Understanding the role of body weight and composition on lung function growth and decline

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Abstract

Background: There is evidence suggesting that body weight is associated with lung function, but results are contradictory and suffer from important limitations. We aimed to assess the association of body weight and composition with lung function growth and decline, overcoming some of the limitations of previous research.

Methods: We used data from three population-based cohorts: the Spanish INfancia y Medio Ambiente ('Environment and Childhood'), the UK Avon Longitudinal Study of Parents and Children and the European Community Respiratory Health Survey. Lung function was measured by spirometry. Body weight was assessed using body mass index (BMI). Body composition (lean body mass and fat mass) was measured using a dual-energy X-ray absorptiometry scanner. We calculated changes over time and group-based trajectories of BMI, lean body mass and/or fat mass.

Results: (1) Independently of birth size, accelerated BMI gain from birth to four years was associated with higher lung function at seven years but also with airflow limitation. In contrast, children with lower birth size and slower BMI gain in early childhood had lower lung function at seven years. (2) Higher lean body mass from nine to fifteen years related to higher lung function at fifteen years in boys and girls. In addition, higher fat mass was associated with lower lung function in boys, and with airflow limitation in boys and girls. (3) The association of higher fat mass with airflow limitation at fifteen years was partly (20%) mediated by insulin resistance, but not by C-

reactive protein. (4) Moderate and high weight gain during adulthood were associated with accelerated lung function decline, while weight loss was related to its attenuation.

Conclusions: Excess body weight and fat mass have deleterious effects on lung function over life span, while higher lean body mass benefits lung function growth. The effects of body weight on lung function seem reversible. This thesis highlights the importance of assessing body composition when studying the effects of body weight on respiratory health and of promoting body weight and fat mass control in order to reduce respiratory morbidity at all ages.

Resumen

Antecedentes: El peso corporal se ha asociado con la función pulmonar, pero hasta ahora los resultados han sido contradictorios y presentan limitaciones importantes. Nuestro objetivo fue evaluar la asociación del peso y la composición corporal con el desarrollo y el declive de la función pulmonar, superando algunas de las limitaciones de los estudios previos.

Métodos: Utilizamos datos de tres cohortes de base poblacional: INfancia y Medio Ambiente, en España, *Avon Longitudinal Study of Parents and Children,* en Inglaterra, y *European Community Respiratory Health Survey*. La función pulmonar se midió mediante espirometría. El peso corporal se evaluó utilizando el índice de masa corporal (IMC). La composición corporal (masa magra y masa grasa) se midió utilizando un escáner de absorciometría de rayos X de energía dual. Calculamos cambios en el tiempo y trayectorias grupales de IMC, masa magra y/o masa grasa.

Resultados: (1) Independientemente del peso al nacer, el aumento acelerado del IMC desde el nacimiento hasta los cuatro años se asoció con una mayor función pulmonar a los siete años, pero también con una limitación del flujo aéreo. En cambio, los niños con un peso al nacer más bajo y un aumento del IMC más lento mostraron una menor función pulmonar a los siete años. (2) Un mayor nivel de masa magra desde los nueve hasta los quince años se asoció con una mayor función pulmonar a los quince años en niños y niñas. Además, un mayor nivel de masa grasa se asoció con una menor función

pulmonar en niños y con una limitación del flujo aéreo en niños y niñas. (3) La asociación entre un mayor nivel de masa grasa y la limitación del flujo aéreo a los quince años fue mediada en parte (20%) por la resistencia a la insulina, pero no por la proteína C-reactiva. (4) El aumento de peso moderado y alto en la edad adulta se asoció con un declive acelerado de la función pulmonar, mientras que la pérdida de peso se relacionó con su atenuación.

Conclusiones: El exceso de peso y masa grasa tienen efectos nocivos sobre la función pulmonar a lo largo de la vida. En cambio, un mayor nivel de masa magra beneficia el desarrollo de la función pulmonar. Los efectos del peso sobre la función pulmonar parecen reversibles. Esta tesis resalta la importancia de evaluar la composición corporal al estudiar los efectos del peso sobre la salud respiratoria y de promover el control del peso y el nivel de masa grasa para reducir la morbilidad respiratoria en todas las edades.

Resum

Antecedents: El pes corporal s'ha associat amb la funció pulmonar, però fins ara els resultats han sigut contradictoris i presenten limitacions importants. El nostre objectiu va ser avaluar l'associació del pes i la composició corporal amb el desenvolupament i el declivi de la funció pulmonar, superant algunes de les limitacions dels estudis previs.

Mètodes: Utilitzàrem dades de tres cohorts de base poblacional: INfància i Medi Ambient, a Espanya, *Avon Longitudinal Study of Parents and Children*, a Anglaterra, i *European Community Respiratory Health Survey*. La funció pulmonar es mesurà mitjançant espirometria. El pes corporal s'avaluà utilitzant l'índex de massa corporal (IMC). La composició corporal (massa magra i greix) es mesurà utilitzant un escàner de absorciometria de raigs X d'energia dual. Calculàrem canvis al llarg del temps i trajectòries grupals d'IMC, massa magra i/o massa greix.

Resultats: (1) Independentment del pes al néixer, l'augment accelerat de l'IMC des del naixement fins als quatre anys va associar-se amb una major funció pulmonar als set anys, però també amb una limitació del flux aeri. En canvi, els nens amb un pes al néixer més baix i un augment de l'IMC més lent mostraren una menor funció pulmonar als set anys. (2) Un major nivell de massa magra des dels nou fins als quinze anys va associar-se amb una major funció pulmonar als quinze anys en nens i nenes. A més, un major nivell de greix va associar-se amb una menor funció pulmonar en nens i amb

una limitació del flux aeri en nens i nenes. (3) L'associació entre un major nivell de greix i la limitació del flux aeri als quinze anys va ser mitjançada en part (20%) per la resistència a la insulina, però no per la proteïna C-reactiva. (4) L'augment de pes moderat i alt en l'edat adulta va associar-se amb un declivi accelerat de la funció pulmonar, mentre que la pèrdua de pes va relacionar-se amb la seva atenuació.

Conclusions: L'excés de pes i greix tenen efectes nocius sobre la funció pulmonar al llarg de la vida. En canvi, un major nivell de massa magra beneficia el desenvolupament de la funció pulmonar. Els efectes del pes sobre la funció pulmonar semblen reversibles. Aquesta tesi ressalta la importància d'avaluar la composició corporal a l'estudiar els efectes del pes sobre la salut respiratòria i de promoure el control del pes i els nivells de greix per reduir la morbiditat respiratòria en totes les edats.

Preface

The present thesis was written at the Barcelona Institute for Global Health (ISGlobal) between June 2016 and April 2020 and was supervised by Dr. Judith Garcia Aymerich. It is an accumulative thesis, consisting of four scientific articles of which the candidate was the first author. The thesis complies with the procedures and regulations of the Biomedicine PhD Program of the Department of Experimental and Health Sciences of the Universitat Pompeu Fabra.

This thesis book is structured into eight sections, including a general introduction, the thesis's rationale and objectives, an overview of the methods, the research results (four original papers, two of them published, one under review and one in preparation), a global discussion, final conclusions and several annexes. The first paper was conducted as part of the INfancia y Medio Ambiente (INMA, 'Environment and Childhood') Project, a network of prospective population-based birth cohorts in Spain that aim to study the role of environmental exposures during pregnancy and early childhood in relation to child growth, health and development. The three remaining papers were carried out under the framework of the Ageing Lung in European Cohorts (ALEC) project (EU H2020 633212), which aimed to improve our understanding of the determinants and risk factors for low lung function, respiratory disability and the development of chronic obstructive lung disease (COPD), through exploitation of information held within existing cohorts. Out of the cohorts included in the ALEC project, the present thesis used data

from the UK population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort and from the multicentre population-based European Community Respiratory Health Survey (ECRHS).

For this thesis, the PhD candidate requested the data to the relevant cohorts, managed the data, conducted statistical analyses, interpreted the findings and wrote scientific articles for publication. In addition, the PhD candidate has been active in research dissemination, presenting the results of this thesis in national and international scientific conferences and in several seminars at ISGlobal. Furthermore, the PhD candidate participated actively in ALEC work packages 3 and 4, attending to regular teleconferences, annual meetings and participating in the writing of project reports. Finally, the PhD candidate also took on leadership roles at ISGlobal. She co-organised the 5th edition of the ISGlobal PhD symposium and the ISGlobal weekly Scientific Seminar Series during the period from September 2017 to June 2018

Abbreviations

ALEC	Ageing Lung in European Cohorts
ALSPAC	Avon Longitudinal Study of Parents and Children
BIA	Bioimpedance analysis
BMI	Body mass index
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DXA	Dual-energy X-ray absorptiometry
ECRHS	European Community Respiratory Health Survey
FEV_1	Forced expiratory volume in one second
FEF_{25-75}	Forced expiratory flow at 25-75% of the FVC
FMI	Fat mass index
FRC	Functional residual capacity
FVC	Forced vital capacity
GEE	Generalised estimating equations
GLI	Global Lung Initiative
GWAS	Genome wide association study

HOMA-IR	Homeostasis model assessment-estimated insulin resistance
IL-6	Interleukin-6
INMA	Infancia y Medio Ambiente (‘Environment and Childhood’)
LBMI	Lean body mass index
LRTI	Lower respiratory tract infection
MVPA	Moderate to vigorous physical activity
PM	Particular matter
SD	Standard deviation
SNPs	Single-nucleotide polymorphisms
TNF-α	Tumour necrosis factor-alpha
URTI	Upper respiratory tract infection
WHO	World Health Organization

Content

1. INTRODUCTION

1.1 Lung function evolution through life

Lung function (how well the lungs work during exhalation) is a powerful marker of overall health and a strong predictor of morbidity and all-cause mortality in the general population [1,2]. Lung function can be measured using a variety of tests. The most basic test and the most generally used in respiratory research is spirometry, which measures the air that is expired and inspired [3,4]. The primary variables obtained from a spirometry test are the forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). The FVC represents the maximum volume of air exhaled in a maximal forced expiratory manoeuvre, initiated after a full inspiration (expressed in litres). The FEV_1 corresponds to the maximal volume of air exhaled in the first second of the FVC manoeuvre (expressed also in litres). In turn, the FEV_1/FVC ratio shows the relation between both parameters and is usually used as a measure of airflow limitation. In addition to these parameters, spirometry also measures flow rate variables. The most widely used is the mid forced expiratory flow ($FEF_{25\%–75\%}$), which is defined as the flow measured between 25% and 75% of the FVC manoeuvre (expressed in litres per second) [4].

Over the lifespan, lung function progresses through different phases (Figure 1). First, there is a grow phase in which lung function increases while lungs complete their development. This growth phase reaches a peak at early adulthood (20-25 years). There is then a

plateau phase that last for few years and is followed by a decline phase due to physiological lung ageing [5].

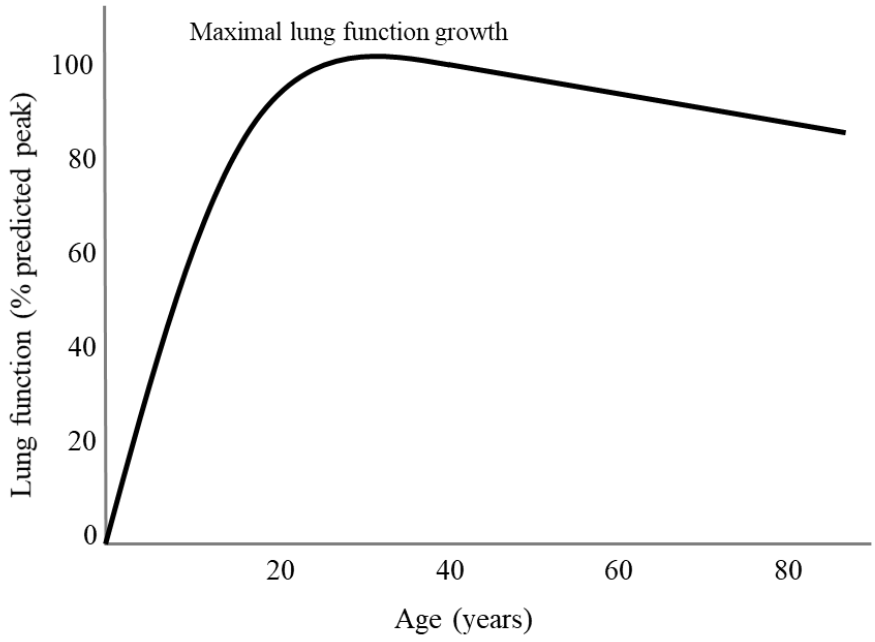

Figure 1. Development of lung function through life

Several genetic and environmental factors can alter any of these phases, resulting in an abnormal lung function growth and/or decline and increasing the risk of poor lung function in adult life. Poor lung function relates to respiratory disability, loss of productive life and loss of active independence [6–8]. At the severe end of the spectrum poor lung function is commonly associated with a diagnosis of chronic obstructive pulmonary disease (COPD), which is a major cause of disability and death worldwide [9,10]. Understanding the determinants of lung function is of relevance because the

demographic pattern is changing around the globe and the prevalence of respiratory disability, low lung function and COPD is expected to increase as population ages [11].

1.1.1 Determinants of lung function growth

Lung development starts in the foetus and comprises five developmental stages: embryonic, pseudoglandular, canalicular, saccular and alveolar [12]. The most substantial structural developments occur during foetal life and the first year after birth, but alveolarisation progresses until early adulthood [12,13]. Since lung development is a continuum process, any alteration of the developmental stages may result in altered lung function and/or in increased risk of respiratory morbidity in later life. Several genetic and environmental factors can affect normal lung function growth and, in consequence, prevent a full growth to maximal lung function in early adulthood.

Genetic factors

Genetic background has been recognised as an important factor for lung function development. Polymorphisms in genes involved in lung growth have been associated with lower lung function levels in childhood as well as with increased risk of wheezing and airway resistance in infancy independently of tobacco smoke exposure [14,15]. Several studies have also reported that genetic alterations in different genes may contribute to genetic predisposition of some individuals to adverse effects of environmental factors such as

tobacco smoke [16]. In addition, a recent genome-wide association study (GWAS) that used data from the UK Biobank concluded that the number of independent genetic associations associated with three lung function parameters (FVC, FEV_1 and FEV_1/FVC) is now 97, representing loci across the whole genome. The total heritability explained by these 97 signals was estimated to 9.6% for FEV_1, 6.4 for FVC and 5.2% for FEV_1/FVC. Importantly, most of the identified single-nucleotide polymorphisms (SNPs) in this study seem to influence lung function both in children and adults [17].

Tobacco smoke exposure

Maternal smoking during pregnancy is a well-established risk factor for impaired lung function growth. Animal studies have shown that exposure to nicotine *in utero* is associated with smaller lungs in offspring, which have fewer, larger alveoli and a low capillary density [18]. Epidemiological studies have reported that maternal smoking during pregnancy is associated with poor lung function, at birth, during childhood and in early adulthood [19–21].. Similar effects on lung function have been reported for postnatal exposure to tobacco smoke [22], which also persists until adult life [23]. In addition, active smoking during adolescence has also been associated with slowed lung function growth, especially in girls [24].

Premature birth

Premature birth (<37 weeks of gestations) is the most common cause of abnormal lung development. The lungs of preterm children are not fully developed and therefore they are susceptible to suboptimal

further development and to lung injury due to artificial ventilation, oxygen therapy and other perinatal factors [25,26]. Despite advances in neonatal care, the prevalence of bronchopulmonary dysplasia (BPD), a neonatal chronic lung disease, has remained high over time and continues to be among the most common diseases in premature children [27,28]. The burden of respiratory problems associated with this chronic disease are high and go far beyond the neonatal period [29]. Longitudinal studies have shown that premature survivors, with or without BPD, have three times higher risk of wheezing disorders and have lower lung functions values than children born at term [30,31]. Other studies also showed that preterm birth is associated with significant lung function deficits at least up to adolescence, particularly for airflow limitations measures [32,33]. In addition, premature birth is an important contributing factor to increased susceptibility to injury by environmental factors [12].

Diet and physical activity

Inadequate availability of nutrients during foetal development has been linked with intrauterine growth retardation and structural alterations in the lungs [34,35]. In particular, vitamin D has been shown to play a key role in lung development [36], and maternal deficiency has been reported to be associated with impaired lung development in school-aged offspring [37,38]. Postnatal nutrition also plays an important role on lung function growth. Children who are breastfeed have higher lung function volumes than children that are formula-fed in early life [39,40]. Consumption of fresh fruit during childhood has also been associated with higher lung function

values in childhood [41,42]. Finally, in the last years, several cross-sectional and longitudinal studies have also shown that physical activity is associated with higher lung function values in childhood, adolescence and early adulthood [43–47].

Environmental pollution

The developing lungs are highly susceptible to damage from exposure to environmental pollutants, including oxidant gases (e.g. ozone), traffic-related emissions and particular matter from biomass fuel combustion [48]. Ozone exposure in children has been linked to several respiratory-related responses in children, including decrements in lung function, shortness of breath and respiratory symptoms such as wheeze and cough [49,50]. Exposure to traffic-related air pollution during pregnancy and childhood has been negatively associated with lung growth and lung function in children and young adults in several studies [51–54]. Finally, childhood exposure to biomass fuels combustion, the main source of indoor air pollution in developing countries, has been clearly linked to respiratory morbidity and mortality [55].

Lower respiratory tract infections and asthma

It is well stablished that children with severe lower tract respiratory infections (LRTI) during early infancy are at risk for later respiratory symptoms and/or lung function impairment. Several studies have reported that both a history of bronchiolitis and wheezing illness are associated with lower lung function in infancy [56–58]. Other longitudinal studies also showed that wheezing and asthma

symptoms during the first years of life are associated with impaired lung function in later childhood [59–61]. In addition, children that develop recurrent wheeze or asthma after a LRTI in infancy are more susceptible to later noxious environmental exposures [62,63] and have an increased risk of low lung function at peak [64].

1.1.2 Determinants of lung function decline

Ageing is accompanied by changes in lung function due to factors such as loss of lung elasticity, weakened muscles of respiration and decreased surface area for alveolar gas exchange [65,66]. This 'natural' age-related decline can be enhanced by several behavioural and environmental factors, most of which take place during adulthood.

Early life factors

In recent years, epidemiological studies have suggested that early life factors (e.g. tobacco exposure, premature birth or LRTI during infancy) may have a direct influence on accelerated lung function decline in adult life, for example by increasing susceptibility to the effects of adult life exposures [67–69]. These and other studies [70,71] have provided strong evidence that lung function deficits established in childhood may track into adult life and increase the risk of respiratory morbidity and COPD.

Smoking

Smoking is one of the major risk factors for lung function decline [72]. In the 1970s, Fletcher and colleagues reported that lung function decline was more accelerated in smokers than in non-smokers, and that in a subgroup of 'susceptible smokers' this acceleration lead to development of COPD [73]. Since that, several epidemiological studies have replicated this association in different study populations, showing also that the negative effects of smoking depend on its intensity and duration [74,75]. Other studies have also showed that smoking cessation is associated with reduced loss of pulmonary function [76]. In addition, there is also evidence that the negative effects of personal smoking are increased in individuals born from mothers that smoked during pregnancy [73].

Diet and physical activity

Several epidemiological studies have studied the effects of diet on adult lung function. Cross-sectional and longitudinal studies have reported a positive association between higher fruit and flavonoid intake and higher lung function levels in middle-aged and elderly adults [77,78]. Similarly, longitudinal studies have showed that a higher intake of fruits and antioxidant nutrients is associated in attenuated lung function decline [79–81]. In addition, a longitudinal study that followed male smokers over a twenty-years periods found that vitamin D deficiency was associated with lower lung function and more rapid decline in smokers [82].

Physical activity has also been investigated in relation to lung function decline. Longitudinal studies have shown that higher physical activity is associated with less lung function decline among smokers [83,84] and adults with asthma [85]. Similarly, another longitudinal study reported that achieving increased fitness from young adulthood to middle age was associated with reduced lung function decline over time [86].

Environmental pollution

There is consistent evidence showing that acute and long-term exposure to outdoor air pollution are associated with decreased lung function values in adults [87,88]. Out of the regulated pollutants, particular matter (PM) has been one of the most extensively studied in relation with lung function decline [89]. Two population-based studies with over a ten-year follow-up showed that exposure to higher long-term concentrations of PM is associated with a meaningful lung function decline in healthy adults [90,91], even if PM concentrations are moderate [90]. There is also evidence showing an association between improvement of air quality (i.e. reduction of PM concentrations) and decreased rate of annual lung function decline [92].

Longitudinal studies have reported that occupational exposures, mainly vapours, gases, dust, fumes and pesticides, are a risk factor for accelerated lung function decline [93–96]. More recently, a population-based study reported that adults exposed to aromatic solvents and metals have greater lung function decline, compared

with those without exposure [97]. Similarly, another study suggested that women cleaning at homer or working as occupational cleaners have accelerated decline in lung function [98].

Other factors

Asthma is a well stablish risk factor for accelerated lung function decline, independently of smoking [99–101]. Recently, longitudinal studies have shown that menopausal status and use of hormonal replacement therapy in menopause are associated with the rate of lung function decline in women, independently of smoking status [102,103]. Other longitudinal population-based studies have also suggested that frequent snoring [104] and exposure to mould [105] can increase the risk of accelerated lung function decline. Finally, there is also evidence that some genetic risk factors (such as the α_1 antitrypsin type) are associated with the rate of lung function decline in adulthood [106].

1.2 The link of body weight and composition with lung function

1.2.1 Body weight and body composition

Body weight is a key characteristic to individual's health. It is defined as a person's mass or weight and is composed of lean body mass, fat mass, bone mass and water. The distinction of the components of body weight, specifically of lean body mass and fat mass, is of relevance because different components have different physiological functions and may play a different role on health outcomes [107].

Body weight that is higher than what is considered normal or healthy for a given height and age is described as overweight or obesity and is usually attributed to an excessive accumulation of fat mass [108,109].

The effects of body weight on health are commonly assessed by means of the body mass index (BMI), calculated by dividing body weight (kg) by height (m) squared. BMI is also commonly used as an indirect measure of body composition, specifically of fat mass as, in general, persons with high BMI tend to have higher levels of fat mass [110]. Fat mass can also be assessed using other indirect measures such as skinfolds, body weight circumferences and bioelectric impedance [111]. In addition, there are also direct measures of body composition such as dual-energy X-ray absorptiometry (DXA), which in addition to fat mass also provides measures for lean body mass, bone mass and water [111].

Body weight and composition change over time. Body weight increases steadily until young adulthood, period in which it tends to stabilize [112]. From mid-childhood onwards, annual increases in body weight are largely due to increases in lean body mass rather than to increases in fat mass [113], but there are important differences by sex [114] The age-related increase in lean body mass is steeper in boys than in girls, especially during puberty [114,115]. In contrast, during late childhood and adolescence, girls exhibit a higher age-related increase in fat mass than boys [114]. In addition, boys and girls differ in terms of the distribution of fat mass. Girls have

considerably more peripheral fat, while boys tend to accumulate fat in the abdominal area [116]. These differences increase with sexual maturation and persist until adulthood [116]. In late adulthood and elderly there are also important changes in terms of body composition. As individuals age, lean body mass decreases while fat mass increases, mainly in the abdominal area [117,118].

Several genetic and environmental factors influence body weight and composition [119,120]. In the last decades, a shift towards a more sedentary lifestyle and a change in dietary patterns has led to a steadily increase of mean body weight [121]. Nowadays, the prevalence of overweight and obesity in children and adults has reached pandemic levels globally [120,121], which is of major concern as these factors are associated with serious health effects. Childhood overweight is associated with lifelong overweight and obesity [122] and with early onset of chronic conditions [123,124]. In addition, overweight and obesity are major risk factors for noncommunicable diseases including cardiovascular diseases, cancer and diabetes mellitus [125]. Obesity is also associated with decreased life expectancy and might lead to reduced quality of life, unemployment, lower productivity and social disadvantages [126,127].

1.2.2 Body weight and composition and lung function growth

Birth weight is an important determinant of lung function growth. Several longitudinal studies have reported that low birth weight (<2,500 grams) is associated with reduced lung function levels in infancy, childhood and adulthood independently of other risk factors such as maternal smoking during pregnancy [128–132]. In the last years, several studies have also assessed the association of post-natal growth characteristics and lung function in childhood (mostly measured by means FVC, FEV_1 and the FEV_1/FVC ratio). The majority of these studies have suggested that accelerated weight growth during infancy and early childhood is associated with higher FEV_1 and FVC but lower FEV_1/FVC ratio (i.e. higher risk of airflow limitation) [33,133–135]. However, these previous studies are limited by their definition of weight growth. Some studies calculated the difference between only two time points [134,136], which does not fully capture weight growth. Other studies derived complex growth patterns (e.g. peak weight and height velocity) [135] that are difficult to interpret and apply in clinical settings.

Overweight and obesity, as measured by BMI, during childhood and adolescence have also been associated with lung function. Although most of the studies have reported an association between higher BMI and lower FEV_1/FVC [137–146], the association with FVC and FEV_1 has been inconsistent. Some studies have reported an association between higher BMI and higher FEV_1 and/or FVC [137,139,140,142,144], whereas other studies have shown that higher

BMI is negatively associated with these lung function parameters [138,143,146]. An important limitation of these studies is the use of BMI to define overweight and obesity, which did not allow the distinction of lean body mass and fat mass. The few studies that have examined body composition in relation to lung function have generally reported than lean body mass is associated with increased lung function levels while fat mass is associated with decreased lung function [147–154]. However, these studies were all cross-sectional and most focused on specific populations (cystic fibrosis, obese children or children with asthma). In addition, most of these studies did not consider relevant potential confounders such as pubertal status, physical activity or diet.

1.2.3 Body weight and composition and lung function decline

There is consistent evidence showing that overweight and obesity are detrimental for adult lung function, mainly described by FEV_1 and FVC [137,155]. Several population-based and occupational cohort studies have shown that excessive weight gain in adult life is associated with lower lung function levels and with accelerated lung function decline independently of age and smoking status [156–162]. Similarly, another population-based study analysing the effects of changes in obesity status on lung function reported that remaining of becoming obese accelerated lung function decline over an eight-year period, while becoming non-obese was related to its attenuation [163]. All these previous studies have been limited to relatively short

follow-up periods (up to 10 years) and most of them investigated this link only up to 50 years of age. This precludes a more comprehensive understanding of the role of weight change on lung function decline and evidences the need for further studies with longer follow-up periods extending into late adult life.

Some cross-sectional studies have also examined the association of body composition and lung function levels in adulthood. These studies have reported that higher lean body mass is associated with higher lung function levels, while higher fat mass is associated with lower lung function [164–171]. However, so far only one study has assessed the association of body composition with lung function decline. In a longitudinal study of 77 elderly subjects (mean age at baseline 72 years), it was reported that loss of lean mass and gain of abdominal fat mass were associated with accelerated lung function decline, and that subjects developing both abdominal fat mass gain and lean body mass loss showed the highest probability of developing worsening in lung function [172].

1.2.4 Mechanism underlying the association of body weight and composition with lung function

Body weight can influence lung function through several mechanisms, which may be specific for each body component:

Lean body mass

Lean body mass is likely to be associated with lung function by means of muscle strength, as higher lean body mass may reflect

increased strength of the diaphragm and chest wall during expansion and contraction during breathing. This hypothesis is supported by several studies showing an association between higher muscle strength (measured mainly using handgrip strength) and higher lung function values in children, adolescents and adults [173–176]. Also, there is evidence showing that respiratory muscle training can improve lung function in adults with chronic conditions [177,178]. In addition, it has been shown that age-related loss of lean body mass is associated with accelerated lung function decline in elderly [172].

Fat mass

Fat mass can affect lung function through mechanical effects on lungs. Abdominal and thoracic fat mass can cause a reduction of the expiratory reserve volume, with an associated reduction in functional residual capacity (FRC) from changes in elastic properties of the chest wall [155,179]. The reduction of FRC may lead to a reduction of airway calibre and to an increase of airway resistance [180]. In addition, fat mass has been associated with a reduction in respiratory system compliance and with and increased work of breathing [180,181].

Fat mass can also impair lung function by inflammatory processes, as adipose tissue is a source of inflammatory mediators [182,183] that can damage lung tissue and reduce airway diameter [184]. There is evidence showing that obese subjects have increased levels of various inflammatory mediators such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) or C-reactive protein (CRP) [185]. Epidemiological studies have reported that systemic inflammation

(measured mainly using CRP) is associated with reduced lung function levels in the general population [186–188]. In addition, fat mass is strongly associated with metabolic alterations [189,190], which can also induce systemic inflammation [191]. In the last years, several large studies have reported an association between metabolic syndrome and lung function impairment in children and adults [191,192]. Finally, higher levels of fat mass are also associated with dysregulation of leptin and adiponectin, hormones produced by the adipose tissue, which may have metabolic effects on the lungs and affect lung function [191].

2. RATIONALE

Lifetime lung function is related with quality of life and all-cause mortality in the general population. Over the lifespan, lung function progresses through phases of growth and decline, which can be disrupted by several genetic and environmental factors resulting in abnormal lung function growth and/or decline. Considering the steadily increase of mean body weight and the pandemic levels of overweight and obesity around the globe, several studies have assessed the effects of body weight on lung function. There is some evidence showing that post-natal weight growth characteristic can affect lung function in childhood. Childhood overweight and obesity have also been related to lung function levels in childhood and adolescence, but the reported associations remain inconsistent. In addition, overweight and obesity, as well as excessive weight gain, during adult life have been suggested to be detrimental to lung function and to increase the risk of accelerated lung function decline.

However, all these previous studies have important limitations that preclude a comprehensive understanding of the role of body weight on lung function over life span. First, the effects of overweight and obesity have been assessed mainly using body mass index (BMI), which does not allow to distinguish the different effects of lean body mass and fat mass on lung function. Second, there is scarce data on the potential mechanisms underlying the association between body weight components and lung function. Finally, the studies on the

effects of weight change over time on lung function have limited interpretation and applicability.

Consequently, there is a strong need for further longitudinal studies on the role of body weight and composition on lifetime lung function that overcome the limitations of previous research.

3. OBJECTIVES

The general objective of this thesis is to assess the association of body weight and composition with lung function growth and decline.

The specific research objectives are:

1. To assess the association of body mass index (BMI) trajectories from birth to four years with lung function at seven years using data from the population-based INfancia y Medio Ambiente (INMA, 'Environment and Childhood') birth cohort in Spain.

2. To assess the association of body weight and composition trajectories, defined using repeated anthropometric and dual-energy X-ray absorptiometry (DXA) scanner measures taken from age seven to fifteen years, with lung function at fifteen years and lung function growth between eight and fifteen years, using data from the UK population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort.

3. To assess whether C-reactive protein (CRP) levels and/or insulin resistance mediate (at least in part) the association of mid-childhood fat mass and FEV_1/FVC at fifteen years in the ALSPAC birth cohort.

4. To assess the lung function trajectories of adults of the population-based European Community Respiratory Health Survey (ECRHS) study according to different weight change profiles over a twenty-year period.

4. METHODS

This section provides a brief overview of the methods used in the thesis. Further methodological details can be found in the methods section of each paper, included in the results section of this thesis.

4.1 Study population

Objective 1 was carried out within the **INfancia y Medio Ambiente (INMA, 'Environment and Childhood') Project** (www.proyectoinma.org), which is a network of population-based birth cohorts in Spain that aim to study the role of environmental exposures during pregnancy and early childhood in relation to child growth, health and development [193]. The analysis presented in this thesis is based on data of three regions of the INMA Project (Sabadell, Gipuzkoa and Valencia). In these regions, 2,270 pregnant women were recruited at prenatal visits at public health care centres or referral hospitals, from 2004 to 2008. After recruitment women were followed up during the pregnancy, and their offspring were evaluated at different timepoints during infancy and childhood.

Objectives 2, 3 and 4 were carried out within the **Ageing Lung in European Cohorts (ALEC) Project** (www.alecstudy.org), which aimed to improve our understanding of risk factors for low lung function, respiratory disability and the development of chronic obstructive lung disease (COPD), by using information held within existing cohort studies. The ALEC project put together data form several international birth and adult population-based cohorts. For

objectives 2 and 3, we used data from the UK population-based **Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort**. ALSPAC recruited 14,541 pregnant women residents in Avon, UK, with expected dates of delivery between the April 1991 and the December 1992. After birth, children have been assessed repeatedly during childhood, adolescence and early adulthood [194,195]. For objective 4, we used data from the multicentre population-based **European Community Respiratory Health Survey (ECRHS)**. ECRHS started in 1991–1993 (ECRHS I), when over 18,000 young adults aged 20-44 years were randomly recruited from available population-based registers (population-based arm), with an oversampling of asthmatics (symptomatic arm). Participants were followed-up in 1999-2003 (ECRHS II) and 2010-2014 (ECRHS III) [196–198].

4.2 Lung function

Lung function was measured by spirometry according to the American Thoracic Society and/or the European Respiratory Society guidelines [199,200], depending on each cohort. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and the FEV_1/FVC ratio were the main outcome variables. For objective 2, we also assessed the forced expiratory flow at 25-75% of the FVC (FEF_{25-75}) as outcome variable and, for objective 3, we only considered the FEV_1/FVC ratio (based on results of objective 2).

4.3 Body weight and composition

For objectives 1 and 4, we used body mass index (BMI), calculated by dividing measured weight (kg) by measured height (m) squared, as the main measure of body weight. Weight change over time was addressed in objective 1, using BMI trajectories previously defined using latent class growth analysis [201], and in objective 4, computing weight change over the follow-up period and classifying it in weight change categories (weight loss, stable weight, moderate weight gain, high weight gain). For objectives 2 and 3, in addition to BMI, we also assessed body composition (total lean body mass and total fat mass), which was measured using a dual-energy X-ray absorptiometry (DXA) scanner [202]. We calculated lean body mass index (LBMI) and fat mass index (FMI) by dividing total lean body mass and total fat mass (kg) by height (m) squared, respectively.

4.4 Statistical analyses

For each research objective, we used appropriate statistical methods to assess the association of body weight and/or composition with lung function measures. For objective 1, we used multivariable mixed linear regression models with random intercepts for participants nested within regions. For objective 2, we used Group-Based Trajectory Modeling for identifying body weight and body composition trajectories, and then multivariable linear regression models to assess the association of these trajectories with lung function. For objective 3, we performed a mediation analysis using the 'mediation' package in 'R'. Finally, for objective 4, we estimated trajectories of lung function over time as a function of weight change

profiles using population-averaged generalised estimating equations. All analyses were adjusted for relevant potential confounders as described in the papers.

5. RESULTS

Paper I: Peralta GP, Abellan A, Montazeri P, Basterrechea M, Esplugues A, González S, Roda C, Santa Marina L, Sunyer J, Vrijheid M, Casas M, Garcia-Aymerich J. Early childhood growth is associated with lung function at seven years: a prospective population-based study. Under major revision in the *European Respiratory Journal.*

Paper II: Peralta GP, Fuertes E, Granell R, Mahmoud O, Roda C, Serra I, Jarvis D, Henderson J, Garcia-Aymerich J. Childhood body composition trajectories and adolescent lung function: Findings from the ALSPAC study. *Am J Respir Crit Care Med* 2019;200:75-83.

Paper III: Peralta GP, Granell R, Bédard A, Howe L, Carsin A-E, Jarvis D, Garcia-Aymerich J. The mediating role of CRP and insulin resistance on the association of fat mass and airflow limitations. In preparation.

Paper IV: Peralta GP, Marcon A, Carsin A-E, Abramson MJ, Accordini S, Amaral AFS, Antó JM, Bowatte G, Burney P, Corsico A, Demoly P, Dharmage S, Forsberg B, Fuertes E, Garcia-Larsen V, Gíslason T, Gullón JA, Heinrich J, Holm M, Jarvis DL, Janson C, Jogi R, Johannessen A, Leynaert B, Martínez-Moratalla Rovira J, Nowak D, Probst-Hensch N, Raherison C, Sánchez-Ramos J, Sigsgaard T, Siroux V, Squillacioti G, Urrutia I, Weyler J, Zock JP, Garcia-Aymerich J. Body mass index and weight change are

associated with adult lung function trajectories: the prospective ECRHS study. *Thorax* 2020;75:313-320.

5.1 Paper I

Peralta GP, Abellan A, Montazeri P, Basterrechea M, Esplugues A, González S, Roda C, Santa Marina L, Sunyer J, Vrijheid M, Casas M, Garcia-Aymerich J.

Early childhood growth is associated with lung function at seven years: a prospective population-based study.

Under major revision in the *European Respiratory Journal*.

Early childhood growth is associated with lung function at seven years: a prospective population-based study

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'Take home' message: Independently of birth size, children with accelerated BMI gain in early childhood had higher lung function at 7 years but showed airflow limitation. Children with lower birth size and slower BMI gain in early childhood had lower lung function at 7 years.

ABSTRACT

Previous studies have related early postnatal growth with later lung function but their interpretation is limited. We aimed to assess the association of early childhood growth, measured by body mass index (BMI) trajectories up to four years, with lung function at seven years.

We included 1,257 children from the Spanish Infancia y Medio Ambiente population-based birth cohort. Early childhood growth was classified in five categories based on BMI trajectories up to four years previously identified using latent class growth analysis. These trajectories differed in birth size ('lower', 'average', 'higher') and in BMI gain velocity ('slower', 'accelerated'). We related these trajectories with lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flow at 25-75% (FEF_{25-75})) at seven years, using multivariable mixed regression.

Compared to children with average birth size and slower BMI gain (reference), children with higher birth size and accelerated BMI gain had higher percent predicted FVC (3.3% [95% CI: 1.0; 5.6]) and lower percent predicted FEV_1/FVC (-1.5% [-2.9; -0.1]) at seven years. Similar associations were observed for children with lower birth size and accelerated BMI gain. Children with lower birth size and slower BMI gain had lower percent predicted FVC at seven years. No association was found for FEF_{25-75}.

Independently of birth size, children with accelerated BMI gain in early childhood had higher lung function at seven years but showed airflow limitation. Children with lower birth size and slower BMI gain in early childhood had lower lung function at seven years.

Keywords: children, epidemiology, INMA, lung function, postnatal growth

BACKGROUND

Early childhood is a critical period for lung function growth [1–3]. The respiratory system starts to develop *in utero* but the airways, particularly the alveoli, continue to develop until early adulthood [1,3,4]. Therefore, early life events can affect normal lung growth and increase the risk of respiratory morbidity in later life [5]. In the last years, several studies have assessed the association between early growth characteristics and lung function in childhood. There is consistent evidence showing that low birth weight is associated with poor lung function (mostly measured by means of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1)) in childhood [6–11]. In addition, previous studies suggested that accelerated weight gain during infancy and childhood is associated with higher FEV_1 and FVC levels but lower FEV_1/FVC ratio, i.e., higher risk of airflow limitation [10–13].

These previous studies are limited by the methods used to assess weight growth. Some studies calculated the differences between only two time points [6,11], which does not fully capture the growth of the infant. Other studies derived complex growth patterns (e.g. peak height and weight growth velocity)[13] and are therefore difficult to interpret and apply in clinical settings. Other analytical strategies that integrate repeated weight information and are, at the same time, easy to interpret for paediatricians and the general public, have not yet been tested in relation to lung function.

In the present study we aimed to assess the association of body mass index (BMI) trajectories from birth to four years with lung function at seven years using data from the population-based INfancia y Medio Ambiente (INMA, "Environment and Childhood") birth cohort in Spain. We previously identified BMI z-score trajectories from birth to four years based on repeated measures of weight and height during early childhood from routine paediatric charts [14], which allow for an accurate assessment of early childhood growth and easier interpretation.

METHODS

Study population

Pregnant women (n=2,270) were recruited at prenatal visits at public health care centres or referral hospitals, from 2004 to 2008, in three regions (Sabadell, Valencia and Gipuzkoa) participating in the Spanish INMA birth cohort [15]. Inclusion criteria were: ≥16 years of age, singleton pregnancy, intention to deliver at reference hospital, and no assisted conception or communication issues. In the present study, we included children who had available information for the identification of BMI z-score trajectories from birth to four years and lung function data at seven years (Figure S1).

The study was approved by the hospital and institutional Ethics Committees in each region. All mothers signed a written consent for themselves and their child's participation.

BMI z-score trajectories

Repeated measurements of child height and weight from birth until four years were extracted from routine paediatric charts (mean [SD] number of measurements per child 11 [3.4]). We calculated BMI by dividing weight in kilograms by height squared in centimetres, and age and sex specific BMI z-scores by using the WHO Child Growth Standards [16]. We previously identified five BMI z-score trajectories (hereon referred to as BMI trajectories) using latent class growth analysis [14,17]. These trajectories differed in birth size (labelled for comparison as 'lower', 'average' or 'higher') and in BMI gain velocity (labelled as 'slower' or 'accelerated') (Figure 1). We used the trajectory with average birth size and slower BMI gain as the reference category in our analysis. The distribution of weight and length/height according to the BMI trajectories in our study sample is presented in Table S1.

Lung function

At seven years, trained nurses measured lung function by spirometry according to American Thoracic Society and the European Respiratory Society guidelines [18]. FVC, FEV_1 and forced expiratory flow 25-75% of the FVC (FEF_{25-75}) were measured, and the FEV_1/FVC ratio was calculated. All children included in the present study had at least one acceptable manoeuvre. We calculated percent predicted lung function parameters by using the Global Lung Function Initiative 2012 prediction equations [19], and we used these variables as the main outcome of the analysis.

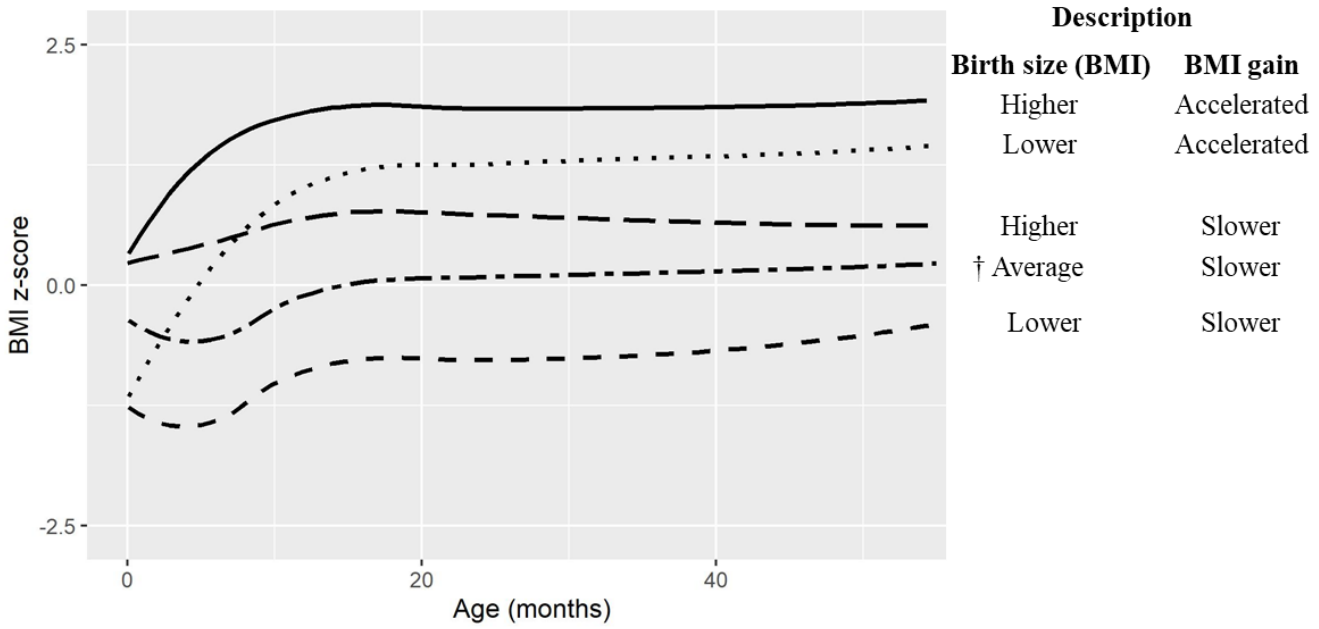

Figure 1. Body mass index (BMI) z-score trajectories from birth to four years

Adapted from Montazeri P., et al. Obesity 2018. † Reference category

Other relevant characteristics

We obtained the following additional information: maternal characteristics (age at delivery, pre-pregnancy BMI, smoking status, educational level and history of allergy-related disease [at least one of the following: allergic asthma, atopic dermatitis, eczema or allergic rhinitis]) using questionnaires during pregnancy; child birth characteristics (sex, gestational age and weight at birth) from medical records; child exposures (duration of any breastfeeding and lower respiratory tract infections) during the first year by postnatal questionnaires; asthma at seven years through questionnaires completed by parents and defined as previously agreed in the MeDALL (Mechanisms of the Development of Allergy) project (see online supplement) [20]; and height at seven years by trained nurses.

Statistical analysis

We assessed the association of BMI trajectories from birth to four years with lung function (FVC, FEV_1, FEV_1/FVC and FEF_{25-75}) at seven years using multivariable mixed linear regression models with random intercepts for participants nested within regions (Sabadell, Valencia and Gipuzkoa). All models were adjusted for maternal age at delivery, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year. We selected covariates based on previous research [10–13] and on subject matter knowledge. We used Direct Acyclic Graphs to identify the

minimum set of covariables required to adjust our models (Figure S2).

