considered statistically significant.

Results

The study population consisted of 341 (45% male) apparently lung-healthy subjects (i.e. no chronic lung diseases or pulmonary medication intake, and $FEV_1/FVC \geq 0.7$) with a mean age of 57 years (Table 1). The prevalence of current smoking was 14%, while 47% of the participants reported to be never smokers. Despite a lower prevalence of females among all ex–/current smokers than among never smokers (50.0% and 61.6%, respectively), 70.2% of current smokers were female. BMI was comparable between never and ex–/current smokers. Mean z-scores were lower among ex–/current smokers compared to never smokers, being statistically significant for z-score FEF_{25-75}. Nevertheless, smoking status did not affect PA (Additional file 1: Table S1). Included subjects were slightly younger (mean age of 57 years vs. 58 years, respectively) and more often never smokers (46.6% vs. 37.8%, respectively) compared to all other subjects performing spirometry (Additional file 1: Table S2).

Overall, participants spent a median of 31 min/day in MVPA with a range from 1 to 111 mean min/day, being lower for females than for males (median 28 vs. 35 min, respectively). In total, 66% of subjects achieved at least one 10-min bout of MVPA, and 15% achieved the recommended 150 min of MVPA/week in at least 10-min bouts (Table 1).

Table 1 Population characteristics, lung function and physical activity measurements

	Males ($n = 152$)	Females ($n = 189$)
Age		
mean years (SD)	57.1 (5.8)	57.5 (5.3)
Height *		
mean cm (SD)	177.0 (6.0)	162.1 (6.0)
Weight *		
mean kg (SD)	88.8 (13.5)	71.5 (14.4)
BMI*		
n normal (BMI < 25) (%)	27 (17.8)	79 (41.8)
n overweight (≥ 25 BMI <30) (%)	83 (54.6)	61 (32.3)
n obese (BMI ≥ 30) (%)	42 (27.6)	49 (25.9)
Smoking status*		
n never smokers (%)	61 (40.1)	98 (51.9)
n ex-smokers (%)	77 (50.7)	58 (30.7)
n current smokers (%)	14 (9.2)	33 (17.5)
Education*		
n low (< 10 years of school) (%)	68 (44.7)	84 (44.4)
n medium (10 years of school) (%)	34 (22.4)	66 (34.9)
n high (> 10 years of school) (%)	50 (32.9)	39 (20.6)
Hay fever		
n yes (%)	22 (14.5)	43 (22.8)
Problems in walking about, and/or pain or discomfort		
n not at all/slight (%)	135 (88.8)	154 (81.9)
n moderate/extreme (%)	17 (11.2)	34 (18.1)
Lung function		
FEV_1*		
mean l (SD)	3.76 (0.57)	2.66 (0.42)
FVC*		
mean l (SD)	4.88 (0.71)	3.39 (0.56)
FEV_1/FVC*		
mean % (SD)	77.08 (3.93)	78.5 (4.14)
FEF_{25-75}*		
mean l/s (SD)	3.16 (0.91)	2.37 (0.63)
Z-score FEV_1		
mean (SD)	0.25 (0.86)	0.32 (0.91)
Z-score FVC		
mean (SD)	0.29 (0.80)	0.35 (0.87)
Z-score FEV_1/FVC		
mean (SD)	−0.12 (0.58)	−0.15 (0.63)
Z-score FEF_{25-75}		
mean (SD)	−0.01 (0.78)	−0.01 (0.80)
TLCO, hemoglobin adjusted*		
mean mmol/min/kPa (SD)	9.88 (1.50)	6.90 (1.07)
TLCO/VA*		
mean mmol/min/kPa/l (SD)	1.45 (0.16)	1.38 (0.18)

Table 1 Population characteristics, lung function and physical activity measurements *(Continued)*

	Males ($n = 152$)	Females ($n = 189$)
PI_{max}*		
mean kPa (SD)	9.77 (2.53)	6.67 (2.12)
Physical activity		
MVPA*		
median of mean min/day (1st; 3rd quartile)	35.2 (21.6; 49.9)	28.3 (17.2; 46.7)
10-min bout of MVPA achieved		
n yes (%)	104 (68.4)	120 (63.5)
WHO threshold achieved		
n yes (%)	24 (15.8)	26 (13.8)

SD standard deviation, *BMI* body mass index, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, FEF_{25-75} forced expiratory flow between 25% and 75% of FVC, *TLCO/VA* transfer factor of the lung for carbon monoxide adjusted for hemoglobin and divided by alveolar volume, PI_{max} maximum inspiratory mouth pressure, *MVPA* moderate to vigorous physical activity
*$p < 0.05$ (males vs. females)

Physical activity and spirometric parameters

In the total population, being in the most active MVPA quartile was associated with higher FEV_1, FVC, FEV_1 z-score and FVC z-score (Table 2, Additional file 1: Table S3). FEV_1 was 142 ml higher in the most active subjects, i.e. females that engaged > 47 min/day and males that engaged > 50 min/day in MVPA, than in the least active quartile, i.e. < 17 min/day for females or < 21 min/day for males. Stratified analyses revealed that these associations remained in ex–/current smokers, but not in never smokers (Table 2).

The results for FVC were comparable to those observed for FEV_1, except for an interaction effect between the third MVPA quartile and sex that was present for FVC only. After stratification an association was found for females only (Additional file 1: Table S4). Sensitivity analyses, e.g. further adjustment for walking difficulties and/or discomfort, and exclusion of subjects with stroke and/or myocardial infarction did not substantially change our results. Adjusting for BMI instead of weight led to the very similar results (Additional file 1: Table S5).

When MVPA was quantified as achieving at least one 10-min bout, an association with lung function was found in sex-stratified analyses for FEV_1, FVC, z-scores for FEV_1 and FVC in females only (Additional file 1: Tables S4 and S6). Reaching the recommended 150 min of MVPA/week in at least 10-min bouts was negatively associated with FEV_1, FVC,

Table 2 Association of physical activity with spirometric parameters

	MVPA	Total population ($n = 341$)		Never smokers ($n = 159$)		Ex- and current smokers ($n = 182$)	
	Quartile[a]	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
FEV_1, ml	2	72 (−44, 188)	0.22	44 (−129, 218)	0.62	81 (−78, 240)	0.32
	3	**124 (7, 242)**	**0.04**	167 (−7, 341)	0.06	60 (−104, 224)	0.47
	4	**142 (23, 260)**	**0.02**	84 (−89, 257)	0.34	**195 (29, 360)**	**0.02**
FVC, ml	2	91 (−52, 235)	0.21	48 (−160, 256)	0.65	114 (−87, 316)	0.27
	3	107 (−38, 251)	0.15	190 (−18, 398)	0.08	11 (−196, 219)	0.92
	4	**155 (10, 301)**	**0.04**	75 (−132, 282)	0.48	**227 (18, 437)**	**0.04**
FEV_1/FVC, %	2	0.01 (−1.18, 1.21)	0.98	−0.03 (−1.86, 1.80)	0.97	−0.10 (−1.72, 1.51)	0.90
	3	0.87 (−0.34, 2.07)	0.16	0.33 (−1.50, 2.17)	0.72	1.07 (−0.59, 2.74)	0.21
	4	0.64 (−0.57, 1.85)	0.30	0.70 (−1.12, 2.52)	0.45	0.56 (−1.12, 2.24)	0.51
FEF_{25-75}, ml/s	2	100 (−120, 319)	0.37	61 (−266, 388)	0.71	101 (−201, 403)	0.51
	3	**277 (56, 499)**	**0.01**	239 (−89, 566)	0.16	246 (−65, 558)	0.12
	4	161 (−63, 384)	0.16	106 (−220, 433)	0.52	213 (−102, 527)	0.19

MVPA moderate to vigorous physical activity, *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
[a]Least active MVPA quartile (1st quartile) was used as reference. All models were adjusted for sex, age, height, weight, education level, a doctor's diagnosis of hay fever and depending on the population analyzed also by smoking status (never, ex- or current)
Statistically significant associations ($p < 0.05$) are shown in bold

and z-scores for FEV_1 and FVC in males only (Additional file 1: Tables S4 and S7).

Physical activity and inspiratory muscle strength

Subjects who engaged in at least one 10-min bout of MVPA had an estimated increase of PI_{max} by 0.6 kPA (Table 3). However, in analyses stratified by smoking status, this association was significant only in never smokers (Additional file 1: Table S8).

Physical activity and pulmonary gas exchange

PA was not associated with TLCO/VA in any analysis, except for a negative association found with the third MVPA quartile among never smokers (Table 3, Additional file 1: Table S8).

