Influence of early life factors on later ventilatory function:

Interpreting associations with inflammation, cardiometabolic function and ethnicity

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Declaration of originality

I herewith certify that this dissertation is my original work and that all material included that is not my own work has been appropriately acknowledged.

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Abstract

Poor ventilatory function, as measured by spirometry, is strongly related to mortality and is the primary characteristic of several chronic lung diseases.

This thesis investigates the influence of early life factors, in particular birth weight, on later ventilatory function and elucidates the associations with inflammation, cardiometabolic function and ethnicity.

First, I performed a systematic review and meta-analysis on birth weight and ventilatory function. The results provide strong evidence for a positive association of birth weight with forced vital capacity (FVC), a 59.4mL increase in FVC per kg increase in birth weight (95% CI: 43.3 to 75.5). Much weaker evidence was found to support a positive association of birth weight with the ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC), particularly among children.

Second, I investigated the association of cardiometabolic and inflammatory markers with FVC and FEV_1/FVC in young adulthood in the Northern Finland 1966 birth cohort. The associations of inflammatory and cardiometabolic markers differed between FVC and FEV_1/FVC, as well as by sex. These associations were strongly influenced by adjustment for important confounders (height and sex) and by mutual adjustment for inflammatory and cardiometabolic markers. These associations were not explained by their common link to low birth weight, nor by socio-economic factors, systemic inflammation or selected prenatal influences, suggesting the involvement of other environmental or genetic factors.

Finally, I conducted a pilot investigation on ethnic differences in ventilatory function between White and South Asian British young adults. This study found a reduction of 860 mL (95% CI: -1320 to -400 mL) in FVC among South Asian British, identified parental immigration as an important predictor of FVC, and provided evidence against the hypotheses that differences in birth weight or trunk size can explain ethnic differences in ventilatory function. This study showed the feasibly of similar investigations in larger population-based studies.

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Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
ATS	American Thoracic Society
BMI	Body mass index
BOLD	Burden of Obstructive Lung Disease
bpm	beats per minute
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DASH	Determinants of Adolescent Social well-being and Health
DELBYA	Diversity in Ethnicity, Lung function and Birth weight in Young Adults
ERS	European Respiratory Society
FEV_1	forced expiratory volume in one second
FEV_1/FVC	ratio of FEV_1 to FVC
FVC	forced vital capacity
GP	general practitioner
HSCIC	Health and Social Care Information Centre
ISCO	International Standard Classification of Occupations
MAR	missing at random

MCAR	missing completely at random
MI	multiple imputation
MICE	Multiple Imputation by Chained Equation
MNAR	missing not at random
NFBC66	Northern Finland 1966 birth cohort
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NOS	Newcastle-Ottawa Quality Assessment Scale
ONS	Office for National Statistics
OR	odds ratio
RV	residual volume
SD	standard deviation
SES	socio-economic status
SMD	standardised mean difference
TLC	total lung capacity
UK	United Kingdom
USA	United States of America

CHAPTER 1

INTRODUCTION

1.1 Rationale

Poor ventilatory function, as measured by spirometry, is the primary characteristic of several chronic lung diseases, which include diseases that are responsible for some of the highest global burden of morbidity and mortality [205]. Moreover, low ventilatory function itself is strongly related with mortality [46, 49, 138]. Research to improve understanding of chronic lung diseases and poor ventilatory function has long centered on identifying adult causes or adult risk factors although, recently, this has shifted to also assess the importance of early life factors [136, 254, 299, 318].

Birth weight is a marker of intrauterine development. Birth weight is easily assessed and, in clinical practice, newborns' health status is immediately determined by measuring their birth weight. Increased birth weight has been associated with improved ventilatory function in later life, during both childhood and adulthood [14, 38, 54, 272, 309]. Moreover, weight at one year of life has been suggested to be a strong predictor of ventilatory function in later life [14], with findings showing an association of increased weight at one year and weight gain in the first year of life with ventilatory function in adulthood [14, 54]. However, the relation of weight in early life with different components of ventilatory function has neither been systematically assessed nor quantified. Despite this, low birth weight has been reported as an important early life risk factor for later chronic lung disease [265, 317].

Cardiometabolic diseases are frequently observed as comorbid diseases among individuals with poor ventilatory function [2, 93, 102, 290]. Although the biological mechanisms that might explain this observed relation remain unknown, common adult risk factors and systemic inflammation have been proposed as potential explanatory factors [19]. An alternative explanation is that birth weight represents a common early life risk factor, as low birth weight is associated with both poor ventilatory function and cardiometabolic diseases [146, 354]. Similarly, it is not known what explains the relation

of poor ventilatory function with systemic inflammation but a possible explanation is again birth weight, since low birth weight is associated with both poor ventilatory function and systematic inflammation [55, 252, 284].

The role of birth weight in relation to ventilatory function and cardiometabolic disease is further confounded by ethnicity. Birth weight is markedly lower for individuals from ethnic minorities [165, 319] and these minority groups have a high burden of non-communicable disease, including chronic lung and cardiometabolic disease. The prevalence, morbidity and mortality of non-communicable diseases are not the same across ethnic minorities [61, 69, 334], which further complicates the elucidation of the relation. A debate has arisen on what might explain the greater burden of non-communicable disease among ethnic minorities, with one view focused on the role of genetics while the other is centered on the importance of the socio-economic environment [32, 195]. Socio-economic status is a strong determinant of health and the parental socio-economic environment will affect an infant's birth weight [242, 337, 369]. Thus, the difference in birth weight between ethnic groups might explain the differences in both poor ventilatory function and cardiometabolic disease, and could explain the association between them.

In summary, birth weight is an important factor in early life but the relation with different measures of ventilatory function has not been systematically assessed or quantified. Moreover, birth weight could potentially explain the relation of low ventilatory function with cardiometabolic diseases or the difference in poor ventilatory function and cardiometabolic diseases among different ethnic groups.

1.2 Aim and objectives

The overall aim of this thesis is to determine the influence of early life factors, in particular birth weight, on later ventilatory function and elucidate the associations with

inflammation, cardiometabolic function and ethnicity.

The specific objectives are to:

1. Summarise currently available evidence on the relationship of birth weight, weight at one year and weight gain in the first year of life with ventilatory function in later life

2. Determine whether

   - the association between ventilatory function and cardiometabolic markers is (a) due to a common association with weight in early life, or can be explained by (b) shared adult risk factors, (c) inflammatory markers, or (d) prenatal factors
   - the association between ventilatory function and inflammatory markers is (a) due to a common association with weight in early life, or can be explained by (b) shared adult risk factors or (c) prenatal factors

3. Conduct a pilot study that identifies factors which could influence and explain the difference in ventilatory function and cardiometabolic markers between young White and South Asian British adults in the United Kingdom (UK)

1.3 Thesis outline

Chapter 2 provides a brief background on the life course trajectory of ventilatory function, the early life risk factors affecting ventilatory function, the relation of cardiometabolic markers and ventilatory function, and ethnic disparities in ventilatory function. Chapter 3 is a systematic review and meta-analysis of weight in early life and later ventilatory function. Chapter 4 focuses on explaining the association between ventilatory function and cardiometabolic or inflammation markers in the Northern Finland 1966

Birth Cohort. Chapter 5 describes a pilot study to identify factors that influence the diversity in ventilatory function and birth weight among different ethnic groups, and aims to explain this diversity. Finally, Chapter 6 discusses the findings of my PhD project and future perspectives for the study of early life influences on later ventilatory function.

CHAPTER 2

BACKGROUND

2.1 Measuring ventilatory function

Ventilation is the process by which air is transported in and out of the respiratory system. Ventilatory function is commonly assessed using three important measures: (1) Forced vital capacity (FVC), the maximum volume of air that can be forcefully exhaled after a full inspiration, (2) Forced expiratory volume in one second (FEV_1), the volume of air that can be forcefully exhaled in the first second after maximal inspiration, and (3) the ratio of FEV_1 to FVC (FEV_1/FVC), a measure of airway narrowing for which higher and lower values indicate normal and narrowed airways, respectively.

Impaired ventilatory function can be classified into (1) obstruction, where the lung airways are narrowed (i.e. low FEV_1/FVC), and (2) restriction, where lung volumes are reduced. Restriction is commonly characterised by low FVC, but this disregards the volume of air that remains in the lungs after forced exhalation, termed residual volume (RV). The RV can be increased with severe obstruction as a consequence of reduced elastic recoil resulting in a lower FVC while the overall lung volume remains constant or even increased. Thus, ideally, restriction should be assessed by measuring the overall lung volume, termed total lung capacity (TLC). However, it is not practicable to measure TLC in large epidemiological studies and a markedly increased RV is only found in those with relatively advanced obstruction and in the elderly [48], which makes low FVC a good marker of restriction in the general population. FEV_1 alone cannot discriminate between restriction and obstruction, as low FEV_1 could be a result of low lung volume (low FVC) or airway narrowing (low FEV_1/FVC) [48]. Two important chronic lung diseases that are primarily characterised by airflow obstruction are chronic obstructive pulmonary disease (COPD) and asthma. In asthma airflow obstruction is largely reversible, while in COPD the obstruction is largely irreversible. Thus, the forced expiratory manoeuvres would ideally be assessed after the administration of a bronchodilator (post-bronchodilator spirometry), to enable a distinction between reversible and irreversible

airflow obstruction.

2.2 Ventilatory function through the life course

Following birth, lung volumes will increase with age due to lung development and somatic growth. Ventilatory function will increase exponentially from birth, until a plateau is reached around 20-25 years of age, and will subsequently decline with increasing age [269, 306].

This pattern of development has led to the identification of four critical periods: (1) lung development in utero, (2) lung function in the first years of life, (3) airway growth in childhood and early adulthood and (4) ventilatory function decline after the plateau is reached [255, 314]. Lung development commences at three to four weeks of gestational age and continues throughout the intrauterine period [160]. Poor intrauterine growth has been associated with wheeze at three years of age [251] and increased risk of asthma and lower FEV_1 at age 10 [339]. The second period is important because ventilatory function is considered to track throughout the life course, meaning that an individual will tend to remain in the same centile of ventilatory function over time [24, 147, 225]. Ventilatory function immediately after birth has been shown to be associated with later respiratory disease [121] and, although catch-up growth in ventilatory function is possible, this only appears to occur within the first 4-6 years of life [225, 239, 311]. During the second critical period, throughout childhood, adolescence and early adulthood, the ventilatory system will continue to develop further with the growth of airways and maturation of alveoli [228], which results in attaining maximal ventilatory function in early adulthood. Failure to achieve maximum ventilatory function is a risk factor for the development of later respiratory insufficiency, as a lower peak given any specific rate of ventilatory function decline will result in a more rapid attainment of respiratory insufficiency [187]. The rate of ventilatory function decline, during the third period, will

depend on genetic, environmental and lifestyle factors.

2.3 Early life risk factors of ventilatory function

Ventilatory function is determined and influenced by genetic, environmental and behavioral factors. A risk factor's influence will depend on the occurrence, duration, intensity, and, potentially, interactions with other factors. In this section, the current evidence of early life influences, defined here as factors that affect later ventilatory function and occur prenatally or during early childhood, is summarised.

2.3.1 Genetic and epigenetic influences

Family, twin and genome-wide association studies have estimated that 40-71% and 24-66% of variation in FVC and FEV_1/FVC, respectively, is due to genetic factors [11, 126, 171, 240, 365]. However, genetic studies have failed to identify polymorphisms that might wholly explain this variation. For FVC, a recent genome-wide association study identified eight loci, of which two were previously known, that explain 1.8% of the variation in FVC [204]. For FEV_1/FVC, multiple loci have been discovered although these explain only 3.2% of variation in FEV_1/FVC [266, 300, 359].

In addition, it has been suggested that intergenerational epigenetic factors may influence adult ventilatory function. Epigenetic factors act upon genes by regulating their expression, that is switching genes on and off [156]. Two studies have reported an increased risk of asthma in grandchildren if the grandmother smoked during the pregnancy of the children's mother regardless of the mother's own smoking status [198, 207]. A similar analysis conducted in the Avon Longitudinal Study of Parents and Children (ALSPAC) did not find an increased asthma risk among the grandchildren if grandmothers smoked during the pregnancy of the grandchildren's parents. The ALSPAC authors did however find a sex-specific association. A higher risk was observed, only among

girls, when the fathers were exposed to grandmaternal smoking and when the mother did not smoke [219]. It has been suggested that these transgenerational factors could be a result of gene methylation that, in turn, might affect ventilatory function [37, 245, 264].

2.3.2 Weight in early life

Low birth weight, an important marker of intrauterine development, has been associated with reduced ventilatory function in later life during both childhood and adulthood, but results are somewhat conflicting. In younger children, FVC and FEV_1 appear to be positively associated with birth weight, whereas for older children weaker evidence was observed [9, 38, 59, 216, 272]. For adults, a meta-analysis found an association of birth weight with FEV_1 and some studies have also reported an association with FVC [14, 54, 193, 309]. Reports of the relation of birth weight to FEV_1/FVC are inconsistent: FEV_1/FVC was found to be significantly lower in low birth weight boys [216], while one study in adulthood did not find an association [309] and another study did, although only in women [54].

Barker et al. [14] suggested that weight at one year of life could also be a strong predictor of ventilatory function in adulthood. His underlying hypothesis was that early infections associated with poverty would cause poor growth in the first 12 months of life, which in turn would predispose to later chronic lung disease [18]. In the Hertfordshire cohort, increased weight at one year was associated with higher FVC and FEV_1 in adulthood [14] whereas in a Finnish study only a positive association between weight gain in the first year and FVC was reported [54]. Thus not only the prenatal environment but also the early postnatal environment could be of importance for later ventilatory function.

2.3.3 Gestational age

Gestational age is the time, which the offspring spends in the womb of the mother. Birth will normally occur between the 37th and 43rd week of gestation, while births before and after that period are defined as preterm and late term births, respectively [28].

Preterm birth is associated with poor ventilatory function in later life. A recent systematic review and meta-analysis showed that preterm birth was related to reduced FEV_1 in later childhood and adulthood [177]. However, being born prematurely has been further classified in extremely preterm (≤28 weeks' gestational age), very preterm (29-32 weeks) and late preterm (33-36 weeks) [28]. In children age 8-9, being born extremely to very (25-32 weeks) and late (33-34 weeks) preterm resulted in lower FVC and FEV_1/FVC compared to being born at term (37-43 weeks) whereas being born near term (35-36 weeks gestation) resulted in similar ventilatory function as controls born at term [175]. The influence of prematurity persists into adolescence and adulthood, with preterm adolescents and adults having lower ventilatory function compared to controls born at term [281, 347, 348]. However, distinguishing the effect of low birth weight and gestational age is complex, as gestational age is tightly coupled with birth weight. Low birth weight can be the result of poor intrauterine growth or, despite normal growth, being born prematurely (i.e. having small lungs) or both being premature and having failed to develop normally [28, 250]. Moreover, perinatal events, such as potential treatment damage from ventilation or respiratory infections, might either hinder catch-up growth or interfere with further development of the small or immature ventilatory system [28, 250].

2.3.4 Parental smoking

Studies of the effects of parental smoking have focused on maternal smoking during pregnancy, which is associated with poor ventilatory function in childhood [110, 139,

227, 315] and adulthood [133, 326], but postnatal parental smoking in early life also adversely affects later ventilatory function [227, 326]. In animal models, in utero exposure to tobacco smoke affects lung growth and lung development [188, 282], with studies in mice showing changes in lung tissues similar to those observed in some preterm infants and mediated through nicotine acetylcholine receptors in the fetal lung [298, 363]. Xiao et al. [364] also found that nicotine exposure in pregnant mice resulted in poor lung function and lung development in the offspring, and they discovered elevated concentrations of inflammatory markers in mice exposed to nicotine prenatally compared with mice either not exposed or exposed after birth. Another mechanism by which tobacco smoke could affect lung development and ventilatory function is dysregulated cytokine production. It has been suggested that maternal smoking may interfere with the regulation of cytokine production in the fetus, resulting in increased inflammation which could result in poor subsequent lung function and lung development [206]. The findings from animal models strongly support the associations found in epidemiological studies and suggest that maternal smoking could indeed affect ventilatory function. However, the potential molecular mechanism remains unclear.

2.3.5 Parental socio-economic status

Socio-economic status (SES) is a complex construct, associated with occupation, education and income, and historically assessed by the father's occupational status. Other assessments that combine both parents' SES or select the highest SES from either parent have since been employed. However, the relative importance of father's and mother's SES remains unresolved [132, 210].

In respiratory research both paternal and maternal SES have been investigated as have a wide range of occupational, educational or income variables. Moreover, research has focused on the relation between poor adult SES and reduced adult ventilatory function [43, 50, 66, 297, 307]. Recently, more studies have examined the relation of child-

hood socio-economic factors and later ventilatory function. Lawlor et al. [190] examined the association between childhood SES and FEV_1 and FVC in elderly women. Childhood poverty was related with poor FEV_1 and FVC in later life and the associations persisted after adjustment for adult SES and smoking [190]. Jackson et al. [149] complemented the work by Lawlor and coworkers by examining the effect of low childhood SES on ventilatory function among young adults, aged 18 to 30 years. They reported that childhood deprivation was associated with lower ventilatory function at baseline and earlier onset of ventilatory function decline, while adjusting for adult SES and smoking [149]. Bartley et al. [20] attempted to ascertain the effect of childhood SES (between birth and age 11) on ventilatory function in mid adulthood (age 44-46), while trying to elucidate the mediating variables. They confirmed the effect of low childhood SES on FEV_1 in midlife and showed that the association was largely mediated by poor housing in childhood [20]. Ramsay et al. [259] further expanded the evidence by showing that low childhood SES was associated with higher decline in FEV_1 and FVC in adulthood, although the effect estimates were attenuated after adjustment for adult SES and smoking. An association between childhood poverty and low ventilatory function in childhood was also described [107, 258]. Although these studies did not specifically investigate the role of the prenatal SES, the combined evidence is suggestive of an effect of deprivation in early life on later ventilatory function that persists across the life course.

2.3.6 Maternal nutrition

Limited availability of maternal nutrients during pregnancy has resulted in poor lung development and lung function of offspring in rats and guinea pigs [97, 115, 163, 194]. Epidemiological findings from the Dutch Winter Hunger study show that reduced caloric intake by mothers during pregnancy was associated with later cardiovascular and doctor diagnosed obstructive airways disease in the offspring [203, 263]. On the other hand, the study, which recruited participants that were (1) exposed in utero to the Dutch famine in

1945, (2) born just prior to the famine and (3) conceived immediately after the famine, did not show that reduced caloric intake was associated with poor ventilatory function in the adult offspring [203].

Devereux et al. [82] investigated the relation of maternal vitamin E, plasma α-tocopherol and zinc during pregnancy with respiratory disease in children at age five years. They found that reduced maternal vitamin E and zinc during pregnancy was associated with a higher risk of wheeze and asthma while reduced α-tocopherol was associated with lower FEV_1 [82]. Moreover, Shaheen et al. [294] found that a processed diet in pregnancy, which mainly included meat, sausages, fast food, crisps, eggs and baked beans, was associated with reduced FVC in the offspring at age 8-9 years in a group of children born in and around Bristol in the 1990s. Evidence from the same cohort study has also shown that reduced maternal iron status was associated with reduced ventilatory function and increased risk of wheeze and atopy of the offspring at age 10 years [231]. Two randomized control trials have been conducted to evaluate the effect of nutrient supplementation in pregnancy on ventilatory function in the offspring in Nepal. One showed that offspring of pregnant mothers who were given vitamin A supplementation had significantly higher FVC and FEV_1 at age 9 to 13 years compared to children in the placebo group [62]. Contrastingly, the other trial found no difference in ventilatory function among children aged 8.5 years when pregnant mothers were administered multivitamin supplementation, which consisted of several vitamins and other nutrients albeit at a lower dose than the former trial, compared to only iron and folic acid supplements [80].

2.3.7 Other early life risk factors

Other early life risk factors have also been suggested to influence later ventilatory function, though they have been less frequently studied.

First, air pollutants have emerged as a potential early life risk factor [84, 167]. Two

recent studies investigated the role of prenatal and postnatal exposure, in the first year of life, to traffic-related air pollutants on later ventilatory function. Schultz et al. [291] reported that exposure in the first year of life was associated with reduced FEV_1 at age 16, regardless of pre- and postnatal maternal smoking exposure. Morales et al. [224] found that prenatal exposure to traffic-related air pollutants was associated with lower FEV_1 in children (mean age of 4.5 years). Second, respiratory infections in early childhood have been suggested to influence later ventilatory function [125]. Some studies have reported an association of respiratory infection with reduced FEV_1 and FVC in later life [83, 157, 202] while other studies could not find any association [122, 211], suggesting that the issue remains unresolved. Finally, other components of maternal health status, such as maternal atopy, hypertension or diabetes, use of medications and history of miscarriage, have been implicated as influencing the offspring's later ventilatory function [81, 280, 315].

2.3.8 Summary

Several early life risk factors are associated with later ventilatory function, with some of the most commonly investigated being weight in early life, gestational age, parental smoking, parental SES and maternal nutrition. Other factors, such as exposure to air pollution, childhood respiratory infections and maternal health status, have also been suggested to influence later ventilatory function.

Although the evidence from epidemiological studies is increasingly supportive of the role of early life influences on later ventilatory function and, as a direct consequence, respiratory health, the biological pathways by which these early life factors have a life-long impact on the respiratory system are largely unknown and are only now being described. This is further complicated by the fact that early life factors interact with one another. For example, parental smoking in early life is associated with both later ventilatory function and low birth weight, which, in turn, is also associated with reduced

ventilatory function in later life. Hayatbakhsh et al. [133] showed that the effect of maternal smoking on later FEV_1 was not completely mediated through low birth weight. This suggested that parental smoking affects later ventilatory function not only through low birth weight but also via other pathways, which is likely to hold true for other early life factors.

2.4 Relation between ventilatory and cardiometabolic function

Poor ventilatory function has been associated with an increased risk of cardiovascular [2, 290] and metabolic conditions [93, 102]. Common risk factors are shared between cardiometabolic diseases and poor ventilatory function or respiratory disease. However, the relation of ventilatory function with cardiometabolic markers persists when taking these common factors into account [94, 196, 304]. Therefore, alternative hypotheses have attempted to explain the observed associations. This section summarises the available evidence on two possible explanations of the relation of ventilatory function with cardiometabolic markers: (1) the systemic inflammation hypothesis, whereby this relation is mediated by systemic inflammation, which is associated with both poor ventilatory function and cardiometabolic markers, and (2) the fetal origins hypothesis, whereby factors in early life, again associated with both ventilatory function and cardiometabolic markers, explain the relation.

However, one important factor that should be taken into account when investigating the relation of ventilatory function with cardiometabolic markers is obesity. Obesity is associated with low FVC and high FEV1/FVC [68, 308] as well as with increased systematic inflammation [91, 346] and with increased risk of cardiovascular disease [75, 166, 201, 229, 274] and type II diabetes [58, 75, 173]. Therefore, obesity itself may explain some of the associations of ventilatory function and cardiometabolic markers.

2.4.1 Systemic inflammation

Systemic inflammation, is inferred from a heightened concentration of inflammatory markers in blood or serum, has been commonly assessed by measuring acute phase proteins, such as C-reactive protein or fibrinogen in blood [73, 249]. Inflammatory markers are elevated in individuals with cardiovascular disease [92, 123, 244, 267], type II diabetes [21, 89, 244, 351] and poor ventilatory function [10, 113, 215], as well as many other acute and chronic conditions. Hence it has been postulated that systemic inflammation might explain the observed co-occurrence of the diseases [19].

However, the relation of systemic inflammation with ventilatory function has been the subject of ongoing debate. Population-based cross-sectional studies confirmed the association of C-reactive protein, fibrinogen, white blood cell count and other inflammatory markers, with FVC or FEV_1, independent of smoking [10, 113, 215]. On the other hand, other cross-sectional studies, among adolescents, adults and the elderly, found no association between C-reactive protein and FEV_1/FVC, while increased fibrinogen concentration has been associated with reduced FEV_1/FVC in adults [113, 154, 232]. A longitudinal study by Rasmussen et al. [262] found a higher C-reactive protein concentration at age 20 associated with decline in FEV_1 and FVC among 1,000 Danes aged between 20 and 29 years, after taking the effects of smoking into account. Among middle-aged adults, C-reactive protein and fibrinogen concentration were associated with a decline in both FEV_1 and FVC between 5 and 20 years from the baseline measurements of the study [161]. Gimeno et al. [112] confirmed these findings in the Whitehall II study, where both C-reactive protein and interleukin six at baseline were predictive of a greater decline in FEV_1 and FVC at 12 years follow-up, after adjusting for adult smoking and socioeconomic factors.

Nonetheless, other studies have been unable to replicate the temporal association between systemic inflammation and FVC or FEV_1. Fogarty et al. [101] found that middle-

aged adults with low FVC or FEV_1 had increased concentration of C-reactive protein at baseline, but found no association between baseline C-reactive protein and decline in either FVC or FEV_1 . Similarly, in adolescents, increased C-reactive protein concentration at age 14 was not associated with lower growth in FVC or FEV_1 between 14 and 20 years [232]. The absence of temporal associations between inflammatory markers and ventilatory function has been confirmed in a large study of over 18,000 adult participants: cross-sectionally C-reactive protein was inversely associated with FVC and FEV_1 but baseline concentration of C-reactive protein were not associated with longitudinal changes in either ventilatory marker [3]. This lack of temporal associations for C-reactive protein was also observed for the relation with FEV_1/FVC [154] .

This evidence from the above studies appears to suggest a cross-sectional relation between systemic inflammation and FVC or FEV_1 while the effect of inflammatory markers on ventilatory function decline does not appear sufficiently supported by the current evidence. FEV_1/FVC has not been frequently studied but findings suggest a cross-sectional association with fibrinogen rather than C-reactive protein.

Recent Mendelian randomization studies have indicated that the observed association of C-reactive protein with ventilatory function or COPD may not be causal. Mendelian randomization is a technique whereby information on genes is leveraged to avoid the potential confounding of findings from observational studies. An individual's genes are randomly acquired from their parents and, if associated with an exposure of interest, can be used as an unconfounded proxy for this exposure. A strong assumption of Mendelian randomization studies is that the genes must only affect the outcome through the exposure of interest and not through any other exposures [44, 74]. Two studies employed Mendelian randomization to assess the causality of the relation between C-reactive protein and ventilatory function or respiratory disease. Both studies found that the genetic variants of C-reactive protein were not associated with the ventilatory function or respiratory disease and that therefore the association was unlikely to be causal [27, 72].

Similarly, a large genetic consortium found no association of C-reactive protein with coronary heart disease [51].

In summary, some observational studies show an association of inflammation with reduced ventilatory function, thus supporting the hypothesis that systemic inflammation might explain the relation between poor ventilatory function and cardiovascular disease or type II diabetes. However, the inconsistent evidence for ventilatory function, combined with recent Mendelian randomization studies assessing the association of C-reactive protein with FVC and with coronary heart disease suggest that this association is not causal. Nonetheless, relatively few markers of inflammation have been investigated, and other inflammatory markers might explain the relation between ventilatory function and cardiovascular disease or type II diabetes.

2.4.2 Fetal origins hypothesis

The fetal origins hypothesis, championed by David Barker and often termed the Barker hypothesis, postulates that influences during early life may program an individual, and that this programming could lead to disease in later life [15]. Barker and coworkers primarily focused on cardiovascular disease and type II diabetes in later life [13, 17, 218, 237, 238, 263] but also, to a lesser extent, investigated the relation with ventilatory function and respiratory disease [14, 203, 309].

Barker and Osmond [18] first reported a geographical relation between high childhood mortality from bronchitis and pneumonia and mortality in adulthood, at least 30 years later, from chronic lung disease. They subsequently showed that increased birth weight and weight at one year were positively associated with FVC and FEV_1 [14]. Thus, not only the early postnatal environment (respiratory infection or weight gain) but also the prenatal environment (birth weight) was thought to influence later respiratory health. As the critical period encompassed both pre-and postnatal events, the term “fetal origins hypothesis” was inadequate and it is now generally referred to as the

"developmental origins of health and disease hypothesis" [16, 350].

Meta-analyses have shown that increased birth weight is associated with a lower risk of cardiovascular disease and type II diabetes. A one kilogram increase in birth weight has been associated with a 16% reduced risk of developing ischemic heart disease [146] and a 25% reduced risk of type II diabetes [354]. Conflicting results have been reported for the association of birth weight and later ventilatory function, but it appears that birth weight is associated with FVC while less evidence supports a relation of birth weight with FEV_1/FVC (see section 2.3.2). Barker postulated that during periods of poor nutritional availability, the fetus would prioritise nutrient flow to certain organs, thereby disadvantaging the development of others [124]. Animal studies confirmed that insults during the fetal period resulted in reduced ventilatory function and lung development [162, 325].

Several criticisms have been levelled at these conclusions [178, 186, 241, 323]. First, some of the earlier studies in support of Barker's theory had relatively large loss to follow-up, substantial number of missing data and insufficient number of variables to control for confounding. Subsequent studies addressed these issues, but residual confounding remains a persistent problem. Observing an association does not imply causality and, unless confounding variables are sufficiently taken into account, the association might not reflect a causal association. Some of the potential confounders are readily collected, in particular those in adult life. Unfortunately, several confounding factors, which are believed to be important to adjust for, refer to early life. For example, parental factors, such as health status, educational level, occupation, diet, physical activity, smoking, in particular maternal smoking during pregnancy, were not commonly available or have not been adequately ascertained. This is, in part, due to not collecting this information in cohort studies, potential bias in assessing prenatal factors in historical cohort studies and potential recall bias in case-control studies.

2.4.3 Summary

Poor ventilatory function is associated with cardiometabolic markers that are strongly related to cardiovascular disease and type II diabetes. This association persists after taking common adult risk factors into account, and therefore two alternative hypotheses have emerged with factors that might explain the observed relation: (1) systemic inflammation, associated with both poor ventilatory function and cardiometabolic disease, or (2) a common association of ventilatory function and cardio-metabolic disease with birth weight or prenatal factors.

2.5 Elucidating ethnic disparities in ventilatory function

Historically, race was associated with fixed biological characteristics that were inherited and perceived to be immutable. With time, many observed that the associations of race were strongly determined by a shared culture, which led to a redefinition in terms of ethnicity. Throughout this thesis the term ethnicity will be employed as it includes an individual's social and cultural environment in contrast to race, which is largely based on physical characteristics and has historically implied a hierarchy among races [34].

Ethnic disparities in ventilatory function are well recognized. For example, in the United States of America (USA), African and Hispanic Americans, have lower FVC and higher FEV_1/FVC in childhood and adulthood compared to White Americans [23, 47, 114, 130, 169, 302]. Similarly, in the United Kingdom (UK), South Asian British and Black Caribbean/African British, have lower FVC and greater FEV_1/FVC compared to White British individuals across the life course [142, 319, 357]. Nonetheless, ethnic differences in ventilatory function have, to date, not been fully explained. A systematic review by Braun et al. [35] examined how the differences in ventilatory function were explained, and found that only 6% examined socio-economic status as a potential explanatory factor. Moreover, 24% of studies did not provide any explanation for the observed differ-

ence while 22% cited inherent differences as an explanation. However, more than half of the studies provided either anthropometric differences (30%) or environmental differences (23%) as explanation [35].

Explanatory studies have focused on elucidating the ethnic differences in FVC and FEV_1. The difference in FEV_1/FVC between ethnic groups is very small and, as such, has largely been ignored. Therefore, in the following subsections, when reviewing the potential anthropometric, environmental or genetic explanatory factors, FEV_1/FVC will be rarely mentioned.

2.5.1 Anthropometric differences

Differences in ventilatory function between ethnic groups persist after adjustment for height, age and sex. Attempts to explain these differences based on anthropometric differences between ethnic groups have mostly focused on a difference in sitting height or a difference in the ratio of sitting to standing height (also termed leg to trunk ratio).

In a study population of young never-smoking adults, Jacobs et al. [150] attempted to explain the difference in FVC between African Americans and White Americans by differences in body proportions. They employed five anthropometric variables for body proportions: standing height, sitting height, leg length, elbow length, measured from the joint of the elbow to the wrist, and shoulder width, the length between the acromial processes. Standing and sitting height were lower in African Americans, whereas leg height, elbow length and shoulder width were lower in White Americans. Adjusting FVC for four body size variables (sitting height, leg length, elbow breadth and shoulder width) rather than height resulted in a higher percentage of variation in FVC explained in both ethnicities (around 40%). However, despite the improved percentage of variance explained in FVC, after adjustment for sitting height, leg length, elbow breadth and shoulder width rather than for height, the difference in FVC between African Americans and White Americans was only reduced marginally [150]. In young Asian American and

White American adults, sitting height also did not explain the difference in FVC although no difference in sitting to standing height ratio between the ethnic groups was observed [174]. Whittaker et al. [358] conducted similar research in Asian British and White British children, and found that ethnic differences in FVC or FEV_1 were not explained by differences in chest size, measured by chest height, circumference, antero-posterior and transverse diameters.

On the other hand, in the National Health and Nutrition Examination Survey (NHANES) the difference in FVC between African and White American children and nonsmoking adults was partially explained by sitting height. The percentage of the ethnic difference in FVC explained by sitting height was 16% in NHANES II [292] and 37% and 39% for women and men, respectively, in NHANES III [130]. Moreover, in 1,800 children of Hispanic, African and White American ethnicity, sitting height explained the difference in FVC fully [144]. The Determinants of Adolescent Social well-being and Health (DASH) study in the UK, which recruited 2,560 British children aged 11-13 of White, Black (Black Caribbean or Black African) and South Asian (Indian or Pakistani/Bangladeshi) ethnicity, reported lower sitting height, lower FVC and higher FEV_1/FVC for Black British and South Asian British compared to White British. In line with the NHANES findings, the DASH study found that adjusting for sitting height reduced the difference in FVC between White British and Black British or White British and South Asian British children by 25-30% and 40-50%, respectively [357]. Lower sitting height compared to standing height (i.e. having relatively longer legs) has thus been found in some studies to explain the difference in ventilatory function. However, an interesting conundrum is that while relatively longer legs, and a relatively shorter thorax, are thought to negatively affect respiratory outcomes; for cardiovascular outcomes, commonly prevalent as comorbidity for those with poor ventilatory function, relatively longer legs are associated with improved outcomes [119, 192, 288, 356].

Body mass index (BMI) has been evaluated as a potential explanatory factor, al-

though BMI was only assessed after adjusting for sitting height (i.e. BMI was always mutually adjusted for sitting height). In both children and adults, in the UK and USA, BMI contributed only marginally, if at all, to further explaining the difference in FVC between the observed ethnic groups [130, 292, 357].

Although numerous anthropometric variables have been proposed, none of the suggested body measurements has fully explained the difference in ventilatory function. One reason why sitting height or other anthropometric variables do not fully explain the ethnic difference may be that they are an imperfect proxy for thoracic size. However, more detailed adjustment for body size only marginally explained the difference in FVC between White American and African Americans [150] and did not explain the difference in FVC between Asian British and White British children [358] . Therefore, other factors are (at least) partially responsible for the difference in ventilatory function.

2.5.2 Environmental differences

Poverty is an important determinant of poor ventilatory function (see subsection 2.3.5) and all other ethnic groups have lower income, educational or socio-economic status compared to White British or American individuals [353, 360, 361], which contributes to ethnic disparities in respiratory health [212, 332, 345].

Harik-Khan et al. [130] investigated 2,326 adults of White and African American ethnicity in the NHANES III survey, and found that African Americans had lower FVC, higher FEV_1/FVC, lower educational status and higher rates of poverty (based on family income) compared to White Americans. Low educational status was associated with reduced FVC in men and women. Among women, poverty was also associated with lower FVC, whereas in men, poverty was not (in African American) or only weakly (in White American) associated with FVC. An attempt to explain the difference in FVC between White and African Americans using poverty or educational status was only made after adjusting for sitting height (i.e. poverty or educational status were mutually adjusted

for sitting height). Thus environmental differences as explanatory factor were only assessed after anthropometric differences were accounted for. In women, poverty and educational status explained 12% and 3%, respectively, whereas in men 4% and 7% of the ethnic difference in FVC was explained by poverty and educational status, respectively, compared to the model with sitting height [130].

In the UK DASH study, among 2,560 children aged 11 to 13 years, Black Caribbean British, Black African British, Indian British or Pakistani/Bangladeshi British children were more disadvantaged, with the exception of Indian British girls, and more likely to live in overcrowded households, except for Black Caribbean British boys, compared to White British children. Similarly to the NHANES III findings, the effect of socio-economic factors on reducing ethnic inequality in FVC was only evaluated after adjusting for sitting height, immigration status (born in/out of the UK) and exposure to tobacco smoke. Further adjusting for socio-economic factors reduced the difference in FVC between the ethnic groups, from 3 to 11% for boys and from 7 to 19% for girls [357]. Another UK study of 1,363 White British and South Asian British children aged 9 to 14 years similarly reported lower socio-economic status among South Asian British compared to White British children, but found that socio-economic factors (parental education, single parenthood, Townsend deprivation score and crowding) reduced the difference in FVC only minimally (by 2%) [319].

The UK study of 1,363 children by Strippoli et al. [319] also investigated other potential explanatory factors that might explain the ethnic difference in ventilatory function: (1) cultural factors (mother's country of birth, language and religion), (2) intrauterine growth (birth weight and gestational age), (3) environmental exposures (pre- and postnatal tobacco exposure, breastfeeding, cooking, heating, number of older siblings, early child care, pets), and (4) personal or family history of wheeze (frequency of wheeze,, doctor diagnosis of asthma, shortness of breath asthma treatment parental history of asthma, parental history of hay fever). However, none of these factors explained the

difference in FVC between White and South Asian British children [319].

Birth weight is another important potential factor because it is associated with later ventilatory function (see subsection 2.3.2) and is significantly lower among all ethnic minorities compared with whites [104, 165, 209, 226, 331]. However, Strippoli et al. [319] did not find any explanatory effect of birth weight on the difference in FVC in a population of White and South Asian British children. Similarly, a cohort study in Brazil, which employed genetically defined African ancestry in lieu of self-identified ethnic/racial categories, did not find that birth weight explained or substantially reduced the difference in FVC [217].

2.5.3 Genetic differences

In biomedical science a debate exists about how to interpret differences in health outcomes between ethnic groups. One view emphasizes the common culture and history that define the different groups. The contrasting view emphasizes the genetic differences between ethnic groups [195], arguing that there is substantial genetic variation between ethnic groups which allows for self-identified racial and ethnic categories to cluster with specific genetic polymorphisms [42, 268].

In contrast to the latter view, genomic studies have shown that ethnicity is a poor proxy for genetic homogeneity and that genetic clustering by ethnic groups has been exaggerated [33]. In particular, genetic diversity is larger within, rather than between, ethnic groups [271, 273, 310]. To overcome the crude approximations of earlier studies, researchers have moved away from attributing genetic homogeneity to crude ethnic phenotypes towards an analysis based on genetic markers indicating ancestry.

Kumar et al. [181] first reported an ancestry-based analysis to explain the difference in ventilatory function among African Americans, for whom they determined the percentage of African ancestry based on ancestry informative markers. One percent increase in African ancestry was associated with a reduction of 12 and 5mL in FVC in men

and women, respectively [181]. Kumar et al. [180] also evaluated the relation of ancestry in a multi-ethnic population of White, African American and Hispanic individuals with recurrent wheezing, in which they reported a positive association of African ancestry with recurrent wheeze. Brehm et al. [36] replicated the ancestry-based analysis in Puerto Rican children with and without asthma born in the USA and in Puerto Rico and showed that the negative association between African ancestry and ventilatory function (FVC and FEV_1) persist after adjustment for socio-economic factors. Recently Menezes et al. [217] examined the association of African ancestry in a population of Brazilian young adults and reported a difference in ventilatory function (FVC and FEV_1) by African ancestry. However, the difference in ventilatory function was halved after adjustment for sitting height, but further adjustment for a wide range of social and early life factors did not markedly affect the difference [217].

Ancestry-based analysis has also received criticism [285], much of which is similar to the critique of the idea that ethnicity implies genetic homogeneity. Although African ancestry, based on genetic markers, is associated with reduced ventilatory function, to date no ancestry related polymorphism has been associated with ventilatory function. Moreover, the reference markers used for genetic ancestry analysis are based on selected populations with limited sample size, which do not necessarily reflect the wide diversity within ethnic groups. The issue of spurious associations between specific polymorphisms and outcome of interests is not novel and well recognized in genetic epidemiology, which is why, in genetic association studies, cases and controls are usually stratified by ancestry, termed population stratification [170, 349]. The stratification reduces the chance of mistaking any association with an outcome of interest with a specific gene as a causal association, when it is simply a non-causal association arising because one population is at higher risk for the outcome for entirely other reasons. For instance, ethnic minorities have lower ventilatory function and thus any genes more common among these minorities will be more associated with poor ventilatory function independent of

any specific genetic effect [170, 349]. Population stratification is designed to adjust for unmeasured differences in lifestyle and environmental factors when examining genetic associations. Association of ancestry genes with an outcome is not, therefore, an indication of a genetic cause unless the outcome is also associated with a specific gene. Finally, attributing the residual difference in ventilatory function, after adjustment for anthropometric and social factors, to ethnicity or to "inherent" differences between ethnic groups does not account for the many other unmeasured or poorly measured environmental factors that were not considered in the analysis [33, 70, 87, 164].

2.5.4 Migration studies

Migration studies, which are studies that include recently migrated participants and participants with a migration ancestry, may clarify some questions related to the ethnic difference in ventilatory function and the role of genetics or environmental factors. Unfortunately, few such studies have been performed.

Fulambarker et al. [105] investigated the difference in ventilatory function among adult USA-born and immigrant Asian Indians who were healthy lifelong nonsmokers. USA-born Asian Americans were taller and had higher FVC, FEV_1 and FEV_1/FVC, after adjusting for height and age, compared to immigrant Asian Indians, but both groups had similar socio-economic status, suggesting that the difference in ventilatory function might still be the result of (early life) environmental factors [105].

On the other hand, in a UK study of 275 South Asian British children, Kuehni et al. [179] investigated the role of the migratory background of the children's mothers, which they classified into UK-born and immigrant mothers, on the ventilatory function of the children. UK-born mother's offspring did not have larger FVC or FEV_1 than children of immigrant mothers. There was also no difference in FEV_1/FVC, birth weight or age-adjusted height between both groups. However, children from UK-born vs. immigrant mothers had a higher socio-economic status. If higher socio-economic status had a pos-

itive effect on ventilatory function, then children of UK-born mothers would have shown higher ventilatory function compared to children of immigrant mothers. The authors argued, however, that the difference in socio-economic status might have been too small and the generational effects, with only two generations considered, potentially not sufficient to show a positive effect on ventilatory function in their small study [179].

Another children's study recently compared the ventilatory function of South Asian British children in London with those of children in urban, semiurban and rural areas in Karnataka, India. South Asian British children in London had higher FVC and FEV_1 compared to children in India, while no difference was observed in FEV_1/FVC [301]. However, further stratification by place of residence revealed no difference in FVC and FEV_1 between South Asian British children in London and urban Indian children, while urban Indian children did have significantly higher FVC and FEV_1 compared to semiurban and rural Indian children. This difference between urban and rural Indian children was slightly reduced, but not fully explained, after adjustment for weight, BMI, tobacco and biomass smoke exposure and children's socio-economic status, which according to the authors suggested that other environmental factors might be responsible for this difference [301].

2.5.5 Summary

Ethnic differences in FVC and FEV_1 are well established, while the difference in FEV_1/FVC between ethnic groups is very small. However, over 45% of studies identified in a systematic review did not attempt to explain the differences or attributed them to inherent differences between the ethnic groups. Genetic, anthropometric and environmental factors have been investigated as potential explanatory factors. Although some studies have reported that anthropometric or environmental factors could explain some of the ethnic variation in ventilatory function, the findings have not been consistently replicated. Attributing the difference in ventilatory function to genetic differences is the

subject of debate, and equating ethnicity to genetic homogeneity has been criticized as going beyond the current evidence. Migration studies could resolve questions regarding the role of genetic and environmental factors but only a handful of these exist.

CHAPTER 3

WEIGHT IN EARLY LIFE AND VENTILATORY FUNCTION IN LATER LIFE: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 Aim and objectives

The overall aim of this chapter is to summarise currently available evidence, from epidemiological studies of any design, on the relationship of birth weight, weight at one year and weight gain in the first year of life with ventilatory function in later life in the general population.

The specific objectives are to:

1. Quantify the relation of birth weight, weight at one year and weight gain in the first year of life with FVC and FEV_1/FVC in children.
2. Assess the relation of birth weight, weight at one year and weight gain in the first year of life with FVC and FEV_1/FVC in adults.
3. Evaluate the heterogeneity across studies of the relation of birth weight, weight at one year and weight gain in the first year of life with (a) FVC and FEV_1/FVC in children and (b) FVC and FEV_1/FVC in adults.

3.2 Methods

I devised the protocol of the the systematic review, identified the studies, extracted the data and performed the meta-analyses, under the supervision of Dr. Cosetta Minelli and Prof. Peter Burney. Jaymini Patel acted as the duplicate data extractor and as second reviewer for the screening of articles and cross-checking of references.

All methods used for study identification, data extraction and meta-analysis were conducted using a strict methodology specified a priori in a detailed protocol, and reporting followed the guidelines from the MOOSE statement [320].

3.2.1 Search strategy and inclusion criteria

Studies were considered for inclusion if they were population-based and assessed the association between birth weight, weight at one year or weight gain in the first year of life, and FVC or FEV_1/FVC in the general population. Studies were excluded if participants were selected based on their gestational age or presence of bronchopulmonary dysplasia.

Three electronic databases, MEDLINE, EMBASE and Web of Science, were searched on the 27th of January 2015 for population-based epidemiological studies of any design in humans without date or language restriction. Search terms were organised in two blocks: (1) for the exposure, terms related to birth weight, weight at one year and weight gain were used, and (2) for the outcome, terms related to airflow obstruction, FVC, FEV_1 and spirometry were included. In MEDLINE and EMBASE, both free text and controlled vocabulary were used, whereas in Web of Science only free text searching was available (Table A.1 and Figure A.1).

Articles were initially screened for inclusion based on title and abstract by myself, with full text retrieved whenever in doubt. Editorials and commentaries, case reports and reviews were excluded, as well as conference abstracts. A random sample of 100 articles was screened independently by a second reviewer, who identified no omitted articles that should have been included. Identification of further studies through cross-checking of references from included articles and related reviews was performed in duplicate.

3.2.2 Data extraction

Data were extracted in duplicate using a pre-piloted data extraction form (Table A.2). Differences in extracted data were discussed and resolved through consensus and, if necessary, through discussion with Dr. Cosetta Minelli. All studies were in English, with

the exception of one study in Mandarin Chinese, which was translated by a colleague who is a Chinese native speaker.