To assess whether associations differed by sex, we tested for interaction and stratified models by this variable. We performed several sensitivity analyses to assess the robustness of results to various assumptions regarding inclusion of susceptible subgroups (e.g. children born prematurely or with asthma) and quality of lung function measures (see the online supplement).

Missing data accounted for 4.9% of total observations. We used a complete case strategy and reported missing data in the Table 1 footnotes. All analyses were conducted in Stata/SE 14.0 (StataCorp, College Station, TX, USA). Statistical significance was set at p-value<0.05 for multivariate analyses, and at p-value<0.2 for interaction tests.

RESULTS

Sample description

We included 1,257 children in the present analysis. Mothers of these children were older at pregnancy, had higher educational level and breastfed for a longer period than mothers of children not included in the present analysis (Table S2). Table 1 shows the main characteristics of the study sample. Approximately 17% of mothers reported that they smoked during pregnancy and 37% of them had a high educational level (university). Approximately 5% of the children had low birth weight (<2500 g) and 38% of them were

classified in the BMI trajectory with average birth size and slower BMI gain (reference category).

Table 1. Characteristics of the study sample (n=1,257) *

	n (%), mean (SD) or median (P_{25}-P_{75})
Maternal characteristics	
Age at delivery (years)	30.9 (0.1)
Pre-pregnancy BMI (kg/m^2)	22.6 (20.8 to 25.2)
History of allergy-related disease †	335 (26.7)
Smoking during pregnancy	
Never smoker	573 (46.2)
Smoking before pregnancy	458 (37.0)
Smoking during pregnancy	208 (16.8)
Educational level	
Primary or less	263 (21.2)
Secondary	515 (41.4)
University	465 (37.4)
Child characteristics	
Sex: girl	622 (49.5)
Birth weight (g)	3,258 (458)
Low birth weight (<2,500 g)	65 (5.2)
Gestational age (weeks)	39.9 (38.9 to 40.7)
Preterm birth (<37 weeks)	48 (3.8)
Duration of any breastfeeding (weeks)	25.9 (10.7 to 43.4)
LRTI during the first year	438 (35.4)
Age at 7 years (years)	7.5 (7.0 to 7.8)
Height at 7 years (cm)	124.7 (6.3)
Asthma at 7 years **	115 (9.2)

(Continued)

Table 1. *(Continued)*

	n (%), mean (SD) or median (P_{25}-P_{75})
BMI trajectories from birth to four years	
Higher birth size – accelerated BMI gain	137 (10.9)
Lower birth size – accelerated BMI gain	145 (11.5)
Higher birth size – slower BMI gain	332 (26.4)
Average birth size – slower BMI gain (Ref.)	483 (38.4)
Lower birth size – slower BMI gain	160 (12.7)
Lung function at 7 years ǂ	
Percent predicted FVC (%)	101.8 (12.0)
Percent predicted FEV_1 (%)	104.8 (11.9)
Percent predicted FEV_1/FVC (%)	96.7 (7.5)
Percent predicted FEF_{25-75} (%)	95.1 (23.8)

**Some variables had missing values: Maternal characteristics: 6 in age at delivery, 8 in pre-pregnancy BMI, 1 in allergy-related disease, 18 in smoking, 14 in educational level; Child characteristics: 3 in birth weight, 17 in duration of any breastfeeding, 18 in lower respiratory tract infections during the first year, 3 in asthma at 7 years, 2 in FEF_{25-75} at 7 years.*

† Defined as reporting at least one of the following: allergic asthma, atopic dermatitis, eczema or allergic rhinitis.

*** Asthma was defined as previously agreed in the MeDALL (Mechanisms of the Development of Allergy) project.*

ǂ Calculated by using Global Lung Function Initiative (GLI) 2012 prediction equations.

Abbreviations: BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FEF_{25-75}: forced expiratory flow at 25-75% of the pulmonary volume; FVC: forced vital capacity; LRTI: lower respiratory tract infections; Ref.: reference.

Associations of early childhood BMI trajectories with lung function at seven years

Figure 2 and Table S3 show the adjusted associations between BMI trajectories up to four years and lung function at seven years. Compared to children with average birth size and slower BMI gain (reference), children with higher birth size and accelerated BMI gain had higher percent predicted FVC (3.3% [95% CI: 1.0 to 5.6]) and lower percent predicted FEV_1/FVC ratio (-1.5% [-2.9 to -0.1]) at seven years. Similarly, children with lower birth size and accelerated BMI gain had higher percent predicted FVC (2.8% [0.5 to 5.0]) and tended to have lower percent predicted FEV_1/FVC ratio (-1.3% [-2.7 to 0.1]) than children in the reference category. In contrast, children with lower birth size and slower BMI gain had lower percent predicted FVC (-3.1% [-5.2 to -0.9]) and tended to have lower FEV_1 (-1.9% [-4.1 to 0.3]), but higher percent predicted FEV_1/FVC (1.1% [-0.2 to 2.4]) than children at the reference category. Finally, children with higher birth size and slower BMI gain did not differ from the reference category in lung function values. We found no significant associations of BMI trajectories with FEF_{25-75}.

We observed a statistically significant interaction by sex of the association between accelerated BMI gain and higher FEV_1, which was only present in girls (p=0.075, Table S4). The association of accelerated BMI gain with FVC was stronger in girls than in boys, while the association with FEV_1/FVC was stronger in boys, without presence of statistical interaction.

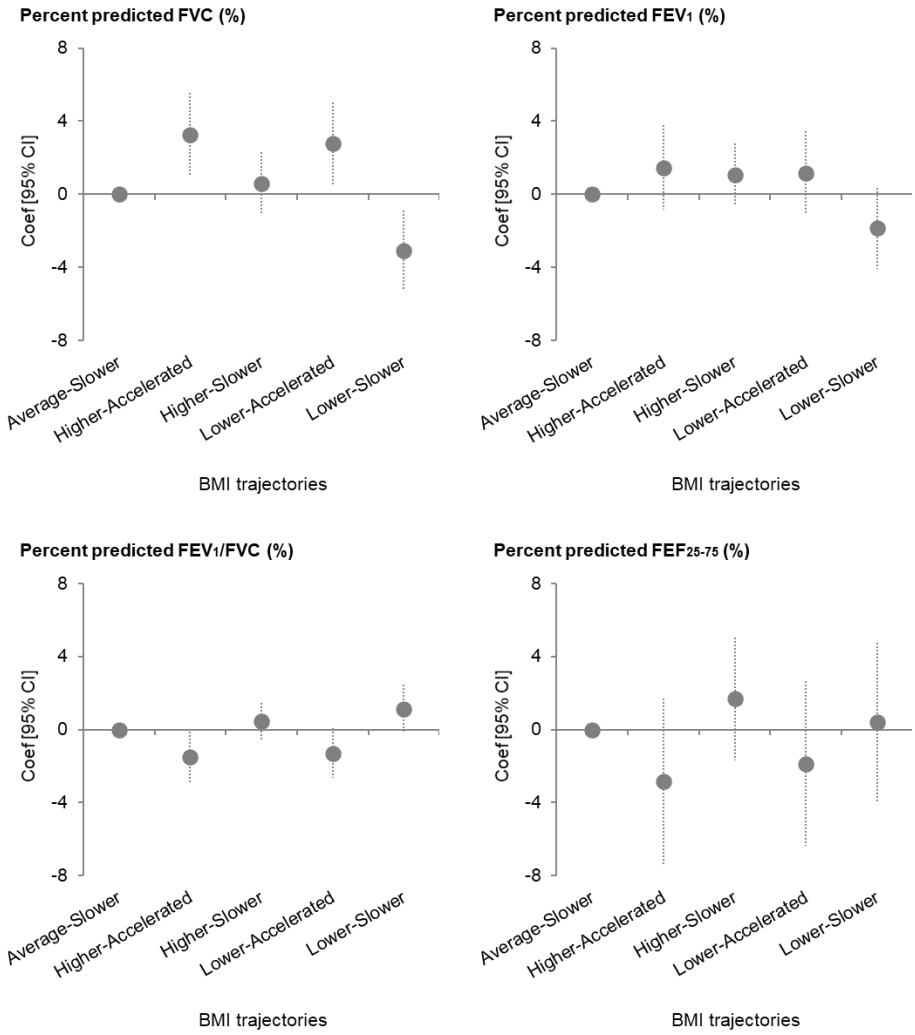

Figure 2. Adjusted associations of early childhood body mass index (BMI) trajectories and lung function at seven years.

All models were adjusted for maternal age at delivery, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year. Abbreviations: FEF_{25-75}: forced expiratory flow 25-75%; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient; 95% CI: 95% confidence intervals.

The direction of the observed associations remained stable in all sensitivity analyses (Tables S5 to S9). However, exclusion of children with extreme lung function values resulted in the attenuation of some FEV_1/FVC effect estimates (Table S7). Also, models restricted to children with at least two acceptable manoeuvres reproducible within 150 mL showed increased effect estimates for the group with higher birth size and accelerated BMI gain (Table S9).

DISCUSSION

Main findings

In this prospective population-based study we found that BMI trajectories from birth to four years relate to lung function at seven years. Specifically, we found that: (i) children with accelerated BMI gain had higher FVC and lower FEV_1/FVC ratio at seven years either if they departed from lower or higher birth size, (ii) children with lower birth size and slower BMI gain had lower FVC and FEV_1, but higher FEV_1/FVC ratio at seven years (although the effect estimates for FEV_1 and FEV_1/FVC were imprecise), and (iii) we found no associations of BMI trajectories with FEF_{25-75} at seven years.

Comparison with previous studies

Our finding that accelerated BMI gain in the first four years of life is associated with higher FVC and lower FEV_1/FVC ratio at seven years is in line with previous longitudinal studies [10–13], which measured early childhood growth using different parameters. The

most recent study using data from the Generation R Study showed that peak weight velocity and BMI at adiposity peak, derived from individual growth trajectories in the first three years of life, were associated with higher FVC and FEV_1 but lower FEV_1/FVC ratio at ten years [13]. Peak weight velocity and BMI at adiposity peak represent accelerated BMI gain particularly in the first year of life, which is the period of fastest growth, as reflected in our trajectories (Figure 1). Similarly, another study using data from the same cohort found that accelerated foetal growth followed by accelerated infant weight growth up to one year (defined as growth percentile change between time periods) were associated with higher FVC and lower FEV_1/FVC ratio at ten years [12]. An important contribution from our study is that, because we distinguished two patterns of accelerated BMI gain (departing from higher and lower birth size), we were able to demonstrate that the effects of accelerated weight gain on lung function do not depend on birth size. Specifically, we observed that accelerated BMI gain was associated with higher FVC at 7 years even if children departed from low birth size. This finding is in line with a previous study showing that children with intrauterine growth restriction who showed weight catch-up growth in the first nine years of life (calculated as the difference between two time points) had higher spirometry measures at age nine years than those without catch-up [6]. Another study also showed that weight gain during the first year of life (defined as the difference between two time points) was associated with higher adult lung function independently of birth weight [21].

We also found that children in the trajectory with lower birth size and slower BMI gain had lower FVC and FEV_1 at seven years than the reference trajectory (although the estimate for FEV_1 was imprecise), which is consistent with existing literature. Previous studies have reported that children with low birth weight or smaller birth size have decreased lung function compared to children with normal birth weight in childhood [6–11]. In addition, these children had higher FEV_1/FVC ratio at seven years (although the estimate was imprecise), which is in line with previous research reporting an association between smaller birth size and higher ratio in childhood [10,11].

We found no association between early childhood growth and FEF_{25-75} at seven years. This finding is in contrast with a previous study showing that rapid weight gain during the first three months of life (derived from individual growth trajectories) was associated with a decreased FEF_{25-75} at eight years [10]. This discrepancy may be attributed to different definitions of childhood growth and different exposure assessment periods (i.e. first three months *vs.* first four years), as well as to differences in sample size.

Interpretation of results

There are three potential mechanisms to explain the associations of accelerated BMI gain in early childhood with higher FVC and lower FEV_1/FVC in later childhood. First, it is possible that accelerated BMI gain during early childhood has greater influence on lung volume than airway growth. This phenomenon is known as

dysanapsis and reflects an incongruence between (faster) growth in lung volume and airway length, and (slower) increase in airway calibre [22,23]. Dysanapsis has been linked with clinical alterations in children with asthma [23] and may be a risk factor for respiratory diseases in later life. Second, it is plausible that accelerated BMI gain is accompanied by accumulation of adipose tissue, which could lead to airflow limitation (as measured by a lower FEV_1/FVC) by means of inflammatory processes. Adipose tissue is a source of pro-inflammatory factors, which can have local effects on the lungs causing structural alterations of the airways [24–26]. This inflammatory hypothesis is supported by a previous longitudinal study showing that higher fat mass during childhood was associated with lower FEV_1/FVC levels in adolescence [27], and by another study showing that subjects with higher BMI had higher adipose tissue and inflammatory cells within the airway wall [26]. Finally, we cannot rule out the possibility that the association of accelerated BMI gain with lower FEV_1/FVC ratio is due to mathematical artefact, since accelerated BMI gain was more strongly associated with FVC than with FEV_1 in the present study. Further studies with available measures of early growth, inflammatory markers, adipose tissue levels and lung structure are needed to understand the potential underlying mechanisms of this association.

A potential explanation for the association of lower birth size and slower BMI gain with lower FVC and FEV_1 at seven years is restricted foetal growth since it may be a common cause of both lower birth size and disrupted lung function. Although the

respiratory system continues developing until early adulthood, the majority of airway and alveoli development takes place *in utero* [3,28]. Several animal studies have reported that restricted foetal growth affects normal lung development causing structural alterations [29,30], which may affect lung function in childhood. In contrast to children with lower birth size and accelerated BMI gain, children with lower birth size and slower BMI gain may not be able to compensate for these lung alterations during the first years of life.

Implications

The findings of the present study have important implications for research and public health. Our study shows that early childhood BMI trajectories are a useful tool to identify growth patterns associated with poor respiratory health. BMI trajectories, which can be estimated using information collected routinely in medical records, represent an accurate way to study early growth that can be easily interpreted for paediatricians and the general public. In addition, our findings, together with existing literature, support that early childhood growth impacts lung function development, and therefore may affect future respiratory health. Since weight growth is affected by modifiable factors, public health interventions promoting healthy lifestyles (e.g. healthy eating and physical activity) in early childhood may help to improve lung function and reduce respiratory morbidity in adulthood.

Strengths and limitations

Strengths of the present study are the longitudinal design and the population-based nature of the INMA cohort. Also, the availability of BMI trajectories from birth to four years allowed us to estimate the association of early growth with lung function accounting simultaneously for birth size and BMI gain. In addition, by using BMI trajectories as a marker of early growth we took into account weight and height changes during the first years of life simultaneously, while most of previous studies have focused only on weight growth [11,12], or have analysed weight and height separately [10,13].

Our study also has some limitations, which include the potential selection bias due to the fact that mothers of children included in the study were older at pregnancy and had a higher educational level than mothers of children not included but participated in the INMA birth cohort. Although we were able to account for a wide range of potential confounders (including gestational age), residual confounding may be a concern as we did not have information on physical activity or diet before four years nor on non-allergic maternal asthma, all of which could be related to BMI growth and lung function. Another potential limitation of this study is the regional basis of the sample which may not allow the generalizability of our results to populations with different environmental and lifestyle factors. Finally, we used BMI as a marker of body growth but BMI is limited by its inability to distinguish between muscle and fat mass, which have different

effects on lung function [27]. Although BMI trajectories in early childhood could be a good predictor of later body composition [31], further research using detailed measures of body composition is needed to provide insight into the effect of body composition during early childhood on later respiratory health.

Conclusion

In conclusion, we found that, independently of birth size, children with accelerated BMI gain in early childhood had higher lung function at seven years but also showed airflow limitation. In contrast, children with lower birth size and slower BMI gain in early childhood had lower lung function at seven years. This study shows that BMI trajectories during the first years of life can identify growth patterns associated with poor respiratory health in later childhood. Our results, together with existing literature, support that early postnatal growth is likely to play a role in lung function development during childhood, and therefore can affect respiratory health in later life. Public health strategies aiming to reduce respiratory health problems may need to target early weight growth.

CONTRIBUTORS

GPP, MC and JG-A designed the study. GPP conducted the statistical analyses and wrote the initial draft. MC and JG-A had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work, revised the manuscript for important intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

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COMPETING INTERESTS

JG-A reports personal fees from Esteve, Chiesi and AstraZeneca, outside the submitted work. Other authors declare no competing interests related to this work

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ONLINE SUPPLEMENT

Contents

Table S9. Adjusted associations of early childhood BMI trajectories with lung function at seven years – Restricting models to children with at least two acceptable manoeuvres reproducible within 150 mL

Definition of asthma at 7 years

Information on asthma at seven years was collected through questionnaires completed by parents. As done in the MeDALL (Mechanisms of the Development of Allergy) project, we defined current asthma based on a positive answer to at least two of the following questions: 1) 'Has your child ever been diagnosed by a doctor as having asthma?'; 2) 'Has your child taken any medicines for asthma (including inhalers, nebulizers, tablets or liquid medicines) or breathing difficulties (chest tightness, shortness of breath) in the last 12 months?'; 3) Has your child had wheezing or whistling in the chest at any time in the last 12 months?'[1].

Reference:

1 Hohmann C, Keller T, Gehring U, *et al.* Sex-specific incidence of asthma, rhinitis and respiratory multimorbidity before and after puberty onset: individual participant meta-analysis of five birth cohorts collaborating in MeDALL. *BMJ Open Resp Res* 2019;6:460. doi:10.1136/bmjresp-2019-000460

Methods: Sensitivity analyses

To assess the robustness of our results we performed several sensitivity analyses. We excluded children with current asthma at seven years, children from mothers who smoked during pregnancy, children with extreme lung function values (below percentile one and above percentile 99) and children born prematurely in separate analyses to assess whether the observed associations were

influenced by these subsamples. We also restricted models to children with at least two acceptable manoeuvres reproducible within 150 mL to account for potential misclassification in lung function.

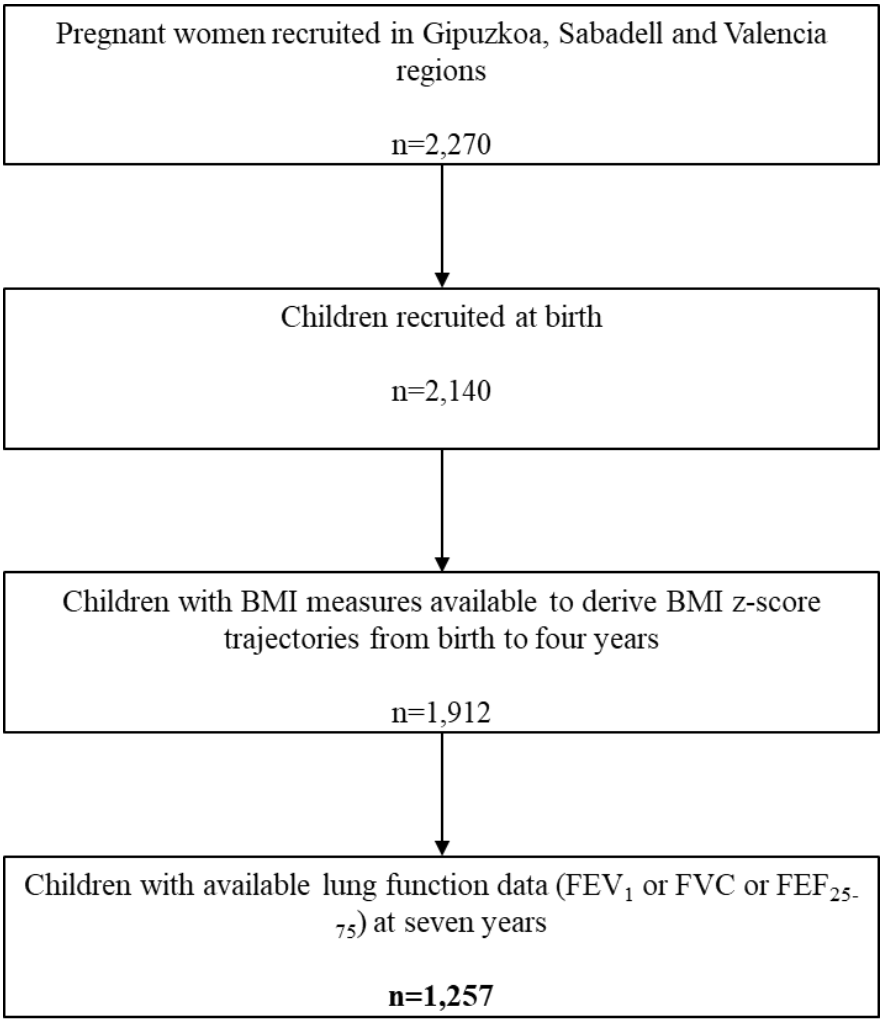

Figure S1. Flowchart of the study sample

Abbreviations: BMI, body mass index; FEV_1: forced expiratory volume in 1 second; FEF_{25-75}: forced expiratory flow at 25-75% of the pulmonary volume; FVC: forced vital capacity

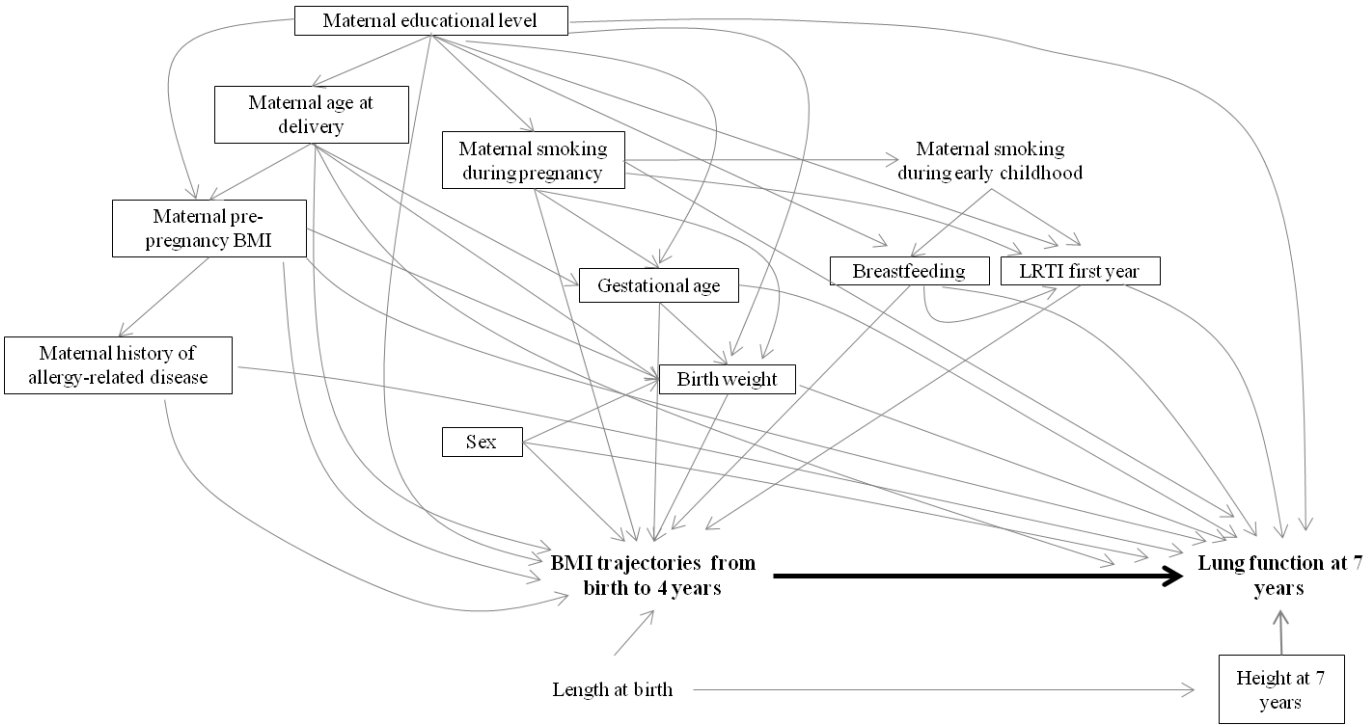

Figure S2. Directed acyclic graph of hypothesised associations between study variables

Variables with black squares represent the minimal adjustment set of covariables required to study the association of BMI trajectories from birth to four years with lung function at seven years. Abbreviations: BMI, body mass index; LRTI, lower respiratory tract infections

Table S1. Distribution of weight and length/height at birth and at one and four years according to BMI trajectories

	n	Higher birth size, accelerated BMI gain n = 137 (10.9%)	Higher birth size, slower BMI gain n= 145 (11.5%)	Lower birth size, accelerated BMI gain n = 332 (26.4%)	Average birth size, slower BMI gain n = 483 (38.4%)	Lower birth size, slower BMI gain n = 160 (12.7%)	Overall n = 1,257 (100%)
Weight							
Birth weight (kg)	1,254	3.5 (0.5)	3.4 (0.4)	3.1 (0.4)	3.2 (0.4)	3.0 (0.5)	3.3 (0.5)
Weight at 1 year (kg)	1,143	11.5 (1.1)	10.3 (0.9)	11.0 (1.1)	9.7 (0.9)	9.1 (0.9)	10.1 (1.2)
Weight at 4 years (kg)	1,200	20.7 (2.9)	18.2 (2.1)	20.2 (3.1)	17.6 (2.1)	16.1 (1.9)	18.2 (2.7)
Height							
Birth length (cm)	1,224	49.8 (2.0)	49.9 (1.9)	49.1 (2.4)	49.6 (2.1)	49.0 (2.6)	49.6 (2.2)
Height at 1 year (cm)	1,143	77.7 (3.0)	76.7 (2.9)	77.2 (3.3)	76.4 (2.9)	76.3 (3.0)	76.7 (3.0)
Height at 4 years (cm)	1,200	106.7 (4.4)	105.2 (4.3)	107.2 (4.7)	105.5 (4)	104.6 (4.4)	105.6 (4.3)

Values are means and standard deviations. Abbreviations: BMI: body mass index

Table S2. Characteristics of included and non-included participants

	Participants (n=1,257) n (%), mean (SD) or median (P_{25}-P_{75})	Non-participants (n=1,013) n (%), mean (SD) or median (P_{25}-P_{75})	*p*-value*
Maternal characteristics			
Age at delivery (years)	30.9 (0.1)	29.7 (0.2)	<0.001
Pre-pregnancy BMI (kg/m^2)	22.6 (20.8 to 25.2)	22.5 (20.7 to 25.1)	0.559
History of allergy-related disease †	335 (26.7)	246 (25.2)	0.417
Smoking during pregnancy			
Never smoker	573 (46.2)	361 (41.6)	0.061
Smoking before pregnancy	458 (37.0)	334 (38.5)	
Smoking during pregnancy	208 (16.8)	173 (20.0)	
Educational level			
Primary or less	263 (21.2)	312 (33.4)	<0.001
Secondary	515 (41.4)	376 (40.3)	
University	465 (37.4)	245 (26.3)	
Child characteristics			
Sex: girls	622 (49.5)	415 (47.2)	0.302
Birth weight (grams)	3,258 (458)	3,256 (521)	0.764
Low birth weight (<2,500 g)	65 (5.2)	45 (5.2)	0.994
Gestational age (weeks)	39.9 (38.9 to 40.7)	39.9 (38.9 to 40.6)	0.959
Preterm birth (<37 weeks gestation)	48 (3.8)	40 (4.6)	0.390
Duration of any breastfeeding (weeks)	25.9 (10.7 to 43.4)	21.8 (5.7 to 39)	0.001
LRTI during the first year	438 (35.4)	240 (34.3)	0.637

† Defined as reporting at least one of the following: allergic asthma, atopic dermatitis, eczema or allergic rhinitis.
** p-value for chi-squared, t-test or U-Mann Witney tests*
Abbreviations: BMI: body mass index; LRTI: lower respiratory tract infections

Table S3. Adjusted associations of early childhood BMI trajectories with lung function at seven years

	Percent predicted FVC (%)		Percent predicted FEV_1 (%)		Percent predicted FEV_1/FVC (%)		Percent predicted FEF_{25-75} (%)	
BMI trajectories	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**
n	1,195		1,195		1,195		1,193	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	3.3 (1.0 to 5.6)	0.005	1.5 (-0.9 to 3.8)	0.215	-1.5 (-2.9 to -0.1)	0.031	-2.8 (-7.4 to 1.7)	0.222
Higher birth size - Slower BMI gain	0.6 (-1.1 to 2.3)	0.480	1.1 (-0.6 to 2.8)	0.214	0.4 (-0.6 to 1.5)	0.407	1.7 (-1.7 to 5.1)	0.325
Lower birth size - Accelerated BMI gain	2.8 (0.5 to 5.0)	0.016	1.2 (-1.1 to 3.5)	0.315	-1.3 (-2.7 to 0.1)	0.064	-1.9 (-6.4 to 2.6)	0.417
Lower birth size - Slower BMI gain	-3.1 (-5.2 to -0.9)	0.006	-1.9 (-4.1 to 0.3)	0.098	1.1 (-0.2 to 2.4)	0.096	0.4 (-3.9 to 4.7)	0.858

All models were adjusted for maternal age at delivery, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year
Abbreviations: BMI: body mass index; FEF_{25-75}, forced expiratory flow 25-75%; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

Table S4. Adjusted associations of early childhood BMI trajectories with lung function at seven years - Stratified by sex

BMI trajectories	Percent predicted FVC (%)		Percent predicted FEV_1 (%)		Percent predicted FEV_1/FVC (%)		Percent predicted FEF_{25-75} (%)	
	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value
Girls								
n	590		590		590		588	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	5.6 (2.2 to 8.9)	0.001	4.5 (1.2 to 7.7)	0.007	-0.9 (-2.8 to 1.0)	0.370	0.3 (-5.9 to 6.5)	0.928
Higher birth size - Slower BMI gain	1.9 (-0.5 to 4.3)	0.120	1.6 (-0.8 to 4)	0.186	-0.2 (-1.6 to 1.2)	0.806	0.8 (-3.7 to 5.3)	0.732
Lower birth size - Accelerated BMI gain	4.5 (1.2 to 7.8)	0.007	3.2 (0 to 6.5)	0.051	-1.0 (-2.9 to 0.9)	0.316	0.5 (-5.7 to 6.7)	0.883
Lower birth size - Slower BMI gain	-3.3 (-6.6 to -0.1)	0.045	-2.1 (-5.4 to 1.1)	0.193	1.4 (-0.4 to 3.3)	0.134	-0.9 (-7.1 to 5.2)	0.768
Boys								
n	605		605		605		605	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	1.3 (-1.8 to 4.4)	0.420	-1.4 (-4.7 to 1.9)	0.395	-2.3 (-4.4 to -0.3)	0.025	-6.3 (-13 to 0.3)	0.062

(Continued)

Table S4. *(Continued)*

BMI trajectories	Percent predicted FVC (%)		Percent predicted FEV_1 (%)		Percent predicted FEV_1/FVC (%)		Percent predicted FEF_{25-75} (%)	
	Coef (95% CI)	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**
Higher birth size - Slower BMI gain	-0.3 (-2.7 to 2.1)	0.803	0.8 (-1.7 to 3.2)	0.543	1.0 (-0.5 to 2.6)	0.190	2.4 (-2.6 to 7.4)	0.340
Lower birth size - Accelerated BMI gain	1.3 (-1.7 to 4.4)	0.388	-0.6 (-3.8 to 2.6)	0.727	-1.5 (-3.5 to 0.5)	0.146	-3.9 (-10.4 to 2.6)	0.239
Lower birth size - Slower BMI gain	-3.2 (-6.1 to -0.3)	0.030	-2.3 (-5.3 to 0.8)	0.148	0.7 (-1.2 to 2.6)	0.471	-0.2 (-6.3 to 6.0)	0.957
p-value for sex interaction		0.216		0.075		0.385		0.410

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year
Abbreviations: BMI: body mass index; FEF_{25-75}, forced expiratory flow 25-75%; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

Table S5. Adjusted associations early childhood BMI trajectories with lung function at seven years – Excluding children with current asthma at seven years

	Percent predicted FVC (%)		Percent predicted FEV_1 (%)		Percent predicted FEV_1/FVC (%)		Percent predicted FEF_{25-75} (%)	
BMI trajectories	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**
n	1,087		1,087		1,087		1,085	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	3.6 (1.2 to 5.9)	0.003	1.8 (-0.6 to 4.2)	0.149	-1.5 (-3.0 to -0.1)	0.038	-3.0 (-7.7 to 1.7)	0.214
Higher birth size - Slower BMI gain	0.9 (-0.9 to 2.6)	0.323	1.1 (-0.6 to 2.9)	0.209	0.2 (-0.8 to 1.3)	0.662	1.3 (-2.2 to 4.8)	0.466
Lower birth size - Accelerated BMI gain	3.1 (0.8 to 5.4)	0.009	1.5 (-0.9 to 3.9)	0.215	-1.3 (-2.7 to 0.1)	0.069	-1.8 (-6.5 to 2.9)	0.453
Lower birth size - Slower BMI gain	-2.7 (-4.9 to -0.4)	0.020	-1.9 (-4.2 to 0.4)	0.108	0.7 (-0.7 to 2.1)	0.307	-0.4 (-5.0 to 4.1)	0.846

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year
Abbreviations: BMI: body mass index; FEF_{25-75}, forced expiratory flow 25-75%; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

Table S6. Adjusted associations of early childhood BMI trajectories with lung function at seven years – Excluding children from mothers who smoked during pregnancy

	Percent predicted FVC (%)		Percent predicted FEV_1 (%)		Percent predicted FEV_1/FVC (%)		Percent predicted FEF_{25-75} (%)	
BMI trajectories	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**
n	995		995		995		993	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	2.7 (0.2 to 5.3)	0.036	1.0 (-1.6 to 3.6)	0.448	-1.5 (-3.0 to 0.1)	0.064	-3.0 (-8.1 to 2.1)	0.247
Higher birth size - Slower BMI gain	0.6 (-1.2 to 2.5)	0.511	0.9 (-1.0 to 2.8)	0.352	0.2 (-0.9 to 1.4)	0.683	0.8 (-2.9 to 4.5)	0.664
Lower birth size - Accelerated BMI gain	2.4 (-0.1 to 5.0)	0.064	1.6 (-1.0 to 4.2)	0.228	-0.7 (-2.2 to 0.9)	0.402	-0.4 (-5.4 to 4.7)	0.886
Lower birth size - Slower BMI gain	-2.8 (-5.1 to -0.4)	0.020	-1.4 (-3.8 to 0.9)	0.236	1.2 (-0.2 to 2.6)	0.086	1.2 (-3.4 to 5.8)	0.615

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year
Abbreviations: BMI: body mass index; FEF_{25-75}, forced expiratory flow 25-75%; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

Table S7. Adjusted associations of early childhood BMI trajectories with lung function at seven years – Excluding children with extreme lung function values (<p1 & >p99)

	Percent predicted FVC (%)		Percent predicted FEV_1 (%)		Percent predicted FEV_1/FVC (%)		Percent predicted FEF_{25-75} (%)	
BMI trajectories	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**
n	1,172		1,171		1,174		1,172	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	2.7 (0.6 to 4.8)	0.013	1.3 (-0.9 to 3.4)	0.247	-0.8 (-2.1 to 0.5)	0.230	-0.9 (-5.3 to 3.4)	0.672
Higher birth size - Slower BMI gain	0.2 (-1.4 to 1.7)	0.825	0.8 (-0.7 to 2.4)	0.293	0.6 (-0.4 to 1.5)	0.218	1.0 (-2.2 to 4.2)	0.534
Lower birth size - Accelerated BMI gain	2.7 (0.6 to 4.8)	0.011	1.6 (-0.5 to 3.7)	0.136	-0.9 (-2.2 to 0.4)	0.157	-0.3 (-4.6 to 4.0)	0.889
Lower birth size - Slower BMI gain	-2.8 (-4.8 to -0.8)	0.007	-1.6 (-3.6 to 0.4)	0.107	1.3 (0.1 to 2.6)	0.033	1.0 (-3.1 to 5.1)	0.637

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year
Abbreviations: BMI: body mass index; FEF_{25-75}, forced expiratory flow 25-75%; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence intervals

Table S8. Adjusted associations of early childhood BMI trajectories with lung function at seven years – Excluding preterm children

	Percent predicted FVC (%)		Percent predicted FEV_1 (%)		Percent predicted FEV_1/FVC (%)		Percent predicted FEF_{25-75} (%)	
BMI trajectories	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**
n	1,151		1,151		1,151		1,149	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	2.8 (0.5 to 5.1)	0.015	1.1 (-1.2 to 3.5)	0.335	-1.4 (-2.8 to 0.0)	0.046	-2.8 (-7.4 to 1.7)	0.222
Higher birth size - Slower BMI gain	0.6 (-1.1 to 2.3)	0.495	1.2 (-0.5 to 2.9)	0.181	0.5 (-0.5 to 1.6)	0.315	2.1 (-1.3 to 5.4)	0.235
Lower birth size - Accelerated BMI gain	2.8 (0.5 to 5.1)	0.017	1.4 (-1.0 to 3.7)	0.257	-1.2 (-2.6 to 0.2)	0.103	-1.4 (-6.0 to 3.2)	0.546
Lower birth size - Slower BMI gain	-3.0 (-5.2 to -0.8)	0.008	-1.6 (-3.9 to 0.6)	0.161	1.3 (-0.1 to 2.6)	0.064	1.2 (-3.2 to 5.7)	0.581

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year
Abbreviations: BMI: body mass index; FEF_{25-75}, forced expiratory flow 25-75%; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

Table S9. Adjusted associations of early childhood BMI trajectories with lung function at seven years – Restricting models to children with at least two acceptable manoeuvres reproducible within 150 mL

	Percent predicted FVC (%)		Percent predicted FEV_1 (%)		Percent predicted FEV_1/FVC (%)		Percent predicted FEF_{25-75} (%)	
BMI trajectories	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**	**Coef (95% CI)**	***p*-value**
n	939		939		939		939	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	4.9 (2.4 to 7.4)	<0.001	2.7 (0.2 to 5.2)	0.033	-1.9 (-3.4 to -0.4)	0.014	-2.4 (-7.4 to 2.6)	0.354
Higher birth size - Slower BMI gain	0.0 (-1.8 to 1.8)	0.994	0.2 (-1.6 to 2.0)	0.809	0.2 (-0.9 to 1.3)	0.711	0.7 (-2.9 to 4.2)	0.701
Lower birth size - Accelerated BMI gain	2.4 (0.0 to 4.8)	0.046	0.9 (-1.5 to 3.3)	0.453	-1.4 (-2.8 to 0.1)	0.062	-2.6 (-7.4 to 2.2)	0.280
Lower birth size - Slower BMI gain	-2.6 (-4.9 to -0.3)	0.025	-1.7 (-3.9 to 0.6)	0.154	0.9 (-0.5 to 2.2)	0.210	0.0 (-4.6 to 4.6)	0.997

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year
Abbreviations: BMI: body mass index; FEF_{25-75}, forced expiratory flow 25-75%; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

5.2 Paper II

Peralta GP, Fuertes E, Granell R, Mahmoud O, Roda C, Serra I, Jarvis D, Henderson J, Garcia-Aymerich J.

Childhood body composition trajectories and adolescent lung function: Findings from the ALSPAC study.

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ORIGINAL ARTICLE

Childhood Body Composition Trajectories and Adolescent Lung Function

Findings from the ALSPAC study

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Abstract

Rationale: Body composition changes throughout life may explain the inconsistent associations reported between body mass index and lung function in children.

Objectives: To assess the associations of body weight and composition trajectories from 7 to 15 years with lung function at 15 years and lung function growth between 8 and 15 years.

Methods: Sex-specific body mass index, lean body mass index, and fat mass index trajectories were developed using Group-Based Trajectory Modeling on data collected at least twice between 7 and 15 years from 6,964 children (49% boys) in the UK Avon Longitudinal Study of Parents and Children birth cohort. Associations of these trajectories with post-bronchodilation lung function parameters at 15 years and with lung function growth rates from 8 to 15 years were assessed using multivariable linear regression models, stratified by sex, in a subgroup with lung function data ($n = 3,575$).

Measurements and Main Results: For all body mass measures we identified parallel trajectories that increased with age. There was no consistent evidence of an association between the body mass index trajectories and lung function measures. Higher lean body mass index trajectories were associated with higher levels and growth rates of FVC, FEV_1, and forced expiratory flow, midexpiratory phase in both sexes (e.g., boys in the highest lean body mass index trajectory had on average a 0.62 L [95% confidence interval, 0.44–0.79; P trend < 0.0001] higher FVC at 15 yr than boys in the lowest trajectory). Increasing fat mass index trajectories were associated with lower levels and growth rates of FEV_1 and forced expiratory flow, midexpiratory phase only in boys and lower levels of FEV_1/FVC in both sexes.

Conclusions: Higher lean body mass during childhood and adolescence is consistently associated with higher lung function at 15 years in both sexes, whereas higher fat mass is associated with lower levels of only some lung function parameters.

Keywords: ALSPAC; children; epidemiology; respiratory health

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At a Glance Commentary

Scientific Knowledge on the Subject: Previous studies have shown inconsistent results regarding the association of overweight/obesity with lung function in children and adolescents, likely because most have defined overweight/obesity using the body mass index. However, the body mass index does not distinguish between different components of body weight (e.g., fat mass and lean body mass). The few studies that have assessed the role of body composition on lung function in children and adolescents are all cross-sectional and based on specific populations (subjects with asthma, obese children, cystic fibrosis), and most did not consider the role of relevant confounders, such as previous lung function levels, pubertal status, physical activity, and diet.

What This Study Adds to the Field: This longitudinal study uses data from a large population-based birth cohort with repeated objective measures of body composition and information on numerous relevant confounders to show that higher lean body mass during childhood and adolescence is associated with higher levels of FEV_1, FVC, and forced expiratory flow, midexpiratory phase at 15 years and with higher growth rates of these parameters from 8 to 15 years. Higher fat mass was associated with lower levels and growth rates of FEV_1 and forced expiratory flow, midexpiratory phase only in boys and lower levels of FEV_1/FVC in both sexes. Our study highlights the importance of assessing body composition, and not just body mass index, when studying the respiratory health effects of body weight in children and adolescents.

Lung function is a powerful marker of overall health and a significant predictor of future morbidity and mortality in the general population (1). Because lung function levels in childhood predict adult lung function, identifying factors that influence the development of lung function in childhood is important. Given the current global increase of childhood overweight and obesity, several studies have assessed their associations with lung function, but findings are inconsistent. Some studies report a positive association of overweight and obesity, as measured by body mass index (BMI), with lung function, whereas others show a negative association (2–8). An important limitation of these studies is that they did not distinguish between lean body mass and fat mass, both of which contribute to the composite measure BMI.

Some studies have examined body composition measures in relation to lung function, but they were all cross-sectional, most focused on specific populations (cystic fibrosis, obese children, or children with asthma) and most did not consider pubertal status, physical activity, or diet as relevant confounders (9–16). Furthermore, they only considered measurements at a single time point, and did not capture changes in the proportion of the different components of body weight (e.g., fat mass, lean body mass, bone mass) that occur over time and vary with sex (17).

Here we assess the association of body weight and composition trajectories, defined using repeated anthropometric and dual-energy X-ray absorptiometry scanner measures taken from age 7 to 15 years, with lung function at 15 years and lung function growth between 8 and 15 years, using data from the UK population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. This approach overcomes the limitations of previous research.

Some of the results of this study have been previously reported in the form of an abstract to the European Respiratory Society annual congress (18).

Methods

Complete details are provided in the online supplement.

Study Population

We used data from the 14,305 singleton births recruited in the population-based UK ALSPAC birth cohort, previously described (19, 20). For the identification of body weight and composition trajectories, we included children with at least two repeated measures of body weight and composition between the ages of 7 and 15 years ($n = 6{,}964$). Children who additionally had lung function measures at age 15 years were used to evaluate associations of body weight and composition trajectories with lung function measures at 15 years ($n = 3{,}575$) (*see* Figure E1 in the online supplement).

The ALSPAC Ethics and Law Committee and the Local Research Ethics Committees gave ethical approval. All participants and their parents/guardians provided written informed consent.

Measures

Body weight, height, and composition were assessed following standardized procedures (21). Weight and height were measured every year from age 7 to 15 years. Body composition (total lean body mass, total fat mass, and total bone mass) was measured using a Lunar Prodigy dual-energy X-ray absorptiometry scanner at age 9, 11, 13, and 15 years. BMI, lean body mass index (LBMI), and fat mass index (FMI) were calculated by dividing body weight, total lean body mass, and total fat mass (kg) by height (m) squared, respectively.

Lung function was measured by spirometry at 8 and 15 years (Vitalograph 2120; Vitalograph) according to American Thoracic Society standards (22). At 15 years, lung function was measured before and after bronchodilation with salbutamol. FVC, FEV_1, and forced expiratory flow, midexpiratory phase ($FEF_{25–75}$) were obtained and the FEV_1/FVC ratio was calculated. The outcomes of the analysis were: post-bronchodilation lung function measures at 15 years and rate of lung function growth from age 8 to 15 years (calculated as [prebronchodilation lung function at 15 yr – prebronchodilation lung function at 8 yr]/time of follow-up in yr).

We collected information, at different time points, on maternal social class, birthweight, gestational age, breastfeeding, tobacco exposure (during pregnancy, childhood, and first hand), total dietary energy intake, physical activity (by accelerometer), asthma doctor-diagnosis, and pubertal status.