Discussion

The present analyses revealed weak positive associations between the most active subjects and volumetric indices in adults without lung function limitation. These associations were primarily observed among ex−/current smokers, but not in never smokers, suggesting that the effect might be driven by smoking behaviour. While PA showed no association with TLCO/VA, PI_{max} was higher in subjects who engaged in at least one 10-min bout of MVPA during the recording period, compared to those who did not.

Compared to current recommendations PA was rather low in our population-based cohort. Median daily MVPA was 31 min, and only 15% of subjects met the WHO PA recommendation. This finding, however, is comparable to results obtained through the questionnaire-based German Health Interview and Examination Survey for Adults where 18% of 50-69 year old participants achieved the WHO activity threshold [32].

Still, weak associations with lung function were present in our analyses.

An association between PI_{max} and the achievement of at least one 10-min bout of MVPA was found in our population, remaining significant in never smokers only. In COPD, twitch mouth pressure has previously been shown to decrease with increasing disease severity and PI_{max} could be improved by exercise training [6, 33]. A study among marathon athletes compared to sedentary controls reported a higher respiratory muscle endurance in the athletes - probably as a result of breath technique, but a similar PI_{max} [19].

In our population, those who reached at least one 10-min bout spent in MVPA showed a higher PI_{max}, while reaching the WHO PA recommendation showed no increase. It might be that the threshold of engaging for at least 10 consecutive minutes in habitual MVPA, i.e. separating subjects with short bouts of activity and those with at least sporadic activity for 10 min, might represent a plateau. However, this result should be interpreted with caution due to the weak associations found and the potentially minor clinical relevance.

While TLCO has previously been shown to be a clinically relevant predictor of exercise capacity determined by 6-min-walking distance test in COPD patients [5], PA was not found to be a predictor of TLCO/VA in our apparently lung-healthy population. The lack of findings might be due to the possibly small effects that could not be detected in habitual PA of middle-aged adults without lung function limitation.

Our results show a weak, but positive association of PA and volumetric lung function indices, primarily seen among ex−/current smokers. Compared to the least active subjects, subjects engaging on average more than about 48 min/day in MVPA had a 142 ml higher FEV_1. Considering an annual decline of around 25 ml of FEV_1

Table 3 Association of physical activity with pulmonary gas exchange and inspiratory muscle strength

	Pulmonary gas exchange (TLCO/VA), 10^{-1} mmol/min/kPa/l		Maximum inspiratory mouth pressure (PI_{max}), kPa	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value
MVPA quartiles,				
1st – least active (reference)	–	–	–	–
2nd	0.01 (−0.47, 0.49)	0.98	0.39 (−0.32, 1.10)	0.28
3rd	−0.30 (−0.80, 0.19)	0.23	0.23 (−0.48, 0.94)	0.53
4th – most active	0.25 (−0.25, 0.75)	0.33	0.05 (−0.68, 0.78)	0.90
10-min bout of MVPA achieved,				
yes vs. no	−0.03 (−0.39, 0.34)	0.88	**0.57 (0.04, 1.10)**	**0.04**
WHO threshold achieved,				
yes vs. no	0.36 (−0.13, 0.84)	0.15	0.00 (−0.71, 0.71)	1.00

The models were adjusted for sex, age, height, weight, smoking status categorized as *never*, *ex-*, or *current* smokers, education level, and a doctor's diagnosis of hay fever

TLCO/VA transfer factor of the lung for carbon monoxide adjusted for hemoglobin and divided by alveolar volume, *PI_{max}* maximum inspiratory mouth pressure, *CI* confidence interval, *MVPA* moderate to vigorous physical activity

in adults [34, 35], our results would correspond to an age-related decline of about 5 years. No causal relationships or long-term effects can be drawn from our cross-sectional analysis, but our results are in line with those from a longitudinal study observing that current smokers with moderate and high PA had a decreased decline in FEV_1 and FVC compared with smokers with low PA [36]; and as in our study, this association was not observed in never smokers. A study including only smokers did not find an association between the achievement of at least 150 min/week of MVPA and spirometric parameters [15]. However, observed differences may be related to diverse designs, population characteristics and definitions of being active [15, 36]. PA was suggested to promote an anti-inflammatory status and to potentially protect against chronic diseases associated with low-grade systemic inflammation [37]. Smokers are at a higher risk for COPD and other smoking-related diseases typically experiencing a low-grade systemic inflammation [38]. In our analysis, the positive associations between being active and volumetric indices were more pronounced among ex–/current smokers, suggesting a higher benefit of PA for subjects being at a higher risk for chronic lung diseases.

Strength and limitations

A major strength of this study is the investigation of a range of standardized lung function parameters obtained by spirometry, as well as less often investigated measures of gas exchange and respiratory muscle strength in apparently lung-healthy adults. We objectively assessed PA by accelerometry, which is rare, as most available studies assessed PA by questionnaires [9–11, 36]. Evidence for the association between PA and lung function in the general population without chronic lung diseases is likewise rare.

Due to the cross-sectional design of our analysis, it is not possible to draw conclusions about long-term effects or causal relations. Although associations were found, these results should be interpreted with caution due to the small effects seen with partly wide confidence intervals. Further, the present results are limited to the pre-selected lung-healthy study population, comprising 48-68 year old residents in the region of Augsburg in southern Germany. Information on chronic lung diseases was assessed via self-report and was not individually verified by a physician.

Conclusions

Objective measurements of physical activity showed a weak, but positive association with slightly higher volumetric lung function indices in lung-healthy adults from southern Germany. This association was mainly observed among ex–/current smokers. Further, engaging in MVPA for at least 10 consecutive minutes was associated with higher PI_{max}, remaining significant in never smokers only. No associations were found for TLCO/VA. Although the effects were small, our results suggest a positive association of PA with lung function of lung-healthy subjects from a population-based cohort.

Additional file

Additional file 1: Results of Tables S1 to S8. (PDF 521 kb)

Abbreviations

BMI: Body mass index; CI: Confidence interval; FEF_{25-75}: Forced expiratory flow between 25% and 75% of FVC; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; GLI: Global Lung Function Initiative; MVPA: Moderate to vigorous physical activity; PA: Physical activity; PI_{max}: Maximum inspiratory mouth pressure; SD: Standard deviation; TLCO/VA: Transfer factor of the lung for carbon monoxide adjusted for hemoglobin and divided by alveolar volume; WHO: World Health Organization

Acknowledgements

The authors express appreciation to all attendees for their active participation in the KORA study. The authors thank the field staff in Augsburg conducting the KORA studies.

Funding

The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. This work was further supported by the Comprehensive Pneumology Center Munich (CPC-M) as member of the German Center for Lung Research and by the Competence Network Asthma and COPD (ASCONET), network COSYCONET (subproject 2, BMBF FKZ 01GI0882) funded by the German Federal Ministry of Education and Research (BMBF).

Availability of data and materials

The authors confirm that, 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. Applications for access to the data sets can be found at the following link: https://www.helmholtz-muenchen.de/en/kora/for-scientists/cooperation-with-kora/index.html. 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.

Authors' contributions

AL, DN and HS were involved in the conception and design of the study. SK, BT, RH, AP and HS contributed with data acquisition and data coding and AL with statistical analyses. AL, DN and HS contributed to the interpretation of the findings. AL drafted the manuscript and all authors revised it critically for important intellectual content and approved the final version.

Ethics approval and consent to participate

The study was approved by the responsible ethics committee of the Bavarian Medical Association. The investigations were carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

[1]Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany. [2]Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Munich (LMU), Ziemssenstr. 1, 80336 Munich, Germany. [3]Institute of Epidemiology II, Helmholtz Zentrum München - German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany. [4]Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Max-Lebsche-Platz 31, 81377 Munich, Germany. [5]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München - German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany.