Data extraction covered the study characteristics (year of publication, study design, study country), study population (size, ethnicity, age, inclusion and exclusion criteria, proportion of male participants, height range, availability and range of gestational age, reporting of bronchopulmonary dysplasia, response rate), weight in early life exposures (which exposures were considered in the study, units of exposure and exposure assessment), ventilatory function outcomes (which outcomes were considered in the study, units of the outcome and assessment of the outcome), statistical analysis (type of analysis, adjustment for covariates, stratified and sensitivity analyses, adjustment for multiple comparisons, sample size and power calculation) and study findings.

3.2.3 Risk of bias

After reviewing the potential tools available for assessment of study quality and risk of bias [283, 312] the studies included were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) [352] after modifying it to fit the research question addressed by this systematic review (Table A.3). In particular, the NOS for cohort studies was modified by (1) removing the question related to the demonstration that the outcome of interest was not present at the start of the study as this does not apply to ventilatory function, (2) the question related to the comparability of cohorts was modified to ensure that the studies controlled for important confounders, (3) the question on the assessment of the outcome was altered to reflect the assessment of spirometry according to American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines at the time of the study, and (4) follow-up was considered adequate if ≥ 70%. Low risk of bias was defined as a NOS score >6, moderate risk between 4 and 6, and high risk <4, consistent with the original NOS [79, 86, 324].

3.2.4 Statistical analysis

Whenever possible study results were translated into differences in mL of FVC and % FEV_1/FVC per kg increase in, for continuous exposures, and per category of, for categorical exposures, birth weight, weight at one year or weight gain in the first year.

For studies that analysed the exposure as a continuous variable (e.g. birth weight, weight at one year or weight in the first year of life, in kg) and used linear regression, the regression coefficient and standard errors were extracted. Ventilatory function expressed as difference in percent of predicted per kg difference in any continuous exposure could not be transformed to either a difference in mL (for FVC) or difference of percentage (for FEV_1/FVC) and were therefore not synthesised. Whenever results from different regression models were reported, data was used from a model adjusted for age, height and sex if available, or from a model judged as similar as possible to this.

For studies that used a categorical exposure (e.g., low vs. normal birth weight), the mean difference in ventilatory function between the two groups and its standard error were extracted (or calculated). In the presence of more than two groups, the exposure was dichotomized to make it consistent across studies. The standardised mean difference (SMD), a unitless measure which is derived as the difference in outcome between the groups divided by the standard deviation (SD) of the outcome was calculated for each study and used for synthesis of results whenever the outcome of at least one study could not be transformed to mL or percent, for FVC and FEV_1/FVC respectively.

In two studies, Lercher and Schmitzberger [197] and Wjst et al. [362], reporting of results was incomplete. In particular, the number of participants in the low and normal birth weight groups who had successfully completed ventilatory function testing was not reported, and this number was derived based on the participants in the original cohort, assuming equal numbers of lost to follow-up for ventilatory function in both groups.

Study estimates were synthesised separately for children and adults and by exposure (continuous or binary) using inverse-variance weighted meta-analysis. The use of a random-effects model was decided a priori to allow for some between-study heterogeneity unless there were fewer than five studies, in which case fixed-effects models were used. The magnitude of the between-study heterogeneity was estimated using the I^2 statistic, which represents the percentage of variation in effect size between studies that is due to heterogeneity rather than chance [137]. Study estimates were not synthesised if the I^2 was higher than 50%, although these results are presented as a secondary analysis.

A priori subgroup analyses by age and country, high- versus low- to middle-income countries (defined using the World Bank classification [333]), as well as sensitivity analyses with exclusion of studies at high risk of bias (NOS score<4) were performed whenever possible. The possibility of reporting bias was assessed using funnel plots. All analyses were performed in Stata 13.1 (StataCorp, LP, College Station, TX, USA) and statistical significance was defined at a p-value threshold of <0.05.

3.3 Results

3.3.1 Inclusion and exclusion of studies

This systematic review identified 1,063 studies from MEDLINE, EMBASE and Web of Science (Figure 3.1). After removal of duplicates from the three databases, 718 records were screened and 71 full-text articles were assessed for eligibility, which included one study identified through cross-checking of references. A total number of 43 studies were included in the review, of which 30 were included in the meta-analysis. Of these 43 studies, 25 were conducted in children and 18 in adults. Reasons for exclusions are reported in Figure 3.1.

All studies reported associations for FVC, but only 7 and 10, in children and adults respectively, also reported FEV_1/FVC. One of the studies in adults reported results from two different study populations [236] and other studies only reported results separately for males and females [54, 88, 131, 256, 309, 321, 341] (Table 3.1). Therefore, the total number of comparisons included in the review was 27 for FVC and 7 for FEV_1/FVC among children (Figure 3.2) and 24 for FVC and 14 for FEV_1/FVC among adults (Figure 3.3). Weight at one year and weight gain in the first year of life were assessed only in three studies while birth weight was investigated in all studies.

Table 3.1: *Reporting of association with FVC or FEV_1/FVC for studies in children and adults*

	Adults		Children	
Number of studies that	FVC	FEV_1/FVC	FVC	FEV_1/FVC
Did not report association by sex	12	6	23	7
Reported association by sex	5	4	2	0
Included two study populations	1	0	0	0
Overall number of studies	18	10	25	7

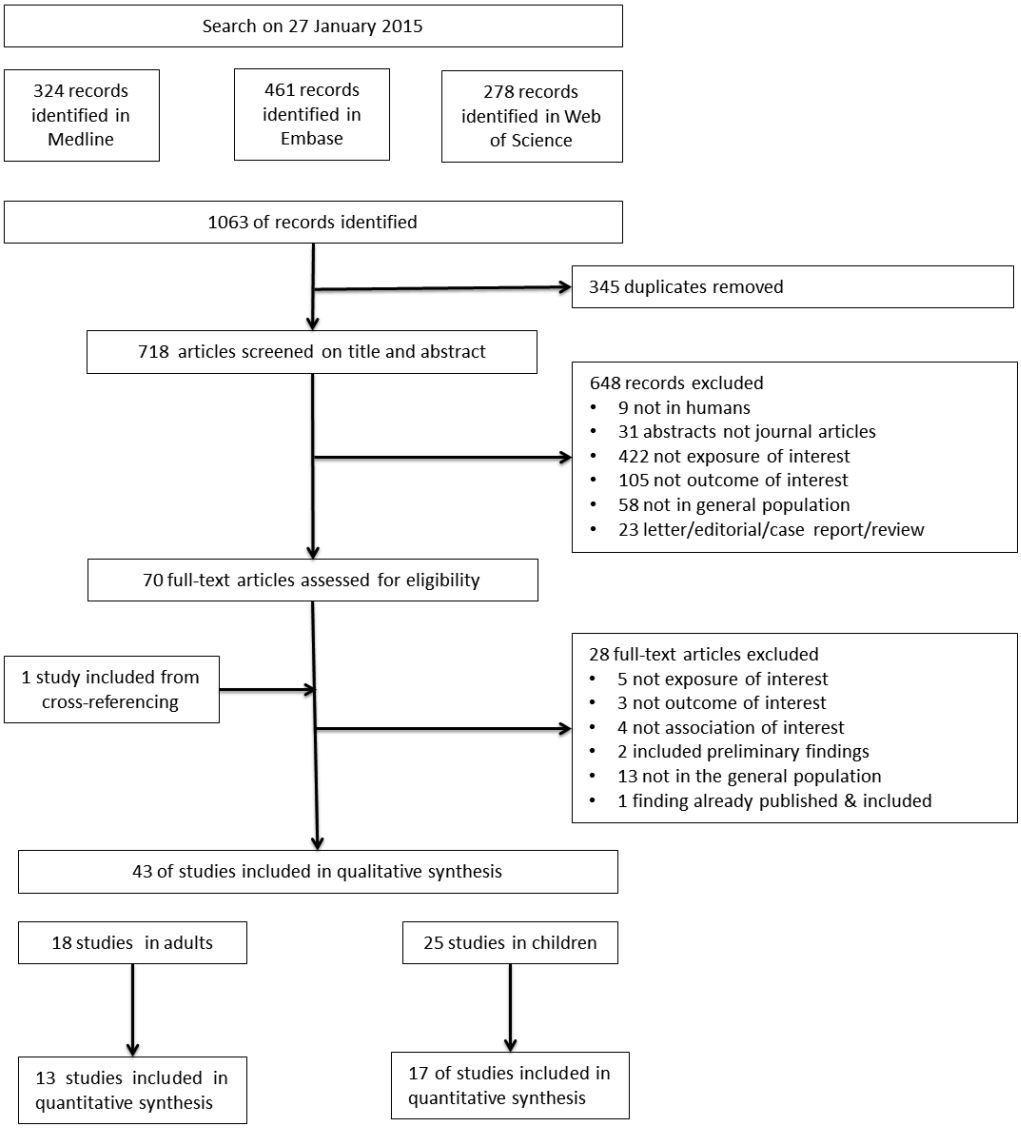


Figure 3.1: *Flow chart of inclusion of studies in the systematic review.*

Figure 3.2: *Flow chart of inclusion of studies in childhood in the meta-analyses for FVC and FEV_1/FVC.*

Figure 3.3: *Flow chart of inclusion of studies in adulthood in the meta-analyses for FVC and FEV_1/FVC.*

3.3.2 Characteristics of the studies included

Characteristic of the studies in childhood are reported in Table 3.2. Birth weight was commonly categorised into low and normal birth weight groups, with the average birth weight ranging from 1.2 to 3.7 kg. Participants were aged from 6 months to 16 years, while the majority of studies consisted of participants aged between 5 to 12 years. FVC and FEV_1/FVC were expressed in litres, percent predicted or as standard deviation scores. FVC varied from 1.1 to 3.6 L and FEV_1/FVC ranged from 84.7 to 96.0 %. The majority of studies were conducted in high-income countries, with only six studies from low to middle income countries (Bulgaria, China, India, Tunisia and Turkey). Sixteen studies provided information on gestational age, although some only reported whether infants were premature.

Table 3.3 details the study characteristics of studies in adulthood. The average birth weight was above 3.0 kg in all studies and varied between 3.1 and 3.6 kg, except for the study from South India [309], where the average was 2.8 kg. Participants' average age lay between 18 and 58 years at the time ventilatory function was measured, with nine studies having a population younger than 40 years and nine studies with a population older than 40 years. The average FVC varied from 2.7 to 5.0 L and FEV_1/FVC ranged from 73.0 to 88.6 %. Studies with older participants had lower average FVC but not always lower FEV_1/FVC compared to studies with younger individuals. Most studies were conducted in high-income countries, with only four studies from low to middle income countries (China, Brazil and India). Gestational age was poorly reported, with only eight studies providing any information; in these studies, only a small number of preterm births were present.

Table 3.2: Characteristics of the 25 childhood studies included. Age, birth weight, gestational age, FVC and FEV_1/FVC are shown as mean and standard deviation (SD); when these were unavailable, median, absolute range (Range) or interquartile range (IQR) were reported instead, as specified in the table; BW: birth weight; NBW: normal birth weight.

Author, year	**Country** (Ethnicity)	**Study population**	**Sample size**	**Age** (yrs)	**Sex** (% male)	**Birth weight** (kg)	**Gestational age** (weeks)	**FVC** (L)	**FEV_1/FVC** (%)
Chandler, 1979 [60]	Australia (aboriginal)	Children from an Aboriginal settlement recruited at school	126	Range: 5-13	52.0[4]	-	-	77.8 (12.4)[1,2]	106.4 (7.8)[1,2]
Chan, 1989 [59]	United Kingdom (White, Asian and Afro -Caribbean)	Newborns born in two London hospitals with BW between 0.5-2.0 kg and a group of age-matched local school children with BW >2.0 kg	250	7.0 (0.3)[1]	-	Low BW: < 2.0 Controls: > 2.0	-	Low BW: 1.4 (0.2) Controls: 1.4 (0.2)[5]	-
Baraldi 1991 [12]	Italy	Newborns with birth weight <1.501 kg born in a hospital and a group of healthy age, sex, height and weight matched term born controls	41	9.8 (1.9)[1]	40.0	Low BW: 1.3 (0.1) Controls: 3.2 (0.2)	Low BW: 32.1 (3.0) Controls: 39.9 (0.6)	Low BW: 92.8 (8.1)[2,4]	-
Tammela, 1991 [327]	Finland	Children with birth weight <1751g, and a paired control of the same age and sex with normal BW from the same class at school	100	Range: 8-10		Low BW: 1.4 Controls: 3.7	Low BW: 32.1 Controls: 40.0	Low BW: 88.5 (11.6)[2] Controls: 92.9 (12.1)[2]	Low BW: 84.7 (6.1) Controls: 86.5 (5.6)
Rona, 1993 [272]	England & Scotland	Annual survey of children selected by stratified random sampling of employment exchange areas with proportionally more children from poorer social groups	2,036	Range: 5-11	-	-	>37 weeks[3]	-	-
Matthes, 1995 [213]	United Kingdom	Participants from Cardiff Birth Survey, cases (BW <2.5kg) and controls (BW: 3.0. -3.8 kg) Cases and controls matched for sex, age, parity, gestational age and hospital	326	15.7 (0.8)[1]	38.7	Low BW: 2.3; Controls: 3.3	≥38 weeks[3]	LBW: 3.2 (0.7) NBW: 3.6 (0.7)	-
McLeod, 1996 [216]	Scotland	Newborns with birth weight <1.5kg born in 1982 and two same sex classroom controls	864	8.8 (0.4)[1]	48.0	-	-	Low BW: 1.8 Controls: 1.9[5]	-
Demissie, 1997 [76]	Canada	School children in Montreal, with a class from each school of age 5-7, age 8-9 and age 10-13	300	Range: 5-13	49.94	3.2 (0.6)	-	-	-
Lercher, 1997 [197]	Austria	Children of second, third and fourth grade from traffic dense and poor communities	644	9.3 (0.9)	-	Low BW: 2.1 (0.3) Controls: 3.4 (0.4)	24.4%[3]	Low BW: 2.0 (0.3) Controls: 2.1 (0.3)[5]	-

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Table 3.2 – continued from previous page

Author, year	**Country**	**Study population**	**Sample size**	**Age** (yrs)	**Sex** (% male)	**Birth weight** (kg)	**Gestational age** (weeks)	**FVC** (L)	**FEV_1/FVC** (%)
Schraeder, 1998 [289]	USA (Black or White)	Newborns from 4 nurseries with birth weight ≤1.5kg and age, gender, race, birth order and parental socio-economic status matched NBW children who were recruited at age 5yrs from the same school or census tract	75	10.81	42.7	Low BW: 1.2 Controls:>2.5	-	Low BW: 85.0 (19)[1,2] Controls: 84.7 (20.8)[1,2]	Low BW: 88.0 (4)[1] Controls: 90.3 (9.3)[1]
Wjst, 1998 [362]	Germany (Caucasian)	School children from two towns and from a subset of schools in a third town	2,470[4]	Range: 5-14	51.5[4]	-	Not preterm[3]	Low BW: 1.6 (1.4) Controls: 2.1 (1.4)	-
Tan, 2001 [329]	China	Newborns with birth weight <2.5 kg and ethnicity, age and sex matched controls with BW >2.5 kg who were recruited from primary schools	70	Range: 6-9	51.4	Low BW: 2.2 (0.3) Controls: 3.2 (0.3)	LBW: 37 (2.0) Controls: 38 (2.0)	Low BW: 1.4 (0.3) Controls: 1.6 (0.3)	Low BW: 95.0 (7) Controls: 96.0 (6)
Harik-Khan, 2004 [131]	USA (White or African American)	Asymptomatic nonsmoking children age 8-17 yrs who participated in NHANES III, a survey conducted between 1988-94	1,462	12.1 (2.6)[1]	52.8	3.3 (0.9) [1]	-	2.8 (0.9)[1]	87.7 (6.0)[1]
Hoo, 2004 [141]	England	Newborns born in 2 London hospitals with BW <10th (low BW group) or >20th centile (controls group) and were born to mothers who did not smoke pre-or postnatally	80	6-9 months	55.0	Low BW: 2.8 (0.3) Controls: 3.5 (0.3)	Low BW: 40.3 (1.0) Controls: 40.0 (1.4)	Low BW: 0.32 (0.06)[6] Controls: 0.35 (0.07)[6]	-
Joseph-Bowen, 2004 [159]	Australia (White, other, aboriginal)	Pregnant mothers and their unborn babies were recruited from antenatal clinics at a Perth Hospital	1,735	5.9 (0.2)	51.5	-	9.9%[3]	1.2 (0.2)	94.0 (7.0)
Mandadzhieva, 2005 [208]	Bulgaria (Romany & Bulgarian)	Fourth and Fifth grade pupils from a primaryschool in Plovdiv, South Bulgaria	124	10.5 (0.5)[4]	52.4	3.3 (0.5)[1]	-	2.6 (0.4)[1,4]	88.4 (5.6)[1,4]
Bucens, 2006 [39]	Australia (Aboriginal)	Newborns born in a hospital were recruited between 1987-90	417	11.6 (1.2)[4]	52.7[4]	3.0 (0.6)[4]	38.8 (2.0)[4]	Median: 2.2 IQR: 1.8-2.6	-
Bostanci, 2008 [30]	Turkey	Newborns with BW <2.5kg born in an Ankara hospital between 1993-94 and a group of age and sex matched term born controls with birth weight >2.5kg	54	8.6 (0.6)[1]	50.0	Low BW: 2.3 (0.1) Controls: 3.5 (0.4)	>38 weeks[3]	Low BW: 86.7 (7.5)[2] Controls: 92.9 (11.6)[2]	Low BW: 89.8 (5.9)[2] Controls: 92.6 (5.0)[2]

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Table 3.2 – continued from previous page

Author, year	**Country**	**Study population**	**Sample size**	**Age** (yrs)	**Sex** (% male)	**Birth weight** (kg)	**Gestational age** (weeks)	**FVC** (L)	**FEV_1/FVC** (%)
Trabelsi, 2008 [338]	Tunisia	Participants randomly selected from 10 elementary and secondary schools	756	Range: 6-16	48.7	3.4 (0.5)[1]	>37 weeks[3]	2.3 (0.7)[1]	87.3 (6.2)[1]
Jindal, 2009 [155]	India	Age-matched participants born in nursing homes located in the vicinity of the research institution	70	14.1 (1.4)[1]	100	Low BW: 2.1 (0.4) Controls: 3.5 (0.4)	-	Low BW: 2.7 (0.7) Controls: 2.8 (0.8)	-
Qi-Quang, 2009 [256]	China	Grade 3 and 4 primary school children from schools in three districts in the Guangzhou province	1,599	10.0 (0.7)[4]	50.3	3.4 (0.8)[4]	Low BW: 12%[3] Controls: 3.9%[3]	Low BW: -0.3 (0.4)[6] Controls: -0.4 (0.4)[6]	-
Jedrychowski, 2010 [153]	Poland	Pregnant non-smoking women, aged 18-35 and their unborn babies were recruited from prenatal clinics	176	5.1 (0.1)	49.4	3.4 (0.42)	39.5 (1.2)	1.1 (0.2)	-
Kotecha, 2010 [176]	United Kingdom	Pregnant women with estimated delivery between 1991-92 were recruited in the county of Avon	576	Range: 8-9	49.3[1]	Low BW: 2.8 (0.3) Controls: 3.5 (0.3)	Low BW: 39.7 (1.2) Controls: 39.8 (1.3)	Low BW: -0.11 (1.0)[6] Controls: 0.03 (1.0)[6]	-
Turner, 2011 [339]	Scotland	Mothers and their unborn babies, born between 1997-99, were recruited from antenatal clinics	393	10.0	51.04	3.5 (0.5)[4]	-	-	-
Brew, 2012 [38]	Australia	Pregnant mothers and their unborn babies recruited between Sept 1997 and Nov 1999 from 2 Sydney hospitals	418	8.0	49.9[4]	3.5 (0.5)[4]	39.6 (1.3)[4]	-	-

[1] Value not reported in the paper but estimates obtained by combining subgroups.
[2] Value reported as percent predicted. Reference equation by Polgar and Promadhat [253] used for Baraldi et al. [12], reference equation by European Respiratory Society [96] used for Bostanci et al. [30], reference equation by Polgar and Promadhat [253] used for Chandler and Dugdale [60], reference equation by Knudson et al. [172] and Hsu et al. [145] used for Schraeder et al. [289] and reference equation by Zapletal et al. [368] used for Tammela et al. [327].
[3] For Joseph-Bowen et al. [159], Lercher and Schmitzberger [197], Qi-qiang et al. [256], only the percentage of preterm births reported with preterm births defined as gestational age <37 weeks. Bostanci et al. [30], Matthes et al. [213], Rona et al. [272], Trabelsi et al. [338] reported whether all participants were above a certain gestational age and Wjst et al. [362] used self-reported prematurity and defined prematurity as being born more than 3 weeks before the due date.
[4]The value refers to the original cohort rather than the subset that performed lung function testing, for which the association with weight in early life was assessed.
For Baraldi et al. [12] the value refers to only the very low birth weight children (n=15) as the information was not available for the whole cohort or the controls.
[5] FVC adjusted for height Chan et al. [59], McLeod et al. [216] or for age, height and weight Lercher and Schmitzberger [197].
[6] Value reported as standard deviation or z-score.

Table 3.3: Characteristics of the 18 adult studies included. Age, birth weight, gestational age, FVC and FEV_1/FVC are shown as mean and standard deviation (SD); when these were unavailable, median, absolute range (Range) or interquartile range (IQR) were reported instead, as specified in the table; BW: birth weight

Author, year	**Country**	**Study population**	**Sample size**	**Age** (yrs)	**Sex** (% male)	**Birth weight** (kg)	**Gestational age** (weeks)	**FVC** (L)	**FEV_1/FVC** (%)
Barker, 1991 [14]	England	Men born in Hertfordshire, England in 1911-30	639	Range: 59-67	100	-	-	3.0 (0.7)[1]	-
Stein, 1997 [309]	India	Subjects born in hospital in 1934-53; identified via house-to-house visits within a radius of hospital	286	47 (4.6)	66	2.8 (0.4)	-	2.7 (0.4)[1]	79.5 (8.5)[1]
Shaheen, 1998 [293]	Scotland	Follow-up study in 1985-86 of children who lived in St Andrews or the Fife or Tayside regions	239	58 (4.3)	53	3.4 (0.6)	-	3.7 (1.0)[3]	-
Lopuhaa, 2000 [203]	Netherlands	Born in hospital in 1943-47; traced and invited for spirometry	733	29 (6.4) [2]	46[2]	3.3 (0.5)[2]	-	4.3 (0.7)[1]	73.0 (11)[1]
Cheung, 2001 [64]	China	Birth cohort in two Hong Kong hospitals in 1967	120	30	49	3.1, range: 2.3-4.1	-	3.8 (0.5)[1,3]	88.6 (6.2)[1,3]
Boezen, 2002 [25]	Netherlands	Random sample of newborns in 1975-78 at hospital	590	20 (0.9)[2]	45	3.3 (0.6)[2]	Median: 40 Range: 28-44	-	-
Edwards, 2003 [88]	Scotland	Follow-up of random community sample of 1 in 5 children who attended school in Aberdeen in 1964	323	48 (1.5)	51	3.3 (0.5)	40.3 (1.7)	-	-
Laerum, 2004 [182]	Denmark, Norway, Iceland, Sweden, Estonia	Random subsample of subjects who had competed screening questionnaire	1,494	Range: 20-47[2]	53	3.5[2]	3.2%[5]	104.7 (13.4)[4]	-
Lawlor, 2005 [193]	United Kingdom	Women randomly selected from 23 British towns between 1999 and 2001	2,257	Range: 60-79	0	3.3 (0.8)	-	-	-
Lima, 2005 [199]	Brazil	All newborns born in 1982 in Pelotas; follow-up in 2000 on all <2.5kg and on two random controls (BW ≥ 2.5kg)	354	18 (0.3)	100	3.0 (0.7)[3]	38.7 (3.3)[3]	4.9 (0.1)[3]	-
Canoy, 2007 [54]	Finland	Birth cohort of individuals born in Northern Finland in 1966	5,39	31	50	3.5 (0.5)	40.3 (1.5)	4.7 (0.7)	84.1 (6.5)
Orfei-1, 2008 [236]	Great Britain	All British children born 1 week in March 1946. At first follow-up a stratified subsample by socio-economic status selected	2,167	43	-	3.4 (0.5)[3]	-	3.7 (0.9)[3]	-
Orfei-2, 2008 [236]	Great Britain	All British children born during 1 week in March 1958 and complemented with immigrants born during the same week	5,947	Range: 44-45	-	3.4 (0.5)[3]	-	4.2 (1.0)[3]	-

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Table 3.3 – continued from previous page

Author, year	**Country**	**Study population**	**Sample size**	**Age** (yrs)	**Sex** (% male)	**Birth weight** (kg)	**Gestational age** (weeks)	**FVC** (L)	**FEV_1/FVC** (%)
Ubilla, 2008 [341]	Chile	Participants randomly selected from those born in the hospital in Limache in 1974-78; follow-up conducted in 2001-03	1,221	Median: 25	45	3.2 (0.5)	-	4.0 (0.5)	87.0 (4.6)
Hancox, 2009 [127]	New Zealand	Birth cohort, born in 1972-73 in a hospital and those living Otago at age 3 invited for follow-up	921	32	53	3.4 (0.5)[3]	4.0%[5]	5.0 (0.7)[3]	78.2 (6.5)[3]
Odberg, 2010 [234]	Norway	All non-handicapped low BW children (<2.0kg) born in 1986-88 and controls (BW>3.0kg)	269	19	54	-	32.2 (3.3)[5]	115.6 (14.2)[3,4]	83.5 (12.3)[3]
Pei, 2010 [247]	China	Born in Hospital in 1948-54, traced if living in Beijing to attend a physical examination in 1995-96	627	45 (1.4)[3]	49	3.1 (0.4)[3]	40 (2.0)[2,3]	3.5 (0.7)[3]	-
Sherrill, 2011 [296]	USA	Healthy newborns enrolled between 1980-84 if parents used a health organisation in Tucson with follow-up	127	22	55	3.6 (0.5)	-	-	-
Suresh, 2012 [321]	Australia	Pregnant women in 1981-83 and their offspring; both followed after up 21 years	2,368	21	50	3.4 (0.5)	-	4.6 (0.7)	-

[1] FVC or FEV_1/FVC adjusted for height and age (Barker et al. [14], Stein et al. [309]), for sex, height and smoking (Cheung et al. [64]) or for sex height and age (Lopuhaä et al. [203]).
[2] The value refers to the original cohort rather than the subset that performed lung function testing, for which the association with weight in early life was assessed. Except for Pei et al. [247], where the information was only available for 611 participants.
[3] Value not reported in the paper but estimates obtained by combining subgroups.
[4] Value reported as percent predicted. Reference equation by European Respiratory Society [95] used for Lærum et al. [182] and reference equation by Quanjer et al. [257] used for Odberg et al. [234].
[5] For Hancox et al. [127] and Lærum et al. [182], only the percentage of preterm births reported. Preterm birth defined as gestational age<37 weeks for Hancox et al. [127] and gestational age<36 weeks for Lærum et al. [182]. For Odberg et al. [234], the mean and standard deviation were only reported for low birth weight participants.

Seventeen of 25 studies in children and 17 of 18 studies in adulthood were either prospective cohort studies where birth weight was obtained in real time or retrospective cohort studies where birth weight was obtained from hospital records. Among adult studies, only Lawlor et al. [193] concurrently measured self-reported birth weight and ventilatory function. Three childhood studies [76, 208, 272] obtained birth weight from parents' self-reporting in studies among children while three other childhood studies [12, 327, 329] that did not provide any information on how birth weight was obtained, were conducted in a local hospital, which suggests that birth weight might have been obtained from hospital records.

Birth weight and ventilatory function were evaluated differently across studies. Birth weight was expressed either as a continuous or as a binary exposure; as a binary exposure, the threshold of 2.5 kg was mostly used, although some comparisons employed other cut-offs (Table A.4 and A.5). FVC was analysed in litres (or mL), in percent predicted or in a standard deviation score while FEV_1/FVC was predominantly expressed in percent though two comparisons used percent predicted (Table A.4 and A.5).

The associations between outcome and exposure were commonly adjusted for different confounders across studies. All different confounders considered in the comparisons, regardless of whether adjustments were made one by one or simultaneously are shown in Table A.6 (children) and Table A.7 (adults). In children, only three comparisons did not adjust the association with FVC for any anthropometric factor and most adjusted for at least one. In adults all comparisons, except one [247], adjusted for age, height and sex, and several also adjusted for adult smoking and adult socio-economic or educational status. However, adjustment for other factors, either childhood factors at examination or prenatal factors, was rare. The association of birth weight with FEV_1/FVC was seldom adjusted in children: less than half of the comparisons adjusted for any anthropometric factor and adjustment for other factors was only observed in two comparisons. Contrastingly, in adults, most comparisons were adjusted for adult anthropometry al-

though adjustment for other adult or prenatal factors was poor. The adjustments used in those models from which the results were extracted are reported in Table A.8 (children) and A.9 (adults) for FVC, and in Table A.10 (children) and A.11 (adults) for FEV_1/FVC.

3.3.3 Association of birth weight with ventilatory function

Birth weight and FVC

For the meta-analyses, nine and six comparisons were excluded, in children and adults respectively, with reasons for reported in Figures 3.2 and 3.3. This resulted in 18 comparisons for both children and adults.

Only two comparisons in children in the meta-analysis evaluated birth weight as a continuous exposure and both comparisons showed a statistically significant positive association with FVC. The combined estimate was an increase of 77.5 mL (95% confidence interval (CI): 37.8 to 117.1 mL, p<0.001) per kg increase in birth weight, with no evidence of between-study heterogeneity (I^2: 0%, p= 0.7) (Figure 3.4a). FVC in children was also higher in normal vs. low birth weight groups in all but 3/18 comparisons. The SMD between normal and low birth weight was 0.23 (95% CI: 0.13 to 0.32, p<0.001; I^2: 47.7%, p= 0.018) (Figure 3.4b). This estimate would relate to a difference of 86 mL (95% CI: 48.8 to 120.0 mL) between normal and low birth weight if a standard deviation of 375 mL was assumed, as reported in McLeod et al. [216].

In the meta-analysis of adult comparisons with birth weight as continuous exposure, the combined estimate was a 59.4 (95%CI: 43.3 to 75.5 mL, p<0.001) mL increase per kg increase in birth weight, with no evidence of between-study heterogeneity (I^2: 0%, p=0.5) (Figure 3.5a). A higher FVC was observed in normal vs. low birth weight groups, the SMD between normal and low birth weight was 0.13 (95% CI: 0.001 to 0.26, p=0.048; I^2: 3.8%, p= 0.4) (Figure 3.5b). This would correspond to a difference of 77 mL (95% CI: 0.6 to 154.0 mL) between normal and low birth weight if we assumed an FVC standard

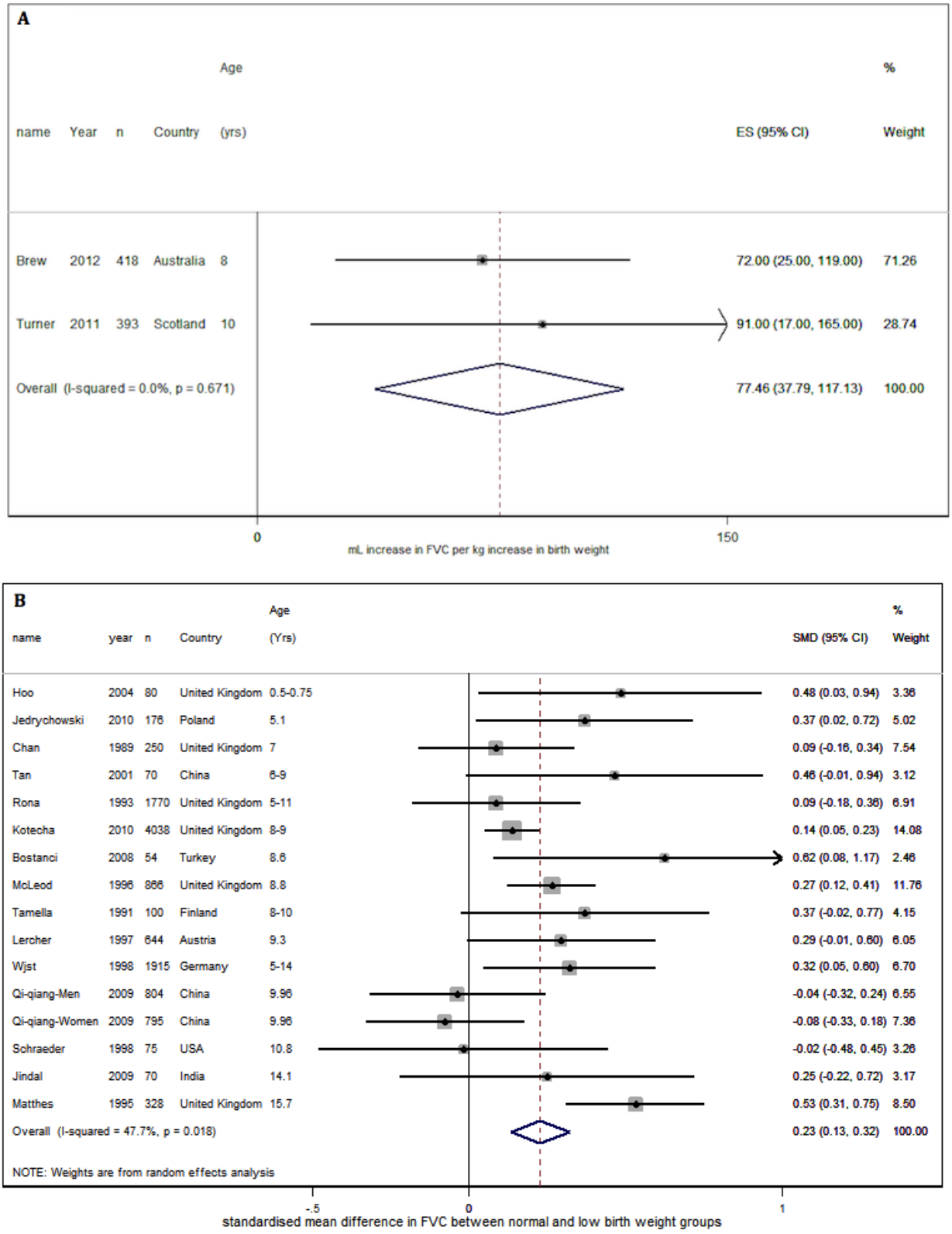


Figure 3.4: *Forest plot for FVC with birth weight in children. A) Birth weight as continuous exposure (2 studies, 2 comparisons); B) Birth weight as binary exposure (above/below 2.5 kg) (15 studies, 16 comparisons). Study estimates were ordered by increasing age. Some associations were reported by sex. Matthes et al. [213] defined birth weight as below 2.5 kg and above 3.0 kg.*

deviation of 592 mL, as reported in the study [199] with the largest weight in the meta-analysis.

Subgroup analysis by age in children was only possible among comparisons with birth weight as a binary exposure as those with birth weight as a continuous exposure were of similar age (Figure 3.2). There was no evidence of a difference (p=0.2) in the association of birth weight with FVC between younger (5-12 yrs) vs older (12-18 yrs) children (Figure A.2). Among adults, subgroup analysis by age (≥ 40 vs <40 years) suggested a smaller effect estimate for older compared to younger individuals for the effect of birth weight as a continuous exposure, p=0.037 (Figure A.3a). For birth weight as a binary exposure among adults, the trend was in the opposite direction, with no apparent effect on FVC for young individuals (based on three studies, two including in 18-19 year olds), p=0.038 (Figure A.3b).

Subgroup analyses by country level income could not be conducted for any comparisons with birth weight as a continuous exposure, in either children or adults, as all studies were conducted in high-income countries (Figures 3.2 and 3.3). Among comparisons with birth weight as a binary exposure, the effect estimates in children from low to middle income countries showed moderate between study heterogeneity (I^2=55.0%, p=0.06) and thus results were not synthesized in the main analysis. A secondary analysis reported a combined estimate of 0.17 (95% CI: -0.08 to 0.42), which was not markedly different (p=0.5) from the combined estimate for children in high income countries (Figure A.4). All studies with birth weight as binary exposure in adulthood, but one [234], were from low- to middle-income countries. For the meta-analysis, results did not change significantly (p=0.69) when excluding the high-income country study [234], 0.17 (95% CI: 0.02 to 0.32) compared with 0.13 (95% CI: 0.001 to 0.26) in the main analysis.

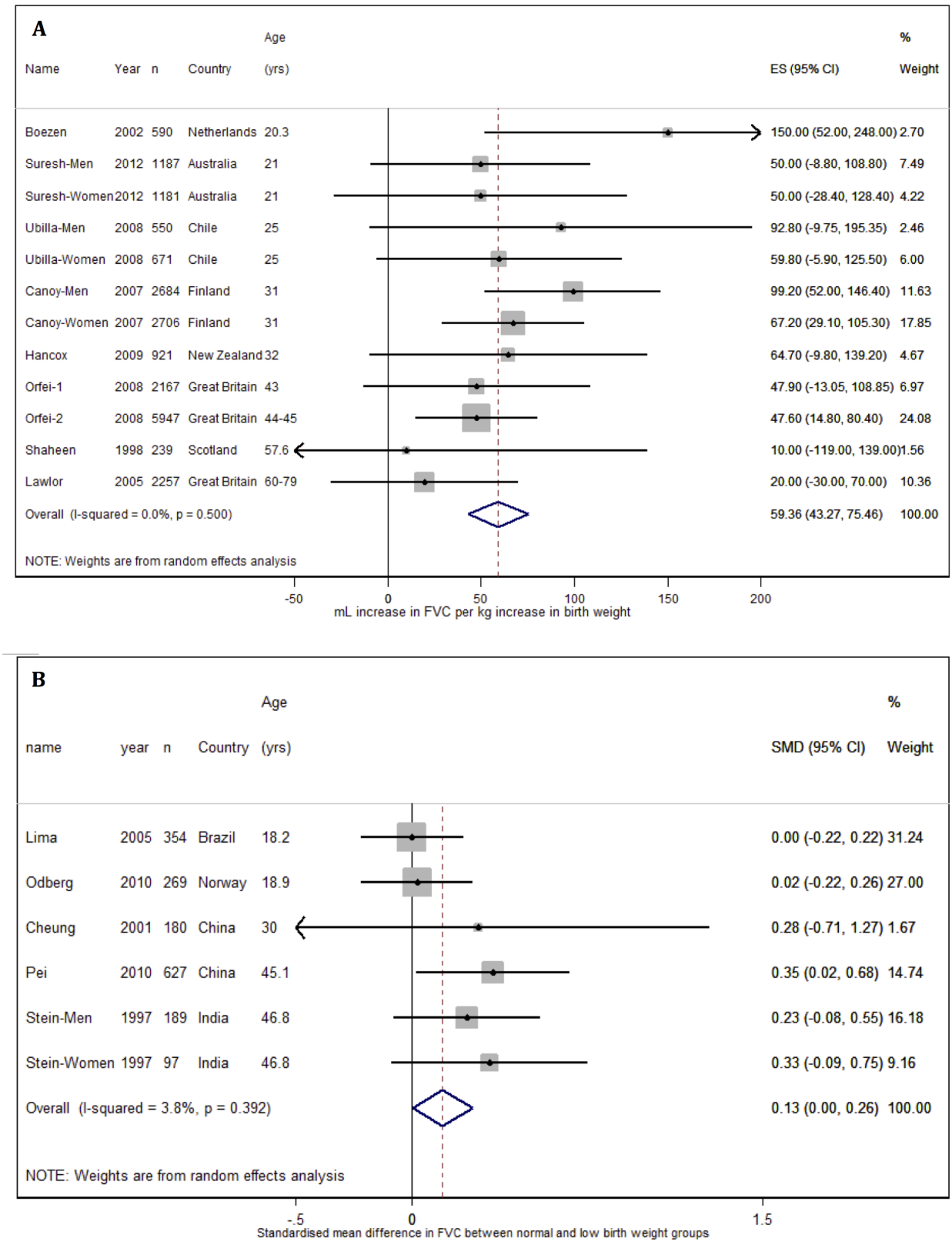


Figure 3.5: *Forest plot for FVC with birth weight in adults. A) Birth weight as continuous exposure (9 studies, 12 comparisons); B) Birth weight as binary exposure (above/below 2.5 kg) (5 studies, 6 comparisons). Study estimates were ordered by increasing age. Some associations were reported by sex and Orfei et al. [236] included two different study populations. Odberg et al. [234] defined birth weight as below 2.5 kg and above 3.0 kg.*

Birth weight and FEV_1/FVC

For the meta-analyses of FEV_1/FVC, three and four comparisons were excluded, for children and adults, respectively, resulting in four childhood and ten adult comparisons included in the meta-analyses, with reasons reported in Figures 3.2 and 3.3.

In children, meta-analysis of comparisons of birth weight as a continuous exposure with FEV_1/FVC was not possible as only one study [76] examined the relation, which showed a non-statistically significant positive association. FEV_1/FVC was higher in normal vs low birth weight groups, although the difference was not statistically significant for any comparison. Combining the effect estimates resulted in a combined SMD of 0.31 (95% CI: 0.08 to 0.54, p=0.009; I^2: 0%, p= 0.8) (Figure 3.6). By using the standard deviation (5.9%) from the study with the largest weight in the meta-analysis [327], this would relate to an increase of 1.8% (95% CI: 0.47 to 3.2 %) for normal vs. low birth weight.

In adults, with birth weight as a continuous exposure, 4/5 comparisons showed a positive association whereas 1/5 comparison found a negative relation. There was evidence of moderate between-study heterogeneity (I^2: 55%, p= 0.06) and therefore results were not synthesized in the main analysis (Figure 3.7a). A meta-analysis performed as a secondary analysis showed no association of birth weight with FEV_1/FVC (0.09 % increase in FEV_1/FVC per kg increase; 95% CI: -0.37 to 0.54 %, p=0.7). However, no between-study heterogeneity was observed for comparisons in adulthood with birth weight as a binary exposure (I^2: 0%, p=0.67) and the meta-analysis showed a statistically significant positive association, with a SMD of 0.21 (95% CI: 0.06 to 0.36, p=0.007) (Figure 3.7b), which corresponds to an increase of 1.9 % (95% CI: 0.5 to 3.2 %) for normal vs. low birth weight if a standard deviation of 8.87% for FEV_1/FVC was assumed, as reported in Stein et al. [309].

All childhood comparisons were obtained from studies with children of similar age while all comparisons of adults with birth weight as continuous exposure contained adults younger than 40 years. Therefore, subgroup analysis by age was only possible

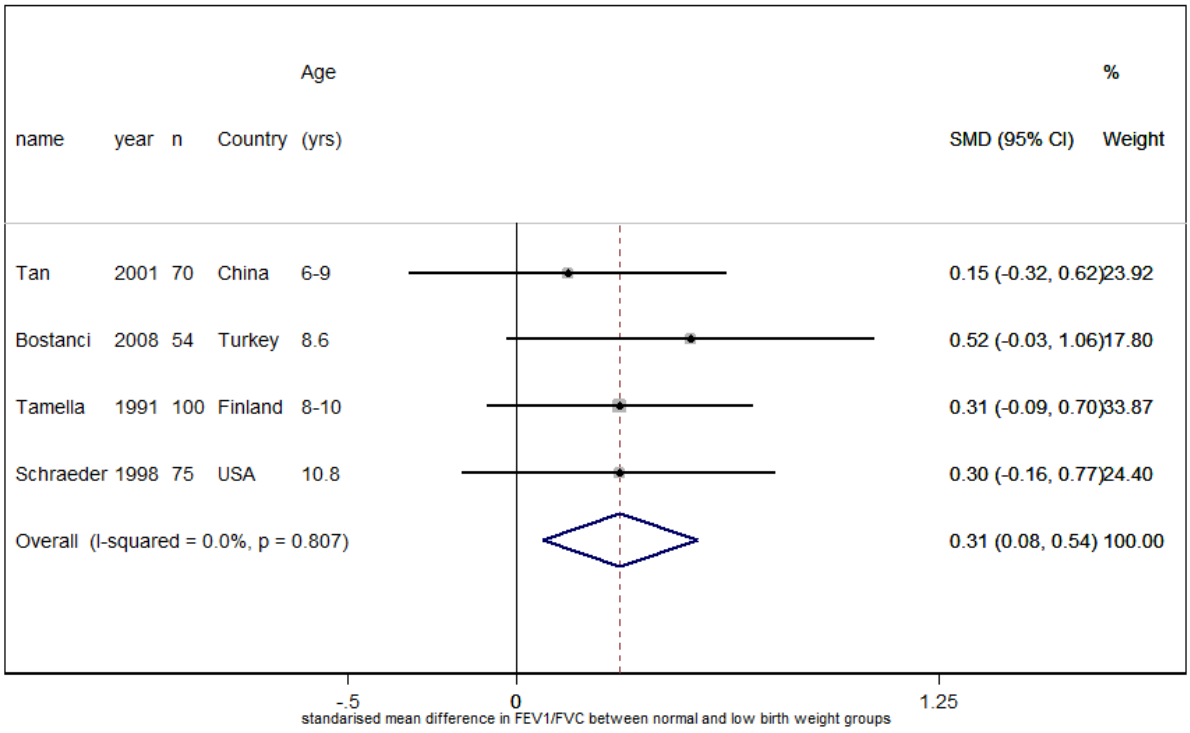


Figure 3.6: *Forest plot for FEV_1/FVC with birth weight in children. Birth weight as binary exposure (above/below 2.5 kg) (4 studies, 4 comparisons). Study estimates were ordered by increasing age. Some associations were reported by sex. Bostanci et al. [30] defined birth weight as below ≤1.75 kg and ≥ 2.5 kg and Schraeder et al. [289] defined birth weight as below ≤1.5 kg and >2.5 kg.*

among adults with birth weight as a binary exposure, where there was no evidence of a difference (p=0.27) (Figure A.5).

Subgroup analysis by income was again not possible for birth weight as a continuous exposure as all adult comparisons were from high-income countries and only one study examined the relation in children. For childhood comparisons with birth weight as a binary exposure, there was no difference in the effect estimate between low- to middle-income and high-income countries (Figure A.6). In adult comparisons, only one study [234] was from a high-income country and the results did not change (p=0.63) when excluding this study, 0.15 (-0.04 to 0.35) compared with 0.21 (0.06 to 0.36) in the main analysis.