Statistical Analysis

We conducted all analyses stratified by sex as body weight and composition as well as lung function have been found to differ across sexes.

We identified BMI trajectories by applying a Group-Based Trajectory Modeling approach (23) using yearly data from ages 7 to 15 years, and LBMI and FMI trajectories using data from ages 9, 11, 13, and 15 years. Because the distribution of BMI and FMI was right-skewed, we applied the natural log-transformation to all body weight and composition measures before the identification of the trajectories. The

assigned trajectory was used as the exposure variable in all subsequent analyses.

Associations of body weight and composition trajectories with post-bronchodilation lung function measures at age 15 years and lung function growth rates from age 8 to 15 years were examined using multivariable linear regression. The final multivariable models included adjustments for maternal social class, maternal smoking during pregnancy, birth weight, any breastfeeding, pubertal status, and age and height at 15 years. We additionally adjusted all models for lung function levels at 8 years to reduce potential reverse causality. The models for the LBMI and FMI trajectories were also mutually adjusted.

We conducted several sensitivity analyses to assess the sensitivity of our estimates to varying assumptions regarding selection bias, information bias, and confounding (*see* online supplement).

All analyses were conducted using Stata/SE version 12.0 (StataCorp).

Results

Characteristics of Study Sample

We included 6,964 children (49.0% boys) in the identification of the body weight and composition trajectories. These children were more likely to be girls, have a higher socioeconomic status, a higher birth weight, a higher proportion of breastfeeding, and lower maternal smoking exposure than the children not included in the present analysis but participating in ALSPAC. Additionally, boys had lower LBMI and girls had lower BMI at 9 years when compared with the children not included in our analysis (*see* Table E1). A subset of the included children with available spirometry was used to analyze the associations of body weight and composition trajectories with lung function at 15 years ($n = 3{,}575$; 47.2% boys). The children in this subgroup were more likely to be girls and have a higher socioeconomic status, a higher proportion of breastfeeding, and lower maternal smoking exposure than those not included, but they did not differ in terms of body weight and composition trajectories or in baseline lung function measures (*see* Table E2).

Table 1 shows the main characteristics of the sample subset used in the association analysis with lung function. Approximately half of the mothers had a high social class and around 16% smoked during pregnancy. Boys had significantly higher lung function levels (FVC, FEV_1, and $FEF_{25–75}$) at 8 and 15 years and higher lung function growth between 8 and 15 years than girls. Figure 1 and Table 2 show the body weight and composition characteristics of the children across ages. Body weight was composed mainly of lean body mass at all ages for both boys and girls. The amount of lean body mass and fat mass changed over time, although this pattern differed by sex. Boys had lower BMI and FMI, but higher LBMI, than girls at all ages.

Body Weight and Composition Trajectories

In both boys and girls, we identified four parallel BMI trajectories from 7 to 15 years. For both sexes, BMI increased with age (Figure 2; *see* Table E3). According to the World Health Organization reference cutoffs (24), we labeled these trajectories as "normal-low," "normal-high," "overweight," and "obese." In boys, the median BMI increased from 14.6 kg/m^2 at age 7 years to 18.3 kg/m^2 at age 15 years in the "normal-low" BMI trajectory and from 20.1 kg/m^2 at age 7 years to 27.7 kg/m^2 at age 15 years in the "obese" BMI trajectory (*see* Table E3).

For LBMI, we identified four parallel trajectories from age 9 to 15 in both sexes (Figure 2; *see* Table E4). According to reference curves for body composition in children (25), we labeled these trajectories as "low," "medium-low," "medium-high," and "high." Median LBMIs were consistently greater in boys than girls for all trajectories. Also, the increase per year of LBMI was steeper in boys than girls, specifically between age 11 and 15 years.

For FMI, we identified four parallel trajectories from age 9 to 15 in both sexes, which we labeled "low," "medium-low," "medium-high," and "high" (Figure 2; *see* Table E5) (25). Median FMIs were consistently greater in girls than boys for all trajectories. In boys, FMI levels consistently increased from age 9 to 11 years and then slightly declined from age 11 years onward. In girls, FMI consistently increased up to 15 years in all trajectories.

Associations of Body Weight and Composition Trajectories with Post-bronchodilation Lung Function at 15 Years

Adjusted associations between the BMI trajectories and post-bronchodilation lung function measures at age 15 years were inconsistent. Significant associations were only apparent for some trajectories and some lung function parameters (Figure 3; *see* Table E6).

Both boys and girls in the highest LBMI trajectories had higher FVC, FEV_1, and $FEF_{25–75}$. The association between the LBMI trajectories and these lung function variables exhibited a linear dose–response pattern (e.g., boys in the "medium-low," "medium-high," and "high" LBMI trajectory groups had on average a 0.24 L 95% confidence interval [0.09–0.39], 0.44 L [0.29–0.59], and a 0.62 L [0.44–0.79] higher FVC respectively than boys in the "low" LBMI trajectory [P-trend < 0.0001]). We did not find any statistically significant association between the LBMI trajectories and the FEV_1/FVC ratio for either sex (Figure 3; *see* Table E6).

Boys in the "high" FMI trajectory had lower FEV_1 (−0.14 L [−0.26 to −0.01]; $P = 0.032$) than boys in the "low" FMI trajectory and there was a trend toward lower $FEF_{25–75}$ with higher FMI trajectories (P-trend = 0.028). We did not find any statistically significant association between FMI trajectories and FEV_1 or $FEF_{25–75}$ in girls, nor between FMI trajectories and FVC in boys or girls. Both boys and girls who were in the highest FMI trajectory exhibited lower FEV_1/FVC ratios (Figure 3; *see* Table E6).

All sensitivity analyses showed very similar results for LBMI (*see* Tables E8–E13), even after additional adjustment for physical activity and total energy intake (*see* Table E8). For the FMI trajectories, the association between a higher FMI trajectory and a lower FEV_1/FVC ratio was maintained in all sensitivity analysis, but the associations with the other lung function parameters were more instable: first, the magnitude of the associations of FMI with FEV_1 and $FEF_{25–75}$ (observed only in boys in the main analysis) was attenuated in some of the analyses and second, an association appeared between the "high" FMI trajectory and post-bronchodilation FVC in girls only in some of the models.

Associations of Body Weight and Composition Trajectories with Prebronchodilation Lung Function Growth Rates from Age 8 to 15 Years

After adjusting for relevant confounders, there was no evidence of a consistent association between BMI trajectories and

Table 1. Characteristics of the Participants Used to Assess Associations of Body Weight and Composition Trajectories with Lung Function at 15 Years

	Total (*n* = *3,575*)	Boys (*n* = *1,687*)	Girls (*n* = *1,888*)	*P* Value
Potential confounders				
Maternal social class	2,941			
Professional and intermediate	1,322	639 (46.2)	683 (43.8)	0.712
Skilled nonmanual	1,179	554 (40.1)	625 (40.1)	
Skilled manual, partly skilled, and unskilled	440	190 (13.7)	250 (16.1)	
Maternal smoking during pregnancy	3,278	260 (16.8)	290 (16.7)	0.930
Birth weight, g	3,381	3,485 (3,160 to 3,860)	3,402 (3,120 to 3,700)	**<0.0001**
Birth weight, *z*-score*	3,366	0.5 (1.1)	0.5 (1.0)	0.686
Gestation, wk	3,425	40 (39 to 41)	40 (39 to 41)	**<0.0001**
Ever breastfed	3,335	1,385 (88.1)	1,521 (86.3)	0.137
Total energy intake at 7 yr, kcal	3,004	1,758 (1,586 to 1,973)	1,630 (1,457 to 1,819)	**<0.0001**
Wear-time in MVPA at 11 yr, min	2,955	24.4 (15.4 to 36.5)	15.6 (9.4 to 24.7)	**<0.0001**
Smoking at 14 yr	2,790	42 (3.4)	109 (7.0)	**<0.0001**
Age at 15 yr, yr	3,575	15.3 (15.3 to 15.5)	15.3 (15.3 to 15.5)	**0.015**
Height at 15 yr, cm	3,538	174.4 (169.4 to 179.2)	164.4 (160.6 to 168.6)	**<0.0001**
Height at 15 yr, *z*-score†	3,538	0.4 (1.0)	0.4 (0.9)	**0.017**
Lifetime doctor-diagnosed asthma	3,573	443 (26.3)	422 (22.4)	**0.006**
Pubertal status				
Age at menarche, yr	1,701	—	12.7 (11.8 to 13.6)	—
Voice break status at age 15 yr	1,649			
Not yet started	218	218 (13.2)	—	—
Starting to break	505	505 (30.6)	—	—
Completely broken	926	926 (56.2)	—	—
Lung function measures (raw data)				
8 yr (prebronchodilation)				
FVC, L	3,078	2.0 (0.3)	1.8 (0.3)	**<0.0001**
FEV_1, L	3,045	1.7 (0.3)	1.6 (0.3)	**<0.0001**
$FEF_{25–75}$, L/s	3,078	2.0 (0.5)	2.1 (0.5)	**0.017**
FEV_1/FVC, %	3,045	87.3 (6.8)	89.4 (6.0)	**<0.0001**
15 yr (post-bronchodilation)				
FVC, L	3,567	4.2 (0.9)	3.3 (0.6)	**<0.0001**
FEV_1, L	3,433	3.8 (0.8)	3.1 (0.6)	**<0.0001**
$FEF_{25–75}$, L/s	3,575	4.7 (1.2)	4.0 (1.0)	**<0.0001**
FEV_1/FVC, %	3,433	91.1 (6.6)	93.0 (6.3)	**<0.0001**
Lung function measures, *z*-scores‡				
8 yr (prebronchodilation)				
FVC, L	2,807	−0.04 (1.1)	−0.03 (1.0)	0.853
FEV_1, L	2,775	−0.03 (1.0)	0.02 (1.0)	0.173
$FEF_{25–75}$, L/s	2,807	−0.11 (1.1)	−0.13 (1.0)	0.736
FEV_1/FVC, %	2,775	0.03 (1.1)	0.07 (1.0)	0.322
15 yr (post-bronchodilation)				
FVC, L	3,245	−0.87 (1.3)	−0.97 (1.3)	**0.024**
FEV_1, L	3,123	−0.34 (1.3)	−0.58 (1.3)	**<0.0001**
$FEF_{25–75}$, L/s	3,253	0.16 (1.1)	0.08 (1.2)	**0.033**
FEV_1/FVC, %	3,123	0.91 (1.1)	0.76 (1.1)	**0.0002**
Prebronchodilation lung function growth rates from age 8 to 15 yr§				
FVC, ml/yr	3,073	325.5 (105.8)	214.4 (72.7)	**<0.0001**
FEV_1, ml/yr	3,013	293.8 (94.3)	200.7 (66.4)	**<0.0001**
$FEF_{25–75}$, (ml/s) · yr	3,070	327.4 (139.8)	234.2 (115.4)	**<0.0001**

Definition of abbreviations: $FEF_{25–75}$ = forced expiratory flow, midexpiratory phase; MVPA = moderate to vigorous physical activity.
Data are shown as mean (SD), median (25th–75th percentiles), or *n* (%). Em dashes indicate "not relevant."
P values were determined by the chi-square test, Student's *t* test, or Mann-Whitney test comparing distributions across sexes. Bold values indicate $P < 0.05$.
*Derived using the International Fetal and New-born Growth Consortium for the 21st Century standards. Note that 15 children had missing values for birth weight *z*-score because they did not have information for gestational age, which should be included in the equation.
†Derived using the World Health Organization Child Growth Standards.
‡Derived using the Global Lung Initiative equations.
§Rate of lung function growth for each parameter was calculated as: (prebronchodilation lung function measure at 15 yr − prebronchodilation lung function measure at 8 yr)/time of follow-up in years.

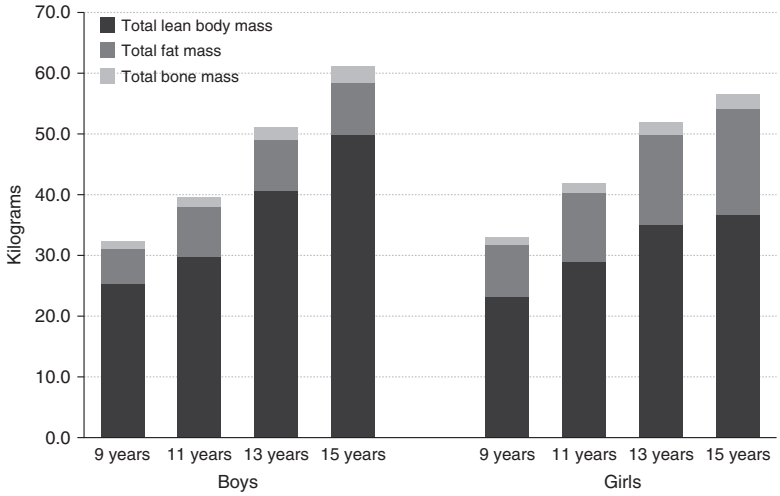

Figure 1. Distribution of body weight components from age 9 to 15 years, stratified by sex. Body weight components were measured using a dual-energy X-ray absorptiometry scanner. The presented values are the median of total lean body mass, total fat mass, and total bone mass.

lung function growth rate (Figure 4; *see* Table E7).

Increasing LBMI was consistently associated with higher growth rates of FVC, FEV_1, and $FEF_{25–75}$ in both sexes, and this association exhibited a linear dose–response pattern (e.g., in boys included in the "high" LBMI trajectory FVC increased 90.3 ml/yr 95% confidence interval [65.0–115.7] higher than in boys in the "low" LBMI trajectory [*P*-trend < 0.0001]).

Boys in the "high" (but not "medium-low" or "medium-high") FMI trajectory exhibited a lower growth rate of FEV_1 (−23.2 ml/yr, 95% confidence interval [−40.7 to −5.8]; *P* value = 0.009) than boys in the "low" FMI and there was a trend toward lower $FEF_{25–75}$ with higher FMI trajectories (*P*-trend = 0.045). We did not find any association between FMI trajectories and growth rate of FEV_1 or $FEF_{25–75}$ in girls, nor between FMI and growth rate of FVC in boys or girls.

All sensitivity analyses showed very similar results for LBMI (*see* Tables E14–E18). For the FMI trajectories, the magnitude of the associations with the growth rate of FEV_1 and $FEF_{25–75}$ (observed only in boys in the main analysis) was attenuated in some of the analyses (*see* Tables E14–E18) and there was a statistically significant linear trend between FMI trajectories and the growth rate of FVC in girls when we used *z*-scores (*see* Table E18).

Table 2. Descriptive Statistics of Body Weight and Composition Measures of the Participants Used to Assess Associations of Body Weight and Composition Trajectories with Lung Function at 15 Years

	n (*N* = 3,575)	Boys (*n* = 1,687) [*Median* (P_{25}–P_{75})]	Girls (*n* = 1,888) [*Median* (P_{25}–P_{75})]	*P* Value
Body weight measures				
BMI, kg/m^2				
7 yr	3,261	15.8 (14.9–16.8)	15.9 (14.9–17.3)	**0.007**
8 yr	2,981	16.5 (15.5–17.9)	16.8 (15.5–18.5)	**0.007**
9 yr	3,323	16.8 (15.6–18.6)	17.3 (15.8–19.2)	**<0.0001**
10 yr	3,363	17.3 (15.9–19.3)	17.7 (16.1–19.9)	**0.002**
11 yr	3,389	18.0 (16.5–20.4)	18.6 (16.8–21.0)	**<0.0001**
12 yr	3,325	18.7 (17.1–21.0)	19.4 (17.6–21.8)	**<0.0001**
13 yr	3,326	19.3 (17.7–21.5)	20.1 (18.4–22.4)	**<0.0001**
15 yr	3,533	20.4 (18.8–22.5)	21.1 (19.4–23.4)	**<0.0001**
Body composition measures				
LBMI, kg/m^2				
9 yr	3,197	13.0 (12.4–13.6)	12.1 (11.5–12.7)	**<0.0001**
11 yr	3,361	13.3 (12.6–14.0)	12.7 (11.9–13.5)	**<0.0001**
13 yr	3,293	14.9 (13.9–16.0)	13.4 (12.7–14.2)	**<0.0001**
15 yr	3,516	16.3 (15.3–17.3)	13.6 (12.8–14.3)	**<0.0001**
FMI, kg/m^2				
9 yr	3,197	3.0 (2.1–4.6)	4.3 (3.1–6.1)	**<0.0001**
11 yr	3,361	3.7 (2.5–5.9)	4.9 (3.5–7.0)	**<0.0001**
13 yr	3,293	3.1 (2.1–5.2)	5.7 (4.2–7.6)	**<0.0001**
15 yr	3,516	2.8 (1.9–4.6)	6.5 (5.0–8.4)	**<0.0001**

Definition of abbreviations: BMI = body mass index; FMI = fat mass index; LBMI = lean body mass index; P_{25}–P_{75} = 25th–75th percentiles.
P values were determined by the Mann-Whitney test comparing distributions across sexes. Bold values indicate $P < 0.05$.

Discussion

To our knowledge, this is the first study to show that body composition trajectories from childhood to adolescence relate to lung function levels at 15 years and lung function growth rates from age 8 to 15 years in a large population-based birth cohort. Specifically, we found that higher LBMI was associated with higher levels and growth rates of FVC, FEV_1, and $FEF_{25–75}$ in both sexes, and higher FMI was related to lower levels and growth rates of FEV_1 and $FEF_{25–75}$ in boys and to a lower FEV_1/FVC ratio in both sexes.

Our finding that a higher lean body mass is related to higher lung function is consistent with observations from previous cross-sectional studies in children and adolescents (9, 14, 15). We show this association longitudinally, reducing the potential for reverse causation, and after adjustment for relevant confounders, such as physical activity, diet, and pubertal status. High lean body mass may reflect increased strength of the diaphragm and chest wall during expansion and contraction during breathing (26), which could produce a greater FVC, FEV_1, and $FEF_{25–75}$ (27). Physical activity (leading to

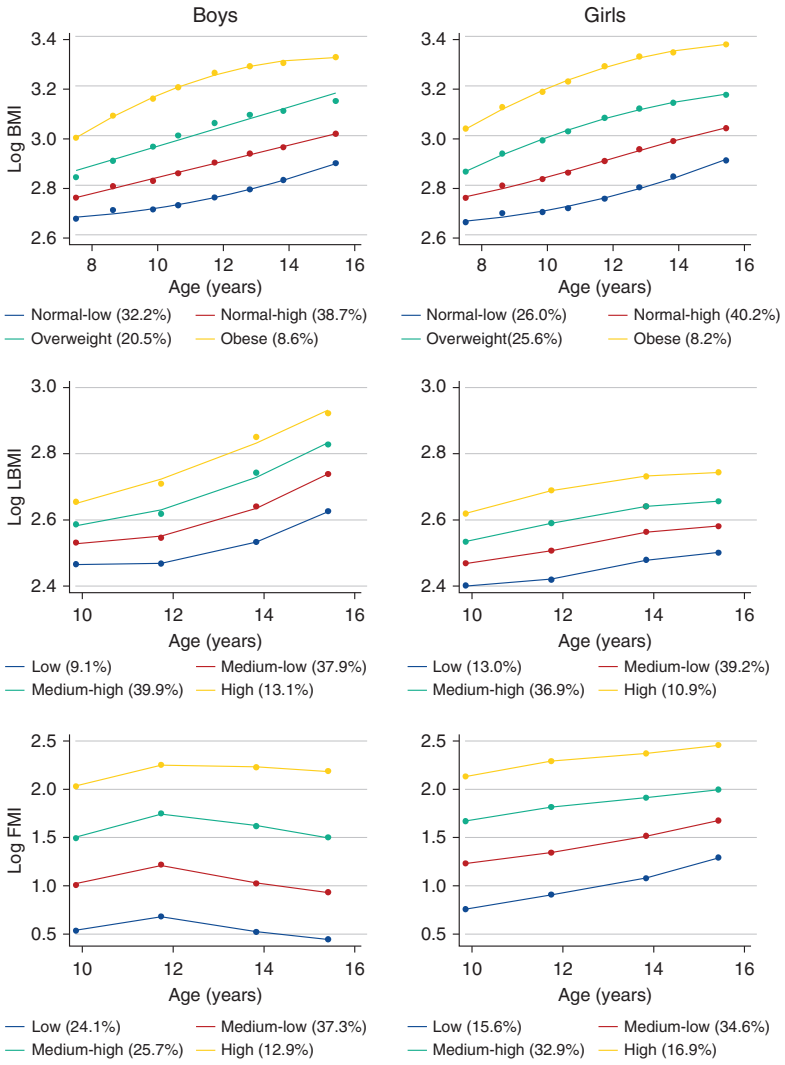

Figure 2. Sex-specific body weight and composition trajectories from 7 to 15 years. The percentage of the sample that is included in each trajectory is reported in the legend. The *y*-axis represents the natural log-transformed levels of body mass index (BMI), lean body mass index, and fat mass index (the equivalent raw values can be calculated by exponentiation of the log-transformed values [i.e., BMI raw value = exp(log BMI)]). FMI = fat mass index; LBMI = lean body mass index.

higher levels of lean body mass) (28) could be the ultimate driver of higher lung function measures, but all associations remained stable after adjustment for physical activity (measured by accelerometer). Consequently, other mechanisms are likely to play a role.

Our study is the first to show an association between higher fat mass and increased airflow limitation (as measured by a lower FEV_1/FVC ratio) in both sexes. This association is difficult to interpret given the inconsistency of the associations between the fat mass trajectories and each of FEV_1 and FVC. Similar inconsistencies have been observed in studies on children that have used BMI as a measure of overweight/obesity; higher BMI seems to be consistently related to a lower FEV_1/FVC ratio (4, 7), but the direction of the associations between BMI with FEV_1 and FVC varies by study. One explanation could be that the fat mass component is the one that is contributing to the inconsistent results observed for BMI. We also hypothesize a mediating role of inflammation, which could explain the stronger effect of fat mass on airway caliber than on lung capacity. Because adipose tissue is a source of inflammatory mediators (29), local effects of inflammation on lung tissues could lead to reductions in airway diameter. A similar mechanism has also been proposed to explain the link between obesity and asthma (30).

Higher FMI trajectories also were related, only in boys, to lower FEV_1 and $FEF_{25–75}$. A previous cross-sectional study also reported an association between body adiposity (assessed through bioelectrical impedance) and FEV_1 and FVC only in boys (15). One explanation could be related to sex differences in fat distribution. Boys, unlike girls, tend to accumulate fat in the abdominal region (31), which via mechanics, may reduce the expiratory reserve volume, in turn leading to expiratory flow limitation (32).

The results of the present study have important research and public health implications. First, our study highlights the importance of assessing body composition, and not just BMI, when studying the health effects of body weight in children and adolescents. Failure to do this has likely contributed to the conflicting findings from multiple studies that have reported associations between overweight/obesity and lung function in children and adolescents (2–8). BMI, a measure based simply on height and total body mass, is unable to distinguish between lean body mass and fat mass, and their relative proportions that vary greatly by age and sex during adolescence as a consequence of puberty (17). In fact, we found important sex differences in the levels and changes over time of lean body mass and fat mass (Figures 1 and 2). Compared with boys, girls had higher levels of fat mass at all ages and showed a higher age-related increase of FMI for all trajectories. In contrast, boys had higher levels of lean body mass at all ages and their age-related increase in LBMI was steeper than in girls. Second, our study shows that body composition in childhood

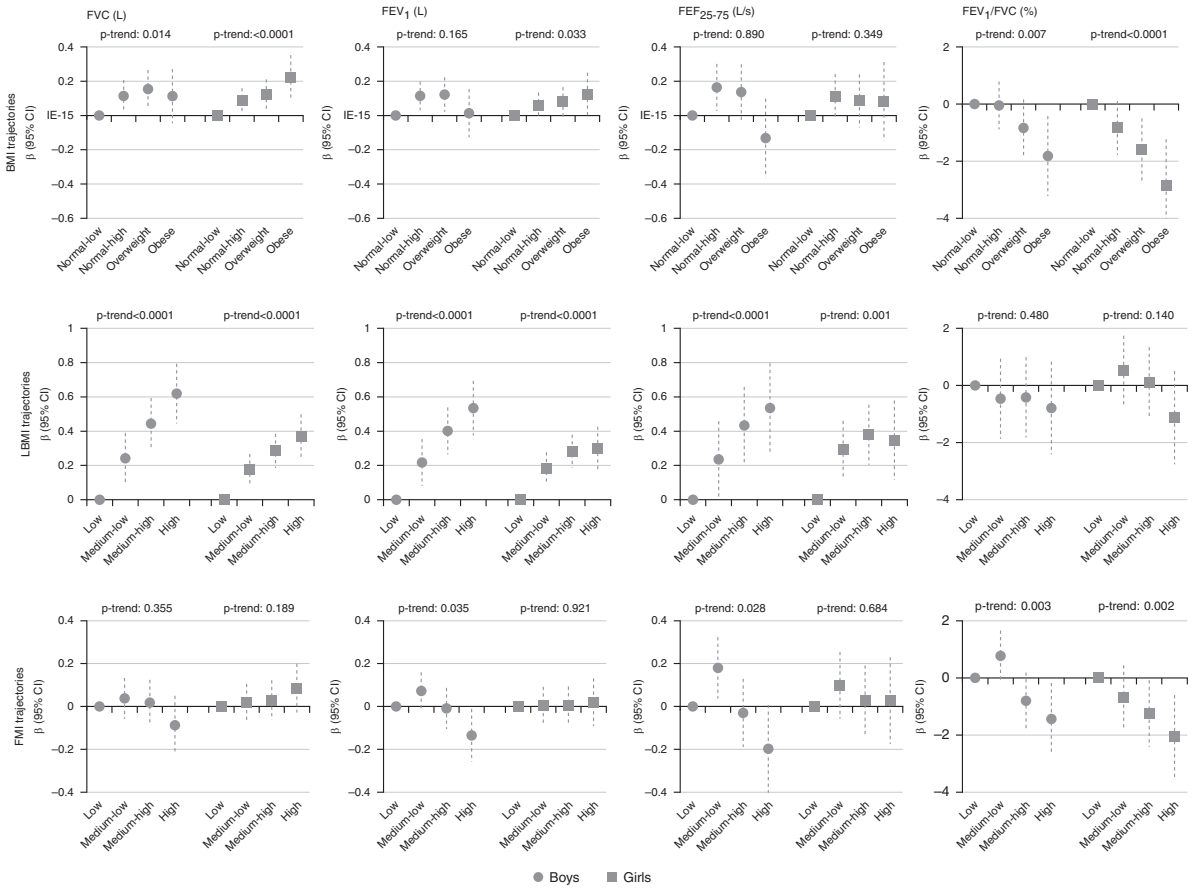

Figure 3. Sex-specific associations of body weight and composition trajectories with post-bronchodilation lung function measures at age 15 years. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years, pubertal status (age at menarche for girls and voice break status at age 15 yr for boys), and age and height at 15 years. Models for fat mass index and lean body mass index are also mutually adjusted. β = estimate of regression coefficient; BMI = body mass index; CI = confidence interval; $FEF_{25–75}$ = forced expiratory flow, midexpiratory phase; FMI = fat mass index; LBMI = lean body mass index.

and adolescence influences the development of lung function and, consequently, may affect future respiratory health. Because body composition tracks from childhood to adulthood (17) and is affected by modifiable lifestyle factors, such as physical activity and diet (21, 28, 33), public health strategies promoting healthy lifestyles in early childhood may improve lung function and reduce respiratory morbidity in adult life.

A limitation of the present study is the potential selection bias produced by the fact that children included in the study were more likely to be girls, have a higher socioeconomic status, a higher birth weight, a higher proportion of breastfeeding, and lower maternal smoking exposure than those excluded. Because these factors have been previously associated with lung function, our associations could be underestimates of the true associations in the general population. However, because most of the attrition occurred between birth and age 7 years, the observed associations (which are based largely on data collected from 7 to 15 yr) are less likely to be affected by the loss to follow-up. Also, the regional basis of the ALSPAC cohort may not allow the generalizability of our results to populations with more ethnic variability. Finally, it is possible that using group-based trajectory modeling for identifying trajectories of body weight and composition may have smoothened the data.

Important strengths of the present research are the large sample size and the longitudinal design, which, together with the adjustment for baseline lung function (both for levels of lung function and lung function growth rates), reduces the possibility of reverse causation. Importantly, we measured body composition using dual-energy X-ray absorptiometry, which is substantially more valid than other methods (e.g., bioelectrical impedance or skinfolds). Finally, we had detailed information of several covariates from both the children

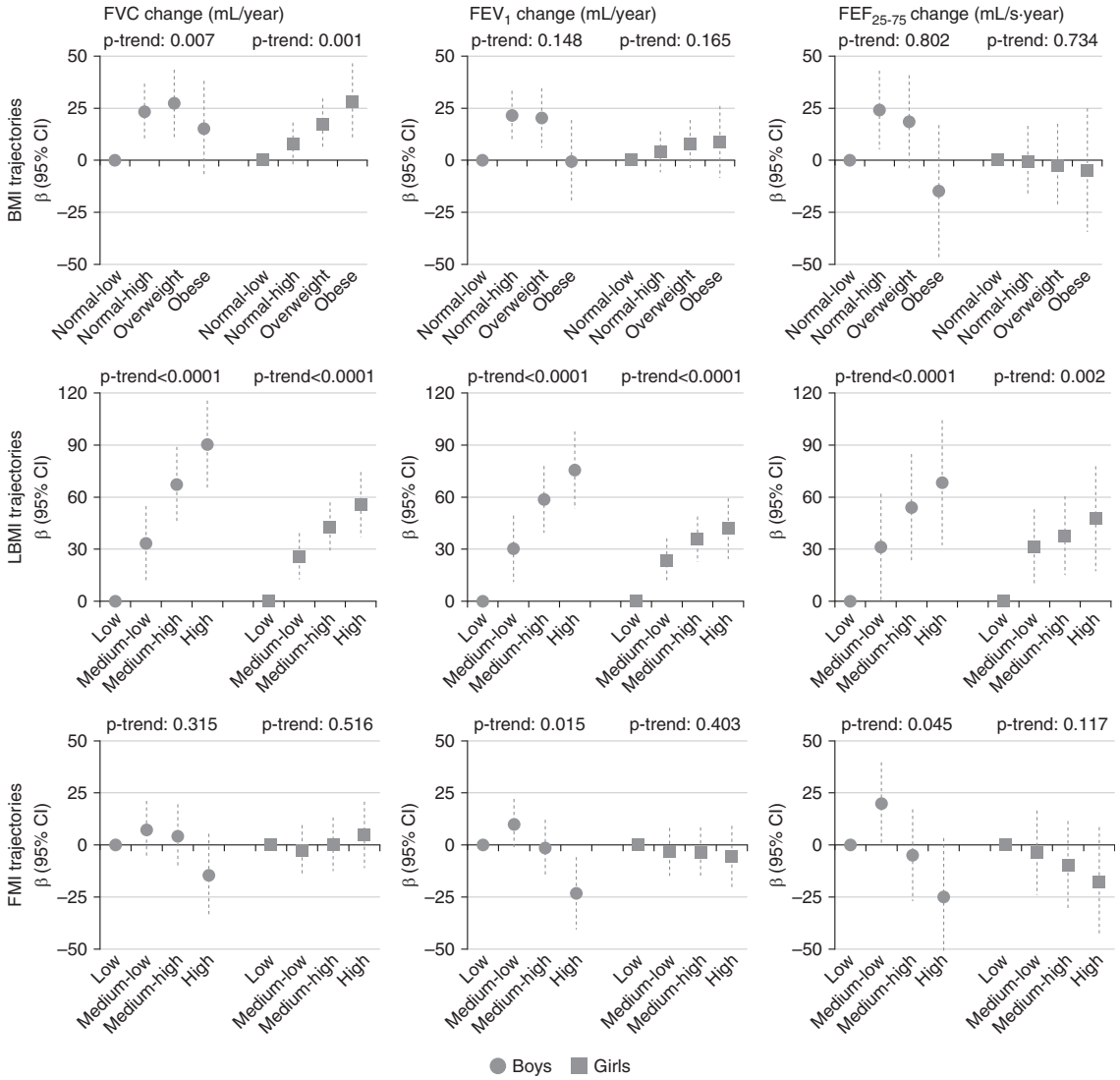

Figure 4. Sex-specific associations of body weight and composition trajectories with prebronchodilation lung function growth rates from age 8 to 15 years. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years, pubertal status (age at menarche for girls and voice break status at age 15 yr for boys), and age and height at 15 years. Models for fat mass index and lean body mass index are also mutually adjusted. For definition of abbreviations, *see* Figure 3.

and their parents, which allowed us to account for a wide range of potential confounders, including physical activity, diet, and baseline lung function.

In conclusion, this cohort study shows that body composition in childhood and adolescence is associated with lung function in adolescence, and consequently, it may also influence respiratory health in later life. Specifically, we found that lean body mass during childhood and adolescence relates to higher lung function in adolescent boys and girls, whereas fat mass relates to lower lung function in boys only. This study shows that public health policies aiming to reduce respiratory morbidity should target body composition in addition to body weight. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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ONLINE SUPPLEMENT

Contents

Study population

ALSPAC recruited 14,541 pregnant women residents in Avon, UK, with expected dates of delivery between the 1st of April, 1991, and the 31st of December 1992. 14,541 is the *initial* number of pregnancies for which the mother enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a "Children in Focus" clinic by 19/07/99. Of these *initial* pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age.

When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper (E1, E2).

The total sample size for analyses using any data collected after the age of seven is therefore 15,247 pregnancies, resulting in 15,458 fetuses. Of this total sample of 15,458 fetuses, 14,775 were live

births and 14,701 (including 14,305 singleton births) were alive at 1 year of age.

The study website contains details of all the data that are available through a fully searchable data dictionary at www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/.

The ALSPAC Ethics and Law Committee and the Local Research Ethics Committees gave ethical approval. A list of the Research Ethics Committee approval references for each of the visits can be found at http://www.bristol.ac.uk/media-library/sites/alspac/documents/governance/Research%20Ethics%20Committee%20approval%20references.pdf.

All participants and their parents/guardians provided written informed consent.

Body weight and composition

From age 7 to 15 years, weight and height were measured at annual clinic visits. Standing height was measured to 0.1 cm using the Harpenden Stadiometer (Holtain, Crymych, Pembs, UK) with shoes and socks removed. Weight was measured to 0.1 kg using the Tanita THF 300GS body fat analyser (Tanita UK Ltd, Yewsley, Middlesex, UK), with clothes largely removed. BMI was calculated by dividing weight (kg) by height (m) squared.

Body composition was measured at the clinic visits at age 9, 11, 13, and 15 years. Total lean body mass, total fat mass, and total bone mass were derived using a Lunar Prodigy DXA scanner (GE Medical Systems Lunar, Madison, WI, USA) following standardized procedures previously described (E3). We calculated a lean body mass index (LBMI) and a fat mass index (FMI) by dividing total lean body mass and total fat mass by height squared, respectively.

Lung function

Lung function was measured by spirometry at 8 and 15 years (Vitalograph 2120; Vitalograph, Maids Moreton, United Kingdom) according to American Thoracic Society standards (E4), as previously reported (E5). At 15 years, lung function was measured before and after bronchodilation with salbutamol (inhalation of a standard dose of 400 µg) (E6). All flow-volume curves were inspected post-hoc to ensure that acceptability criteria were met. Results were obtained from the best of three technically acceptable flow-volume curves repeatable within 200 mL of forced vital capacity (FVC), according to the criteria at that time. The parameters FVC, forced expiratory volume in 1 s (FEV_1), and forced expiratory flow at 25 and 75% of FVC (FEF_{25-75}) were obtained and the FEV_1/FVC ratio was calculated. The outcomes of the analysis were: post-bronchodilation lung function measures at 15 years and rate of lung function growth from age 8 to 15 years (calculated as (pre-bronchodilation lung function at 15 years – pre-

bronchodilation lung function at 8 years)/time of follow-up in years).

Other variables

We collected information on sociodemographic and lifestyle factors at different time points to describe the sample or as potential confounding variables from diverse sources at different time points. At 32 weeks of gestation, the mother recorded her occupation using a self-completed questionnaire, which was used to allocate her to a social class (professional and intermediate, skilled non-manual, skilled manual, partly skilled, and unskilled manual workers) based on the 1991 Office of Population, Censuses and Surveys classifications. Smoking during pregnancy was assessed at 18 and 32 weeks of gestation using self-completed questionnaires and a dichotomous variable was created for any smoking during pregnancy. Birthweight, gestational age and sex were obtained from birth records. Information about breastfeeding was obtained at age 15 months from maternal self-completed questionnaires. Environmental tobacco exposure at age 3 years was recorded by the mother using a self-completed questionnaire. From the 7 years questionnaire, we obtained data on total energy intake of the child based on a 3-day report. At 11 years, physical activity was measured by accelerometer (Actigraph LLC, Fort Walton Beach, FL, USA) and the wear-time spent in moderate to vigorous physical activity (MVPA) (E7) was obtained. Smoking habits at age 14 years were reported by the children themselves using a self-completed questionnaire. At 15 years, children reported if a doctor had ever

diagnosed them with asthma. Finally, pubertal status (age at menarche for girls and state of voice break for boys at 15 years) was obtained from a puberty questionnaire completed by the parents or/and children from age 8 to 15 years. We used the first reported age at onset of menarche, as this report should be least affected by recall bias.

Identification of body weight and composition trajectories

We identified BMI trajectories, using data at ages 7, 8, 9, 10, 11, 12, 13 and 15 years, as well as LBMI and FMI trajectories, using data at ages 9, 11, 13 and 15 years. As the distribution of BMI and FMI was right-skewed, we applied the natural log-transformation to all body weight and composition measures prior to the identification of the trajectories. The trajectories were defined by applying a Group-Based Trajectory Modeling approach (E8, E9) using the Stata plug-in *Traj* (E10). This approach has been previously used to identify anthropometric trajectories both in children (E11- E13) and adults (E14-E16).

Group-Based Trajectory Modeling, a specialized form of finite mixture modeling, uses the trajectory groups as a statistical device for approximating the unknown distribution of trajectories across population members employing a maximum likelihood approach (E9). The detailed steps of model selection have been previously described (E17). We computed a series of models with progressively more trajectory groups (from two to ten) and determined the most appropriate number of groups based on the

Bayesian Information Criterion and the proportion of participants assigned to each trajectory (*a priori* defined to contain at least 5% of the sample). We first fitted the models assuming a cubic relationship and then tested quadratic or linear relationships for any non-significant polynomial term. We selected the final models according to model fit and plausibility of the observed trajectories according to previous research on distribution of body weight and composition in children and adolescents (E18, E19). Finally, individuals were assigned to one trajectory group based on the highest estimated group-membership probability. To further assess model adequacy, we ensured that: (i) we obtained, for each trajectory, a close correspondence between the estimated probability group membership and the proportion assigned to that group based on the posterior probability of group membership; (ii) the average of the posterior probabilities of group membership for individuals assigned to each trajectory exceeded a minimum threshold of 0.7; and (iii) the odds of correct classification based on the posterior probabilities of group membership exceeded a minimum threshold of 5 (E8, E9). The assigned trajectory was used as the exposure variable (i.e., body weight or composition trajectory) in all subsequent analyses.

Analysis of the associations between body weight and composition trajectories and post-bronchodilation lung function at 15 years

Associations of body weight and composition trajectories with post-bronchodilation lung function measures at age 15 years and lung function growth rates from age 8 to 15 years were examined using

multivariable linear regression. We considered as potential confounders: (i) factors related to both the exposure and the outcome in bivariate analyses ($p<0{\cdot}20$); (ii) factors that modified (>10% change in regression coefficient) the estimate of the exposure variable; and (iii) factors deemed relevant in the scientific literature. The final multivariable models included adjustments for maternal social class, maternal smoking during pregnancy, birth weight, any breastfeeding, pubertal status as well as age and height at 15 years. We additionally adjusted all models for lung function levels at 8 years to reduce potential reverse causality. The models for the LBMI and FMI trajectories were also mutually adjusted.

We tested multicollinearity of the models using the variance inflation factor. The p-values for the trend test were obtained by treating the body weight and composition trajectories as continuous variables.

We conducted several sensitivity analyses: (i) additionally adjusting the models by wear-time spent in MVPA at 11 years and total energy intake at 7 years in the subsample with this information available; (ii) excluding children with any lifetime history of doctor-diagnosed asthma; (iii) excluding children with spirometry measures below the first percentile ($<P_1$) or above the highest percentile ($>P_{99}$); (iv) using pre-bronchodilation lung function measures at 15 years (only for the analysis of post-bronchodilation lung function levels at 15 years), (v) not adjusting the models for lung function at 8 years and (vi) using standard deviation scores (z-

scores) derived using the Global Lung Initiative equations (E20) instead of absolute lung function values.