Received: 13 March 2017 Accepted: 15 December 2017
Published online: 28 December 2017

References

1. Warburton DER, Charlesworth S, Ivey A, Nettlefold L, Bredin SSD. A systematic review of the evidence for Canada's physical activity guidelines for adults. Int J Behav Nutr Phys Act. 2010;7:39.
2. Carson KV, Chandratilleke MG, Picot J, Brinn MP, Esterman AJ, Smith BJ. Physical training for asthma. Cochrane Database Syst Rev. 2013(9):Cd001116. DOI:10.1002/14651858.CD001116.pub4.
3. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax. 2006;61(9):772–8.
4. Waschki B, Kirsten A, Holz O, Muller KC, Meyer T, Watz H, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. Chest. 2011;140(2):331–42.
5. Diaz AA, Pinto-Plata V, Hernandez C, Pena J, Ramos C, Diaz JC, et al. Emphysema and DLCO predict a clinically important difference for 6MWD decline in COPD. Respir Med. 2015;109(7):882–9.
6. Cortopassi F, Castro AA, Porto EF, Colucci M, Fonseca G, Torre-Bouscoulet L, et al. Comprehensive exercise training improves ventilatory muscle function and reduces dyspnea perception in patients with COPD. Monaldi Arch Chest Dis. 2009;71(3):106–12.
7. Strasser B, Siebert U, Schobersberger W. Effects of resistance training on respiratory function in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Sleep Breath. 2013;17(1):217–26.
8. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest. 2007;131(5 Suppl):4S–42S.
9. Nystad W, Samuelsen SO, Nafstad P, Langhammer A. Association between level of physical activity and lung function among Norwegian men and women: the HUNT study. Int J Tuberc Lung Dis. 2006;10(12):1399–405.
10. Jakes RW, Day NE, Patel B, Khaw K-T, Oakes S, Luben R, et al. Physical inactivity is associated with lower forced expiratory volume in 1 second: European prospective investigation into cancer-Norfolk prospective population study. Am J Epidemiol. 2002;156(2):139–47.
11. Pelkonen M, Notkola I-L, Lakka T, Tukiainen HO, Kivinen P, Nissinen A. Delaying decline in pulmonary function with physical activity. Am J Respir Crit Care Med. 2003;168(4):494–9.
12. Prince SA, Adamo KB, Hamel ME, Hardt J, Gorber SC, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act. 2008;5:56.
13. Skender S, Ose J, Chang-Claude J, Paskow M, Bruhmann B, Siegel EM, et al. Accelerometry and physical activity questionnaires - a systematic review. BMC Public Health. 2016;16:515.
14. Smith MP, von Berg A, Berdel D, Bauer CP, Hoffmann B, Koletzko S, et al. Physical activity is not associated with spirometric indices in lung-healthy German youth. Eur Respir J. 2016;48(2):428–40.
15. Barboza ML, Barbosa AC, Spina GD, Sperandio EF, Arantes RL, Gagliardi AR, et al. Association between physical activity in daily life and pulmonary function in adult smokers. J Bras Pneumol. 2016;42(2):130–5.
16. Lazovic B, Mazic S, Suzic-Lazic J, Djelic M, Djordjevic-Saranovic S, Durmic T, et al. Respiratory adaptations in different types of sport. Eur Rev Med Pharmacol Sci. 2015;19(12):2269–74.
17. Degens H, Rittweger J, Parviainen T, Timonen KL, Suominen H, Heinonen A, et al. Diffusion capacity of the lung in young and old endurance athletes. Int J Sports Med. 2013;34(12):1051–7.
18. Ramsook AH, Molgat-Seon Y, Schaeffer MR, Wilkie SS, Camp PG, Reid WD, et al. Effects of inspiratory muscle training on respiratory muscle electromyography and dyspnea during exercise in healthy men. J Appl Physiol (1985). 2017;122(5):1267-75.
19. Eastwood PR, Hillman DR, Finucane KE. Inspiratory muscle performance in endurance athletes and sedentary subjects. Respirology. 2001;6(2):95–104.
20. Holle R, Happich M, Lowel H, Wichmann HE. KORA–a research platform for population based health research. Gesundheitsw. 2005;67(Suppl 1):S19–25.
21. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. Ann Med. 2001;33(5):337–43.
22. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–38.
23. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. Am J Respir Crit Care Med. 2001;163(5):1256–76.
24. Luzak A, Heier M, Thorand B, Laxy M, Nowak D, Peters A, et al. Physical activity levels, duration pattern and adherence to WHO recommendations in German adults. PLoS One. 2017;12(2):e0172503.
25. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. Med Sci Sports Exerc. 2011;43(2):357–64.
26. Freedson PS, Melanson E, Sirard J. Calibration of the computer science and applications. Inc accelerometer Med Sci Sports Exerc. 1998;30(5):777–81.
27. World Health Organization. Global recommendations on physical activity for health. Geneva: World Health Organization; 2010. http://www.who.int/dietphysicalactivity/factsheet_recommendations/en/. Accessed 13 Oct 2016
28. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26(4):720–35.
29. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518-624.
30. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324–43.
31. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017. URL https://www.R-project.org
32. Krug S, Jordan S, Mensink GBM, Müters S, Finger JD, Lampert T. English version of "Körperliche Aktivität. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1)" Bundesgesundheitsblatt. 2013;56:765–71.
33. Ju C, Liu W, Chen RC. Twitch mouth pressure and disease severity in subjects with COPD. Respir Care. 2014;59(7):1062–70.
34. Abramson MJ, Kaushik S, Benke GP, Borg BM, Smith CL, Dharmage SC, et al. Symptoms and lung function decline in a middle-aged cohort of males and females in Australia. Int J Chron Obstruct Pulmon Dis. 2016;11:1097–103.
35. Tang W, Kowgier M, Loth DW, Soler Artigas M, Joubert BR, Hodge E, et al. Large-scale genome-wide association studies and meta-analyses of longitudinal change in adult lung function. PLoS One. 2014;9(7):e100776.
36. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. Am J Respir Crit Care Med. 2007;175(5):458–63.
37. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol (1985). 2005;98(4):1154–62.
38. National Center for Chronic Disease P, Health Promotion Office on S, Health. Reports of the surgeon general. In: The health consequences of Smoking-50 years of progress: a report of the surgeon general. Edn. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.

Additional file 1: Results of Tables S1 to S8

Table S1 Population characteristics stratified by smoking status

		Never smokers (n=159)	Ex- and current smokers (n=182)
Sex*	n females (%)	98 (61.6)	91 (50.0)
Age	mean years (SD)	57.6 (5.5)	57.2 (5.5)
Height*	mean cm (SD)	167.5 (9.7)	169.9 (9.3)
Weight*	mean kg (SD)	77.3 (16.6)	80.9 (16.2)
BMI	n normal (BMI <25 BMI) (%)	54 (34.0)	52 (28.6)
	n overweight (≥25 BMI <30) (%)	68 (42.8)	76 (41.8)
	n obese (BMI ≥30) (%)	37 (23.3)	54 (29.7)
Education	n low (<10 years of school) (%)	62 (39.0)	90 (49.5)
	n medium (=10 years of school) (%)	54 (34.0)	46 (25.3)
	n high (>10 years of school) (%)	43 (27.0)	46 (25.3)
Hay fever	n yes (%)	33 (20.8)	32 (17.6)
Problems in walking about/pain/discomfort	n not at all/slight (%)	133 (84.2)	156 (85.7)
	n moderate/extreme (%)	25 (15.8)	26 (14.3)
Lung function			
Z-score FEV_1	mean (SD)	0.34 (0.92)	0.24 (0.86)
Z-score FVC	mean (SD)	0.33 (0.84)	0.32 (0.85)
Z-score FEV_1/FVC	mean (SD)	-0.07 (0.61)	-0.20 (0.60)
Z-score FEF_{25-75}*	mean (SD)	0.08 (0.82)	-0.09 (0.76)
TLCO/VA*	mean mmol/min/kPa/l (SD)	14.39 (1.68)	13.85 (1.82)
PI_{max}*	mean kPa (SD)	7.75 (2.86)	8.36 (2.68)
Physical activity			
MVPA among females	median of mean minutes/day (1^{st}; 3^{rd} quartile)	28.7 (17.2; 49.6)	28.0 (17.5; 46.3)
MVPA among males	median of mean minutes/day (1^{st}; 3^{rd} quartile)	36.6 (23.1; 52.0)	33.0 (21.0; 48.7)
MVPA quartiles	n 1^{st} – least active (%)	38 (23.9)	47 (25.8)
	n 2^{nd} (%)	37 (23.3)	48 (26.4)
	n 3^{rd} (%)	41 (25.8)	44 (24.2)
	n 4^{th} – most active (%)	43 (27.0)	43 (23.6)
10-minute bout of MVPA achieved	n yes (%)	109 (68.6)	115 (63.2)
WHO threshold achieved	n yes (%)	26 (16.4)	24 (13.2)

*p<0.05 between never and ex-/current smokers.

SD: standard deviation. BMI: body mass index. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC. TLCO/VA: transfer factor of the lung for carbon monoxide adjusted for hemoglobin and divided by alveolar volume. PI_{max}: maximum inspiratory mouth pressure. MVPA: moderate to vigorous physical activity. WHO: World Health Organization.