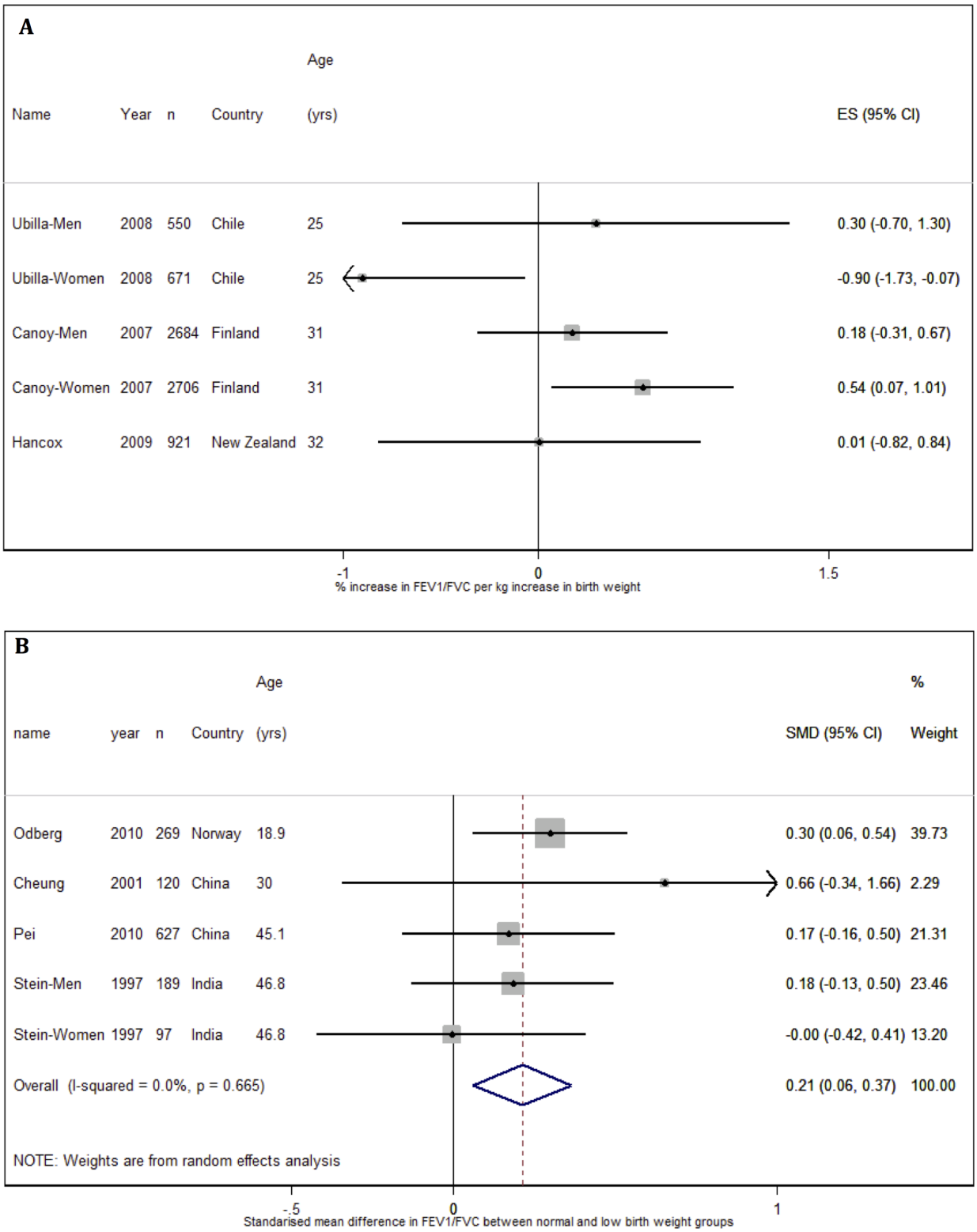


Figure 3.7: *Forest plot for FEV_1/FVC with birth weight in adults. A) Birth weight as continuous exposure (3 studies, 5 comparisons); B) Birth weight as binary exposure (above/below 2.5 kg) (4 studies, 5 comparisons). Study estimates were ordered by increasing age. Some associationas were reported by sex. Odberg et al. [234] defined birth weight as below 2.5 kg and above 3.0 kg.*

3.3.4 Association of weight at one year or weight gain in the first year with ventilatory function

Only three studies were identified that investigated the relation of weight at one year or weight gain in the first year of life, all in relation to FVC. Barker et al. [14] reported a positive association between weight at one year and FVC; for each kg increase in weight at one year, FVC rose by 44 mL (95% CI: 0 to 66 mL). Similarly, Canoy et al. [54] showed that FVC increased by 41.8 mL (95% CI: 16 to 67 mL) and 23.5 mL (95%CI: 4.9 to 42 mL), for men and women respectively, for each kg increase of weight gain in the first year of life. Chandler and Dugdale [60] only reported that weight at one year was not associated with FVC in children (no effect estimate, p-value>0.05). Weight at one year and weight gain in the first year of life were not reported in any other study, so that no meta-analysis could be performed.

3.3.5 Risk of bias and investigation of reporting bias

Table 3.4 shows the number of child- and adulthood studies at high, moderate and low risk of bias while Figure 3.8 shows the percentage of studies, in child- and adulthood, that fulfilled each of the eight NOS criteria. Detailed study-specific results available in Table A.12 (children) and Table A.13 (adults).

Eight childhood studies [12, 59, 60, 141, 216, 289, 327, 329] were of low methodological quality (NOS < 4). Eleven childhood studies (44%) obtained birth weight from birth or hospital records while ten studies did not provide any information on how birth weight was obtained. Thirteen studies (52%) measured ventilatory function according to ATS/ERS criteria, although 11 studies used non-ATS/ERS criteria and one study provided no information (Table A.12). Exclusion of the eight studies at high risk of bias in children affected the findings for both FVC and FEV_1/FVC. For FVC, it resulted in moderate between-study heterogeneity (I^2: 60%, p= 0.07) when examining the association

with birth weight as binary exposure (Figure A.7). The results were only synthesised as a secondary analysis, which resulted in a combined SMD of 0.22 (95% CI: 0.09 to 0.35). For the association with FEV_1/FVC, only one study [30] was retained, which did not find a statistically significant association.

Table 3.4: Number of studies at high (NOS<4), moderate (NOS: 4-6) and low (NOS>6) risk of bias in childhood and adulthood

	Children	**Adults**
High	**8**: Baraldi et al. [12], Chan et al. [59], Chandler and Dugdale [60], Hoo et al. [141], McLeod et al. [216], Schraeder et al. [289], Tammela et al. [327], Tan et al. [329]	**0**: -
Moderate	**11**: Bostanci et al. [30], Bucens et al. [39], Harik-Khan et al. [131], Jedrychowski et al. [153], Jindal et al. [155], Kotecha et al. [176], Lercher and Schmitzberger [197], Mandadzhieva et al. [208], Matthes et al. [213], Rona et al. [272], Wjst et al. [362]	**13**: Barker et al. [14],Canoy et al. [54], Cheung et al. [64], Edwards et al. [88], Hancox et al. [127], Lærum et al. [182], Lawlor et al. [193], Lopuhaä et al. [203], Odberg et al. [234], Pei et al. [247] Shaheen et al. [293], Sherrill et al. [296], Stein et al. [309]
Low	**6**: Brew and Marks [38], Demissie et al. [76], Joseph-Bowen et al. [159], Qi-qiang et al. [256], Trabelsi et al. [338], Turner et al. [339]	**5**: Boezen et al. [25], Lima et al. [199], Orfei et al. [236], Suresh et al. [321], Ubilla et al. [341]

In contrast, there were no studies in adults with high risk of bias. All but two studies [64, 247] selected participants representative of the target populations, and 12/19 studies achieved a follow-up greater than 70%. Most of the studies (78%) ascertained birth weight from birth or hospital records, although 3/18 studies [64, 127, 234] provided no description and 1/18 [193] used self-reported birth weight. Assessment of ventilatory function in adults did also not always adhere to ATS/ERS criteria, with 10/18 studies using non-ATS/ERS criteria (Table A.13).

Investigating of reporting biases was only possible for the association of FVC with birth weight as a binary exposure in childhood studies and with birth weight as a con-

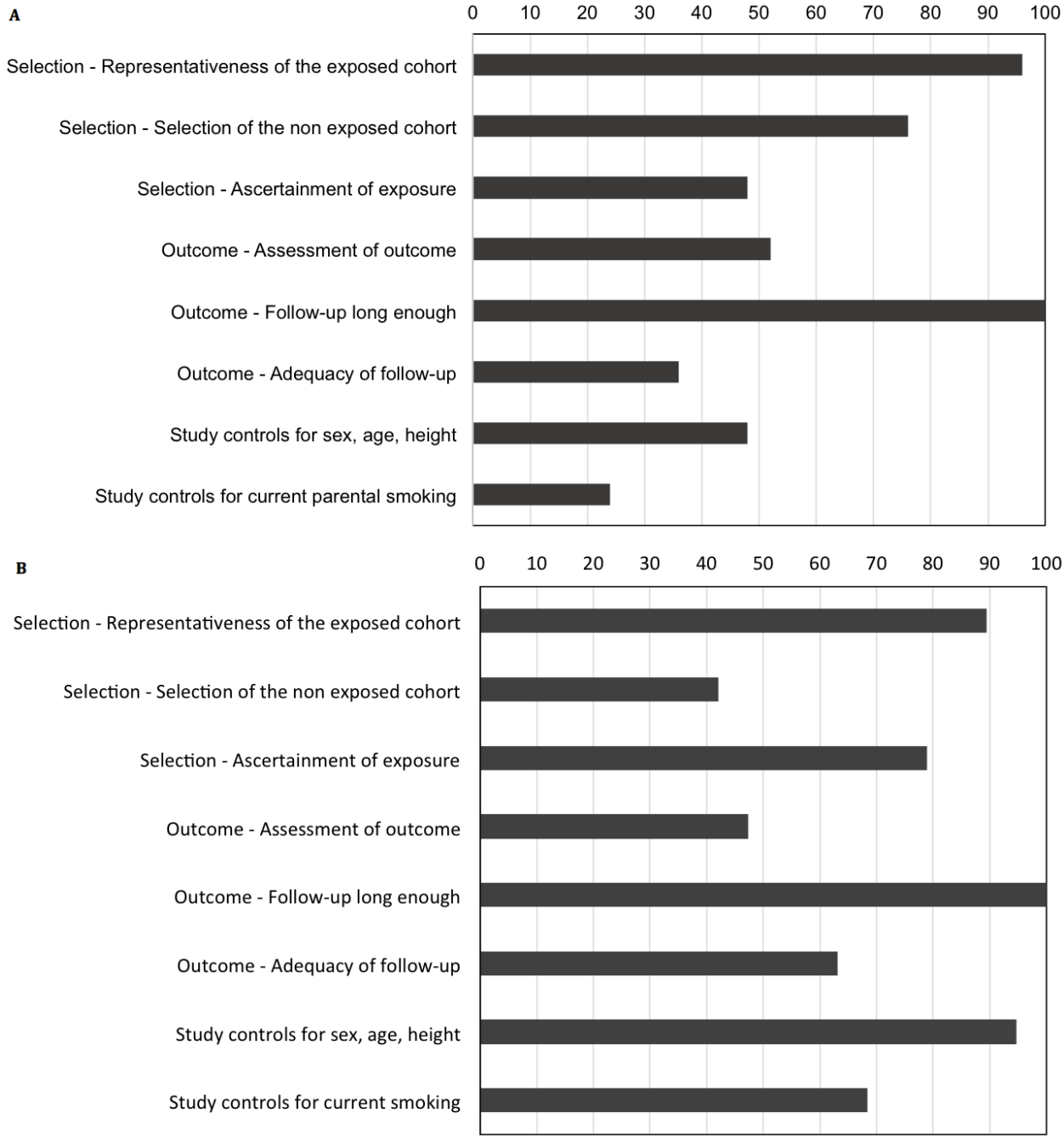


Figure 3.8: *Percentage of studies that fulfilled each of eight NOS criteria. A) Studies in childhood. Regarding adjustment for potential confounders (last two items), 4 studies did not control the association with FEV_1/FVC for sex, age, height or current parental smoking [216, 289, 327, 329], while 1 studies [30] did not control the association with FEV_1/FVC for current parental smoking. B) Studies in adulthood. Regarding adjustment for potential confounders (last two items), 5 studies did not control the association with FEV_1/FVC for sex, age or height [88, 127, 182, 234, 247], while 6 studies [88, 182, 203, 234, 247, 309] did not control the association with FEV_1/FVC for current smoking.*

tinuous exposure in studies in adulthood (Figure 3.9). The funnel plots did not show any evidence of asymmetry. Funnel plots for the other associations were not very informative due to the small number of studies available (2 to 5).

3.4 Discussion

Through meta-analysis, there is strong evidence of a positive relation of birth weight with FVC in both children and adults. The findings also suggest a positive association of birth weight with FEV_1/FVC across the life course, but the evidence is much weaker and more heterogeneity was observed across studies.

The association of birth weight and later FVC might be explained by Barker's hypothesis which postulates that influences during early life may program an individual, and that this programming could cause disease in later life [15]. However, it might also be a result of confounding. Adverse early life influences such as maternal smoking [110, 133, 227] and poor maternal nutrition in pregnancy [62, 67, 214], affect both birth weight and later FVC. Gestational age is also a strong predictor of birth weight and therefore prematurity or adverse early life influences might explain some of the observed association of birth weight and FVC. It was not possible to assess whether these factors mediate the associations as prenatal factors and gestational age were rarely taken into account in the analyses of the included studies.

Subgroup analyses by age did not find any difference in the association of birth weight and FVC in children while a weaker association was observed in older compared to younger adults. This might be the result of lifetime environmental factors, such as smoking, diet or air pollution, which could reduce the relative influence of birth weight on FVC [52]. Subgroup analyses by country level income were not always possible as comparisons with birth weight as a continuous exposure were all conducted in high income countries in both children and adults. However, there was no difference in the

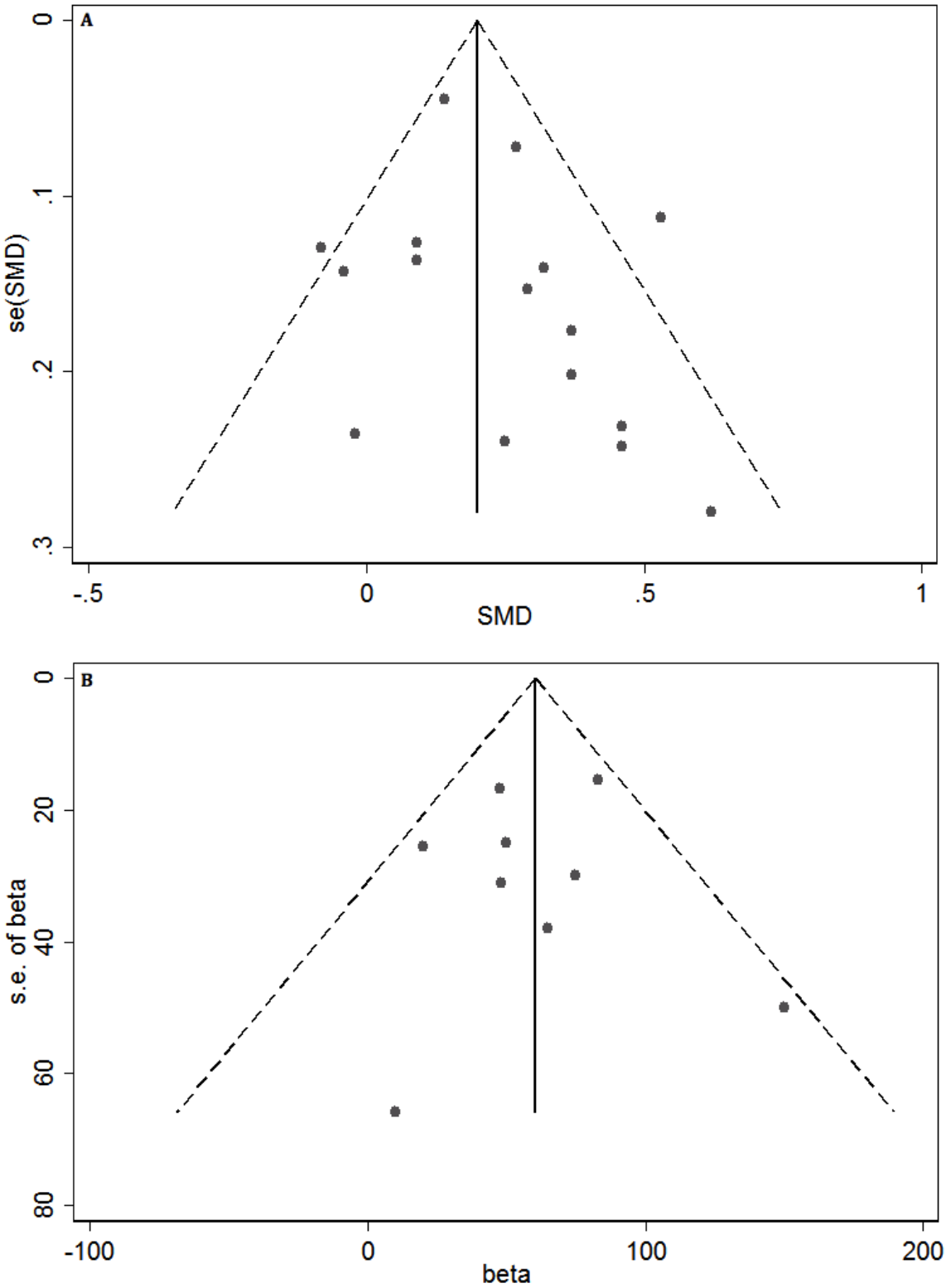


Figure 3.9: *Funnel plot of birth weight with FVC. A) Birth weight as a binary exposure in children (15 studies); B) Birth weight as a continuous exposure in adults (9 studies). SMD is the standardised mean difference, representing the difference in outcome between the groups divided by the standard deviation of the outcome, and beta is the effect estimate from a linear regression of FVC on birth weight. se(SMD) and s.e. of beta are the standard error of the SMD and effect estimate, respectively. The dashed lines represent the pseudo 95% confidence limits.*

effect of birth weight, as binary exposure, on FVC between high and low to middle income countries in children. In adults, comparing the difference was not straightforward because all comparisons with birth weight as binary exposure, except one, were from low to middle income countries. Nonetheless, the meta-analyses by country level income showed associations in the same direction, which suggests that country wealth does not influence the relation.

The findings suggest a positive association of birth weight with FEV_1/FVC but the evidence is much weaker with inconsistency across studies. For both child- and adulthood comparisons, the association of birth weight as a continuous exposure with FEV_1/FVC did not yield a statistically significant association whereas assessing the relation with birth weight as a binary exposure did result in small positive findings. Moreover, the association of birth weight as continuous exposure in adults was marked by moderate heterogeneity (I^2=55%), although none was observed for the associations with birth weight as binary exposure in both children and adults.

All of the individual studies in adulthood were at low risk of bias while eight childhood studies did appear to be at high risk of bias, as defined by the NOS scale. Excluding these childhood studies in sensitivity analyses increased the heterogeneity but did not markedly affect the association of birth weight with FVC. On the other hand, the association of birth weight with FEV_1/FVC was strongly affected as only one comparison remained, which reported a SMD of 0.52 (95% CI: -0.03 to 1.06). These results further weaken the evidence of a positive association of birth weight with FEV_1/FVC, especially in children.

Studies that selected participants based on gestational age or, presence of bronchopulmonary dysplasia, were excluded to ensure that the findings were generalisable. Also, throughout the study strict guidelines for the conduct and reporting of the results were adhered to, according to the MOOSE statement [320], a rigorous quality assessment was undertaken and the risk of biases was reduced through use of a thorough and

detailed protocol. Language bias was reduced by not posing any language restrictions during the search, location bias was minimised by searching multiple databases and multiple publication bias was eliminated by carefully conducting the search and removing any duplicate publications.

Investigation of reporting bias was not always possible due to the small number of studies included in each meta-analysis. Only two funnel plots contained sufficient observations (FVC with birth weight as binary exposure in children and with birth weight as continuous exposure in adults) and both did not show asymmetry. Reporting bias might have occurred for the association of birth weight with FEV_1/FVC. Fourteen of 20 childhood studies and 8 of 18 adult studies did not report on FEV_1/FVC despite reporting the results for both FEV_1 and FVC separately. It is possible that the authors might have selectively reported the results for FVC and FEV_1 while omitting the findings for FEV_1/FVC. However, it cannot be excluded that not reporting FEV_1/FVC could be due to a lack of interest as "airflow obstruction" has commonly been defined in epidemiological studies by FEV_1 alone, although this is not the case in clinical practice. A meta-analysis on birth weight and ventilatory function published ten years ago and including eight studies, analysed only FEV_1 because too few studies reported results for other outcomes [193]. This meta-analysis reported an increase of 48 mL in FEV_1 for one kilogram increase in birth weight [193]. The 1946 and 1958 British national birth cohorts found similar estimates of 41.3 mL and 66.6 mL for FEV_1 per kg increase in birth weight, respectively [236]. These findings seem congruent with the combined estimate in this meta-analysis for the relation between birth weight and FVC, an increase of 59.4 mL in FVC per kilogram difference in birth weight. Low FEV_1 can indicate either restriction or obstruction, it appears that FEV_1 acted as a proxy for FVC. Thus, suggestions that low birth weight is associated with FEV_1/FVC or even COPD [265, 317] are insufficiently supported by the current evidence.

Only three studies were identified that investigated the relation between weight at

one year or weight gain in the first year of life with FVC and none that assessed the relation with FEV_1/FVC. Both studies in adults reported a positive association between both weight at one year and weight gain in the first year of life with FVC whereas the only study in children found no association of weight at one year with FVC. This systematic review was restricted to weight at one year and weight gain in the first year of life. However, in comparison, two studies have reported no the relation of FVC and FEV_1/FVC with weight gain in the first three years of life [127, 296] and one has reported a positive association of FVC with weight gain between birth and age five [322]. Weight at one year has been proposed to be a more important predictor of later ventilatory function than birth weight by Barker et al. [14]. In order to assess this claim, more studies are required to evaluate the importance of weight at one year with later FVC and FEV_1/FVC.

A recent pooled meta-analysis of nearly 25,000 children by Den Dekker et al. [77] corroborated our findings. This study reported positive associations for the relations of birth weight, weight at one year and weight gain in the first year of life with FVC. Birth weight was also associated with FEV_1/FVC in childhood although birth weight adjusted for gestational age was not, suggesting that intra uterine growth retardation is not associated with FEV_1/FVC in childhood. Moreover, when stratified by age no statistically significant association was observed between birth weight and FEV_1/FVC in children older than 11 years. These results further strengthen the evidence for the associations in children but the findings might not be generalisable to all populations as only European cohort studies were included in this meta-analysis [77].

This systematic review identified several gaps and methodological limitations remain that should be addressed in future research. First, prenatal influences and gestational age were seldom reported or taken into account when assessing the association of weight in early life with later ventilatory function. This prevented an investigation of potentially mediating effects in this systematic review. Second, the use of different units for FVC and FEV_1/FVC and measurement of the exposure as either binary or con-

tinuous made comparisons across studies difficult. Use of standard units for FVC (L or percent predicted), FEV_1/FVC (percent or percent predicted) and birth weight (kg) would facilitate comparisons. Also, dichotomising birth weight into a binary exposure leads to loss of information and statistical power [7], which was especially problematic for several studies with relatively small sample sizes in this systematic review. Fourth, little evidence for this systematic review came from studies from low to middle income countries. Moreover, few studies had reported on the association of weight in early life with the mid-expiratory flow (FEF_{25-75}), which measures small airways obstruction, and was therefore not included in the aims. Finally, unmeasured influences affecting birth weight and weight gain in early life as well as later ventilatory function could potentially confound the observed effects. One such factor that was seldom taken into account is ethnicity, which may be of importance in populations of mixed ethnicity as it is associated with both low FVC [46, 142] and low birth weight [165].

3.5 Conclusion

There is strong evidence for a positive association of birth weight with FVC, which was consistent in children and adults. Most of the evidence is from studies conducted in high-income countries, with less data available from low- to middle-income countries. Much weaker evidence, especially among children, was available to support a positive association of birth weight with FEV_1/FVC. Finally, there was currently insufficient evidence to evaluate the association of weight at one year or weight gain in the first year of life with FVC and FEV_1/FVC.

CHAPTER 4

EXPLAINING THE ASSOCIATION OF VENTILATORY FUNCTION WITH CARDIOMETABOLIC AND INFLAMMATORY MARKERS IN THE NORTHERN FINLAND 1966 BIRTH COHORT

4.1 Aim and objectives

The Northern Finland 1966 birth cohort (NFBC66) is a birth cohort of individuals born in Northern Finland in 1966. The NFBC66 is a cohort with numerous follow-ups across the life course, with measurement of ventilatory function at age 31, and detailed information collected on factors from early to adult life.

Previous research using the NFBC66 investigated the relation between weight in early life and ventilatory function in adulthood [54], examined the association of early life factors on systemic inflammation [55, 252], and assessed the influence of early life factors on adult blood pressure [152]. Here, I investigate the relation of ventilatory function with cardiometabolic or inflammatory markers, which has not previously been investigated in this cohort, and assess which early or adult life factors might explain the association between ventilatory function and cardiometabolic markers.

The specific objectives are to:

1. Investigate the association between FVC or FEV_1/FVC (outcomes of interest) and cardiometabolic markers (primary exposure) and inflammatory markers (secondary exposure)

2. Identify whether early or adult life factors can explain the association between the outcomes and exposures, including shared adult risk factors, inflammatory markers, weight in early life and prenatal factors.

4.2 Methods

I was provided with the data from the NFBC66 by Prof. Marjo-Riitta Jarvelin, the principal investigator of the study, and conducted all statistical analyses, under the supervision of Prof. Peter Burney and Dr. Cosetta Minelli.

4.2.1 Study population and design

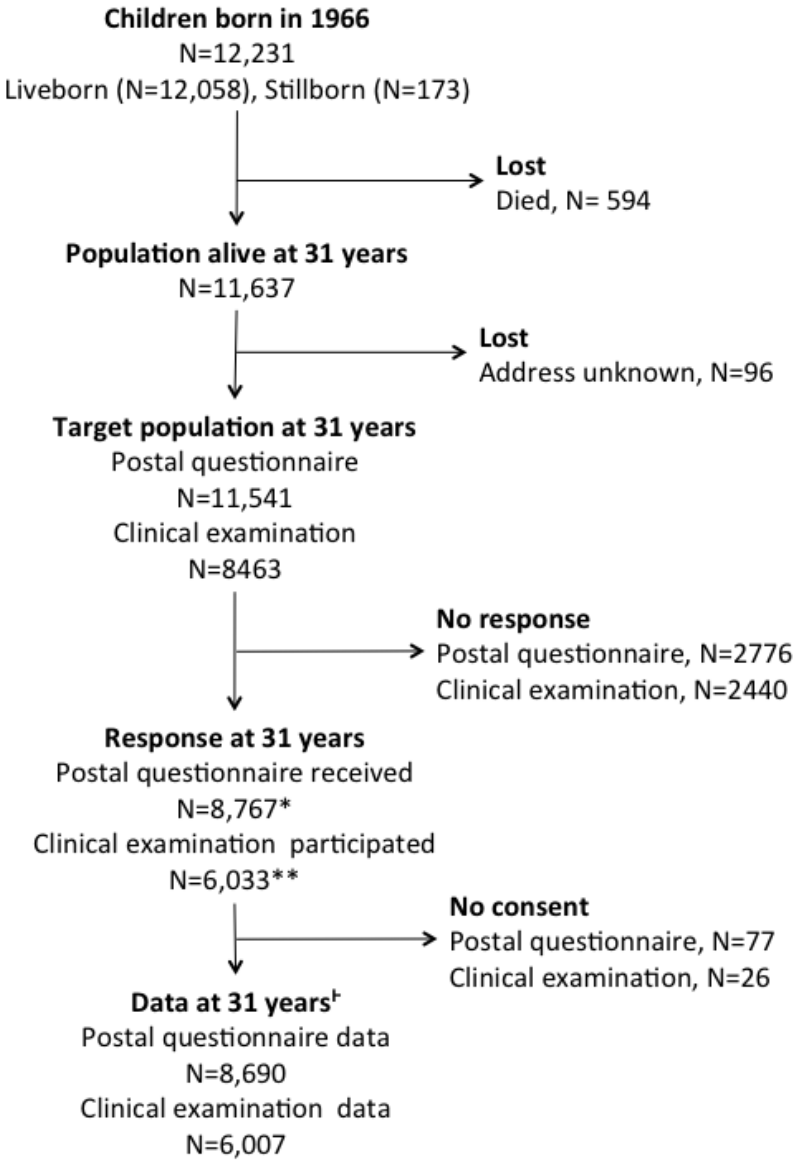
All pregnant mothers, living in the Oulu and Lapland provinces, with expected delivery in 1966 were invited to participate in the study through 157 maternal health clinics in 1965. The study included all births with a birth weight of 600 grams or more. In total, 12,231 births were included in the study, which corresponded to 96.3% of all births (out of 12,527 births) in those provinces during 1966 (Figure 4.1). A more detailed description of the study design and recruitment can be found in publications by Rantakallio et al. [260, 261].

Prenatal data, data on birth and growth outcomes up to the first year of life and follow-up data at age 14 and 31 years were collected (Figure 4.1). Data at age 14 were restricted to a postal questionnaire, whereas follow-up at age 31 included both a postal questionnaire and a clinical examination. The postal questionnaire at age 31 was sent to all participants with known addresses (n=11,541) and was completed by 8,690 (75%) participants. The clinical examination was restricted to 8,463 participants who lived in the original target area (Oulu or Lapland provinces) or the capital (Helsinki). The clinical examination was completed by 6,007 (71%) participants, of whom not all responded to the postal questionnaire (Figure 4.1).

Written informed consent was obtained from all study participants and ethical approval for the study was obtained from the University of Oulu ethics committee.

4.2.2 Study data

Variables were selected a priori based on the literature and on the experience of the research group. An overview of the variables used in this study is available in Table 4.1.



*Two cohort participants outside the target area for the postal questionnaire also responded
**Ten cohort participants outside the target for the clinical examination also responded
[ŀ] Although the target group for the clinical examination was a subgroup of the postal questionnaire target group, not all participants who completed the clinical examination responded to the postal questionnaire

Figure 4.1: *Flow chart of Northern Finland 1966 birth cohort data collection*

Table 4.1: Variables from the Northern Finland 1966 Birth Cohort Study used in the study

Variable	Unit/categories	Note
Adult factors at 31 years		
FVC	Litres	
FEV_1	Litres	
FEV_1/FVC	%	
Doctor diagnosed asthma	a) No; b) Yes	
Gender	a) Male; b) Female	
Height	Metres	
Weight	Kilogram	
Waist circumference	Centimetres	
Socio-economic status	a Professional; b) Skilled worker; c) Unskilled worker; d) Farmer; e) Other	Based on classification by Sovio et al. [303]. The group "Professional" includes entrepreneurs and upper white-collar workers; "Skilled worker" includes lower white-collar workers; "Unskilled worker" includes blue-collar workers; "Farmers" include farmers; "Others" include pensioners, students and long-term unemployed or undefined
Ever smoking	a) No; b) Yes	Response to question "Have you ever smoked in your life?"
Pack years	Number	
Cholesterol	mmol/L	
Low density lipoprotein	mmol/L	
High density lipoprotein	mmol/L	
Triglycerides	mmol/L	
Glucose	mmol/L	
Insulin	mU/L	
Systolic blood pressure	mm Hg	
Diastolic blood pressure	mm Hg	
C-reactive protein	mg/L	
White blood cell count	10^9 cells/L	

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Table 4.1 – continued from previous page

Variable	Unit/categories	Note
Weight in early life		
Birth weight	Kilogram	
Weight gain in the first year	Kilogram	Calculated from weight at one year and birth weight
Gestational age	Weeks	
Early life		
Parity	Number	
Maternal age at delivery	Years	
Maternal height prior to pregnancy	Metres	
Maternal weight prior to pregnancy	Kilogram	
Smoking during pregnancy	a) No; b) Yes	Derived from two questions related to mother's smoking in pregnancy:(1) "Smoking in second month of pregnancy" and (2) "How many cigarettes/pipefuls a day did the mother smoke during the last 3 months of pregnancy?"
Maternal socio-economic status	a) No occupation; b) Professional; c) Skilled worker; d) Unskilled worker; e) Farmer	Based on classification by Sovio et al. [303]. The group "No occupation" includes no occupation (housewife);"Professional" includes occupations with high education and prestige (class I) and those with lower prestige than class I and shorter education (class II); "Skilled worker" includes skilled workers; "Unskilled worker" includes unskilled workers; "Farmer" includes farmers

4.2.2.1 Prenatal, birth and infant growth data

Questionnaires administered by midwives at local antenatal clinics from the 24th to the 28th week of gestation collected data on maternal anthropometry, health and social status. The questionnaire collected maternal data on smoking before and during pregnancy, height and weight, maternal age, parity, marital status and maternal socioeconomic status. Newborn (participant) data on gestational age, birth weight and gender were obtained from hospital birth records. Gestational age was defined as the number of completed weeks from date of mother's last menstrual period to delivery. Weight at one year was ascertained in welfare clinics, which were attended by all participants, and recorded from medical records.

4.2.2.2 Adult data

In the follow-up visit at age 31, trained nurses conducted the clinical examination according to standardised operating procedures and with continuous quality control. Height (0.1 cm accuracy), weight (0.1 kg accuracy), and waist circumference, measured at the level midway between the lowest rib margin and the iliac crest (0.5 cm accuracy) [183]. A mercury sphygmomanometer was used to measure blood pressure twice from the participants' right arm when seated after 15 minutes of rest and the average blood pressure was used for the analysis [152].

A blood sample was taken following overnight fasting. Blood samples for serum lipids (total, high and low density lipoprotein cholesterol, and triglyceride), glucose and leukocyte count were stored at +4°C and analysed within 24h at the laboratory of Oulu University Hospital. The absolute leukocyte count was determined using automatic electronic cell counter (Coulter Corp., Miami, FL) [55], serum lipid concentration was measured using a Hitachi 911 automatic analyzer and commercial reagents (Roche Molecular Biochemicals, Mannheim, Germany) [53, 55], and glucose concentration was measured by a glucose dehydrogenase method (Granutest 250m Diagnostic Merck, Darm-

stadt, Germany) [330]. Blood samples for insulin and serum C-reactive protein were stored at -20°C and -80°C, respectively. Insulin concentration was analysed within seven days by radioimmunoassay with commercial reagents (Pharmacia Diagnostics, Uppsala, Sweden) [55], and C-reactive protein was measured using a high-sensitivity immunoenzymometric assay (Medix Bio- chemica, Espoo, Finland) [340].

FEV_1 and FVC were measured by spirometry using a Vitalograph P-model spirometer (Vitalograph Ltd, Buckingham, UK), which was calibrated regularly using a 1L precision syringe. Three blows were performed but these were repeated if the difference between the two maximum [303]readings was > 4%. The highest FEV_1 and FVC measures were used in this study [54].

Information on adult socio-economic status, smoking and asthma diagnosis was obtained from self-reported postal questionnaires. Classification of adult socio-economic status was based on occupation and current activity [303]. Information on adult smoking included whether the participant had ever smoked (yes/no) and the number of pack-years smoked. Having asthma was defined as a positive response to questions on whether the participant had ever had asthma, and whether this had been verified or treated by a doctor [185].

4.2.3 Multiple imputation of missing data

4.2.3.1 Missing data

In regression analyses, missing data are often dealt with by restricting the analysis to the observations that have complete information on all variables included in the regression (i.e. complete-case analysis). However, complete-case analysis may result in biased and/or imprecise estimates [85, 117, 200].

The risk of bias in the complete-case analysis will depend on the reasons for missingness, which are referred to as missingness mechanism. Missingness mechanisms

can be classified as: (1) missing completely at random (MCAR), (2) missing at random (MAR), and (3) missing not at random (MNAR). Information is MCAR when there are no systematic differences between the observed and missing values (i.e. the probability of missingness is not associated with any of the variables in the data) and therefore the observations with complete information are a random subset of the total population. Data can be MCAR, for instance, due to a random spirometer malfunction or accidental breaking of a blood tube. If the difference between the observed and missing data can be explained by the observed variables, then the missingness is deemed to be MAR (i.e. data is missing at random conditional on the observed data). For example, the missing FVC values might be lower than the observed values because older individuals more commonly refused to perform spirometry; therefore, after taking age into account, there would be no differences between participants with complete and missing data. Finally, data is MNAR when, after taking into account the observed variables, systematic differences between the individuals with missing and complete data persist (i.e. the probability of missingness is dependent on unobserved information). MNAR could occur, for example, if participants with lower ventilatory function more frequently did not attend the study visits due to poor health, and therefore the missing FVC values would depend on the unobserved information on poor health [6, 22, 276].

Complete-case analysis of data that is MAR or MNAR may give biased results, which are also less precise (as only a subset of the data is used), whereas complete-case analysis of data that is MCAR will result in less precise but unbiased estimates [117, 200].

In this study, the missingness mechanism was investigated by assessing the pattern of missingness, described as the proportion of observations with missing information for different variable groups used in the association analyses (see 4.2.4.2). The predictors of missingness for variables with incomplete data were then identified by regressing a binary variable indicating the presence of missingness (1: information missing, 0: information present) on all other available variables (multiple logistic regression).

Although identifying predictors of missingness strengthens the MAR assumption, as it shows that the missingness is conditional on the observed data, solely using observed data does not enable a distinction to be made between MAR and MNAR [117, 200].

4.2.3.2 Multiple imputation

The analysis of datasets with missing data can either discard or replace (impute) the missing values. A common approach which discards information is the complete-case analysis, whereas a wide range of statistical techniques exist for imputing missing data [1, 222, 278, 287, 342]. Many of these different approaches are reviewed by Little [200] and Greenland and Finkle [117].

A popular, effective and commonly used approach is multiple imputation (MI). MI is a statistical method whereby a set of values for the missing data will be generated based on the observed data. It is undertaken in three stages. First, MI creates multiple copies of the dataset in which the values of the missing data are replaced with imputed values using a Bayesian framework. Second, each imputed dataset is analysed separately and, finally, the estimates of each analysis are combined across the imputed datasets to provide overall estimates, taking into account the uncertainty in the imputation of the missing data [277, 286]. However, one important drawback of MI is that it will only produce unbiased estimates if the missingness mechanism is MCAR or MAR [313]. More details on MI, including details on the Bayesian approach, can be found in reviews by Rubin [279] and Kenward and Carpenter [168] and in recently published books by van Buuren [344] and Molenberghs et al. [221].

Different approaches are used for the first step of MI, where the missing values are imputed. However, Multiple Imputation by Chained Equation (MICE) provides better imputation results compared to other methods [270]. MICE will impute the missing values by first randomly filling in all the missing values and, secondly, regressing the variables with missing information on the other variables in the imputation model to

obtain the imputed values. This process is repeated until the imputed values are stabilised. One such cycle, from the random filling of values, the regression of variables and iteration to stabilise the results will generate one imputed dataset. In MI, multiple imputed datasets are generated (see subsection 4.2.3.5 for details on the number of imputed datasets) [343, 355].

MICE has been implemented in different statistical software packages [143] ; here the MICE implementation in Stata [275] with the ice (imputation by chained equation) command was used to impute the missing values. This study also adhered to the reporting guidelines of analyses using imputation[313].

4.2.3.3 Selecting variables for the imputation model

The imputation model is the model that will impute the missing values for variables with incomplete information and will contain all the variables with missing data. The imputation model will also include all the variables in the analysis model, including the outcome variable. If multiple analyses are conducted, then the imputation model should include every variable included in any analysis model [223, 305]. Here, all variables, including those with missing information, that were included in the analyses models were included in the imputation model (see section 4.2.4 for details of the analyses models).

Additional variables, which are not included in the analysis models (auxiliary variables), can be included to improve the imputation [270, 355]; here gestational age and doctor diagnosed asthma were included as auxiliary variables.

In addition to predictors of the variables with incomplete information, imputation quality can be improved by also including predictors of the missingness of data in the imputation model, since this will strengthen the MAR assumption (see section 4.2.3.1) [275, 355].

4.2.3.4 Imputing different types of variables

MICE imputes variables according to the type of variable: categorical variables are imputed using logistic regression, whereas continuous variables are imputed using linear regression.

Imputation of categorical variables

According to the type of categorical variable, a specific logistic regression will be used. Binary variables (e.g. sex: male/female) will be imputed using classical logistic regression. Nominal categorical variables, that is variables with multiple levels but no ordering of the levels, are imputed with multinomial logistic regression, while ordinal categorical variables, that is variables with multiple ordered levels, are imputed using ordered logistic regression.

Imputation of continuous variables

Normally distributed continuous variables are imputed using a linear regression model. Imputation of non-normally distributed variables using linear regression will result in incorrect imputation, as the distribution of imputed values will not resemble the distribution of the observed values [355].

Two solutions for imputation of non-normally distributed variables are available: (1) shifted log transformation, where variables were centred by a scalar and log transformed, and (2) predictive mean matching, where imputed values are sampled from observations with complete information that are matched with observations that contain missing values. Non-normally distributed variables for which a large fraction of the values are equal to zero (termed semi-continuous variables) cannot be transformed to normality, but can be imputed using predictive mean matching. An example of a semi-continuous variable is smoking pack-years [275, 355].

Here, non-normally distributed continuous variables with missing data were identified by visual inspection of histograms and by examining the distribution (mean, standard deviation, median, 25th and 75th percentile). Three different imputation approaches

were evaluated for non-normally distributed continuous variables to determine the optimal imputation approach: (1) predictive mean matching, (2) linear regression after a shifted log transformation, and (3) linear regression (i.e. ignoring the non-normal distribution).

The optimal imputation approach for non-normally distributed continuous variables was determined by comparing the distribution of the imputed values with that of the observed data. When assessing the three different imputation approaches for non-normally distributed continuous variables, categorical variables were imputed as described in the subsection above, and normally distributed continuous variables were imputed using linear regression, with sixty imputations for each imputation model (see section 4.2.3.5 for details on the number of imputations).

4.2.3.5 Specifying and checking the imputation model

The imputation model is described in Table 4.2, with categorical variables imputed according to their type and normally distributed continuous variables imputed using linear regression. Non-normally distributed continuous variables were imputed using their optimal imputation approach (see section 4.3.2 for the results on the optimal approach). Initially, the number of imputed copies of the dataset (number of imputations) was suggested to range between 5 and 10 [286]. However, this has been questioned [116, 305] and a recent rule of thumb recommended that the number of imputations should at least equal the percentage of observations with incomplete information [355], which has been adhered to in this study. The accuracy of the imputation was assessed by comparing the distribution of the imputed with the observed values for all variables with missing data.

Table 4.2: Specification of imputation model for variables with missing data in the NFBC66

Variables	Imputation approach	Reason
FVC	-	No missing data
FEV_1/FVC	-	No missing data
Doctor diagnosed asthma	Logistic regression	Binary variable
Height	-	No missing data
Sex	-	No missing data
Waist circumference	Linear regression	Normally distributed continuous variable
Socio-economic status	Multinomial logistic regression	Nominal categorical variable
Ever smoking	Logistic regression	Binary variable
Pack years	Predictive mean matching	Semi-continuous variable
Low density lipoprotein	Linear regression	Normally distributed continuous variable
High density lipoprotein	Linear regression	Normally distributed continuous variable
Triglycerides	Predictive mean matching	Non-normally distributed continuous variable
Glucose	Linear regression	Normally distributed continuous variable
Insulin	Predictive mean matching	Non-normally distributed continuous variable
Systolic blood pressure	Linear regression	Normally distributed continuous variable
Diastolic blood pressure	Linear regression	Normally distributed continuous variable
C-reactive protein	Predictive mean matching	Non-normally distributed continuous variable
White blood cell count	Linear regression	Normally distributed continuous variable
Birth weight	-	No missing data
Weight gain in the first year	Linear regression	Normally distributed continuous variable
Gestational age	Predictive mean matching	Non-normally distributed continuous variable
Parity	Predictive mean matching	Non-normally distributed continuous variable
Maternal age at delivery	Predictive mean matching	Non-normally distributed continuous variable
Maternal height prior to pregnancy	Linear regression	Normally distributed continuous variable
Maternal weight prior to pregnancy	Linear regression	Normally distributed continuous variable
Smoking during pregnancy	Logistic regression	Binary variable
Maternal socio-economic status	Multinomial logistic regression	Nominal categorical variable

4.2.4 Statistical analysis

Previous findings from the NFBC66 investigated the relation of birth weight with ventilatory function in adulthood and found a statistically significant interaction between sex and birth weight for FVC (p=0.007) [54]. Thus, all statistical analyses were conducted on the whole sample and on a priori defined subgroup analyses by sex.

4.2.4.1 Descriptive statistics

Data were summarised using mean and standard deviation for continuous variables or number and percentage for categorical variables, and the proportion of missing data was reported. Differences by sex and between those who did and did not attend the study visit were investigated using a t-test or Wilcoxon rank sum test, as appropriate, for continuous variables, and a χ^2-test for categorical variables.

4.2.4.2 Association analyses

The outcomes of interest were FVC and FEV_1/FVC, while the primary and secondary exposures of interest were cardiometabolic and inflammatory markers, respectively. Cardiometabolic markers included serum lipids (triglyceride and total, high and low density cholesterol), systolic and diastolic blood pressure, glucose and insulin concentration, waist circumference and weight. Inflammatory markers were the total leukocyte count (i.e. white blood cell count) and the C-reactive protein concentration.

The main analysis aimed to assess and explain the association between the outcomes and both the primary and secondary exposures of interest using multiple linear regression, with a priori specified covariates. Multicollinearity was investigated using the variance inflation factor [316].

For the association between the outcomes and the primary exposures of interest (cardiometabolic markers), seven different linear regression models (Table 4.3) were fit-

ted: (1) Crude (unadjusted) model; (2) Model 1, where all primary or secondary exposures were mutually adjusted for; (3) Model 2, in which Model 1 was further adjusted for sex (except when stratified by sex) and height; (4) Model 3, in which Model 2 was further adjusted for other adult covariates (socio-economic status, ever smoking and pack-years), to assess whether adult factors could explain the association; (5) Model 4, in which Model 3 was further adjusted for inflammatory markers (white blood cell count and C-reactive protein), to examine if inflammatory markers mediate the association; (6) Model 5, in which Model 3 was further adjusted for weight in early life (birth weight and weight gain in the first year of life), to determine whether the association was due to a common association with weight in early life; (7) Model 6, in which Model 3 was further adjusted for maternal covariates measured prior to the birth of the participant, including parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy, to evaluate the influence of prenatal factors. All linear regression models were also fitted for the association of the outcomes and the secondary exposures of interest (inflammatory markers), with the exception of Model 4, since the inflammatory markers had already been mutually adjusted for in Model 1 (Table 4.3).