All analyses were conducted using Stata/SE 12·0 (StataCorp, College Station, TX, USA). Results are expressed as regression coefficients with 95% confidence intervals (95% CI)

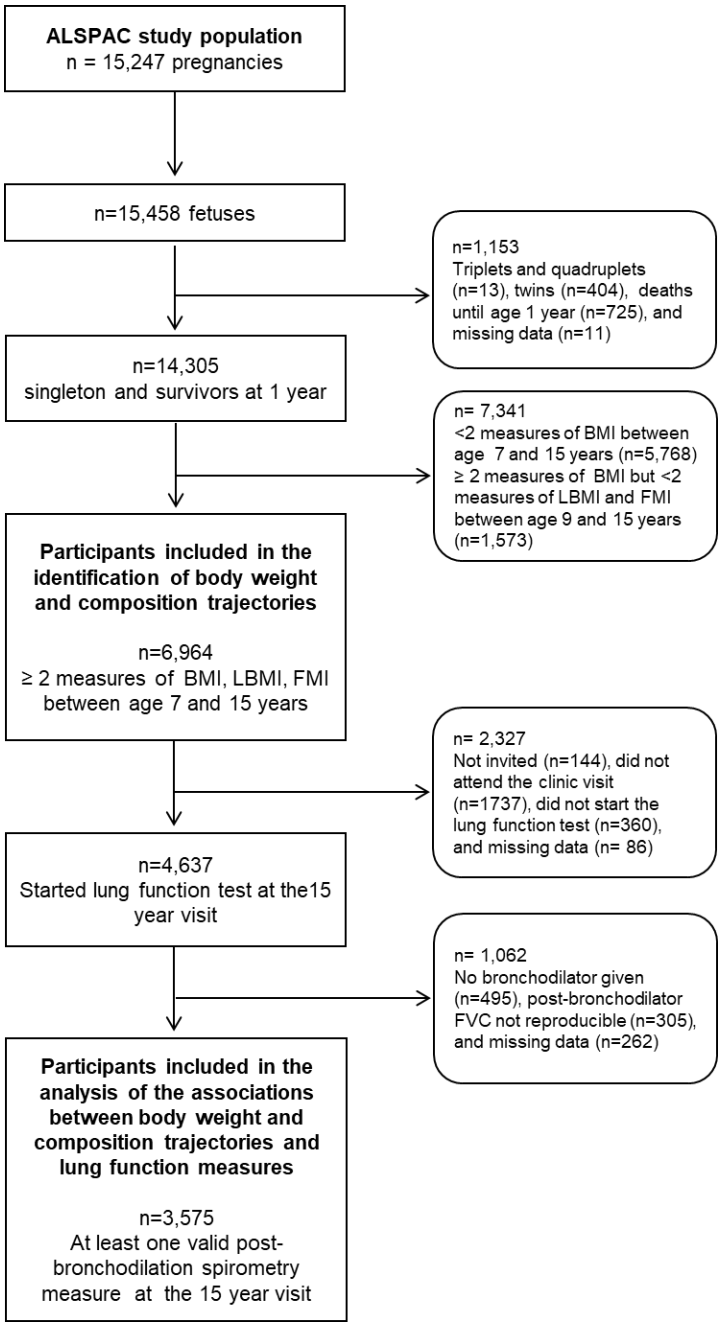

Figure E1. Flow chart of study participants

Definition of abbreviations: BMI, body mass index; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index

Table E1. Characteristics of the children included and excluded from the analysis identifying the body weight and composition trajectories

	Included (n=6,964)	Excluded (n=7,341)	p-value
Mother characteristics			
Maternal social class			
Professional and intermediate	2,124 (40.1)	1,185 (29.3)	**<0.0001**
Skilled non-manual	2,214 (41.7)	1,750 (43.3)	
Skilled manual, partly, and unskilled	962 (18.2)	1,107 (27.4)	
Maternal smoking during pregnancy	1,191 (18.9)	2,276 (38.9)	**<0.0001**
Children characteristics			
Sex. Girls	3,550 (51.0)	3,425 (46.7)	**<0.0001**
Gestation (weeks)	40 (39-41)	40 (39-41)	0.185
Birth weight (Kg)	3.5 (3.1-3.8)	3.4 (3.1-3.7)	**<0.0001**
Ever breastfed	5,424 (84.6)	3,873 (68.9)	**<0.0001**
Spirometry measures at 8 years in boys			
FVC (L)	2.0 (0.3)	2.0 (0.3)	0.766
FEV_1 (L)	1.7 (0.3)	1.7 (0.3)	0.933
FEF_{25-75} (L/s)	2.0 (0.5)	2.0 (0.5)	0.536
FEV_1/FVC (%)	87.5 (6.8)	87.3 (6.7)	0.653
Spirometry measures at 8 years in girls			
FVC (L)	1.8 (0.3)	1.9 (0.4)	**0.010**
FEV_1 (L)	1.6 (0.3)	1.7 (0.3)	**0.037**
FEF_{25-75} (L/s)	2.1 (0.5)	2.1 (0.5)	0.755
FEV_1/FVC (%)	89.4 (6.1)	89.0 (6.1)	0.128
Body weight and composition at 9 years in boys			
BMI (kg/m^2)	16.8 (15.6-18.7)	16.9 (15.7-19.1)	0.212
LBMI (kg/m^2)	12.9 (12.4-13.5)	13.1 (12.5-13.7)	**0.038**
FMI (kg/m^2)	3.0 (2.1-4.7)	3.1 (2.1-5.1)	0.581
Body weight and composition at 9 years in girls			
BMI (kg/m^2)	17.3 (15.8-19.4)	17.5 (15.9-19.9)	**0.008**
LBMI (kg/m^2)	12.1 (11.5-12.7)	12.2 (11.5-12.8)	0.053
FMI (kg/m^2)	4.4 (3.1-6.2)	4.6 (3.2-6.6)	0.059

Some variables had missing values in both the included children (1,664 for maternal social class, 648 for maternal smoking during pregnancy, 338 for gestation, 421 for birthweight and 553 for ever breastfed) and excluded children (3,299 for maternal social class, 1,489 for maternal smoking during pregnancy, 354 for gestation, 442 for birthweight and 1,722 for ever breastfed)

Data are shown as median (P_{25}-P_{75}) or n (%). Definition of abbreviations: P_{25}-P_{75}, 25th and 75th percentiles. p-value for the Chi-squared, Mann-Whitney, or Student's t-test. Bold: p-value <0.05

Table E2. Characteristics of the children included and excluded from the analysis examining associations of body weight and composition trajectories with post-bronchodilation lung function measures at 15 years

	Included (n=3,575)	Excluded (n=3,389)	p-value
Mother characteristics			
Maternal social class			
Professional and intermediate	1,223 (43.5)	901 (36.2)	**<0.0001**
Skilled non-manual	1,114 (39.7)	1,100 (44.2)	
Skilled manual, partly, and unskilled	473 (16.8)	489 (19.6)	
Maternal smoking during pregnancy	550 (16.8)	641 (21.1)	**<0.0001**
Children characteristics			
Sex. Girls	1,888 (52.8)	1,662 (49.0)	**0.002**
Gestation (weeks)	40 (39-41)	40 (39-41)	0.368
Birth weight (grams)	3460 (3140-3760)	3443 (3140-3760)	0.746
Ever breastfed	2,906 (87.1)	2,518 (81.9)	**<0.0001**
Spirometry measures at 8 years in boys			
FVC (L)	2.0 (0.3)	2.0 (0.3)	0.250
FEV_1 (L)	1.7 (0.3)	1.7 (0.3)	0.897
FEF_{25-75} (L/s)	2.0 (0.5)	2.1 (0.5)	0.415
FEV_1/FVC (%)	87.3 (6.8)	87.6 (6.8)	0.215
Spirometry measures at 8 years in girls			
FVC (L)	1.8 (0.3)	1.8 (0.3)	0.988
FEV_1 (L)	1.6 (0.3)	1.6 (0.3)	0.958
FEF_{25-75} (L/s)	2.1 (0.5)	2.1 (0.5)	0.833
FEV_1/FVC (%)	89.4 (6.0)	89.4 (6.1)	0.813
BMI trajectories in boys			
Normal-low	562 (32.5)	537 (31.8)	0.922
Normal-high	670 (38.8)	650 (38.5)	
Overweight	347 (20.1)	354 (21.0)	
Obese	148 (8.6)	146 (8.7)	
BMI trajectories in girls			
Normal-low	435 (26.2)	490 (26.0)	0.871
Normal-high	656 (39.5)	770 (40.8)	
Overweight	432 (26.0)	475 (25.2)	
Obese	139 (8.4)	153 (8.1)	
LBMI trajectories in boys			
Low	164 (9.5)	148 (8.8)	0.343
Medium-low	668 (38.7)	625 (37.1)	
Medium-high	685 (39.7)	678 (40.2)	
High	210 (12.2)	236 (14.0)	

(Continued)

Table E2. Continued

	Included (n=3,575)	Excluded (n=3,389)	p-value
LBMI trajectories in girls			
Low	229 (13.8)	234 (12.4)	0.201
Medium-low	664 (40.0)	728 (38.6)	
Medium-high	583 (35.1)	725 (38.4)	
High	186 (11.2)	201 (10.7)	
FMI trajectories in boys			
Low	416 (24.1)	406 (24.1)	0.850
Medium-low	633 (36.7)	641 (38.0)	
Medium-high	452 (26.2)	427 (25.3)	
High	226 (13.1)	213 (12.6)	
FMI trajectories in girls			
Low	265 (15.9)	288 (15.3)	0.369
Medium-low	564 (33.9)	664 (35.2)	
Medium-high	536 (32.3)	634 (33.6)	
High	297 (17.9)	302 (16.0)	

Some variables had missing values in both the included children (765 for maternal social class, 297 for maternal smoking during pregnancy, 150 for gestation, 194 for birthweight and 240 for ever breastfed) and excluded children (899 for maternal social class, 351 for maternal smoking during pregnancy, 188 for gestation, 227 for birthweight and 313 for ever breastfed)
Data are shown as median (P_{25}-P_{75}) or n (%)
Definition of abbreviations: BMI, body mass index; FMI, fat mass index; LBMI, lean body mass index; P_{25}-P_{75}, 25th and 75th percentiles
p-value for the Chi-squared, Mann-Whitney, or Student's t-test
Bold: p-value <0.05

Table E3. Distribution of BMI according to BMI trajectory

	Boys					Girls				
BMI (Kg/m^2)	**Normal-low n= 1,099 (32.2%)**	**Normal-high n= 1,320 (38.7%)**	**Overweight n=701 (20.5%)**	**Obese n= 294 (8.6%)**	***p-value***	**Normal-low n= 925 (26.0%)**	**Normal-high n= 1,426 (40.2%)**	**Overweight n=907 (25.6%)**	**Obese n= 292 (8.2%)**	***p-value***
7 years	14.6 (14.1-15.1)	15.8 (15.4-16.4)	17.2 (16.4-18.0)	20.1 (18.7-21.5)	**0.0001**	14.4 (13.9-14.9)	15.8 (15.2-16.4)	17.5 (16.7-18.4)	20.8 (19.4-22.4)	**0.0001**
8 years	15.1 (14.7-15.6)	16.6 (16.1-17.1)	18.3 (17.6-19.3)	22.0 (20.6-23.4)	**0.0001**	14.9 (14.4-15.4)	16.6 (16.0-17.2)	18.9 (18.1-19.8)	22.6 (21.5-24.2)	**0.0001**
9 years	15.2 (14.6-15.7)	16.9 (16.4-17.5)	19.4 (18.5-20.4)	23.4 (22.2-25.0)	**0.0001**	15.0 (14.4-15.5)	17.0 (16.3-17.8)	19.9 (18.9-21.1)	24.0 (22.7-25.7)	**0.0001**
10 years	15.4 (14.9-15.9)	17.4 (16.8-18.1)	20.3 (19.4-21.4)	24.4 (23.2-26.1)	**0.0001**	15.2 (14.7-15.8)	17.4 (16.7-18.3)	20.7 (19.6-21.7)	25.1 (23.7-26.7)	**0.0001**
11 years	15.9 (15.3-16.5)	18.1 (17.5-19.0)	21.4 (20.4-22.4)	25.9 (24.7-27.7)	**0.0001**	15.8 (15.1-16.4)	18.3 (17.5-19.2)	21.8 (20.7-23.1)	26.6 (25.2-28.4)	**0.0001**
12 years	16.5 (15.8-17.1)	18.8 (18.1-19.8)	22.0 (20.9-23.3)	26.7 (25.1-28.6)	**0.0001**	16.6 (15.8-17.3)	19.2 (18.3-20.2)	22.6 (21.5-23.9)	27.6 (26.2-29.4)	**0.0001**
13 years	17.1 (16.4-17.8)	19.4 (18.6-20.2)	22.4 (21.3-23.8)	27.1 (25.4-29.2)	**0.0001**	17.3 (16.5-18.1)	19.8 (19-20.8)	23.2 (21.9-24.5)	28.2 (26.6-30.3)	**0.0001**
15 years	18.3 (17.5-19.0)	20.5 (19.6-21.4)	23.2 (22.0-24.7)	27.7 (25.5-30.3)	**0.0001**	18.4 (17.5-19.4)	20.9 (20.0-22.0)	23.9 (22.5-25.5)	29.4 (27.0-31.7)	**0.0001**

Data are shown as median (P25-P75). Definition of abbreviations: BMI, body mass index; P_{25}-P_{75}, 25th and 75th percentiles
p-value for the Kruskal-Wallis test. Bold: p-value <0.05

Table E4. Distribution of LBMI according to LBMI trajectory

	Boys					Girls				
LBMI (Kg/m^2)	**Low n=312 (9.1%)**	**Medium-low n=1,363 (37.9%)**	**Medium-high n=1,293 (39.9%)**	**High n=446 (13.1%)**	**p-value**	**Low n=463 (13.0%)**	**Medium-low n=1,392 (39.2%)**	**Medium-high n=1,308 (36.9%)**	**High n=387 (10.9%)**	**p-value**
9 years	11.8 (11.4-12.0)	12.5 (12.2-12.9)	13.3 (12.9-13.7)	14.2 (13.8-14.7)	**0.0001**	10.9 (10.7-11.2)	11.7 (11.4-12.0)	12.5 (12.2-12.8)	13.6 (13.2-14.0)	**0.0001**
11 years	11.8 (11.4-12.1)	12.7 (12.4-13.1)	13.7 (13.4-14.1)	14.9 (14.6-15.5)	**0.0001**	11.2 (10.8-11.4)	12.2 (11.8-12.5)	13.3 (12.9-13.7)	14.6 (14.2-15.1)	**0.0001**
13 years	12.5 (12.2-13.0)	14.0 (13.5-14.5)	15.6 (15.0-16.1)	17.3 (16.8-17.8)	**0.0001**	11.9 (11.6-12.1)	12.9 (12.6-13.2)	13.9 (13.6-14.4)	15.2 (14.8-15.7)	**0.0001**
15 years	13.9 (13.3-14.4)	15.4 (15-15.9)	16.9 (16.4-17.4)	18.5 (18.1-19.0)	**0.0001**	12.1 (11.8-12.4)	13.1 (12.8-13.5)	14.2 (13.8-14.6)	15.5 (14.9-16.0)	**0.0001**

Data are shown as median (P25-P75). Definition of abbreviations: LBMI, lean body mass index; P_{25}-P_{75}, 25th and 75th percentiles
p-value for the Kruskal-Wallis test
Bold: p-value <0.05

Table E5. Distribution of FMI according to FMI trajectory

	Boys					Girls				
FMI (Kg/m^2)	**Low n=822 (24.1%)**	**Medium-low n=1,274 (37.3%)**	**Medium-high n=879 (25.7%)**	**High n=439 (12.9%)**	**p-value**	**Low n=553 (15.6%)**	**Medium-low n=1,228 (34.6%)**	**Medium-high n=1,170 (32.9%)**	**High n=599 (16.9%)**	**p-value**
9 years	1.7 (1.4-2.0)	2.7 (2.3-3.2)	4.5 (3.7-5.4)	7.7 (6.5-9.3)	**0.0001**	2.3 (2.0-2.6)	3.5 (3.1-4.1)	5.4 (4.7-6.2)	8.5 (7.3-9.8)	**0.0001**
11 years	2.0 (1.7-2.3)	3.4 (2.9-4.0)	5.8 (4.9-6.9)	9.5 (8.1-11.0)	**0.0001**	2.6 (2.3-3.0)	4.0 (3.5-4.5)	6.2 (5.4-7.2)	9.8 (8.7-11.1)	**0.0001**
13 years	1.7 (1.4-2.0)	2.8 (2.3-3.3)	5.2 (4.2-6.2)	9.3 (8.0-11.0)	**0.0001**	3.1 (2.7-3.5)	4.7 (4.1-5.3)	7.0 (6.1-7.8)	10.5 (9.3-12.3)	**0.0001**
15 years	1.6 (1.3-1.8)	2.5 (2.1-3.0)	4.4 (3.6-5.7)	8.9 (7.3-11.0)	**0.0001**	3.8 (3.2-4.4)	5.5 (4.8-6.2)	7.5 (6.7-8.5)	11.4 (10.0-13.6)	**0.0001**

Data are shown as median (P25-P75). Definition of abbreviations: FMI, fat mass index; P_{25}-P_{75}, 25th and 75th percentiles
p-value for the Kruskal-Wallis test
Bold: p-value <0.05

Table E6. Adjusted associations of body weight and composition trajectories with post-bronchodilation lung function measures at age 15 years

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
BOYS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.11 [0.02; 0.21]	**0.017**	0.11 [0.03; 0.2]	**0.008**	0.16 [0.03; 0.30]	**0.019**	-0.05 [-0.89; 0.79]	0.910
	Overweight	0.15 [0.04; 0.27]	**0.007**	0.12 [0.02; 0.22]	**0.018**	0.14 [-0.03; 0.30]	**0.099**	-0.84 [-1.83; 0.16]	0.100
	Obese	0.11 [-0.05; 0.27]	0.161	0.01 [-0.13; 0.15]	0.854	-0.13 [-0.36; 0.10]	0.261	-1.82 [-3.22; -0.42]	**0.011**
		p-trend	**0.014**	*p-trend*	0.165	*p-trend*	0.890	*p-trend*	**0.007**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.24 [0.09; 0.39]	**0.001**	0.22 [0.08; 0.35]	**0.002**	0.24 [0.01; 0.46]	**0.039**	-0.46 [-1.86; 0.94]	0.516
	Medium-high	0.44 [0.29; 0.59]	**<0.0001**	0.40 [0.26; 0.54]	**<0.0001**	0.43 [0.21; 0.66]	**<0.0001**	-0.42 [-1.83; 0.99]	0.560
	High	0.62 [0.44; 0.79]	**<0.0001**	0.53 [0.38; 0.69]	**<0.0001**	0.53 [0.27; 0.80]	**<0.0001**	-0.79 [-2.42; 0.83]	0.339
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.408
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.04 [-0.06; 0.13]	0.440	0.07 [-0.01; 0.16]	0.102	0.18 [0.04; 0.32]	**0.014**	0.77 [-0.12; 1.66]	0.089
	Medium-high	0.02 [-0.09; 0.12]	0.743	-0.01 [-0.11; 0.09]	0.854	-0.03 [-0.19; 0.13]	0.710	-0.80 [-1.79; 0.19]	0.111
	High	-0.09 [-0.22; 0.05]	0.210	-0.14 [-0.26; -0.01]	**0.032**	-0.20 [-0.4; 0.01]	0.059	-1.44 [-2.70; -0.18]	**0.025**
		p-trend	0.355	*p-trend*	**0.035**	*p-trend*	**0.028**	*p-trend*	**0.003**
GIRLS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.08 [0.01; 0.16]	**0.026**	0.06 [-0.01; 0.13]	0.107	0.11 [-0.02; 0.24]	0.098	-0.84 [-1.78; 0.10]	0.080

(Continued)

Table E6. Continued

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
	Overweight	0.12 [0.03; 0.21]	**0.007**	0.08 [-0.01; 0.17]	0.071	0.09 [-0.07; 0.24]	0.277	-1.60 [-2.70; -0.50]	**0.004**
	Obese	0.22 [0.09; 0.35]	**0.001**	0.12 [0.00; 0.25]	0.060	0.08 [-0.15; 0.31]	0.488	-2.85 [-4.47; -1.23]	**0.001**
		p-trend	**<0.0001**	*p-trend*	**0.033**	*p-trend*	0.349	*p-trend*	**<0.0001**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.17 [0.08; 0.27]	**<0.0001**	0.18 [0.09; 0.28]	**<0.0001**	0.29 [0.12; 0.46]	**0.001**	0.53 [-0.68; 1.75]	0.388
	Medium-high	0.28 [0.18; 0.38]	**<0.0001**	0.28 [0.18; 0.38]	**<0.0001**	0.38 [0.2; 0.55]	**<0.0001**	0.09 [-1.16; 1.34]	0.884
	High	0.37 [0.23; 0.50]	**<0.0001**	0.30 [0.17; 0.43]	**<0.0001**	0.35 [0.12; 0.58]	**0.003**	-1.13 [-2.76; 0.51]	0.176
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.001**	*p-trend*	0.140
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.02 [-0.07; 0.11]	0.704	0.01 [-0.08; 0.09]	0.898	0.10 [-0.06; 0.26]	0.218	-0.68 [-1.81; 0.45]	0.236
	Medium-high	0.03 [-0.06; 0.12]	0.525	0.00 [-0.09; 0.09]	0.934	0.03 [-0.13; 0.19]	0.730	-1.25 [-2.41; -0.08]	**0.036**
	High	0.09 [-0.03; 0.20]	0.141	0.02 [-0.09; 0.13]	0.718	0.03 [-0.18; 0.23]	0.793	-2.05 [-3.49; -0.6]	**0.005**
		p-trend	0.189	*p-trend*	0.921	*p-trend*	0.684	*p-trend*	**0.002**

Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

Table E7. Adjusted associations of body weight and composition trajectories with pre-bronchodilation lung function growth rates from age 8 to 15 years

		FVC change (mL/year)		FEV_1 change (mL/year)		FEF_{25-75} change (mL/s·year)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
BOYS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	23.3 [9.7; 36.8]	**0.001**	21.5 [9.6; 33.4]	**<0.0001**	24.1 [5.2; 43.0]	**0.012**
	Overweight	27.4 [11.2; 43.5]	**0.001**	20.3 [6.1; 34.5]	**0.005**	18.5 [-3.9; 40.9]	0.105
	Obese	15.2 [-7.8; 38.1]	0.195	-0.6 [-20.6; 19.3]	0.952	-14.8 [-46.5; 16.9]	0.360
		p-trend	**0.007**	*p-trend*	0.148	*p-trend*	0.802
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	33.3 [11.8; 54.8]	**0.002**	30.3 [11.2; 49.4]	**0.002**	31.2 [0.5; 62.0]	**0.047**
	Medium-high	67.2 [45.6; 88.9]	**<0.0001**	58.7 [39.4; 77.9]	**<0.0001**	54.0 [23.1; 84.9]	**0.001**
	High	90.3 [65.0; 115.7]	**<0.0001**	75.6 [53.2; 98.0]	**<0.0001**	68.3 [32.3; 104.4]	**<0.0001**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	7.2 [-6.7; 21.1]	0.310	9.8 [-2.4; 22.1]	0.114	19.8 [-0.1; 39.7]	0.051
	Medium-high	4.2 [-11.3; 19.6]	0.597	-1.5 [-15.1; 12.1]	0.828	-5.0 [-27.0; 17.1]	0.659
	High	-14.6 [-34.5; 5.3]	0.151	-23.2 [-40.7; -5.8]	**0.009**	-25.0 [-53.3; 3.3]	0.084
		p-trend	0.315	*p-trend*	**0.015**	*p-trend*	**0.045**
GIRLS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	7.6 [-2.9; 18.1]	0.155	4.0 [-5.8; 13.8]	0.426	-0.4 [-17.4; 16.5]	0.960

(Continued)

Table E7. Continued

		FVC change (mL/year)		FEV_1 change (mL/year)		FEF_{25-75} change (mL/s·year)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
	Overweight	17.3 [4.9; 29.7]	**0.006**	7.8 [-3.8; 19.3]	0.186	-2.3 [-22.2; 17.5]	0.818
	Obese	28.0 [9.4; 46.6]	**0.003**	8.8 [-8.4; 26.0]	0.315	-4.7 [-34.4; 25.0]	0.756
		p-trend	**0.001**	*p-trend*	0.165	*p-trend*	0.734
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	25.9 [12.6; 39.2]	**<0.0001**	23.6 [11; 36.2]	**<0.0001**	31.2 [9.3; 53.1]	**0.005**
	Medium-high	43.0 [28.9; 57.0]	**<0.0001**	35.7 [22.5; 48.9]	**<0.0001**	37.8 [15.1; 60.5]	**0.001**
	High	55.8 [37.1; 74.5]	**<0.0001**	41.9 [24.3; 59.4]	**<0.0001**	47.5 [17.2; 77.8]	**0.002**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.002**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	-2.8 [-15.1; 9.5]	0.655	-3.3 [-14.9; 8.2]	0.574	-3.8 [-24.1; 16.5]	0.716
	Medium-high	0.3 [-12.5; 13.2]	0.959	-3.5 [-15.5; 8.5]	0.563	-9.7 [-30.8; 11.5]	0.370
	High	4.9 [-11.1; 20.8]	0.550	-5.7 [-20.5; 9.2]	0.456	-17.7 [-43.9; 8.6]	0.187
		p-trend	0.516	*p-trend*	0.403	*p-trend*	0.117

Rate of lung function growth for each parameter was calculated as: (pre-bronchodilation lung function measure at 15 years - pre-bronchodilation lung function measure at 8 years)/time follow-up. Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

Table E8. Adjusted associations of body weight and composition trajectories with post-bronchodilation lung function measures at age 15 years: Models additionally adjusted for wear-time spent in MVPA and total energy intake

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
BOYS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.17 [0.06; 0.27]	**0.003**	0.15 [0.05; 0.25]	**0.003**	0.20 [0.04; 0.36]	**0.015**	-0.17 [-1.14; 0.81]	0.733
	Overweight	0.21 [0.07; 0.34]	**0.002**	0.16 [0.04; 0.28]	**0.011**	0.17 [-0.03; 0.36]	**0.092**	-0.69 [-1.87; 0.50]	0.257
	Obese	0.19 [-0.01; 0.39]	0.067	0.09 [-0.09; 0.27]	0.334	-0.05 [-0.34; 0.24]	0.738	-1.44 [-3.23; 0.34]	0.112
		p-trend	**0.003**	*p-trend*	**0.035**	*p-trend*	0.421	*p-trend*	0.09
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.28 [0.11; 0.45]	**0.001**	0.25 [0.10; 0.41]	**0.002**	0.26 [0.00; 0.51]	**0.046**	-0.19 [-1.79; 1.41]	0.817
	Medium-high	0.47 [0.3; 0.64]	**<0.0001**	0.43 [0.28; 0.59]	**<0.0001**	0.46 [0.20; 0.71]	**<0.0001**	-0.02 [-1.62; 1.59]	0.984
	High	0.65 [0.45; 0.85]	**<0.0001**	0.56 [0.38; 0.74]	**<0.0001**	0.55 [0.26; 0.85]	**<0.0001**	-0.58 [-2.42; 1.27]	0.539
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.728
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.04 [-0.07; 0.15]	0.452	0.07 [-0.03; 0.18]	0.155	0.18 [0.01; 0.35]	**0.035**	0.68 [-0.36; 1.72]	0.198
	Medium-high	0.05 [-0.08; 0.18]	0.436	0.01 [-0.11; 0.13]	0.859	-0.01 [-0.20; 0.18]	0.945	-0.84 [-2.02; 0.34]	0.162
	High	-0.02 [-0.19; 0.15]	0.805	-0.08 [-0.24; 0.07]	0.304	-0.15 [-0.41; 0.10]	0.246	-1.32 [-2.89; 0.25]	0.099
		p-trend	0.903	*p-trend*	0.342	*p-trend*	0.198	*p-trend*	**0.025**
GIRLS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.07 [-0.02; 0.15]	0.127	0.04 [-0.04; 0.13]	0.308	0.07 [-0.08; 0.23]	0.357	-0.85 [-1.92; 0.23]	0.123

(Continued)

Table E8. Continued

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
	Overweight	0.11 [0.01; 0.22]	**0.032**	0.07 [-0.03; 0.17]	0.193	0.07 [-0.11; 0.25]	0.462	-1.67 [-2.93; -0.41]	**0.009**
	Obese	0.18 [0.03; 0.34]	**0.020**	0.10 [-0.05; 0.25]	0.211	0.06 [-0.21; 0.33]	0.660	-2.56 [-4.43; -0.69]	**0.007**
		p-trend	**0.008**	*p-trend*	0.134	*p-trend*	0.523	*p-trend*	**0.001**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.19 [0.08; 0.30]	**0.001**	0.21 [0.10; 0.32]	**<0.0001**	0.34 [0.14; 0.54]	**0.001**	0.61 [-0.77; 2.00]	0.384
	Medium-high	0.31 [0.19; 0.42]	**<0.0001**	0.30 [0.19; 0.41]	**<0.0001**	0.44 [0.23; 0.64]	**<0.0001**	0.04 [-1.39; 1.46]	0.960
	High	0.36 [0.21; 0.52]	**<0.0001**	0.29 [0.14; 0.44]	**<0.0001**	0.34 [0.06; 0.61]	**0.015**	-1.4 [-3.27; 0.47]	0.142
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.004**	*p-trend*	0.092
FMI	Low	(Reference)		(Reference)		[Reference]		(Reference)	
	Medium-low	0.03 [-0.07; 0.14]	0.501	0.03 [-0.07; 0.13]	0.525	0.12 [-0.06; 0.30]	0.191	-0.44 [-1.72; 0.84]	0.496
	Medium-high	0.02 [-0.09; 0.13]	0.696	0.00 [-0.10; 0.11]	0.931	0.01 [-0.19; 0.20]	0.959	-1.05 [-2.38; 0.28]	0.122
	High	0.09 [-0.04; 0.23]	0.185	0.04 [-0.09; 0.17]	0.535	0.04 [-0.20; 0.28]	0.730	-1.53 [-3.21; 0.15]	0.074
		p-trend	0.392	*p-trend*	0.970	*p-trend*	0.561	*p-trend*	**0.026**

Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, total energy intake at 7 years, lung function measures at 8 years, wear-time spent in MVPA at 11 years, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

Table E9. Adjusted associations of body weight and composition trajectories with post-bronchodilation lung function measures at age 15 years: Excluding children with lifetime doctor-diagnosed asthma (n=865)

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
BOYS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.15 [0.04; 0.26]	**0.009**	0.13 [0.03; 0.23]	**0.011**	0.18 [0.01; 0.34]	**0.037**	-0.28 [-1.23; 0.68]	0.572
	Overweight	0.17 [0.04; 0.31]	**0.009**	0.14 [0.01; 0.26]	**0.029**	0.19 [-0.01; 0.38]	0.059	-0.99 [-2.12; 0.15]	0.089
	Obese	0.07 [-0.12; 0.27]	0.447	-0.06 [-0.23; 0.12]	0.512	-0.22 [-0.5; 0.06]	0.130	-2.55 [-4.2; -0.90]	**0.002**
		p-trend	0.052	*p-trend*	0.453	*p-trend*	0.942	*p-trend*	**0.003**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.24 [0.06; 0.43]	**0.009**	0.19 [0.02; 0.36]	**0.027**	0.17 [-0.11; 0.45]	0.232	-1.05 [-2.71; 0.60]	0.213
	Medium-high	0.48 [0.3; 0.67]	**<0.0001**	0.42 [0.24; 0.59]	**<0.0001**	0.41 [0.13; 0.69]	**0.004**	-0.85 [-2.52; 0.81]	0.314
	High	0.66 [0.44; 0.88]	**<0.0001**	0.51 [0.31; 0.72]	**<0.0001**	0.44 [0.1; 0.77]	**0.010**	-1.98 [-3.92; -0.03]	**0.046**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.140
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.03 [-0.09; 0.14]	0.637	0.07 [-0.04; 0.17]	0.202	0.21 [0.04; 0.39]	**0.015**	0.93 [-0.08; 1.93]	0.072
	Medium-high	0.01 [-0.11; 0.14]	0.844	0.00 [-0.11; 0.12]	0.961	0.06 [-0.13; 0.26]	0.510	-0.47 [-1.60; 0.65]	0.409
	High	-0.12 [-0.29; 0.04]	0.134	-0.18 [-0.33; -0.04]	**0.015**	-0.24 [-0.48; 0.01]	0.061	-1.75 [-3.19; -0.32]	**0.017**
		p-trend	0.269	*p-trend*	**0.038**	*p-trend*	0.117	*p-trend*	**0.008**
GIRLS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.09 [0.00; 0.17]	**0.042**	0.05 [-0.03; 0.13]	0.254	0.12 [-0.03; 0.27]	0.117	-0.98 [-2.04; 0.08]	0.071

Table E9. Continued

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
	Overweight	0.13 [0.03; 0.23]	**0.014**	0.08 [-0.02; 0.18]	0.132	0.06 [-0.11; 0.24]	0.487	-1.94 [-3.21; -0.67]	**0.003**
	Obese	0.26 [0.09; 0.42]	**0.002**	0.18 [0.02; 0.34]	**0.028**	0.18 [-0.11; 0.47]	0.227	-2.68 [-4.72; -0.65]	**0.010**
		p-trend	**0.001**	*p-trend*	**0.028**	*p-trend*	0.279	*p-trend*	**0.001**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.21 [0.10; 0.31]	**<0.0001**	0.21 [0.10; 0.31]	**<0.0001**	0.29 [0.10; 0.48]	**0.003**	0.42 [-0.94; 1.79]	0.542
	Medium-high	0.28 [0.17; 0.39]	**<0.0001**	0.28 [0.17; 0.39]	**<0.0001**	0.40 [0.21; 0.60]	**<0.0001**	0.22 [-1.20; 1.63]	0.764
	High	0.40 [0.25; 0.56]	**<0.0001**	0.34 [0.19; 0.49]	**<0.0001**	0.41 [0.14; 0.68]	**0.003**	-1.14 [-3.06; 0.79]	0.248
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.349
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.01 [-0.09; 0.11]	0.807	-0.02 [-0.12; 0.08]	0.707	0.08 [-0.10; 0.25]	0.401	-0.96 [-2.24; 0.32]	0.140
	Medium-high	0.03 [-0.07; 0.14]	0.547	-0.02 [-0.12; 0.09]	0.770	-0.01 [-0.19; 0.17]	0.913	-1.82 [-3.14; -0.50]	**0.007**
	High	0.11 [-0.03; 0.24]	0.112	0.04 [-0.09; 0.17]	0.531	0.00 [-0.24; 0.24]	0.979	-2.31 [-4.01; -0.60]	**0.008**
		p-trend	0.139	*p-trend*	0.679	*p-trend*	0.534	*p-trend*	**0.001**

Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

Table E10. Adjusted associations of body weight and composition trajectories with post-bronchodilation lung function measures at age 15 years: Excluding children with extreme lung function measures (<p1 and p>99) at age 15 years

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	p-value	Adjusted β [95% CI]	p-value	Adjusted β [95% CI]	p-value	Adjusted β [95% CI]	p-value
BOYS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.11 [0.03; 0.20]	**0.010**	0.10 [0.02; 0.18]	**0.014**	0.15 [0.02; 0.28]	**0.020**	-0.01 [-0.80; 0.79]	0.987
	Overweight	0.19 [0.09; 0.29]	**<0.0001**	0.15 [0.05; 0.24]	**0.002**	0.09 [-0.07; 0.24]	0.263	-0.82 [-1.76; 0.13]	0.091
	Obese	0.15 [0.00; 0.30]	**0.044**	0.03 [-0.1; 0.16]	0.618	-0.12 [-0.33; 0.10]	0.291	-1.94 [-3.28; -0.6]	**0.005**
		p-trend	**0.001**	*p-trend*	**0.042**	*p-trend*	0.894	*p-trend*	**0.004**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.22 [0.08; 0.36]	**0.002**	0.20 [0.07; 0.32]	**0.003**	0.22 [0.02; 0.43]	**0.036**	-0.47 [-1.78; 0.84]	0.484
	Medium-high	0.44 [0.30; 0.58]	**<0.0001**	0.40 [0.27; 0.53]	**<0.0001**	0.46 [0.25; 0.67]	**<0.0001**	-0.47 [-1.79; 0.85]	0.486
	High	0.57 [0.40; 0.73]	**<0.0001**	0.50 [0.35; 0.65]	**<0.0001**	0.49 [0.25; 0.74]	**<0.0001**	-0.74 [-2.27; 0.80]	0.345
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.418
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.02 [-0.07; 0.11]	0.681	0.05 [-0.03; 0.13]	0.228	0.13 [0.00; 0.27]	0.050	0.73 [-0.11; 1.57]	0.089
	Medium-high	0.05 [-0.05; 0.15]	0.334	0.01 [-0.08; 0.10]	0.823	-0.06 [-0.20; 0.09]	0.471	-0.79 [-1.73; 0.14]	0.097
	High	-0.01 [-0.14; 0.11]	0.820	-0.10 [-0.22; 0.01]	0.076	-0.23 [-0.42; -0.04]	**0.018**	-1.37 [-2.57; -0.17]	**0.025**
		p-trend	0.791	*p-trend*	0.131	*p-trend*	**0.008**	*p-trend*	**0.003**
GIRLS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.07 [0.01; 0.14]	**0.035**	0.05 [-0.01; 0.12]	0.129	0.15 [0.03; 0.28]	**0.016**	-0.96 [-1.81; -0.11]	**0.027**

(Continued)

Table E10. Continued

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
	Overweight	0.12 [0.04; 0.20]	**0.003**	0.07 [-0.01; 0.15]	0.078	0.09 [-0.06; 0.23]	0.243	-1.95 [-2.94; -0.96]	**<0.0001**
	Obese	0.19 [0.07; 0.31]	**0.002**	0.11 [-0.01; 0.22]	0.075	0.04 [-0.18; 0.27]	0.695	-2.66 [-4.10; -1.22]	**<0.0001**
		p-trend	**<0.0001**	*p-trend*	**0.039**	*p-trend*	0.468	*p-trend*	
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.14 [0.05; 0.23]	**0.002**	0.13 [0.05; 0.22]	**0.002**	0.24 [0.08; 0.41]	**0.003**	0.39 [-0.71; 1.49]	0.489
	Medium-high	0.26 [0.16; 0.35]	**<0.0001**	0.23 [0.14; 0.32]	**<0.0001**	0.34 [0.17; 0.50]	**<0.0001**	-0.17 [-1.31; 0.96]	0.764
	High	0.27 [0.15; 0.39]	**<0.0001**	0.21 [0.10; 0.33]	**<0.0001**	0.32 [0.09; 0.54]	**0.006**	-1.44 [-2.94; 0.07]	0.061
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.002**	*p-trend*	**0.032**
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.03 [-0.06; 0.11]	0.536	0.02 [-0.06; 0.10]	0.668	0.08 [-0.07; 0.23]	0.304	-0.89 [-1.92; 0.13]	0.088
	Medium-high	0.04 [-0.04; 0.13]	0.329	0.00 [-0.08; 0.08]	0.973	0.03 [-0.12; 0.19]	0.698	-1.55 [-2.60; -0.49]	**0.004**
	High	0.11 [0.00; 0.21]	**0.041**	0.03 [-0.07; 0.13]	0.564	-0.03 [-0.22; 0.17]	0.781	-2.18 [-3.48; -0.87]	**0.001**
		p-trend	0.067	*p-trend*	0.916	*p-trend*	0.502	*p-trend*	**<0.0001**

Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Number of observations deleted from the adjusted models: FVC (boys/girls):32/36; FEV_1: 32/33; FEF_{25-75}:32/36; ratio FEV_1/FVC: 60/113. Bold: p-value <0.05

Table E11. Adjusted associations of body weight and composition trajectories with pre-bronchodilation lung function measures at age 15 years

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
BOYS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.16 [0.07; 0.25]	**0.001**	0.15 [0.07; 0.23]	**<0.0001**	0.16 [0.04; 0.29]	**0.012**	-0.16 [-1.08; 0.76]	0.735
	Overweight	0.18 [0.07; 0.29]	**0.001**	0.13 [0.04; 0.23]	**0.007**	0.11 [-0.04; 0.27]	0.143	-0.82 [-1.91; 0.27]	0.139
	Obese	0.10 [-0.05; 0.26]	0.202	-0.01 [-0.15; 0.12]	0.880	-0.11 [-0.32; 0.11]	0.322	-1.65 [-3.18; -0.11]	**0.036**
		p-trend	**0.008**	*p-trend*	0.190	*p-trend*	0.917	*p-trend*	**0.023**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.23 [0.09; 0.38]	**0.002**	0.21 [0.08; 0.34]	**0.001**	0.23 [0.02; 0.43]	**0.035**	0.17 [-1.35; 1.69]	0.830
	Medium-high	0.47 [0.32; 0.61]	**<0.0001**	0.41 [0.28; 0.54]	**<0.0001**	0.38 [0.17; 0.59]	**<0.0001**	-0.21 [-1.74; 1.32]	0.788
	High	0.63 [0.46; 0.80]	**<0.0001**	0.53 [0.38; 0.68]	**<0.0001**	0.49 [0.24; 0.73]	**<0.0001**	-0.42 [-2.19; 1.36]	0.644
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.362
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.05 [-0.04; 0.15]	0.278	0.07 [-0.01; 0.15]	0.106	0.13 [0.00; 0.27]	0.057	0.22 [-0.75; 1.20]	0.653
	Medium-high	0.03 [-0.07; 0.13]	0.567	-0.01 [-0.10; 0.08]	0.821	-0.04 [-0.19; 0.11]	0.614	-1.07 [-2.15; 0.01]	0.051
	High	-0.10 [-0.24; 0.03]	0.131	-0.17 [-0.28; -0.05]	**0.006**	-0.18 [-0.38; 0.01]	0.060	-1.4 [-2.78; -0.02]	**0.047**
		p-trend	0.294	*p-trend*	**0.010**	*p-trend*	**0.032**	*p-trend*	**0.007**
GIRLS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.05 [-0.02; 0.12]	0.146	0.03 [-0.04; 0.09]	0.448	-0.01 [-0.12; 0.11]	0.906	-0.92 [-1.85; 0.02]	0.055

(Continued)

Table E11. Continued

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
	Overweight	0.12 [0.04; 0.21]	**0.005**	0.05 [-0.03; 0.13]	0.190	-0.02 [-0.16; 0.12]	0.764	-1.73 [-2.83; -0.62]	**0.002**
	Obese	0.20 [0.08; 0.33]	**0.002**	0.06 [-0.05; 0.18]	0.279	-0.03 [-0.24; 0.17]	0.750	-3.25 [-4.88; -1.63]	**<0.0001**
		p-trend	**<0.0001**	*p-trend*	0.151	*p-trend*	0.702	*p-trend*	**<0.0001**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.17 [0.08; 0.26]	**<0.0001**	0.16 [0.07; 0.25]	**<0.0001**	0.21 [0.06; 0.36]	**0.005**	-0.18 [-1.40; 1.04]	0.772
	Medium-high	0.29 [0.20; 0.39]	**<0.0001**	0.24 [0.15; 0.33]	**<0.0001**	0.26 [0.10; 0.41]	**0.001**	-0.62 [-1.88; 0.64]	0.333
	High	0.38 [0.25; 0.51]	**<0.0001**	0.29 [0.17; 0.41]	**<0.0001**	0.33 [0.12; 0.53]	**0.002**	-1.45 [-3.11; 0.22]	0.088
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.002**	*p-trend*	**0.040**
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	-0.02 [-0.10; 0.06]	0.628	-0.02 [-0.10; 0.06]	0.557	-0.03 [-0.17; 0.11]	0.658	-0.64 [-1.75; 0.48]	0.264
	Medium-high	0.00 [-0.09; 0.09]	0.971	-0.03 [-0.11; 0.06]	0.530	-0.07 [-0.22; 0.07]	0.318	-1.13 [-2.29; 0.04]	0.058
	High	0.04 [-0.07; 0.15]	0.495	-0.04 [-0.14; 0.06]	0.466	-0.13 [-0.31; 0.05]	0.166	-2.34 [-3.79; -0.9]	**0.002**
		p-trend	0.462	*p-trend*	0.405	*p-trend*	0.101	*p-trend*	**0.001**

Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

Table E12. Adjusted associations of body weight and composition trajectories with post-bronchodilation lung function measures at age 15 years: Without adjustment for lung function at 8 years

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
BOYS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.18 [0.09; 0.28]	**<0.0001**	0.15 [0.07; 0.24]	**<0.0001**	0.20 [0.06; 0.35]	**0.007**	-0.43 [-1.30; 0.45]	0.338
	Overweight	0.29 [0.18; 0.39]	**<0.0001**	0.21 [0.12; 0.31]	**<0.0001**	0.24 [0.07; 0.41]	**0.007**	-1.18 [-2.21; -0.16]	**0.024**
	Obese	0.26 [0.10; 0.41]	**0.001**	0.09 [-0.05; 0.22]	0.212	-0.10 [-0.34; 0.14]	0.421	-2.68 [-4.12; -1.24]	**<0.0001**
		p-trend	**<0.0001**	*p-trend*	**0.001**	*p-trend*	0.336	*p-trend*	**<0.0001**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.23 [0.09; 0.37]	**0.002**	0.18 [0.05; 0.31]	**0.008**	0.17 [-0.06; 0.40]	0.143	-0.67 [-2.08; 0.74]	0.352
	Medium-high	0.47 [0.33; 0.62]	**<0.0001**	0.39 [0.26; 0.53]	**<0.0001**	0.43 [0.20; 0.66]	**<0.0001**	-0.76 [-2.18; 0.66]	0.295
	High	0.73 [0.56; 0.90]	**<0.0001**	0.59 [0.44; 0.74]	**<0.0001**	0.59 [0.32; 0.86]	**<0.0001**	-1.27 [-2.91; 0.37]	0.128
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.111
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.05 [-0.05; 0.15]	0.312	0.09 [0.00; 0.17]	**0.049**	0.2 [0.05; 0.36]	**0.010**	0.91 [-0.02; 1.84]	0.055
	Medium-high	0.04 [-0.06; 0.15]	0.410	0.02 [-0.07; 0.12]	0.649	0.03 [-0.14; 0.20]	0.755	-0.67 [-1.70; 0.36]	0.201
	High	0.00 [-0.13; 0.14]	0.982	-0.09 [-0.21; 0.03]	0.129	-0.20 [-0.42; 0.01]	0.066	-2.02 [-3.31; -0.73]	**0.002**
		p-trend	0.796	*p-trend*	0.171	*p-trend*	0.067	*p-trend*	**<0.0001**
GIRLS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.16 [0.08; 0.23]	**<0.0001**	0.11 [0.04; 0.19]	**0.003**	0.13 [-0.01; 0.26]	0.066	-1.11 [-2.02; -0.20]	**0.017**

(Continued)

Table E12. Continued

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
	Overweight	0.26 [0.17; 0.35]	**<0.0001**	0.16 [0.07; 0.24]	**<0.0001**	0.08 [-0.08; 0.24]	0.324	-2.43 [-3.49; -1.37]	**<0.0001**
	Obese	0.42 [0.28; 0.55]	**<0.0001**	0.25 [0.13; 0.38]	**<0.0001**	0.09 [-0.15; 0.32]	0.470	-3.88 [-5.43; -2.32]	**<0.0001**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.404	*p-trend*	**<0.0001**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.23 [0.14; 0.33]	**<0.0001**	0.23 [0.13; 0.32]	**<0.0001**	0.34 [0.17; 0.52]	**<0.0001**	0.65 [-0.52; 1.82]	0.277
	Medium-high	0.42 [0.32; 0.52]	**<0.0001**	0.37 [0.27; 0.47]	**<0.0001**	0.43 [0.25; 0.61]	**<0.0001**	-0.22 [-1.43; 0.99]	0.719
	High	0.57 [0.43; 0.70]	**<0.0001**	0.45 [0.33; 0.58]	**<0.0001**	0.44 [0.20; 0.68]	**<0.0001**	-1.43 [-3.02; 0.17]	0.079
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.013**
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.06 [-0.03; 0.15]	0.182	0.04 [-0.05; 0.12]	0.400	0.11 [-0.05; 0.27]	0.189	-0.85 [-1.94; 0.24]	0.127
	Medium-high	0.10 [0.01; 0.20]	**0.030**	0.05 [-0.04; 0.14]	0.296	0.05 [-0.12; 0.21]	0.591	-1.66 [-2.78; -0.54]	**0.004**
	High	0.15 [0.04; 0.27]	**0.010**	0.05 [-0.06; 0.16]	0.387	-0.02 [-0.23; 0.19]	0.865	-2.69 [-4.08; -1.31]	**<0.0001**
		p-trend	**0.007**	*p-trend*	0.450	*p-trend*	0.489	*p-trend*	**<0.0001**

Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

Table E13. Adjusted associations of body weight and composition trajectories with post-bronchodilation lung function measures at age 15 years: Using lung function measures as standard deviation scores derived using the Global Lung Initiative equations