Table S2 Comparison of subjects included in the present analysis compared to all other participants of the "Lung Health & physical activity" study performing spirometry

		Analyzed population (n=341)	**"Lung Health & physical activity" study participants with spirometry (n=669)**
Sex	n female (%)	189 (55.4)	346 (51.7)
Age*	mean years (SD)	57.4 (5.5)	58.4 (5.8)
Height	mean cm (SD)	168.7 (9.6)	169.3 (9.3)
Weight	mean kg (SD)	79.2 (16.4)	81.0 (18.4)
BMI	n normal (BMI <25 BMI) (%)	106 (31.1)	194 (29.0)
	n overweight (≥25 BMI <30) (%)	144 (42.2)	273 (40.8)
	n obese (BMI ≥30) (%)	91 (26.7)	202 (30.2)
Smoking status*	n never smokers (%)	159 (46.6)	253 (37.8)
	n ex-smokers (%)	135 (39.6)	280 (41.9)
	n current smokers (%)	47 (13.8)	136 (20.3)
Education	n low (<10 years of school) (%)	152 (44.6)	325 (48.8)
	n medium (=10 years of school) (%)	100 (29.3)	164 (24.6)
	n high (>10 years of school) (%)	89 (26.1)	177 (26.6)
Hay fever	n yes (%)	65 (19.1)	140 (20.9)
Asthma	n yes (%)	-	98 (14.6)
COPD or emphysema	n yes (%)	-	83 (12.4)
Problems in walking about/pain/discomfort*	n not at all/slight (%)	289 (85.0)	530 (79.3)
	n moderate/extreme (%)	51 (15.0)	138 (20.7)

*p<0.05 between study population analyzed and all other subjects participating in spirometry.
SD: standard deviation. BMI: body mass index. COPD: chronic obstructive pulmonary disease.

Table S3 Association of physical activity with GLI z-scores for spirometric parameters

	MVPA	Total population[a] (n=341)		Never smokers (n=159)		Ex- and current smokers[b] (n=182)	
	Quartile	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Z-score FEV_1	2	0.17 (-0.10, 0.43)	0.21	0.08 (-0.34, 0.49)	0.72	0.26 (-0.08, 0.60)	0.14
	3	**0.27 (0.01, 0.53)**	**0.05**	0.35 (-0.06, 0.76)	0.10	0.20 (-0.15, 0.55)	0.26
	4	**0.34 (0.07, 0.60)**	**0.01**	0.20 (-0.20, 0.60)	0.33	**0.48 (0.12, 0.83)**	**0.01**
Z-score FVC	2	0.18 (-0.06, 0.43)	0.14	0.10 (-0.27, 0.47)	0.60	0.27 (-0.06, 0.60)	0.11
	3	0.21 (-0.04, 0.46)	0.10	0.34 (-0.02, 0.71)	0.07	0.09 (-0.24, 0.43)	0.59
	4	**0.31 (0.06, 0.56)**	**0.01**	0.18 (-0.18, 0.54)	0.33	**0.45 (0.10, 0.80)**	**0.01**
Z-score FEV_1/FVC	2	-0.04 (-0.22, 0.14)	0.65	-0.04 (-0.32, 0.23)	0.76	-0.04 (-0.27, 0.20)	0.77
	3	0.09 (-0.09, 0.26)	0.35	-0.01 (-0.29, 0.26)	0.93	0.17 (-0.07, 0.41)	0.18
	4	0.04 (-0.14, 0.22)	0.63	0.03 (-0.24, 0.30)	0.85	0.06 (-0.19, 0.31)	0.64
Z-score FEF_{25-75}	2	0.08 (-0.16, 0.31)	0.52	-0.01 (-0.38, 0.37)	0.97	0.16 (-0.14, 0.46)	0.31
	3	**0.25 (0.01, 0.48)**	**0.04**	0.21 (-0.16, 0.57)	0.27	0.27 (-0.04, 0.58)	0.09
	4	0.18 (-0.06, 0.41)	0.15	0.01 (-0.27, 0.46)	0.61	0.26 (-0.06, 0.58)	0.11

All models were adjusted for weight, education level, and a doctor's diagnosis of hay fever.

[a]additionally adjusted for smoking status categorized as *never*, *ex-*, or *current* smokers.

[b]additionally adjusted for smoking status categorized as *ex-* or *current* smokers.

GLI: Global Lung Function Initiative. MVPA: moderate to vigorous physical activity. CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table S4 Sex-stratified results of linear regression models

		Males (n=152)		Females (n=189)	
		β (95% CI)	p-value	β (95% CI)	p-value
MVPA	Quartile				
FEV_1, ml	2	44 (-160, 248)	0.68	113 (-22, 247)	0.10
	3	45 (-158, 248)	0.66	**202 (66, 339)**	**0.00**
	4	60 (-148, 268)	0.57	**209 (73, 345)**	**0.00**
FVC, ml	2	52 (-192, 297)	0.67	144 (-26, 314)	0.10
	3	-72 (-315,171)	0.56	**255 (83, 428)**	**0.00**
	4	88 (-161, 337)	0.49	**210 (38, 381)**	**0.02**
FEV_1/FVC, %	2	-0.10 (-1.81, 1.6)	0.90	0.16 (-1.48, 1.80)	0.85
	3	**2.04 (0.34, 3.75)**	**0.02**	0.15 (-1.52, 1.82)	0.86
	4	-0.21 (-1.96, 1.53)	0.81	1.35 (-0.31, 3.01)	0.11
Z-score FEV_1/FVC	2	-0.02 (-0.27, 0.24)	0.90	-0.04 (-0.28, 0.21)	0.77
	3	**0.31 (0.05, 0.56)**	**0.02**	-0.05 (-0.30, 0.20)	0.69
	4	-0.05 (-0.3, 0.21)	0.73	0.17 (-0.08, 0.41)	0.20
10-minute bout of MVPA achieved, yes vs. no					
FEV_1, ml		-70 (-229, 90)	0.39	**154 (49, 259)**	**0.00**
FVC, ml		-121 (-312, 70)	0.22	**157 (23, 290)**	**0.02**
Z-score FEV_1		-0.11 (-0.42, 0.20)	0.48	**0.36 (0.08, 0.64)**	**0.01**
Z-score FVC		-0.15 (-0.43, 0.14)	0.31	**0.30 (0.04, 0.57)**	**0.03**
WHO threshold achieved, yes vs. no					
FEV_1, ml		**-196 (-387, -5)**	**0.05**	105 (-39, 249)	0.15
FVC, ml		**-242 (-472, -12)**	**0.04**	79 (-103, 261)	0.39
Z-score FEV_1		**-0.38 (-0.75, 0.00)**	**0.05**	0.33 (-0.05, 0.71)	0.09
Z-score FVC		**-0.35 (-0.70, -0.01)**	**0.05**	0.25 (-0.12, 0.61)	0.18

The models were adjusted for sex, age, height, weight, smoking status, education level, and a doctor's diagnosis of hay fever.

MVPA: moderate to vigorous physical activity. CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. WHO: World Health Organization.

Table S5 Association of physical activity with spirometric parameters with **adjustment for BMI instead of weight**

	MVPA	Total population[a] (n=341)		Never smokers (n=159)		Ex- and current smokers[b] (n=182)	
	Quartile	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
FEV_1, ml	2	71 (-45, 187)	0.23	43 (-131, 216)	0.63	81 (-79, 240)	0.32
	3	**124 (7, 242)**	**0.04**	163 (-11, 337)	0.07	61 (-103, 225)	0.47
	4	**141 (22, 259)**	**0.02**	79 (-94, 252)	0.37	**197 (31, 363)**	**0.02**
FVC, ml	2	89 (-54, 233)	0.22	45 (-162, 252)	0.67	113 (-89, 315)	0.27
	3	106 (-39, 251)	0.15	183 (-25, 391)	0.09	13 (-195, 222)	0.90
	4	**154 (8, 300)**	**0.04**	68 (-139, 275)	0.52	**231 (21, 441)**	**0.03**
FEV_1/FVC, %	2	0.03 (-1.16, 1.22)	0.96	-0.01 (-1.84, 1.82)	0.99	-0.09 (-1.71, 1.53)	0.91
	3	0.87 (-0.33, 2.07)	0.16	0.36 (-1.48, 2.19)	0.70	1.06 (-0.61, 2.73)	0.21
	4	0.65 (-0.56, 1.86)	0.29	0.73 (-1.09, 2.56)	0.43	0.55 (-1.13, 2.23)	0.52

All models were adjusted for sex, age, height, **body mass index**, education level, and a doctor's diagnosis of hay fever.

[a]additionally adjusted for smoking status categorized as *never*, *ex-*, or *current* smokers.