The main analyses were repeated as sensitivity analyses among full-term participants (gestational age between 37 and 41 weeks) to assess the influence of prematurity on the results, and among participants with no doctor-diagnosed asthma, to reduce the possibility that the association with ventilatory function was due to an association with reversible obstruction.

All analyses were conducted in the imputed datasets. However, as additional analysis the main analyses were conducted in a more limited imputation strategy, where the cardiometabolic and inflammatory markers with missing data were not imputed, and with complete case analyses, and the results compared to the results from the main analyses in the imputed datasets.

All analyses were conducted in Stata 13.1 (StataCorp LP, College Station, TX, USA) and statistical significance was defined as $p<0.05$.

Table 4.3: Specification of linear regression models for association analyses of outcomes of interest with primary (cardiometabolic markers) and secondary (inflammatory markers) exposure of interest

Linear regression models for association of ventilatory function with cardiometabolic markers	
Model	**Adjustment for**
Crude	No adjustment
1	Triglyceride concentration, high-density and low-density lipoprotein, systolic and diastolic blood pressure, glucose and insulin concentration and waist circumference
2	Factors in Model 1 + sex (except when stratified by sex) and adult height
3	Factors in Model 2 + adult socio-economic status, ever smoking and pack-years
4	Factors in Model 3 + C-reactive protein and white blood cell count
5	Factors in Model 3 + birth weight and weight gain in the first year of life
6	Factors in Model 3 + parity, maternal age at delivery, maternal height and weight prior to pregnancy, maternal smoking in pregnancy and maternal socio-economic status during pregnancy
Linear regression models for association of ventilatory function with inflammatory markers	
Model	**Adjustment for**
Crude	No adjustment
1	C-reactive protein concentration and white blood cell count
2	Factors in Model 1 + sex (except when stratified by sex) and adult height
3	Factors in Model 2 + adult socio-economic status, ever smoking and pack-years
4	Factors in Model 3 + birth weight and weight gain in the first year of life
5	Factors in Model 3 + parity, maternal age at delivery, maternal height and weight prior to pregnancy, maternal smoking in pregnancy and maternal socio-economic status during pregnancy

4.3 Results

4.3.1 Cohort follow-up and study population

Participants who attended the clinical examination were more likely to be female, had higher birth weight and gestational age and had mothers who were older at their birth,

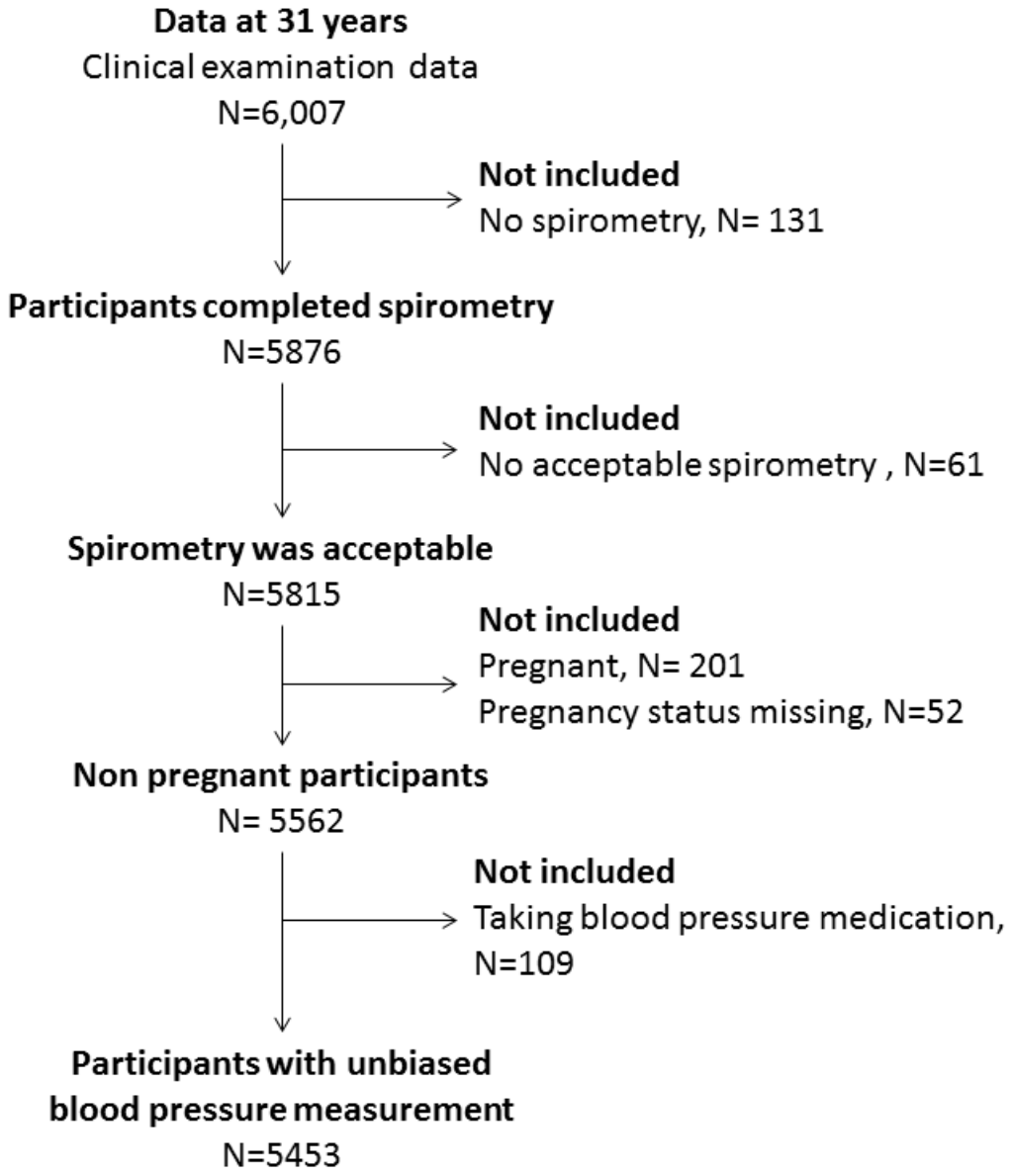


Figure 4.2: *Flow chart of Northern Finland 1966 birth cohort study participants*

were slightly heavier and had had more children (Table 4.4). Of these 6,007 participants, 554 participants were excluded from the analysis because no acceptable spirometry was available, participants were pregnant, information on participants' pregnancy status was missing, or participants used blood pressure medication and thus their actual blood pressure was not known (Figure 4.2).

Table 4.5 shows the characteristics of participants included in the analysis. Men had a higher FVC and FEV_1 and smoked more, but had lower FEV_1/FVC and a lower prevalence of asthma compared with women. Cardiometabolic and inflammatory markers were also more elevated in men compared to women, except for high density lipoprotein and C-reactive protein (which were higher in women) and white blood cell count (no difference between sexes). No difference was observed in the prenatal factors or gestational age, but men did have higher birth weight and weight gain in the first year of life.

Two variables were not included in the multiple regression analyses due to multicollinearity (variance inflation factor >10): total cholesterol concentration and weight. On further inspection, total cholesterol concentration was highly correlated with low density lipoprotein, while weight was strongly correlated with waist circumference. Low density lipoprotein and waist circumference were both retained in the multiple regression analyses.

4.3.2 Missing data and multiple imputation

The percentage of missing data ranged from 0 to 22.7% in the total population. Only five variables had five or more percent missing data: doctor diagnosed asthma (18.8%), pack-years (22.7%), weight gain in the first year of life (12.5%), maternal height (5.0%) and weight prior to pregnancy (5.2%) (Table B.1). In total, 3,067 out of 5,453 observations (56.2%) were incomplete with most observations with missing data having only one variable (29.8% of observations) or two variables (15.3%) missing. Moreover, there did not appear to be a pattern in the missingness of the data (Table B.2).

Table 4.4: Comparison of Northern Finland 1966 Birth Cohort study liveborn participants by attendance at the clinical examination at 31 years

	N (%) with information		N (%) or Mean (SD)		P-value
	Not attending at age 31 yrs (N=6,051)	Attending at age 31 yrs (N=6,007)	Not attending at age 31 yrs (N=6,051)	Attending at age 31 yrs (N=6,007)	difference in mean proportion
Gender (Female)	5,961 (98.5)	6,007 (100.0)	2,721 (45.6)	3,127(52.1)	<0.001
Weight in early life					
Birth weight (kg)	5,960 (98.5)	6,007 (100.0)	3.39 (0.6)	3.46 (0.5)	<0.001
Weight gain in the first year (kg)	4,818 (79.6)	5,263 (87.6)	6.80 (1.2)	6.80 (1.1)	<0.001
Gestational age (weeks)	5,732 (94.7)	5,803 (96.6)	39.79 (2.5)	40.03 (1.9)	<0.001
Prenatal factors (during pregnancy)					
Parity (n)	5,954 (98.4)	5,994 (99.7)	2.82 (2.2)	2.96 (2.3)	<0.001
Maternal age at delivery (years)	5,959 (98.5)	6,006 (99.9)	26.87 (6.6)	27.71 (6.7)	<0.001
Maternal height prior to pregnancy (m)	5,616 (92.8)	5,710 (95.1)	1.60 (0.05)	1.60 (0.05)	0.19
Maternal weight prior to pregnancy (kg)	5,632 (93.1)	5,698 (94.9)	59.18 (8.7)	59.73 (9.0)	<0.001
Maternal smoking during pregnancy (Yes)	5,714 (94.4)	5,741 (95.6)	1,095 (19.2)	876 (15.3)	<0.001
Maternal socio-economic status	5,866 (96.9)	5,916 (98.5)			<0.001
No occupation			2,120 (36.1)	1,952 (33.0)	
I (highest social class)			212 (3.6)	196 (3.3)	
II			535 (9.1)	531 (9.0)	
III			1,265 (21.6)	1,260 (21.3)	
IV (lowest social class)			556 (9.5)	479 (8.1)	
Farmers			1,178 (20.1)	1,498 (25.3)	

Table 4.5: Characteristics of Northern Finland 1966 Birth Cohort Study Population

	Total population (N=5,453)	**Men (N=2,748)**	**Women (N=2,705)**	**P-value for difference in mean/proportion between men & women**
	Mean (SD) or n (%)	**Mean (SD) or n (%)**	**Mean (SD) or n (%)**	
Adult factors at 31 years				
Lung function and asthma				
FVC (L)	4.8 (1.0)	5.5 (0.8)	4.0 (0.6)	<0.001
FEV_1 (L)	4.0 (0.8)	4.5 (0.6)	3.4 (0.5)	<0.001
FEV_1/FVC (%)	83.8 (5.8)	82.9 (5.7)	84.8 (5.8)	<0.001
Doctor diagnosed asthma (ref: Yes)	436 (8.0)	199 (7.2)	237 (8.8)	0.12
Anthropometry				
Height (m)	1.7 (0.1)	1.8 (0.1)	1.6 (0.1)	<0.001
Weight (kg)	72.8 (14.8)	80.0 (12.5)	65.5 (13.3)	<0.001
Waist circumference (cm)	83.8 (12.0)	88.8 (9.7)	78.8 (12.1)	<0.001
Socio-economic status				<0.001
I (highest)	1,276 (24.2)	738 (27.5)	538 (20.7)	
II	1,643 (31.1)	469 (17.5)	1,174 (45.1)	
III (lowest)	1,410 (26.7)	997 (37.2)	413 (15.9)	
Farmers	200 (3.8)	132 (4.9)	68 (2.6)	
Other	752 (14.2)	344 (12.8)	408 (15.7)	
Smoking variables				
Ever smoking (ref: Yes)	3,433 (63.9)	1,812 (67.3)	1,621 (60.6)	<0.001
Pack years (n)	5.4 (7.8)	7.1 (9.1)	3.6 (5.7)	<0.001
Metabolic markers				
Cholesterol (mmol/L)	5.0 (1.0)	5.2 (1.0)	4.9 (0.9)	<0.001
Low density lipoprotein (mmol/L)	3.0 (0.9)	3.2 (0.9)	2.8 (0.8)	<0.001
High density lipoprotein (mmol/L)	1.5 (0.4)	1.4 (0.3)	1.7 (0.4)	<0.001
Triglycerides (mmol/L)	1.2 (0.7)	1.3 (0.8)	1.0 (0.5)	<0.001
Glucose (mmol/L)	5.1 (0.7)	5.2 (0.7)	4.9 (0.7)	<0.001
Insulin (mU/L)	8.6 (5.1)	8.9 (5.3)	8.3 (4.9)	<0.001
Systolic blood pressure (mm Hg)	125.0 (13.5)	130.2 (12.6)	119.9 (12.3)	<0.001
Diastolic blood pressure (mm Hg)	77.6 (11.2)	80.1 (11.3)	75.0 (10.5)	<0.001

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Table 4.5 – continued from previous page

	Total population (N=5,453)	Men (N=2,748)	Women (N=2,705)	P-value for difference in mean/proportion between men & women
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	
Adult factors at 31 years				
Inflammatory markers				
C-reactive protein (mg/L)	1.9 (3.7)	1.6 (3.2)	2.2 (4.1)	<0.001
White blood cell count (109 cells/L)	5.9 (1.6)	5.9 (1.7)	5.8 (1.6)	0.25
Weight in early life				
Birth weight (kg)	3.5 (0.5)	3.5 (0.5)	3.4 (0.5)	<0.001
Weight gain in the first year (kg)	6.8 (1.1)	7.1 (1.1)	6.6 (1.1)	<0.001
Gestational age (weeks)	40.0 (1.9)	40.0 (1.9)	40.1 (1.9)	0.06
Prenatal factors (during pregnancy)				
Parity	3.0 (2.3)	3.0 (2.3)	3.0 (2.3)	0.75
Maternal age at delivery (years)	27.7 (6.7)	27.9 (6.6)	27.6 (6.7)	0.11
Maternal height prior to pregnancy (m)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	0.23
Maternal weight prior to pregnancy (kg)	59.8 (8.9)	59.9 (8.8)	59.6 (9.1)	0.37
Smoking during pregnancy (ref: Yes)	815 (15.6)	418 (15.9)	397 (15.4)	0.62
Maternal socio-economic status				0.93
No occupation	1,776 (33.1)	900 (33.3)	876 (32.9)	
I (highest social class)	181 (3.4)	96 (3.6)	85 (3.2)	
II	488 (9.1)	247 (9.1)	241 (9.1)	
III	1,122 (20.9)	569 (21.0)	553 (20.8)	
IV (lowest social class)	438 (8.2)	223 (8.2)	215 (8.1)	
Farmers	1,363 (25.4)	672 (24.8)	691 (26.0)	

To select the optimal imputation model, the normality of continuous variables was evaluated and the best imputation approach selected for non-normally distributed continuous variables. Seven continuous variables were not normally distributed: insulin, triglyceride and C-reactive protein concentration, pack-years, parity, gestational age and maternal age at delivery (Table B.3 and Figure B.1). Comparison of the distributions of the imputed and observed data for the different imputation approaches identified predictive mean matching as the optimal imputation strategy for these non-normally distributed continuous variables (Table B.4 and Figure B.2–B.8).

I set the number of imputation in MI at sixty, as nearly 60% of observations contained some missing values.

Multiple imputation requires the missingness mechanism to be MCAR or MAR and inclusion of predictors of variables with missing data has been shown to strengthen the imputation [275, 355]. Table B.5 shows (results only shown for variables with ≥5% missing data) that many of the variables in the association analyses were associated with the missingness of data. Thus, the missingness was likely random conditional on the observed data, which strengthens the belief in the validity of the imputation by MI. Moreover, the imputation will have been improved by the large number of variables in the imputation model that were predictors of variables with missing data (Table B.6, results only shown for variables with ≥5% missing data).

Once the optimal imputation model was defined, the accuracy of the final imputation model (see Table 4.2 for specification of the imputation model) was assessed. The distributions of observed and imputed data were compared, which showed that the distributions of the imputed data matched those of the observed data (Table B.7 and Figure B.9).

4.3.3 Association analyses

Association between ventilatory function and cardiometabolic markers

The cardiometabolic markers had different associations with FVC and FEV_1/FVC, and these associations also differed between the sexes.

Nearly all cardiometabolic markers were associated with FVC, in the total population and when stratified by sex, both in the unadjusted analyses and in the analyses mutually adjusted for the other cardiometabolic markers (Crude and Model 1 in Figure 4.3). However, when further adjusting for sex and height (or height only in the stratified analyses), the effect estimates were strongly reduced and became not statistically significant, which shows the important confounding effect of sex and height (Model 2 in Figure 4.3). For example, in the total population, the crude association of low density lipoprotein with FVC changed from a 164 mL increase (95% CI: 134 to 194 mL, p<0.001) to no evidence of an association, a 6.9 mL decrease (95% CI: -24.7 to 10.7 mL, p=0.44) per mmol/L increase in low density lipoprotein, after mutually adjusting for the other cardiometabolic markers, together with height and sex. Nonetheless, several cardiometabolic markers remained associated with FVC after further adjustment for these important confounders (Model 2 in Figure 4.3). Insulin concentration and diastolic blood pressure were negatively associated with FVC, in the total population and when stratified by sex. Also, in the total population, triglyceride, glucose concentration and high density lipoprotein were negatively associated with FVC, but this was driven by the association in men. Waist circumference was not associated with FVC in the total population, although it showed negative association with FVC in men and borderline positive association in women (p=0.049) (Model 2 in Figure 4.3). In addition, systolic blood pressure was not associated with FVC in the adjusted analyses (Model 2 in Figure 4.3), in either the total population or when stratified by sex.

Of all cardiometabolic markers, triglyceride concentration was the strongest predic-

tor of FVC in both the total population (-67 mL; 95% CI: -91 to -43mL, p<0.001) and among men (-78 mL; 95% CI: -111 to -45 mL, p<0.001). On the other hand, insulin concentration was the strongest predictor of FVC in women, with a reduction of 9 mL (95% CI: -13 to -4 mL, p<0.001) per mmol/L increase in insulin concentration in the adjusted analyses (Model 2 in Figure 4.3).

Further adjustments of the association analysis of FVC with the cardiometabolic markers made no further difference compared with mutually adjusting for other cardiometabolic markers and adjusting for sex and height, with the effect estimates only marginally altered (Model 3 to 6 in Figure 4.3).

All cardiometabolic markers, except for insulin concentration, were associated with FEV_1/FVC in the crude analyses in the total population. However, after mutually adjusting for the other cardiometabolic markers and further adjusting for height and sex (Model 2 in Figure 4.4), only four markers remained associated with FEV_1/FVC, waist circumference, high density lipoprotein, insulin concentration and systolic blood pressure. High density lipoprotein and systolic blood pressure showed only a borderline statistically significant association. The associations for the cardiometabolic markers with FEV_1/FVC differed markedly between the sexes, with all the associations observed in the total population being observed in women but not in men, except for insulin concentration which also showed association in men (Figure 4.4). The strongest predictor of FEV_1/FVC in women was high density lipoprotein concentration, with an effect estimate of 0.99% increase in FEV_1/FVC (95% CI: 0.35 to 1.63, p=0.002) per mmol/L increase in high density lipoprotein when mutually adjusting for the other cardiometabolic markers and for height.

Similarly to FVC, further adjusting the relation of the cardiometabolic markers with FEV_1/FVC barely changed the effect estimates (Model 3 to 6 in Figure 4.4).

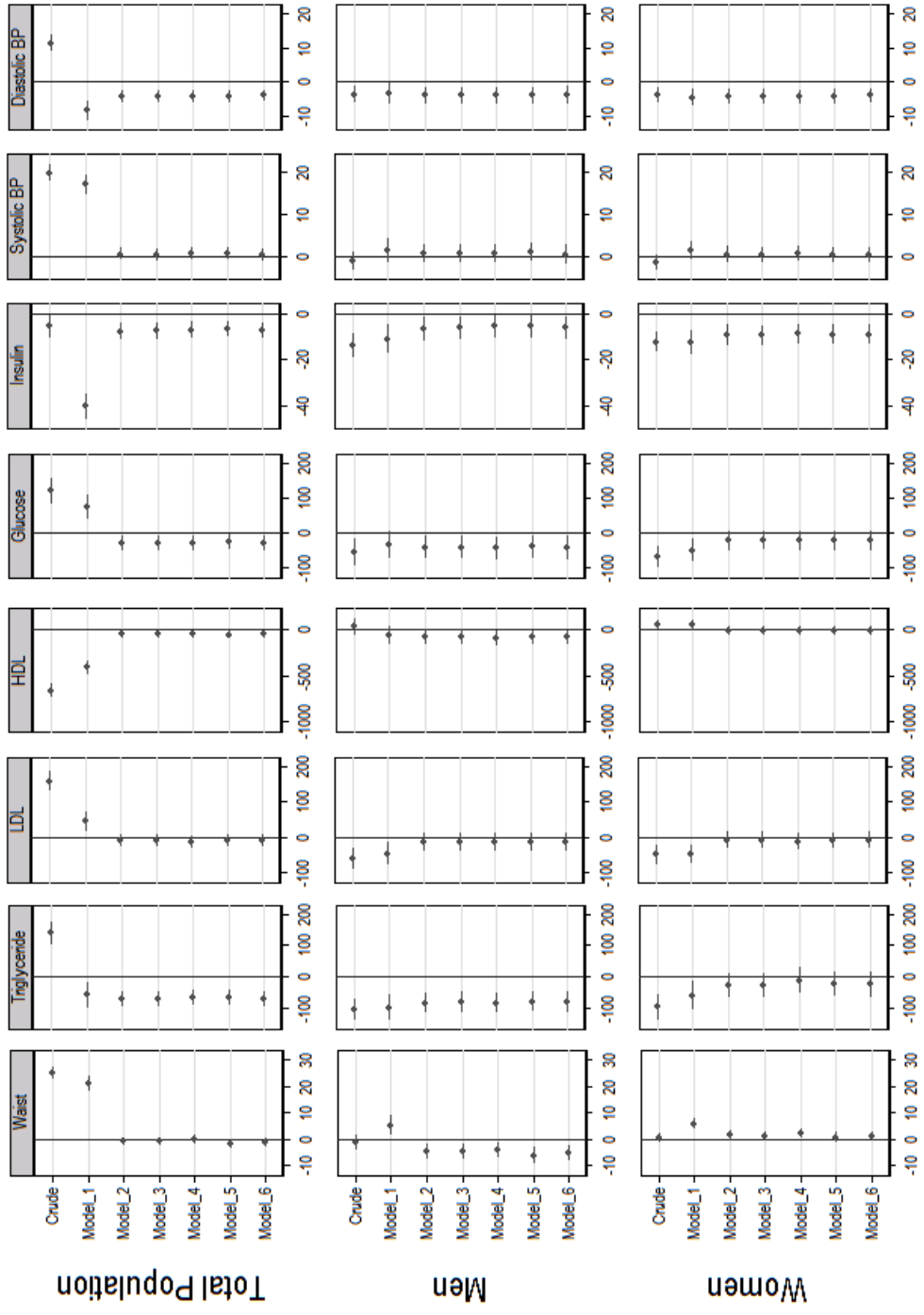


Figure 4.3: Associations between FVC (mL) and cardiometabolic markers (waist circumference in cm (Waist), triglyceride concentration in mmol/L (Triglyceride), low density lipoprotein in mmol/L (LDL), high density lipoprotein in mmol/L (HDL), glucose concentration in mmol/L (Glucose), insulin concentration in mU/L (Insulin), systolic blood pressure in mm Hg (systolic BP) and diastolic blood pressure in mm Hg (Diastolic BP)) in the total population and stratified by sex. Model 1: Mutually adjusted for other cardiometabolic markers; Model 2: Model 1 further adjusted for sex (except when stratified by sex) and adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for C-reactive protein and white blood cell count; Model 5: Model3 further adjusted for birth weight and weight gain in the first year of life; Model 6: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy

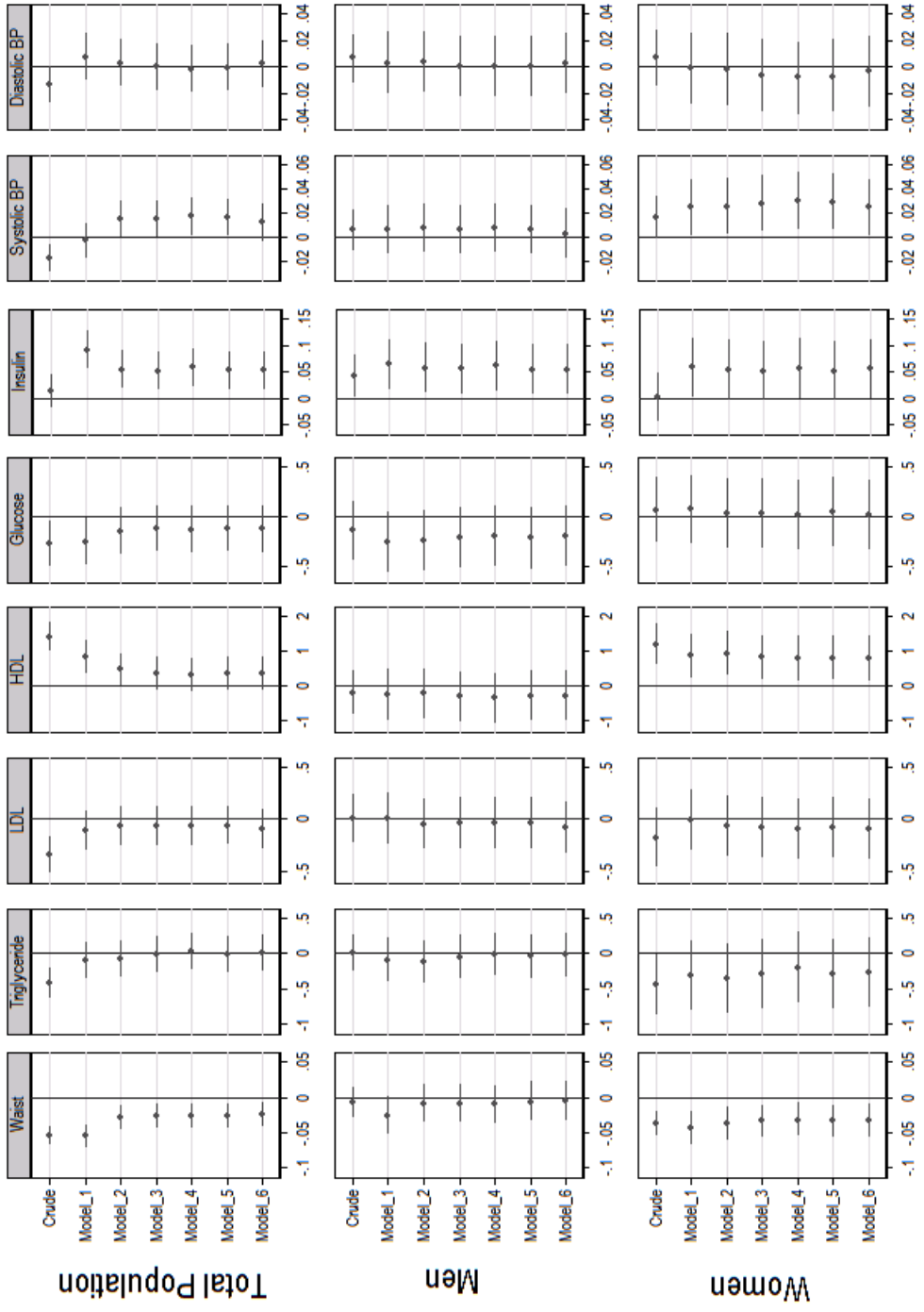


Figure 4.4: Associations between FEV_1/FVC (%) and cardiometabolic markers (waist circumference in cm (Waist), triglyceride concentration in mmol/L (Triglyceride), low density lipoprotein in mmol/L (LDL), high density lipoprotein in mmol/L (HDL), glucose concentration in mmol/L (Glucose), insulin concentration in mU/L (Insulin), systolic blood pressure in mm Hg (systolic BP) and diastolic blood pressure in mm Hg (Diastolic BP)) in the total population and stratified by sex. Model 1: Mutually adjusted for other cardiometabolic markers; Model 2: Model 1 further adjusted for sex (except when stratified by sex) and adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for C-reactive protein and white blood cell count; Model 5: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 6: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy

Association between ventilatory function and inflammatory markers

FVC was strongly associated with both the inflammatory markers in the total population and when stratified by sex (Figure 4.5). The strength of the association with white blood cell count was reduced after mutually adjusting for C-reactive protein, and vice versa (Model 1 in Figure 4.5), especially in the total population, and after further adjusting for height and sex (Model 2 in Figure 4.5). However, the association was not further reduced or explained by adjusting for adult socio-economic status and smoking, weight in early life or prenatal covariates (Model 3 to 5 in Figure 4.5).

The associations of FVC with the inflammatory markers were consistent in men and women although the 95%CI was slightly wider for the association of FVC with white blood cell count (Figure 4.5). Moreover, the association of FVC with white blood cell count among women became not statistically significant after adjusting for both C-reactive protein and height (Model 2 in Figure 4.5), from a decrease of 30.2 mL (95 %CI: -43.2 to -17.2 mL, p<0.001) in the crude analysis, to no evidence of an association, a decrease of 6.1 mL (95 % CI: -17.3 to 5.1 mL, p=0.29) per unit increase in white blood cell count after adjustment.

FEV_1/FVC was not associated with C-reactive protein in any of the analyses, while lower FEV_1/FVC was associated with an increase in white blood cell count, both in the whole sample and when stratified by sex (Figure 4.6). The pattern of association between FEV_1/FVC and white blood cell count did not differ between sexes, and was not markedly altered by adjustment for potential confounders (Model 3 to 5 in Figure 4.6). However, the strength of the overall and sex-specific associations was slightly reduced when taking socio-economic status and smoking into account, mainly due to the adjustment for smoking. Solely adjusting for smoking showed that a unit increase in white blood cell count was associated with a decrease of 0.19 % (95% CI: -0.29 to -0.09 %), after adjustment for adult smoking, height, sex and mutually adjusting for the other inflammatory marker, in the total population.

Figure 4.5: *Associations between FVC (mL) and C-reactive protein (CRP) (mg/L) and white blood cell count (WBC) (10^9 cells/L). Model 1: Adjusted for other inflammatory marker (i.e. either CRP or WBC); Model 2: Model 1 further adjusted for sex (except when stratified by sex) and adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 5: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy*

Figure 4.6: *Associations between FEV_1/FVC (%) and C-reactive protein (CRP) (mg/L) and white blood cell count (WBC) (10^9 cells/L). Model 1: Adjusted for other inflammatory marker (i.e. either CRP or WBC); Model 2: Model 1 further adjusted for sex (except when stratified by sex) and adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 5: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy*

Sensitivity and additional analyses

The majority of the associations did not change markedly when restricting the analyses those born full term or without a diagnosis of asthma (Table B.8–B.13).

Similarly, most associations did not change substantially when comparing the results from the main analyses with those performed using a more limited imputation strategy and with complete case analyses (Table B.14–B.19).

Even for the few associations where the sensitivity and additional analyses provided different effect estimates, 95% CI and statistical significance, these differences were limited.

Finally, in an additional complete case analysis, the results for the assocations of FVC with diastolic blood pressure, glucose, insulin and triglyceride concentration and the results for the association of FEV_1/FVC with insulin concentration and systolic blood pressure were substantially unaltered when substituting waist circumference with weight in the association analyses.

4.4 Discussion

The cardiometabolic and inflammatory markers were associated with FVC and FEV_1/FVC and with sex but a common association with weight in early life did not explain the association nor did adult smoking, socio-economic factors and systemic inflammation, or prenatal factors. These findings suggest that in young adults the association of cardiometabolic or inflammatory markers with FVC or FEV_1/FVC is not mediated by any of these factors, nor is it the result of a common association with them.

Ventilatory function and cardiometabolic markers

Many studies have previously investigated the relation of ventilatory function with cardiometabolic markers. These studies, the majority of which were conducted in adults older

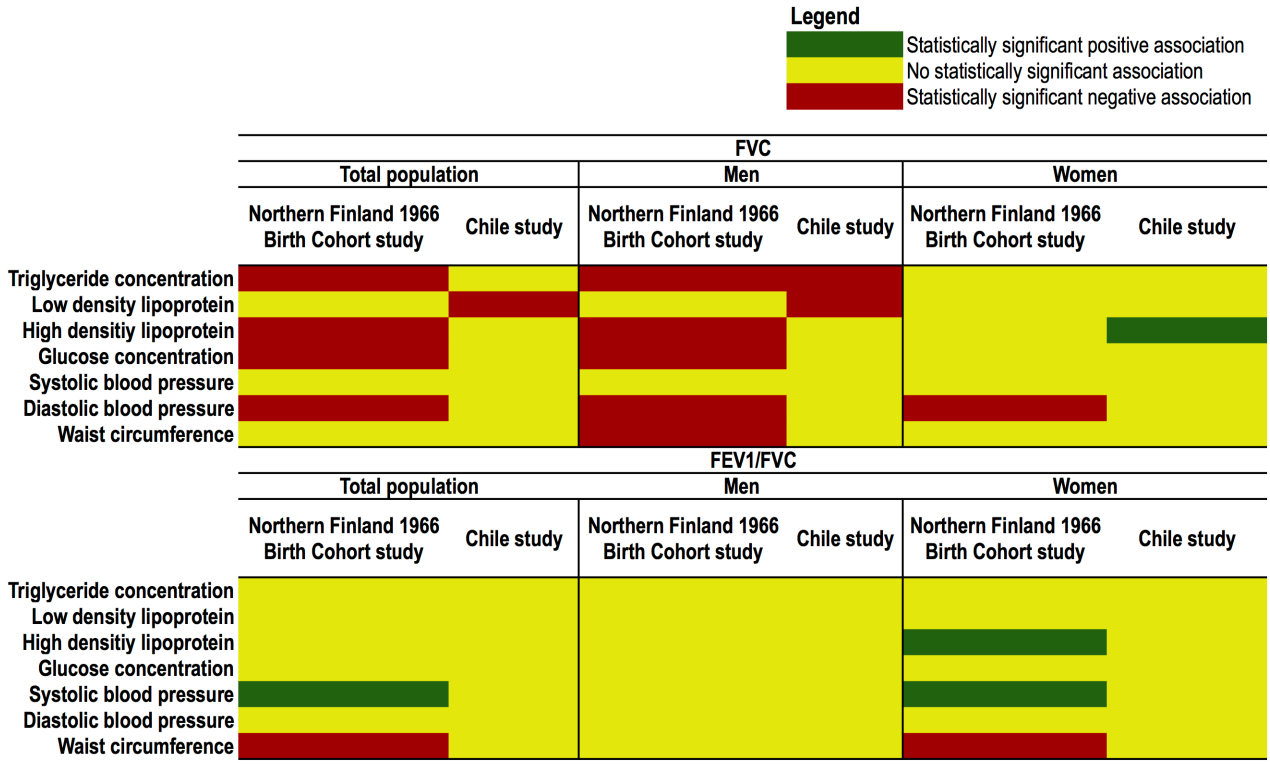


Figure 4.7: *Comparison of findings for the association of FVC and FEV_1/FVC with cardiometabolic markers in the Northern Finland 1966 birth cohort study and the Chilean study by Garcia-Larsen et al. [108]. Colors, green, yellow and red, indicate a postive statistically significant association, no statistically significant association and a negative statistically significant association, respectively. Findings of the NFBC66 are adjusted for sex, adult height, adult smoking and adult socio-economic status, birth weight and weight gain in the first year of life and mutually adjusted for the other cardiometabolic markers. The findings for the Chile study are adjusted for age, gender, height, weigh at birth, educational level, smoking, socio-economic status and body-mass index.*

than 40 years, provided very different and contradictory results (Table 4.6). Only one study of 970 participants from Chile by Garcia-Larsen et al. [108] assessed the relation in young adults aged 25, and was thus particularly relevant for comparison with our study in 31 year-olds. Figure 4.7, compares the findings from this study with those from the Chilean study.

Our findings for triglyceride concentration and low and high density lipoprotein are at odds with those from the young adults in Chile [108]. In the latter study, among all participants, triglyceride concentration and high density lipoprotein were not associ-

ated with FVC, while low density lipoprotein was associated with a lower FVC, after adjustment for adult and early life factors. In our analyses, we found the exact opposite: a strong negative association of FVC with triglyceride concentration and high density lipoprotein but no association with low density lipoprotein. However, when stratified by sex, some of the findings in this study were congruent with the results from the Chilean study, in particular the negative association of triglyceride concentration with FVC in men, and the absence of an association for triglycerides and low density lipoprotein in women [108]. In this study, systolic blood pressure was not associated with FVC, while diastolic blood pressure was consistently negatively associated with FVC, both in the total population and in men and women separately. Blood pressure is commonly dichotomised and analysed as a binary variable (high/low blood pressure), thus complicating the comparisons. Nonetheless, high blood pressure was not associated with FVC among young adults in Chile [108].

Our findings show that FVC was adversely associated with insulin concentration, in the total population and when stratified by sex. On the other hand, the negative association of glucose concentration with FVC in the total population was driven by the negative association in men. In contrast, Garcia-Larsen et al. [108] did not find an association between elevated glucose concentration and lower FVC among Chilean young adults, in either the total population or when stratified by sex.

In the NFBC66, FVC was not associated with waist circumference in the total population, while a higher waist circumference was associated with a lower FVC in men but with a trend towards a higher FVC in women. On the contrary, in the Chilean study no association was found among young adults for waist circumference and FVC, in the total population or when stratified by sex [108].

Table 4.6: Overview of studies in older adults for association of ventilatory function with cardiometabolic markers

Author, year	Study description	Association of cardiometabolic markers with	
		FVC	**FEV_1/FVC**
Engstrom, 2001 [94]	Prospective cohort study (Men born in 1914 study) in Sweden of 375 participants with 13-year follow-up and average age at baseline 55	Association of high FVC at baseline with lower increase in blood pressure, systolic and diastolic, between baseline and follow-up	-
Griffith, 2001 [118]	Prospective cohort study (Cardiovascular Health study) in USA of 5281 participants with 3-year follow-up and average age at baseline >65	High systolic blood pressure (>160 mm Hg) associated with low FVC	-
Engstrom, 2002 [93]	Prospective cohort study (Men born in 1914 study) in Sweden of 382 participants with 13-year follow-up and average age at baseline 55	Association of high FVC at baseline with low glucose concentration at follow-up	-
Lawlor, 2004 [191]	Cross-sectional study of 3,911 women in Great Britain, average age >60 years	Association of high density lipoprotein and triglyceride concentration with FVC No association of systolic blood pressure with FVC	-
Yeh, 2005 [367]	Prospective cohort study (ARIC study) in the USA of 11,479 participants with 9-year follow-up and average age at baseline 54 years	Association at baseline of FVC with fasting glucose, fasting insulin and triglyceride concentration, high density lipoprotein and systolic blood pressure in men and women No association at baseline for FVC with diastolic blood pressure in men and women Association of increased diabetes incidence with low FVC in men and women during follow-up	No association of diabetes incidence with FEV_1/FVC during follow-up
Ochs-Balcom, 2006 [233]	Cross-sectional study of 2,153 participants in the USA with average age >50 years	Association of waist circumference with FVC % predicted in men and women	Association of waist circumference with FEV_1/FVC in men and women
Fimognari, 2007 [99]	Cross-sectional study of 159 participants in Italy with average age 70 years	Elevated waist circumference in participants with low FVC (FVC<0.8 and FEV_1/FVC >0.7) No difference in systolic or diastolic blood pressure, glucose or triglyceride concentration between participants with normal ventilatory function and low FVC	No difference in systolic or diastolic blood pressure, waist circumference, glucose or triglyceride concentration between participants with normal ventilatory function and low FEV_1/FVC (FEV_1/FVC <0.7)
Leone, 2009 [196]	Cross-sectional study of 121,965 participants in France with average age 46 years	Association of large waist circumference, low high density lipoprotein, high triglyceride and high glucose concentration and high blood pressure with low FVC (FVC≤ lower limit of normal) in men and women	Association of large waist circumference with low FEV_1/FVC (FEV_1/FVC <LLN) in men and women No association of other cardiometabolic markers with low FEV_1/FVC

Continued on next page

Table 4.6 – continued from previous page

Author, year	Study description	Association of cardiometabolic markers with	
		FVC	**FEV_1/FVC**
Burkart, 2010 [45]	Cross-sectional study (MESA Lung study) in the USA of 3,630 participants, average age 61 years	-	No association of high or low density lipoprotein with FEV_1/FVC
Choi, 2011 [65]	Cross-sectional study of 2,614 Korean adults, average age >45 years	Association of waist circumference, glucose concentration, high density lipoprotein and systolic blood pressure with FVC % predicted in men No association of triglyceride concentration with FVC % predicted in men Association of waist circumference with FVC % predicted in women No association of glucose or triglyceride concentration, high density-lipoprotein or systolic blood pressure with FVC % predicted in women	Negative association of systolic blood pressure with FEV_1/FVC in men. Negative association of glucose and total cholesterol concentration and systolic blood pressure with FEV_1/FVC in women. No association of waist circumference, glucose or triglyceride concentration and high density-lipoprotein with FEV_1/FVC in men No association of waist circumference or triglyceride concentration with FEV_1/FVC in women
Heianza, 2012 [135]	Prospective cohort study in Japan of 5,346 men with 4-year follow-up and average age at baseline 49 years	Association of high FVC at baseline with low glucose concentration at baseline and at follow-up	No association of high FVC at baseline with low glucose concentration at follow-up
Jacobs, 2012 [151]	Prospective cohort study in USA of 3,205 participants with 20-year follow-up and average age at baseline 35 years	Association of decline in FVC with incidence in hypertension between baseline and follow-up	No association of decline in FVC with incidence in hypertension between baseline and follow-up
Yamane, 2013 [366]	Prospective cohort study in Japan of 1,058 participants with 28-year follow-up and average age at baseline 50 years	No association with FVC at baseline and glucose concentration at baseline or at follow-up	No association with FEV_1/FVC at baseline and glucose concentration at baseline or at follow-up
Chen, 2014 [63]	Cross-sectional study (NHANES III) in the USA of 8602 participants aged 20-65 years	Negative association of high waist circumference, high blood pressure, high triglyceride and high glucose concentration and low high density lipoprotein with FVC % predicted in men and women	
Buchman, 2015 [40]	Cross-sectional study (Berlin Aging Study II) of 697 participants, average age 68 years	Negative association of waist circumference and FVC	Association of low waist circumference with low FEV_1/FVC (FEV_1/FVC <0.7)
Colak, 2015 [68]	Cross-sectional analysis of prospective study (Copenhagen City Heart study) with 10,135 adults, average age >55 years	Negative association of waist circumference with % predicted FVC	Negative association of waist circumference with FEV_1/FVC

The Chilean study did not find any association of FEV_1/FVC with triglyceride concentration, high or low density lipoprotein, blood pressure or waist circumference [108], while in the NFBC66 systolic blood pressure, waist circumference and high density lipoprotein concentration were associated with FEV_1/FVC (Figure 4.7).

Our study findings are at odds with those by the Garcia-Larsen et al. [108] study but the associations in older adults were also not uniform across studies (Table 4.6).

Nonetheless, the combined evidence from this study and from studies in older adults for an association of FVC with cardiometabolic markers is moderately strong, although almost half of the evidence in older adults is derived from cross-sectional studies as is the evidence for both studies in young adults (Table 4.6).

Few studies have assessed the relation of FEV_1/FVC with cardiometabolic markers (Table 4.6). Those studies show only weak evidence for associations with cardiometabolic markers, with the exception of some evidence for waist circumference being inversely associated with FEV_1/FVC, a finding that is consistent with the results from this study.

Explaining the relation of ventilatory function and cardiometabolic markers

No study in young adults has previously attempted to explain the association of ventilatory function with cardiometabolic markers, with all previous studies having been conducted in older adults and having rarely considered the full range of risk factors which have been examined in our study. Lawlor et al. [191] attempted to explain the association of ventilatory function with cardiometabolic disease in women older than 60, with similar factors as in this study. They also could not explain the association of ventilatory function and insulin resistance or type II diabetes by adult or early life factors. They reported a negative association for FVC with insulin resistance, diabetes prevalence and triglyceride concentration among non-smokers. However, these associations persisted and were not markedly altered after further adjustment for adult and early life factors which included adult socio-economic status, physical activity and white blood

cell count, or birth weight [191].

Some studies have attempted to explain the relation of ventilatory function with arterial stiffness. Although measuring arterial stiffness is not a substitute for other cardiometabolic markers, all are predictors of later cardiovascular disease [57]. Bolton et al. [26] reported negative associations for FEV_1 and FVC in midlife with arterial stiffness in later life, but found no association between FEV_1/FVC and arterial stiffness. Similarly to our findings, further adjusting for smoking, inflammatory (C-reactive protein) or cardiometabolic (triglyceride concentration, systolic blood pressure and HOMA) markers, or early life factors (birth weight and father's socio-economic status) did not explain the observed associations [26]. The findings by Bolton et al. [26] were confirmed in the Burden of Obstructive Lung Disease (BOLD) London study, where TLC and FVC were negatively associated with arterial stiffness, independently of airflow limitation. This association was also not explained by confounding with smoking [8].

Our findings, combined with the limited evidence from existing studies, appears to suggest that adult socio-economic influences, systemic inflammation or early life factors are not responsible for the association of cardiometabolic markers with FVC or FEV_1/FVC.

Ventilatory function and inflammatory markers

Both inflammatory markers, C-reactive protein and white blood cell count, were associated with FVC in this study, whereas only white blood cell count was associated with FEV_1/FVC. The associations of the inflammatory markers were similar for men and women, except for the relation of white blood cell count with FVC, which did not show a significant association among women. Our findings are consistent with previous results that investigated the association of increased concentration of C-reactive protein or white blood cell count with poor ventilatory function [10, 111, 215], but few studies have investigated this in young adults, looked specifically at the relation with FEV_1/FVC, or stratified the analyses by sex.

Taking account of important confounders by adjusting the association of one inflammatory marker with ventilatory function for the other one (i.e. mutual adjustment) and for height and sex (when not stratified) did change most associations with FVC, in particular the relation of white blood cell count and FVC in women and the association of C-reactive protein with FVC in the total population.

Further adjustments did not explain the relation of C-reactive protein and white blood cell count with FVC or FEV_1/FVC. The exception was the association of white blood cell count with FEV_1/FVC, which was moderately affected by adjusting for smoking albeit it did not fully explain the association. No previous studies have attempted to assess whether weight in early life or prenatal factors explain the association of ventilatory function with inflammatory markers.

Strengths and limitations

This is the largest study to date of ventilatory function with cardiometabolic and inflammatory markers in young adults, for which the current evidence base, especially for the relation with cardiometabolic markers, is particularly sparse. This did complicate comparisons with similar studies as these were mostly conducted on middle-age or elderly adults. Other major strengths of this study were the regular follow-ups and availability of information from gestation into adulthood on study participants and their parents. The assessment of study participants in young adulthood also allowed for the investigation of the associations without the potential confounding of numerous environmental influences, the effects of which accumulate with age. Moreover, analyses were conducted on the total population and stratified by sex, which enabled the identification of sex-specific associations. In addition, the full range of factors that were assessed as potentially explanatory factors have seldom been considered previously.