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
BOYS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.36 [0.18; 0.54]	**<0.0001**	0.38 [0.2; 0.56]	**<0.0001**	0.25 [0.11; 0.39]	**0.001**	0.01 [-0.15; 0.16]	0.935
	Overweight	0.51 [0.29; 0.73]	**<0.0001**	0.42 [0.2; 0.63]	**<0.0001**	0.18 [0.01; 0.36]	**0.037**	-0.18 [-0.37; 0.01]	0.058
	Obese	0.61 [0.31; 0.92]	**<0.0001**	0.44 [0.13; 0.75]	**0.006**	0.12 [-0.13; 0.37]	0.335	-0.30 [-0.56; -0.04]	**0.025**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.070	*p-trend*	**0.009**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.56 [0.27; 0.84]	**<0.0001**	0.55 [0.26; 0.85]	**<0.0001**	0.27 [0.04; 0.50]	**0.024**	-0.10 [-0.36; 0.15]	0.433
	Medium-high	0.95 [0.66; 1.23]	**<0.0001**	0.99 [0.69; 1.28]	**<0.0001**	0.53 [0.30; 0.76]	**<0.0001**	-0.04 [-0.29; 0.22]	0.763
	High	1.32 [0.99; 1.65]	**<0.0001**	1.28 [0.94; 1.62]	**<0.0001**	0.64 [0.37; 0.91]	**<0.0001**	-0.17 [-0.46; 0.12]	0.247
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.614
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.13 [-0.06; 0.31]	0.176	0.19 [0.00; 0.38]	**0.045**	0.19 [0.04; 0.34]	**0.011**	0.13 [-0.03; 0.29]	0.110
	Medium-high	0.17 [-0.04; 0.38]	0.107	0.06 [-0.15; 0.27]	0.549	-0.01 [-0.18; 0.16]	0.917	-0.18 [-0.37; 0.00]	**0.046**
	High	0.10 [-0.18; 0.37]	0.487	-0.07 [-0.34; 0.21]	0.637	-0.12 [-0.34; 0.10]	0.302	-0.27 [-0.51; -0.03]	**0.025**
		p-trend	0.255	*p-trend*	0.633	*p-trend*	0.174	*p-trend*	**0.002**
GIRLS									
BMI	Normal-low	(Reference)		(Reference)		(Reference)		(Reference)	
	Normal-high	0.34 [0.16; 0.51]	**<0.0001**	0.33 [0.14; 0.52]	**0.001**	0.25 [0.08; 0.41]	**0.003**	-0.07 [-0.23; 0.10]	0.425

Table E13. Continued

		FVC (L)		FEV_1 (L)		FEF_{25-75} (L/s)		FEV_1/FVC (%)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
	Overweight	0.59 [0.4; 0.78]	**<0.0001**	0.54 [0.32; 0.75]	**<0.0001**	0.26 [0.07; 0.44]	**0.007**	-0.25 [-0.44; -0.07]	**0.008**
	Obese	0.94 [0.65; 1.23]	**<0.0001**	0.79 [0.47; 1.11]	**<0.0001**	0.35 [0.07; 0.63]	**0.014**	-0.48 [-0.76; -0.20]	**0.001**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.003**	*p-trend*	**<0.0001**
LBMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.44 [0.22; 0.65]	**<0.0001**	0.50 [0.25; 0.74]	**<0.0001**	0.40 [0.19; 0.61]	**<0.0001**	0.07 [-0.14; 0.29]	0.503
	Medium-high	0.71 [0.48; 0.94]	**<0.0001**	0.78 [0.53; 1.03]	**<0.0001**	0.56 [0.34; 0.78]	**<0.0001**	0.02 [-0.20; 0.24]	0.839
	High	1.13 [0.83; 1.43]	**<0.0001**	1.04 [0.71; 1.37]	**<0.0001**	0.55 [0.26; 0.83]	**<0.0001**	-0.26 [-0.55; 0.03]	0.076
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.069
FMI	Low	(Reference)		(Reference)		(Reference)		(Reference)	
	Medium-low	0.17 [-0.04; 0.37]	0.105	0.19 [-0.04; 0.42]	0.103	0.20 [0.00; 0.39]	0.052	-0.02 [-0.22; 0.18]	0.862
	Medium-high	0.26 [0.05; 0.47]	**0.014**	0.25 [0.02; 0.48]	**0.030**	0.11 [-0.09; 0.31]	0.266	-0.13 [-0.33; 0.08]	0.216
	High	0.45 [0.19; 0.71]	**0.001**	0.37 [0.08; 0.65]	**0.011**	0.15 [-0.10; 0.40]	0.230	-0.29 [-0.55; -0.04]	**0.023**
		p-trend	**<0.0001**	*p-trend*	**0.013**	*p-trend*	0.603	*p-trend*	**0.006**

Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years and pubertal status (age at menarche for girls and voice break for boys status at age 15 years for boys). Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

Table E14. Adjusted associations of body weight and composition trajectories with pre-bronchodilation lung function growth rates from age 8 to 15 years: Models additionally adjusted for wear-time spent in MVPA and total energy intake

		FVC change (mL/year) Adjusted β [95% CI]	p-value	FEV_1 change (mL/year) Adjusted β [95% CI]	p-value	FEF_{25-75} change (mL/s·year) Adjusted β [95% CI]	p-value
BOYS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	28.7 [13.0; 44.5]	**<0.0001**	25.7 [11.7; 39.7]	**<0.0001**	26.5 [4.1; 48.9]	**0.021**
	Overweight	36.2 [16.9; 55.5]	**<0.0001**	26.6 [9.5; 43.7]	**0.002**	23.1 [-4.0; 50.3]	0.095
	Obese	20.5 [-8.7; 49.6]	0.168	6.0 [-19.7; 31.6]	0.647	-9.6 [-50.6; 31.4]	0.646
		p-trend	**0.002**	*p-trend*	**0.036**	*p-trend*	0.473
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	40.0 [15.4; 64.7]	**0.002**	34.6 [12.4; 56.8]	**0.002**	36.8 [0.9; 72.8]	**0.044**
	Medium-high	72.2 [47.4; 97.1]	**<0.0001**	63.4 [41.1; 85.7]	**<0.0001**	59.9 [23.9; 96.0]	**0.001**
	High	95.0 [66.1; 124]	**<0.0001**	79.3 [53.4; 105.1]	**<0.0001**	73.9 [32.1; 115.7]	**0.001**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	6.0 [-10.3; 22.3]	0.470	7.4 [-7.1; 21.9]	0.318	17.2 [-6.5; 40.8]	0.155
	Medium-high	8.1 [-10.5; 26.6]	0.393	0.5 [-15.9; 17.0]	0.948	-0.6 [-27.5; 26.3]	0.963
	High	-10.1 [-35.0; 14.9]	0.429	-21.0 [-43.1; 1.0]	0.062	-22.2 [-58.2; 13.8]	0.226
		p-trend	0.832	*p-trend*	0.132	*p-trend*	0.235
GIRLS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	2.8 [-9.4; 14.9]	0.654	-0.5 [-11.8; 10.8]	0.933	-10.9 [-30.6; 8.9]	0.282

(Continued)

Table E14. Continued

		FVC change (mL/year) Adjusted β [95% CI]	p-value	FEV_1 change (mL/year) Adjusted β [95% CI]	p-value	FEF_{25-75} change (mL/s·year) Adjusted β [95% CI]	p-value
	Overweight	11.9 [-2.4; 26.2]	0.103	3.4 [-9.9; 16.7]	0.615	-13.7 [-36.8; 9.4]	0.244
	Obese	20.8 [-0.8; 42.4]	0.059	3.9 [-16.2; 23.9]	0.706	-11.4 [-46.3; 23.5]	0.520
		p-trend	**0.028**	*p-trend*	0.558	*p-trend*	0.301
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	27.4 [12.1; 42.7]	**<0.0001**	25.3 [10.9; 39.8]	**0.001**	33.0 [7.7; 58.3]	**0.011**
	Medium-high	43.5 [27.4; 59.6]	**<0.0001**	35.5 [20.4; 50.6]	**<0.0001**	33.9 [7.5; 60.2]	**0.012**
	High	50.7 [29.4; 72]	**<0.0001**	36.6 [16.7; 56.5]	**<0.0001**	34.6 [-0.2; 69.4]	0.052
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	0.056
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	-3.9 [-18.0; 10.2]	0.588	-2.8 [-16.1; 10.5]	0.676	-4.0 [-27.5; 19.5]	0.738
	Medium-high	-4.7 [-19.5; 10.1]	0.534	-7.1 [-20.9; 6.7]	0.316	-16.9 [-41.4; 7.6]	0.177
	High	2.5 [-16.1; 21.2]	0.792	-5.1 [-22.6; 12.4]	0.569	-16.5 [-47.4; 14.5]	0.296
		p-trend	0.973	*p-trend*	0.295	*p-trend*	0.098

Rate of lung function growth for each parameter was calculated as: (pre-bronchodilation lung function measure at 15 years - pre-bronchodilation lung function measure at 8 years)/time follow-up. Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, total energy intake at 7 years, lung function measures at 8 years, wear-time spent in MVPA at 11 years, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

Table E15. Adjusted associations of body weight and composition trajectories with pre-bronchodilation lung function growth rates from age 8 to 15 years: Excluding children with lifetime doctor-diagnosed asthma (n=865)

		FVC change (mL/year)		FEV_1 change (mL/year)		FEF_{25-75} change (mL/s·year)	
		Adjusted β [95% CI]	p-value	Adjusted β [95% CI]	p-value	Adjusted β [95% CI]	p-value
BOYS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	26.8 [10.7; 42.9]	**0.001**	23.5 [9.2; 37.7]	**0.001**	27.5 [5.2; 49.7]	**0.016**
	Overweight	30.8 [11.5; 50.0]	**0.002**	21.4 [4.2; 38.6]	**0.015**	20.2 [-6.2; 46.6]	0.134
	Obese	10.9 [-17.1; 38.8]	0.446	-8.8 [-33.4; 15.8]	0.482	-24.4 [-62.8; 14.0]	0.212
		p-trend	**0.026**	*p-trend*	0.404	*p-trend*	0.985
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	33.1 [6.4; 59.7]	**0.015**	27.8 [3.5; 52.0]	**0.025**	26.0 [-12.0; 64.0]	0.179
	Medium-high	71.5 [44.6; 98.3]	**<0.0001**	58.4 [34.0; 82.8]	**<0.0001**	49.5 [11.3; 87.7]	**0.011**
	High	98.7 [66.9; 130.4]	**<0.0001**	77.3 [48.6; 106.0]	**<0.0001**	67.3 [22.3; 112.3]	**0.003**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	7.5 [-8.9; 23.9]	0.369	12.6 [-2.0; 27.2]	0.092	29.1 [5.7; 52.4]	**0.015**
	Medium-high	6.2 [-12.1; 24.5]	0.505	2.8 [-13.5; 19.2]	0.736	5.7 [-20.4; 31.7]	0.669
	High	-17.5 [-41.0; 6.0]	0.144	-28.5 [-49.3; -7.7]	**0.007**	-32.0 [-65.3; 1.3]	0.059
		p-trend	0.368	*p-trend*	**0.030**	*p-trend*	0.088
GIRLS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	7.1 [-4.7; 18.9]	0.237	1.7 [-9.3; 12.8]	0.757	-1.9 [-20.5; 16.8]	0.844

(Continued)

Table E15. Continued

		FVC change (mL/year)		FEV_1 change (mL/year)		FEF_{25-75} change (mL/s·year)	
		Adjusted β [95% CI]	**p-value**	**Adjusted β [95% CI]**	**p-value**	**Adjusted β [95% CI]**	**p-value**
	Overweight	16.5 [2.3; 30.7]	**0.023**	6.6 [-6.6; 19.9]	0.327	-2.3 [-24.6; 20.0]	0.839
	Obese	30.4 [7.3; 53.4]	**0.010**	13.6 [-7.7; 34.9]	0.210	10.3 [-26.0; 46.5]	0.578
		p-trend	**0.003**	*p-trend*	0.169	*p-trend*	0.846
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	29.5 [14.7; 44.3]	**<0.0001**	24.8 [10.7; 38.8]	**0.001**	28.5 [4.8; 52.2]	**0.018**
	Medium-high	43.5 [27.7; 59.2]	**<0.0001**	36.3 [21.5; 51.2]	**<0.0001**	42.6 [17.9; 67.3]	**0.001**
	High	58.2 [36.7; 79.8]	**<0.0001**	43.7 [23.4; 64.0]	**<0.0001**	50.5 [16.3; 84.6]	**0.004**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.001**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	-3.6 [-17.5; 10.3]	0.613	-5.7 [-18.8; 7.3]	0.387	-6.4 [-28.8; 16.0]	0.576
	Medium-high	0.7 [-13.8; 15.1]	0.928	-4.8 [-18.3; 8.7]	0.487	-12.5 [-35.7; 10.8]	0.294
	High	5.6 [-13.1; 24.3]	0.559	-3.8 [-21.3; 13.6]	0.668	-16.0 [-46.1; 14.2]	0.299
		p-trend	0.484	*p-trend*	0.651	*p-trend*	0.194

Rate of lung function growth for each parameter was calculated as: (pre-bronchodilation lung function measure at 15 years - pre-bronchodilation lung function measure at 8 years)/time follow-up. Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

Table E16. Adjusted associations of body weight and composition trajectories with pre-bronchodilation lung function growth rates from age 8 to 15 years: Excluding children with extreme lung function growth rates (<p1 and p>99)

		FVC change (mL/year) Adjusted β [95% CI]	p-value	FEV_1 change (mL/year) Adjusted β [95% CI]	p-value	FEF_{25-75} change (mL/s·year) Adjusted β [95% CI]	p-value
BOYS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	22.0 [9.5; 34.4]	**0.001**	17.8 [6.8; 28.8]	**0.002**	22.8 [4.5; 41.1]	**0.015**
	Overweight	30.2 [15.4; 45.0]	**<0.0001**	21.9 [8.6; 35.1]	**0.001**	24.8 [2.9; 46.7]	**0.026**
	Obese	24.9 [3.5; 46.2]	0.023	1.5 [-17.0; 20.0]	0.876	-13.7 [-44.4; 17.0]	0.381
		p-trend	**<0.0001**	*p-trend*	0.06	*p-trend*	0.523
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	28.9 [9.1; 48.7]	**0.004**	28.2 [10.5; 45.8]	**0.002**	25.7 [4.9; 46.5]	**0.016**
	Medium-high	63.6 [43.7; 83.6]	**<0.0001**	57.4 [39.6; 75.2]	**<0.0001**	34.0 [12.5; 55.5]	**0.002**
	High	83.0 [59.5; 106.4]	**<0.0001**	70.4 [49.6; 91.2]	**<0.0001**	42.1 [13.8; 70.4]	**0.004**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.003**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	4.9 [-7.9; 17.7]	0.450	3.3 [-8.0; 14.6]	0.566	6.1 [-12.7; 25.0]	0.523
	Medium-high	4.7 [-9.5; 18.9]	0.518	-2.8 [-15.4; 9.8]	0.659	-4.0 [-23.6; 15.6]	0.688
	High	-5.3 [-23.8; 13.2]	0.572	-21.4 [-37.6; -5.3]	**0.009**	-13.3 [-37.5; 10.9]	0.281
		p-trend	0.814	*p-trend*	**0.018**	*p-trend*	0.127
GIRLS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	7.1 [-2.3; 16.6]	0.140	4.7 [-4.1; 13.5]	0.297	-0.1 [-16.0; 15.8]	0.990

(Continued)

Table E16. Continued

		FVC change (mL/year) Adjusted β [95% CI]	p-value	FEV_1 change (mL/year) Adjusted β [95% CI]	p-value	FEF_{25-75} change (mL/s·year) Adjusted β [95% CI]	p-value
	Overweight	14.5 [3.3; 25.7]	**0.011**	6.5 [-3.9; 16.8]	0.219	-3.2 [-21.7; 15.3]	0.734
	Obese	25.4 [8.5; 42.3]	**0.003**	9.9 [-5.8; 25.6]	0.215	-0.4 [-28.3; 27.5]	0.979
		p-trend	**0.001**	*p-trend*	0.148	*p-trend*	0.810
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	18.6 [6.5; 30.7]	**0.003**	18.7 [7.3; 30.1]	**0.001**	31.3 [10.9; 51.6]	**0.003**
	Medium-high	35.0 [22.2; 47.8]	**<0.0001**	30.2 [18.3; 42.1]	**<0.0001**	33.5 [12.4; 54.7]	**0.002**
	High	43.8 [26.8; 60.9]	**<0.0001**	32.5 [16.6; 48.4]	**<0.0001**	43.9 [15.6; 72.1]	**0.002**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.005**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	-0.9 [-12.0; 10.2]	0.875	1.4 [-9.0; 11.8]	0.793	0.6 [-18.3; 19.5]	0.950
	Medium-high	0.3 [-11.3; 12.0]	0.955	-0.7 [-11.5; 10.1]	0.897	-4.6 [-24.2; 15.1]	0.649
	High	6.2 [-8.3; 20.7]	0.399	-1.7 [-15.2; 11.7]	0.801	-9.3 [-33.8; 15.2]	0.455
		p-trend	0.462	*p-trend*	0.573	*p-trend*	0.303

Rate of lung function growth for each parameter was calculated as: (pre-bronchodilation lung function measure at 15 years - pre-bronchodilation lung function measure at 8 years)/time follow-up. Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Number of observations deleted from the adjusted models: FVC (boys/girls):262/303; FEV_1: 282/340; FEF_{25-75}:263/304. Bold: p-value <0.05

Table E17. Adjusted associations of body weight and composition trajectories with pre-bronchodilation lung function growth rates from age 8 to 15 years: Without adjustment for lung function at 8 years

		FVC change (mL/year) Adjusted β [95% CI]	p-value	FEV_1 change (mL/year) Adjusted β [95% CI]	p-value	FEF_{25-75} change (mL/s·year) Adjusted β [95% CI]	p-value
BOYS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	21.4 [8.0; 34.9]	**0.002**	20.6 [8.8; 32.4]	**0.001**	24.9 [6.0; 43.7]	**0.010**
	Overweight	24.3 [8.3; 40.2]	**0.003**	18.7 [4.7; 32.7]	**0.009**	19.7 [-2.6; 42.1]	0.083
	Obese	10.8 [-11.8; 33.4]	0.349	-2.4 [-22.2; 17.4]	0.812	-14.1 [-45.9; 17.6]	0.382
		p-trend	**0.022**	*p-trend*	0.209	*p-trend*	0.728
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	32.9 [11.3; 54.4]	**0.003**	30.3 [11.2; 49.5]	**0.002**	31.0 [0.2; 61.7]	**0.048**
	Medium-high	64.9 [43.2; 86.6]	**<0.0001**	57.6 [38.4; 76.9]	**<0.0001**	54.7 [23.7; 85.6]	**0.001**
	High	86.0 [60.8; 111.3]	**<0.0001**	73.8 [51.5; 96.1]	**<0.0001**	69.3 [33.3; 105.3]	**<0.0001**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	7.0 [-7.0; 20.9]	0.326	9.6 [-2.6; 21.9]	0.122	20.1 [0.2; 40.1]	0.047
	Medium-high	3.4 [-12.1; 18.9]	0.666	-1.9 [-15.5; 11.7]	0.782	-4.9 [-26.9; 17.2]	0.665
	High	-17.6 [-37.5; 2.2]	0.082	-24.7 [-42.0; -7.3]	**0.005**	-24.5 [-52.9; 3.8]	0.090
		p-trend	0.195	*p-trend*	**0.009**	*p-trend*	**0.048**
GIRLS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	7.0 [-3.4; 17.4]	0.186	4.1 [-5.7; 13.9]	0.411	-0.5 [-17.4; 16.5]	0.959

(Continued)

Table E17. Continued

		FVC change (mL/year) Adjusted β [95% CI]	p-value	FEV_1 change (mL/year) Adjusted β [95% CI]	p-value	FEF_{25-75} change (mL/s·year) Adjusted β [95% CI]	p-value
	Overweight	16.2 [4.1; 28.4]	**0.009**	7.9 [-3.5; 19.4]	0.173	-2.2 [-22.1; 17.7]	0.829
	Obese	26.3 [8.1; 44.5]	**0.005**	9.2 [-7.8; 26.1]	0.290	-5.7 [-35.4; 24.0]	0.707
		p-trend	**0.001**	*p-trend*	0.146	*p-trend*	0.710
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	24.5 [11.2; 37.8]	**<0.0001**	23.2 [10.6; 35.7]	**<0.0001**	30.6 [8.7; 52.5]	**0.006**
	Medium-high	40.0 [26.3; 53.8]	**<0.0001**	34.9 [21.9; 47.9]	**<0.0001**	36.9 [14.2; 59.6]	**0.001**
	High	51.6 [33.3; 69.9]	**<0.0001**	40.6 [23.4; 57.7]	**<0.0001**	45.1 [15.0; 75.2]	**0.003**
		p-trend	**<0.0001**	*p-trend*		*p-trend*	**0.003**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	-3.7 [-16.1; 8.6]	0.550	-3.6 [-15.1; 8.0]	0.545	-3.9 [-24.2; 16.4]	0.706
	Medium-high	-1.2 [-14; 11.6]	0.850	-3.9 [-15.8; 8.1]	0.527	-9.4 [-30.5; 11.8]	0.386
	High	3.4 [-12.6; 19.3]	0.679	-5.9 [-20.8; 9.0]	0.436	-17.1 [-43.3; 9.2]	0.202
		p-trend	0.669	*p-trend*	0.381	*p-trend*	0.131

Rate of lung function growth for each parameter was calculated as: (pre-bronchodilation lung function measure at 15 years - pre-bronchodilation lung function measure at 8 years)/time follow-up Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, pubertal status (age at menarche for girls and voice break status at age 15 years for boys), as well as age and height at 15 years. Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

Table E18. Adjusted associations of body weight and composition trajectories with pre-bronchodilation lung function growth rates from age 8 to 15 years: Using lung function measures as standard deviation scores derived using the Global Lung Initiative equations

		FVC change (mL/year) Adjusted β [95% CI]	p-value	FEV_1 change (mL/year) Adjusted β [95% CI]	p-value	FEF_{25-75} change (mL/s·year) Adjusted β [95% CI]	p-value
BOYS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	50.9 [26.4; 75.5]	**<0.0001**	51.6 [27.7; 75.5]	**<0.0001**	33.8 [13.9; 53.7]	**0.001**
	Overweight	71.9 [42.8; 101.0]	**<0.0001**	60.1 [31.7; 88.5]	**<0.0001**	36.2 [12.6; 59.9]	**0.003**
	Obese	54.6 [13.6; 95.7]	**0.009**	31.9 [-7.8; 71.7]	0.115	26.0 [-7.3; 59.3]	0.125
		p-trend	**<0.0001**	*p-trend*	0.001	*p-trend*	0.008
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	61.4 [21.5; 101.2]	**0.003**	60.7 [21.5; 99.8]	**0.002**	32.2 [-0.6; 65.1]	0.055
	Medium-high	124.7 [84.5; 164.8]	**<0.0001**	120.5 [81.1; 160.0]	**<0.0001**	58.3 [25.3; 91.3]	**0.001**
	High	170.8 [124.3; 217.3]	**<0.0001**	157.8 [112.4; 203.3]	**<0.0001**	75.3 [37.2; 113.5]	**<0.0001**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**<0.0001**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	18.7 [-6.8; 44.1]	0.150	23.3 [-1.4; 48.1]	0.065	24.7 [3.7; 45.8]	**0.021**
	Medium-high	26.6 [-1.7; 54.8]	0.065	12.1 [-15.4; 39.7]	0.387	9.3 [-14; 32.6]	0.433
	High	-6.4 [-42.7; 30.0]	0.731	-23.6 [-58.9; 11.7]	0.189	4.5 [-25.6; 34.5]	0.771
		p-trend	0.629	*p-trend*	0.369	*p-trend*	0.882
GIRLS							
BMI	Normal-low	(Reference)		(Reference)		(Reference)	
	Normal-high	24.0 [0.1; 47.9]	**0.049**	16.5 [-8.2; 41.1]	0.189	3.7 [-17.1; 24.5]	0.727

(Continued)

Table E18. Continued

		FVC change (mL/year) Adjusted β [95% CI]	p-value	FEV_1 change (mL/year) Adjusted β [95% CI]	p-value	FEF_{25-75} change (mL/s·year) Adjusted β [95% CI]	p-value
	Overweight	59.2 [31.1; 87.3]	**<0.0001**	40.0 [11.1; 68.9]	**0.007**	11.2 [-13.3; 35.6]	0.371
	Obese	95.2 [53.3; 137.1]	**<0.0001**	61.9 [19; 104.8]	**0.005**	22.6 [-13.9; 59.1]	0.224
		p-trend	0.369	*p-trend*	0.001	*p-trend*	0.192
LBMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	58.1 [27.9; 88.4]	**<0.0001**	55.7 [24.2; 87.2]	**0.001**	34.4 [7.8; 61.1]	**0.011**
	Medium-high	95.0 [63.1; 126.9]	**<0.0001**	86.4 [53.5; 119.3]	**<0.0001**	45.9 [18.2; 73.6]	**0.001**
	High	139.5 [96.9; 182.2]	**<0.0001**	120.3 [76.2; 164.3]	**<0.0001**	63.0 [25.8; 100.3]	**0.001**
		p-trend	**<0.0001**	*p-trend*	**<0.0001**	*p-trend*	**0.001**
FMI	Low	(Reference)		(Reference)		(Reference)	
	Medium-low	-1.9 [-30.1; 26.2]	0.892	-0.7 [-29.8; 28.4]	0.962	6.4 [-18.5; 31.4]	0.613
	Medium-high	11.8 [-17.6; 41.1]	0.431	4.8 [-25.4; 35.0]	0.756	2.6 [-23.4; 28.6]	0.842
	High	34.2 [-1.9; 70.4]	0.063	14.1 [-23.2; 51.4]	0.458	5.1 [-27.0; 37.1]	0.755
		p-trend	**0.040**	*p-trend*	0.448	*p-trend*	0.951

Rate of lung function growth for each parameter was calculated as: (pre-bronchodilation lung function measure at 15 years - pre-bronchodilation lung function measure at 8 years)/time follow-up Definition of abbreviations: BMI, body mass index; FEF_{25-75} forced expiratory flow at 25-75%; FEV_1, volume expired in the first second; FMI, fat mass index; FVC, forced vital capacity; LBMI, lean body mass index; 95% CI, 95% confidence intervals; β, estimate of regression coefficient. Models are adjusted for maternal social class, maternal smoking during pregnancy, birth weight, breastfeeding, lung function measures at 8 years and pubertal status (age at menarche for girls and voice break for boys status at age 15 years for boys). Models for FMI and LBMI are also mutually adjusted. Bold: p-value <0.05

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5.3 Paper III

Peralta GP, Granell R, Bédard A, Howe L, Carsin A-E, Jarvis Deborah, Garcia-Aymerich J.

The mediating role of CRP and insulin resistance in the association of mid-childhood fat mass and airflow limitation at 15 years.

In preparation.

The mediating role of CRP and insulin resistance in the association of mid-childhood fat mass and airflow limitation at 15 years

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ABSTRACT

Background: We previously reported an association of high fat mass levels from age 9 to 15 years with lower forced expiratory flow in one second (FEV_1)/forced vital capacity (FVC) ratio (i.e. increased risk of airflow limitation) at 15 years. Here we aimed to assess whether C-reactive protein (CRP) or/and insulin resistance at 15 years mediate (at least in part) this association.

Methods: We included 2,263 children from the UK Avon Longitudinal Study of Parents and Children birth cohort. Four fat mass index (FMI) trajectories ('low', 'medium-low', 'medium-high', 'high') from 9 to 15 years were previously identified using Group-based Trajectory Modelling. Data on CRP, glucose, insulin and FEV_1/FVC were available at 15 years. We defined insulin resistance by means the homeostasis model assessment-estimated insulin resistance (HOMA-IR) index. We used adjusted linear regression models and the 'mediate' package in 'R' to assess the presence of mediation.

Results: There was no evidence for a role of CRP levels in the association between FMI trajectories and FEV_1/FVC. HOMA-IR appeared to mediate 20% of the association between fat mass and FEV_1/FVC in the 'medium-high' and 'high' trajectories (indirect effect [95%CI]: -0.17% [-0.35 to -0.01] and -0.38% [-0.72 to -0.04], per one standard deviation increase in HOMA-IR, respectively) compared to the 'low' FMI trajectory.

Conclusion: The association of mid-childhood fat mass with the FEV_1/FVC ratio at 15 years may be mediated in part by insulin resistance. We found no evidence of mediation by CRP.

Keywords: ALSPAC, CRP, epidemiology, insulin resistance, mediation

BACKGROUND

Obesity is a major public health problem associated with several adverse health outcomes, including detrimental effects on respiratory health [1,2]. In children and adolescents, obesity (as measured by body mass index (BMI), waist circumference or fat mass) has been related with the levels of lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and the ratio between them) [3–7]. Although results for FEV_1 and FVC vary depending on the measures used, a consistent association has been reported between obesity and the FEV_1/FVC ratio, the primary index of airflow limitation. Systemic inflammation, induced by fat mass, has been proposed as a potential mechanism underlying this association. Several studies have reported positive associations between body fat mass and levels of C-reactive protein levels (CRP), a commonly systemic inflammation marker, in children and adolescents [8–10]. Higher CRP levels have also been associated with impaired lung function [11–13]. In addition, in the last years several studies have suggested that obesity may impair lung function also by means of metabolic derangements [14]. There is growing evidence that insulin resistance, a common consequence of childhood obesity [9,15], is associated with reduced lung function levels and asthma-like symptoms in children [16–18]. However, despite this evidence, no previous study has explicitly assessed whether childhood obesity leads to lower FEV_1/FVC via CRP or insulin resistance.

We previously reported an association of high fat mass levels from age 9 to 15 years with lower FEV_1/FVC at 15 years in children

participating in the UK population-based Avon Longitudinal study of Parents and Children (ALSPAC) birth cohort [6]. Here we aimed to explore the underlying mechanisms of this association. Specifically, we assessed whether CRP levels and/or insulin resistance at 15 years mediate (at least in part) the association of fat mass and FEV_1/FVC, using a casual mediation analysis approach. Identifying the biological underlying mechanisms is of utmost importance to strengthen causal inference between obesity and respiratory health.

METHODS

Study population

We used data from the UK ALSPAC birth cohort, previously described [19,20]. Briefly, ALSPAC recruited 14,541 pregnant women residents in Avon, UK, with expected dates of delivery between the 1st of April 1991, and the 31st of December 1992. Since age 7, surviving offspring has attended to regular follow-up clinic visits. The present analysis was restricted to children from singleton births with available information for the identification of fat mass index trajectories from 9 to 15 years and with lung function, CRP and insulin resistance data at 15 years (Figure S1). The ALSPAC Ethics and Law Committee and the Local Research Ethics Committees gave ethical approval.

All participants and their parents/guardians provided written informed consent.

Fat mass index trajectories

Body composition and height were measured at clinic visits at age 9, 11, 13 and 15 years. Total fat mass was derived using a Lunar Prodigy DXA scanner (GE Medical Systems Lunar, Madison, WI, USA) following standardized procedures previously described [21]. We calculated fat mass index (FMI) by diving total body fat mass (kg) by height squared (m). We previously identified four FMI trajectories from 9 to 15 years ('low', 'medium-low', 'medium-high' and 'high') using a Group-Based Trajectory Modelling approach [6] (Figure 1). We used these trajectories as the exposure variable.

Lung function

Lung function was measured by spirometry at 8 and 15 years (Vitalograph 2120; Vitalograph, Maids Moreton, UK) according to American Thoracic Society standards [22], as described previously [23]. At 15 years, lung function was measured before and after bronchodilation with salbutamol. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were obtained and the FEV_1/FVC ratio was calculated. We used post-bronchodilation FEV_1/FVC at 15 years as the main outcome variable. We also calculated FEV_1/FVC standard deviation score (z-score) using the Global Lung Initiative (GLI) equation references, [24] and used this variable in sensitivity analyses.

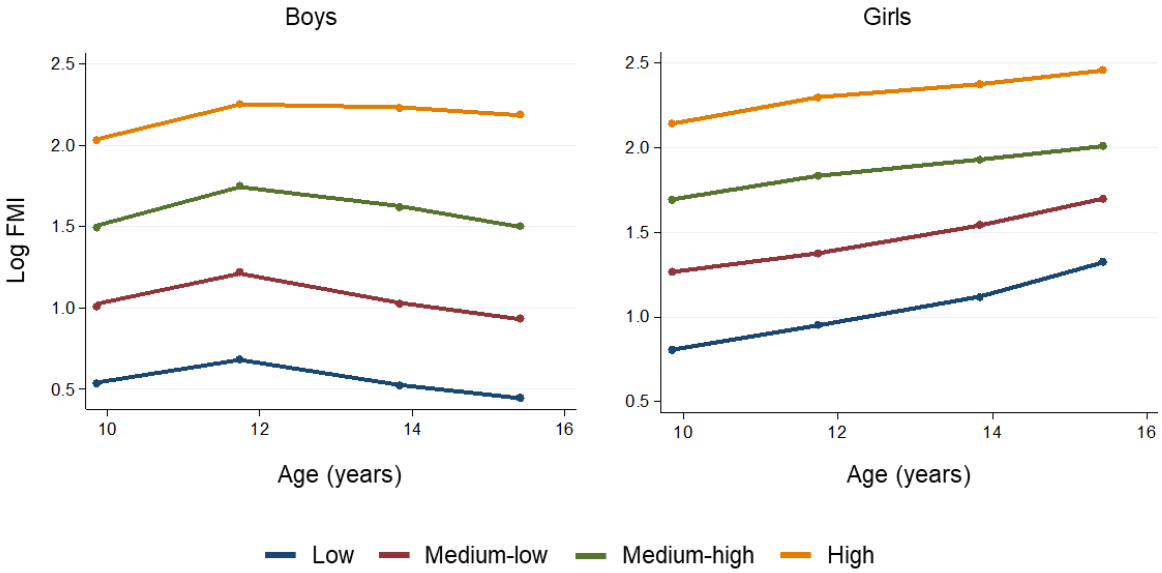

Figure 1. Sex-specific FMI trajectories from 9 to 15 years.

The y-axis represents the natural log-transformed levels of FMI (the equivalent raw value can be calculated by exponentiation of the log transformed value). Abbreviations: FMI: fat mass index. Adapted from Peralta GP, et al. Am J Respir Crit Care Med. 2019;200(1):75-83.

CRP and insulin resistance

Blood samples were obtained during the 15 years clinic visit. Participants fasted overnight before attending the clinic visit if seen in the morning, or at least for 6 h if seen in the afternoon. Blood samples were immediately frozen and stored at -80 ºC, which were assayed three to nine months after blood sampling with not freeze-thaw cycles in between. High sensitivity CRP was measured by automated particle-enhanced immunoturbidimetric assay (Roche UK, Welwyn Garden City, UK). Insulin was measured with an enzyme linked immunosorbent assay (ELISA) (Mercodia, Uppsala, Sweden) that does not cross-react with proinsulin, and plasma glucose was measured with an auto-mated assay. Insulin resistance was calculated as a continuous measure from insulin and glucose by using the homeostasis model assessment-estimated insulin resistance (HOMA-IR), which is calculated by multiplying fasting plasma glucose (mmol/L) and fasting serum insulin (mU/L) and dividing by 22.5 [18,25]. As CRP and HOMA-IR data did not follow a normal distribution, we applied the natural log-transformation to these variables and used log-transformed CRP and HOMA-IR in mediation analysis.

Other relevant characteristics

We collected data on sociodemographic and lifestyle factors at different time points. Information on maternal social class and smoking status was obtained using questionnaires during pregnancy. Birthweight, gestational age and sex were obtained from birth records. Data on breastfeeding, total energy intake of the child at 7

years and environmental tobacco exposure at 8 years were obtained using questionnaires. At 11 years, physical activity was measured by accelerometer and the wear-time spent in moderate to vigorous physical activity (MVPA) [21] was obtained. At 15 years, children reported if a doctor had ever diagnosed them with asthma and if they had had chest infection, upper respiratory tract infection (URTI) or cold with fever in past three weeks before the spirometry test. Finally, puberty at 15 years was assessed using self-completed Tanner questionnaires. We defined pubertal status based on pubic hair development stage for boys and girls. Full details on how these variables were measured are provided in the online supplement.

Statistical analysis

To assess the potential mediating role of CRP and HOMA-IR on the association of FMI trajectories with FEV_1/FVC at 15 years we used a causal inference analysis approach, which is based on a counterfactual framework [26]. We performed the mediation analysis following several steps. First, we fit two mediator models, where CRP and HOMA-IR levels were modelled as a function of FMI trajectories in separate models, after adjusting for relevant confounders (maternal social class and smoking during pregnancy, and child's sex, age, height and pubertal status at 15 years). Then, we built the outcome model, which model FEV_1/FVC as a function of CRP and HOMA-IR, in separate models, including FMI trajectories and the same covariates used in the mediator models plus FEV_1/FVC at 8 years. We used linear regression models to estimate both the mediator and outcome models.

The mediator and outcome models were then incorporated into the 'mediation' package in the statistical program 'R' (version 3.6.3), which estimates the amount of the association between FMI trajectories and FEV_1/FVC that occurs through changes in CRP or HOMA-IR. Using previously developed algorithms [26], the 'mediation' package provides three effect estimates: the indirect effect (the population average causal mediation effect that is occurring through the mediator, i.e. through changing CRP or HOMA-IR levels), the direct effect (the remaining population average effect that is not occurring through changes in CRP or HOMA-IR) and the total effect (the sum of the indirect and direct effects). Confidence intervals around these effect estimates are calculated using a quasi-Bayesian Monte Carlo method based on normal approximation. Further details of the statistical procedures have been published elsewhere [27].

We performed several sensitivity analyses. Children who reported lifetime doctor-diagnosed asthma, those with chest infection, URTI or cold with fever in past three weeks before spirometry and those with CRP/HOMA-IR levels equal or above the 95^{th} percentile were excluded in separate analyses. We also repeated the analysis additionally adjusting mediator and outcome models for child's energy intake at 7 years, environmental tobacco exposure at 8 years and wear-time spent in MVPA at 11years. In addition, we repeated models using FEV_1/FVC z-score instead of the absolute value as outcome variable. Finally, we tested the robustness of the indirect effects to violation of the sequential ignorability assumption (i.e.

unmeasured residual confounding) using the ‘medsens’ function of the ‘mediation’ package [27].

RESULTS

Sample description

We included 2,263 children in the present analysis. Mother of these children were older at pregnancy, had higher educational level, were less likely to smoke during pregnancy and more likely to breastfed than mothers of children not included in the analysis (Table S1). In addition, included children had higher birth weight and gestational age and lower FEV_1/FVC at 8 years than children not included. Table 1 shows the main characteristics of the study sample. Approximately 46% of the mothers had a high social class (professional and intermediate) and 17% smoked during pregnancy. Approximately 24% of the children reports lifetime doctor-diagnosed asthma and 19% of them were classified in the ‘low’ FMI trajectory.

Table 1. Characteristics of the study sample (n=2,263) *

	n (%), mean (SD) or median (P_{25}-P_{75})
Maternal characteristics	
Age at delivery (years)	29.2 (4.5)
Social class	
Professional and intermediate	815 (45.6)
Skilled nonmanual	672 (37.6)
Skilled manual, partly skilled and unskilled	299 (16.7)
Smoking during pregnancy: yes	343 (16.6)
Child characteristics	
Sex: girl	1,144 (50.6)
Birth weight (grams)	3,466 (515)
Gestation (weeks)	39.6 (1.7)
Pre-term delivery (<37 weeks gestation)	80 (3.7)
Ever breastfed: yes	1,865 (88.5)
Total energy intake (kcal) at 7 years	1,733 (306)
Wear-time in MVPA (minutes) at 11 years	19.5 (11.7 - 30.7)
Lifetime doctor-diagnosed asthma: yes	534 (23.6)
Age at 15 years (years)	15.4 (0.3)
Height at 15 years (metres)	1.7 (0.1)
Pubertal status 15 years: Tanner stage for pubic hair	
Stage 1-3	105 (5.2)
Stage 4	918 (45.4)
Stage 5	1,001 (49.4)
FMI trajectories from 9 to 15 years	
Low	422 (18.7)
Medium-low	835 (36.9)
Medium-high	686 (30.3)
High	320 (14.1)
CRP (mg/L)15 years	0.4 (0.2 - 0.9)
Log CRP 15 years	-0.7 (1.1)
HOMA-IR 15 years	2.1 (1.5 - 2.8)
Log HOMA-IR 15 years	0.7 (0.5)

(Continued)

Table 1. Continued	**n (%), mean (SD) or median (P_{25}-P_{75})**
Lung function measures	
8 years (pre-bronchodilation)	
FVC (L)	1.9 (0.3)
FEV_1 (L)	1.7 (0.3)
FEV_1/FVC (%)	88.1 (6.5)
15 years (post -bronchodilation)	
FVC (L)	3.8 (0.9)
FEV_1 (L)	3.5 (0.8)
FEV_1/FVC (%)	92.1 (6.5)

** Some variables had missing values: Maternal characteristics: 477 in maternal social class, 191 in smoking during pregnancy, 93 in age at delivery; Child characteristics: 93 in gestational age, 121 in birthweight, 155 in ever breastfed, 348 in total energy intake at 7 years, 376 in wear-time in MVPA at 11 years, 20 in height at 15 years, 239 in pubertal status, 307 in FVC at 8 years, 328 in FEV_1 at 8 years and 328 in FEV_1/FVC at 8 years.*

Abbreviations: CRP: C-reactive protein; CSE: certificate of secondary education; FEV_1: forced expiratory volume in one second; FMI: fat mass index; FVC: forced vital capacity; HOMA-IR: homeostasis model assessment-estimated insulin resistance; MVPA: moderate to vigorous physical activity; P25-P75, 25th and 75th percentiles.

Mediating role of CRP and HOMA-IR on the association between FMI trajectories and FEV_1/FVC at 15 years

FMI trajectories were positively associated with CRP and HOMA-IR levels at 15 years (Table S2). CRP was not associated with FEV_1/FVC at 15 years (estimate coefficient and 95% confidence intervals: -0.16% [-0.46 to 0.14]; p-value: 0.309, per one standard deviation increase in log-CRP), while HOMA-IR levels were negatively associated with FEV_1/FVC (-0.74% [-1.40 to -0.08]; p-value: 0.029, per one standard deviation increase in log-HOMA-IR).

Compared to children in the 'low' FMI trajectory, children in the 'medium-high' and 'high' FMI trajectories had lower FEV_1/FVC at 15 years (although the effect estimate for the 'medium-high' trajectory was imprecise). There was no evidence for a role of CRP levels in this association (Table 2). In contrast, HOMA-IR appeared to mediate 20% of the total effect of fat mass on FEV_1/FVC in these trajectories (Table 3). The effect mediated via HOMA-IR (i.e. indirect effect) was -0.17% [-0.35 to -0.01] and -0.38% [-0.72 to -0.04], per one standard deviation increase in log HOMA-IR, for the 'medium-high' and 'high' trajectories, respectively.

Sensitivity analyses yielded similar findings for a null role of CRP (Table S3 to S7) and a mediating role of HOMA-IR (Table S8 to S12). However, the effect mediated via HOMA-IR was imprecise when excluding children with HOMA-IR values equal of above the 95^{th} percentile (Table S10) and when models were additionally adjusted for child's energy intake, environmental tobacco exposure and physical activity in a subsample (Table S11). Finally, the analysis

assessing the sequential ignorability assumption suggested that an unmeasured confounder that is correlated by -0.1 with both HOMA-IR and FEV_1/FVC could explain away the observed indirect effects.

Table 2. Mediating role of log-CRP on the association between FMI trajectories and FEV_1/FVC (%) at 15 years (n=1,404)

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via CRP)	-0.03 [-0.11 to 0.03]	0.320
	Direct (not via CRP)	0.11 [-0.72 to 1.03]	0.840
	Total	0.08 [-0.78 to 0.99]	0.890
	Proportion mediated	-0.02 [-1.00 to 1.23]	0.920
Medium-high vs. low	Indirect (via CRP)	-0.08 [-0.24 to 0.08]	0.310
	Direct (not via CRP)	-0.73 [-1.66 to 0.17]	0.128
	Total	-0.81 [-1.72 to 0.08]	0.078
	Proportion mediated	0.09 [-0.51 to 0.99]	0.368
High vs. low	Indirect (via CRP)	-0.18 [-0.51 to 0.17]	0.310
	Direct (not via CRP)	-1.69 [-2.84 to -0.43]	0.006
	Total	-1.87 [-2.98 to -0.65]	0.004
	Proportion mediated	0.10 [-0.10 to 0.41]	0.310

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC at 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; CRP: C-reactive protein; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity.

Table 3. Mediating role of log-HOMA-IR index on the association between FMI trajectories and FEV_1/FVC (%) at 15 years (n=1,404)

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via HOMA-IR)	-0.05 [-0.13 to 0.01]	0.082
	Direct (not via HOMA-IR)	0.13 [-0.70 to 1.05]	0.820
	Total	0.08 [-0.77 to 0.98]	0.888
	Proportion mediated	-0.03 [-1.46 to 1.59]	0.890
Medium-high vs. low	Indirect (via HOMA-IR)	-0.17 [-0.35 to -0.01]	0.032
	Direct (not via HOMA-IR)	-0.63 [-1.55 to 0.27]	0.180
	Total	-0.81 [-1.74 to 0.07]	0.084
	Proportion mediated	0.20 [-1.14 to 1.70]	0.112
High vs. low	Indirect (via HOMA-IR)	-0.38 [-0.72 to -0.04]	0.032
	Direct (not via HOMA-IR)	-1.47 [-2.62 to -0.20]	0.018
	Total	-1.85 [-2.96 to -0.62]	0.004
	Proportion mediated	0.20 [0.02 to 0.69]	0.036

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC at 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity; HOMA-IR: homeostasis model assessment-estimated insulin resistance

DISCUSSION

To our knowledge, this is the first study to examine the potential mediating role of CRP and insulin resistance on the association between high fat mass levels in mid-childhood and lower FEV_1/FVC ratio at 15 years. Our study suggests that insulin resistance at 15 years may mediate part of this association, but we found no evidence of a mediating role of CRP.