[b]additionally adjusted for smoking status categorized as *ex-* or *current* smokers.

BMI: body mass index. MVPA: moderate to vigorous physical activity. CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table S6 Association of at least one 10-minute bout of MVPA achieved with spirometric parameters

	10-minute bout of MVPA achieved, yes vs. no					
	Total population[a] (n=341)		Never smokers (n=159)		Ex- and current smokers[b] (n=182)	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
FEV_1, ml	36 (-52, 125)	0.42	74 (-59, 207)	0.28	22 (-98, 141)	0.72
FVC, ml	27 (-82, 136)	0.62	44 (-116, 203)	0.59	33 (-118, 185)	0.67
FEV_1/FVC, %	0.39 (-0.51, 1.29)	0.40	1.19 (-0.18, 2.57)	0.09	-0.23 (-1.43, 0.98)	0.71
FEF_{25-75}, ml/s	49 (-118, 216)	0.57	157 (-92, 405)	0.22	-28 (-253, 197)	0.81
Z-score FEV_1	0.13 (-0.07, 0.33)	0.21	0.16 (-0.16, 0.47)	0.33	0.12 (-0.15, 0.38)	0.39
Z-score FVC	0.11 (-0.08, 0.30)	0.24	0.08 (-0.20, 0.36)	0.58	0.15 (-0.11, 0.41)	0.25
Z-score FEV_1/FVC	0.03 (-0.10, 0.17)	0.63	0.12 (-0.09, 0.33)	0.26	-0.04 (-0.22, 0.14)	0.64
Z-score FEF_{25-75}	0.08 (-0.10, 0.26)	0.38	0.17 (-0.11, 0.45)	0.23	-0.01 (-0.24, 0.22)	0.94

The models were adjusted for sex, age, height, weight, education level, and a doctor's diagnosis of hay fever.

[a]additionally adjusted for smoking status categorized as *never*, *ex*-, or *current* smokers.

[b]additionally adjusted for smoking status categorized as *ex*- or *current* smokers.

MVPA: moderate to vigorous physical activity. CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table S7 Association of the achievement of WHO threshold with spirometric parameters

	WHO threshold achieved, yes vs. no					
	Total population[a] (n=341)		Never smokers (n=159)		Ex- and current smokers[b] (n=182)	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
FEV_1, ml	-35 (-153, 82)	0.56	60 (-107, 226)	0.48	-142 (-312, 27)	0.10
FVC, ml	-69 (-214, 75)	0.35	56 (-143, 254)	0.58	**-220 (-434, -6)**	**0.05**
FEV_1/FVC, %	0.45 (-0.75, 1.65)	0.46	0.42 (-1.31, 2.15)	0.64	0.65 (-1.07, 2.37)	0.46
FEF_{25-75}, ml/s	-31 (-255, 193)	0.79	18 (-299, 335)	0.91	-62 (-383, 260)	0.71
Z-score FEV_1	0.01 (-0.25, 0.28)	0.93	0.24 (-0.15, 0.63)	0.23	-0.24 (-0.61, 0.13)	0.20
Z-score FVC	-0.01 (-0.26, 0.24)	0.91	0.21 (-0.14, 0.55)	0.24	-0.26 (-0.62, 0.10)	0.16
Z-score FEV_1/FVC	0.04 (-0.14, 0.22)	0.66	0.01 (-0.25, 0.27)	0.94	0.07 (-0.18, 0.33)	0.57
Z-score FEF_{25-75}	0.01 (-0.22, 0.25)	0.92	0.08 (-0.27, 0.43)	0.66	-0.06 (-0.39, 0.26)	0.70

The models were adjusted for sex, age, height, weight, education level, and a doctor's diagnosis of hay fever.

[a]additionally adjusted for smoking status categorized as *never*, *ex-*, or *current* smokers.

[b]additionally adjusted for smoking status categorized as *ex-* or *current* smokers.

WHO: World Health Organization. CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table S8 Association of physical activity with pulmonary gas exchange and inspiratory muscle strength according to smoking status

	Pulmonary gas exchange (TLCO/VA), 10^{-1} mmol/min/kPa/l				**Maximum inspiratory mouth pressure (PI_{max}),** kPa			
	Never smokers (n=151)		Ex- and current smokers[a] (n=171)		Never smokers (n=155)		Ex- and current smokers[a] (n=176)	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
MVPA quartiles[a]								
1st – least active vs.								
2nd	-0.26 (-0.93, 0.42)	0.45	0.22 (-0.47, 0.91)	0.53	0.85 (-0.21, 1.92)	0.12	0.01 (-0.96, 0.98)	0.98
3rd	**-0.81 (-1.50, -0.13)**	**0.02**	0.12 (-0.61, 0.85)	0.75	0.84 (-0.22, 1.91)	0.12	-0.20 (-1.20, 0.80)	0.70
4th – most active	-0.05 (-0.73, 0.64)	0.90	0.47 (-0.27, 1.20)	0.21	0.17 (-0.90, 1.23)	0.76	-0.01 (-1.05, 1.02)	0.98
10-minute bout of MVPA achieved, yes vs. no	0.00 (-0.54, 0.53)	0.99	-0.09 (-0.61, 0.42)	0.72	**0.93 (0.11, 1.74)**	**0.03**	0.37 (-0.35, 1.09)	0.32
WHO threshold achieved, yes vs. no	0.12 (-0.55, 0.79)	0.72	0.56 (-0.16, 1.28)	0.13	0.50 (-0.51, 1.51)	0.33	-0.51 (-1.55, 0.53)	0.33

All models were adjusted for sex, age, height, weight, education level, and a doctor's diagnosis of hay fever.

[a]additionally adjusted for smoking status categorized as *ex*- or *current* smokers.

TLCO/VA: transfer factor of the lung for carbon monoxide adjusted for hemoglobin and divided by alveolar volume. PI_{max}: maximum inspiratory mouth pressure. CI: confidence interval. MVPA: moderate to vigorous physical activity. WHO: World Health Organization.

6.5 Publication V

Original title:

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

Authors:

Agnes Luzak, Stefan Karrasch, Margarethe Wacker, Barbara Thorand, Dennis Nowak, Annette Peters, Holger Schulz

Journal:

Quality of Life Research

Volume:

27 (3)

Pages:

735-745

Year:

2018

DOI:

https://doi.org/10.1007/s11136-017-1763-6

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

Agnes Luzak[1], Stefan Karrasch[1,2,5], Margarethe Wacker[3], Barbara Thorand[4], Dennis Nowak[2,5], Annette Peters[4], Holger Schulz[1,5]

[1]Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

[2]Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Munich (LMU), Ziemssenstr. 1, 80336 Munich, Germany

[3]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München - German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

[4]Institute of Epidemiology II, Helmholtz Zentrum München - German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

[5]Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Max-Lebsche-Platz 31, 81377 Munich, Germany

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 second (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 -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.

Key words: 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 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 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 three-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 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 months a year, or (IV) 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.

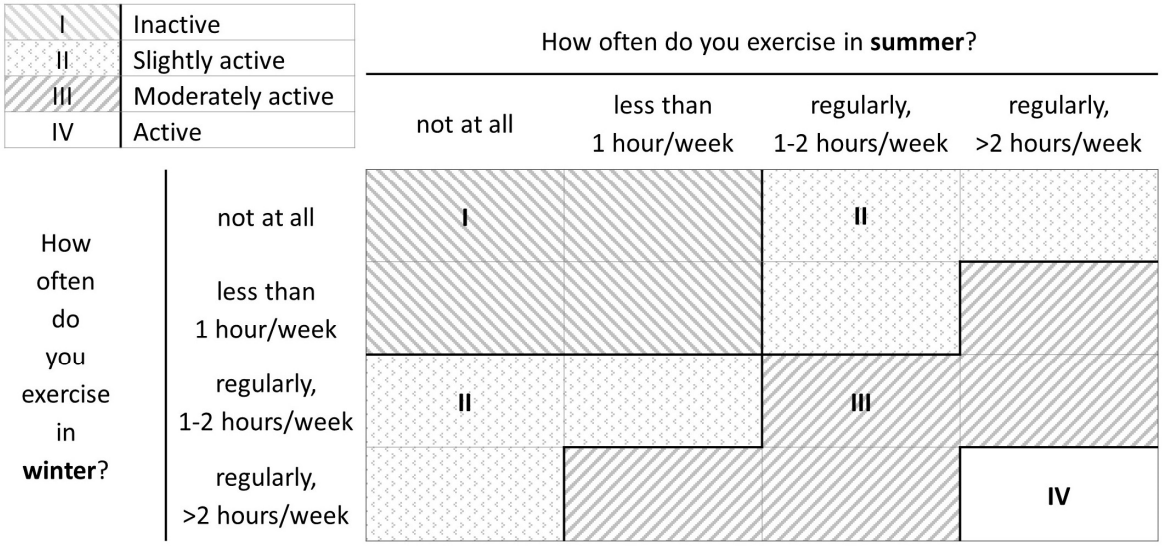
EQ-5D and physical inactivity

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 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 Figure 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 hours/week, (b) regularly, 1-2 hours/week, (c) less than 1 hour/week, (d) not at all. A categorization matrix is displayed in Figure 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 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 [28], were used as the reference category to determine if less activity is associated with lower lung function.