Data in the NFBC66 were collected meticulously and according to standardised protocols. However, ventilatory function and the inflammatory and cardiometabolic mark-

ers were measured at the same time, despite the NFBC66 study being longitudinal by design. Hence, temporality of the relations could not be deduced. Another limitation was the non-availability of post-bronchodilator ventilatory function. Although this was explored further by conducting a sensitivity analysis among non-asthmatic participants, this cannot entirely compensate for not having measured post-bronchodilator ventilatory function, as doctor diagnosis of asthma is subject to variability. Participants on hypertensive medication were not included in the study population as we only had their post-treatment blood pressure values and these were not comparable with the blood pressure values from the rest of the cohort. The exclusion of this small group is unlikely to have altered substantially the general findings. Finally, despite the extensive availability of demographic, social and clinical information, only a limited set of hypotheses could be assessed with the data in this study. Data that would have allowed more detailed investigation, such as information on maternal nutrition during pregnancy or more information on systemic inflammation were not available for this study. The availability of other inflammatory markers is of particular of importance as systemic inflammation might not be sufficiently reflected by the two inflammatory markers in this study.

Although the NFBC66 is a large population-based cohort study, multiple imputation was employed to increase the sample size available for analysis, which resulted in increased precision of the effect estimates in the association analyses and avoided potentially biased results that would have arisen from a complete case analysis. Moreover, the imputation was thoroughly evaluated and conducted according to strict guidelines [313], which, as shown in a recent systematic review [134], is not commonly the case in studies that employ imputation. The conclusions from this study were further strengthened by the robustness of the findings to sensitivity analyses, in either participants born full term or among those without a diagnosis of asthma, and to the additional analyses, where the analyses were repeated using a more limited imputation strategy or using complete data only and when waist circumference was substituted by weight in the as-

sociation analyses.

4.5 Conclusion

This study is the largest to date and one of the few that has investigated the association of cardiometabolic and inflammatory markers with FVC and FEV_1/FVC in young adulthood.

Low FVC was associated with high diastolic blood pressure, high density lipoprotein, insulin, triglyceride and glucose concentration, in the total population. The associations of FVC with triglyceride, glucose concentration and high density lipoprotein in the total population were driven by the association in men. A low FVC was also associated with high C-reactive protein and white blood cell count, but the association with white blood cell count was driven by the association in men.

Reduced FEV_1/FVC was associated with increased waist circumference, insulin concentration, systolic blood pressure, and with low high density lipoprotein,. These associations differed markedly between the sexes, with all the associations observed in the total population being observed in women but not in men, except for insulin concentration. Further, lower FEV_1/FVC was associated with an increase in white blood cell count but not with C-reactive protein .

The effect estimates of the associations were strongly influenced by adjustment for important confounders, height and sex, and by mutually adjusting for the other inflammatory or cardiometabolic markers. Socio-economic factors, systemic inflammation, as well as weight in early life and prenatal influences, did not explain the relation of cardiometabolic markers with FVC or FEV_1/FVC. As for the inflammatory markers, only smoking partially explained the association of white blood cell count with FEV_1/FVC. This appears to suggest that other environmental or genetic factors are responsible for the observed association of cardiometabolic and inflammatory markers with measures

of both restrictive and obstructive ventilatory function.

CHAPTER 5

THE DIVERSITY IN ETHNICITY, LUNG FUNCTION AND BIRTH WEIGHT AMONG YOUNG ADULTS (DELBYA) STUDY: A PILOT STUDY

5.1 Aim and objectives

The aim of the Diversity in Ethnicity, Lung function and Birth weight in Young Adults (DELBYA) study is to investigate ethnic differences in ventilatory function and a limited list of cardiometabolic markers among young adults in the UK, and to identify factors, in particular birth weight and other early life influences, that might explain these differences.

Here I describe a pilot investigation aimed to assess the feasibility of such a study and to obtain preliminary results on both ethnic differences in ventilatory function and the cardiometabolic markers between two ethnic groups, White and South Asian British, and on potential explanatory factors that might account for these differences.

The specific objectives of this pilot investigation are to:

1. Evaluate the study design and protocol of the DELBYA study and assess the feasibility of conducting it in a larger sample. In particular:

    a) Determine the recruitment rate and ideal route of recruitment of young adults

    b) Assess the willingness of young adults to travel to the study centre and to take part in all study procedures and questionnaires

    c) Identify the potential missingness in questionnaire answers, in particular related to parental and grandparental information

    d) Evaluate feasibility of data linkage to obtain birth weight from birth records

2. Obtain preliminary results on:

    a) Differences between the two ethnic groups in ventilatory function measures (primary outcomes) and cardiometabolic markers (secondary outcomes)

b) Identifying explanatory factors for differences in both primary and secondary outcomes, using:

   i. Linear regression analysis of a priori defined factors, including long bone length, birth weight or material deprivation as measured by parental and grandparental socio-economic status

   ii. Penalised regression analysis testing all factors for which information was available

5.2 Methods

I was responsible for the design and conduct of the DELBYA study, under the supervision of Prof. Peter Burney and Dr. Cosetta Minelli. I obtained all the necessary ethical approvals, designed the study documentation, questionnaires and recruitment advertisements, communicated with participants, scheduled and conducted the study visits, managed the study data and performed all statistical analyses.

5.2.1 Study population and recruitment

The DELBYA study was a cross-sectional study of Imperial College London students who were aged 18-23 years, born in the UK, defined themselves as White or South Asian British ethnicity and had at least three grandparents who were born either in the UK or other European countries, or in South Asia (Pakistan, India, Nepal, Bangladesh, Bhutan, Sri Lanka) or East Africa (Kenya, Tanzania, Uganda). Participants were excluded if they had any contraindication to undertaking a forced respiratory manoeuvre.

Participants were recruited from Imperial College London through advertisements (Figures C.1 and C.2) on noticeboards in College buildings, and on online College noticeboards, advertisements in Imperial College Union Club & Society newsletters, shout-

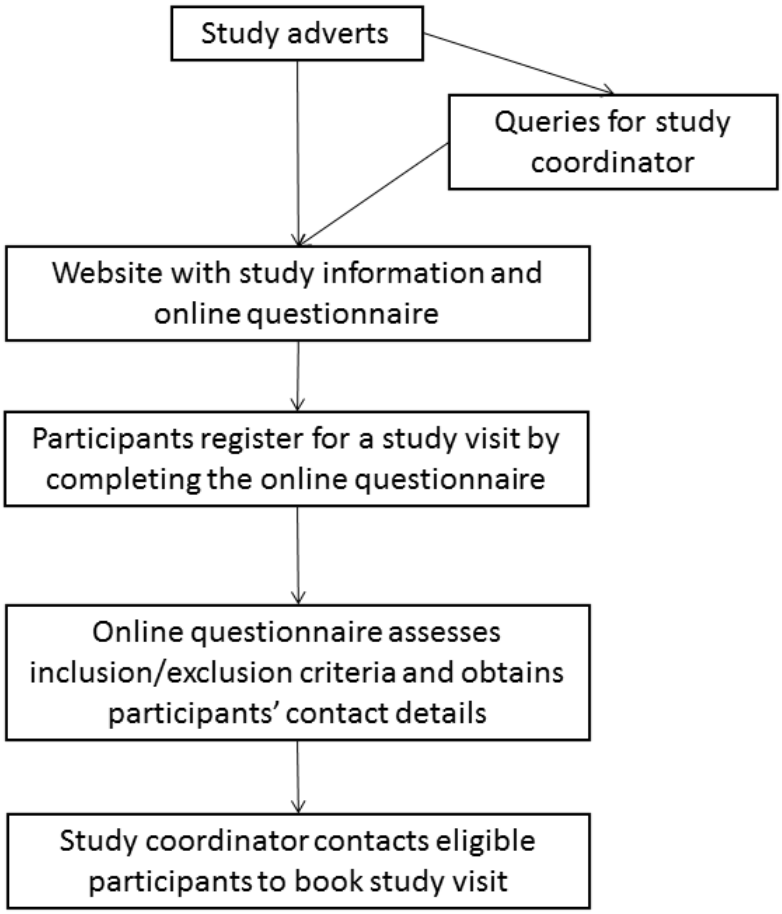


Figure 5.1: *Recruitment process*

outs after lectures following the approval of the lecturer, and advertisements on social media (Facebook and Twitter).

Figure 5.1 provides an overview of the recruitment process. The advertisements directed interested participants to a website (Figure C.3 shows a screenshot of the website) which contained more information about the study and an online questionnaire for the registration of participants into the study. Participants were offered a cash incentive of £15 for participation in the study, which was based on the UK minimum hourly wage and the total time the participants spent travelling and undergoing the clinical examination.

5.2.2 Study visit

I received the BOLD spirometry training and further training by Prof. Peter Burney for dealing with study participants and conducting the study visits. I had several practice visits with members of the research group, and Prof. Peter Burney was present at several initial study visits in order to monitor the conduct and provide feedback.

All study visits took place in the respiratory biomedical research unit at the Royal Brompton Hospital, London, UK, and Figure 5.2 provides an overview of the procedures conducted during the visit. After the initial registration, assessment of contraindications for a forced expiratory manoeuvre (exclusion criteria) and study consent, participants' cardiovascular and anthropometric measurements were taken, as was pre-bronchodilator ventilatory function. The core questionnaire was completed after the administration of the bronchodilator, which was followed by the measurement of the post-bronchodilator ventilatory function. The study visit was concluded by checking the participants' blood pressure and pulse rate before they left the hospital.

5.2.3 Study data

Study data were recorded on five questionnaires: (1) an online registration questionnaire prior to the study visit, which assessed the inclusion/exclusion criteria and obtained participants' contact details to book the study visit; (2) a paper-based safety questionnaire during the study visit, which reassessed the exclusion criteria; (3) a paper-based measurement questionnaire during the study visit, which was used to record the results from the anthropometric and cardiovascular measurements and the compliance of, or adverse events to, spirometry; (4) a paper-based core questionnaire during the study visit, which recorded information on respiratory symptoms, smoking, parental and grandparental socio-economic status and educational attainment, and parental and grandparental upbringing and place of birth [41]; (5) an online feedback questionnaire

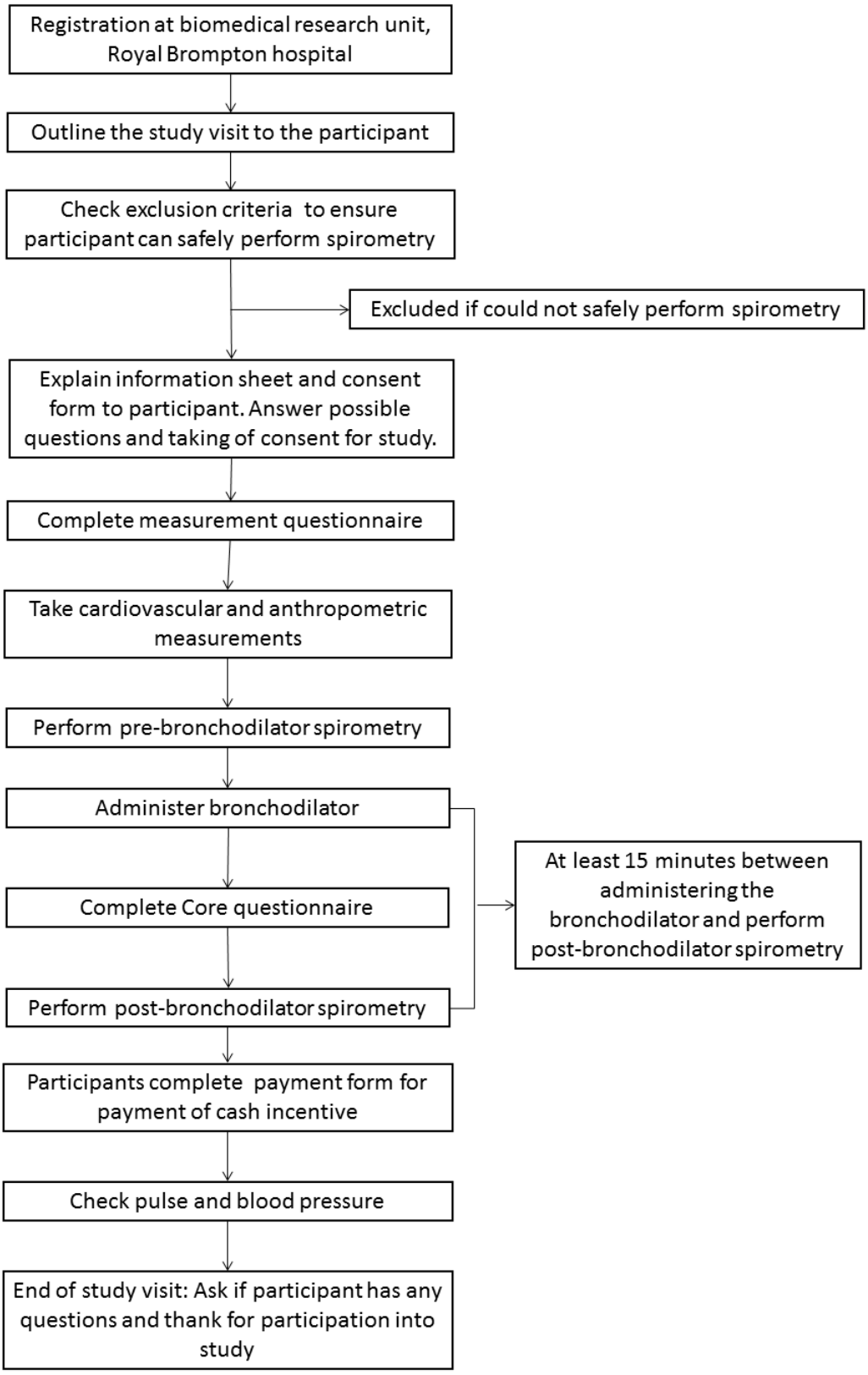


Figure 5.2: *Overview of the study visit*

after the study visit, which collected feedback on the study conduct and procedures. All questionnaires are available in Appendix C.2.

General information

Information on the inclusion and exclusion criteria described in Section 5.2.1 was obtained to determine the eligibility of participants and whether participants could safely perform spirometry. Contact details were collected to book the study visit for the participants.

Participants' sex was recorded during the study visit and age was calculated by subtracting the date of birth from the date of the study visit. Participants self-defined their ethnicity, based on the ethnic group question and categories, as recommended by the Office for National Statistics [235]. By study design, participants were either White or South Asian British.

Clinical measurements

All clinical measurements were recorded on the measurement questionnaire with the exception of ventilatory function, which was stored in the spirometer and subsequently linked. All clinical measurements (spirometry, cardiovascular and anthropometry) were performed according to standard operating procedures, and an overview of the clinical measurements is shown in Table 5.1.

Blood pressure, pulse rate, height and weight measurements were obtained according to Royal Brompton and Harefield NHS Foundation Trust standard operating protocols. Blood pressure and pulse rate were measured thrice using a Dinamap on the right upper arm, when seated after 15 minutes of rest and with the arm positioned at heart level. Height (0.1 cm accuracy) and weight (0.1 kg accuracy) were measured once, using a stadiometer (Leicester) and weighing scales (Marsden), respectively, with participants asked to remove shoes, items from their pockets or heavy clothing.

Table 5.1: Overview and description of clinical measurements in the DELBYA study

Variable	Units/Categories	Note	Obtained from
Systolic and diastolic blood pressure	mm Hg	Measured thrice, average used in the analyses. Also measured before the end of the study visit to check the participants' status before concluding the study visit	Measurement questionnaire
Pulse	Beats per minute (bpm)	Measured thrice, average used in the analyses. Also measured before the end of the study visit to check the participants' status before concluding the study visit	Measurement questionnaire
Height	Centimetres		Measurement questionnaire
Weight	Kilogram		Measurement questionnaire
Body mass index	kg / m^2	Derived from current height and weight by dividing weight by height (in $metres^2$)	Measurement questionnaire
Demispan	Centimetres	Measured twice, average used in the analyses	Measurement questionnaire
Ulna	Centimetres	Measured twice, average used in the analyses	Measurement questionnaire
FVC	Litres	Measured according to ATS/ERS criteria	Spirometer
FEV_1	Litres	Measured according to ATS/ERS criteria	Spirometer
FEV_1/FVC	Percent	Derived from FEV_1 and FVC by taking the ratio of FVC to FEV_1	

Long bone length (demispan and ulna) were measured twice using a measuring tape (Seca) according to standardised procedures. Demispan was measured standing, with the right arm extended horizontally from the shoulder, from between the middle and ring finger of the right hand to the mid-point of the sternal notch. The ulna was measured on the left arm, while the participant was seated and with the participant bending the arm across the chest with the palm flat and fingers pointing toward the right shoulder, from the point of the elbow to the mid-point of the prominent bone of the wrist.

Spirometery was performed according to ATS/ERS guidelines [220] both pre- and

post-bronchodilator. Participants were seated and performed spirometry, using the ndd EasyOne Spirometer (ndd Medizintechnik AG, Zurich, Switzerland), while wearing a noseclip. Participants performed at least three acceptable blows but could attempt up to eight blows. The spirometry procedure was first explained and demonstrated to the participant by myself before pre-bronchodilator spirometry was measured. Participants had the administration of the bronchodilator explained to them and were given two 100 micrograms puffs of salbutamol (Salamol, IVAX pharmaceuticals UK) via a valved spacer (ABLE spacer, Clement Clarke International, England). Participants inhaled the salbutamol via the spacer and held their breath for 10 seconds before exhaling. Following both inhalations, participants waited at least 15 minutes before performing the post-bronchodilator spirometry.

Questionnaire data on symptoms and risk factors

Information on chronic cough, asthma, wheezing, exacerbations, dyspnea and hospitalisation for breathing problems were collected. Table 5.2 provides an overview and description of the respiratory symptoms collected in the study. Active smoking, exposure to passive smoking and exposure to parental smoking throughout the life course were assessed. Table 5.3 shows the definitions used in the DELBYA study for the different smoking variables. Spirometry compliance, adverse events related to spirometry and factors that might influence spirometry (recent use of breathing medications, recent respiratory infection or recent smoking) were also recorded and are shown in Table 5.4. Parental and grandparental socio-economic and ancestry information is shown in Table 5.5. An International Standard Classification of Occupations (ISCO) code was allocated, according to the ISCO-88 classification [148], based on the description of the usual job or occupation, type of work and industry. In the analyses the major groups of the ISCO-88 classification were used to group the parents and grandparents.

Birth weight

Birth weight was obtained from the Health and Social Care Information Centre (HSCIC), a UK governmental agency that holds data, including birth weight data, on behalf of the Office for National Statistics (ONS). Participants' birth weight was obtained through linkage of participants' name, date of birth and National Health Service (NHS) number.

Study feedback

Participants who attended the study visit, as well as those who provided contact details but did not attend the study visit, were contacted by email and asked to complete an online feedback questionnaire. Feedback was obtained on the recruitment, the study visit and procedures, and the overall participant's study experience. Table 5.6 provides an overview and description of the information collected.

Table 5.2: Description of respiratory symptoms employed in the DELBYA study

Variable	Units/Categories	Note	Obtained from
Chronic cough	a) No; b) Yes	Affirmative answer to all subsequent questions: a)Do you usually cough when you don't have a cold? b)Are there months in which you cough on most days? c)Do you cough on most days for as much as three months each year? And confirmation that coughs lasts at least 2 years in a single choice question: For how many years have you had this cough?	Core questionnaire
Asthma, ever	a) No; b) Yes	Answer to "Has a doctor or other health care provides ever told you that you have asthma, asthmatic bronchitis or allergic bronchitis?"	Core questionnaire
Asthma, current	a) No; b) Yes	Answer to "Do you still have asthma, asthmatic bronchitis or allergic bronchitis?"	Core questionnaire
Wheezing, last year	a) No; b) Yes	Answer to "Have you had wheezing or whistling in your chest at any time in the last 12 months?"	Core questionnaire
Wheezing, last year not only when a cold	a) No; b) Yes	Answer to "Have you had this wheezing or whistling only when you have a cold?"	Core questionnaire
Wheezing, last year made you feel short of breath	a) No; b) Yes	Answer to "In the last 12 months, have you ever had an attack of wheezing or whistling that has made you feel short of breath?"	Core questionnaire
Any exacerbation, ever	a) No; b) Yes	Answer to "Have you ever had a period when you had breathing problems that got so bad that they interfered with your usual daily activities or caused you to miss work?"	Core questionnaire
Any exacerbation, last year	a) No; b) Yes	Derived from the question "How many such episodes have you had in the past 12 months", which relates to any exacerbation. "Yes" was defined as having any exacerbation in the past year.	Core questionnaire
Dyspnea	1-5	Five point Modified Medical research council scale [100]	Core questionnaire
Hospitalised as child for breathing problems	a) No; b) Yes	Answer to "Where you hospitalized as a child for breathing problems prior to the age of 10?"	Core questionnaire

Table 5.3: Description of smoking variables employed in the DELBYA study

Variable	Units/Categories	Note	Obtained from
Ever smoked cigarettes	a) No; b) Yes	Answer to "Have you ever smoked cigarettes?" with "Yes" meaning more than 20 packs of cigarettes in a lifetime or more than 1 cigarette each day for a year	Core questionnaire
Pack-years		Derived from the number of years smoked and number of packs of cigarettes smoked per year.	Core questionnaire
Passive smoke, people smoke where you live	a) No; b) Yes	Derived from the question "Not counting yourself, how many people in your household smoke regularly?" "Yes" means at least one person smokes in the household	Core questionnaire
Passive smoke, exposed to tobacco smoke at home	a) No; b) Yes	Derived from the question "How many hours per day are you exposed to other people's tobacco smoke at home?" "No" means not exposed (i.e. 0 hours/day)	Core questionnaire
Passive smoke, exposed to tobacco smoke in social settings	a) No; b) Yes	Derived from the question "How many hours per day are you exposed to other people's tobacco smoke in bars, restaurants, cinemas or similar social settings?" "No" means not exposed (i.e. 0 hours/day)	Core questionnaire
Passive smoke, exposed to tobacco smoke elsewhere	a) No; b) Yes	Derived from the question "How many hours per day are you exposed to other people's tobacco smoke elsewhere"? "No" means not exposed (i.e. 0 hours/day)	Core questionnaire
Maternal smoking, before pregnancy	a) No; b) Yes	Derived from the question "Did your mother smoke regularly before your pregnancy?"	Core questionnaire
Paternal smoking, before pregnancy	a) No; b) Yes	Derived from the question "Did your father smoke regularly before your pregnancy?"	Core questionnaire
Parental smoking, before pregnancy	a) No; b) Yes	Derived from the questions "Did your mother smoke regularly before your pregnancy?" and "Did your father smoke regularly before your pregnancy?""Yes" means at least one parent smoked	Core questionnaire

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Table 5.3 – continued from previous page

Variable	Units/Categories	Note	Obtained from
Maternal smoking, during pregnancy	a) No; b) Yes	Derived from the question "Did your mother smoke regularly during your pregnancy?"	Core questionnaire
Paternal smoking, during pregnancy	a) No; b) Yes	Derived from the question "Did your father smoke regularly during your pregnancy?"	Core questionnaire
Parental smoking, during pregnancy	a) No; b) Yes	Derived from the questions "Did your mother smoke regularly during your pregnancy?" and "Did your father smoke regularly during your pregnancy?""Yes" means at least one parent smoked	Core questionnaire
Maternal smoking, during childhood	a) No; b) Yes	Derived from the question "Did your mother smoke regularly during your childhood?"	Core questionnaire
Paternal smoking, during childhood	a) No; b) Yes	Derived from the question "Did your father smoke regularly during your childhood?"	Core questionnaire
Parental smoking, during childhood	a) No; b) Yes	Derived from the questions "Did your mother smoke regularly during your childhood?" and "Did your father smoke regularly during your childhood?""Yes" means at least one parent smoked	Core questionnaire
Maternal smoking, nowadays	a) No; b) Yes	Derived from the question "Did your mother smoke regularly nowadays?"	Core questionnaire
Paternal smoking, nowadays	a) No; b) Yes	Derived from the question "Did your father smoke regularly nowadays?"	Core questionnaire
Parental smoking, nowadays	a) No; b) Yes	Derived from the questions "Did your mother smoke regularly nowadays?" and "Did your father smoke regularly nowadays?" "Yes" means at least one parent smoked	Core questionnaire

Table 5.4: Description of variables that convery information related to ventilatory function

Variable/ Data	Description and/or Units/Categories	Note	Obtained from
Respiratory infection	a) No; b) Yes	Answer to "Have you had a respiratory infection (cold) in the last three weeks?"	Measurement questionnaire
Medications for breathing	a) No; b) Yes	Answer to "Have you taken any medications for breathing in the last 24 hours?"	Measurement questionnaire
Smoking last	a) No; b) Yes	Derived from the question "When did you last smoke?" and "Yes" was defined as smoking the last month.	Measurement questionnaire
Spirometry compliance and adverse events	a)Recording of compliance with spirometry b)Noting of any adverse events related to spirometry c)Describing of any condition that might affect spirometry		Measurement questionnaire
Bronchodilator compliance	a) No; b) Yes	Recording of administration of bronchodilator	Measurement questionnaire

Table 5.5: Overview of immigration, upbringing, ancestry, educational and socio-economic variables in the DELBYA study

Immigration, upbringing and ancestry			
Variable	**Units/Categories**	**Note**	**Obtained from**
Immigration status	a) Both parents born in the UK; b) One parent born in the UK; c) No parent born in the UK	Derived from the place of birth of the parents	Core questionnaire
Mother, upbringing	a) Rural; b) Urban	Derived from the question "What term best describes the place your parent/ grandparent lived most of the time during her childhood?" "Rural" is defined as farm or village in a rural area. "Urban" is defined as small town or suburb or city	Core questionnaire
Maternal grandmother, upbringing	a) Rural; b) Urban		Core questionnaire
Maternal grandfather, upbringing	a) Rural; b) Urban		Core questionnaire
Father, upbringing	a) Rural; b) Urban		Core questionnaire
Paternal grandmother, upbringing	a) Rural; b) Urban		Core questionnaire
Paternal grandfather, upbringing	a) Rural; b) Urban		Core questionnaire
Grandparental ancestry	At least 3 born in: UK; Western-Europe (WE); UK or WE; South-Asia; South-Asia or East-Africa	Derived from the place of birth of the grandparents	Core questionnaire
(Grand)parental educational attainment and socio-economic status			
Variable	**Units/Categories**	**Note**	**Obtained from**
Mother	a) ≤ High School; b) >High School	Derived from the question "What is the highest level of schooling your parent/ grandparent has completed?"	Core questionnaire
Maternal grandmother	a) ≤ High School; b) >High School		Core questionnaire
Maternal grandfather	a) ≤ High School; b) >High School		Core questionnaire

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Table 5.5 – continued from previous page

(Grand)parental educational attainment and socio-economic status			
Variable	**Units/Categories**	**Note**	**Obtained from**
Father	a) ≤ High School; b) >High School		Core questionnaire
Paternal grandmother	a) ≤ High School; b) >High School		Core questionnaire
Paternal grandfather	a) ≤ High School; b) >High School		Core questionnaire
Maternal grandparents farming	a) No; b) Yes	Derived from the questions "Has your grandmother been a farmer?" and "Has your	Core questionnaire
Paternal grandparents farming	a) No; b) Yes	grandfather been a farmer?" "Yes" means at least one grandparent was a farmer	Core questionnaire
(Grand)parental occupation	Classified in "Did not work" or ISCO-88 major groups: a) Armed forces; b) Legislators, senior officials and managers; c) Professionals; d) Technicians and associate professionals; e) Clerks; f) Service works and shop and market sales workers; g) Skilled agricultural and fisher workers; h) Craft and related trade workers; i)Plant and machine operators and assemblers; j) Elementary occupations	Derived from questions on usual occupation or job, description of job and industry they worked in	Core Questionnaire

Table 5.6: Overview and description of study obtained from the online feedback questionnaire

Data	Categories	Note
Means of recruitment	a) Recruitment flyer; b) Word of mouth; c) Shout-out during lecture;d) Facebook or Twitter; e) Email from Imperial College Society or Club	Derived from question "How did you learn about the DELBYA study?"
Participant information sheet adequate	a) No; b) Yes	Derived from question "Was the study information in the participant information sheet adequate?"
Reason for study participation	a) Interested in helping medical research; b) Interested in knowing my lung function; c) For the reimbursement	Derived from question "Why did you want to participate in the study?"
Study visit attendance	a) No; b) Yes	Derived from question "Did you attend the study visit?"
Reason non attendance	a) No longer interested;b) No time of the study visit; c) Did not want to travel to the hospital; d) Reimbursement not enough;e) Other	Derived from question "Why did you no longer want to attend the study visit?"
Difficulty traveling	a) No; b) Yes	Derived from question "Was traveling to the hospital for the study visit difficult for you?"
Comfort procedures study visit	a) Very comfortable; b) Somewhat comfortable; c) Not comfortable	Derived from question "How comfortable were you with the following procedures of the study visit?" for each study procedure
Study visit duration	a) No; b) Yes	Derived from question "Did the study visit last longer than you expected?"
Reimbursement	a) About right; b) Too little;c) Too much	Derived from question "How did you find the reimbursement for participating?"
Study visit experience	a) Very good; b) Fair; c) Poor	Derived from question "Overall, how would you rate your experience of the study visit?"
Recommend friends	a) No; b) Yes	Derived from question "Did you recommend the study to your friends?"
Future participation	a) No; b) Yes	Derived from question "Would you attend similar studies in the future?"

5.2.4 Data quality control and management

Both online questionnaires were administered via Qualtrics, an online survey platform recommended and supported by Imperial College London, and all paper-based questionnaires were interviewer-led. I entered the data from the paper-based questionnaires twice (double data entry) using EpiData 3.1 (EpiData Association, Odense, Denmark) to identify any data entry errors.

The participants' spirograms were reviewed at two intermediate time points during the study by a respiratory physiologist who provided feedback on my conduct of measuring spirometry. The calibration of the spirometer was checked daily using a 3 litres syringe. After all study visits were completed, a physician (Prof. Peter Burney), who was blinded to the birth weight status, reviewed each spirogram using the ndd EasyWare software (ndd Medizintechnik AG, Zurich, Switzerland) and assigned a quality score based on the ATS/ERS acceptability and reproducibility criteria. The highest of the acceptable post-bronchodilator FVC and FEV_1 values were used in the statistical analyses.

5.2.5 Ethical approval, informed consent and data linkage/sharing

Ethical approval for the study was obtained from the Imperial College research ethics committee (ref: ICREC 13 6 16) and the Imperial College medical education ethics committee (ref: MEEC 1314 – 07). Both approval letters are available in Appendix C.3.

Written informed consent was obtained from each participant after explaining the participant information sheet and consent form and answering of any questions. Approval for the linkage to personal information, which was needed to obtain birth weight data, was requested in the consent form.

Study results were provided to the participants or their general practitioner, as per the participants' request indicated on the consent form. Participants were also provided with a summary of the main findings of the study if requested on the consent form. The

participant information sheet and consent form are available in Appendix C.3.

5.2.6 Statistical analysis

Descriptive statistics

Data were summarised using mean and standard deviation for continuous variables or number and percentage for categorical variables, and the proportion of missing data was reported. Differences between the two ethnic groups and differences between those who did and did not have birth weight data were investigated using the non-parametric Wilcoxon rank sum test for continuous variables due to the low number of participants, and Fisher's exact test for categorical variables, as the expected cell frequencies were generally low due to the small sample size. Estimates of the association of risk factors with respiratory symptoms by ethnicity were expressed in terms of odds ratio (OR). Lung function reversibility was assessed by comparing the difference of pre- to post-bronchodilator ventilatory function relative to the post-bronchodilator ventilatory function [328].

Association analyses

The primary outcomes of the association analyses were post-bronchodilator FVC and FEV_1/FVC, while the secondary outcomes were blood pressure, BMI and pulse rate. For the adjusted analysis of differences between the two ethnic groups in the primary outcomes multiple linear regression was used, with covariates specified a priori. The variance inflation factor was employed to evaluate multicollinearity [316].

Penalised regression was conducted as an additional analysis for both the primary and secondary outcomes. Standard linear regression can result in overfitting when the sample size is small relative to the number of variables tested in the model [246]. Penalised regression methods represent an alternative approach that addresses the issue

of overfitting by shrinking the regression coefficients towards zero. From the available penalised regression methods, I chose the lasso (least absolute shrinkage and selection operator) regression since, in addition to parameter estimation, it simultaneously performs variable selection by shrinking some of the coefficients exactly to zero and therefore removing them from the model [246]. The value of the parameter which controls the amount of shrinkage was chosen based on cross-validation. In the lasso analysis of the primary outcomes (ventilatory function), secondary outcomes (cardiometabolic markers) were not considered as potential predictors, and vice versa. Also not included as predictors in the lasso were variables with less than five observations (smoking of waterpipe, maternal smoking during pregnancy and maternal smoking now), as well as grandparental socio-economic and educational variables, as these contained missing observations which would have reduced the sample size and power of the analysis. All other variables in Table 5.7 and Table C.1 were considered as potential predictors for the lasso regression. The predictors retained by the lasso regression were those that result in the best model fit [246].

All analyses were conducted in Stata 13.1 (StataCorp LP, College Station, TX, USA), apart from the lasso regression, which was performed using the glmnet package [103] in R 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $p<0.05$.

5.3 Results

5.3.1 Recruitment, study visit completion and birth weight linkage

Figure 5.3 provides an overview of the recruitment, with details on dropouts and exclusions. Over 3,800 students at Imperial College London were a UK national, which was considered as a proxy for being born in the UK, of White or South Asian British ethnicity and aged between 18 and 23 during the recruitment period.

Of the 311 individuals who started the online eligibility & safety questionnaire, 172 individuals were eligible for inclusion in the study and could safely perform spirometry. The main reason for not fulfilling the inclusion criteria was not being born in the UK (n=55, 47% of all excluded), while two students were excluded for recent surgery on chest or abdomen. Contact details were obtained for 135 students who were invited to the study visit of whom 112 attended. Thus overall 112 (3%) participants were recruited into the study from a target population of 3,863 UK students at Imperial College London, aged 18-23, and of White or South Asian British ethnicity during the period of the study. There was no difference in recruitment by ethnicity: 86 White participants took part (2.9%, 2,931 in the target population) vs 26 South Asian British students (2.8%, 932 in the target population).

All 112 participants attending the study visit accepted and signed the consent form, completed the visit, completed all procedures and did not refuse to respond to any questions (Figure 5.4). However, three White participants that did not fulfil the ancestry inclusion criterion were excluded from the subsequent analyses while poor ventilatory function test quality excluded a further 10 participants. Birth weight was successfully obtained for 90 participants with acceptable lung function, which resulted in a study population of 68 White and 22 South Asian British participants (Figure 5.4). Those without birth weight data did not differ in FVC, FEV_1, FEV_1/FVC or height from those with birth weight data. However, participants without birth weight were slightly older compared to those with birth weight data (21.2 yrs (SD:1.1) vs 20.4 yrs (SD:1.3); p=0.0499, Wilcoxon rank-sum test).

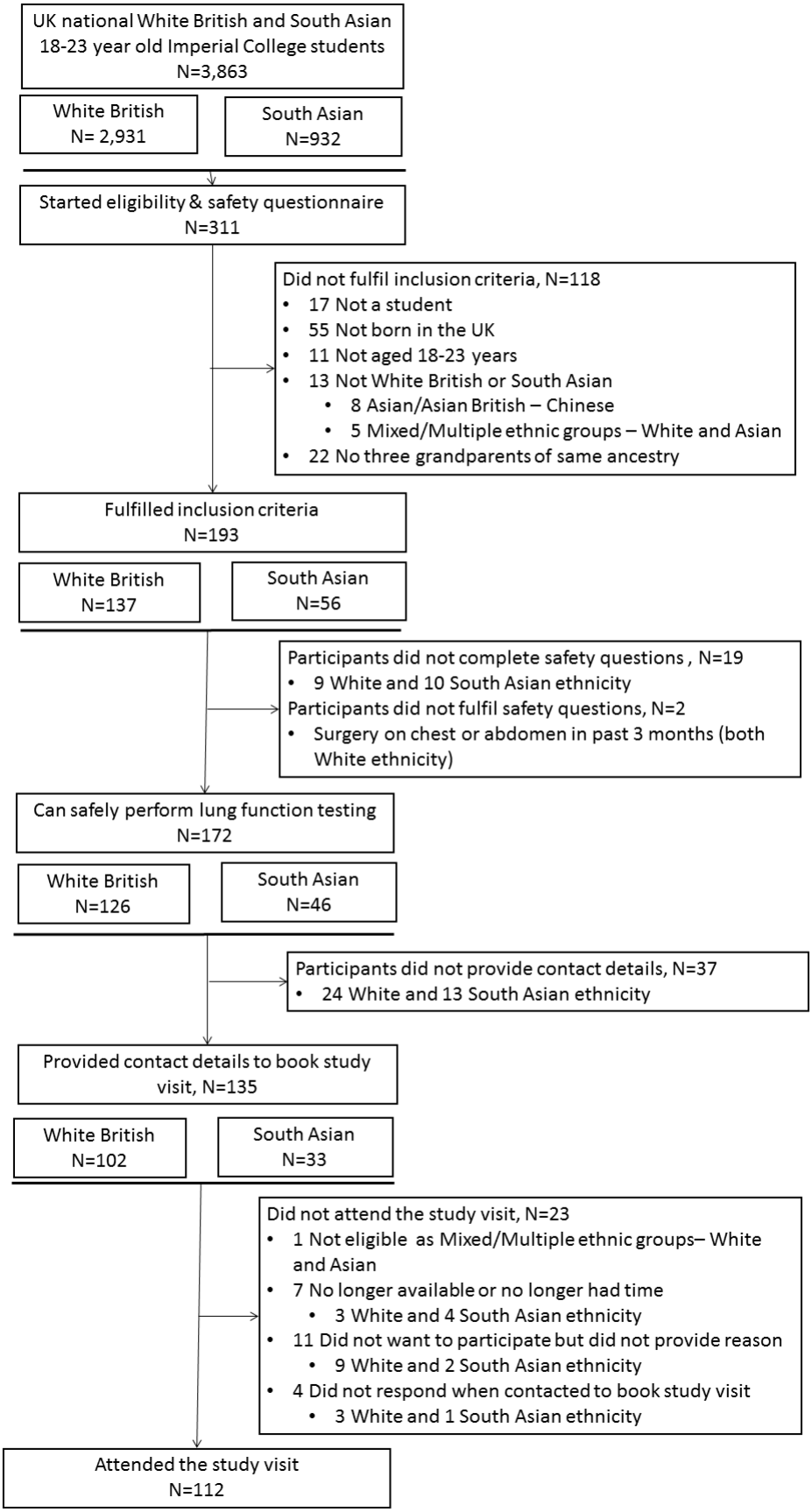


Figure 5.3: *Flow chart of participants during the recruitment*

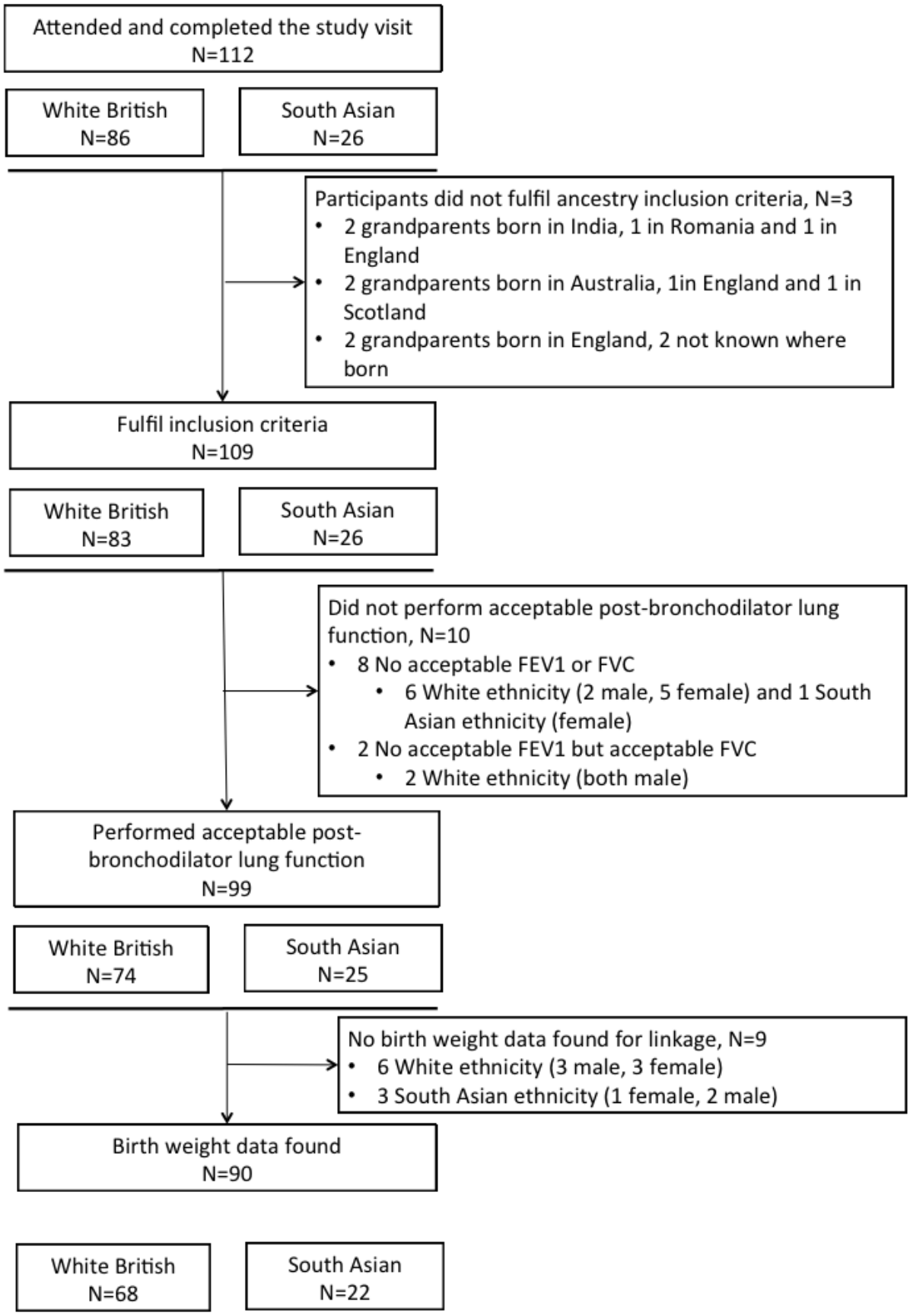


Figure 5.4: *Flow chart of participants who attended the study visit*

5.3.2 Study population

Table 5.7 provides an overview of the study population by ethnicity. Half of the study population were women, equally divided among White and South Asian British students. White participants were younger, taller, heavier and had higher birth weight but had lower BMI, shorter demispan and ulna length compared to South Asian British participants although none of these differences were statistically significant. No participant reported having ever been diagnosed with diabetes.

Only seven participants (8% of all participants), had ever smoked cigarettes, defined as smoking more than 20 packs of cigarettes in a lifetime or more than 1 cigarette each day for a year, and only one South Asian British participant had ever smoked a waterpipe. Similarly, exposure to passive smoke did not differ between White and South Asian British participants. Almost a quarter to a third of parents smoked before the participant was conceived but parental smoking lessened during pregnancy and childhood and current parental smoking was about 9% in both ethnic groups. None of the South Asian British participants' parents smoked during pregnancy. However, none of the differences in proportions of smoking of either parents or of a parent, mother or father, differed significantly between the two ethnic groups (Table 5.7 or Table C.1).

Nearly all South Asian British participants were second-generation immigrants (n=18 (82%), neither parent born in the UK) whereas for the majority of White participants both parents were born in the UK (n=54, 79%). Parents and grandparents of South Asian British participants were also more likely to have had a rural upbringing compared to White participants (Table 5.7). When examining the ancestry of the grandparents, for 95% of South Asian British participants three or more grandparents were born in South-Asia (n=21) while for one South Asian British participant, the grandparents were born in in South-Asia or East-Africa (where many South-Asians had migrated to).

Table 5.7: Characteristics of the DELBYA study population

	White (N=68) Mean (SD) or N (%)	South Asian British (N=22) Mean (SD) or N (%)	P-value
Sex (Female)	35 (51.5)	12 (54.2)	0.8
Age (yrs)	20.3 (1.2)	20.9 (1.5)	0.08
Anthropometry			
Height (cm)	173.7 (8.3)	169.5 (12.5)	0.07
Weight (kg)	67.3 (10.3)	67.0 (11.3)	0.92
BMI (kg/m^2)	22.2 (2.7)	23.3 (2.9)	0.07
Demispan (cm)	80.6 (4.4)	80.9 (6.0)	0.92
Ulna (cm)	26.2 (1.8)	26.7 (2.5)	0.73
Cardiovascular			
Pulse (bpm)	70.2 (11.0)	75.8 (10.8)	0.026
Systolic blood pressure (mm Hg)	115.4 (8.6)	110.8 (8.9)	0.046
Diastolic blood pressure (mm Hg)	64.2 (7.4)	61.5 (5.6)	0.22
Smoking			
Ever smoked, cigarettes	6 (8.8)	1 (4.5)	1.00
Ever smoked, pack-years (n)	0.5 (0.5)	2.5 (-)	-
Passive smoke, people smoke where you live	11 (16.2)	3 (13.6)	1.00
Passive smoke, exposed to tobacco smoke at home	4 (5.9)	1 (4.6)	1.00
Passive smoke, exposed to tobacco smoke in social settings	12 (17.7)	6 (27.3)	0.36
Passive smoke, exposed to tobacco smoke elsewhere	7 (10.3)	3 (13.6)	0.70
Parental smoking, before pregnancy	22 (32.4)	5 (22.7)	0.44
Parental smoking, during pregnancy	8 (11.8)	0 (0)	0.19
Parental smoking, during childhood	9 (13.2)	3 (13.6)	1.00
Parental smoking, nowadays	6 (8.8)	2 (9.1)	1.00
Early life influence			
Birth weight (kg)	3.4 (0.5)	3.3 (0.6)	0.32
Parental immigration status			
Both parents born in the United Kingdom	54 (79.4)	1 (4.6)	<0.001
One parent born in the United Kingdom	13 (19.1)	3 (13.6)	
No parent born in the United Kingdom	1 (1.5)	18 (81.8)	
(Grand)Parental upbringing* (urban/rural)			
Mother, rural	16 (23.5)	8 (36.4)	0.27
Maternal grandmother, rural	21 (35.6)	14 (73.7)	0.007
Maternal grandfather, rural	21 (40.4)	13 (68.4)	0.059
Father, rural	13 (19.1)	9 (40.9)	0.049
Paternal grandmother, rural	19 (33.9)	15 (75.0)	0.003
Paternal grandfather, rural	14 (26.9)	16 (80.0)	<0.001
(Grand)Parental educational attainment*			
Mother (≤High School)	15 (22.1)	4 (18.2)	1.00
Maternal grandmother (≤High School)	40 (71.4)	11 (73.3)	1.00
Maternal grandfather (≤High School)	31 (58.5)	9 (52.9)	0.78
Father (≤High School)	14 (20.6)	4 (18.2)	1.00
Paternal grandmother (≤High School)	36 (67.9)	12 (85.7)	0.32
Paternal grandfather (≤High School)	31 (62.0)	11 (64.7)	1.00
Grandparental farming*			
Maternal grandparents farming	7 (10.5)	4 (19.1)	0.29
Paternal grandparents farming	2 (3.03)	8 (36.4)	<0.001

*Missing data for these variables (see Table C.4 for details on missing data)

For White participants, 88% had at least three grandparents who were born in the UK (n=60) while the remaining participants had at least three grandparents who were born in either the UK or Western Europe (n=6) or were born solely in Western Europe (n=2).