Interpretation

Our finding that insulin resistance mediates part of the association between fat mass and FEV_1/FVC is biologically plausible. Obesity is one of the most important risk factors for insulin resistance in childhood [15]. Insulin receptors are expressed in the lung and there is evidence that insulin can influence lung structure and function at different stages of life [28]. Previous research has also suggested that insulin has a direct effect on human airways by influencing airway smooth muscle and airway epithelial cells [14]. Results from a three-year randomized control trial on the safety and direct effects of inhaled human insulin showed that those receiving the drug were more likely to exhibit respiratory symptoms and reduced lung function [29]. Similarly, a previous cross-sectional study found that insulin resistance (measured also using the HOMA-IR index) was associated with significant worsened lung function in overweight/obese adolescents [18].

Although previous studies have reported an association between higher CRP levels and decreased lung function [11–13], we found no

evidence of a role of CRP on the association between mid-childhood fat mass and FEV_1/FVC at 15 years. There are two potential explanations for this negative finding. First, it is possible that CRP affects in a similar magnitude FVC and FEV_1, leading mathematically to a null effect on the ratio of these two parameters. This would be consistent with all previous studies on the topic, which have reported an association of CRP levels with FEV_1 and/or FVC, but not with FEV_1/FVC. Second, it is possible that CRP levels are so low in adolescence, that even those with higher levels would not have levels high enough to affect lung function. This is plausible because adolescents have been reported to have lower levels of CRP than adults [30] and all previous research on the association of CRP with lung function has been studied in adult samples only. In fact, our finding is in line with a previous study that reported no association between BMI status and airway inflammation (measured by FE_{NO}) at 16 years [5]. Further research is needed to replicate our finding in other populations and to explore if CRP levels in other periods of childhood and adolescence could affect FEV_1/FVC.

Implications

The results of the present study have important implications for future research. Since the adipose tissue is involved in the secretion of several proinflammatory markers other than CRP [31], future research should also consider other biomarkers of systemic inflammation such as interleukin-6 (IL-6) or tumour necrosis factor alpha (TNF-α), which have also been linked to lung function [11,32]. In addition, our study suggested that the association of high fat mass

with airflow limitation at 15 years is mediated by insulin resistance only in part (20% of the total effect). Therefore, future studies that also examine other potential mechanisms, such as the mechanical effects of fat mass on lungs [33], are needed to fully understand how fat mass affects lung function in adolescence A better understanding of the underlying biological mechanisms will help to strengthen causal inference between obesity and respiratory health. In turn, this will be of relevance for the development of public health strategies aiming to reduce respiratory morbidity, as determining that an association is causal indicates the possibility for interventions [31].

Strengths and limitations

Important strengths of this study are the population-based nature of the ALSPAC birth cohort and the availability of metabolic and inflammatory biomarkers, which allow us to examine two potential mechanisms for the association between fat mass and FEV_1/FVC.

A limitation of the present study is that the associations of CRP and insulin resistance with FEV_1/FVC were assessed cross-sectionally and therefore are subject to potential reverse causation. However, it is unlikely that lung function levels affect CRP levels/insulin resistance. Another limitation is the potential selection bias produced by the fact that children included had a higher socioeconomic status, a higher birth weight, a higher gestational age, a higher proportion of breastfeeding and lower maternal smoking exposure than those excluded. In addition, the regional basis of the ALSPAC cohort may not allow the generalizability of our finding to populations with more ethnic variability and with different environmental and lifestyle

factors. Finally, although we account for a wide range of potential confounders, we cannot exclude residual confounding by unmeasured (e.g. genetic factors) or insufficiently measured confounders.

Conclusion

In conclusion, in this population-based study we found that insulin resistance may mediate part of the association between mid-childhood fat mass and the FEV_1/FVC ratio in adolescence, but we found no evidence of a role of CRP levels. Further longitudinal studies that evaluate other biomarkers of systemic inflammation and examine other potential mechanisms are needed to better understand the pathways linking obesity and respiratory health in adolescence.

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AUTHOR'S CONTRIBUTIONS

GPP carried out the statistical analysis. GPP and JGA prepared the first draft of the paper. RG and LD contributed to data collection. All authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work, revised the manuscript for important intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

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COMPETING INTERESTS

JG-A reports personal fees from Esteve, Chiesi and AstraZeneca, outside the submitted work. Other authors declare no competing interests related to this work

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ONLINE SUPPLEMENT

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Study population

ALSPAC recruited 14,541 pregnant women residents in Avon, UK, with expected dates of delivery between the 1st of April, 1991, and the 31st of December 1992. 14,541 is the *initial* number of pregnancies for which the mother enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a "Children in Focus" clinic by 19/07/99. Of these *initial* pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age.

When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper [1,2].

The total sample size for analyses using any data collected after the age of seven is therefore 15,247 pregnancies, resulting in 15,458 fetuses. Of this total sample of 15,458 fetuses, 14,775 were live births and 14,701 (including 14,305 singleton births) were alive at 1 year of age.

The study website contains details of all the data that are available through a fully searchable data dictionary at www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/.

The ALSPAC Ethics and Law Committee and the Local Research Ethics Committees gave ethical approval. A list of the Research Ethics Committee approval references for each of the visits can be found at http://www.bristol.ac.uk/media-library/sites/alspac/documents/governance/Research%20Ethics%20Committee%20approval%20references.pdf. All participants and their parents/guardians provided written informed consent.

Other relevant characteristics

We collected data on sociodemographic and lifestyle factors at different time points from diverse sources. At 32 weeks of gestation, the mother recorded her occupation using a self- completed questionnaire, which was used to allocate her to a social class (professional and intermediate, skilled non-manual, skilled manual, partly skilled, and unskilled manual workers) based on the 1991 Office of Population, Censuses and Surveys classifications. Smoking during pregnancy was assessed at 18 and 32 weeks of gestation using self-completed questionnaires and a dichotomous variable was created for any smoking during pregnancy. Birthweight, gestational age and sex were obtained from birth records. Information about breastfeeding was obtained at age 15 months from maternal self-completed questionnaires. From the 7 years questionnaire, we obtained data on total energy intake of the child based on a 3-day report. Environmental tobacco exposure at age 8 years was recorded

by the mother using a self-completed questionnaire. At 11 years, physical activity was measured by accelerometer (Actigraph LLC, Fort Walton Beach, FL, USA) and the wear-time spent in moderate to vigorous physical activity (MVPA)[3] was obtained. At 15 years, children reported if a doctor had ever diagnosed them with asthma and if they had had chest infection, upper respiratory tract infection or cold with fever within three weeks before the spirometry test. Finally, puberty at 15 years was assessed using self-completed Tanner questionnaires. We defined pubertal status based on pubic hair development stage for boys and girls.

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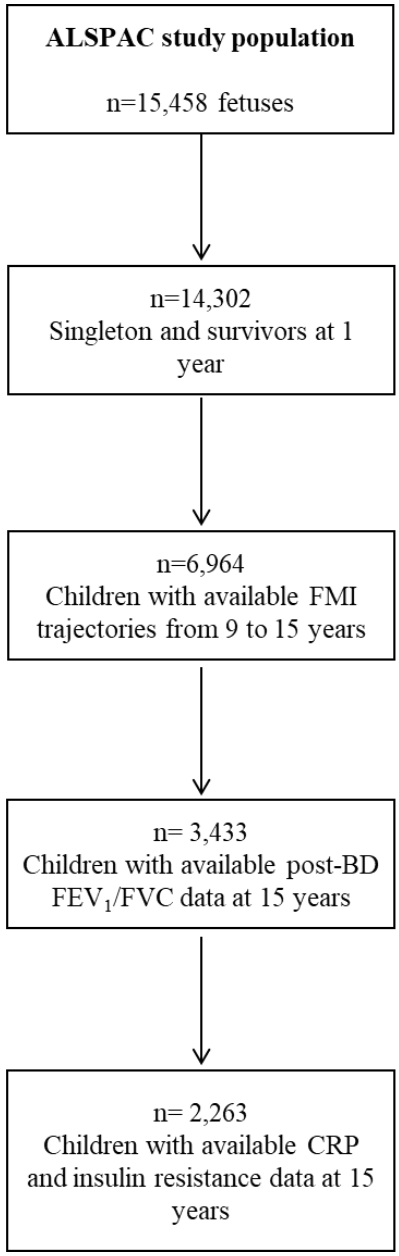

Figure S1. Flowchart of study participants

Abbreviations: CRP: C-reactive protein; FMI: fat mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; post-BD: post-bronchodilator

Table S1. Characteristics of children included and excluded from the analysis*

	Included (n=2,263)	Excluded (n=12,039)	*p*-value
Maternal characteristics			
Age at delivery (years)	29.2 (4.5)	27.7 (5.0)	<0.001
Social class			
Professional and intermediate	815 (45.6)	2,612 (33.2)	<0.001
Skilled nonmanual	672 (37.6)	3,3409 (43.4)	
Skilled manual, partly skilled and unskilled	299 (16.7)	1,837 (23.4)	
Smoking during pregnancy: yes	343 (16.6)	3,119 (30.9)	<0.001
Child characteristics			
Sex: girl	1,144 (50.6)	5,830 (48.4)	0.063
Birth weight (grams)	3,466 (515)	3404 (544)	<0.001
Gestation (weeks)	39.6 (1.7)	39.4 (1.9)	0.001
Pre-term delivery (<37 weeks gestation)	80 (3.7)	605 (5.3)	0.002
Ever breastfed: yes	1,865 (88.5)	7,431 (74.9)	<0.001
Lung function measures 8 years			
FVC (L)	1.9 (0.3)	1.9 (0.3)	0.093
FEV_1 (L)	1.7 (0.3)	1.7 (0.3)	0.541
FEV_1/FVC (%)	88.1 (6.5)	88.5 (6.5)	0.029

Values are n (%), mean (SD) or median (P25-P75). p-value for the Chi-squared, Mann-Whitney, or Student's t-test.

** Some variables had missing values in both the included (148 in maternal educational level, 191 in maternal smoking during pregnancy, 93 in maternal age at delivery, 93 in gestational age, 121 in birthweight, 155 in ever breastfed, 307 in FVC at 8 years, 328 in FEV_1 at 8 years and 328 in FEV_1/FVC at 8 years) and excluded children (4,484 in maternal educational level, 1,949 in maternal smoking during pregnancy, 599 in maternal age at delivery, 599 in gestational age, 742 in birthweight, 2,119 in ever breastfed, 7,181 in FVC at 8 years, 7,261 in FEV_1 at 8 years and 7,261 in FEV_1/FVC at 8 years).*

Abbreviations: CSE: certificate of secondary education; FEV1: forced expiratory volume in one second; FVC: forced vital capacity.

Table S2. Adjusted associations between FMI trajectories and log-CRP and log-HOMA-IR at 15 years

	log-CRP		log-HOMA-IR	
FMI trajectories	**Coef. [95%CI]**	**p-value**	**Coef. [95%CI]**	**p-value**
Low	Reference		Reference	
Medium-low	0.21 [0.06 to 0.36]	0.006	0.07 [0.00 to 0.14]	0.058
Medium-high	0.51 [0.35 to0.67]	<0.001	0.23 [0.16 to 0.30]	<0.001
High	1.11 [0.91 to 1.31]	<0.001	0.51 [0.42 to 0.60]	<0.001

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height and pubertal status at 15 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; CRP: C-reactive protein; HOMA-IR: homeostasis model assessment-estimated insulin resistance.

Table S3. Mediating role of CRP index on the association between FMI trajectories and FEV_1/FVC (%) at 15 years: Excluding children with ever doctor-diagnosed asthma (n=1,071)

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via CRP)	-0.03 [-0.11 to 0.03]	0.380
	Direct (not via CRP)	0.06 [-0.88 to 1.11]	0.930
	Total	0.04 [-0.95 to 1.09]	0.960
	Proportion mediated	0.00 [-1.33 to 0.76]	0.940
Medium-high vs. low	Indirect (via CRP)	-0.08 [-0.25 to 0.08]	0.300
	Direct (not via CRP)	-0.81 [-1.88 to 0.22]	0.130
	Total	-0.89 [-1.94 to 0.14]	0.096
	Proportion mediated	0.08 [-0.63 to 0.8]	0.376
High vs. low	Indirect (via CRP)	-0.21 [-0.60 to 0.19]	0.300
	Direct (not via CRP)	-1.75 [-3.09 to -0.28]	0.014
	Total	-1.96 [-3.25 to -0.55]	0.004
	Proportion mediated	0.11 [-0.11 to 0.53]	0.300

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC at 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; CRP: C-reactive protein; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity.

Table S4. Mediating role of CRP index on the association between FMI trajectories and FEV_1/FVC (%) at 15 years: Excluding children with chest infection/URTI/cold with fever in past 3 weeks before the spirometry test (n=1,319)

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via CRP)	-0.04 [-0.12 to 0.03]	0.260
	Direct (not via CRP)	0.17 [-0.67 to 1.11]	0.740
	Total	0.14 [-0.74 to 1.07]	0.800
	Proportion mediated	-0.03 [-1.43 to 1.46]	0.830
Medium-high vs. low	Indirect (via CRP)	-0.09 [-0.26 to 0.06]	0.250
	Direct (not via CRP)	-0.62 [-1.58 to 0.30]	0.200
	Total	-0.72 [-1.66 to 0.19]	0.130
	Proportion mediated	0.11 [-0.84 to 1.22]	0.360
High vs. low	Indirect (via CRP)	-0.21 [-0.55 to 0.15]	0.248
	Direct (not via CRP)	-1.71 [-2.89 to -0.41]	0.008
	Total	-1.92 [-3.06 to -0.66]	0.004
	Proportion mediated	0.11 [-0.08 to 0.44]	0.248

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC at 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; CRP: C-reactive protein; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity; URTI: upper respiratory tract infection.

Table S5. Mediating role of CRP index on the association between FMI trajectories and FEV_1/FVC (%) at 15 years: Excluding children with log-CRP ≥ percentile 95th (n=1,338)

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via CRP)	-0.06 [-0.15 to 0.03]	0.180
	Direct (not via CRP)	0.01 [-0.83 to 0.94]	0.990
	Total	-0.05 [-0.91 to 0.87]	0.900
	Proportion mediated	0.02 [-2.25 to 1.91]	0.930
Medium-high vs. low	Indirect (via CRP)	-0.13 [-0.31 to 0.06]	0.180
	Direct (not via CRP)	-0.59 [-1.55 to 0.34]	0.250
	Total	-0.71 [-1.65 to 0.18]	0.130
	Proportion mediated	0.15 [-1.14 to 1.61]	0.290
High vs. low	Indirect (via CRP)	-0.27 [-0.66 to 0.14]	0.176
	Direct (not via CRP)	-1.36 [-2.57 to -0.05]	0.040
	Total	-1.64 [-2.79 to -0.37]	0.006
	Proportion mediated	0.16 [-0.09 to 0.86]	0.182

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVCat 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; CRP: C-reactive protein; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity.

Table S6. Mediating role of CRP index on the association between FMI trajectories and FEV_1/FVC (%) at 15 years: Models additionally adjusted for energy intake, physical activity and environmental tobacco exposure (n=1,048)

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via CRP)	-0.05 [-0.15 to 0.02]	0.160
	Direct (not via CRP)	0.10 [-0.95 to 1.00]	0.830
	Total	0.05 [-1.04 to 0.95]	0.890
	Proportion mediated	-0.02 [-1.63 to 1.18]	0.910
Medium-high vs. low	Indirect (via CRP)	-0.14 [-0.34 to 0.04]	0.130
	Direct (not via CRP)	-0.72 [-1.82 to 0.32]	0.170
	Total	-0.86 [-1.97 to 0.16]	0.110
	Proportion mediated	0.14 [-1.13 to 1.22]	0.230
High vs. low	Indirect (via CRP)	-0.29 [-0.66 to 0.08]	0.126
	Direct (not via CRP)	-1.55 [-3.01 to -0.07]	0.038
	Total	-1.84 [-3.23 to -0.44]	0.012
	Proportion mediated	0.16 [-0.06 to 0.73]	0.138

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, energy intake at 7 years, environmental tobacco exposure at 8 years, physical activity at 11 years and age, height and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC at 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; CRP: C-reactive protein; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity.

Table S7. Mediating role of CRP index on the association between FMI trajectories and FEV_1/FVC at 15 years: Using FEV_1/FVC z-score* as outcome variable

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via CRP)	-0.01 [-0.02 to 0.01]	0.350
	Direct (not via CRP)	0.03 [-0.12 to 0.18]	0.650
	Total	0.03 [-0.12 to 0.18]	0.690
	Proportion mediated	-0.02 [-1.45 to 0.99]	0.820
Medium-high vs. low	Indirect (via CRP)	-0.01 [-0.04 to 0.01]	0.348
	Direct (not via CRP)	-0.18 [-0.33 to -0.03]	0.016
	Total	-0.19 [-0.34 to -0.03]	0.008
	Proportion mediated	0.07 [-0.09 to 0.43]	0.356
High vs. low	Indirect (via CRP)	-0.03 [-0.09 to 0.03]	0.350
	Direct (not via CRP)	-0.33 [-0.52 to -0.13]	<0.001
	Total	-0.36 [-0.55 to -0.16]	<0.001
	Proportion mediated	0.08 [-0.09 to 0.30]	0.350

** Calculated using Global Lung Initiative equation references 2012.*
Models are adjusted for maternal social class and smoking during pregnancy, and child's pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC z-score at 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; CRP: C-reactive protein; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity.

Table S8. Mediating role of HOMA-IR index on the association between FMI trajectories and FEV_1/FVC (%) at 15 years: Excluding children with lifetime doctor-diagnosed asthma (n=1,071)

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via HOMA-IR)	-0.05 [-0.16 to 0.03]	0.200
	Direct (not via HOMA-IR)	0.09 [-0.86 to 1.14]	0.890
	Total	0.04 [-0.94 to 1.07]	0.950
	Proportion mediated	-0.01 [-1.76 to 1.29]	0.960
Medium-high vs. low	Indirect (via HOMA-IR)	-0.22 [-0.43 to -0.04]	0.024
	Direct (not via HOMA-IR)	-0.67 [-1.73 to 0.37]	0.220
	Total	-0.89 [-1.95 to 0.12]	0.100
	Proportion mediated	0.22 [-1.74 to 1.75]	0.120
High vs. low	Indirect (via HOMA-IR)	-0.47 [-0.88 to -0.07]	0.024
	Direct (not via HOMA-IR)	-1.48 [-2.8 to -0.03]	0.046
	Total	-1.95 [-3.26 to -0.54]	0.004
	Proportion mediated	0.24 [0.03 to 0.95]	0.028

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVCat 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity; HOMA-IR: homeostasis model assessment-estimated insulin resistance.

Table S9. Mediating role of HOMA-IR index on the association between FMI trajectories and FEV_1/FVC (%) at 15 years: Excluding children with chest infection/URTI/cold with fever in past 3 weeks before the spirometry test (n=1,319)

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via HOMA-IR)	-0.04 [-0.13 to 0.01]	0.130
	Direct (not via HOMA-IR)	0.18 [-0.67 to 1.11]	0.720
	Total	0.14 [-0.73 to 1.06]	0.790
	Proportion mediated	-0.03 [-1.97 to 1.37]	0.810
Medium-high vs. low	Indirect (via HOMA-IR)	-0.17 [-0.35 to 0.00]	0.048
	Direct (not via HOMA-IR)	-0.54 [-1.48 to 0.39]	0.280
	Total	-0.71 [-1.67 to 0.19]	0.138
	Proportion mediated	0.21 [-1.41 to 1.91]	0.178
High vs. low	Indirect (via HOMA-IR)	-0.36 [-0.70 to -0.01]	0.048
	Direct (not via HOMA-IR)	-1.55 [-2.74 to -0.26]	0.014
	Total	-1.91 [-3.06 to -0.65]	0.004
	Proportion mediated	0.18 [0.00 to 0.63]	0.052

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC at 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity; HOMA-IR: homeostasis model assessment-estimated insulin resistance; URTI: upper respiratory tract infection.

Table S10. Mediating role of HOMA-IR index on the association between FMI trajectories and FEV_1/FVC (%) at 15 years: Excluding children with log-HOMA-IR ≥ percentile 95th (n=1,338)

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via HOMA-IR)	-0.04 [-0.12 to 0.01]	0.130
	Direct (not via HOMA-IR)	0.27 [-0.56 to 1.19]	0.540
	Total	0.23 [-0.62 to 1.14]	0.610
	Proportion mediated	-0.04 [-1.89 to 1.33]	0.650
Medium-high vs. low	Indirect (via HOMA-IR)	-0.13 [-0.30 to 0.02]	0.094
	Direct (not via HOMA-IR)	-0.70 [-1.63 to 0.21]	0.138
	Total	-0.83 [-1.78 to 0.06]	0.072
	Proportion mediated	0.15 [-0.25 to 1.40]	0.158
High vs. low	Indirect (via HOMA-IR)	-0.24 [-0.54 to 0.04]	0.094
	Direct (not via HOMA-IR)	-1.54 [-2.72 to -0.23]	0.014
	Total	-1.78 [-2.96 to -0.48]	0.004
	Proportion mediated	0.13 [-0.03 to 0.57]	0.098

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC at 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity; HOMA-IR: homeostasis model assessment-estimated insulin resistance.

Table S11. Mediating role of HOMA-IR index on the association between FMI trajectories and FEV_1/FVC (%) at 15 years: Models additionally adjusted for energy intake, physical activity and environmental tobacco exposure (n=1,048)

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via HOMA-IR)	-0.03 [-0.12 to 0.03]	0.340
	Direct (not via HOMA-IR)	0.09 [-0.96 to 0.98]	0.850
	Total	0.05 [-1.02 to 0.97]	0.880
	Proportion mediated	0.00 [-0.85 to 0.79]	0.940
Medium-high vs. low	Indirect (via HOMA-IR)	-0.13 [-0.29 to 0.01]	0.080
	Direct (not via HOMA-IR)	-0.72 [-1.82 to 0.32]	0.180
	Total	-0.85 [-1.96 to 0.19]	0.110
	Proportion mediated	0.13 [-0.98 to 1.11]	0.190
High vs. low	Indirect (via HOMA-IR)	-0.33 [-0.71 to 0.03]	0.080
	Direct (not via HOMA-IR)	-1.49 [-2.97 to 0.04]	0.052
	Total	-1.82 [-3.22 to -0.45]	0.012
	Proportion mediated	0.19 [-0.03 to 0.81]	0.092

Models are adjusted for maternal social class and smoking during pregnancy, and child's sex, energy intake at 7 years, environmental tobacco exposure at 8 years, physical activity at 11 years and age, height and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC at 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity; HOMA-IR: homeostasis model assessment-estimated insulin resistance.

Table S12. Mediating role of HOMA-IR index on the association between FMI trajectories and FEV_1/FVC at 15 years: Using FEV1/FVC z-score* as outcome variable

FMI trajectories	Effect	Coef. [95% CI]	p-value
Medium-low vs. Low	Indirect (via HOMA-IR)	-0.01 [-0.02 to 0.00]	0.120
	Direct (not via HOMA-IR)	0.04 [-0.11 to 0.18]	0.610
	Total	0.03 [-0.12 to 0.18]	0.670
	Proportion mediated	-0.03 [-1.24 to 1.27]	0.730
Medium-high vs. low	Indirect (via HOMA-IR)	-0.03 [-0.06 to 0.00]	0.044
	Direct (not via HOMA-IR)	-0.16 [-0.32 to -0.01]	0.038
	Total	-0.19 [-0.33 to -0.04]	0.014
	Proportion mediated	0.13 [0.00 to 0.77]	0.058
High vs. low	Indirect (via HOMA-IR)	-0.06 [-0.12 to 0.00]	0.044
	Direct (not via HOMA-IR)	-0.29 [-0.49 to -0.09]	0.002
	Total	-0.35 [-0.54 to -0.16]	<0.001
	Proportion mediated	0.17 [0.00 to 0.49]	0.044

** Calculated using Global Lung Initiative equation references 2012.*
Models are adjusted for maternal social class and smoking during pregnancy, and child's pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC z-score at 8 years.
Abbreviations: CI: confidence intervals; Coef.: regression coefficient; FEV_1: forced expiratory volume in one second, FMI: fat mass index: FVC: forced vital capacity; HOMA-IR: homeostasis model assessment-estimated insulin resistance.

5.4 Paper IV

Peralta GP, Marcon A, Carsin A-E, Abramson MJ, Accordini S, Amaral AFS, Antó JM, Bowatte G, Burney P, Corsico A, Demoly P, Dharmage S, Forsberg B, Fuertes E, Garcia-Larsen V, Gíslason T, Gullón JA, Heinrich J, Holm M, Jarvis DL, Janson C, Jogi R, Johannessen A, Leynaert B, Martínez-Moratalla Rovira J, Nowak D, Probst-Hensch N, Raherison C, Sánchez-Ramos J, Sigsgaard T, Siroux V, Squillacioti G, Urrutia I, Weyler J, Zock JP, Garcia-Aymerich J.

Body mass index and weight change are associated with adult lung function trajectories: the prospective ECRHS study.

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ORIGINAL RESEARCH

Body mass index and weight change are associated with adult lung function trajectories: the prospective ECRHS study

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ABSTRACT

Background Previous studies have reported an association between weight increase and excess lung function decline in young adults followed for short periods. We aimed to estimate lung function trajectories during adulthood from 20-year weight change profiles using data from the population-based European Community Respiratory Health Survey (ECRHS).

Methods We included 3673 participants recruited at age 20–44 years with repeated measurements of weight and lung function (forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1)) in three study waves (1991–93, 1999–2003, 2010–14) until they were 39–67 years of age. We classified subjects into weight change profiles according to baseline body mass index (BMI) categories and weight change over 20 years. We estimated trajectories of lung function over time as a function of weight change profiles using population-averaged generalised estimating equations.

Results In individuals with normal BMI, overweight and obesity at baseline, moderate (0.25–1 kg/year) and high weight gain (>1 kg/year) during follow-up were associated with accelerated FVC and FEV_1 declines. Compared with participants with baseline normal BMI and stable weight (±0.25 kg/year), obese individuals with high weight gain during follow-up had −1011 mL (95% CI −1.259 to −763) lower estimated FVC at 65 years despite similar estimated FVC levels at 25 years. Obese individuals at baseline who lost weight (<−0.25 kg/year) exhibited an attenuation of FVC and FEV_1 declines. We found no association between weight change profiles and FEV_1/FVC decline.

Conclusion Moderate and high weight gain over 20 years was associated with accelerated lung function decline, while weight loss was related to its attenuation. Control of weight gain is important for maintaining good lung function in adult life.

Key questions

What is the key question?
- Is weight change over a 20-year period associated with lung function trajectories in adult life?

What is the bottom line?
- Moderate and high weight gain over a 20-year period was associated with accelerated FVC and FEV_1 decline, while weight loss was related to its attenuation.

Why read on?
- This study, which is based on data collected as part of the multicentre prospective ECRHS study, reinforces the public health message that overweight and obesity have deleterious effects on respiratory health. However, these negative effects can be reversed by weight loss even later in adult life.

BACKGROUND

Lung function is a significant predictor of future morbidity and mortality in the general population.[1] Maintaining good lung function across adult life is important to prevent chronic respiratory diseases, which nowadays represent a serious public health problem around the world.[2] There is consistent evidence showing that overweight, obesity and weight gain in adulthood are detrimental to lung function, as described by the forced vital capacity (FVC) and/or forced expiratory volume in 1 s (FEV_1). Previous population-based and occupational cohort studies have shown that excessive weight gain in adulthood is associated with lower lung function levels and with an increased rate of lung function decline independently of age and

smoking status.[3–8] Another longitudinal study in healthy young adults (age range at baseline 18–30 years) showed that lung function was lower both with higher baseline body mass index (BMI) and with increasing BMI over a 10-year period.[9] Similarly, a population-based study of young adults (mean age at baseline 41 years) analysing the effects of changes in obesity status on lung function found that remaining or becoming obese accelerated lung function decline over an 8-year follow-up, while becoming non-obese was related to its attenuation.[10]

All these previous studies have had relatively short follow-up periods (up to 10 years) and most investigated this link only up to 50 years of age. This precludes a more comprehensive understanding of the role of weight change on lung function during adulthood and older life and supports the need for further studies with longer follow-up periods extending into late adult life. Understanding the effects of weight changes on lung function during adult life is of utmost importance given the epidemic levels of overweight and obesity globally.[11]

The European Community Respiratory Health Survey (ECRHS) is a large multicentre population-based study with available measures of weight, height and lung function at three time points over a 20-year period, as well as detailed information of sociodemographic and lifestyle factors from adults living across Europe and Australia.[12–14] Under the framework of the Ageing Lungs in European Cohorts (ALEC) consortium (www.alecstudy.org), we aimed to assess the lung function trajectories of adults of the ECRHS study according to different weight change profiles that combined BMI at baseline and weight change over a 20-year period.

METHODS

Study population

The ECRHS started in 1991–1993 (ECRHS I), when over 18 000 young adults aged 20–44 years were randomly recruited from available population-based registers (population-based arm), with an oversampling of asthmatics (symptomatic arm). Participants were followed up in 1999–2003 (ECRHS II) and 2010–2014 (ECRHS III) when they were aged 27–57 and 39–67 years, respectively. More details of the study design are available elsewhere.[12–14] In this analysis we included participants who had weight at ECRHS I and III and lung function and base covariates (sex, age, height and smoking status) at all three surveys (3673 participants from 26 centres in 12 countries) (see online supplementary figure S1).

Ethical approval was obtained from the ethics committees of all participating institutions and all participants provided informed written consent.

Lung function

Lung function was measured by spirometry at ECRHS I, II and III. Centres used different spirometers at ECRHS I and II, but almost all centres used the same spirometer at ECRHS III (see online supplementary table S1). In the three examinations, forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), repeatable to 150 mL from at least two of a maximum of five correct manoeuvres that met the American Thoracic Society and European Respiratory Society recommendations,[15] were used as the primary outcomes. The FEV_1/FVC ratio was also analysed. In the present analysis, we used lung function measurements collected pre-bronchodilator. We also calculated lung function SD scores (z-scores) using the Global Lung Initiative (GLI) equation references,[16] and used these variables as secondary outcomes.

Weight change profiles

BMI was calculated by dividing measured weight (kg) by measured height (m) squared. We defined categories of BMI at ECRHS I (baseline) as 'underweight' (BMI $<20\,kg/m^2$), 'normal weight' ($20\,kg/m^2 \leq BMI < 25\,kg/m^2$), 'overweight' ($25\,kg/m^2 \leq BMI < 30\,kg/m^2$) and 'obese' (BMI $\geq 30\,kg/m^2$), as in previous ECRHS studies.[8] We computed weight change during follow-up as the difference between weight measured at ECRHS III and ECRHS I divided by the total time of follow-up (in years) and categorised it into stable weight, weight loss and weight gain. Since there are no standard references for weight change in adults, we used similar weight change categories as in a recent longitudinal long-term population-based study[17]: 'weight loss' (<-0.25 kg/year), 'stable weight' (± 0.25 kg/year), 'moderate weight gain' (>0.25 to ≤ 1 kg/year) and 'high weight gain' (>1 kg/year). We combined baseline BMI categories with weight change categories to classify participants in weight change profiles. This combined variable was used as the main exposure variable in the analysis.

Other relevant variables

Sociodemographic and other health data were collected using questionnaires. These included sex, age, age completed full-time education (<17 years; 17–20 years;>20 years), smoking status (never smoker; ex-smoker; current smoker), secondhand smoke exposure (yes; no) and asthma (yes; no). Current asthma was defined as having reported physician-diagnosed asthma and at least one of the following: asthma-like symptoms (wheeze, nocturnal chest tightness, attacks of breathlessness after activity/at rest/at night-time), asthma attacks, use of inhaled/oral medicines for breathing problems (in the last 12 months), or current use of inhalers, aerosols or tablets for asthma. Leisure-time vigorous physical activity was assessed at ECRHS II by asking participants how often and for how many hours per week they usually exercised so much that they got out of breath or sweaty. Participants were categorised as being active if they exercised with a frequency of two or more times a week and with a duration of about 1 hour a week or more, and non-active otherwise.[18] Finally, at ECRHS II participants reported if they presented any of the following long-term limiting illnesses: hypertension, heart disease, diabetes, cancer or stroke.

Statistical analysis

We used population-averaged generalised estimating equations (GEE) to estimate lung function trajectories from age 20 to 67 years (the full age range of the study sample) as a function of weight change profiles. Prior to stratifying models by weight change profiles, we tested the interaction between age, BMI at baseline and weight change, and we found that it was statistically significant for all lung function parameters (p value <0.01 for all models). All GEE models had the individuals as the clustering factor (to account for repeated lung function measurements at ECRHS I, II and III) and an unstructured within-cluster correlation. GEE models had FVC, FEV_1 or FEV_1/FVC as the outcome variables. Interaction terms between age (or age squared) and weight change profiles were entered to allow for different trajectories of lung function with ageing across weight change profiles. We entered sex as a fixed covariate and height, age, age squared, smoking status, current asthma and spirometer type as time-specific covariates. We also included an interaction term between smoking status and age (to account for a faster decline over time in smokers). We centred continuous variables at the mean (over the data from the three examinations) before modelling. Adjusted lung function over age was calculated by

setting continuous and categorical variables equal to the mean and proportion, respectively (calculated over the study sample).

In a secondary analysis we repeated the models using lung function z-scores instead of absolute lung function values. To assess whether estimated lung function trajectories differed by sex we tested for sex interactions (by including an interaction term between sex and weight change profiles) and we stratified final models by sex. We performed several sensitivity analyses to assess the robustness of the estimated lung function trajectories to various assumptions regarding confounding, change of spirometry devices or weight change categorisation (see online supplementary file).

All analyses were conducted following a complete case approach in Stata/SE 14.0 (StataCorp, College Station, Texas, USA).

RESULTS

Characteristics of the study sample

Compared with those not included in the present analysis (n=12 909), individuals who were included were slightly older, less likely to be current smokers, be exposed to secondhand smoke and had higher educational levels at ECRHS I, but they did not differ in terms of weight, BMI and lung function (see online supplementary table S2). Table 1 shows the main characteristics of the study sample (n=3673). Mean (SD) age of the study sample was 34.3 (7.1) years at baseline and 54.3 (7.1) years at the last follow-up. Approximately half of the study sample were women (53.3%) and 40% had completed full-time education when they were 20 years of age or older.

At baseline, 12% of the sample was underweight, 57% normal weight, 24% overweight and 6% obese. During follow-up almost 4% of the sample lost weight, 34% had stable weight, 53% had a moderate weight gain and 9% had a high weight gain. Table 2 shows descriptive statistics of the 16 weight change profiles identified. Almost 20% of the sample was classified in the weight change profile with baseline normal BMI and stable weight during follow-up. Out of the groups who lost weight during follow-up, obese participants at baseline were those who lost more weight over time (median −0.6 kg/year, P_{25}–P_{75} −0.9 to −0.4), while among those who experienced a moderate increase in weight, median weight gain was the same in the different categories of baseline BMI. Among those with high weight gain during follow-up, overweight and obese participants at baseline were those who gained more weight. Underweight participants who lost weight or had a high weight gain represented less than 1% of the study sample and therefore were excluded from further analyses.

Table 1 Characteristics of the study sample*

Characteristics	ECRHS I N (%) or mean (SD)	ECRHS II N (%) or mean (SD)	ECRHS III N (%) or mean (SD)
Symptomatic study arm	544 (14.8)	–	–
Women	1956 (53.3)	–	–
Age in years	34.3 (7.1)	43.0 (7.0)	54.3 (7.1)
Height in cm	170.6 (9.4)	170.3 (9.4)	169.4 (9.5)
Weight in kg	69.5 (13.5)	74.0 (15.1)	77.9 (16.1)
BMI			
Continuous, in kg/m^2	23.8 (3.7)	25.4 (4.3)	27.1 (4.9)
Underweight	453 (12.3)	222 (6.1)	119 (3.2)
Normal weight	2097 (57.1)	1676 (45.8)	1224 (33.3)
Overweight	892 (24.3)	1298 (35.5)	1481 (40.3)
Obese	231 (6.3)	461 (12.6)	849 (23.1)
Smoking status			
Non-smoker	1651 (45.0)	1576 (42.9)	1518 (41.3)
Ex-smoker	818 (22.3)	1119 (30.5)	1500 (40.8)
Current smoker	1204 (32.8)	978 (26.6)	655 (17.8)
Secondhand smoke exposure, yes	1939 (52.9)	1321 (36.1)	680 (18.6)
Current asthma, yes†	378 (10.5)	491 (13.8)	570 (16.2)
Age completed full-time education			
<17 years	675 (21.5)	–	–
17–20 years	1205 (38.4)	–	–
>20 years	1256 (40.1)	–	–
Physical activity. Active status‡	–	1363 (52.2)	–
Any long-term limiting illness, yes§	–	405 (17.1)	–
Lung function			
FVC (mL)	4516 (988)	4354 (980)	3964 (948)
FEV_1 (mL)	3702 (798)	3485 (790)	3006 (753)
FEV_1/FVC (%)	82.3 (6.9)	80.3 (6.5)	75.8 (6.5)
Lung function (z-scores)¶			
FVC z-score	0.01 (0.95)	0.02 (1.00)	−0.08 (0.94)
FEV_1 z-score	−0.01 (1.06)	−0.03 (1.08)	−0.34 (1.04)
FEV_1/FVC z-score	−0.06 (1.03)	−0.10 (1.00)	−0.48 (0.89)

*Some variables had missing values. Number of missing values for ECRHS I: 10 in secondhand smoke exposure, 78 in current asthma, and 537 in age completed full-time education. Number of missing values for ECRHS II: 18 in secondhand smoke exposure, 118 in current asthma, 1062 in physical activity and 1300 in any long-term limiting illness. Number of missing values for ECRHS III: 14 in secondhand smoke exposure and 163 in current asthma.
†Current asthma was defined as having reported physician-diagnosed asthma and at least one of the following: asthma-like symptoms (wheeze, nocturnal chest tightness, attacks of breathlessness after activity/at rest/at night-time), asthma attacks, use of inhaled/oral medicines for breathing problems (in the last 12 months), or current use of inhalers, aerosols or tablets for asthma.
‡Individuals were categorised as being active if they exercised with a frequency of two or more times a week and with a duration of about 1 hour a week or more.
§The following illnesses were considered: hypertension, heart disease, diabetes, cancer or stroke.
¶Lung function z-scores were derived using Global Lung Initiative 2012 equations.
BMI, body mass index; FEV_1, volume expired in the first second; FVC, forced vital capacity.

Associations between weight change profiles and lung function trajectories

To facilitate interpretation of results, the estimated trajectories of lung function by weight change profiles are presented separately for normal BMI, overweight and obese categories at baseline (figures 1–3). Among adults with baseline normal BMI, overweight and obesity, those with moderate and high weight gain during follow-up exhibited significantly steeper FVC decline than those with stable weight (Panels A, B and C in figure 1). Estimated differences in FVC at 25 and 65 years by weight change profiles (see online supplementary table S3) show that, in comparison with participants with baseline normal BMI and stable weight, baseline overweight and obese participants with high weight gain had lower estimated FVC at 65 years (−677 mL (95% CI −841 to −512); p<0.001 and −1.011 mL (−1.259 to −763); p<0.001, respectively) despite similar estimated FVC levels at age 25 (see online supplementary table S3).

In contrast to weight gain, obese (but not overweight or normal BMI) adults at baseline who lost weight during follow-up exhibited an attenuation of FVC decline (panel C in figure 1). We estimated that, at age 25 years, obese participants had lower FVC levels than normal BMI participants. However, obese individuals who lost weight during follow-up were estimated to have not significantly different FVC values at age 65 years than participants with baseline normal BMI and stable weight (see online supplementary table S3).

Table 2 Descriptive statistics of weight change profiles

Weight change profiles*		N (%)	Weight ECRHS I (kg) Median (P_{25}; P_{75})	Weight ECRHS III (kg) Median (P_{25}; P_{75})	Weight change during follow-up (kg/year) Median (P_{25}; P_{75})
Underweight	Weight loss	2 (0.1)†	55.5 (54; 57)	48.5 (45; 52)	−0.3 (−0.4; −0.3)
	Stable weight	167 (4.6)	53 (50; 56)	55 (51; 59)	0.1 (0; 0.2)
	Moderate weight gain	259 (7.1)	53 (50; 58)	65.3 (60; 70.4)	0.5 (0.4; 0.7)
	High weight gain	25 (0.7)†	52 (50; 57)	78 (74; 85)	1.2 (1.1; 1.5)
Normal BMI	Weight loss	38 (1)	63.5 (60; 74)	55 (52; 65)	−0.4 (−0.4; −0.3)
	Stable weight	715 (19.5)	64 (59; 72)	65.8 (60; 74)	0.1 (0.0; 0.2)
	Moderate weight gain	1164 (31.7)	65 (60; 72)	76 (70; 84)	0.5 (0.4; 0.7)
	High weight gain	180 (4.9)	66 (60; 72)	92.4 (86; 98)	1.2 (1.1; 1.4)
Overweight	Weight loss	52 (1.4)	80 (76; 87)	71 (66; 75.8)	−0.4 (−0.6; −0.3)
	Stable weight	291 (7.9)	79 (73; 85)	80 (73; 86.8)	0.1 (−0.1; 0.2)
	Moderate weight gain	454 (12.4)	80 (73; 86)	90.9 (84; 97.1)	0.5 (0.4; 0.7)
	High weight gain	95 (2.6)	79 (70; 85)	103 (96.4; 113.9)	1.3 (1.1; 1.5)
Obese	Weight loss	46 (1.3)	95 (87; 105)	85 (72; 93)	−0.6 (−0.9; −0.4)
	Stable weight	65 (1.8)	90 (85; 100)	92 (85; 101)	0.1 (−0.1; 0.1)
	Moderate weight gain	85 (2.3)	93 (87; 103)	105 (97.1; 114)	0.5 (0.4; 0.7)
	High weight gain	35 (1)	95 (85; 109)	125 (112; 135)	1.3 (1.1; 1.8)
Overall		3673 (100)	68 (59; 78)	76 (66; 87.3)	0.4 (0.1; 0.7)

*Weight change profiles were defined combining BMI at baseline and weight change during follow-up. BMI categories at baseline: underweight: BMI <20 kg/m^2; normal weight: 20 kg/m^2≤BMI<25 kg/m^2; overweight: 25 kg/m^2 ≤BMI <30 kg/m^2; obese: BMI ≥30 kg/m^2. Weight change was computed as the difference between weight measured at ECRHS III and ECRHS I divided by the total duration follow-up (in years). Weight change categories: weight loss: <−0.25 kg/year; stable: within ±0.25 kg/year; moderate weight gain: 0.25–1 kg/year; high weight gain: >1 kg/year.
†Not analysed further because of small sample size.

Supplementary figure S2 shows lung function trajectories for subjects with baseline underweight. In young adulthood, participants with baseline underweight had lower estimated FVC values than baseline normal BMI participants (see online supplementary figure S2). However, baseline underweight participants with stable weight during follow-up were estimated to have very similar FVC values at age 65 to participants with baseline normal BMI and stable weight.

We found very similar results for estimated FEV_1 trajectories (figure 2, online supplementary figure S2 and table S4). We found no evidence that FEV_1/FVC ratio trajectories were different by weight change profiles, except for two groups. Subjects with baseline underweight who had stable weight or moderate weight gain showed a steeper decline in FEV_1/FVC ratio than participants with baseline normal BMI and stable weight during follow-up (figure 3, online supplementary figure S2 and table S5).

Secondary analysis using lung function z-scores instead of absolute lung function showed similar results to the main analysis for all lung function parameters (see online supplementary figure S3). Stratification by sex showed that FVC and FEV_1 decline was steeper in men who gained weight than in

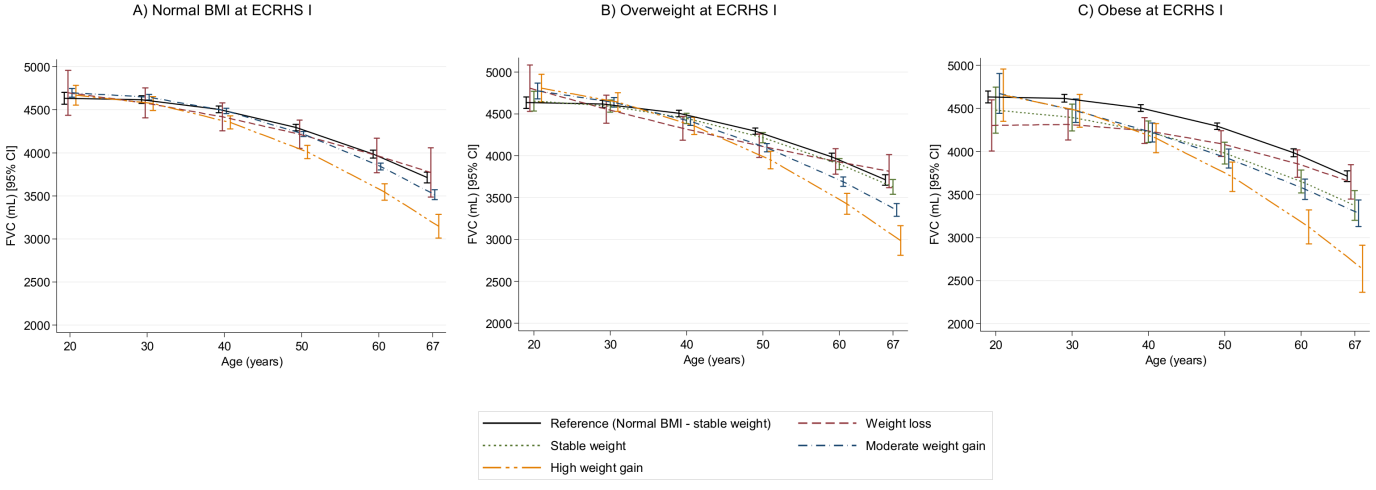

Figure 1 Estimated trajectories of FVC (in mL) decline by weight change profiles. The figure shows estimated FVC values and their corresponding 95% CI. Models are adjusted for sex, height, age, age squared, smoking status, an interaction term between smoking status and age, current asthma and spirometer type. Reference category: normal BMI at baseline and stable weight during follow-up. All graphs are presented with a 'jitter' (0.05) to avoid overlap of CI bars. BMI, body mass index; FVC, forced vital capacity.