Figure 1 Categorization of activity levels



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

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 to 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 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 Pearsons'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 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. 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 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 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 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) 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 Figure A1, S2 Table A1). Further, subjects in the lowest 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 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 hours/week) in physical activity, while 24% were categorized as inactive, i.e. engaging in physical activity <1 hour/week or not at all ($p<0.01$).

Table 1 Population characteristics

	Males (n=545)	**Females (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)	5.0 (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)

	Males (n=545)	Females (n=587)	Total (n=1132)
	Mean (SD) or % (N)		
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)
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)

*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)

SD: standard deviation. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

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 FEV1 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 FEV1/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 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: β= -81 ml, p=0.04; FVC: β= -109 ml, p=0.03; usual activities: FEV_1: β= -86 ml, p=0.04; FVC: β=-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: 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) (S2 Tables 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 indice. 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).

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.
CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

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 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 hours/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.

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, 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 to 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.

References

1. Wacker ME, Jörres RA, Karch A, Koch A, Heinrich J, Karrasch S, et al: Relative impact of COPD and comorbidities on generic health-related quality of life: a pooled analysis of the COSYCONET patient cohort and control subjects from the KORA and SHIP studies. Respir Res. 2016;17(1):81.
2. Pickard AS, Wilke C, Jung E, Patel S, Stavem K, Lee TA: Use of a preference-based measure of health (EQ-5D) in COPD and asthma. Respir Med. 2008;102(4):519-536.
3. Janson C, Marks G, Buist S, Gnatiuc L, Gislason T, McBurnie MA, et al: The impact of COPD on health status: findings from the BOLD study. Eur Respir J. 2013;42(6):1472.
4. Anokye NK, Trueman P, Green C, Pavey TG, Taylor RS: Physical activity and health related quality of life. BMC Public Health. 2012;12(1):624.
5. Choi M, Prieto-Merino D, Dale C, Nüesch E, Amuzu A, Bowling A, et al: Effect of changes in moderate or vigorous physical activity on changes in health-related quality of life of elderly British women over seven years. Qual Life Res. 2013;22(8):2011-2020.
6. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM: Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax. 2006;61(9):772-778.
7. Brumpton BM, Langhammer A, Henriksen AH, Camargo CA, Jr., Chen Y, Romundstad PR, et al: Physical activity and lung function decline in adults with asthma: The HUNT Study. Respirology. 2017;22(2):278-283.
8. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al: Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-1343.
9. Dyer C: The interaction of ageing and lung disease. Chron Respir Dis. 2012;9(1):63-67.
10. Merkus PJ: Effects of childhood respiratory diseases on the anatomical and functional development of the respiratory system. Paediatr Respir Rev. 2003;4(1):28-39.
11. Weiss ST: Lung function and airway diseases. Nat Genet. 2010;42(1):14-16.
12. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al: Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med. 2008;177(3):253-260.
13. Myint PK, Luben RN, Surtees PG, Wainwright NWJ, Welch AA, Bingham SA, et al: Respiratory function and self-reported functional health: EPIC-Norfolk population study. Eur Respir J. 2005;26(3):494-502.
14. Singh-Manoux A, Dugravot A, Kauffmann F, Elbaz A, Ankri J, Nabi H, et al: Association of lung function with physical, mental and cognitive function in early old age. Age. 2011;33(3):385-392.
15. Rabin R, de Charro F: EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337-343.
16. König HH, Heider D, Lehnert T, Riedel-Heller SG, Angermeyer MC, Matschinger H, et al: Health status of the advanced elderly in six European countries: results from a representative survey using EQ-5D and SF-12. Health Qual Life Outcomes. 2010;8:143.
17. Wacker ME, Hunger M, Karrasch S, Heinrich J, Peters A, Schulz H, et al: Health-related quality of life and chronic obstructive pulmonary disease in early stages - longitudinal results from the population-based KORA cohort in a working age population. BMC Pulm Med. 2014;14:134.
18. König HH, Bernert S, Angermeyer MC, Matschinger H, Martinez M, Vilagut G, et al: Comparison of population health status in six european countries: results of a representative survey using the EQ-5D questionnaire. Med Care. 2009;47(2):255-261.
19. Mielck A, Vogelmann M, Schweikert B, Leidl R: [Health status of adults in Germany: results from a representative survey using the EuroQol 5D (EQ-5D)]. Gesundheitswesen. 2010;72(8-9):476-486.

20. Jakes RW, Day NE, Patel B, Khaw K-T, Oakes S, Luben R, et al: Physical Inactivity Is Associated with Lower Forced Expiratory Volume in 1 Second: European Prospective Investigation into Cancer-Norfolk Prospective Population Study. Am J Epidemiol. 2002;156(2):139-147.
21. Nystad W, Samuelsen SO, Nafstad P, Langhammer A: Association between level of physical activity and lung function among Norwegian men and women: the HUNT study. Int J Tuberc Lung Dis. 2006;10(12):1399-1405.
22. Holle R, Happich M, Löwel H, Wichmann HE: KORA--a research platform for population based health research. Gesundheitswesen. 2005;67 Suppl 1:S19-25.
23. Peters A, Döring A, Ladwig KH, Meisinger C, Linkohr B, Autenrieth C, et al: [Multimorbidity and successful aging: the population-based KORA-Age study]. Z Gerontol Geriatr. 2011;44 Suppl 2:41-54.
24. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al: Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338.
25. Report (2017) From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org. Assessed on 13/10/2017.
26. Greiner W, Claes C, Busschbach JJ, von der Schulenburg JM: Validating the EQ-5D with time trade off for the German population. Eur J Health Econ. 2005;6(2):124-130.
27. Wacker ME, Jörres RA, Karch A, Wilke S, Heinrich J, Karrasch S, et al: Assessing health-related quality of life in COPD: comparing generic and disease-specific instruments with focus on comorbidities. BMC Pulm Med. 2016;16(1):70.
28. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva, World Health Organization, 2010. http://www.who.int/dietphysicalactivity/factsheet_recommendations/en/. Accessed 13 Oct 2016.
29. Karrasch S, Flexeder C, Behr J, Holle R, Huber RM, Jörres RA, et al: Spirometric reference values for advanced age from a South german population. Respiration. 2013;85(3):210-219.
30. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C: Lung volumes and forced ventilatory flows. Eur Respir J. 1993;6(Suppl 16):5-40.
31. Simon MR, Chinchilli VM, Phillips BR, Sorkness CA, Lemanske RF, Szefler SJ, et al: FEF_{25-75} and FEV_1/FVC in Relation to Clinical and Physiologic Parameters in Asthmatic Children with Normal FEV_1 Values. J Allergy Clin Immunol. 2010;126(3):527-534.e528.
32. Krug S JS, Mensink GBM, Müters S, Finger JD, Lampert T: English version of “Körperliche Aktivität. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1)” Bundesgesundheitsbl. 2013;56:765–771.

Acknowledgments

The authors thank the study personnel for their excellent work and all attendees for their participation in the KORA surveys. They thank Carla Harris (Institute of Epidemiology I, Helmholtz Zentrum München, Germany) for editorial assistance in preparation of this manuscript.