Despite the difference in upbringing and immigration status between ethnic groups, the educational attainment of parents or grandparents did not differ between South Asian British and White participants. However, occupational status did show some variation between ethnic groups. Grandmothers of South Asian British participants were much more likely to never have worked (Tables C.2 and C.3). No difference was observed in the father or mother's occupation nor in the paternal or maternal grandfathers' jobs (Table C.2 and C.3) while paternal grandparents of South Asian British participants were more likely to have been farmers compared with those of White participants (Table 5.7).

Although all participants who completed the study visit responded to all questions and participated in all procedures or measurements, missing information occurred when participants did not know the answer to a question or, in the case of ventilatory function, because the measurement did not meet the quality standard. No post-bronchodilator FVC or FEV_1 was available for ten participants (9.2% of those who fulfilled the inclusion criteria, Figure 5.4). Table C.4 provides an overview of the other missing information in the study. There was no missing information for any of the questions related to respiratory symptoms or smoking history. All participants but one were aware of their parents' smoking history, but up to a quarter of participants could not recall information on their grandparents' upbringing, educational attainment or occupational status.

5.3.3 Respiratory symptoms and ventilatory function

Wheezing was markedly different between White and South Asian British participants (Table 5.8). South Asian British participants showed a higher prevalence of wheezing or whistling in the last year, OR of 3.6 (95% CI: 1.2 to 10.4), wheezing not only when having a cold (OR: 3.7; 95% CI: 1.0 to 14.3) and more serious wheezing that made participants

feel short of breath (OR: 6.4; 95% CI: 1.4 to 29.4). Despite the difference in wheezing, no difference in the prevalence of ever being diagnosed with asthma by a physician was observed, which ranged from 16 to 23%, and just six participants reported a current diagnosis of asthma. Few participants reported any other respiratory symptoms (exacerbation in the last year, chronic cough, being hospitalised as a child, breathlessness) and these did not differ between the ethnic groups (Table 5.8).

Table 5.8: Respiratory function and symptoms by ethnicity

	White (N=68) **Mean (SD) or N (%)**	**South Asian British (N=22)** **Mean (SD) or N (%)**	**OR (95% CI)** (ref: White)	**P-value**[1]
FVC (L)	4.7 (0.9)	3.8 (0.9)	-	0.0008
FVC (% predicted[2])	97.1 (10.3)	94.8 (10.4)	-	0.35
FEV_1 (L)	4.1 (0.8)	3.4 (0.9)	-	0.0014
FEV_1 (% predicted[2])	99.6 (10.7)	97.2 (9.9)	-	0.30
FEV_1/FVC (%)	87.6 (5.4)	88.1 (6.3)	-	0.49
Chronic cough	1 (1.5)	1 (4.5)	3.2 (0.2;53.2)	0.42
Asthma, ever	11 (16.2)	5 (22.7)	1.5 (0.5;5.0)	0.49
Asthma, current	4 (5.9)	2 (9.1)	1.6 (0.3;9.4)	0.6
Wheezing, last year	11 (16.2)	9 (40.9)	3.6 (1.2;10.4)	0.02
Wheezing, last year not only when a cold	5 (7.4)	5 (22.7)	3.7 (1.0;14.3)	0.06
Wheezing, last year made you feel short of breath	3 (4.4)	5 (22.7)	6.4 (1.4;29.4)	0.02
Any exacerbation, ever	8 (11.1)	1 (4.5)	0.4 (0.04;3.0)	0.35
Any exacerbation, last year	2 (2.9)	0 (-)	-	-
Dyspnea (MRC scale)			3.2	0.42
1	67 (98.5)	21 (95.5)	(0.2;53.2)	
>1	1 (1.5)	1 (4.0)		
Hospitalised as child for breathing problems	4 (5.9)	2 (9.1)	1.6 (0.3;9.4)	0.6

[1] P- value for difference in FVC, FEV_1 and FEV_1/FVC between both ethnic groups determined by Wilcoxon ranksum test

[2] % Predicted obtained using NHANES III reference equations with a correction factor of 0.88 for South Asian participants [128, 129, 248]

Results from the crude analysis showed lower ventilatory function among South Asian British participants, who had a lower FVC of -0.86 L (95% CI: -1.32 to -0.40 L) and a lower FEV_1 of -0.71 L lower (95% CI: -1.10 to -0.32 L) compared to White participants (Table 5.8 and 5.9). However, no difference was observed in FVC or FEV_1 when expressed as % predicted, which is not suprising given that the reference equation for % predicted is adjusted for ethnicity. FVC was also lower among women, while both anthropometric measures (height and demispan) and birth weight showed a positive relation with FVC, with all of these associations being statistically significant except for birth weight. As all participants were aged between 18 and 23 years, age did not influence FVC. Paternal and maternal educational and socio-economic variables were also positively associated with FVC, but this was only statistically significant for maternal educational attainment (Table 5.9). In contrast, FEV_1/FVC did not show a statistically significant crude association with ethnicity (95% CI: -2.2 to 3.3%), sex, age, birth weight or any reported anthropometric or parental measures (Table 5.9).

In the adjusted analyses, the difference in FVC between the ethnic groups was slightly reduced from 0.86 L (95% CI: -1.32 to -0.40 L) to 0.81 L (95% CI: -1.01 to -0.54 L). The effect estimates of sex and height on FVC were reduced while the association of demispan with FVC became not statistically significant. Maternal educational attainment remained positively associated with FVC in the adjusted model but, in contrast, father's occupational status negatively affected FVC (Table 5.9). Figure 5.5 shows the effect of the adjustment of individual covariates on the difference in FVC between both ethnic groups. None of the socio-economic influences (father's occupational status, maternal educational attainment or maternal upbringing) nor birth weight was able to explain the difference in FVC. Moreover, adjusting for demispan increased the difference in FVC between ethnic groups by 15% (Figure 5.5).

Table 5.9: Crude and adjusted difference in FVC and FEV_1/FVC across categories (categorical variables) and per unit (continuous variables).

	FVC (L)				**FEV_1/FVC (%)**			
	Crude		**Adjusted***		**Crude**		**Adjusted***	
	Difference (95% CI)	**P-value**	**Difference (95% CI)**	**P-value**	**Difference (95% CI)**	**P-value**	**Difference (95% CI)**	**P-value**
Ethnicity (South Asian)	-0.86 (-1.32;-0.40)	<0.001	-0.81 (-1.01;-0.54)	<0.001	0.56 (-2.2;3.3)	0.69	0.38 (-3.07;3.84	0.83
Sex (female)	-1.51 (-1.81;-1.27)	<0.001	-0.9 (-1.23;-0.56)	<0.001	0.30 (-2.05;2.66)	0.8	-1.00 (-5.27;3.28)	0.64
Age (yrs)	-0.10 (-0.26;0.05)	0.19	0.047 (-0.029;0.12)	0.22	0.053 (-0.83;0.94)	0.91	-0.035 (-1.02;0.95)	0.94
Height (cm)	0.09 (0.07;0.10)	<0.001	0.025 (-0.005;0.055)	0.1	-0.067 (-0.19;0.057)	0.29	-0.064 (-0.45;0.32)	0.74
Demispan (cm)	0.15 (0.12;0.18)	<0.001	-0.036 (-0.016;0.089)	0.17	-0.12 (-0.37;0.12)	0.33	-0.068 (-0.75;0.61)	0.84
Father occupational status (≥ professional category)	0.027 (-0.53; 0.58)	0.92	-0.27 (-0.53;-0.0069)	0.044	1.02 (-2.05;4.09)	0.51	0.92 (-2.45;4.29)	0.54
Birth weight (kg)	0.29 (-0.10;0.68)	0.14	0.052 (-0.15;0.26)	0.61	-1.19 (-3.35;0.98)	0.28	-0.78 (-3.40;1.84)	0.56
Maternal educational attainment (>High school)	0.58 (0.076;1.09)	0.025	0.33 (0.064;0.59)	0.015	-0.031 (-2.91;2.85)	0.98	0.22 (-3.19;3.62)	0.9
Maternal upbringing (urban)	0.12 (-0.35;0.60)	0.6	-0.077 (-0.31;0.15)	0.5	-0.11 (-2.77;2.55)	0.93	-0.0075 (-2.95;2.93)	0.99

*Difference of predictor adjusted for all other predictors reported in the crude analysis

Figure 5.5: *Crude and adjusted difference in L (FVC) or % (FEV_1/FVC) of South Asian British vs White participants. Baseline adjustment includes adult height and sex. The adjusted model includes adult height, sex, demispan, father's occupation, birth weight, maternal educational attainment and maternal upbringing.*

No difference in FEV_1/FVC was shown in the adjusted model (Table 5.9 and Figure 5.5) while similar results to FVC were obtained for FEV_1 after repeating the association analyses (data not shown). Ulna length was specified a priori for inclusion in the association analyses but was not included due to multicolinearity.

The lasso regression in the additional analysis identified six predictors of FVC, in addition to ethnicity (Figure 5.6). Results for sex, height, demispan and maternal educational attainment are consistent with those of the linear regression in the main analysis which included predictors specified a priori, although the effect estimates were attenuated, as expected, due to the shrinkage of the lasso regression. Two additional predictors, not included in the main analysis, were retained by the lasso regression: the immigration status of the mother and of the father. Either of the parents not being born in the UK, mutually adjusted for the other predictors, strongly adversely affected participant's FVC. Moreover, the mutually adjusted combined effect of the parents' immigration status on FVC was more pronounced than an individual's self-defined ethnicity. Consistent with the a priori defined linear regression, the lasso regression did not identify ethnicity as a predictor of FEV_1/FVC.

Pre-and post-bronchodilator lung function did differ slightly. However, only one participant varied by more than 12.5% in FEV_1 (Table C.5). No participant had a family history of COPD, emphysema or chronic bronchitis. Post-bronchodilator FVC, FEV_1 or FEV_1/FVC were also not influenced by a cold in the last three weeks, by whether participants had smoked in the last month, or by any medications for breathing in the last 24 hours before performing spirometry ($p>0.05$, Wilcoxon rank-sum test).

5.3.4 Pulse rate, blood pressure and body mass index

Table 5.10 and 5.11 show the crude and adjusted association analyses for pulse rate, blood pressure and BMI. The crude associations show a higher pulse rate in South Asian British participants (5.5 beats per minute (bpm), 95%CI: 0.2 to 10.9 bpm), whereas sys-

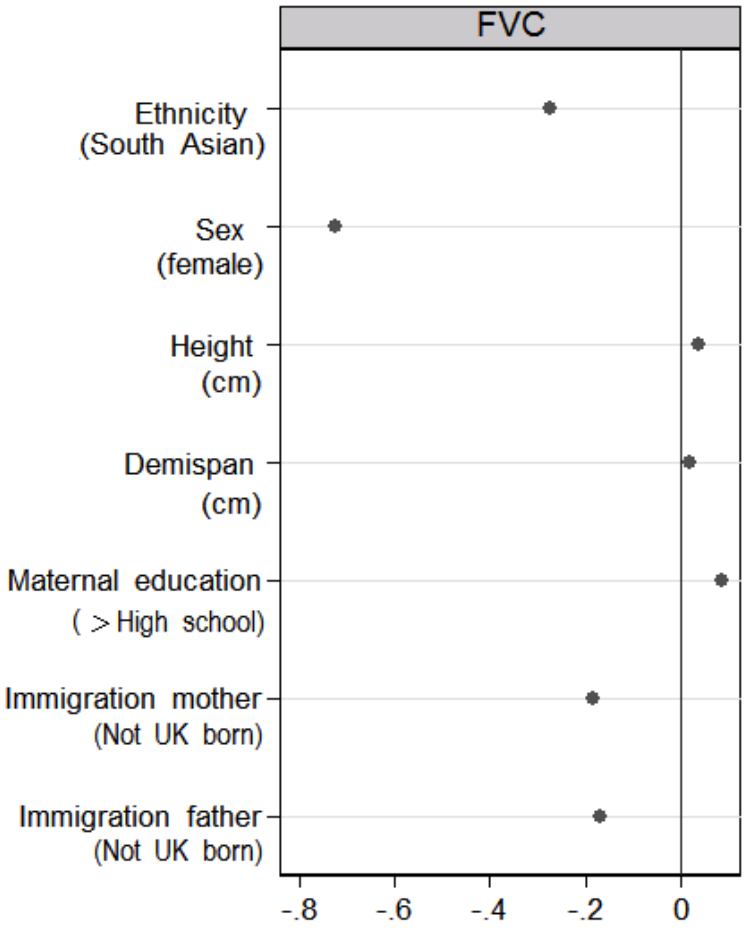


Figure 5.6: *Adjusted difference in L for FVC for predictors identified by lasso regression*

tolic blood pressure was lower (-4.6 mm Hg, 95% CI: -8.9 to -0.4) compared to Whites. Diastolic blood pressure and BMI did not differ between the two ethnicities. Only systolic blood pressure was lower in women, while pulse rate, diastolic blood pressure and BMI did not differ between sexes. The difference in pulse rate between the two ethnic groups persisted and further increased after adjustment. On the other hand, the difference in systolic blood pressure was marginally reduced and became of only borderline significance. No statistically significant difference in either diastolic blood pressure or BMI was shown after adjustment. In the additional analyses with the lasso regression, ethnicity was not identified as a predictor for any of the cardiometabolic outcomes.

Table 5.10: Crude and adjusted difference in systolic and diastolic blood pressure across categories (categorical variables) and per unit (continuous variables)

	Systolic blood pressure (mm Hg)				**Diastolic blood pressure (mm Hg)**			
	Crude		**Adjusted***		**Crude**		**Adjusted***	
	Difference (95% CI)	**P-value**	**Difference (95% CI)**	**P-value**	**Difference (95% CI)**	**P-value**	**Difference (95% CI)**	**P-value**
Ethnicity (South Asian)	-4.63 (-8.86;-0.40)	0.032	-4.17 (-8.76;0.41)	0.07	-2.62 (-6.03;0.80)	0.13	-1.94 (-5.98;2.10)	0.34
Sex (female)	-7.9 (-11.24;-4.55)	<0.001	-3.03 (-8.70;2.65)	0.29	2.8 (-0.12;5.71)	0.06	6.63 (1.63;11.64)	0.01
Age (yrs)	-1.05 (-2.44;0.33)	0.13	-0.33 (-1.64;0.97)	0.61	-0.52 (-1.63;0.60)	0.36	-0.58 (-1.74;0.57)	0.32
Height (cm)	0.45 (0.28;0.62)	<0.001	0.14 (-0.37;0.65)	0.59	-0.033 (-0.19;0.12)	0.68	0.26 (-0.19;0.71)	0.25
Demispan (cm)	0.81 (0.45;1.16)	<0.001	0.33 (-0.57;1.24)	0.74	-0.12 (-0.43;0.19)	0.43	-0.085 (-0.88;0.71)	0.83
Father occupational status (≥ professional category)	-1.23 (-6.11;3.64)	0.62	-3.02 (7.49;1.46)	0.18	-2.02 (-5.88;1.85)	0.3	-2.67 (-6.62;1.27)	0.18
Birth weight (kg)	0.19 (-3.27;3.64)	0.91	-2.05 (-5.53;1.42)	0.24	-0.71 (-3.46;2.03)	0.61	-2.79 (-5.85;0.28)	0.07
Maternal educational attainment (>High school)	4.22 (-0.27;8.70)	0.065	3.38 (-1.14;7.89)	0.14	1.89 (-1.73;5.51)	0.3	3.85 (-0.13;7.84)	0.06
Maternal upbringing (urban)	2.97 (-2.13;6.27)	0.33	0.79 (-3.11;4.69)	0.69	-0.27 (-3.63;3.09)	0.87	-1.51 (-4.95;1.93)	0.39

*Difference of predictor adjusted for all other predictors reported in the crude analysis

Table 5.11: Crude and adjusted difference in body mass index and pulse rate across categories (categorical variables) and per unit (continuous variables)

	Body mass index (kg/m^2)				**Pulse (bpm)**			
	Crude		**Adjusted***		**Crude**		**Adjusted***	
	Difference (95% CI)	**P-value**	**Difference (95% CI)**	**P-value**	**Difference (95% CI)**	**P-value**	**Difference (95% CI)**	**P-value**
Ethnicity (South Asian)	1.05 (-0.30;2.40)	0.13	-0.31 (-1.87;1.26)	0.7	5.53 (0.20;10.86)	0.04	6.56 (0.056;13.06)	0.048
Sex (female)	-0.065 (-1.24;1.11)	0.91	-1.1 (-3.04;0.85)	0.27	4.07 (-0.55;8.68)	0.08	5.88 (-2.18;13.93)	0.15
Age (yrs)	0.05 (-0.39;0.49)	0.82	0.19 (-0.26;0.64)	0.4	0.31 (-1.45;2.07)	0.73	-0.64 (-2.49;1.22)	0.5
Height (cm)	-0.024 (-0.086;0.037)	0.43	-0.27 (-0.44;-0.090)	0.003	-0.2 (-0.44;0.040)	0.1	0.094 (-0.63;0.82)	0.8
Demispan (cm)	0.024 (-0.99;0.15)	0.7	0.39 (0.077;0.70)	0.015	-0.28 (-0.77;0.21)	0.26	0.13 (-1.16;1.41)	0.85
Father occupational status (≥ professional category)	-0.53 (-2.06;1.00)	0.5	-0.97 (-2.50;0.56)	0.21	-3.47 (-9.56;2.62)	0.26	-1.06 (-7.41;5.29)	0.74
Birth weight (kg)	0.25 (-0.84;1.33)	0.65	0.39 (-0.80;1.58)	0.51	-2.41 (-6.72;1.90)	0.27	-2.76 (-7.69;2.17)	0.2
Maternal educational attainment (>High school)	1.64 (0.24;3.04)	0.022	1.85 (0.31;3.40)	0.019	-4.2 (-9.88;1.48)	0.15	-4.19 (-10.60;2.22)	0.2
Maternal upbringing (urban)	0.85 (-0.47;2.17)	0.2	0.91 (-0.42;2.25)	0.18	1.78 (-3.51;7.07)	0.51	3.68 (-1.86;9.22)	0.19

*Difference of predictor adjusted for all other predictors reported in the crude analysis

5.3.5 Participant feedback

Twenty-six participants provided feedback for the study, of which 23 had attended the study visit (20.5% of those who attended the study visit) and 3 had not (13% of those who provided contact details but did not attend the study visit). The majority of participants were recruited through recruitment flyers (Figure 5.7) and participant's motivation to take part was equally divided between helping medical research, being interested in knowing their lung function and for the reimbursement (Figure 5.8). All participants agreed that the participant information sheet provided sufficient information and those who did not attend the study visit cited lack of time as a reason.

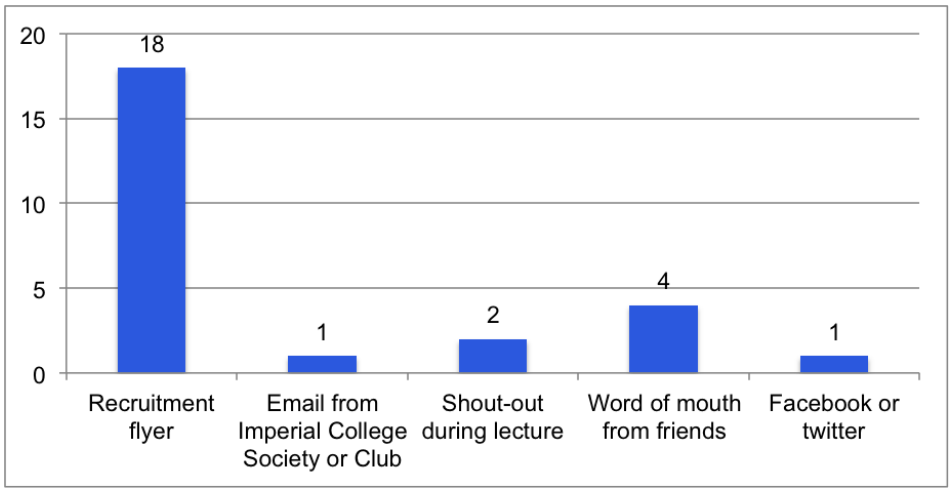


Figure 5.7: *Means of recruitment*

The study visit did not take place at the Imperial College London main campus but only one participant found travelling to the Royal Brompton Hospital difficult. Participants also described how comfortable they were with the procedures conducted during the study visit (blood pressure and pulse rate, height and weight measurements, ventilatory function and questionnaires) (Figure 5.9). All participants, except one, were very comfortable with blood pressure, pulse rate and the height and weight measurements. However, some participants did find ventilatory function measurement and the ques-

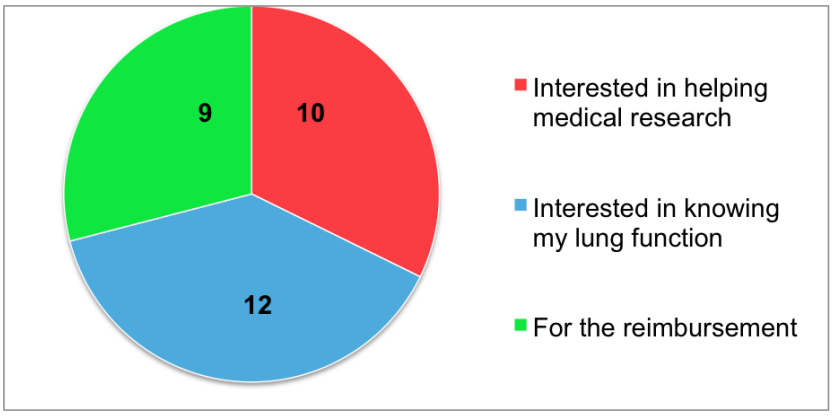


Figure 5.8: *Reason for participation. Some participants indicated multiple reasons for participation and therefore the numbers do not add up to 26*

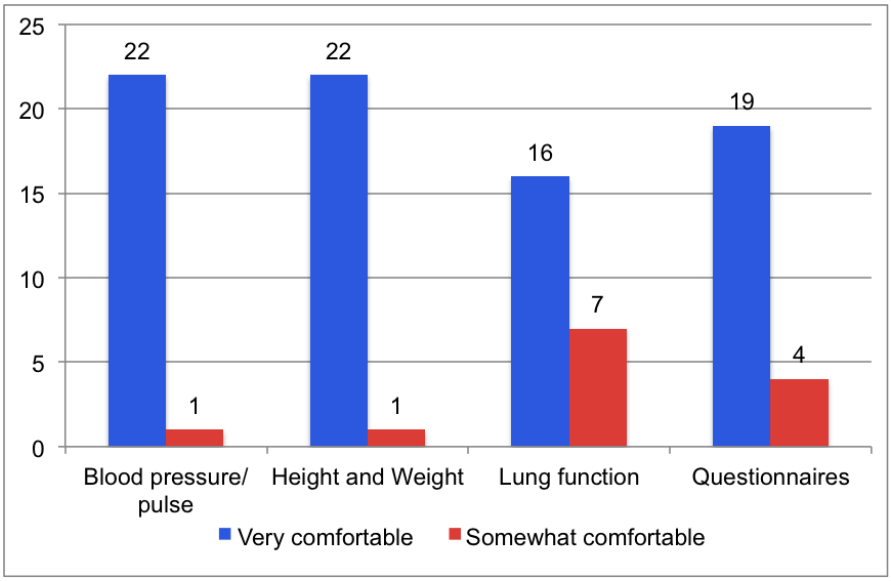


Figure 5.9: *Comfort of procedures during study visit*

tionnaires only "somewhat comfortable". No participant reported that any procedure was "not comfortable" and no adverse effects to spirometry were observed in any participant during the study visit.

A third of participants (n=7) found that the study visit lasted longer than expected and four participants reported that the reimbursement was too little. These participants suggested a reimbursement ranging from £20 to £30.

Overall, 22 participants rated their experience of the study visit as very good and one participant scored their experience as fair. However, all participants recommended the study to their friends and indicated a willingness to take part in similar future studies.

5.4 Discussion

The DELBYA pilot investigation demonstrated that population-based studies into the disparities in ventilatory function and cardiometabolic markers among young adults of different ethnicities are feasible. The study found a difference in FVC despite the similar parental socio-economic environment between the two ethnic groups and lack of difference in birth weight. Therefore, it is unlikely that the difference in birth weight or parental socio-economic variables is the explanation for the difference in FVC between the ethnic groups in this study population. This pilot investigation also found evidence against the hypothesis that a difference in trunk size can explain ethnic differences in ventilatory function and identified parental immigration as an important predictor of FVC.

5.4.1 Evaluation of pilot study design

Only 112 (3%) participants were recruited into the study from a target population of 3,863 UK students at Imperial College London, aged 18-23, and of White or South Asian British ethnicity during the period of the study. The information on the target population was obtained through a freedom of information request to Imperial College London and is an approximation, as it was not possible to obtain information on the country of birth of the students or of the grandparents. Therefore, the recruitment percentage will be underestimated and should be considered as a lower bound estimate. Nonetheless, participation into epidemiological studies has severely declined in the past decades [106], with the recruitment rate in this study similar to that of a recent cohort study in

the UK, the UK COSMOS study [336].

Recruitment flyers appeared the most successful for the recruitment of study participants, while the other methods, through friends, shout-outs during lectures, clubs and societies or social media, performed markedly worse. Only one participant was recruited through social media, which was surprising given that young adults are routine users of these platforms. However, the abundance of information on, and fast pace of, social media, which has been shown to result in a shortened attention span [140], could also have contributed to the low recruitment number using this medium. In addition, the results from the feedback questionnaire may not be representative as only 21% of those who attended the study visit responded.

Recruitment could be improved by shortening the online registration questionnaire, which might result in greater retention of participants, as 56 participants did not provide any information after completing and fulfilling the inclusion questions of the online questionnaire. Second, although those who attended the study visit did not find travelling to the hospital cumbersome, performing the study at the Imperial College main campus would have eliminated the travel time for participants and increased the study presence on campus. Finally, another way to expand the study population could be to include other London academic institutions, London regions or other UK regions.

Compliance with the study procedures and the response rate of the questionnaires was very good. Only a small number of participants were unable to perform acceptable post-bronchodilator lung function after coaching due to poor coordination of in- and exhalation, while other missing data were observed for questions pertaining to grandparental occupational history, upbringing and educational attainment. The increased missingness of answers to questions about grandparents could be explained by reduced contact with the grandparents due to geographic distance, early death or for other reasons.

Birth weight was obtained from birth records from the HSCIC, which was a very pro-

tracted process. The initial application was submitted on the 13th of August 2015 and birth weight information was provided on the 2nd of March 2016. However, the linkage of the DELBYA study data with the birth weight data only took 10 days. Birth weight was obtained from the ONS birth dataset, which is considered the most complete dataset for birth weight information [109]. Two other datasets (Hospital Episode Statistics birth and Hospital Episode Statistics deliveries), both also managed by the HSCIC, exist but these contain markedly more missing data. A third, and more recent, dataset, the NHS numbers for babies, only contains information from 2006 onwards and was therefore not suitable for this study [109]. An alternative approach could be to obtain birth weight from general practitioner (GP) practices. However, in the Size and Lung function In Children study, 33% of GPs did not respond to data requests, and birth weight information was only obtained for 47% of participants. Moreover, GPs non-response or presence of missing birth weight information was higher for children of non-White British ethnicity and with lower family socio-economic status [29]. Finally, participants could have been asked for self-reported birth weight. However, the reliability of self-reported birth weight for young adults is unknown, although mother's recall of children's birth weight and recall by elderly women of their own birth weight has been shown to be trustworthy [29, 189].

The DELBYA study was conducted by researchers from Imperial College London at the Royal Brompton Hospital. Therefore, the study required approval from both Imperial College London and the Royal Brompton and Harefield NHS foundation trust, as the Royal Brompton hospital is not a part of the Imperial College Healthcare NHS trust. Moreover, ethical approval at Imperial College had to be obtained from two committees: the Imperial College research ethics committee and the medical education ethics committee. Approval from the medical education ethics committee must be sought when advertising in Imperial College London medical school buildings or when medical students may take part in the research. This is because participating in certain studies, such

as those related to HIV or hepatitis, may have life-long repercussions for the medical students' careers. However, coordinating and responding to different amendments from both ethics committees, with the Imperial College joint research compliance office and with the Royal Brompton hospital research and development office, was complicated as no communication occurs between these entities.

Finally, a significant period of time was spent on data entry of the questionnaires. Although data entry errors were minimised by use of double data entry, the process was very time-consuming. This study employed online registration and feedback questionnaires, created and hosted by Qualtrics, an Imperial College approved questionnaire tool. These online questionnaires were easily designed and managed, with safeguards to prevent data entry errors, such as forced response to questions and range of plausible values for a response. Qualtrics allows the design of questionnaires for use on tablets and such use would eliminate the need for data entry and strongly reduce the possibility of data entry errors. Recently, several epidemiological studies have abandoned paper-based questionnaires and embraced digital tools [4, 90].

5.4.2 Interpreting pilot study findings

Despite the small sample size, with only 22 South Asian British participants, this pilot study showed a significantly lower ventilatory function in South Asians compared with Whites, with a crude difference of 0.86 L in FVC, which was reduced to 0.63 L after taking into account height and sex. No statistically significant difference was observed for FEV_1/FVC between the two ethnic groups in either crude or adjusted analyses.

These findings are in line with two previous studies, which assessed the difference in ventilatory function between White and South Asian British subjects, although in different age groups. Hooper et al. found a lower FVC and FEV_1 among South Asian British vs Whites in the BOLD London study among subjects older than 40. They reported a crude difference of 0.79 L and 0.49 L in FVC and of 0.44 L and 0.28 L in FEV_1, in men

and women respectively [142]. Strippoli et al. [319] equally observed a lower FVC, of 0.31 L, and FEV_1, of 0.23 L, adjusted for age, sex, weight and height, in 9 to 14 year old South Asian British vs White British children. No difference in FEV_1/FVC between White and South Asian British subjects was observed in the BOLD London study [142], while a higher FEV_1/FVC was reported by Strippoli et al. [319] in South Asian British children.

South Asian British students were 3.6 times more likely to experience wheezing in the last year compared to White students. However, there was no significant difference in doctor-diagnosed asthma between the two ethnic groups. This could be a result of (1) over-reporting, due to differences in the perception and experience of wheezing or (2) a true difference in environmental and genetic risk factors between the two groups that results in more wheezing among South Asian British students without adversely affecting ventilatory function reversibility, as there was no difference in ventilatory function reversibility between both ethnic groups. A meta-analysis found a similar discrepancy in children: although the prevalence of doctor-diagnosed asthma and recent history of wheeze were lower in South Asian British children compared to White British children, South Asian children showed higher risk of asthma admission [230], and this finding was corroborated by an analysis of Scottish health records. Sheikh et al. [295] found in a 9-year analysis of health records that Indian and Pakistani individuals had the highest age-adjusted rates of asthma admission. The discrepancy in prevalence of asthma and history of wheeze with hospital admissions has been attributed to barriers to health care such as poor knowledge of asthma and compliance with medication [184].

Few parental and grandparental factors differed between the two ethnic groups. South Asian British paternal and grandparental upbringing was more likely to have occurred in a rural environment, South Asian British paternal grandparents were more likely to have been farmers and South Asian British grandmothers were more likely to have been housewives. However, no differences in educational attainment of parents and grandparents or in occupational status of parents or grandfathers between the two ethnic

groups were observed. Seldom were both parents of South Asian British participants born in the UK but, given the information on occupational status and educational attainment, the parents were neither without means nor lacking in education. Therefore, it can be assumed that the study participants of both ethnic groups will have grown up in similar socio-economic but different cultural environments. This is in contrast with the low parental socio-economic environment of South Asian British compared to White children in the study by Strippoli et al. [319]. The similar socio-economic environment in the DELBYA pilot study may reflect patterns of recruitment at an elite university.

Birth weight did not differ significantly between the two ethnic groups, but this may be explained by the lack of power to detect differences unless they were large or by the similar socio-economic environment of both White and South Asian British participants. Strippoli et al. [319] observed a significantly lower birth weight, of 226 grams, of birth weight in South Asian British vs White children. Similarly, Kelly et al. [165] reported a lower birth weight for Indian, Pakistani and Bangladeshi British children compared to White British children in the Millennium cohort study, with a difference of 344, 306 and 327 grams, respectively. Moreover, the findings from the meta-analysis reported in Chapter 3 show a significant relation between birth weight and FVC and therefore failure to detect an association of birth weight with FVC in this pilot study is very likely due to the small sample size as demonstrated by the broad confidence intervals, which include the central estimate of the meta-analysis in Chapter 3.

Long bone length relative to other aspects of body size, commonly assessed as either the ratio of armspan to height or the ratio of sitting to standing height, are markers of social advantage and associated with reduced disease risk and lower mortality [78, 98, 120, 158]. Relatively longer long bones will reduce the relative length of the trunk (and hence of the thorax). Ethnic minorities compared to Whites have relatively longer long bones [47, 243] and therefore differences in ventilatory function between ethnic groups were thought to be a direct consequence of the reduced thoracic size. This

resulted in sitting height being employed as a predictor of ventilatory function when comparing different ethnic groups [144, 292, 357]. However, sitting height is difficult to measure accurately and in this pilot study two measures were assessed that include a measurement of long bone length; ulna length and demispan, which measures both long bone length (humerus, radius and ulna) and chest width. In this pilot study, further adjusting the height and sex adjusted ethnic difference in FVC for long bone length (demispan) increased the difference in FVC between ethnic groups by 15%. Thus, the ethnic difference was not explained by adjusting for sex and height relative to long bone length (e.g. trunk size) and runs contrary to previous observations that accounting for trunk size (sitting height) partly explains the ethnic difference [144, 292, 357].

Neither birth weight nor any of the a priori defined parental socio-economic factors seemed to explain the difference in FVC between the two ethnic groups, which is probably a consequence of the lack of difference in these factors and socio-economic similarities of participants' parents and grandparents. However, the difference in FVC between ethnic groups was observed despite the similar socio-economic environment and lack of difference in birth weight. Therefore, it is very unlikely that the difference in birth weight or parental socio-economic variables is the explanation for the difference in FVC between the ethnic groups in this study population.

The additional analyses with the lasso regression also identified the immigration status of the mother and father as important predictors of FVC; the sum of their effects was larger than the effect estimate for (self-defined) ethnicity. This could be suggestive of an environmental influence explaining the difference in ventilatory function between ethnic groups. Carey et al. [56] did identify westernisation, defined by dietary habits, as an important environmental influence that explained the risk of bronchial hyperactivity, measured using methacholine challenge, and the risk of atopy between White and Asian British school children.

Pulse rate and systolic blood pressure differed between ethnic groups, although the

difference in systolic blood pressure became only borderline significant in the fully adjusted model. I am not aware of any study in young adults that has assessed the difference in cardiometabolic markers between White and South Asian British. However, a study of 4,000 middle-aged participants in London, did find a higher systolic and diastolic blood pressure in South Asian vs White British while BMI was significantly lower and higher, in men and women, respectively, of South Asian vs White British [335]. This pilot study was probably underpowered to detect all differences in the cardiometabolic markers although the ability to identify some disparities in the cardiometabolic markers in a small study population might indicate that these differences are relatively large.

5.5 Conclusion

This pilot study shows that large population-based studies into the disparities in ventilatory function and cardiometabolic markers among young adults of different ethnicities are feasible, but that these should be mindful of recruitment rates, missing information related to questions concerning grandparents, and practical issues when acquiring birth weight through data linkage.

Differences in ventilatory function and cardiometabolic markers between ethnic groups exist, but findings to date have not provided conclusive answers on what might explain them.

This pilot investigation identified parental immigration as an important predictor of FVC, and provided evidence against the hypotheses that differences in birth weight or trunk size can explain ethnic differences in ventilatory function.

Although genetic, anthropometric and environmental influences might hold the key to explain ethnic disparities in ventilatory and cardiometabolic function, particular attention in future studies should be paid to the role of broader environmental influences, including factors related to the immigration status of each parent.

CHAPTER 6

CONCLUSION

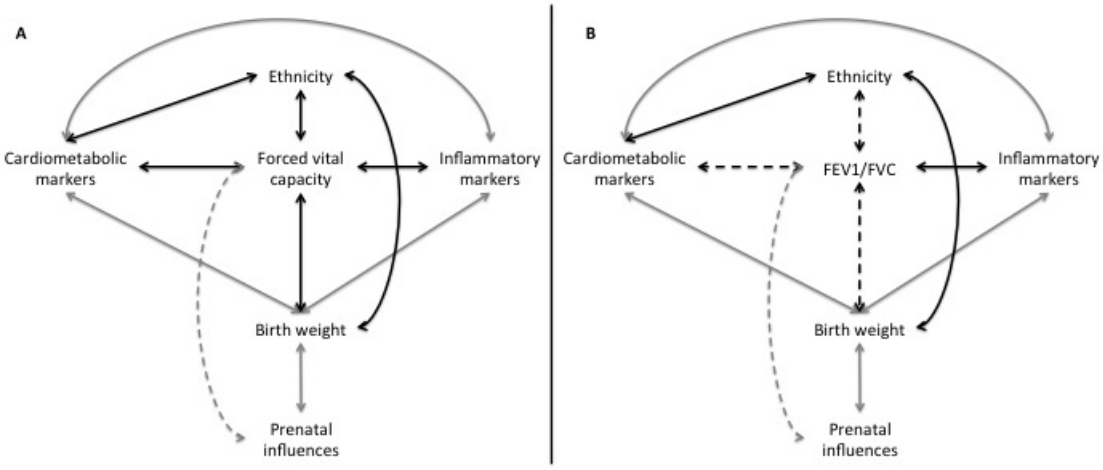


Figure 6.1: *Overview of relevant associations outlined in this thesis for FVC (A) and FEV1/FVC (B). Black and grey colour(s) indicate associations directly investigated and not directly investigated, respectively; a full line indicates strong to moderate evidence in support of the association, while a dashed line indicates weak or no evidence.*

Low ventilatory function is strongly related to increased mortality and is the primary defining characteristic of several chronic lung diseases [46, 49, 138]. Ventilatory function is considered to track throughout the life course, meaning that an individual will tend to remain in the same centile of ventilatory function over time [24, 147, 225]. Adverse influences in early life may lead to lower ventilatory function. Thus, lower ventilatory function in early life can, due to tracking, lead to lower maximum ventilatory function attained and, in turn lead to respiratory disease in later life [187].

This thesis aimed to determine the influence of early life factors, with a particular focus on birth weight, on later ventilatory function, and to elucidate the associations with inflammatory and cardiometabolic markers, and with ethnicity. Birth weight is a marker of intrauterine development, with low birth weight representing an indicator of potential adverse early life influences. Figure 6.1A and 6.1B provide an overview of the associations with FVC and FEV1/FVC, respectively, relevant to this thesis.

Low birth weight and reduced growth in the first year of life are known to be associated with poor ventilatory function in later life [14, 38, 54, 272, 309]. However, the

available evidence has not been systematically evaluated with the aim of assessing their specific effects on FVC and FEV1/FVC, as measures of restrictive and obstructive impairment, respectively.

In Chapter 3, I conducted a systematic review and meta-analysis of birth weight, weight at one year and weight gain in the first year of life with ventilatory function in later life in the general population. This provided strong evidence for a positive association of birth weight with FVC throughout childhood and adulthood, while I found much weaker evidence for association with FEV1/FVC. The finding from the meta-analysis for an association of birth weight with FVC is strong, with results remarkably consistent across studies in different populations. The evidence for an association with FEV1/FVC was much weaker, with more limited data available and potential for reporting bias. These findings suggest that past claims of a positive association with airflow obstruction, which were defined using FEV1, were due to the confounding effect of the association with FVC, given the strong correlation between FEV1 and FVC. Moreover, this is supported by a similar effect estimate for an association of birth weight with FEV1 from a previous meta-analysis [193] with that for FVC from the meta-analysis in this thesis. Thus, it appears that FEV_1 acted as a proxy for FVC rather than FEV_1/FVC. Interpreting the causality of the observed association of birth weight with FVC in later life is difficult, and alternative explanations include the presence of prenatal influences associated with both low birth weight and lower FVC. An initial aim of my systematic review was to assess whether early life factors mediated the association between birth weight and FVC, but this was not possible as these factors were seldom reported. Similarly, I was unable to provide a reliable assessment of the relation of weight at one year, or weight gain in the first year of life, with later ventilatory function due to the limited evidence available.

Poor ventilatory function has been associated with an increased risk of cardiovascular and metabolic conditions [2, 93, 102, 290]. Previous findings have shown that the relation of ventilatory function with cardiometabolic markers persists when taking shared

adult risk factors into account [94, 196, 304]. Therefore, an explanation for this association remains elusive. The elucidation of this relation has been further complicated because these associations were commonly investigated in older participants. This increases potential confounding by numerous environmental influences, the effects of which accumulate with age.

The results from the meta-analysis in this thesis on the association of birth weight with FVC, and to a lesser extent with FEV_1/FVC, combined with the existing evidence on an association of birth weight with cardiometabolic function led to the hypothesis that the relation of ventilatory function with cardiometabolic markers might be explained by a common association with birth weight. This was investigated in Chapter 4 in the Northern Finland 1966 birth cohort among young adults of 31 years old. These analyses identified sex-specific associations of cardiometabolic markers with ventilatory function among young adults, as well as differences in the association of cardiometabolic markers with FVC and FEV_1/FVC, with only few cardiometabolic markers being associated with FEV_1/FVC. In line with findings from a previous study [191], the effect estimates for these associations were not markedly altered after adjusting for birth weight, which suggests that other factors mediate the association of cardiometabolic markers with ventilatory function. One such factor could be systemic inflammation, which is associated with both ventilatory function and cardiometabolic markers, and this was also investigated in Chapter 4. Adjustment for systemic inflammation did not explain the relation of ventilatory function and cardiometabolic markers, and this could have three possible explanations: (1) systemic inflammation is truly associated with both ventilatory function and cardiometabolic markers, but does not mediate that relation; (2) systemic inflammation does mediate the relation, but was insufficiently captured by adjusting for only two inflammatory markers (C-reactive protein and white blood cell count); and (3) systemic inflammation is not causally associated with either ventilatory function or the cardiometabolic measurements, and cannot therefore explain the rela-

tion. Systemic inflammation has been commonly measured by levels of C-reactive protein, but it is not known how to best capture systemic inflammation and which, or how, many inflammatory markers would accurately reflect the inflammatory process. Moreover, the lack of statistically significant findings from longitudinal studies [3, 101, 154], combined with evidence from Mendelian randomization studies [27, 51, 72], appear to indicate that the association of C-reactive protein with poor ventilatory function, and also with cardiometabolic markers, is not causal. Therefore, since this thesis mostly focused on C-reactive protein, the possibility that systemic inflammation might explain the relation of ventilatory function with cardiometabolic markers cannot be ruled out.

I further sought to assess the relation of ventilatory function with systemic inflammation in the Northern Finland 1966 birth cohort in order to determine if this relation could be explained by common adult risk factors or, again, by a common association with birth weight. The findings show that only adult smoking partially explains the association of white blood cell count with FEV_1/FVC, while the effect estimates were not markedly altered after adjustment for other adult factors or birth weight.

The problems encountered in the findings described above are inherent to all observational studies, where the effects of unknown or unmeasured confounding factors cannot be excluded. An alternative approach would be to employ Mendelian randomisation analyses, which use genes as proxy for the risk factor of interest. Because genes are randomly allocated at conception, this approach can provide indirect unconfounded estimates of the effect [44, 74]. Future studies employing Mendelian randomisation might be conducted in large epidemiological studies in adults, such as UK biobank [5], or children, such as the MEDALL [31] and STELAR [71] consortia, which have a large sample size and contain detailed genetic and epidemiological information across the life course.

The relation of ventilatory function, cardiometabolic markers and birth weight can be confounded by ethnicity. Ethnic minorities have a higher burden of some cardiometabolic diseases and lower ventilatory function, as well as lower birth weight, compared

to Whites [47, 61, 142, 165, 319, 334]. However, what might explain these ethnic disparities is the subject of debate. A common explanation is that the difference in thoracic size, commonly measured by a difference in body proportions, is responsible for the lower ventilatory function among ethnic minorities. However, as reviewed in Chapter 2, the evidence in support of this hypothesis is inconclusive. An alternative hypothesis is that a reduced birth weight among ethnic minorities, reflecting adverse early life influences, could explain these differences. Therefore, in Chapter 5 I assessed in a pilot study whether a difference in birth weight could explain differences in ventilatory function between ethnic groups.

Consistent with previous findings and despite the small number of South Asian British participants in the study, the pilot study showed a large difference in FVC. However, the limited sample size and the similar socio-economic status of participants in both ethnic groups prevented the identification of a possible difference in birth weight between ethnic groups. Thus, I could not assess whether a difference in birth weight might explain the difference in ventilatory function between the two ethnic groups. However, the difference in FVC between ethnic groups was observed despite the lack of difference in birth weight. Therefore, it is very unlikely that the difference in birth weight is the explanation for the difference in FVC between the ethnic groups in this study population. Nonetheless, the pilot study did identify the immigration status of the mother and father as important predictors of FVC in an ethnically diverse population. I also assessed the role of thoracic size in potentially explaining ethnic differences in ventilatory function, and did not find evidence in support of this hypothesis. Importantly, this pilot study demonstrated the feasibility of future large population-based studies of ethnic disparities in ventilatory function and cardiometabolic markers among young adults, and highlighted possible issues and solutions for their implementation. In particular, Chapter 5 provides practical insight in the recruitment rate, potential missingness for questions related to parental and grandparental factors and linkage of birth weight data

for the conduct of future studies.