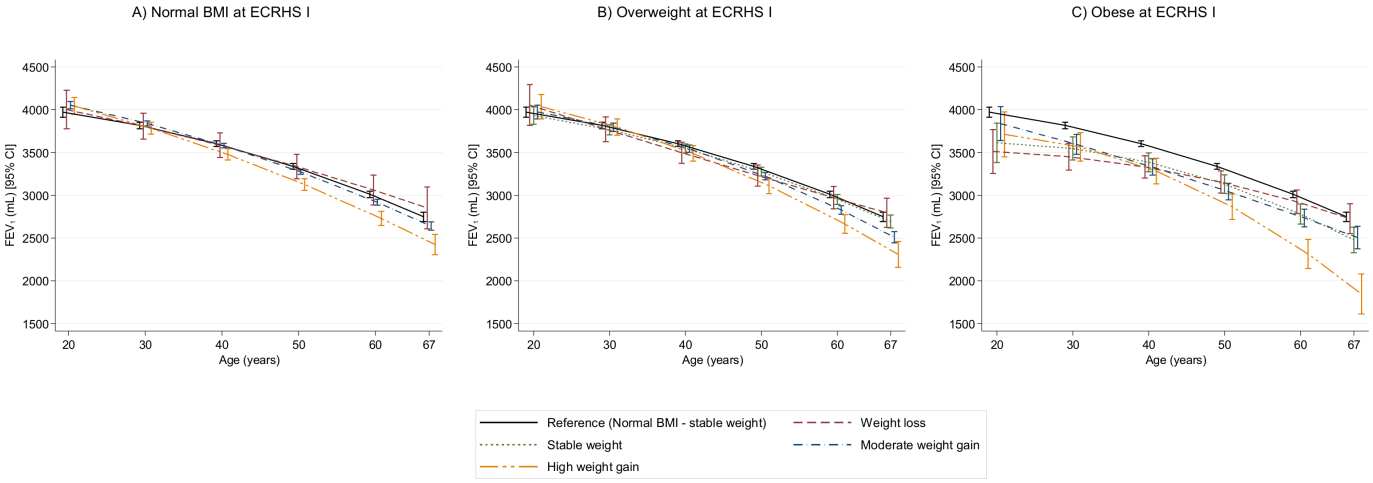

Figure 2 Estimated trajectories of FEV_1 (mL) decline by weight change profiles. The figure shows estimated FEV_1 values and their corresponding 95% CI. Models are adjusted for sex, height, age, age squared, smoking status, an interaction term between smoking status and age, current asthma and spirometer type. Reference category: normal BMI at baseline and stable weight during follow-up. All graphs are presented with a 'jitter' (0.05) to avoid overlap of CI bars. BMI, body mass index; FEV_1, forced expiratory volume in 1 s.

their female counterparts, particularly in the obese category (see online supplementary figure S4 and S5), but there was no difference with regard to the FEV_1/FVC ratio (see online supplementary figure S6). All sensitivity analyses showed very similar results (see online supplementary figure S7–S12). However, the lung function differences between the reference category and some overweight/obese weight change profiles were attenuated when the analyses were restricted to participants who reported to be non-smokers at all examinations and when additionally adjusting for physical activity, educational level and any long-term limiting illness.

DISCUSSION

In this population-based study we found that weight change over a 20-year period was associated with the rate of lung function decline in adulthood. Specifically, we found that: (1) in participants with baseline normal BMI, overweight and obesity in young adulthood, moderate and high weight gain during follow-up were associated with accelerated FVC and FEV_1 decline; (2) in participants with obesity in young adulthood, weight loss during follow-up was associated with attenuated FVC and FEV_1 decline; (3) in underweight participants in young adulthood, stable weight during follow-up was associated with an attenuation of FVC and FEV_1 decline; and (4) we found no evidence of an association between weight change and FEV_1/FVC ratio decline, with the exception of underweight participants with either stable weight or moderate weight gain, both of whom exhibited accelerated FEV_1/FVC ratio decline over follow-up.

Interpretation

Our findings that moderate and high weight gain accelerates FVC and FEV_1 decline and that weight loss attenuates it are consistent with previous research in young adults.[3–10] This demonstrates how weight changes can affect lung function until late adulthood. Our approach of combining baseline BMI categories with weight change over time let us distinguish the effects of different weight change profiles on lung function throughout

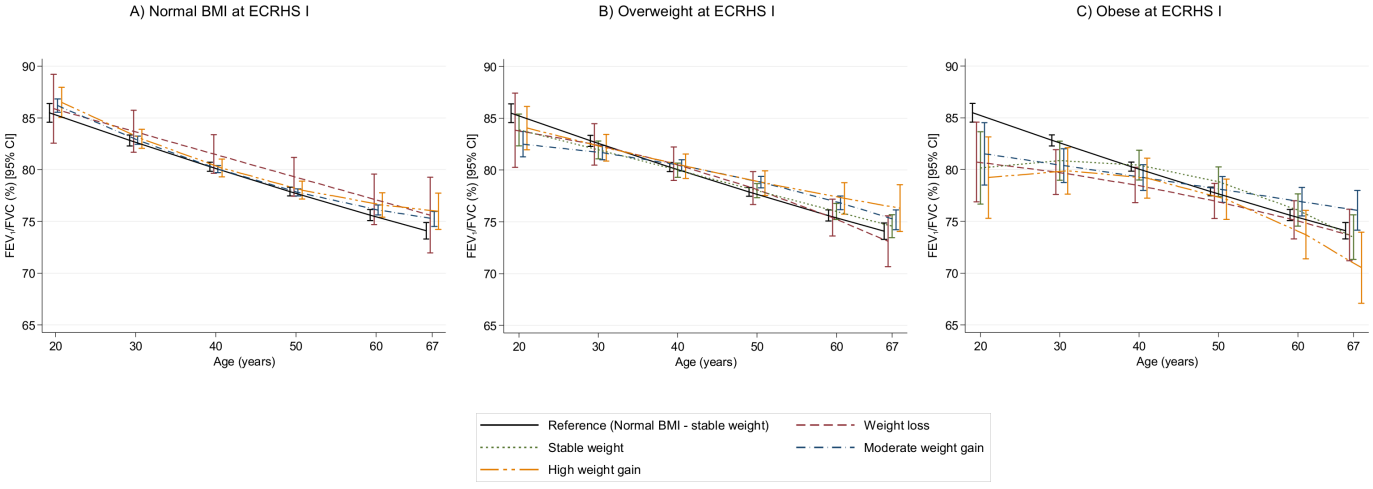

Figure 3 Estimated trajectories of FEV_1/FVC (%) decline by weight change profiles. The figure shows estimated FEV_1/FVC values and their corresponding 95% CI. Models are adjusted for sex, height, age, age squared, smoking status, an interaction term between smoking status and age, current asthma and spirometer type. Reference category: normal BMI at baseline and stable weight during follow-up. All graphs are presented with a 'jitter' (0.05) to avoid overlap of CI bars. BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

adult life. Two potential mechanisms have been proposed to explain the association of weight gain with accelerated lung function decline. First, weight gain can affect lung function through mechanical effects on lungs. Abdominal and thoracic fat mass are likely to reduce vital capacity by limiting the room for lung expansion during inspiration, in turn leading to expiratory flow limitation.[19] These mechanical effects may also explain the observed sex differences in relation to lung function decline, consistent with previous studies,[4 8 20] as men tend to accumulate more fat mass in the abdominal area than women.[21] Second, weight gain can impair lung function by inflammatory processes, as adipose tissue is a source of inflammatory mediators[22 23] that can damage lung tissue and reduce airway diameter.[24] Unfortunately, we did not have measures of chest compliance or markers of systemic inflammation related to obesity, and therefore we could not disentangle the mechanical effects of body mass on lung function from the inflammatory effects.

There are some potential mechanisms that can explain the association between weight loss and attenuation of lung function decline in obese subjects. First, it is possible that weight loss reverses the mechanical effects of overweight/obesity on the respiratory system allowing the recovery of lung function. Second, weight loss may relate to a reduction of inflammatory processes in the lung which in turn can help to attenuate lung function decline related to excessive weight. This hypothesis is supported by previous research showing that lung function decline associated with air pollution, which likely affects lung function via inflammation, could be attenuated with improvement of air quality.[25] Third, weight loss may be accompanied by improvement of metabolic alterations related to excess body weight, such as insulin dysregulation, high fasting glucose levels, hyperlipidaemia or systemic hypertension, which are also related to impaired lung function.[26 27] Fourth, the observed association between weight loss and attenuated lung function decline could be related to confounding by changes in lifestyle (eg, increasing physical activity or changing diet) that can follow awareness of the harmful effects of overweight/obesity. Indeed, quitting smoking and becoming physically active in adulthood has been related to better lung function levels and/or attenuated lung function decline.[8 18 28 29] Although we accounted for changes in smoking status during follow-up, levels of physical activity and presence of long-term limiting illness that could be accompanied by metabolic alterations (hypertension, heart disease, diabetes, cancer or stroke) at ECRHS II in sensitivity analyses, we did not have information on physical activity or diet at baseline. Further studies with repeated measures of lifestyle factors and indicators of metabolic dysregulation associated with weight changes are needed to disentangle the mechanisms underlying the association of weight loss and attenuated lung function decline.

We also found that stable weight during follow-up in individuals underweight in young adulthood was associated with attenuated FVC and FEV_1 decline, while those with baseline underweight and moderate weight gain had a parallel FVC and FEV_1 decline to individuals with baseline normal BMI in late adulthood. These findings contrast with results of a previous longitudinal study showing that increasing BMI in initially thin adults (aged 18–30) was associated with lung function improvement over 10 years.[9] This inconsistency could be related to differences in the definition of weight gain (ie, the use of BMI gain vs weight change) and to a different baseline age range. The relationship between weight change and lung function has received little attention in healthy underweight individuals, so further research is needed to understand the effects of weight change in underweight individuals and their underlying mechanisms.

In the present analysis we did not observe statistically different FEV_1/FVC ratio trajectories by weight change profiles, except for underweight subjects with either stable weight or moderate weight gain during follow-up, both of whom exhibited a faster FEV_1/FVC decline over follow-up. The observed associations in underweight subjects are in line with findings of one previous study in healthy adults[9] and allow us to hypothesise that underweight subjects could be more susceptible to the development of airflow limitation with ageing. Also, the lack of association of weight gain with the FEV_1/FVC ratio in the present analysis is in line with previous studies showing that the FEV_1/FVC ratio is normal in overweight and obese individuals.[19] The lack of association of weight gain with the FEV_1/FVC ratio could be attributed to the fact that both FVC and FEV_1 declines were accelerated with weight gain, which could lead to a null net effect on the ratio of these two measures (as both denominator and numerator were equally affected). This pattern suggests that weight gain is likely to be related to a restrictive pattern characterised by a reduction of lung volumes with no effect on airflow limitation. This hypothesis is supported by previous evidence showing that obesity is more likely to be associated with a restrictive ventilatory pattern than an obstructive one.[30]

Strengths and limitations

A strength of the current study is the long follow-up (up to 20 years) and the width of age distribution covering early to late adulthood. The population-based nature of the ECRHS and broad geographical representation of participants (26 centres in 12 countries in Europe and Australia) support external validity of our results. Finally, we had lung function measures at three time points, which allowed us to estimate lung function trajectories.

A limitation of this study is the use of total body weight as the main exposure. Although total body weight has been largely used in epidemiological studies as a marker of overweight and obesity, it is limited by its inability to distinguish between fat and muscle mass, which vary with age and sex[31 32] and could have different effects on lung function, as previously shown in children.[33] Also, we defined weight change categories using only weight measures at baseline and last follow-up to capture 'stable' weight change patterns and facilitate the interpretability of our results. Of note, the correlation between individual weight change per year (taking into account three weight measurements) and the weight change variable used in our analysis was 0.998, which justifies our approach. However, we recognise that our approach precludes us from determining how long it takes for a change in weight to affect lung function decline. Given the lack of standard references for weight change in adults, we categorised weight change based on a previous longitudinal study,[17] limiting the interpretation of our findings to our definition of 'stable weight' (±0.25 kg/year). However, the results were very similar when repeating our analysis using a wider category for 'stable weight' (±0.50 kg/year), suggesting that our findings are robust even with a less restrictive definition of 'stable weight'. Our results may also be affected by selection bias, as participants were more likely to be highly educated and less likely to be current smokers or to be exposed to secondhand smoke than those lost to follow-up. Because these factors have been previously associated with lung function, our associations could be underestimates of the true associations in the general population. Although we accounted for a wide range of confounders, our results could be affected by potential residual confounding by, for example, dietary intake, which affects both body weight and lung function, as the available data on diet were limited to a small subset of the study sample at ECRHS II and III. Moreover, the spirometers used for

lung function assessment were changed in some centres, which could have led to systematic differences inherent in lung function measurement that may differ by age and height.[34] However, when we adjusted our analysis for spirometer type and when we replicated the analyses using lung function values corrected for change in spirometer we obtained consistent results. Finally, we used three repeated measures of lung function from a sample aged 20–44 years (mean (SD) age 34.3 (7.1) years) at baseline and 39–67 years (mean (SD) age 54.3 (7.1) years) at the last follow-up to estimate lung function trajectories throughout adulthood. However, few participants were aged around 20 years at baseline and around 67 years at the last follow-up, and in consequence the models had fewer observations at the age ends than between 30 and 60 years, where most of the observations were.

CONCLUSION

In conclusion, this prospective population-based study shows that moderate and high weight gain over a 20-year period was associated with accelerated lung function decline in adulthood, while weight loss was related to its attenuation. Our findings, together with the existing literature, reinforce the public health message that overweight and obesity have deleterious effects on health, including respiratory health. However, the negative effects of overweight and obesity on lung function can be reversed by weight loss even later in adult life. Therefore, public health policies that promote healthy lifestyles and body weight may be important for maintaining good lung function in adult life.

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Contributors GPP, AM, A-EC and JG-A designed the study. GPP wrote the initial draft and conducted the statistical analyses. JG-A had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work, revised the manuscript for important intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

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Competing interests JG-A reports personal fees from Esteve, Chiesi and AstraZeneca, outside the submitted work. MJA reports grants from Pfizer, grants from Boehringer-Ingelheim and personal fees from Sanofi, outside the submitted work. PD reports personal fees from ALK, Stallergenes Greer, IQVIA, Chiesi, AstraZeneca, Thermo Fisher Scientific, Menarini, Bausch & Lomb, Mylan, ASIT Biotech, Novartis, Sanofi and Regeneron, outside the submitted work. RJ reports grants from Estonian Research Council (Personal Research Grant no 562) and personal fees from GSK, Boehringer and Novartis, outside the submitted work.

Patient consent for publication Not required.

Ethics approval Each participating centre obtained ethical approval from their local ethics committees and followed the rules for ethics and data protection from their country, which were in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

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ONLINE SUPPLEMENT

Contents

Figure S4. Estimated trajectories of FVC (mL) decline, by weight change profiles - Stratified by sex

Figure S5. Estimated trajectories of FEV_1 (mL) decline, by weight change profiles - Stratified by sex

Figure S6. Estimated trajectories of FEV_1/FVC (%) decline, by weight change profiles - Stratified by sex

Figure S7. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline, by weight change profiles - Excluding participants with current asthma at any visit (n= 709)

Figure S8. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline, by weight change profiles - Excluding the symptomatic arm of ECRHS (n=536)

Figure S9. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline, by weight change profiles – Restricting models to participants who reported to be non-smokers at all visits (n=1,491)

Figure S10. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline, by weight change profiles – Models additionally adjusted for educational level at ECRHS I and physical activity and any long-term limiting illness (hypertension/heart disease/diabetes/cancer/stroke) at ECRHS II (n=1,525)

Figure S11. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline, by weight change profiles – Using lung function values corrected for change in spirometer

Figure S12. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline, by weight change profiles – Using alternative categories for weight change (weight loss: <-0.5 kg/year; stable weight ±0.5 kg/year; moderate weight gain: 0.5 to 1 kg/year; high weight gain: >1kg/year)

Local Principal Investigators, senior scientific teams and funding agencies for the European Community Respiratory Health Survey (ECRHS

Methods: sensitivity analyses

To assess the robustness of our results, we performed several sensitivity analyses. First, we excluded subjects with asthma and subjects from the symptomatic arm of the ECRHS in separate analyses to assess whether results were sensitive to the exclusion of these subsamples. Second, we restricted the final models to participants who reported being non-smokers at the three examinations to account for potential residual confounding by smoking and weight change related to change in smoking status. Third, we additionally adjusted models for educational level, physical activity and presence of any long-term limiting illness to rule out potential residual confounding. These variables were not included in the main models because they reduced the statistical power without substantially altering the results. Fourth, to account for potential misclassification in lung function due to change in spirometers over time we replicated our models using lung function values corrected for change in spirometer. These corrected values were derived using a similar methodology as previously described for another similar adult cohort.[1] Finally, we repeated our analysis defining 'stable weight' as change over time ±0.50kg/year [2] to account for potential misclassification in weight change categories (i.e., using a less restrictive definition of change 'stable weight').

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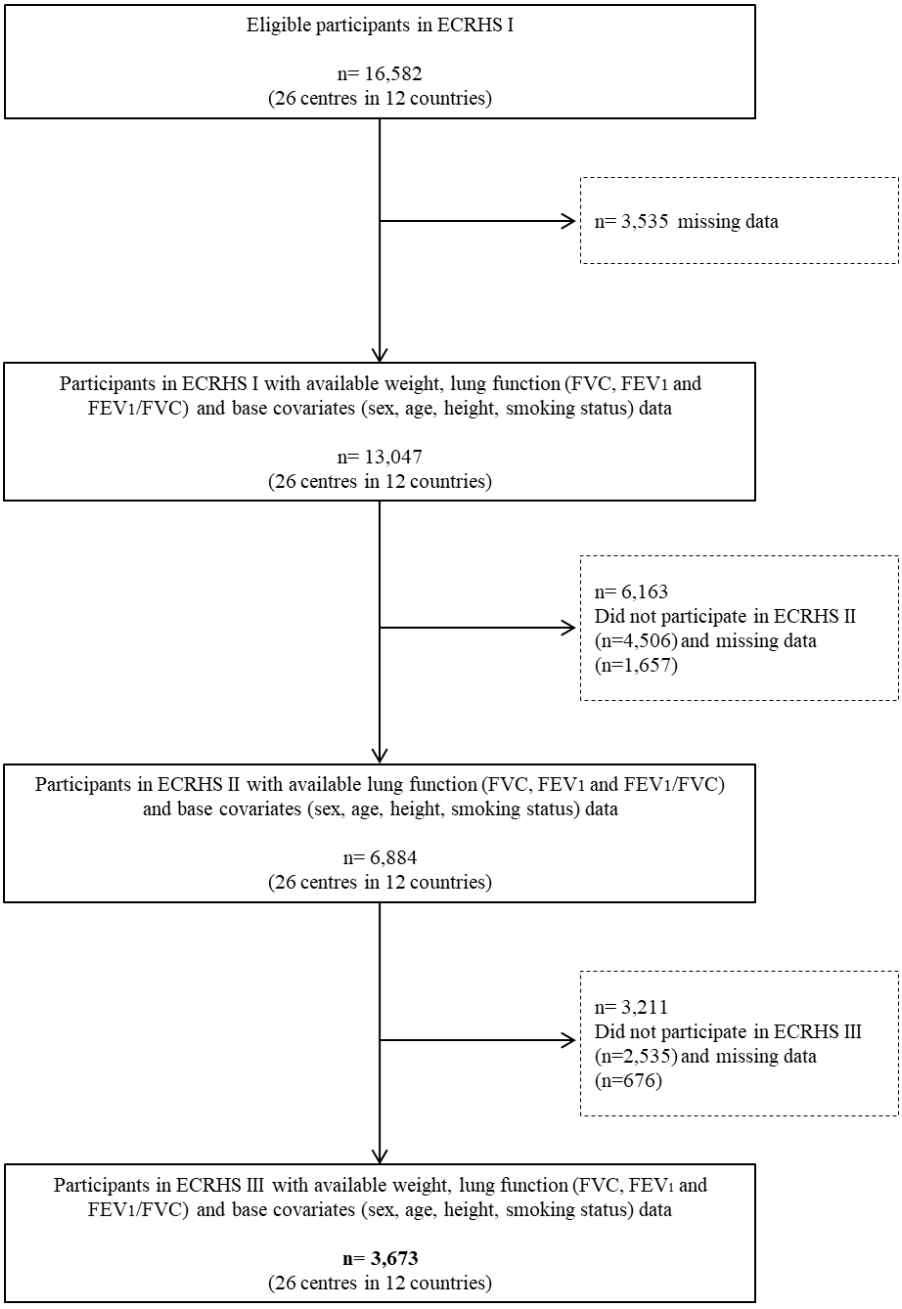

Figure S1. Flowchart of the study sample

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity

Table S1. Instruments used at spirometry examinations in the ECRHS

Study centre	Instrument used at ECRHS I	Instrument used at ECRHS II	Instrument used at ECRHS III
Albacete	Biomedin spiro	Biomedin spiro	NDD
Anterwep City	SensorMedics displacement	Jaeger pneum	NDD
Anterwep South	SensorMedics displacement	Jaeger pneum	NDD
Barcelona	Biomedin spiro	Biomedin spiro	NDD
Basel	SensorMedics hot wire	SensorMedics hot wire	NDD
Bergen	SensorMedics displacement	SensorMedics displacement	NDD
Bordeaux	Vitalograph spiro	Vitalograph spiro	NDD
Erfurt	Jaeger pneum	Jaeger pneum	NDD
Galdakao	Biomedin spiro	Biomedin spiro	NDD
Gothenburg	SensorMedics displacement	SensorMedics displacement	NDD
Grenoble	Biomedin spiro	Biomedin spiro	NDD
Hamburg	Jaeger pneum	Jaeger pneum	NDD
Huelva	Biomedin spiro	Biomedin spiro	NDD
Ipswich	Biomedin spiro	Biomedin spiro	NDD
Melbourne	Fleisch pneumotach	SensorMedics displacement	NDD
Montpellier	Biomedin spiro	Biomedin spiro	NDD
Norwich	Biomedin spiro	Biomedin spiro	NDD
Oviedo	Biomedin spiro	Biomedin spiro	NDD
Paris	Biomedin spiro	Biomedin spiro	NDD

(Continued)

Table S1. Continued

Study centre	Instrument used at ECRHS I	Instrument used at ECRHS II	Instrument used at ECRHS III
Pavia	Biomedin spiro	Biomedin spiro	NDD
Reykjavik	SensorMedics displacement	SensorMedics displacement	NDD
Tartu	Jaeger pneum	Jaeger pneum	NDD
Turin	Biomedin spiro	Biomedin spiro	Biomedin spiro
Umea	SensorMedics displacement	SensorMedics displacement	NDD
Uppsala	SensorMedics displacement	SensorMedics displacement	NDD
Verona	Biomedin spiro	Biomedin spiro	Biomedin spiro

Table S2. Baseline (ECRHS I) characteristics of participants included and excluded of the analysis

Characteristics	Included (n=3,673) n (%) or mean (SD)	Excluded (n=12,909) n (%) or mean (SD)	p-value
Symptomatic study arm	544 (14.8)	1,842 (14.3)	0.409
Sex. Women	1,956 (53.3)	6,6694 (51.9)	0.134
Age in years	34.3 (7.1)	33.4 (7.2)	<0.001
Height in cm	170.6 (9.4)	170.7 (9.7)	0.557
Weight in kg	69.5 (13.5)	69.5 (13.9)	0.842
BMI			
Continuous, in kg/m2	23.8 (3.7)	23.8 (3.9)	0.864
Underweight	453 (12.3)	1,412 (13.3)	0.512
Normal weight	2,097 (57.1)	5,987 (56.2)	
Overweight	892 (24.3)	2,562 (24.1)	
Obese	231 (6.3)	684 (6.4)	
Smoking status			
Non-smoker	1,651 (45.0)	5,199 (40.3)	<0.001
Ex-smoker	818 (22.3)	2,545 (19.7)	
Current smoker	1,204 (32.8)	5,149 (39.9)	
Second-hand smoke exposure. Yes	1,939 (52.9)	7,526 (58.6)	<0.001
Current asthma*. Yes	378 (10.5)	1,329 (10.6)	0.880
Age completed full time education			
<17 years	675 (21.5)	2,644 (24.3)	<0.001
17-20 years	1,205 (38.4)	4,514 (41.5)	
>20 years	1,256 (40.1)	3,709 (34.1)	

(Continued)

Table S2. Continued

Characteristics	Included (n=3,673) n (%) or mean (SD)	Excluded (n=12,909) n (%) or mean (SD)	p-value
Lung function			
FVC (ml)	4,516 (988)	4,517 (1,038)	0.957
FEV_1 (ml)	3,702 (798)	3,716 (845)	0.360
FEV_1/FVC (%)	82.3 (6.9)	82.5 (7.5)	0.080

**Current asthma was defined as having reported physician-diagnosed asthma and at least one of the following: asthma-like symptoms (wheeze, nocturnal chest tightness, attacks of breathlessness after activity/at rest/at night-time), asthma attacks, use of inhaled/oral medicines for breathing problems (in the last 12 months), or current use of inhalers, aerosols or tablets for asthma*
Abbreviations: BMI, body mass index; FEV1, volume expired in the first second; FVC, forced vital capacity; SD, standard deviation

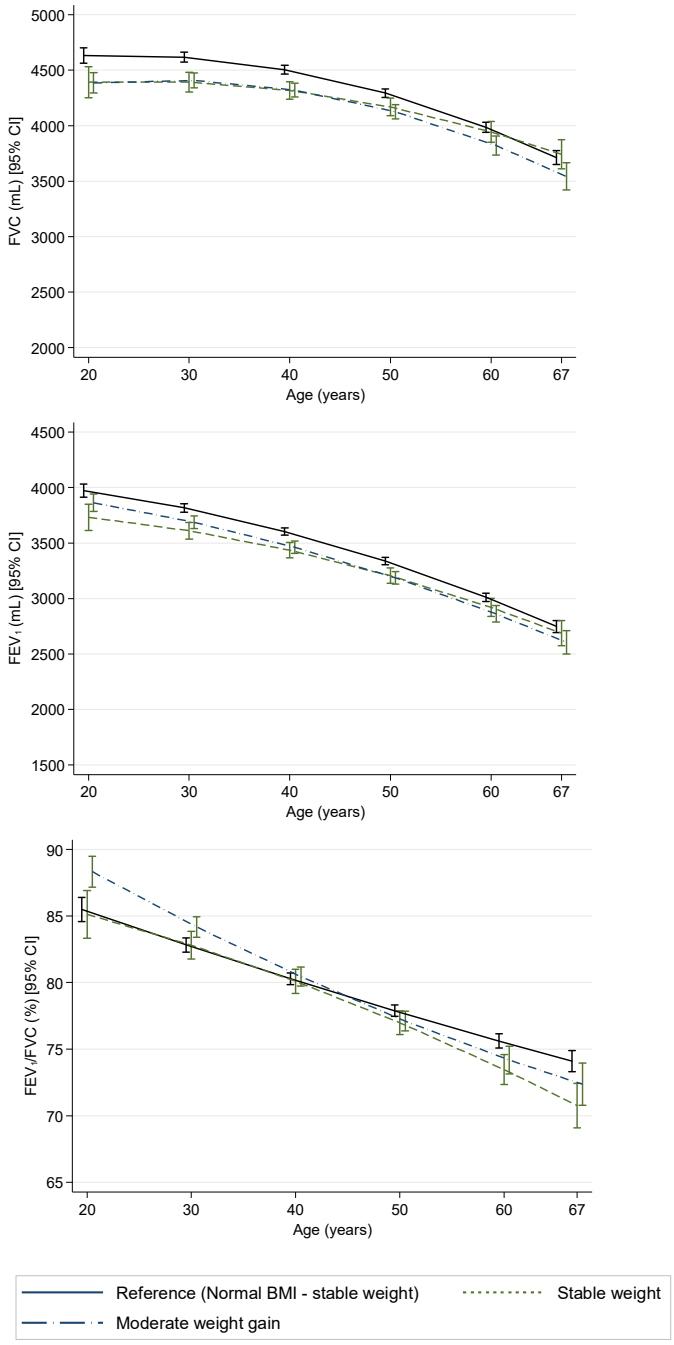

Figure S2. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline in baseline underweight participants with stable weight and moderate weight gain during follow-up. *Models are adjusted for the same variables than main models (see Figures 1 to 3).*

Table S3. Estimated FVC (mL) differences among weight change profiles at age 25 years and 65 years

		25 years		65 years	
Weight change profiles		**Coef (95% CI)**	**p-value**	**Coef (95% CI)**	**p-value**
Normal BMI	Stable weight	Reference		Reference	
Underweight †	Stable weight	-236 [-354 to -118]	<0.001	9 [-117 to 134]	0.891
	Moderate weight gain	-228 [-318 to -138]	<0.001	-167 [-285 to -50]	0.005
Normal BMI	Weight loss	6 [-204 to 216]	0.957	36 [-223 to 294]	0.788
	Moderate weight gain	47 [-17 to 112]	0.150	-182 [-249 to -115]	<0.001
	High weight gain	-2 [-106 to 102]	0.971	-528 [-658 to -398]	<0.001
Overweight	Weight loss	40 [-176 to 256]	0.716	53 [-132 to 238]	0.574
	Stable weight	-5 [-107 to 98]	0.930	-84 [-176 to 8]	0.073
	Moderate weight	79 [-9 to 166]	0.077	-342 [-423 to -260]	<0.001
	High weight gain	100 [-39 to 239]	0.158	-677 [-841 to -512]	<0.001
Obese	Weight loss	-320 [-552 to -87]	0.007	-84 [-274 to 107]	0.389
	Stable weight	-189 [-396 to 18]	0.074	-338 [-502 to -174]	<0.001
	Moderate weight	-58 [-238 to 122]	0.529	-429 [-576 to -282]	<0.001
	High weight gain	-58 [-296 to 180]	0.632	-1,011 [-1,259 to -763]	<0.001

Coefficients represent the estimated differences of FVC (mL) for each one of the weight change profiles compared to individuals with baseline normal BMI and stable weight during follow-up. Models are adjusted for sex, height, age, age squared, smoking status, an interaction term between smoking status and age, current asthma and spirometer type.

† Underweight who lost weight and underweight with high weight gain were excluded from multivariate analyses because of small sample size.

Abbreviations: FVC, forced vital capacity; 95% CI, 95% confidence interval

Table S4. Estimated FEV_1 (mL) differences among weight change profiles at age 25 years and 65 years

		25 years		65 years	
Weight change profiles		**Coef (95% CI)**	**p-value**	**Coef (95% CI)**	**p-value**
Normal BMI	Stable weight	Reference		Reference	
Underweight †	Stable weight	-222 [-324 to -120]	<0.001	-70 [-178 to 39]	0.208
	Moderate weight gain	-119 [-197 to -41]	0.003	-146 [-247 to -45]	0.005
Normal BMI	Weight loss	7 [-175 to 189]	0.940	87 [-136 to 309]	0.445
	Moderate weight gain	53 [-3 to 108]	0.064	-105 [-163 to -47]	<0.001
	High weight gain	19 [-72 to 109]	0.688	-313 [-424 to -201]	<0.001
Overweight	Weight loss	12 [-174 to 199]	0.899	19 [-141 to 179]	0.817
	Stable weight	-44 [-133 to 44]	0.327	-57 [-136 to 22]	0.159
	Moderate weight	-7 [-82 to 69]	0.861	-222 [-293 to -152]	<0.001
	High weight gain	25 [-96 to 145]	0.687	-413 [-554 to -271]	<0.001
Obese	Weight loss	-412 [-612 to -211]	<0.001	-41 [-205 to 124]	0.628
	Stable weight	-308 [-487 to -130]	0.001	-257 [-399 to -115]	<0.001
	Moderate weight	-181 [-337 to -26]	0.022	-254 [-381 to -127]	<0.001
	High weight gain	-245 [-451 to -40]	0.019	-839 [-1,053 to -626]	<0.001

Coefficients represent the estimated differences of FEV_1 (mL) for each one of the weight change profiles compared to individuals with baseline normal BMI and stable weight during follow-up. Models are adjusted for sex, height, age, age squared, smoking status, an interaction term between smoking status and age, current asthma and spirometer type.

† Underweight who lost weight and underweight with high weight gain were excluded from multivariate analyses because of small sample size.

Abbreviations: FEV_1, volume expired in the first second; 95% CI, 95% confidence interval.

Table S5. Estimated FEV_1/FVC (%) differences among weight change profiles at age 25 years and 65 years

		25 years		65 years	
Weight change profiles		**Coef (95% CI)**	**p-value**	**Coef (95% CI)**	**p-value**
Normal BMI	Stable weight	Reference		Reference	
Underweight†	Stable weight	-0.1 [-1.6 to 1.3]	0.872	-3 [-4.5 to -1.4]	0.000
	Moderate weight gain	2.1 [1 to 3.2]	0.000	-1.7 [-3.2 to -0.2]	0.028
Normal BMI	Weight loss	0.7 [-1.9 to 3.2]	0.617	1.5 [-1.8 to 4.8]	0.364
	Moderate weight gain	0.3 [-0.5 to 1.1]	0.440	0.9 [0.1 to 1.8]	0.028
	High weight gain	0.5 [-0.8 to 1.8]	0.432	1.6 [0.0 to 3.2]	0.055
Overweight	Weight loss	-0.9 [-3.6 to 1.8]	0.509	-0.7 [-3 to 1.5]	0.527
	Stable weight	-1.2 [-2.5 to 0.1]	0.063	0.5 [-0.7 to 1.6]	0.425
	Moderate weight	-2 [-3.1 to -0.9]	0.000	1.1 [0.1 to 2.2]	0.026
	High weight gain	-1.1 [-2.8 to 0.6]	0.221	2.1 [0.0 to 4.1]	0.051
Obese	Weight loss	-3.9 [-6.8 to -0.9]	0.010	-0.4 [-2.7 to 1.9]	0.726
	Stable weight	-3.5 [-6.1 to -0.9]	0.009	-0.2 [-2.2 to 1.7]	0.807
	Moderate weight	-3.2 [-5.5 to -0.9]	0.006	1.8 [0.0 to 3.6]	0.053
	High weight gain	-4.4 [-7.4 to -1.5]	0.003	-3 [-6.1 to 0.1]	0.055

Coefficients represent the estimated differences of FEV_1/FVC (%) for each one of the weight change profiles compared to individuals with baseline normal BMI and stable weight during follow-up. Models are adjusted for sex, height, age, age squared, smoking status, an interaction term between smoking status and age, current asthma and spirometer type.

† Underweight who lost weight and underweight with high weight gain were excluded from multivariate analyses because of small sample size.

Abbreviations: FEV_1, volume expired in the first second; FVC, forced vital capacity; 95% CI, 95% confidence interval.

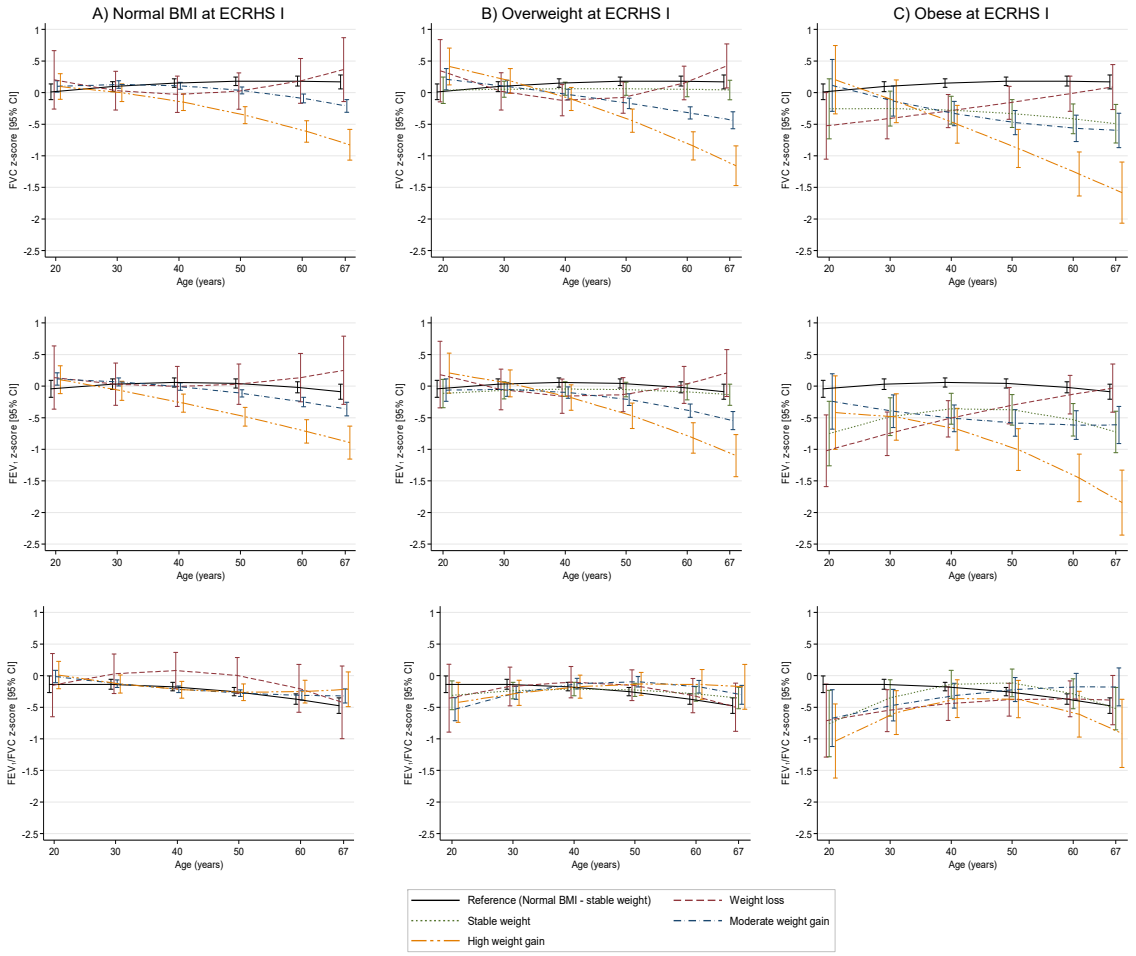

Figure S3. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline by weight change profiles– Using lung function standard deviation score (z-score) as outcome variable. *Models are adjusted for the same variables as in the main models, except sex and height (see Figures 1 to 3).*

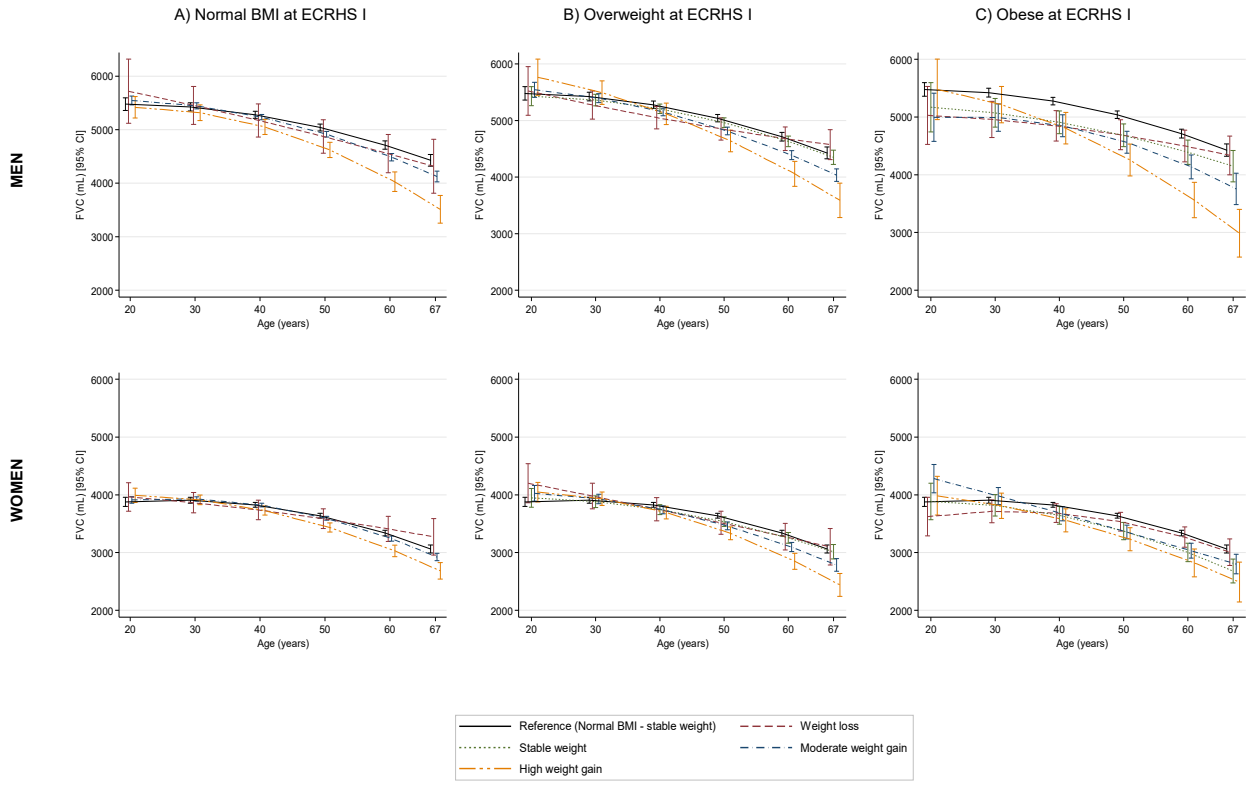

Figure S4. Estimated trajectories of FVC (mL) decline by weight change profiles – Stratified by sex

Models are adjusted for the same variables as in the main models, except sex (see Figure 1). P-value for sex interaction: 0.124

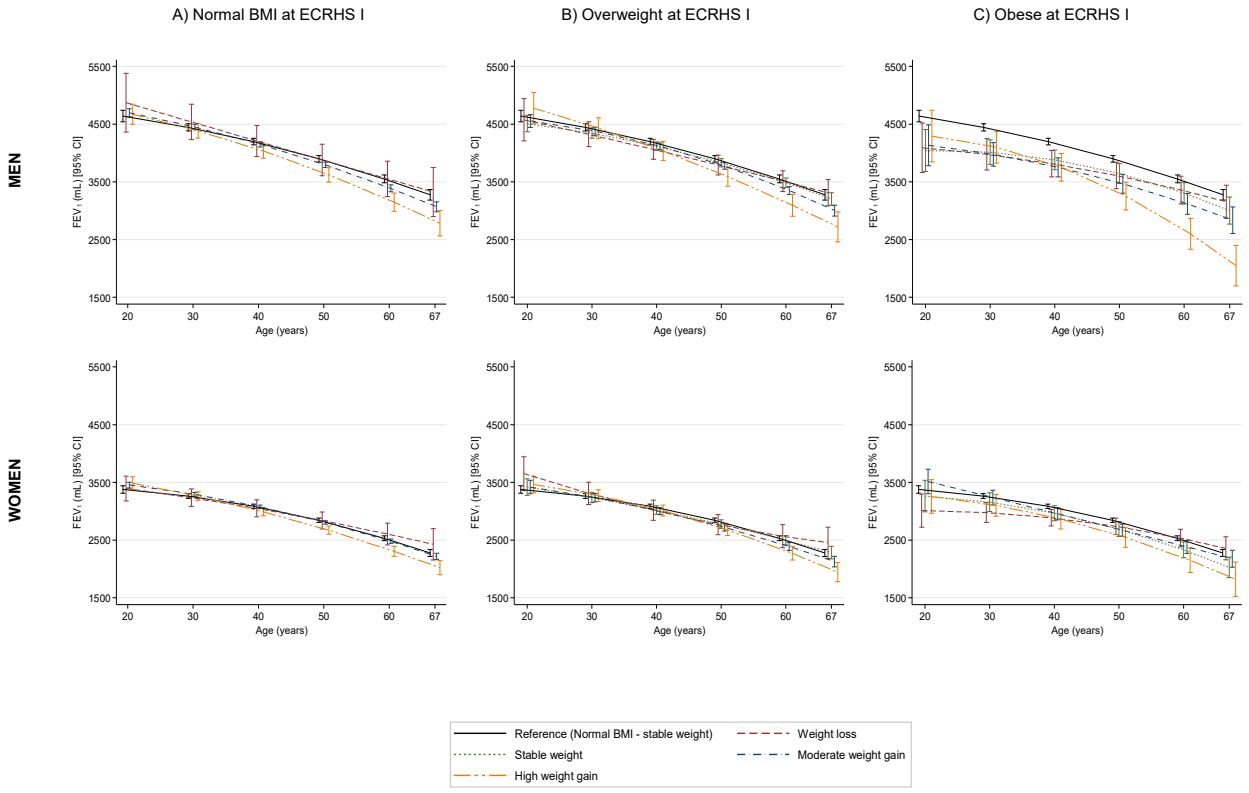

Figure S5. Estimated trajectories of FEV_1 (mL) decline by weight change profiles– Stratified by sex