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: Figure A1
S1_Figure_A1.pdf

Supplement S2: Tables A1 to A10
S2_Tables_A1_to_A10.pdf

Compliance with Ethical Standards

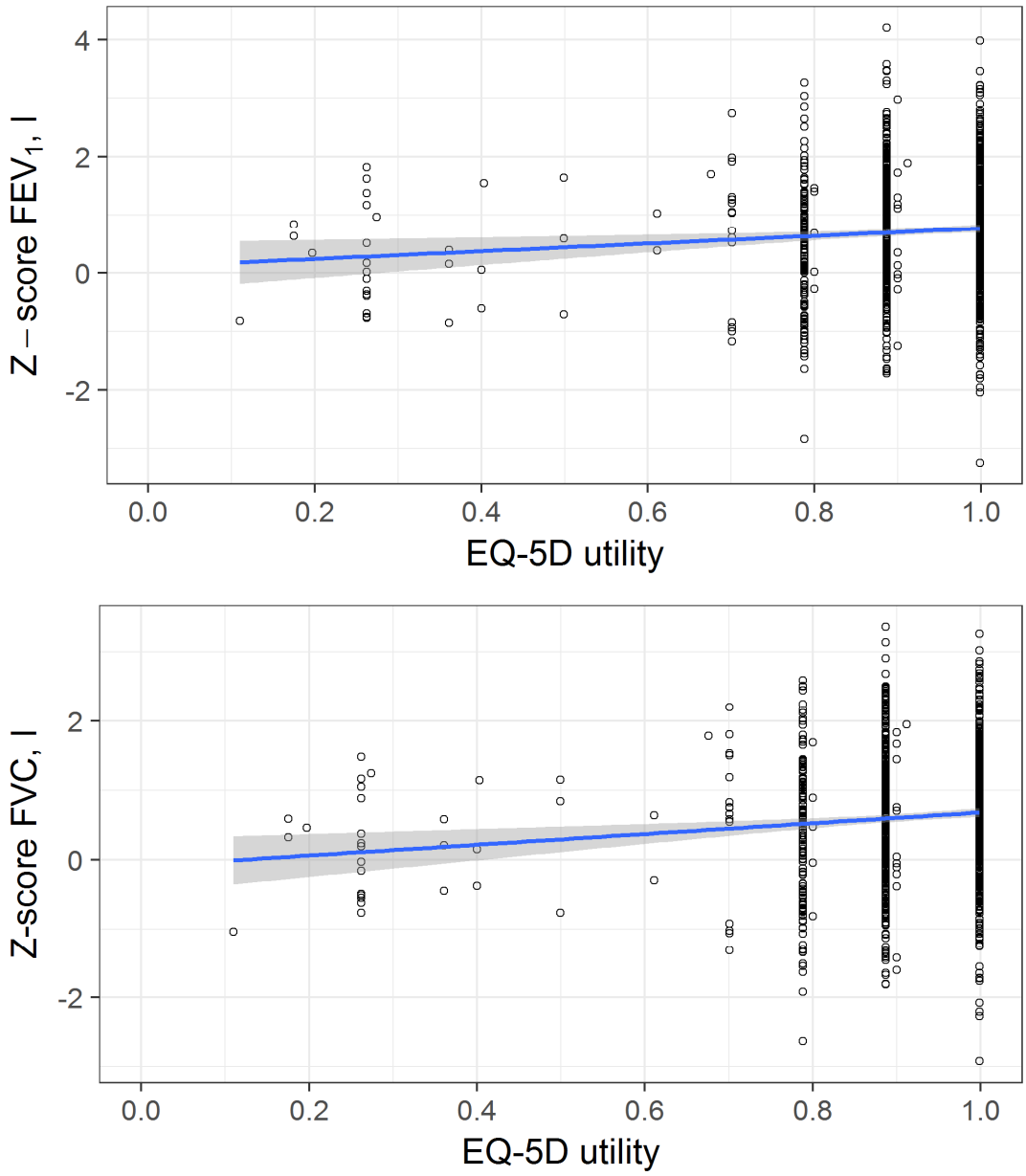
Disclosure of potential conflicts of interest: The authors declare that they have no competing interests.

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.

Funding: The KORA study was initiated and financed by the Helmholtz Zentrum München - German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria.

Authors AP and HS received research grants from the German Federal Ministry of Education and Research (BMBF FKZ 01ET0713 and 01ET1003A) for the KORA Age project. Author HS has further received grants from the BMBF through the German Center for Lung Research (DZL), Comprehensive Pneumology Center Munich (CPC-M) and by the Competence Network Asthma and COPD (ASCONET), network COSYCONET (subproject 2, BMBF FKZ 01GI0882) funded by the BMBF.

Figure A1 Distribution of EQ-5D utility and z-scores for FEV_1 and FVC with corresponding linear regression line (blue line) and 95% confidence interval (shaded area)



Supplement S2 Tables A1 to A10

Table A1 Results of multiple linear regression models with EQ-5D utility as exposure

	FEV_1, ml		FVC, ml		FEV_1/FVC, %		FEF_{25-75}, ml/s	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
EQ-5D utility, continuous	**209 (12; 405)**	**0.04**	229 (-19; 478)	0.07	1.35 (-0.75; 3.46)	0.21	265 (-93; 622)	0.15
EQ-5D utility, categorized								
=0.999	ref.		ref.		ref.		ref.	
≥0.887	25 (-29; 79)	0.37	10 (-59; 78)	0.78	0.46 (-0.12; 1.04)	0.12	64 (-35; 162)	0.20
<0.887	**-87 (-160; -15)**	**0.02**	**-96 (-187; -4)**	**0.04**	-0.50 (-1.27; 0.28)	0.21	-111 (-243; 20)	0.10

The models were adjusted for sex, age, height, weight and one EQ-5D utility variable (continuous or categorized).

CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table A2 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_{25-75}	
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/unable to	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/unable to	**-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
Pain/Discomfort								
no	ref.		ref.		ref.		ref.	
moderate/extreme	-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
Anxiety/Depression								
no	ref.		ref.		ref.		ref.	
moderate/extreme	**-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)**	**0.047**	**-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.

CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table A3 Results of selected sensitivity analyses

	Linear regression models were adjusted for sex, age, height, weight, one EQ-5D dimension or physical activity and additionally for									
	Hay fever		Season		Stroke		Myocardial infarction		Multimorbidity	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
FEV_1, ml										
Mobility										
no problems	ref.		ref.		ref.		ref.		ref.	
some problems	**-99 (-166; -31)**	**<0.01**	**-100 (-168; -33)**	**<0.01**	**-93 (-160; -25)**	**0.01**	**-80 (-148; -12)**	**0.02**	**-85 (-153; -17)**	**0.01**
Usual activities										
no problems	ref.		ref.		ref.		ref.		ref.	
some/unable to	**-97 (-169; -26)**	**0.01**	**-99 (-170; -28)**	**0.01**	**-87 (-158; -15)**	**0.02**	**-76 (-148; -4)**	**0.04**	**-80 (-153; -8)**	**0.03**
Physical activity										
Active	ref.		ref.		ref.		ref.		ref.	
Moderately active	-51 (-112; 10)	0.10	-50 (-111; 10)	0.10	-50 (-111; 10)	0.10	-52 (-112; 9)	0.09	-52 (-113; 9)	0.09
Slightly active	-58 (-136; 19)	0.14	-58 (-135; 19)	0.14	-56 (-133; 21)	0.16	-63 (-140; 14)	0.11	-64 (-141; 13)	0.11
Inactive	-51 (-117; 15)	0.13	-51 (-117; 14)	0.13	-44 (-110; 22)	0.19	-48 (-114; 17)	0.15	-46 (-111; 20)	0.17
FVC, ml										
Mobility										
no problems	ref.		ref.		ref.		ref.		ref.	
some problems	**-109 (-194; -24)**	**0.01**	**-112 (-197; -26)**	**0.01**	**-98 (-184; -13)**	**0.02**	**-88 (-174; -1)**	**0.047**	**-94 (-180; -7)**	**0.03**
Usual activities										
no problems	ref.		ref.		ref.		ref.		ref.	
some/unable to	**-124 (-215; -34)**	**0.01**	**-126 (-217; -36)**	**0.01**	**-105 (-196; -14)**	**0.02**	**-99 (-191; -8)**	**0.03**	**-105 (-197; -13)**	**0.03**
Physical activity										
Active	ref.		ref.		ref.		ref.		ref.	
Moderately active	**-82 (-158; -5)**	**0.04**	**-80 (-157; -4)**	**0.04**	**-80 (-157; -4)**	**0.04**	**-83 (-159; -7)**	**0.03**	**-84 (-161; -8)**	**0.03**
Slightly active	**-112 (-209; -15)**	**0.02**	**-111 (-208; -14)**	**0.03**	**-111 (-208; -14)**	**0.03**	**-118 (-215; -21)**	**0.02**	**-119 (-216; -22)**	**0.02**
Inactive	**-85 (-168; -2)**	**0.046**	**-87 (-170; -4)**	**0.04**	-75 (-158; 8)	0.08	-83 (-165; 0)	0.05	-80 (-163; 3)	0.06

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

Table A4 Results of multiple linear regression models – Females

	FEV_1, ml		FVC, ml		FEV_1/FVC, %		FEF_{25-75}, 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/unable to	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/unable to	**-86 (-167; -5)**	**0.04**	**-106 (-209; -3)**	**0.04**	-0.34 (-1.40; 0.73)	0.54	-101 (-254; 53)	0.20
Pain/Discomfort								
no	ref.		ref.		ref.		ref.	
moderate/extreme	-4 (-63; 54)	0.89	-13 (-87; 61)	0.73	0.23 (-0.54; 0.99)	0.56	0 (-110; 111)	0.99
Anxiety/Depression								
no	ref.		ref.		ref.		ref.	
moderate/extreme	-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)	0.70	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 models were adjusted for age, height, weight and one EQ-5D dimension or physical activity variable at a time.

CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table A5 Results of multiple linear regression models – Males

	FEV_1, ml		FVC, ml		FEV_1/FVC, %		FEF_{25-75}, 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	**-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/unable to	-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/unable to	-119 (-240; 2)	0.05	-151 (-304; 1)	0.05	-0.24 (-1.35; 0.88)	0.68	-130 (-345; 84)	0.23
Pain/Discomfort								
no	ref.		ref.		ref.		ref.	
moderate/extreme	-12 (-92; 69)	0.78	-13 (-115; 88)	0.80	-0.25 (-0.98; 0.49)	0.51	3 (-139; 146)	0.96
Anxiety/Depression								
no	ref.		ref.		ref.		ref.	
moderate/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 models were adjusted for age, height, weight and one EQ-5D dimension or physical activity variable at a time.

CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table A6 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_{25-75}	
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/unable to	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/unable to	**-0.23 (-0.46; 0)**	**0.049**	**-0.26 (-0.47; -0.05)**	**0.02**	0.04 (-0.12; 0.19)	0.65	-0.08 (-0.27; 0.11)	0.42
Pain/Discomfort								
no	ref.		ref.		ref.		ref.	
moderate/extreme	-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
Anxiety/Depression								
no	ref.		ref.		ref.		ref.	
moderate/extreme	-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)**	**0.045**	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.

CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table A7 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_{25-75}	
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/unable to	-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/unable to	**-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
Pain/Discomfort								
no	ref.		ref.		ref.		ref.	
moderate/extreme	-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
Anxiety/Depression								
no	ref.		ref.		ref.		ref.	
moderate/extreme	-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 ethnicity, sex, age, and height were adjusted only for weight and one EQ-5D dimension or physical activity variable at a time.

CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table A8 Linear regression results after exclusion of subjects reporting ***extreme problems*** or being ***unable to***

	FEV_1, ml		FVC, ml		FEV_1/FVC, %		FEF_{25-75}, 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	**-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	3 (-155; 161)	0.97	-5 (-205; 195)	0.96	-0.75 (-2.47; 0.97)	0.39	58 (-228; 344)	0.69
Usual activities								
no	ref.		ref.		ref.		ref.	
some	**-101 (-173; -29)**	**0.01**	**-131 (-222; -40)**	**<0.01**	-0.20 (-0.97; 0.57)	0.61	-101 (-232; 29)	0.13
Pain/Discomfort								
no	ref.		ref.		ref.		ref.	
moderate	2 (-48; 53)	0.92	-3 (-67; 61)	0.93	0.07 (-0.47; 0.61)	0.80	17 (-74; 108)	0.71
Anxiety/Depression								
no	ref.		ref.		ref.		ref.	
moderate	-43 (-102; 15)	0.15	-63 (-137; 11)	0.09	0.12 (-0.50; 0.75)	0.70	-20 (-126; 86)	0.71

*None of the participants reported to be confined to bed, therefore all participants remained in the models.

The models were adjusted for sex, age, height, weight and one EQ-5D dimension at a time.

CI: confidence interval. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow between 25% and 75% of FVC.

Table A9 Results of multiple linear regression models with 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						
EQ-5D						
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.

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

Table A10 Results of multiple linear regression models with adjustment for problems with *usual activities* 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/unable to	**-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						
EQ-5D						
Problems with *Usual activities*						
no	ref.		ref.		ref.	
some/unable to	**-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 activities* and physical activity.
[b]Model was adjusted for age, height, weight, *usual activities* and physical activity.

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

7 Acknowledgements

First, I would like to thank my supervisors Prof. Dr. Dennis Nowak, director of the Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Munich, Ludwig-Maximilians-University, and Prof. Dr. Holger Schulz, head of the working group Lung Epidemiology, Institute of Epidemiology, Helmholtz Zentrum München, who made this work possible and always provided professional supervision. I am very grateful for their motivation and excellent scientific advice.

I thank the KORA, GINIplus and LISAplus study groups, and the team members of all study centers for their excellent work, and all attendees for the active participation in these studies.

Further, I am grateful to all my colleagues for their help, patience and the overall enjoyable working environment at the Institute of Epidemiology.

I would like to send special thanks to my family and friends for their great support, especially to my mother and Sebastian who were very patient during all ups and downs and encouraged me constantly. Furthermore, I would like to thank Sebastian for his great help with illustrations and formatting.

8 Publications

Publications comprised within this thesis

Luzak A, Flexeder C, von Berg A, et al. Relation of lung function and current inhalant allergen-specific immunoglobulin E concentrations in adolescents (GINIplus cohort). Ann Allergy Asthma Immunol. 2015;115(3):183-190.

Luzak A, Fuertes E, Flexeder C, et al. Which early life events or current environmental and lifestyle factors influence lung function in adolescents? - results from the GINIplus & LISAplus studies. Respir Res. 2017;18(1):138.

Luzak A, Heier M, Thorand B, et al. Physical activity levels, duration pattern and adherence to WHO recommendations in German adults. PLoS One. 2017;12(2):e0172503.

Luzak A, Karrasch S, Thorand B, et al. Association of physical activity with lung function in lung-healthy German adults: results from the KORA FF4 study. BMC Pulm Med. 2017;17(1):215.

Luzak A, Karrasch S, Wacker M, et al. 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. Qual Life Res. 2018;27(3):735-745.

Further publications

Jaeschke L*, **Luzak A***, Steinbrecher A, et al. 24 h-accelerometry in epidemiological studies: automated detection of non-wear time in comparison to diary information. Sci Rep. 2017;7(1):2227. *These authors contributed equally to this work.

Jaeschke L, Steinbrecher A, **Luzak A**, et al. Socio-cultural determinants of physical activity across the life course: a 'Determinants of Diet and Physical Activity' (DEDIPAC) umbrella systematic literature review. Int J Behav Nutr Phys Act. 2017;14(1):173.

O'Donoghue G, Kennedy A, Puggina A, …, **Luzak A**, …, et al. Socio-economic determinants of physical activity across the life course: a "DEterminants of DIet and Physical ACtivity" (DEDIPAC) umbrella literature review. PLoS One. 2018;13(1):e0190737.

Condello G, Puggina A, Aleksovska K, ..., **Luzak A**, …, et al. Behavioral determinants of physical activity across the life course: a "DEterminants of DIet and Physical ACtivity" (DEDIPAC) umbrella systematic literature review. Int J Behav Nutr Phys Act. 2017;14(1):58.

Carlin A, Perchoux C, Puggina A, ..., **Luzak A**, …, et al. A life course examination of the physical environmental determinants of physical activity behaviour: A "Determinants of Diet and Physical Activity" (DEDIPAC) umbrella systematic literature review. PLoS One. 2017;12(8):e0182083.

Puggina A, Aleksovska K, Buck C, ..., **Luzak A**, …, et al. Policy determinants of physical activity across the life course: a 'DEDIPAC' umbrella systematic literature review. Eur J Public Health. 2017. doi: 10.1093/eurpub/ckx174.

Cortis C, Puggina A, Pesce C, ..., **Luzak A**, …, et al. Psychological determinants of physical activity across the life course: A "DEterminants of DIet and Physical ACtivity" (DEDIPAC) umbrella systematic literature review. PLoS One. 2017;12(8):e0182709.

Luzak A, Schnell-Inderst P, Bühn S, et al. Clinical effectiveness of cancer screening biomarker tests offered as self-pay health service: a systematic review. Eur J Public Health. 2016;26(3):498-505.

Gothe H, Schall I, Saverno K, ..., **Luzak A**, …, et al. The Impact of Generic Substitution on Health and Economic Outcomes: A Systematic Review. Appl Health Econ Health Policy. 2015;13 Suppl 1:S21-33.

9 Affidavit

Hiermit erkläre ich, Agnes Luzak, des Eides statt, dass ich die vorliegende Dissertation zum Thema „Associations of environmental and lifestyle factors with lung function in youth and adulthood“ selbstständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 10.07.2018

Agnes Luzak