This thesis has shown that the evidence from epidemiological studies is increasingly supportive of the role of early life influences on later ventilatory function, and in particular of the influence of birth weight. Nonetheless, the biological pathways by which early life factors have a lifelong impact on the respiratory system remain largely unknown. Nor could the relation between ventilatory function, cardiometabolic markers, systemic inflammation, early life influences or ethnicity be fully elucidated in this thesis. This is further complicated by the fact that early life factors interact with one another, and with factors in adulthood, which also affect each other (Figure 6.1). The interrelatedness of these associations, combined with the inherent problem of confounding in observational studies, makes the interpretation of causes and effects among these associations difficult. Therefore, future studies might benefit from adopting causal methods, such as Mendelian randomisation.

Adverse early life influences may lead to lower ventilatory function, prevent the attaining of maximum ventilatory function and result in respiratory inequalities between ethnic groups. Identifying the causal role of early life influences, which could be a target for prevention, remains of the utmost importance.

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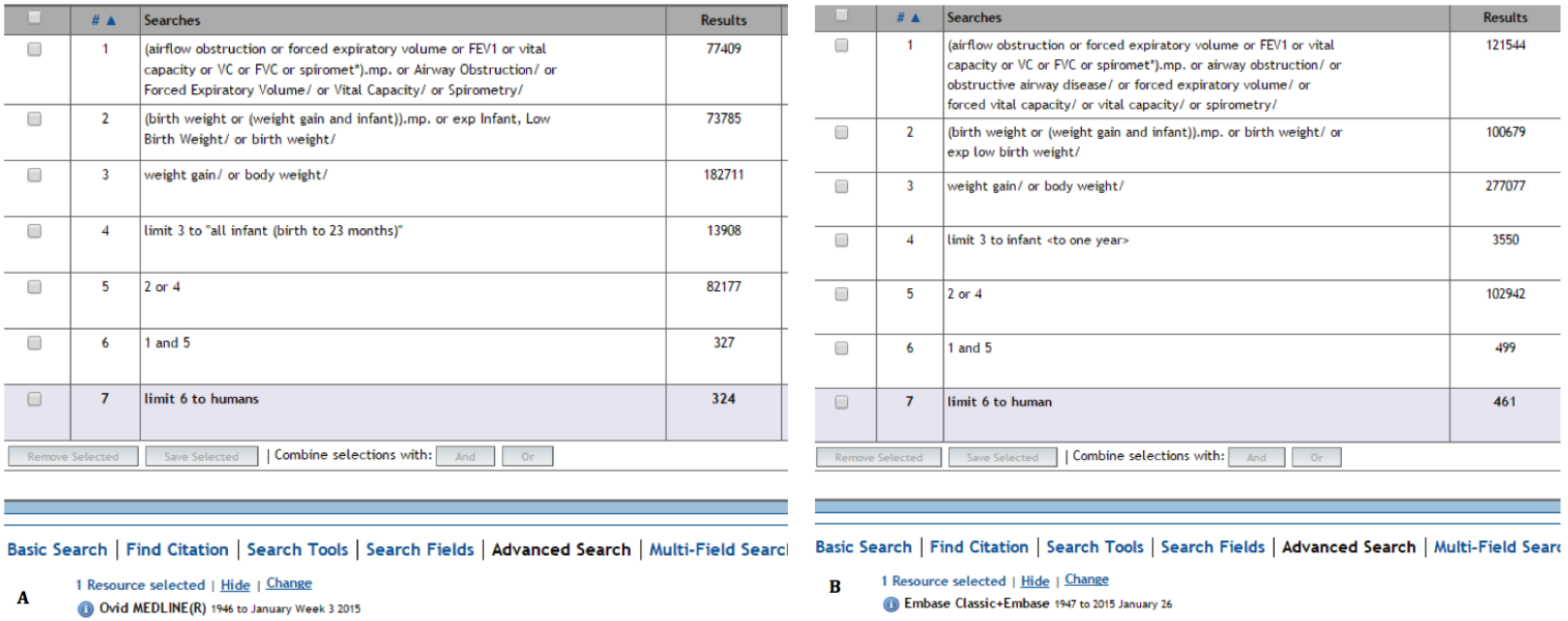
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WEIGHT IN EARLY LIFE AND VENTILATORY FUNCTION

A.1 Figures



	# ▲	Searches	Results
☐	1	(airflow obstruction or forced expiratory volume or FEV1 or vital capacity or VC or FVC or spiromet*).mp. or Airway Obstruction/ or Forced Expiratory Volume/ or Vital Capacity/ or Spirometry/	77409
☐	2	(birth weight or (weight gain and infant)).mp. or exp Infant, Low Birth Weight/ or birth weight/	73785
☐	3	weight gain/ or body weight/	182711
☐	4	limit 3 to "all infant (birth to 23 months)"	13908
☐	5	2 or 4	82177
☐	6	1 and 5	327
☐	7	limit 6 to humans	324

Remove Selected | Save Selected | Combine selections with: And | Or

Basic Search | Find Citation | Search Tools | Search Fields | Advanced Search | Multi-Field Searcl

A

1 Resource selected | Hide | Change

Ovid MEDLINE(R) 1946 to January Week 3 2015

	# ▲	Searches	Results
☐	1	(airflow obstruction or forced expiratory volume or FEV1 or vital capacity or VC or FVC or spiromet*).mp. or airway obstruction/ or obstructive airway disease/ or forced expiratory volume/ or forced vital capacity/ or vital capacity/ or spirometry/	121544
☐	2	(birth weight or (weight gain and infant)).mp. or birth weight/ or exp low birth weight/	100679
☐	3	weight gain/ or body weight/	277077
☐	4	limit 3 to infant <to one year>	3550
☐	5	2 or 4	102942
☐	6	1 and 5	499
☐	7	limit 6 to human	461

Remove Selected | Save Selected | Combine selections with: And | Or

Basic Search | Find Citation | Search Tools | Search Fields | Advanced Search | Multi-Field Searc

B

1 Resource selected | Hide | Change

Embase Classic+Embase 1947 to 2015 January 26

C

# 3	278	#2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 2	76,473	TS= ((birth weight) or (weight gain and infant)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 1	48,710	TS=((airflow obstruction) or (forced expiratory volume) or FEV1 or (vital capacity) or VC or FVC or spiromet*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*

Figure A.1: *Search strategy in the three databases. A) MEDLINE; B) Embase and C) Web of Science*

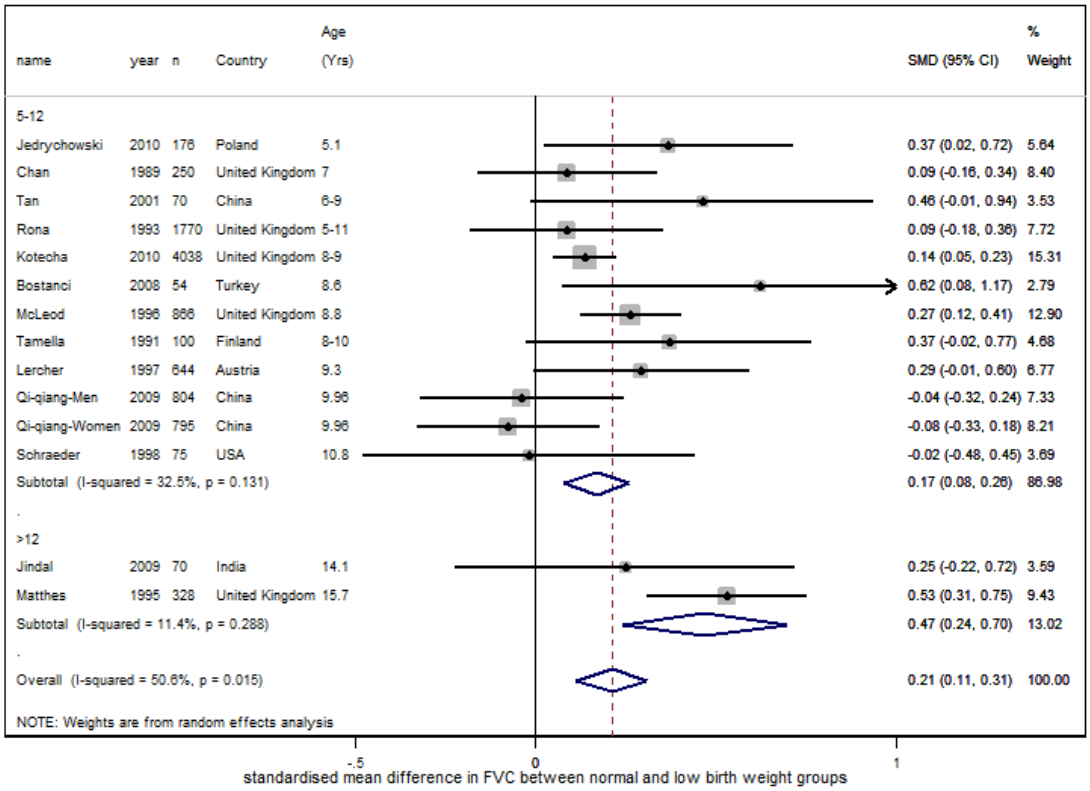


Figure A.2: *Forest plot for subgroup analysis by age for the association of FVC with birth weight as binary exposure (above/below 2.5 kg) in children (13 studies, 14 comparisons). Study estimates were ordered by increasing age. Some associations were reported by sex. Matthes et al. [213] defined birth weight as below 2.5 kg and above 3.0 kg.*

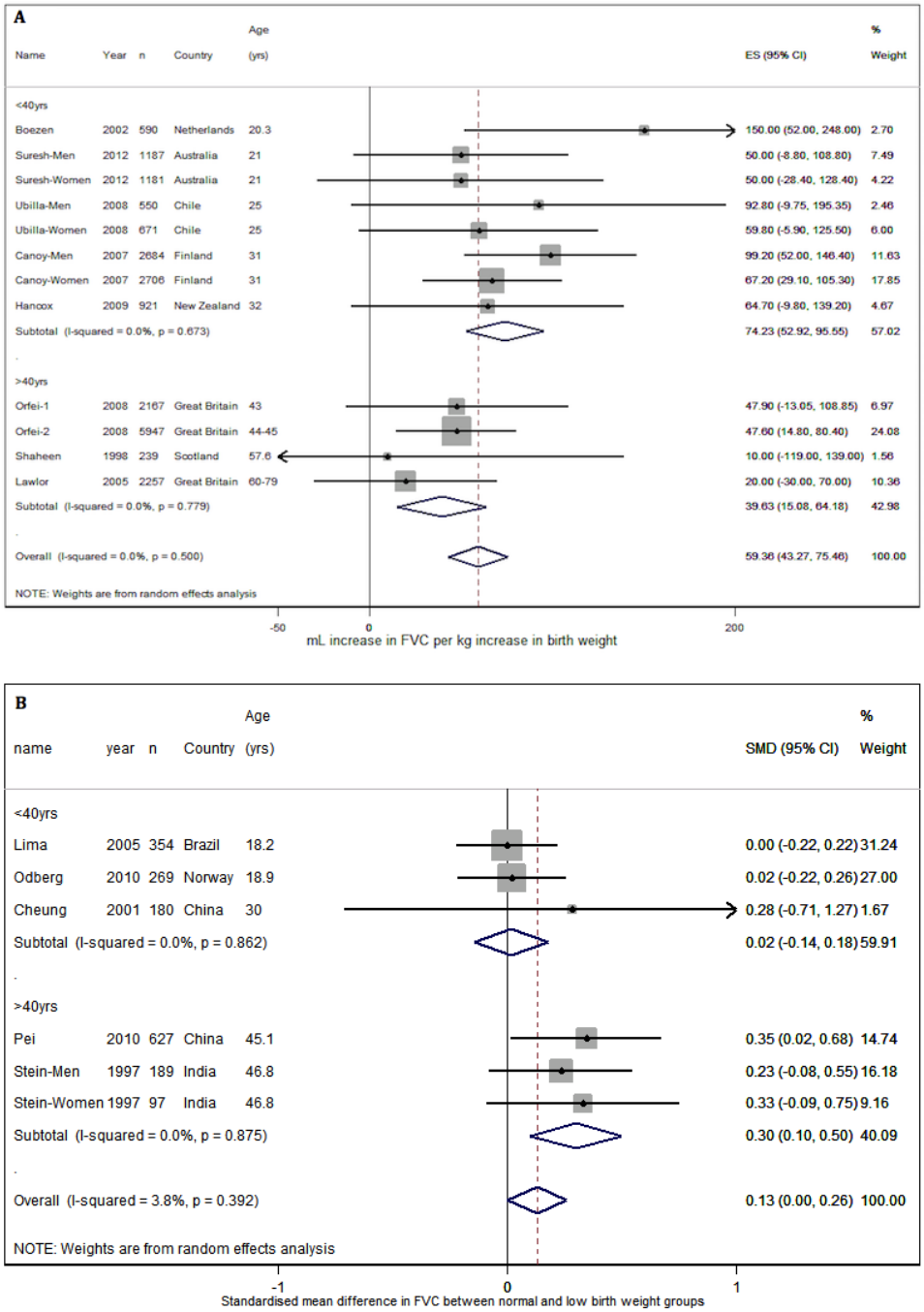


Figure A.3: *Forest plot for subgroup analysis by age for the association of FVC with birth weight in adults as: a) continuous exposure; b) binary exposure (above/below 2.5 kg). Some associations were reported by sex and Orfei et al (12). included two different study populations. Odberg et al. (11) defined birth weight as below 2.5 kg and above 3.0 kg.*

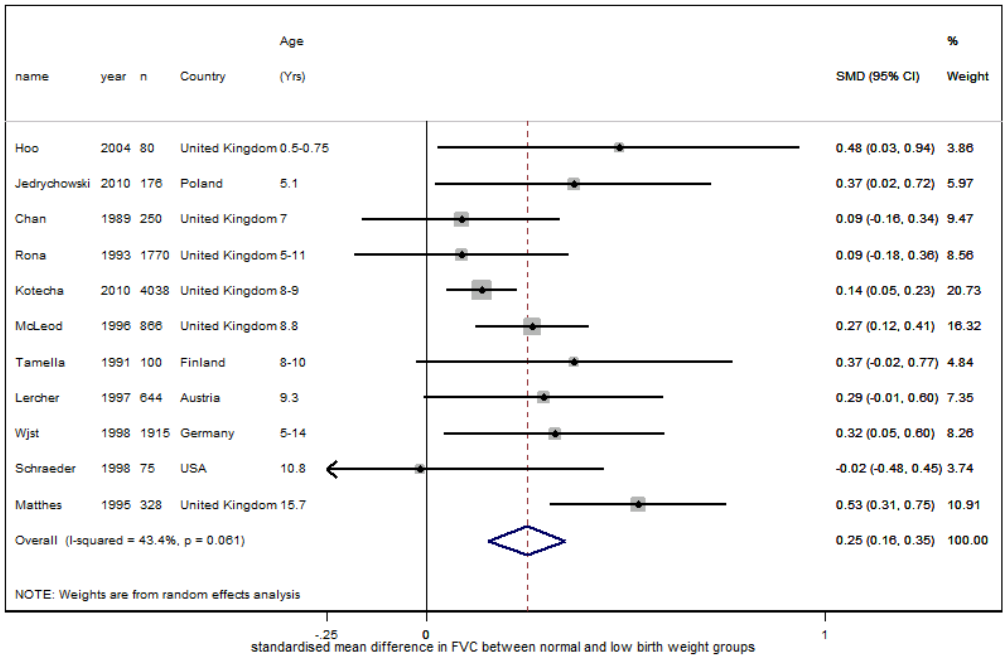


Figure A.4: *Forest plot for the association of FVC with birth weight as binary exposure (above/-below 2.5 kg) in children in high-income countries (11 studies, 11 comparisons). Study estimates were ordered by increasing age. Matthes et al. [213] defined birth weight as below 2.5 kg and above 3.0 kg.*

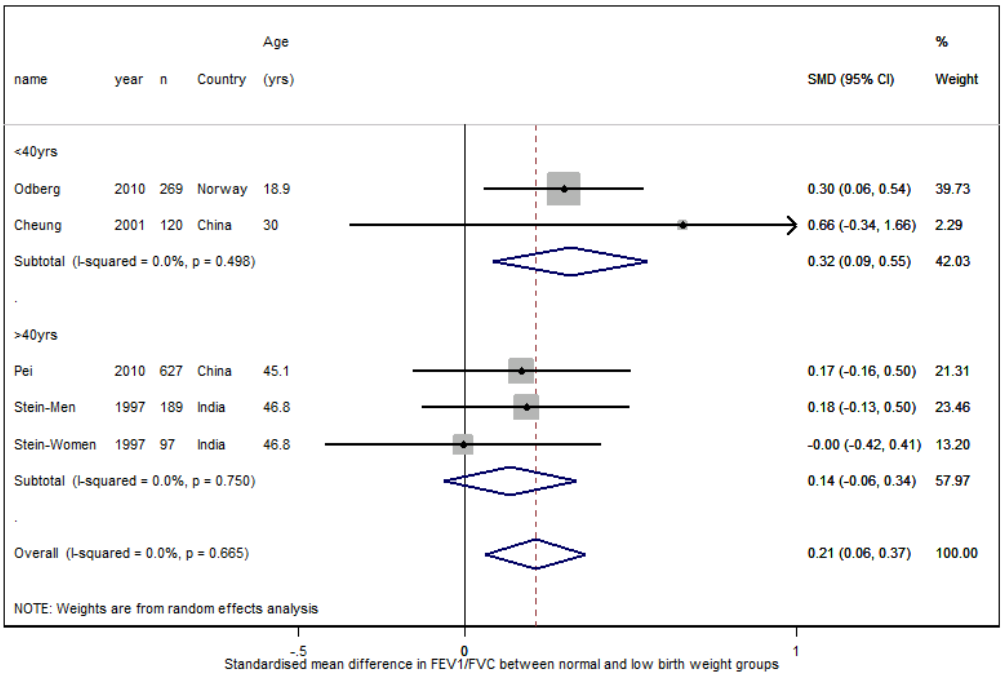


Figure A.5: *Forest plot for subgroup analysis by age for the association of FEV_1/FVC with birth weight as binary exposure (above/below 2.5 kg) in adults (4 studies, 5 comparisons). Study estimates were ordered by increasing age. Some associations were reported by sex. Odberg et al. [234] defined birth weight as below 2.5 kg and above 3.0 kg.*

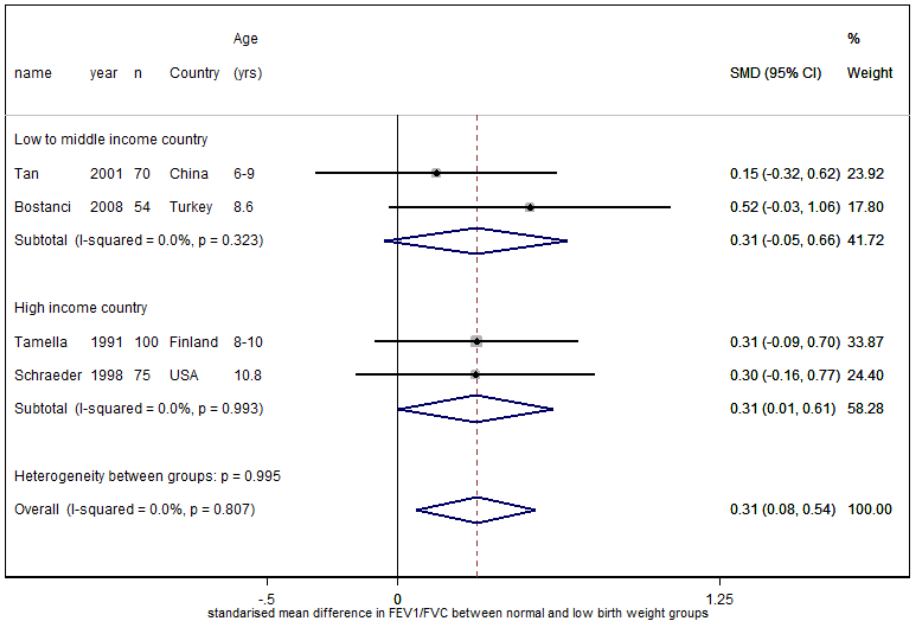


Figure A.6: *Forest plot for subgroup analysis by income for the association of FEV_1/FVC with birth weight as binary exposure (above/below 2.5 kg) in children (4 studies, 4 comparisons). Study estimates were ordered by increasing age. Some associations were reported by sex. Bostanci et al. [30] defined birth weight as below ≤1.75 kg and ≥ 2.5 kg and Schraeder et al. [289] defined birth weight as below ≤1.5 kg and >2.5 kg.*

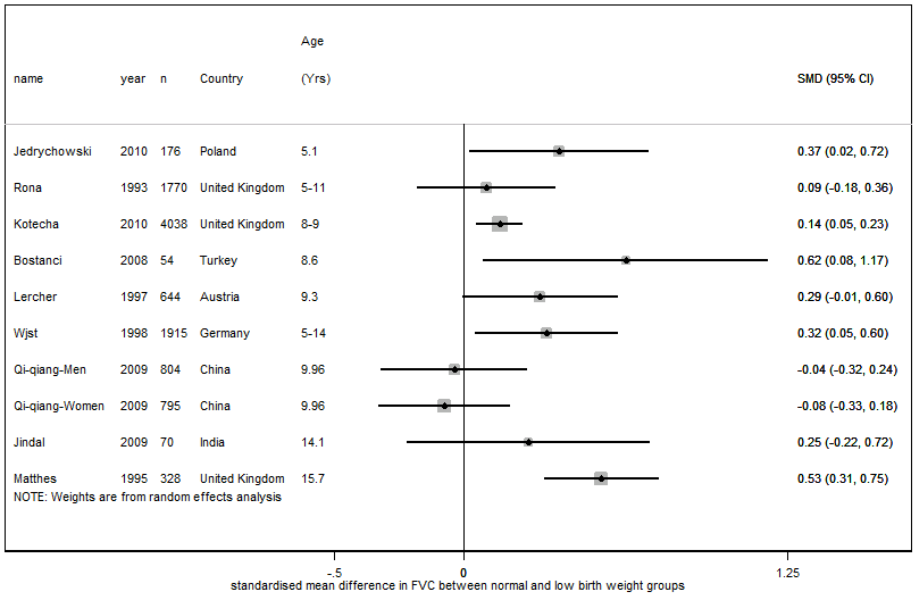


Figure A.7: *Forest plot for sensitivity analysis by exclusion of studies at high risk of bias for the association of FVC with birth weight as binary exposure (above/below 2.5 kg) in children (9 studies, 10 comparisons). Some associations were reported by sex. Study estimates were ordered by increasing age. Matthes et al. [213] defined birth weight as below 2.5 kg and above 3.0 kg.*

A.2 Tables

Table A.1: *Search strategy for the systematic review in three databases (Embase, Medline and Web of Science).*

Embase (Ovid)	**Medline (Ovid)**	**Web of Science**)
Database: Embase Classic+Embase 1947 to 2015 January 26	**Database**: Ovid MEDLINE(R) 1946 to January Week 3 2015	**Database**: Web of ScienceTM Core Collection (1970-present) • Social Sciences Citation Index 1970-present • Science Citation Index Expanded 1970-present •Arts & Humanities Citation Index 1975-present • Conference Proceedings Citation Index Science 1990-present • Conference Proceedings Citation Index Social Science & Humanities -1990-present **Limits**: • No timespan limit (i.e. searched all years) • All databases in the Core Collection
Search terms: free text (FT) and controlled vocabulary (CV)		
Block 1: **FT**: ((airflow obstruction) or (forced expiratory volume) or FEV1 or (vital capacity) or VC or FVC or spiromet*).mp. **CV**: airway obstruction/ or obstructive airway disease/ or forced expiratory volume/ or forced vital capacity/ or vital capacity/ or spirometry/	**Block 1**: **FT**: ((airflow obstruction) or (forced expiratory volume) or FEV1 or (vital capacity) or VC or FVC or spiromet*).mp. or **CV**: Airway Obstruction/ or Forced Expiratory Volume/ or Vital Capacity/ or Spirometry/	**Block 1**: **FT**: ((airflow obstruction) or (forced expiratory volume) or FEV1 or (vital capacity) or VC or FVC or spiromet*) or
Block 2: **FT**: ((birth weight) or (weight gain and infant)).mp. or **CV**: birth weight/ or exp low birth weight/ or **CV**: weight gain/ or body weight/ (limit to infant<to one year)	**Block 2**: **FT**: ((birth weight) or (weight gain and infant)).mp. or **CV**: exp Infant, Low Birth Weight/ or birth weight/ or **CV**:weight gain/ or body weight/ (limited by Age Groups from birth to 23 months)	**Block 2**: **FT**: ((birth weight) or (weight gain and infant))

Table A.2: *Data extraction form*

Reviewer		**Statistical analysis**	
Article ID number		**Adjustment for covariates**	
First Author, year		**Stratified analyses**	
Design		**Sensitivity analyses**	
Cohort study Cross-sectional study Other (specify) *If cohort study:* selection of the study population average follow-up time lost to follow-up (%) *If cross-sectional study:* selection of the study population		**Adjustment for multiple comparisons**	
		Other issues	
		Sample size/power calculations Extra-material available on-line	
		Outcomes definition and assessment	
		FVC units FEV1/FVC units Reference equation Lung function assessment Type of spirometer Quality control Bronchodilator	
Study population		**Exposures definition and assessment**	
Ethnicity Country Inclusion and/or exclusion criteria Age (mean & SD/ median & IQR/ simple range) Sex (% male) Height (mean & SD/ median & IQR/ simple range), if possible by sex Gestational age reported Broncho-pulmonary Dysplasia reported Other participant characteristics reported Response rate		Birth weight units Weight in the first year of life units Weight gain in the first year of life units Assessement	
		Extractable data	
		BW-FVC BW-FEV1/FVC W1Y-FVC W1Y-FEV1/FVC WG1Y-FVC WG1Y-FEV1/FVC	
Total sample size (on which the analyses were performed)			
Disease outcomes			
Primary outcomes Seconday outcomes			
Exposures			
Main exposures Other exposures		**Additional references**	
		Notes	

Table A.3: *Original and modified Newcastle-Ottawa Quality Assessment Scale (NOS)*

Original Newcastle-Ottawa Quality Assessment Scale	**Modified Newcastle-Ottawa Quality Assessment Scale**
Selection	**Selection**
1) Representativeness of the exposed cohort	**1) Representativeness of the exposed cohort**
a) truly representative of the average (describe) in the community *	a) truly representative of the average in the target community (all subjects or random sampling) *
b) somewhat representative of the average (describe) in the community *	b) somewhat representative of the average in the target community (non-random sampling) *
c) selected group of users eg nurses, volunteers	c) selected group of users eg nurses, volunteers
d)no description of the derivation of the cohort	d)no description of the derivation of the cohort
2) Selection of the non exposed cohort	**2) Selection of the non exposed cohort**
a)drawn from the same community as the exposed cohort*	a)drawn from the same community as the exposed cohort*
b) drawn from a different source	b) drawn from a different source
c)no description of the derivation of the non exposed cohort	c)no description of the derivation of the non exposed cohort
3) Ascertainment of exposure	**3) Ascertainment of exposure**
a)secure record (eg surgical records)*	a)secure record (eg birth or hospital records)*
b) structured interview*	b) structured interview *
c) written self report	c) written self report
d)no description	d)no description
4) Demonstration that outcome of interest was not present at start of study	
Yes*; No	
Comparability	**Comparability**
1) Comparability of cohorts on the basis of the design or analysis	**1) Comparability of cohorts on the basis of the design or analysis**
a)study controls for (select the most important factor) *	a) study controls for sex, age and height*
b)study controls for any additional factor *	b) study controls for current smoking*
Outcome	**Outcome**
1) Assessment of outcome	**1) Assessment of outcome**
a)independent blind assessment*	a) ATS/ERS guidelines and bronchodilator used and blind assessment*
b)record linkage*	b) ATS/ERS guidelines or non-ATS/ERS assessment and with bronchodilator or non-ATS/ERS assessment and blind assessment*
c) self report	c) Non-ATS/ERS guidelines
d)no description	d)no description
2) Was follow-up long enough for outcomes to occur	**2) Was follow-up long enough for outcomes to occur**
Yes*;No	Yes*;No
3) Adequacy of follow up of cohorts	**3) Adequacy of follow up of cohorts**
a)complete follow up - all subjects accounted for*	a)complete follow up - all subjects accounted for*
b)subjects lost to follow up unlikely to introduce bias small number lost - > % (select an adequate %) follow up, or description provided of those lost)*	b)subjects lost to follow up or response rate unlikely to introduce bias - small number lost/did not respond - >70% (description of those lost in note)*
c)follow up rate < % (select an adequate %) and no description of those lost	c) follow up/response rate < 70% (description of those lost in note)
d)no statement	d)no statement

Table A.4: *Type of variable and unit of measurement used across childhood studies for birth weight, FVC and FEV_1/FVC*

	Birth weight - FVC relation		Birth weight - FEV_1/FVC relation	
	Exposure	**Outcome units**	**Exposure**	**Outcome units**
Baraldi, 1991 [12]	Binary (⩽ 1.5kg; ⩾2.1kg)	Percent predicted	-	-
Bostanci, 2008 [30]	Binary (<2.5kg;>2.5kg)	Percent predicted	Binary (<2.5kg;>2.5kg)	Percent predicted
Brew, 2012 [38]	Continuous (kg)	mL	-	-
Bucens, 2006 [39]	Text only, no estimates available		-	-
Chan, 1989 [59]	Binary (<2.0kg;>2.0kg)	L	-	-
Chandler, 1979 [60]	Continuous (not specified)	Percent predicted	-	-
Demissie, 1997 [76]	Continuous (kg)	Percent	Continuous (kg)	Percent
Harik-Khan, 2004 [131]	Continuous (100 g)	mL	-	-
Hoo, 2004 [141]	Binary (<10th centile; >20th centile)	mL	-	-
Jedrychowski, 2010 [153]	Binary (⩽3.165kg; >3.165kg)	mL	-	-
Jindal, 2009 [155]	Binary (<2.5kg;⩾ 2.5kg)	L	-	-
Joseph-Bowen, 2004 [159]	Continuous (kg)	mL	-	-
Kotecha, 2010 [176]	Binary (<10th centile;⩾ 10th centile)	Standard deviation score	-	-
Lercher, 1997 [197]	Binary (<2.5kg;>2.5kg)	L	-	-
Mandadzhieva, 2005 [208]	Text only, no estimates available		-	-
Matthes, 1995 [213]	Binary (<2.5kg; ⩾3.0kg)	L	-	-
McLeod, 1996 [216]	Binary (<1.5kg; not specified)	L	Binary (<1.5kg; not specified)	Not specified
Qi-qiang, 2009 [256]	Binary (⩽ 2.5kg;>2.5kg)	Standard deviation score	-	-
Rona, 1993 [272]	Binary (<2.5kg;>2.5kg)	Standard deviation score	-	-
Schraeder, 1998 [289]	Binary (⩽1.5kg;>2.5kg)	Percent predicted	Binary (⩽1.5kg;>2.5kg)	Percent
Tammela, 1991 [327]	Binary (⩽1.75kg;>2.49kg)	Percent predicted	Binary (⩽1.75kg;>2.49kg)	Percent
Tan, 2001 [329]	Binary (<2.5kg;>2.5kg)	L	Binary (<2.5kg;>2.5kg)	Percent
Trabelsi2008 [338]	Continuous (kg)	L	Continuous (kg)	Percent
Turner, 2011 [339]	Continuous (kg)	mL	-	-
Wjst, 1998 [362]	Binary (⩽2.5kg; >2.5kg)	L	-	-

Table A.5: *Type of variable and unit of measurement used across adult studies for birth weight, FVC and FEV_1/FVC*

	Birth weight - FVC relation		**Birth weight - FEV_1/FVC relation**	
	Exposure	**Outcome units**	**Exposure**	**Outcome units**
Barker, 1991 [14]	Categorical	L	-	-
Boezen, 2002 [25]	Continuous (100 g)	L	-	-
Canoy, 2007 [54]	Continuous (500 g)	mL	Continuous (500 g)	Percent
Cheung, 2001 [64]	Binary (⩽ 2.5kg;>2.5kg)	L	Binary (⩽ 2.5kg;>2.5kg)	Percent
Edwards, 2003 [88]	Categorical	L	Text only, no data given	
Hancox, 2009 [127]	Continuous (kg)	mL	Continuous (kg)	Percent
Laerum, 2004 [182]	Continuous (500 g)	Percent predicted	Text only, no data given	
Lawlor, 2005 [193]	Continuous (kg)	L	-	-
Lima, 2005 [199]	Binary (<2.5kg;⩾2.5kg)	L	-	-
Lopuhaa, 2000 [203]	Categorical	L	Categorical	Percent
Odberg, 2010 [234]	Binary (⩽ 2.5kg;>3.0kg)	Percent predicted	Binary (⩽ 2.5kg;>3.0kg)	Percent
Orfei-1, 2008 [236]	Continuous (kg)	mL	-	-
Orfei-2, 2008 [236]	Continuous (kg)	mL	-	-
Pei, 2010 [247]	Binary (<2.5kg;⩾2.5kg)	L	Binary (<2.5kg;⩾2.5kg)	Percent predicted
Shaheen, 1998 [293]	Continuous (kg)	L	-	-
Sherrill, 2011 [296]	Categorical	Percent predicted	-	-
Stein, 1997 [309]	Binary (⩽ 2.5kg;>2.5kg)	L	Binary (⩽ 2.5kg;>2.5kg)	Percent
Suresh, 2012 [321]	Continuous (100 g)	L	-	-
Ubilla, 2008 [341]	Continuous (kg)	mL	Continuous (kg)	Percent

Table A.6: *Potential confounders considered for adjustments of the associations of birth weight with FVC and with FEV_1/FVC in childhood studies. Numbers in the table correspond to number of variables for each category of potential confounders*

	Childhood Factors at examination					Prenatal Factors						Other Factors		
	anthropometry	ethnicity	smoking	socio-economic/education	other	gestational age	parental anthropometry	parental smoking	parental socioeconomic/education	parental nutrition	other	Comorbidities	Study design	Other
	FVC													
Baraldi, 1991 [12]	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Bostanci, 2008 [30]	4	-	-	-	-	-	-	-	-	-	-	-	-	-
Brew, 2012 [38]	3	-	-	-	-	1	-	1	2	-	2	-	-	2
Bucens, 2006 [39]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chan, 1989 [59]	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Chandler, 1979 [60]	3				1		-	-	-	-	-	-	-	1
Demissie, 1997 [76]	4	1	1	1		1	-	-	-	-	-	-	-	2
Harik-Khan, 2004 [131]	2	1	-	-	-	-	-	-	-	-	-	-	-	-
Hoo, 2004 [141]	2		-	-	-	-	-	-	-	-	-	-	-	-
Jedrychowski, 2010 [153]	3		1		1			1			1			
Jindal, 2009 [155]	4	-	-	-	-	-	-	-	-	-	-	-	-	-
Joseph-Bowen, 2004 [159]	3	1			-				-	-	-	-	-	-
Kotecha, 2010 [176]	1			1	-	1		1	-	-	-	-	-	-
Lercher, 1997 [197]	3	-	-	-	-	-	-	-	-	-	-	-	-	-
Mandadzhieva, 2005 [208]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Matthes, 1995 [213]	3	-	-	-	-	-	-	-	-	-	-	-	-	-
McLeod, 1996 [216]	2	-	-	-	-	-	-	-	-	-	-	-	-	-
Qi-qiang, 2009 [256]	2	-	1	-	1	1	-	-	1	-	-	-	-	2
Rona, 1993 [272]	3	-	-	-	-	-	-	-	-	-	-	-	-	-
Schraeder, 1998 [289]	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Tammela, 1991 [327]	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Tan, 2001 [329]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Trabelsi2008 [338]	4	-	1	1	4	1	-	-	-	-	-	-	-	1
Turner, 2011 [339]	3	-	1	1	-	1	1	1			1	-	-	1
Wjst, 1998 [362]	3	-	-	-	-	-	-	-	-	-	-	-	-	-
	FEV_1/FVC													
Bostanci, 2008 [30]	4	-	-	-	-	-	-	-	-	-	-	-	-	-
Demissie, 1997 [76]	4	1	1	1	-	1	-	-	-	-	-	-	-	2
McLeod, 1996 [216]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schraeder, 1998 [289]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tammela, 1991 [327]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tan, 2001 [329]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Trabelsi2008 [338]	4		1	1	4	1	-	-	-	-	-	-	-	1

Table A.7: *Potential confounders considered for adjustments of the associations of birth weight with FVC and with FEV_1/FVC in adult studies. Numbers in the table correspond to number of variables for each category of potential confounders*

	Adult Factors at examination					Prenatal Factors						Other Factors		
	anthropometry	ethnicity	smoking	socio-economic/education	other	gestational age	parental anthropometry	parental smoking	parental socioeconomic/education	parental nutrition	other	Comorbidities	Study design	Other
	FVC													
Barker, 1991 [14]	3	-	-	-	-	-	-	-	-	-	-	-	-	-
Boezen, 2002 [25]	3	-	1	-	-	-	-	1	-	-	1	5	-	-
Canoy, 2007 [54]	3	-	1	1	1	1	-	1	1	-	-	5	-	-
Cheung, 2001 [64]	3	-	1	-	-	-	-	-	-	-	-	-	-	-
Edwards, 2003 [88]	3	-	1	1	-	-	-	-	-	-	-	-	1	-
Hancox, 2009 [127]	4	-	1	-	-	1	-	1	-	-	-	1	-	3
Laerum, 2004 [182]	4	-	2	-	-	-	-	-	-	-	1	1	1	1
Lawlor, 2005 [193]	2	-	1	5	-	-	-	-	4	-	-	-	1	1
Lima, 2005 [199]	3	1	-	2	-	1	2	-	-	-	1	-	-	1
Lopuhaa, 2000 [203]	3	-	-	-	-	-	-	-	-	-	-	-	-	-
Odberg, 2010 [234]	3	-	-	-	-	-	-	-	-	-	-	-	-	-
Orfei-1, 2008 [236]	4	-	1	-	-	-	-	-	-	-	-	-	-	3
Orfei-2, 2008 [236]	4	-	1	-	-	-	-	-	-	-	-	-	-	3
Pei, 2010 [247]	2	-	1	-	1	1	1	-	-	-	1	6	-	-
Shaheen, 1998 [293]	3	-	1	-	-	-	-	-	-	-	-	-	-	1
Sherrill, 2011 [296]	3	-	-	-	-	-	-	-	-	-	-	-	-	-
Stein, 1997 [309]	2	-	-	-	-	-	-	-	-	-	-	-	-	-
Suresh, 2012 [321]	3	-	1	-	-	-	1	1	1	2	-	-	-	-
Ubilla, 2008 [341]	2	-	1	1	1	1	-	-	-	-	-	-	-	-
	FEV_1/FVC													
Canoy, 2007 [54]	3	-	1	1	1	1	-	1	1	-	-	5	-	-
Cheung, 2001 [64]	3	-	1	-	-	-	-	-	-	-	-	-	-	-
Edwards, 2003 [88]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hancox, 2009 [127]	3	-	1	-	-	1	-	1	-	-	-	1	-	3
Laerum, 2004 [182]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lopuhaa, 2000 [203]	3	-	-	-	-	-	-	-	-	-	-	-	-	-
Odberg, 2010 [234]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pei, 2010 [247]	2	-	1	-	1	1	1	-	-	-	1	6	-	-
Stein, 1997 [309]	2	-	-	-	-	-	-	-	-	-	-	-	-	-
Ubilla, 2008 [341]	2	-	1	1	1	1	-	-	-	-	-	-	-	-

Table A.8: *Study-specific results for the association of birth weight with FVC and adjustments used for the analysis in childhood studies*

Author, year	Association with birth weight	Adjustment for covariates	Included in Meta-analysis
Baraldi, 1991 [12]	No data [Mean FVC only reported for low birth weight group]	Age, sex, height [by % predicted]	No, no data
Bostanci, 2008 [30]	Birth weight as binary exposure with mean FVC reported for each group; p-value<0.05	Age, sex, height and weight [by % predicted]	Yes
Brew, 2012 [38]	Increase of 72 mL (95%CI: 25 to 119) per kg increase in birth weight (pre-bronchodilator)	Age [by design], sex, height, maternal asthma, maternal age, breastfeeding for geq 6 months, mother's education, father's education, gestational age, parity and mother smoked in pregnancy	Yes
Bucens, 2006 [39]	No statistically significant association [no data, only in text]	-	No, no data
Chan, 1989 [59]	No statistically significant association [birth weight as binary exposure with mean FVC reported for each group]	Height	Yes
Chandler, 1979 [60]	No statistically significant association [no estimates; only p-value reported]	Age, height, weight, nutrition index, weight at one year	No, no data
Demissie, 1997 [76]	Increase of 2.8% (95% CI: 0.5 to 5.2) per kg increase in birth weight	Age, sex, height, body mass index and ethnicity [by logarithmic transformation]	No, FVC transformed into logarithmic scale and birth weight as continuous exposure
Harik-Khan, 2004-Women [131]	Increase of 6.0 mL per 100 gram increase in birth weight	Age, sitting height and race	No, no standard error or 95% confidence interval available
Harik-Khan, 2004-Men [131]	Increase of 6.4 mL per 100 gram increase in birth weight	Age, sitting height and race	No, no standard error or 95% confidence interval available
Hoo, 2004 [141]	Effect of low vs normal birth weight: -32.5 mL (95% CI: -64.1 to -0.8;p-value:0.05)	-	Yes
Jedrychowski, 2010 [153]	Birth weight categorised into four groups with mean FVC reported for each; p-value for trend:0.0003	Age [by design]	Yes
Jindal, 2009 [155]	No statistically significant association [Effect of low vs normal birth weight: -0.19L (95%CI: -0.55 to 0.16)]	-	Yes
Joseph-Bowen, 2004 [159]	Increase of 20 mL (95% CI: 4 to 36; p-value<0.05) per gram increase in birth weight	Age, sex, height and race	No
Kotecha, 2010 [176]	Effect of low vs normal birth weight: -0.14 SD (95% CI: -0.23 to -0.048)	Sex and gestational age [by standard deviation score transformation]	Yes
Lercher, 1997 [197]	No statistically significant association [birth weight as binary exposure with mean FVC reported for each group; p-value>0.05]	Age, height and weight	Yes
Mandadzhieva, 2005 [208]	No statistically significant association [no data, only in text]	-	No, no data

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Table A.8 – continued from previous page

Author, year	Association with birth weight	Adjustment for covariates	Included in Meta-analysis
Matthes, 1995 [213]	Birth weight as binary exposure with mean FVC reported for each group	-	Yes
McLeod, 1996 [216]	Birth weight as binary exposure with mean FVC reported for each group; p-value<0.001	Age [by design] and height	Yes
Qi-qiang, 2009- Women [256]	No statistically significant association [birth weight as binary exposure with mean FVC reported for each group; p-value:0.47]	Height [by standard deviation score transformation]	Yes
Qi-qiang, 2009-Men [256]	No statistically significant association [birth weight as binary exposure with mean FVC reported for each group; p-value:0.88]	Height [by standard deviation score transformation]	Yes
Rona, 1993 [272]	Birth weight categorised into four groups with mean FVC reported for each	Age, sex and height [by standard deviation score transformation]	Yes
Schraeder, 1998 [289]	No statistically significant association [Birth weight categorised into three groups with mean FVC reported for each; p-value: 0.66]	Age, sex and height [by % predicted]	Yes
Tammela, 1991 [327]	No statistically significant association [birth weight as binary exposure with mean FVC reported for each group]	Height [by % predicted]	Yes
Tan, 2001 [329]	Birth weight as binary exposure with mean FVC reported for each group; p-value<0.05	-	Yes
Trabelsi2008 [338]	No statistically significant association [no estimates; only p-value reported]	Sex, age, height, weight, gestational age, birth height, maximal inspiratory and expiratory thoracic perimeter, socio-economic status, type of heating used at home, total passive smokinga and physical activity	No, no data
Turner, 2011 [339]	Increase of 91 mL (95% CI: 17 to 165; p-value:0.02) per kg increase in birth weight	Age [by design], sex, child's height aged ten years, gestation at birth, maternal smoking status at first trimester scan, exposure to tobacco smoke at ten years, history of maternal asthma,maternal height, maternal first trimester plasma alpha tocopherol and Scottish Index of Multiple Deprivation	Yes
Wjst, 1998 [362]	Birth weight as binary exposure with mean FVC reported for each group	Height, sex and age (using logarithmic transformation)	Yes

Table A.9: *Study-specific results for the association of birth weight with FVC and adjustments used for the analysis in adult studies*

Author, year	Association with birth weight	Adjustment for covariates	Included in Meta-analysis
Barker, 1991 [14]	No statistically significant association [birth weight categorised into six groups with mean FVC reported for each group; no significant trend]	Age, sex [by study design] and height	No, no standard errors or 95% confidence interval available
Boezen, 2002 [25]	Increase of 0.015 L (95%CI: 0.0052 to 0.025; p-value: <0.05) per 100 gram increase in birth weight	Age, sex, height, mother smoke during pregnancy, being first born, severe respiratory tract infection, current smoker, family history of asthma or allergy and asthmatic symptoms and bronchitic symptoms	Yes
Canoy, 2007 - Women [54]	Increase of 33.6 mL (95%CI: 14.5 to 52.6) per 500 gram increase in birth weight	Age [by study design] and height	Yes
Canoy, 2007 - Men [54]	Increase of 49.6 mL (95%CI: 26.0 to 73.2) per 500 gram increase in birth weight	Age [by study design] and height	Yes
Cheung, 2001 [64]	No statistically significant association [birth weight categorised into seven groups with mean FVC reported for each group; p-value for trend: 0.87]	Age [by study design], sex, height and smoking	Yes
Edwards, 2003- Women [88]	Increase of mean FVC per categories of birth weight (p-value for trend<0.01)	Age, height, weight, current smoking status, deprivation category and childhood group	No, no standard error or 95% confidence interval available
Edwards, 2003 - Men [88]	Increase of mean FVC per categories of birth weight (p-value for trend<0.01)	Age, height, weight, current smoking status, deprivation category and childhood group	No, no standard error or 95% confidence interval available
Hancox, 2009 [127]	No statistically significant association [increase of 64.7 mL (95%CI:-10 to 139; p-value: 0.088) per kilogram increase in birth weight]	Age [by study design], sex and height	Yes
Laerum, 2004 [182]	No statistically significant association [increase of 0.47 % predicted (95%CI:-0.52 to 1.46) per 500 gram increase in birth weight]	Age, sex, height [by percent predicted], age, sex, birth length, study centre, adult body mass index, allergic rhinitis parental and adult environmental, ex- and current smoking	No, unable to pool as FVC in percent predicted and birth weight as continuous exposure
Lawlor, 2005 [193]	No statistically significant association [Increase of 0.02 L (95% CI: -0.03 to 0.07) per kilogram increase in birth weight]	Age, sex [by study design], examining nurse and height^2	Yes
Lima, 2005 [199]	No statistically significant association [effect of low vs normal birth weight: 0.002 L (95%CI: -0.12 to 0.12); p-value: 0.97]	Age, sex [both by study design] and height	Yes
Lopuhaa, 2000 [203]	No statistically significant association [birth weight categorised into four groups with mean FVC reported for each group; p-value for trend: 0.60]	Age, sex and height	No, no standard error or 95% confidence interval available
Odberg, 2010 [234]	No statistically significant association [effect of normal vs low birth weight: 0.3 % predicted (95%CI: -3.1 to 3.7); p-value: 0.90]	Age, sex and height [all by percent predicted]	Yes