Models are adjusted for the same variables as in the main models, except sex (see Figure 2). P-value for sex interaction: 0.006

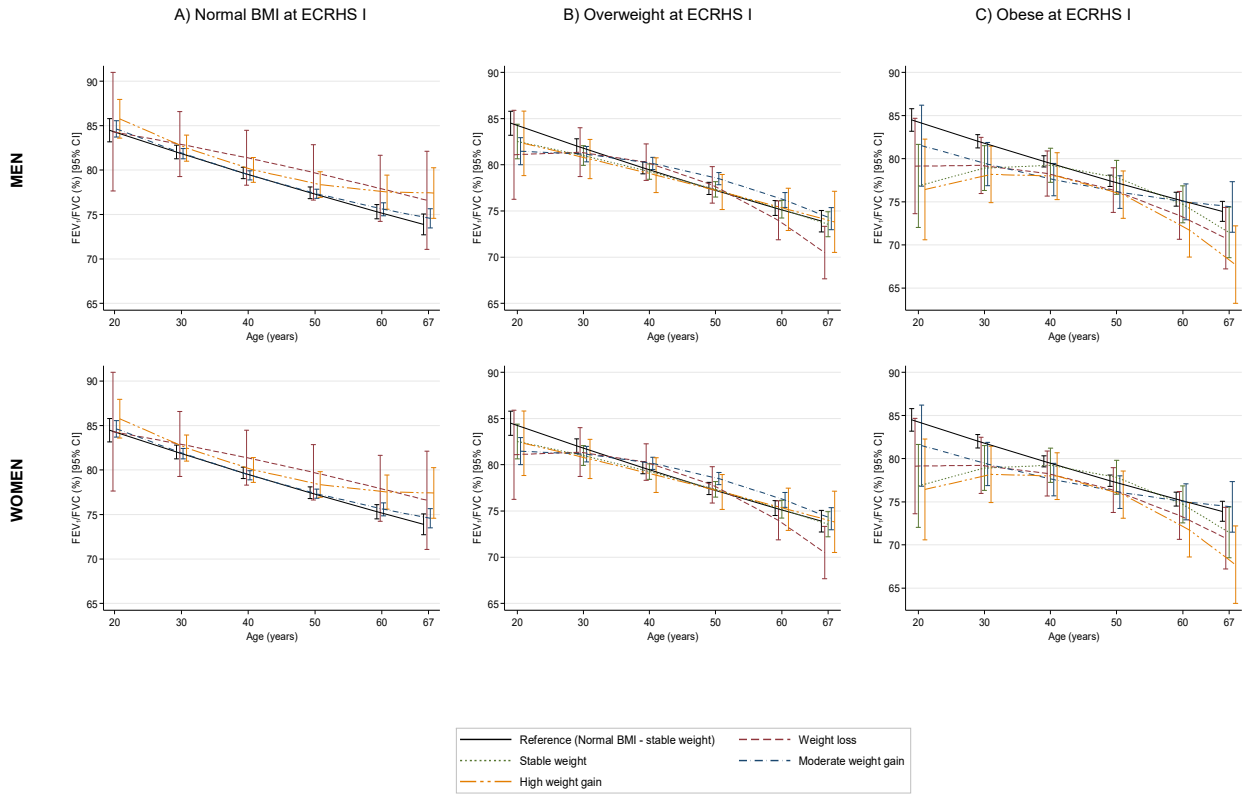

Figure S6. Estimated trajectories of FEV_1/FVC (%) decline by weight change profiles– Stratified by sex.
Models are adjusted for the same variables as in the main models, except sex (see Figure 3). P-value for sex interaction: 0.247

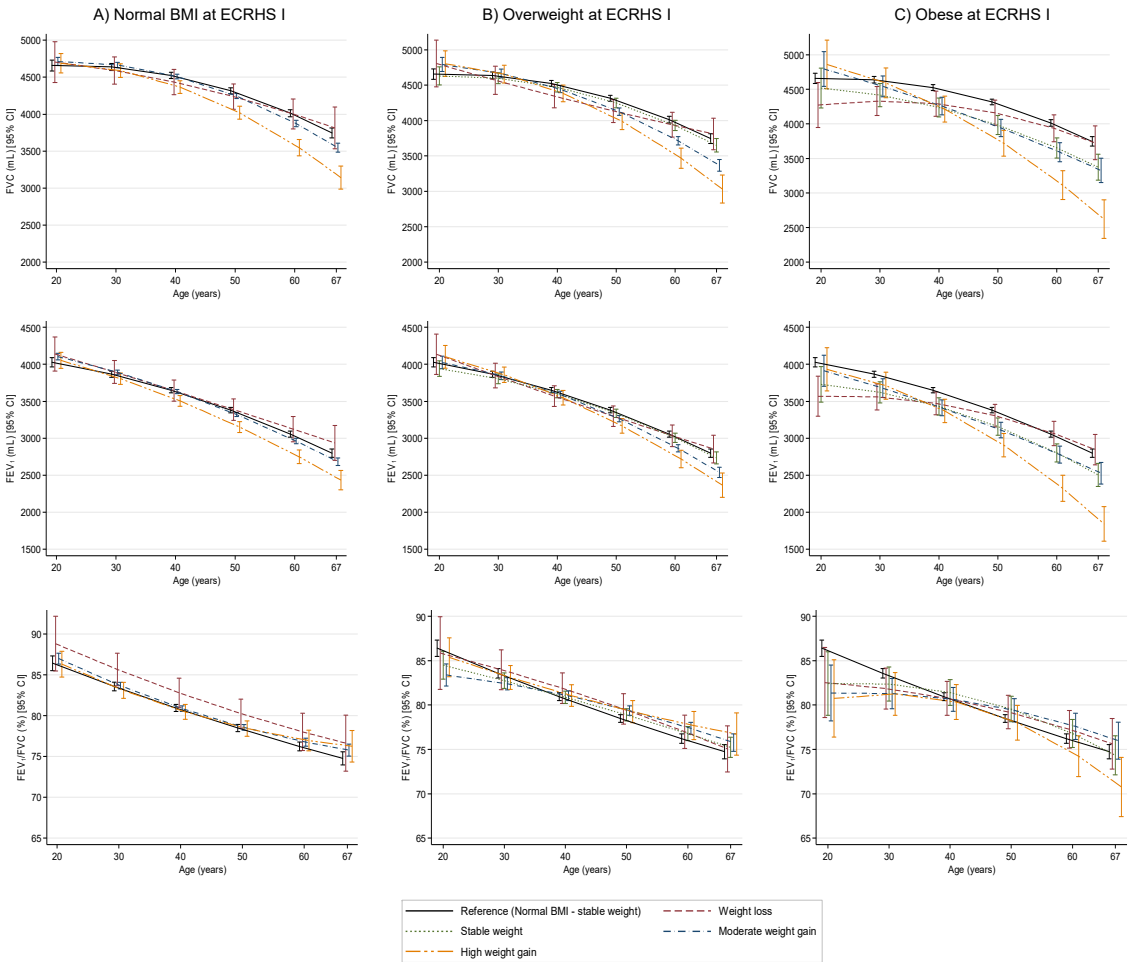

Figure S7. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline by weight change profiles– Excluding participants with current asthma at any visit (n= 709). *Models are adjusted for the same variables as in the main models (see Figures 1 to 3).*

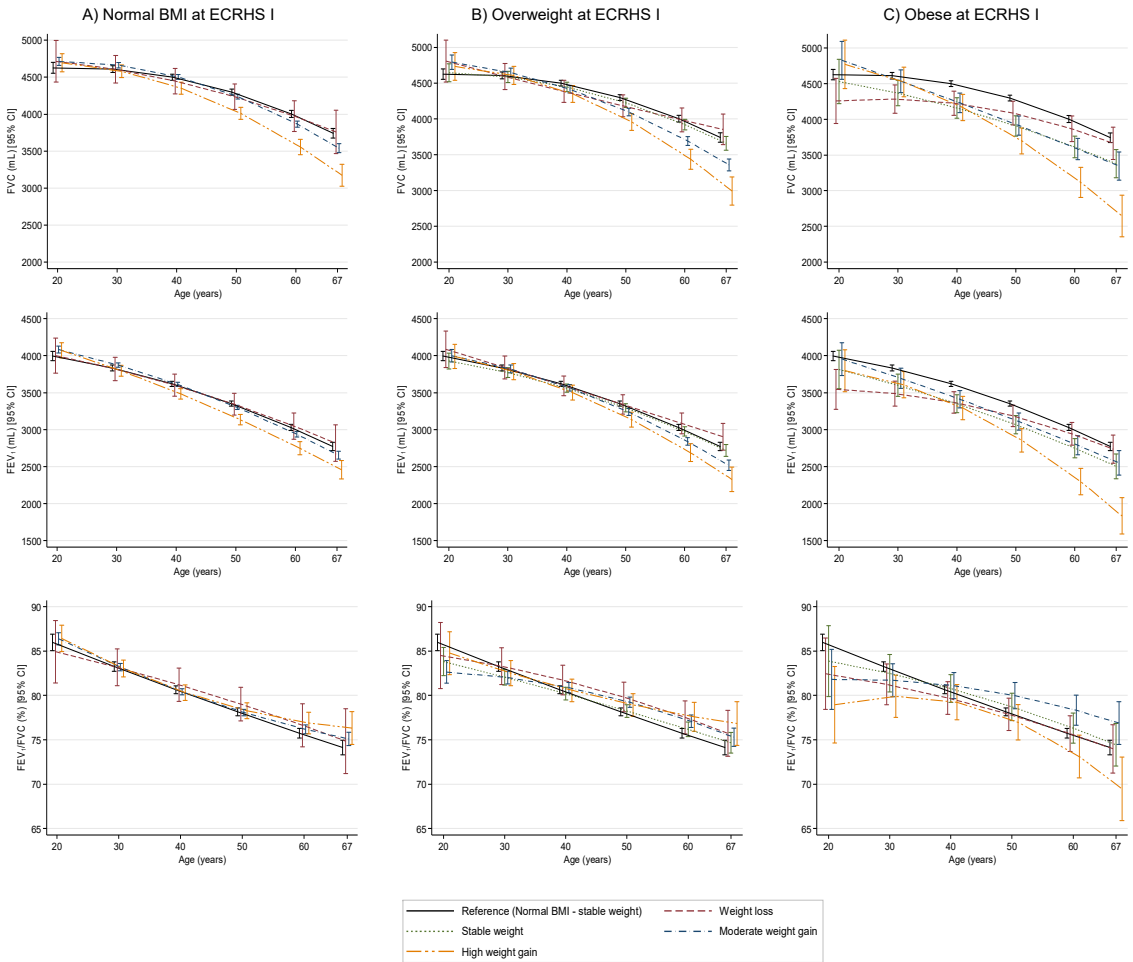

Figure S8. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline by weight change profiles– Excluding the symptomatic arm of ECRHS (n=536). *Models are adjusted for the same variables as in the main models (see Figures 1 to 3).*

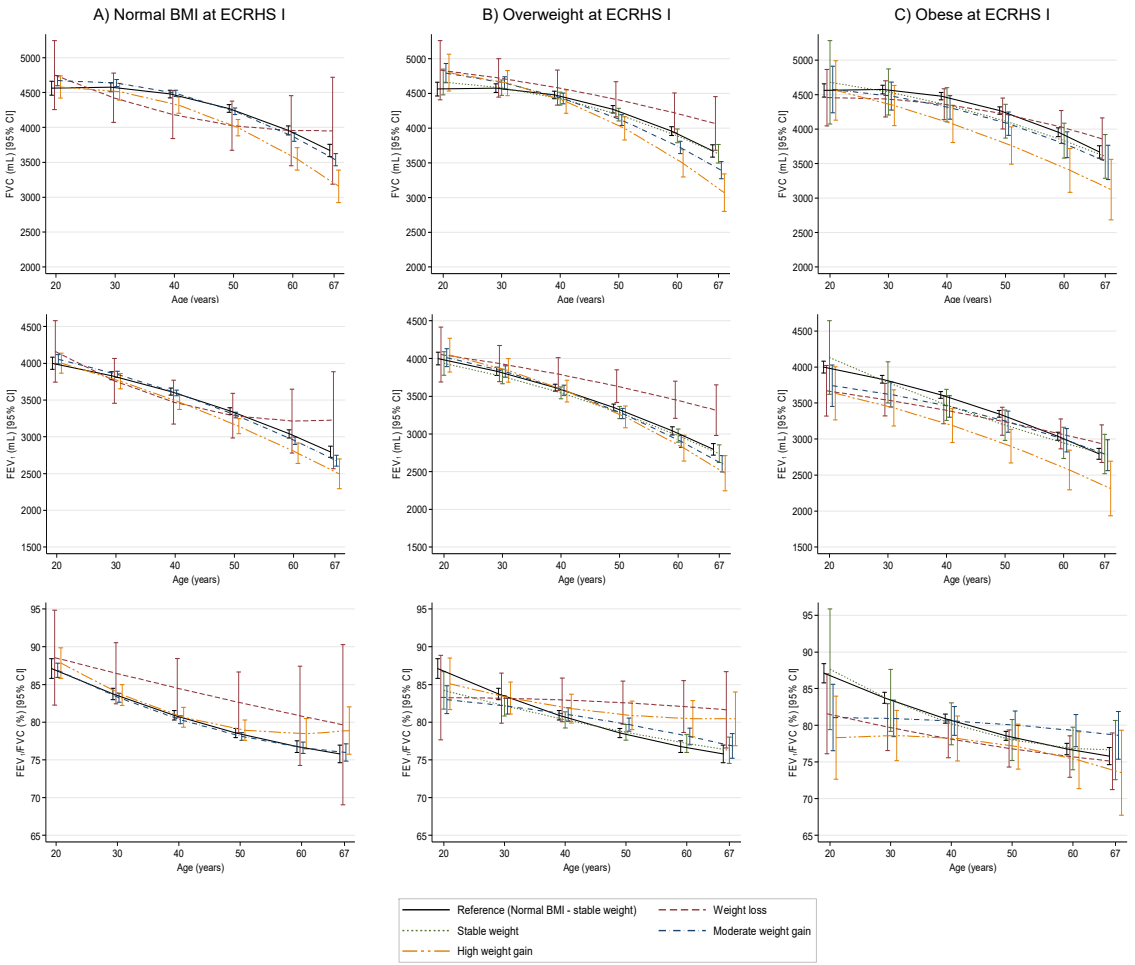

Figure S9. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline by weight change profiles–Restricting models to participants who reported to be non-smokers at all visits (n=1,491). *Models are adjusted for the same variables as in the main models (see Figures 1 to 3).*

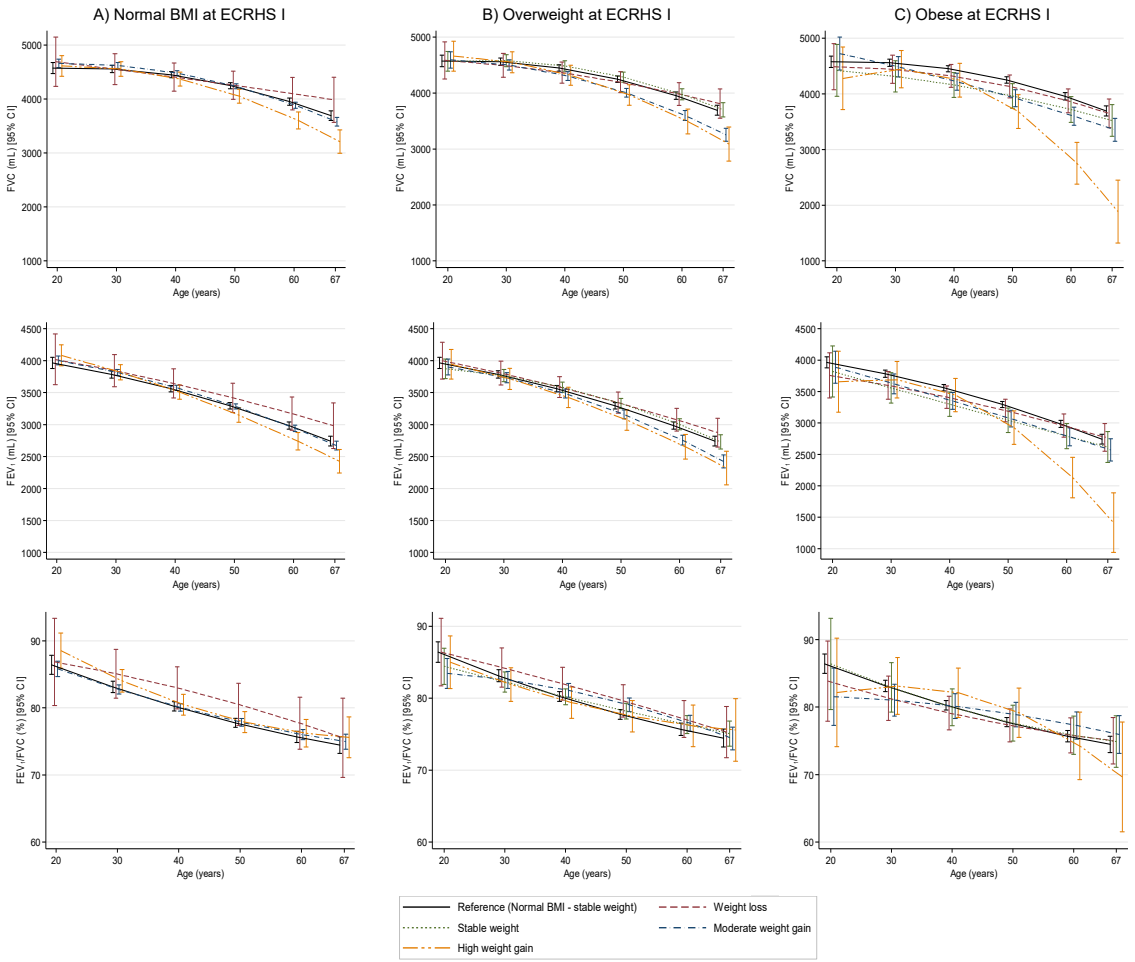

Figure S10. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline by weight change profiles–Models additionally adjusted for educational level at ECRHS I and physical activity and any long-term limiting illness (hypertension/heart disease/diabetes/cancer/stroke) at ECRHS II (n=1,525). *Models are adjusted for the same variables as in the main models (see Figures 1 to 3).*

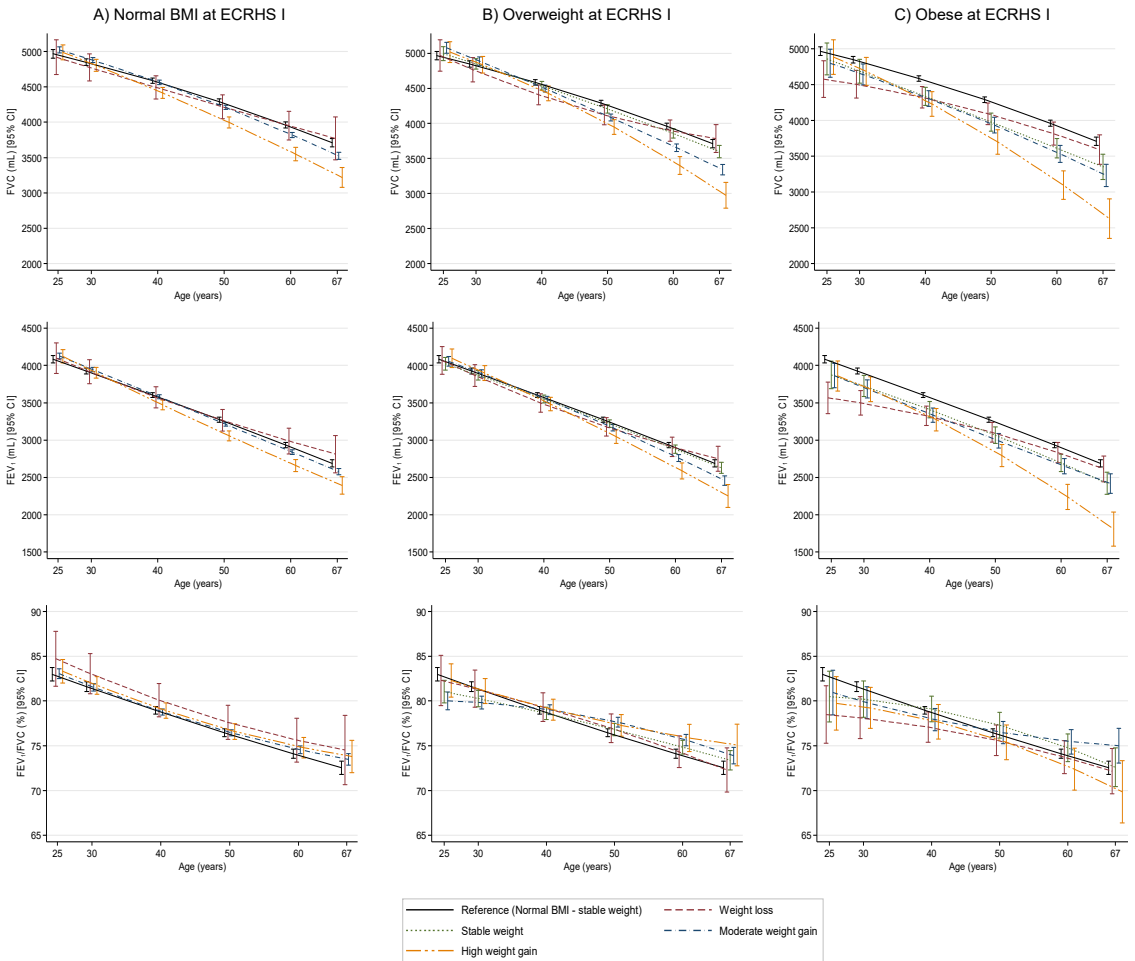

Figure S11. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline by weight change profiles–Using lung function values corrected for change in spirometer. *Models are adjusted for the same variables as in the main models, except for spirometer type (see Figures 1 to 3). Lung function trajectories start at age 25 years because corrected values were calculated only for subjects aged ≥25 year at baseline.*

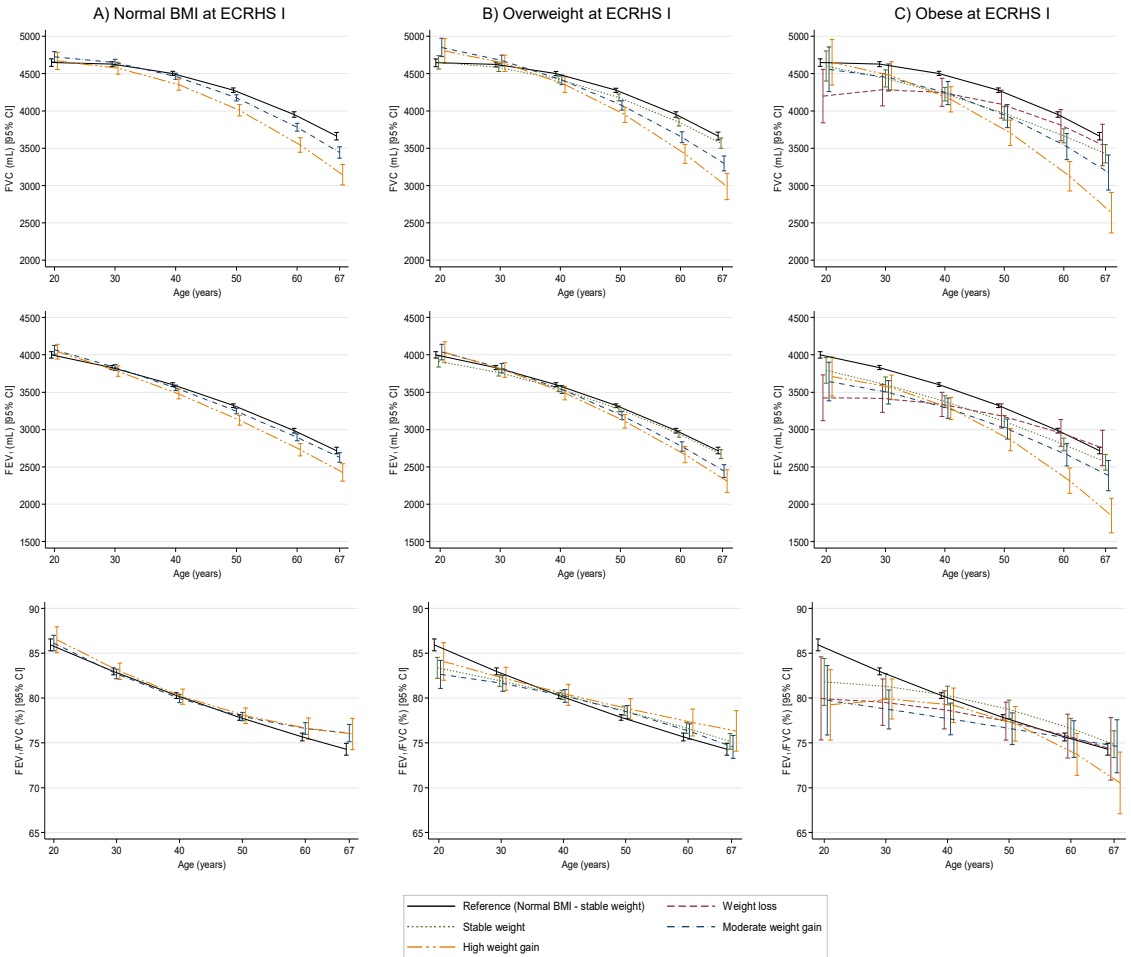

Figure S12. Estimated trajectories of FVC (first panel), FEV_1 (second panel) and FEV_1/FVC (third panel) decline by weight change profiles–Using alternative categories for weight change (weight loss: <-0.5 kg/year; stable weight ±0.5 kg/year; moderate weight gain: 0.5 to 1 kg/year; high weight gain: >1kg/year). *Models are adjusted for the same variables as in the main models (see Figures 1 to 3). Normal BMI and overweight subjects who lost weight were excluded due to small sample size.*

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ECRHS II

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(SEPAR R01 HL62633-01) Red de Centros de Epidemiología y Salud Pública (C03/09), Red de Bases moleculares y fisiológicas de las Enfermedades Respiratorias (C03/011) and Red de Grupos Infancia y Medio Ambiente (G03/176);97/0035-01, 99/0034-01, and99/0034-02); **Sweden: Göteborg, Umea, Uppsala**: Swedish Heart Lung Foundation, Swedish Foundation for Health Care Sciences and Allergy Research, Swedish Asthma and Allergy Foundation, Swedish Cancer and Allergy Foundation, Swedish Council for Working Life and Social Research (FAS); **Switzerland: Basel** Swiss National Science Foundation, Swiss Federal Office for Education and Science, Swiss National Accident Insurance Fund; **UK: Ipswich and Norwich**: Asthma UK (formerly known as National Asthma Campaign).

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ECRHS III

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6. DISCUSSION

The results of the four papers included in this thesis have been discussed in depth in the corresponding section of each paper. This section aims to complement previous discussion sections by expanding on two of the main contributions of this thesis: the potential reversibility of the effects of body weight on lung function and the assessment and interpretation of body composition in epidemiological research. This section also reflects on the implications of this thesis for future research and public health and provides a global discussion of the strengths and limitations of the thesis.

6.1 Reversibility of the effects of body weight on lung function

One of the key findings of this thesis is that the effects of body weight on lung function seem to be reversible both in early childhood and in adulthood (*Papers I and IV*, respectively). These findings are relevant as they help to reinforce causality between body weight and respiratory health and may open the door for public health interventions over the life course.

In *Paper I*, we found that accelerated BMI gain in early childhood was associated with higher FVC at seven years even if children departed from low birth size. In contrast, children with low birth size and slow BMI gain in early childhood had lower FVC and FEV_1 at seven years. Low birth size is likely to be a consequence of intrauterine growth retardation, which in turn can lead to abnormal

lung and airway development [203,204]. However, as alveolar development continues after birth [205], it is possible that postnatal growth could help to overcome previously reduced lung growth. This hypothesis is supported by previous longitudinal research showing that children with intrauterine growth restriction who showed weight catch-up growth in childhood had higher spirometry measures at age nine years than those without catch-up [136]. Similarly, another longitudinal study showed a positive contribution of catch-up growth in early life to adult lung function [145]. Overall, results of *Paper I*, as well as previous research, suggest that the effects of low birth weight on lung function are not fixed, and that may be reverted by postnatal growth. However, it is important to highlight that we found that children with accelerated BMI gain in early childhood also showed lower FEV_1/FVC at seven years, which is line with previous research [33,133–135]. Although we cannot rule out the possibility that this association is due to a mathematical artefact (due to a higher effect on FVC than on FEV_1), it may also indicate that accelerated weight gain relates to later airflow limitation. Further research into the biological mechanisms is needed to understand the opposite effects of accelerated weight gain on FVC and FEV_1/FVC.

In *Paper II*, we aimed also to consider body weight and composition changes over mid-childhood and adolescence in relation to lung function growth, however it was not possible because our analytical approach did not identify changing patterns but parallel trajectories only. It is likely that changes in body weight and the proportion of body weight components during these periods are not heterogeneous enough to allow the identification of changing patterns at a

population-level. Further studies using other analytical approaches should examine if changes in body weight and composition affect lung function growth during adolescence.

In *Paper IV*, we found that in participants with obesity in young adulthood, weight loss during a twenty-year period was associated with attenuated FVC and FEV_1 decline, which is consistent with previous research [156–163]. It possible that these associations are explained by an reduction of abdominal fat mass, which in turn may reverse the mechanical effects of fat mass on the respiratory system [206]. In addition, weight loss may relate to reduction of inflammatory processes and metabolic alterations related to obesity, both of which have been associated with decreased lung function in adults [186,191]. In fact, there is evidence showing that weight loss also relates to improvement of asthma status [207] and cardiovascular outcomes [208,209], conditions in which inflammation and/or metabolic derangements are also likely to play an important role. Finally, the association of weight loss with attenuated lung function decline could be due to confounding by changes in physical activity and/or diet, which can affect both body weight and lung function [79,83,210]. There is evidence that lifestyle interventions targeting physical activity and/or diet are effective for weight reduction [208,211], and that these interventions may be also effective to reduce premature mortality in adults with obesity [208]. Despite further research is needed to elucidate the mechanisms underlying the association between weight loss and lung function, results of *Paper IV*, as well as previous research, suggest that public health policies

promoting healthy lifestyles and body weight may be important for reducing respiratory morbidity in adult life.

6.2 Assessment and interpretation of body composition in epidemiological research

One of the main contributions of this thesis is elucidating a potential reason why previous research assessing the association between overweigh/obesity, as measured by BMI, and lung function in children and adolescents had reported conflicting findings. BMI considers total body weight only and is unable to distinguish between lean body mass and fat mass, which, as we shown, have different effects on lung function. Specifically, we found that higher lean body mass from nine to fifteen years were associated with higher levels and growth rates of FVC, FEV_1 and FEF_{25-75} in both sexes at fifteen years, while higher fat mass levels were associated with lower FEV_1 and FEF_{25-75} in boys and to lower FEV_1/FVC in both sexes (*Paper II*). Similarly, other epidemiological studies have consistently shown that lung function is positively related to lean mass but negatively related to fat mass in adulthood and elderly [165,166,168–170,172]. Overall, these results show that body composition relates to lung function over the life span and that lean body mass and fat mass have opposite effects. This highlights the importance of assessing the different components of body weight (i.e. body composition) when studying the effects of body weight on respiratory health.

The assessment of body composition in epidemiological research requires to take into consideration some important factors. Body composition can be measured by a variety of methods, which vary in

their accuracy, feasibility and cost. Dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging (MRI) are considered to be among the most accurate methods to measure body composition as they allow to obtain separate measures of fat and lean tissues, as well as regional estimates of these tissues [111,212]. However, these methods require large expensive equipment and specialized technicians [213], which limit their use in large epidemiological studies. In contrast, bioelectrical impedance analysis (BIA) is a relatively simple method to measure body composition and requires inexpensive portable equipment, characteristics that have made it really appealing in epidemiological research [214]. BIA provides indirect measures of body composition by measuring the body resistance to a small electrical current, from which total fat-free mass (FFM, all non-fat tissues) can be calculated. Then, fat mass can by derived as the subtraction of FFM to total body weight. A potential limitation of BIA is that the calculation of FFM requires population specific equations, which are useful only for those populations with characteristics similar to those of the reference population [111,214]. In addition, BIA relies on constant body hydration and thus may be affected by clinical conditions, levels of physical activity, hormonal status and levels of obesity [214,215]. Finally, indirect measures of body composition can also be obtained using anthropometric measures such as skinfolds and body circumferences. These methods are simple and inexpensive, but have some important limitations including large measurement error due to lack of agreement on the optimal site for measurement and the lack of accuracy in subjects with severe obesity [216]. Researchers should consider the

limitations of available methods and select the best suited according to the research question and to the context of the study.

Apart from difficulties in the assessment, body composition results in (generally) healthy populations are often difficult to interpret because of limited availability of reference values [217]. Over the last decades, several studies have derived references values for different methods both for paediatric [217] and adult populations [218–220]. However, there are several factors that need to be considered when using these references. Body composition measures can be compared only to those obtained with the same method, and preferably with the equipment of the same manufacturer, as there are important variations in the theorical assumptions used to calculate final values [111]. In addition, it is important to consider that body composition levels vary greatly by ethnic background [221,222], and that may also be affected by environmental factors [217]. Thus, the comparison of reference values is population specific. Finally, existing reference values have been derived for specific age ranges and, although some of them include both childhood and adulthood, there are periods of life that have not been examined yet, especially in early childhood and elderly.

Overall, the interpretation of body composition results in the general population is still challenged by the diversity in assessment methods and scarcity of reference values. This challenge is likely more relevant for prevalence than for inference studies. In any case, researchers may consider combining different equations, internal

validation substudies and/or sensitivity analyses in order to increase internal and external validity of their results.

6.3 Implications for future research and public health

The findings presented in this thesis have substantial implications both for future research and public health. First, our findings increase the knowledge on the association between body weight and lung function over the life course and reinforce the public health message that obesity has deleterious effects on health, including respiratory health. Importantly, the findings presented in *Paper IV*, show that the negative effects of obesity on lung function can be reversed by weight loss even later in adult life. Therefore, public health policies that promote healthy lifestyles and body weight control may be important for maintaining good lung function over life span.

A relevant message for future research is the importance of assessing body composition when studying the health effects of body weight on respiratory health. As shown in *Paper II,* lean body mass and fat mass have different effects on lung function, and measures that consider total body weight only, such as BMI, are unable to distinguish these differences and can lead to conflicting findings. In addition, since there is research suggesting that abdominal fat mass may drive the association of obesity with lung function [165,166,223], future research should also include regional measures of body composition. Our findings also suggest that public health policies and clinical interventions aiming to reduce respiratory morbidity should target body composition in addition of body weight.

In fact, there is evidence showing that respiratory muscle training interventions can improve lung function [177,178]. However, previous research has been limited to adults with chronic conditions and there is a lack of research on the potential benefits of gaining lean body mass for lung function in healthy populations. More research is needed to understand the independent effects of gaining lean body mass and losing fat mass on respiratory outcomes.

The results presented in this thesis also evidence the need of future studies that examine the biological mechanism underlying the association of body weight and composition with lung function. These studies will help to strengthen causal inference between obesity and respiratory health and to identify intermediate treatment targets for interventions aiming to reduce respiratory morbidity. In *Paper III*, we examine for the first time the potential mediating role of systemic inflammation (measured by CRP levels) and insulin resistance in the association between high fat mass and airflow limitation in adolescence. We found that insulin resistance may mediate part of this association, but no evidence of a role of CRP. Future research should confirm our results and examine other inflammatory markers as well as other potential mechanisms (e.g. mechanical effects or structural alterations of fat mass on the respiratory system). In addition, we strongly recommend that future research includes detailed information on physical activity and diet, as they are related both with body weight/composition and lung function. This will help to elucidate the independent contribution of weight change and lifestyles factors to improvement in respiratory

health, and to design informed and effective public health interventions.

6.4 Strengths and limitations

An important strength of the present thesis is the population-based nature of the INMA, ALSPAC and ECRHS cohorts, which ensures external validity of our findings. The long follow-up of these cohorts allowed us to study the effects of not only levels of body weight and composition but also changes over time. Similarly, the availability of repeated measures of lung function allowed us to assess not only levels but also growth and decline of lung function. In addition, accounting for baseline lung function, together with the longitudinal design of the studies, reduced the possibility of reverse causation in the association of body weight and composition with lung function. Moreover, the availability of detailed information on several sociodemographic and environmental factors made possible to control for a wide range of potential confounders of the studied associations. Finally, the use of body composition measurements obtained using dual-energy X-ray absorptiometry (DXA) is also an important strength of this thesis. DXA is substantially more accurate than other methods used in previous research, such as bioelectric impedance or skinfolds, and therefore it reduces the possibility of misclassification of the exposure variables.

Although the limitations of the studies included in this thesis are detailed in each paper, certain limitations deserve to be highlighted also in this section. In *Papers I and IV,* we assessed body weight change using BMI and therefore we could not consider changes in

the proportion of lean body mass and fat mass over time neither distinguish the different effects of these body weight components on lung function. In addition, the findings of this thesis may be affected by selection bias as, in general, participants included in the four studies tended to have a higher socioeconomic status than those excluded. Also, the regional basis of the INMA and ALSPAC cohorts may not allow the generalizability of the findings of *Papers I, II and III* to populations with more ethnic variability and different lifestyles and environmental exposures. Finally, the findings of *Paper III* may be subject to potential reverse causation as the associations of CRP and insulin resistance with airflow limitation were assessed cross-sectionally. However, it is unlikely that lung function levels affect CRP levels/insulin resistance.

7. CONCLUSIONS

The results presented in this thesis show that excess body weight and fat mass have deleterious effects on lung function over life span, while higher lean body mass benefits lung function growth. The effects of body weight on lung function seem reversible. This thesis highlights the importance of assessing body composition when studying the effects of body weight on respiratory health and of promoting body weight and fat mass control in order to reduce respiratory morbidity at all ages.

More in detail, the specific conclusions of each of the manuscripts of this doctoral thesis are:

1. Independently of birth size, children with accelerated BMI gain in early childhood had higher lung function at seven years but also showed airflow limitation. In contrast, children with lower birth size and slower BMI gain in early childhood had lower lung function at seven years

2. Higher lean body mass during childhood and adolescence was consistently associated with higher lung function at fifteen years in both sexes, whereas higher fat mass was associated with lower levels of only some lung function parameters.

3. Insulin resistance may mediate part of the association between mid-childhood fat mass and the FEV_1/FVC ratio in adolescence, but we found no evidence of mediation by CRP.

4. Moderate and high weight gain over a 20-year period was associated with accelerated lung function decline in adulthood, while weight loss was related to its attenuation.

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ANNEXES

Other co-authored papers

Roda C, Mahmoud O, **Peralta GP**, et al. Physical-activity trajectories during childhood and lung function at 15 years: findings from the ALSPAC cohort. *Int J Epidemiol* 2019 pii: dyz128 [Epub ahead of print]

Bédard A, Carsin A-E, Fuertes E, Accordini S, Dharmage S, Garcia-Larsen V, Heinrich J, Janson C, Johannessen A, LeynaertB, Maldonado Pérez JA, **Peralta GP**, Pin I, Squillacioti G, Weyler J, Jarvis DL, Garcia-Aymerich J. Physical activity and lung function - cause or consequence? Resubmitted after review to *PLoS ONE* on April 9th, 2019 (Manuscript ID: PONE-D-19-25355)

Mahmoud O, Granell R, **Peralta GP**, Garcia- Aymerich J, Jarvis DL, Henderson H, Sterne J. Early-life and health behaviour influences on lung function in early-adulthood. Submitted to the *European Respiratory Journal* on Abril 21st, 2020 (Manuscript ID: ERJ-01316-2020)

Presentations at national and international conferences

Peralta GP et al. Early infancy BMI trajectories and lung function and asthma during childhood. **Oral presentation at the European**

Respiratory Society International Congress. September 28th – October 2nd, 2019, Madrid, Spain

Peralta GP et al. Body mass index trajectories during adult life and lung function decline. **Oral presentation at the European Respiratory Society International Congress.** September 16-19th, 2018, Paris, France

Peralta GP et al. La masa magra se asocia positivamente con la función pulmonar a los 15 años [Spanish]. **Oral presentation at the 51st National Congress of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).** May 31st - June 3rd, 2018, Palma de Mallorca, Spain

Peralta GP et al. Lean mass is positively associated with lung function at age 15. **Oral presentation at the European Respiratory Society International Congress.** September 9-13th, 2017, Milan, Italy

Grants and awards

ERS Young Scientist Sponsorship to attend the ERS International Congress. September 28th – October 2nd, 2019, Madrid, Spain. Abstract No 1721 'Early infancy BMI trajectories and lung function and asthma during childhood'.

Best abstract in Paediatric Pneumology at the 51st National Congress of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), May 31st - June 3rd, 2018, Palma de Mallorca, Spain

Best oral presentation at the 4th ISGlobal PhD Symposium. November 28th, 2017, Barcelona, Spain.

Institutional responsibilities and outreach activities

Co-manager of the Twitter account of the INfancia y Medio Ambiente (Environment and Childhood) Project (@ProyectoINMA) since June 2019

Co-organizer of the 5th ISGlobal PhD Symposium, held in Barcelona, Spain, on the 6th November 2018

Co-organizer of the ISGlobal weekly Scientific Seminar Series during the period September 2017- June 2018

Mentor of a nutrition course for high-school students held in the Institut XXV Olimpiada (Barcelona, Spain) during the period March – June 2017. Course organized by the Barcelona City Council in the framework of the Global STEM Alliance

Media attention

Papers II and IIII received national and international media attention, resulting in online published news articles and radio interviews. Below some examples of headlines.


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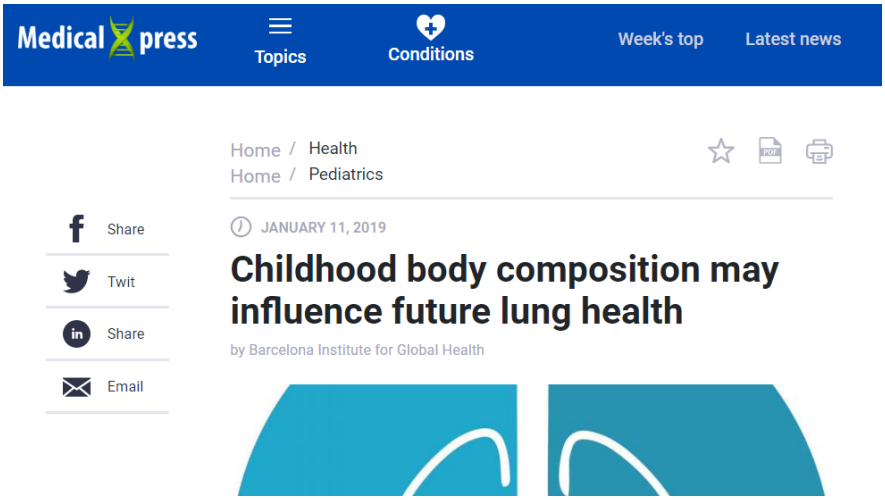
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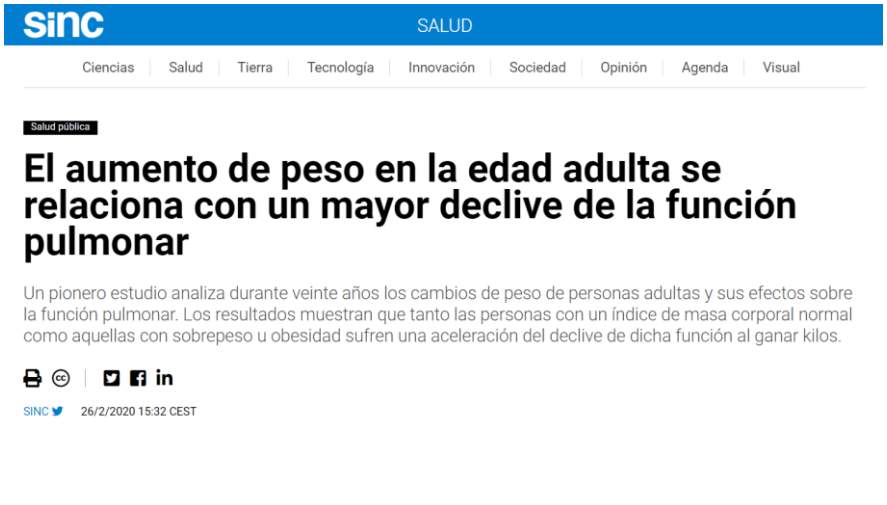

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