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Table A.9 – continued from previous page

Author, year	Association with birth weight	Adjustment for covariates	Included in Meta-analysis
Orfei-1, 2008 [236]	No statistically significant association [increase of 47.9 mL (95%CI:-13.0 to 108.9) per kilogram increase in birth weight]	Age [by study design], sex, adult height, adult sitting height, height at 7 years, smoking status, childhood social class and air pollution exposure	Yes
Orfei-2, 2008 [236]	Increase of 47.6 mL (95%CI: 14.8 to 80.4; p-value: <0.01) per kilogram increase in birth weight	Age [by study design], sex, adult height, adult sitting height, height at 7 years, smoking status, childhood social class and air pollution exposure	Yes
Pei, 2010 [247]	Increase of mean FVC per categories of birth weight (p-value for trend: 0.001)	Maternal age, gestation week, offspring's sex, birth height, history of dyspnea and asthma, lung disease before 16 yrs of age, lung diseases after measles and pneumonia before 16 yrs of age, cough with sputum within 2 years, current asthma, taking medicine for asthma, adult body mass index, male use of alcohol and male smoking	Yes
Shaheen, 1998 [293]	No statistically significant association [increase of 0.010 L (95%CI:-0.119 to 0.139; p-value: 0.88) per kilogram increase in birth weight]	Age, sex, height, smoking and type of spirometer	Yes
Sherrill, 2011 [296]	No statistically significant association [birth weight categorised in tertiles with mean FVC reported for each group; p-value for trend >0.05]	Age, sex and height [all by percent predicted]	No, unable to pool as exposure expressed in tertile and mean birth weight for each tertile unknown
Stein, 1997 - Women [309]	No statistically significant association [birth weight categorised into six groups with mean FVC reported for each group; p-value for trend: 0.05]	Age and height	Yes
Stein, 1997 - Men [309]	Birth weight categorised into six groups with mean FVC reported for each group; p-value for trend: 0.02	Age and height	Yes
Suresh, 2012 - Women [321]	No statistically significant association [increase of 0.005 L (95%CI:-0.0009 to 0.011) per 100 gram increase in birth weight]	Age [by study design], offspring's height and weight	Yes
Suresh, 2012 - Men [321]	No statistically significant association [increase of 0.005 L (95%CI:-0.0028 to 0.013) per 100 gram increase in birth weight]	Age [by study design], offspring's height and weight	Yes
Ubilla, 2008 - Women [341]	No statistically significant association [increase of 59.8 mL (95%CI:-5.9 to 125.5) per kilogram increase in birth weight]	Age, height, smoking, number of siblings, years of full time school and gestational age	Yes
Ubilla, 2008 - Men [341]	No statistically significant association [increase of 92.8 mL (95%CI:-9.7 to 195.4) per kilogram increase in birth weight]	Age, height, smoking, number of siblings, years of full time school and gestational age	Yes

Table A.10: *Study-specific results for the association of birth weight with FEV_1/FVC and adjustments used for the analysis in childhood studies*

Author, year	Association with birth weight	Adjustment for covariates	Included in Meta-analysis
Bostanci, 2008 [30]	No statistically significant association [Birth weight categorised into two groups with mean FEV_1/FVC reported for each group p-value>0.05)]	Sex, age, height and weight [by % predicted]	Yes
Demissie, 1997 [76]	No statistically significant association [Increase of 0.5% (95% CI: -0.7 to 1.7) per kilogram increase of birth weight]	Sex, age, height, body mass index and ethnicity [by logarithmic transformation]	No, unable to pool as FEV_1/FVC transformed into logarithmic scale and birth weight as continuous exposure
McLeod, 1996 [216]	Effect of low BW vs normal BW [no estimates; p-value<0.05]	-	No, no data
Schraeder, 1998 [289]	No statistically significant association [Birth weight categorised into three groups with mean FEV_1/FVC reported for each; p-value: 0.09]	-	Yes
Tammela, 1991 [327]	No statistically significant association [birth weight as binary exposure with mean FEV_1/FVC reported for each group]	-	Yes
Tan, 2001 [329]	No statistically significant association [birth weight as binary exposure with mean FEV_1/FVC reported for each group; p-value: 0.53]	-	Yes
Trabelsi, 2008 [338]	No statistically significant association [no data only p-value:0.41]	Sex, age, height, weight, gestational age, birth height, maximal inspiratory and expiratory thoracic perimeter, socio-economic status, type of heating used at home,total passive smoking and physical activity	No, no data

Table A.11: *Study-specific results for the association of birth weight with FEV_1/FVC and adjustments used for the analysis in adult studies*

Author, year	Association with birth weight	Adjustment for covariates	Included in Meta-analysis
Canoy, 2007 - Women [54]	Increase of 0.27 % (95%CI: 0.07 to 0.54) per 500 gr increase in birth weight	Age [by study design] and height	Yes
Canoy, 2007 - Men [54]	No statistically significant association [Increase of 0.09 % (95%CI: -0.16 to 0.33) per 500 gr increase in birth weight]	Age [by study design] and height	Yes
Cheung, 2001 [64]	No statistically significant association [birth weight categorised into six groups with mean FEV_1/FVC reported for each group; p-value for trend: 0.30]	Age [by study design], sex, height and smoking	Yes
Edwards, 2003 - Women [88]	No statistically significant association [no data, only in text]	-	No, no data
Edwards, 2003 - Men [88]	No statistically significant association [no data, only in text]	-	No, no data
Hancox, 2009 [127]	No statistically significant association [Increase of 0.01 % (95%CI: -0.82 to 0.84; p-value:0.97) per kg increase in birth weight]	Age [by study design] and sex	Yes
Laerum, 2004 [182]	No statistically significant association [no data, only in text]	-	No, no data
Lopuhaa, 2000 [203]	No statistically significant association [birth weight categorised into four groups with mean FEV_1/FVC reported for each group; p-value for trend: 0.80]	Age, sex and height	No, no standard error or 95% confidence interval available
Odberg, 2010 [234]	Increase of 0.03 % (95%CI: 0.01 to 0.04; p-value: <0.01) for normal vs low birth weight	-	Yes
Pei, 2010 [247]	No statistically significant association [birth weight categorised into four groups with mean FEV_1/FVC reported for each group; p-value for trend>0.05]	Maternal age, gestation week, offspring's sex, birth height, history of dyspnea and asthma, lung disease before 16 yrs of age, lung diseases after measles and pneumonia before 16 yrs of age, cough with sputum within 2 years, current asthma, taking medicine for asthma, adult body mass index, male use of alcohol and male smoking	Yes
Stein, 1997 - Women [309]	No statistically significant association [birth weight categorised into six groups with mean FEV_1/FVC reported for each group; p-value for trend: 0.76]	Age and height	Yes
Stein, 1997 - Men [309]	No statistically significant association [birth weight categorised into six groups with mean FEV_1/FVC reported for each group; p-value for trend: 0.32]	Age and height	Yes
Ubilla, 2008 - Women [341]	Decrease of -0.9 % (95%CI: -1.7 to -0.03; p-value: <0.05) per kg increase in birth weight	Age, height, smoking, number of siblings, years of full time school and gestational age	Yes
Ubilla, 2008 - Men [341]	No statistically significant association [Increase of 0.3 % (95%CI: -0.7 to 1.3) per kg increase in birth weight]	Age, height, smoking, number of siblings, years of full time school and gestational age	Yes

Table A.12: *Study-specific results for the quality assessment according to the NOS scale in childhood studies*

Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Baraldi, 1991 [12]	B*	C	D	No	No	D	A*	C/D	1	Selection 1: Participants who, at birth, had been admitted to the neonatal intensive care unit Selection 2: No details as to how controls were selected Selection 3: No description of ascertainment of birth weight Comparability 1 & 2: Lung function only adjusted for height and only lung function outcomes available for low birth weight group. However, participants in low and normal birth weight group were age, sex, height and weight matched Outcome 1: No description of lung function assessment Outcome 3: 15 out of 76 low birth weight children were included in the study. No description of non-responders. No information on the follow-up or response for the normal birth weight children
Bostanici, 2008 [30]	B*	A*	A*	Yes*	No	B*	A*	C/D	6	Selection 1: Participants were born to a Turkish mother who did not smoke in pregnancy Comparability 1 & 2: Adjusted by using reference equations for % predicted. No adjustment for smoking Outcome 1: ATS criteria used Outcome 3: 25 of 55 SGA participants took part (45.4%). No description on response rate/follow-up for AGA participants. No description of those lost
Brew, 2012 [38]	B*	A*	A*	Yes*	No	B*	A*	B*	7	Selection 1: Pregnant mothers with either parent or an older sibling had a history of asthma or recurrent wheeze, and that the child was born at >36 weeks gestation were recruited into the study Comparability 2: Association not adjusted for current parental smoking although they did adjust for maternal smoking in pregnancy Outcome 1: ATS criteria used with bronchodilator Outcome 3: 73% of children (449/616) available at follow-up and description of those lost

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Table A.12 – continued from previous page

Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Bucens, 2006 [39]	B*	A*	A*	No	No	B*	A*	B*	6	Selection 1: Neonatal paediatrician visited the Aboriginal mothers within four days of delivery. Recruitment was dependent primarily on the whether the neonatal paediatrician was in town. She was intermittently absent for a total of 5 months during this time. Recruitment was also dependent on whether mothers could be found as they often absented themselves for extended periods of time. All the mothers found and interviewed agreed to participate. For the whole cohort there were no significant differences in mean birth weight, or gender ratio between those recruited and not recruited using the unpaired t-test. Therefore, the selection is considered to be non-random sampling. Comparability 1 & 2: Relation between FVC and birth weight only assessed in crude analysis. Birth weight was not statistically significantly associated with FVC and therefore was not included in further analyses Outcome 1: ATS criteria used Outcome 3: 80% of children available at follow-up and description of those lost
Chan, 1989 [59]	B*	B	D	No	No	C	A*	B*/D	2	Selection 1: Participants of birth weight between 500g and 200g born between June 1979 and May 1980 were recruited at birth or on admission to the neonatal units Selection 2: Normal birth weight participants obtained from a different setting (schools) that low birth weight participants. Selection 3: No description of birth weight ascertainment. Comparability 1 & 2: Lung function by birth weight group was adjusted for height and age but not for sex or smoking. Outcome 1: Non ATS/ERS guidelines were used. Outcome 3: 134 children out of 189 LBW children (71%) attended the study visit. No description of those lost to follow-up. No description of response rate for NBW children.
Chandler, 1979 [60]	B*	A*	D	No	No	C	A*	D	3	Selection 1: Children selected from primary school setting. Selection 3: No description of birth weight ascertainment. Comparability 1 & 2: Only p-value given for FVC-BW association from multiple linear regression and adjustment for Age, height, weight, nutrition index, weight at one year. Outcome 1: non ATS/ERS guidelines were used. A subgroup of 38 children did have a bronchodilator administered and had post bronchodilator spirometry performed. Outcome 3: No description of follow-up/response rate.

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Table A.12 – continued from previous page

Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Demissie, 1997 [76]	B*	A*	B*	Yes*	Yes*	B*	A*	B*	8	Selection 1: Children selected from school setting. Schools were selected to represent a broad range of socio-economic status. Selection 3: Birth weight information was obtained through interview-led questionnaire with the parents. Comparability 2: Children do not smoke but adjustment for passive smoking (not specified whether this refers to parental smoking). Outcome 1: ATS guidelines used. Outcome 3: 83.9% response rate. Description of those who did not participate and comparison between participants and non-participants
Harik-Khan, 2004 [131]	B*	A*	D	No	No	B*	A*	D	4	Selection 1: Study population obtained from a survey of US noninstitutionalised population. Selection 3: No description of birth weight ascertainment. Comparability 1 & 2: Association stratified by gender and adjusted for age, sitting height and race. Outcome 1: ATS guidelines used. Outcome 3: No description of response rate. However, of 4140 children, only 1462 met the quality criteria for spirometry and only 752 the relation between birth weight and lung function was assessed.
Hoo, 2004 [141]	B*	A*	D	No	No	C	A*	C	3	Selection 1: Healthy singleton infants (>35 weeks) were eligible for inclusion if born to a white northern European mother who did not smoke in pregnancy or postnatally. Selection 3: No description of birth weight ascertainment. Comparability 1 & 2: Only adjusted for infant length and sex. Not for age or smoking. Outcome 1: Own guidelines used. Outcome 3: Of the initial cohort, 139 participants were eligible for follow-up (59%). No description of those lost.
Jedrychowski, 2010 [153]	B*	A*	D	Yes*	Yes*	B*	A*	C	6	Selection 1: Women 18-35 years of age, who claimed to be non-smokers, with singleton pregnancies, with no history of illicit drug use or HIV infection, free from chronic diseases such as diabetes or hypertension and who had resided in Krakow for at least 1 year prior to pregnancy were eligible for the study. Selection 3: No description of birth weight ascertainment. Comparability 2: Association has been adjusted for pre- and postnatal environmental tobacco smoke. Outcome 1: ATS/ERS criteria used Outcome 3: 176 of 481 children at follow-up and description of those lost.

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Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Jindal, 2009 [155]	B*	A*	A*	No	No	C	A*	D	4	Selection 1: Participants were born in nursing homes, located in the vicinity of the institution and having their complete birth records. Comparability 1 & 2: Estimates not adjusted for age, height, sex or smoking but P-value shown in Table that is adjusted for sex (by design), age, height, weight and BMI. Outcome 1: Own criteria used Outcome 3: No description of follow-up or response rate
Joseph-Bowen, 2004 [159]	A*	A*	A*	Yes*	Yes*	B*	A*	B*	8	Comparability 2: Children are 6 years so don't smoke but association has been adjusted for maternal smoking at a child age 6. Outcome 1: ATS criteria used. Outcome 3: 78% of children (1995/2537) conducted physical examination at follow-up and description of those lost.
Kotecha, 2010 [176]	A*	A*	A*	Yes*	No	B*	A*	C	6	Comparability 1 & 2: Z-scores were used, which were adjusted for age, sex and height Outcome 1: ATS/ERS criteria used. Outcome 3: Of the 14049 participants, 7394 had lung spirometry at age 8-9 years (53%). Description of those lost and comparison with whole study cohort.
Lercher, 1997 [197]	B*	A*	A*	No	No	B*	A*	B*	6	Selection 1: Children selected from school setting. Schools selected based on traffic density. Comparability 1 & 2: Association adjusted for age, height and weight but not for sex or smoking. Outcome 1: ATS criteria used. Outcome 3: Response rate was 796 of 940 (85%). Of these 644 were included in the study (69%) as information was available on all variables. Comparison with whole cohort.
Mandadzhieva, 2005 [208]	B*	A*	C	No	No	B*	A*	B*	5	Selection 1: Children selected from school setting. No detailed description of how schools were selected. Selection 3: Parents reported the birth weight using self-reported questionnaires. Comparability 1 & 2: No association between birth weight and FVC. Only mentioned in text. No adjustment mentioned or data provided. Outcome 1: ATS/ERS criteria used. Outcome 3: 210 out of 250 children successfully completed the study. However, birth weight information was only available for 124 children.

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Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Matthes, 1995 [213]	B*	A*	D	No	No	C	A*	B*	4	Selection 1: Participants selected from the two large obstetric departments. Comparability 1 & 2: Association only adjusted for height, weight and age. Outcome 1: Own criteria used Outcome 3: 163 out of 222 (74.3%) of matched pairs participated in the study. No description of those lost.
Mcleod, 1996 [216]	A*	B	A*/D	No	No	C	A*	B*/D	2	Selection 1: All liveborn children born in Scotland in 1984 weighting less than 1750g at birth were eligible. Selection 2: Normal birth weight participants obtained from a different setting (schools) that low birth weight participants. Selection 3: No clear description of birth weight ascertainment mentioned perinatal data abstracted from maternal and infant case records for VLBW infants. Comparability 1 & 2: FVC-birth weight association only adjusted for height. Outcome 1: Own criteria used Outcome 3:300 of VLBW children (88%) and 590 controls were assessed. No description of those lost or any information on response rate for controls.
Qi-quang, 2009 [256]	B*	A*	C	Yes*	Yes*	B*	A*	B*	7	Selection 1: Children selected from school setting. Schools selected on air pollution monitoring/vicinity industry. Selection 3: Parents reported the birth weight using self-reported questionnaires. Comparability 2: Children do not smoke but adjustment for passive smoking (not specified whether this refers to parental smoking). Outcome 1: ATS/ERS criteria used Outcome 3: 92.8% of children (2760/2975) participated in study. 78.9% of children returned the questionnaires and participated in the anthropometric and lung function tests. Description of lost to follow-up.
Rona, 1993 [272]	A*	A*	C	Yes*	No	C	A*	C	4	Selection 1: Children selected from school setting. Schools selected by stratified random sampling. Selection 3: Parents reported the birth weight using self-reported questionnaires. Outcome 1: Own criteria used Outcome 3: 2036 out of 3036 participants (67%) had useful information on all variables. Description of those lost.

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Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Schraeder, 1998 [289]	B*	B	A*	No	No	C	A*	C/D	3	Selection 1: Children selected by reviewing census books. Selection 2: Two comparison groups. First group are school based peers and second group are siblings of very low birth weight participants. Selection 3: Birth weight was obtained by chart review in infancy. Comparability 1 & 2: Lung function expressed as percent predicted, which adjusted only for standing height. No other adjustments made. Outcome 1: Own criteria used Outcome 3: 41 out of 64 (64%) VLBW participants agreed to take part. Description of those lost for VLBW. 30 out of 32 NBW peers participated in the study. No response rate for NBW siblings.
Tamella, 1991 [327]	B*	B	D	FVC: Yes* FEV_1/FVC: No	No	C	A*	C/D	FVC: 3 FEV_1/FVC: 2	Selection 1: 93 LBW (BW<1751gram) who survived in the neonatal intensive care unit of Oulu University Central Hospital but only 50 were included in the study. Selection 2: Normal birth weight participants obtained from a different setting (schools) that low birth weight participants. Selection 3: No description of birth weight ascertainment. Comparability 1 & 2: Lung function presented as & predicted based on body height. LBW and NBW groups matched on age and sex. No other variables adjusted for. For FEV_1/FVC, the association was not adjusted for height, age or sex. Outcome 1: Own criteria used Outcome 3: 50 out of 93 LBW children participated in the study (54%). Description of LBW lost to follow-up. 50 control participants were recruited but no information on response rate.
Tan, 2001 [329]	D	B	D	No	No	C	A*	D	1	Selection 1: Children selected from hospital. No description of selection criteria. Selection 2: Normal birth weight participants obtained from a different setting (schools) that low birth weight participants. Selection 3: No description of birth weight ascertainment. Comparability 1 & 2: Lung function reported in both L or % and % predicted. But no reporting of adjustment or no reference for the prediction equation.
Trabelsi, 2008 [338]	A*	A*	A*	Yes*	Yes*	B*	A*	D	7	Selection 1: Children selected from school setting. Schools and classes were selected by two level cluster sampling. Comparability 2: Children do not smoke but adjustment for passive smoking (not specified whether this refers to parental smoking). Outcome 1: ATS/ERS criteria used Outcome 3: No description of response rate. Only that 919 children were selected and that 116 were excluded due to the inclusion criteria and in total 756 out of 919 children (82%) were included in the study. Description of those lost/not included.

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Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Turner, 2011 [339]	A*	A*	A*	Yes*	Yes*	B*	Yes*	C	7	Comparability 2: Children are 10 years so don't smoke but association has been adjusted for exposure to tobacco smoke at 10 years Outcome 1: ERS criteria used Outcome 3: 927 participants out of 1924 returned the questionnaire (48%) and 449 attended the clinical visit (23%). Lung function available for 393 children out of 1924 children. Comparison of participants to whole cohort but no description of those lost.
Wjst, 1998 [362]	B*	A*	A*	Yes*	No	C	A*	B*	6	Selection 1: Children selected from school setting. Comparability 2: Association adjusted for height, sex and age in logarithmic transformation. Outcome 1: Own criteria used Outcome 3: 2470 children participated out of 2773 (89.1%) and 2082 children completed lung function testing out of 2773 children (75%). Authors give description of those lost to follow-up.

Table A.13: *Study-specific results for the quality assessment according to the NOS scale in adult studies*

Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Barker, 1991 [14]	A*	A*	A*	Yes*	No	C	A*	B*	6	Outcome 1: Lung function measured according to their own guidelines Outcome 3: Follow-up study of all male infants born in Hertfordshire between 1911-30 of which 5718 were traced (74%). Of those born during 1920-30, 1157 still lived there and 845 (73%) agreed to participate. However, no description of those who did not participate
Boezen, 2002 [25]	B*	A*	A*	Yes*	Yes*	B*	A*	C	7	Outcome 2: Participants are aged 18-22 years Outcome 3: Birth cohort follow-up. Participants were invited to complete a questionnaire and from the responders (n=1568, 59%) a random sample of 597 participants was invited for lung function testing. There was no significant difference between questionnaire responders and non-responders for perinatal risk factors, except for maternal smoking during pregnancy which was higher among non-responders Lung function was obtained in 590 subjects (99%) but no description given if any refused or did not participate in the lung function
Canoy, 2007 [54]	A*	A*	A*	Yes*	Yes*	C	A*	C	6	Outcome 1: Lung function assessment similar to ATS/ERS criteria but authors did not explicitly mention that they followed ATS/ERS criteria Outcome 3: In 1997 of the 12058 live births, 11637 were alive and 8463 lived in Helsinki or northern Finland area. These 8463 were invited for clinical examination and 5390 participated (64%). Participants had higher birth weight and gestational age compared to the remaining cohort members
Cheung, 2001 [64]	D	A*	D	Yes*	Yes*	B*	A*	C	5	Selection 1: Originally, 523 babies born in two hospitals between 24 Feb and 1 April 1967 were included and were followed up until the age of 5. In 1995, study was reopened and 171 participants were traced (33%) of which 133 agreed to participate (75%). No description of how babies in hospitals were selected Selection 3: Authors state that "Weight and length at birth were taken for the construction of independent variables" but no clear description was given with regards to the ascertainment of the exposure Outcome 3: Only 33% traced and 175 agreed to participate. No statement concerning lost to follow up or those who refused to participate after being traced

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Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Edwards, 2003 [88]	A*	A*	A*	FVC: Yes* FEV_1/FVC No	FVC: Yes* FEV_1/FVC No	C	A*	C	FVC 6 FEV_1/FVC 4	Comparability 1 & 2: No description of adjustment factors was given for the association of birth weight and FEV_1/FVC Outcome 1: Lung function assessment similar to ATS/ERS criteria but authors did not explicitly mention that they followed ATS/ERS criteria Outcome 3: In 1964, a random community survey included 2511 participants and in 2001 a follow-up of 605 was conducted. Of these, 592 were traced and 381 (63% of 605) agreed to participate. No statement concerning lost to follow up or those who refused to participate after being traced
Hancox, 2009 [127]	A*	A*	D	FVC: Yes* FEV_1/FVC: No	Yes*	B*	A*	B*	FVC: 7 FEV_1/FVC: 6	Selection 3: Authors state that birth weight was measured for all study members but no clear description was given with regards to the exposure ascertainment Comparability 1: The association was only adjusted for age and sex but not for height Outcome 3: Of those participated in the birth cohort, 94% of those living (953/1015) took part in the follow-up at 32 yrs. No description of those who did not participate
Laerum, 2004 [182]	A*	A*	A*	FVC: Yes* FEV_1/FVC: No	FVC: Yes* FEV_1/FVC: No	B*	A*	B*	FVC: 8 FEV_1/FVC: 6	Selection 1: Spirometry was performed according to European Respiratory Society [95] Comparability 1 & 2: No description of adjustment factors was given for the association of birth weight and FEV_1/FVC Outcome 3: ECHRS randomly selected participants to complete a questionnaire. A randomly selected subsample was invited for a clinical examination. Of the 440 participatns who completed the screening questionnaire, 72% (n=3201) responded to take part in the clinical examination. For 1683 of 3201 (53%) who attended the clinical examination birth weight information was obtained. Difference between responders and non-responders was assessed.
Lawlor, 2005 [193]	A*	A*	C	Yes*	Yes*	C	A*	B*	6	Selection 3: Birth weight (exposure) was self-reported Outcome 1: Lung function assessment similar to ATS/ERS criteria but authors did not explicitly mention that they followed ATS/ERS criteria Outcome 3: From 23 British towns, 4286 women were randomly selected of which 3941 (91%) completed lung function and 2431 (57%) had self-reported birth weight. However, only 2257 had completed data on both lung function and birth weight (53%). Difference between those with/without lung function and/or birth weight assessed.
Lima, 2005 [199]	A*	A*	A*	Yes*	Yes*	B*	A*	B*	8	Outcome 2: Participants' average age is 18yr Outcome 3: All births in 1982 in the city of Pelotas, Brazil, were studied and 99.2% of deliveries were included in the study. In 2000, male subjects identified during compulsary military enlistment. Of the 3307 boys born, 2250 were interviewed (74%). Lung function was performed on those <2.5 kg and two randomly selected controls with BW >2.5kg. No comparision of those lost to follow-up.

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Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Lopuhaa, 2000 [203]	A*	A*	A*	Yes*	No	C	A*	B*	6	Comparability 1b: Adjustment for smoking mentioned in text but not data given Outcome 1: Lung function assessment similar to ATS/ERS criteria but authors did not explicitly mention that they followed ATS/ERS criteria Outcome 3: Of the 912 that lived in the Amsterdam area, 741 attended the clinical examination (81%). Brief description also of those who attended the examination compared to original cohort
Odberg, 2010 [234]	A*	B	D	FVC: Yes* FEV_1/FVC: No	No	B*	A*	B*	FVC: 5 FEV_1/FVC: 4	Selection 2: Controls were selected via random sampling from a defined geographical region and partly as every 40th child born at the regional hospital Selection 3: No information on how birth weight was obtained Comparability 1 & 2: The association of birth weight and FEV_1/FVC was not adjusted for height, age, sex or smoking Outcome 2: Participants' average age is 19 years Outcome 3: For the LBW participants, 134 of 173 (77%) participated and for the controls, 135 of 170 (79%) participated. Description of non-participants and lost to follow up
Orfei, 2008a [236]	A*	A*	A*	Yes*	Yes*	C	A*	B*	7	Outcome 1: Lung function assessment similar to ATS/ERS criteria but authors did not explicitly mention that they followed ATS/ERS criteria Outcome 3: At age 43, 3262 of 5362 participants (85%) provided data. Description of reason for lost to follow-up (death, refusal, move abroad)
Orfei, 2008b [236]	A*	A*	A*	Yes*	Yes*	C	A*	B*	7	Outcome 1: Lung function assessment similar to ATS/ERS criteria but authors did not explicitly mention that they followed ATS/ERS criteria Outcome 3: At age 44-45, 9377 of 12069 participants (78%) provided data
Pei, 2010 [247]	C	A*	A*	No	No	C	A*	B*	4	Selection 1: Authors examined obstetric records of 1921 women who had sequential singleton live births and identified 885 women living in Beijing. The authors traced 725 offspring through the women of whom 627 agreed to participate (86%). No description of criteria used for selection of mothers/babies in the hospital Comparability 1a: No adjustment not for height, age but association was adjusted for BMI and age only differed by 6 years Comparability 1b: No adjustment for current smoking but adjustment for male smoking Outcome 1: Lung function assessment similar to ATS/ERS criteria but authors did not explicitly mention that they followed ATS/ERS criteria Outcome 3: Of the traced participants, 86% agreed to take part. No description of those not traced

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Table A.13 – continued from previous page

Author, year	Selection			Comparability		Outcome			NOS	Note
	1	2	3	1a	1b	1	2	3	Score	
Shaheen, 1998 [293]	B*	A*	A*	Yes*	Yes*	C	A*	C	6	Selection 1: Follow-up study based on 70% of all children born in the Burgh of St Andrews between 1921-35 Outcome 1: Lung function assessment similar to ATS/ERS criteria but authors did not explicitly mention that they followed ATS/ERS criteria Outcome 3: Of the 653 participants traced out of 1070 (61%), 468 (78%) responded to the questionnaire of which 414 were still living in the local region. These 414 individuals were invited for lung function testing, which was agreed to by 243 individuals. No description of questionnaire non-responders or those that did not have lung function testing
Sherill, 2011 [296]	B*	A*	A*	Yes*	No	B*	A*	D	6	Note: Lung function available at 16 and 22 years. Only lung function at 22 years assessed Comparability 1b: No adjustment for current smoking Outcome 2: Participants' average age is 16-22 years Outcome 3: Analysis was restricted to subjects that had at least four well visit weight measures, who were of non-Hispanic white ethnicity and who had at least one acceptable pulmonary function test at age 16 or 22yrs. Short description of participants with lung function data at both time points and whether they full the other criteria but no description of how the participants relate to the original cohort
Stein, 1997 [309]	B*	A*	A*	Yes*	No	C	A*	B*	6	Comparability 1b: Adjustment for smoking only presented as p-value but not as estimates Outcome 1: Lung function assessment similar to ATS/ERS criteria but authors did not explicitly mention that they followed ATS/ERS criteria Outcome 3: 517 of the 536 (96%) agreed to participate in the study. No description of follow up but description of those who refused spirometry
Suresh, 2012 [321]	B*	A*	A*	Yes*	Yes*	B*	A*	C	7	Outcome 2: Participants aged 21yrs Outcome 3: At age 14, 5185 participants had agreed to be contacted again, of which 3800 responded to a questionnaire. A subsample of 2612 individuals was invited for physical assessment and data was obtained for 2368 participants (46%). Comparison of initial cohort and study sample made but no description of questionnaire non-responders
Ubilla, 2008 [341]	A*	A*	A*	Yes*	Yes*	B*	A*	B*	8	Outcome 2: Age of participants 21-28 Outcome 3: A sampling frame based on all births in the Hospital of Limache in Chile between 1974 and 1978 (5 years) was used for randomly selecting 1232 subjects. Very small number lost (n=11) and reason given for inclusion of 1221 participants is that information was available for these participants



EXPLAINING THE ASSOCIATION OF VENTILATORY FUNCTION WITH CARDIOMETABOLIC AND INFLAMMATORY MARKERS IN THE NORTHERN FINLAND 1966 BIRTH COHORT

B.1 Figures

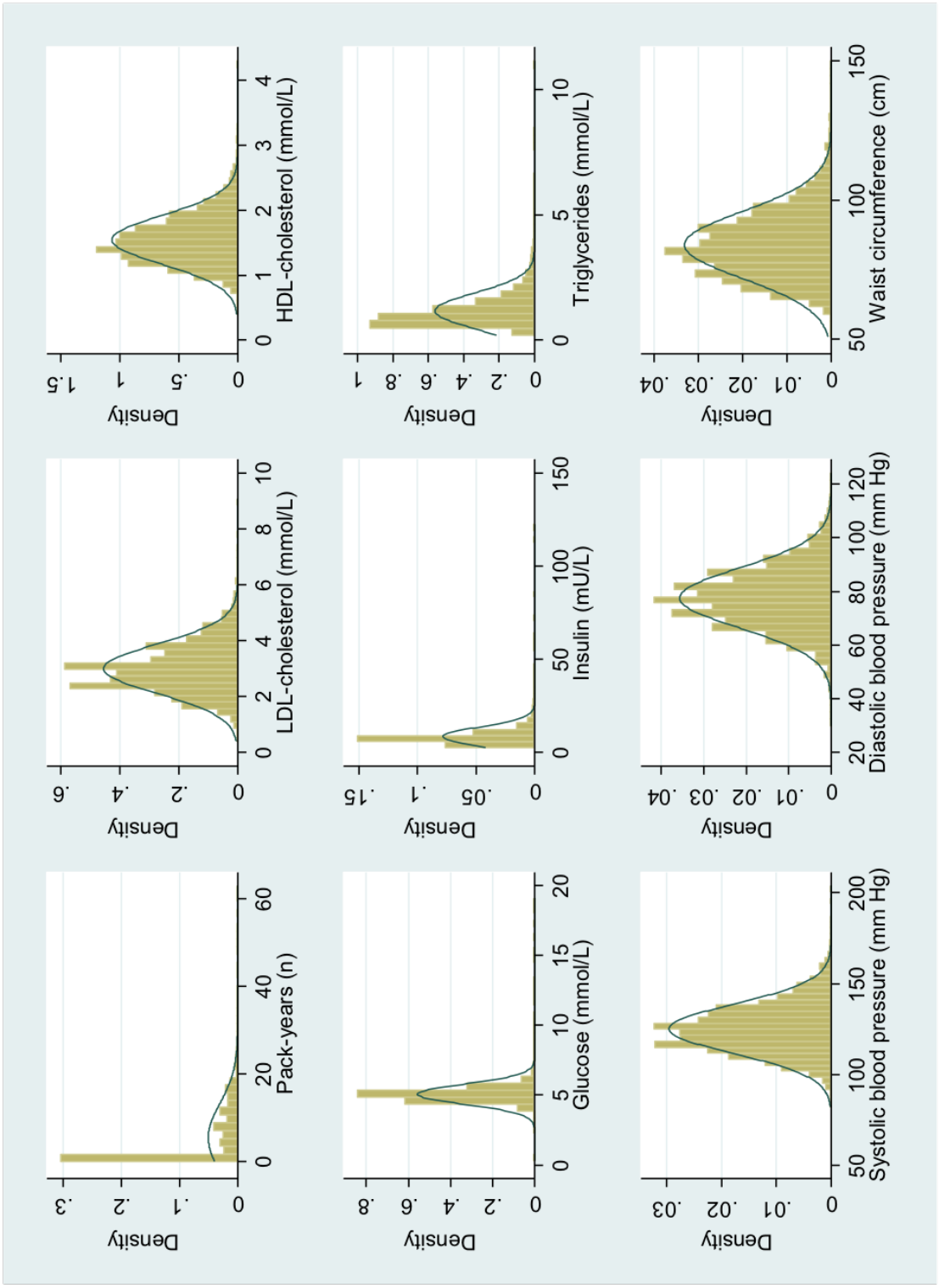


Figure B.1: *Histogram of continuous variables in Northern Finland 1966 birth cohort.* ***Continued on next page***

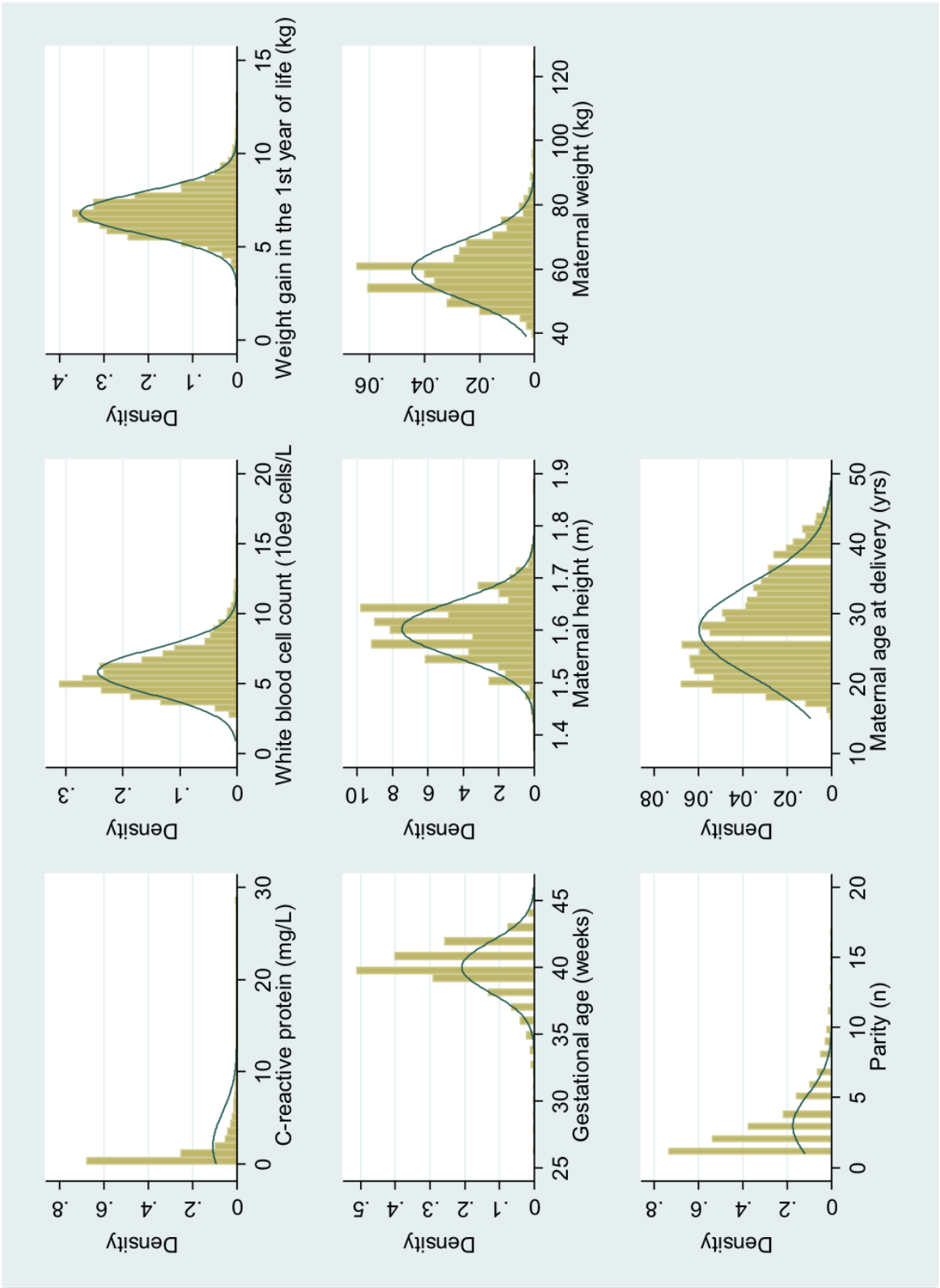


Figure B.1 – continued from previous page

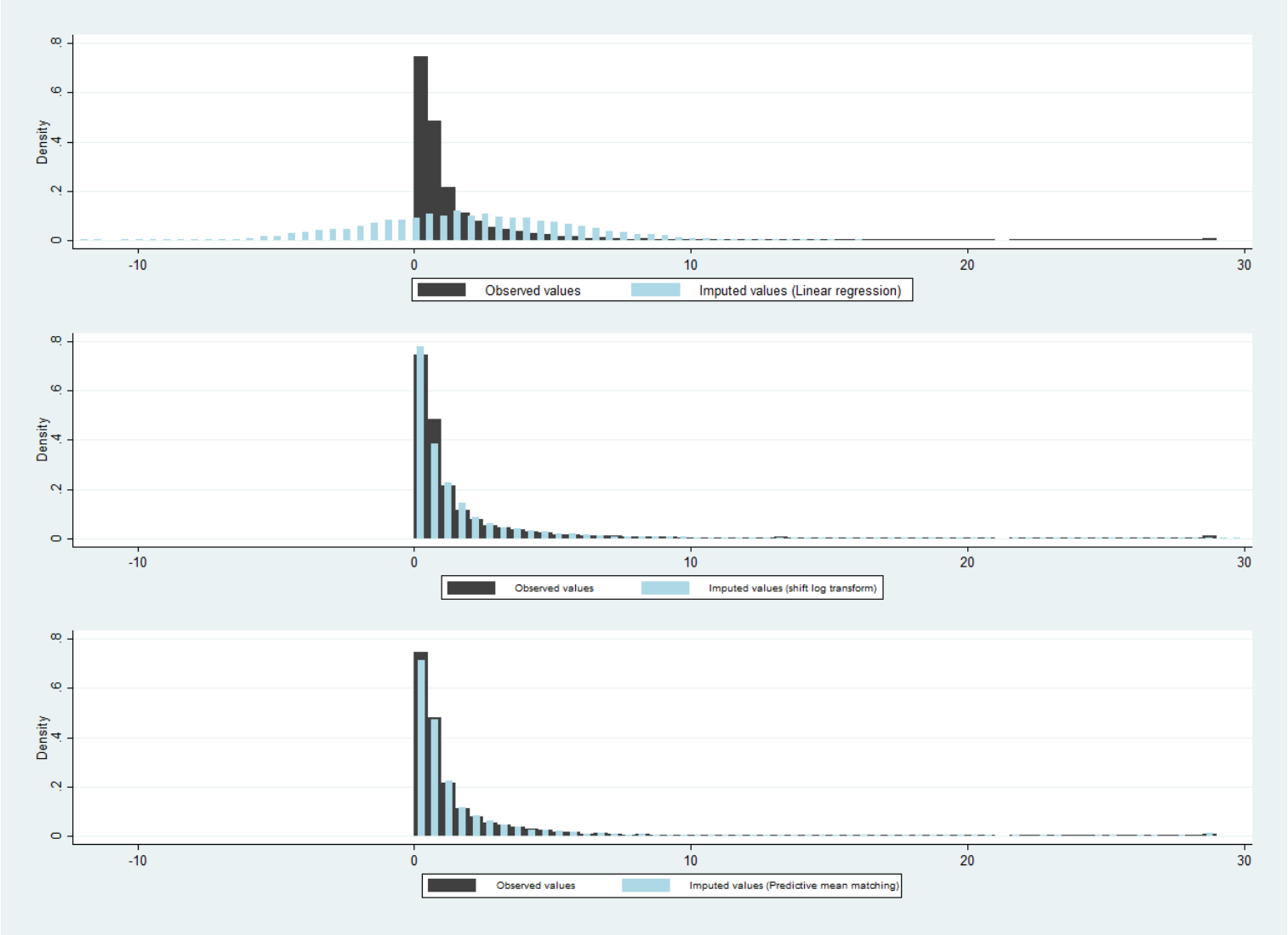


Figure B.2: *Three different strategies for imputation of C-reactive protein. Top subfigure: imputation using linear regression; Middle subfigure: imputation using shifted log transformation; Bottom subfigure: imputation using predictive mean matching. Values larger than 30 not shown on the histogram. Light blue bars represent the imputed values; dark gray bars represent the observed values.*

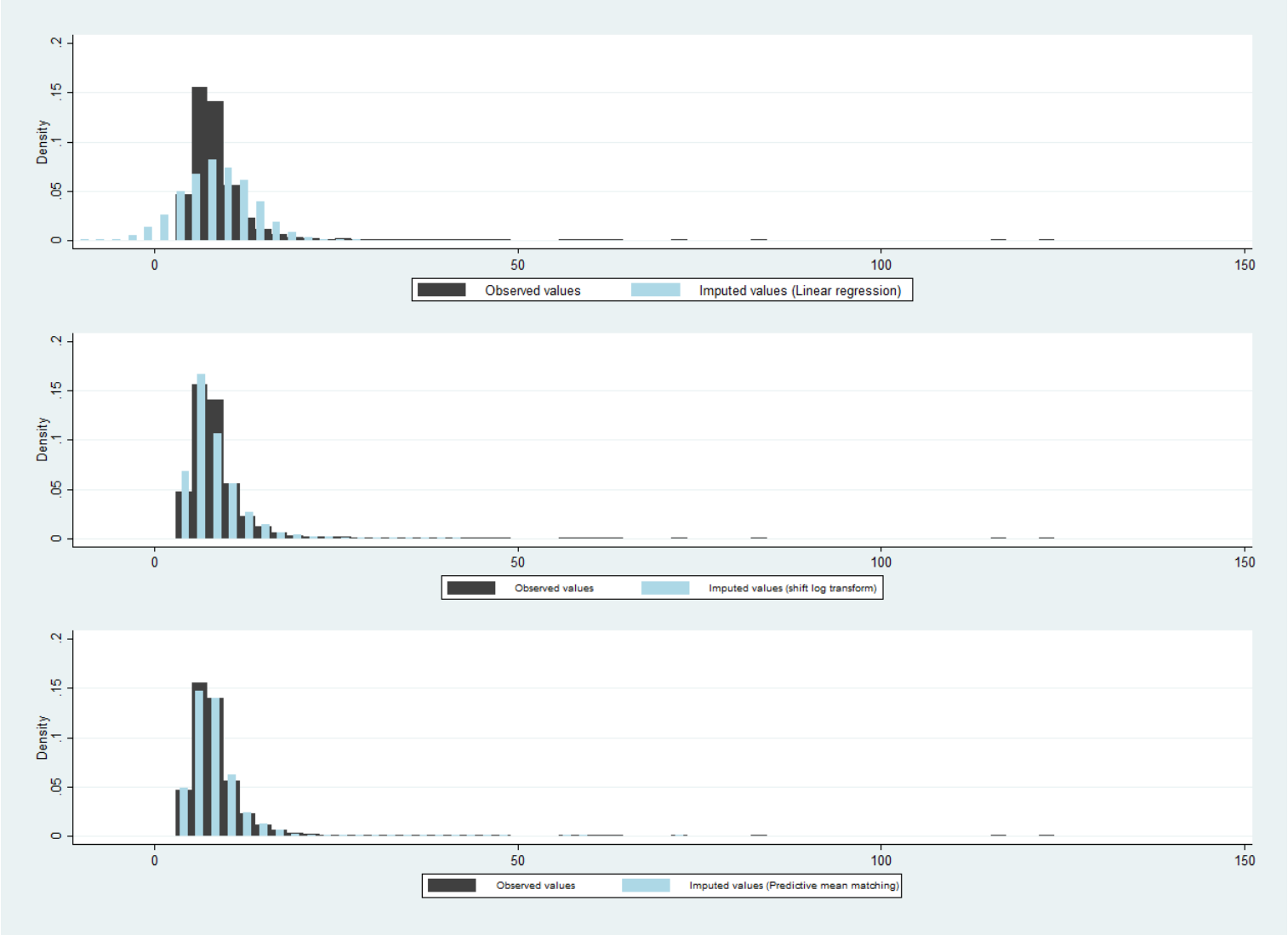


Figure B.3: *Three different strategies for imputation of insulin concentration. Top subfigure: imputation using linear regression; Middle subfigure: imputation using shifted log transformation; Bottom subfigure: imputation using predictive mean matching. Light blue bars represent the imputed values; dark gray bars represent the observed values.*

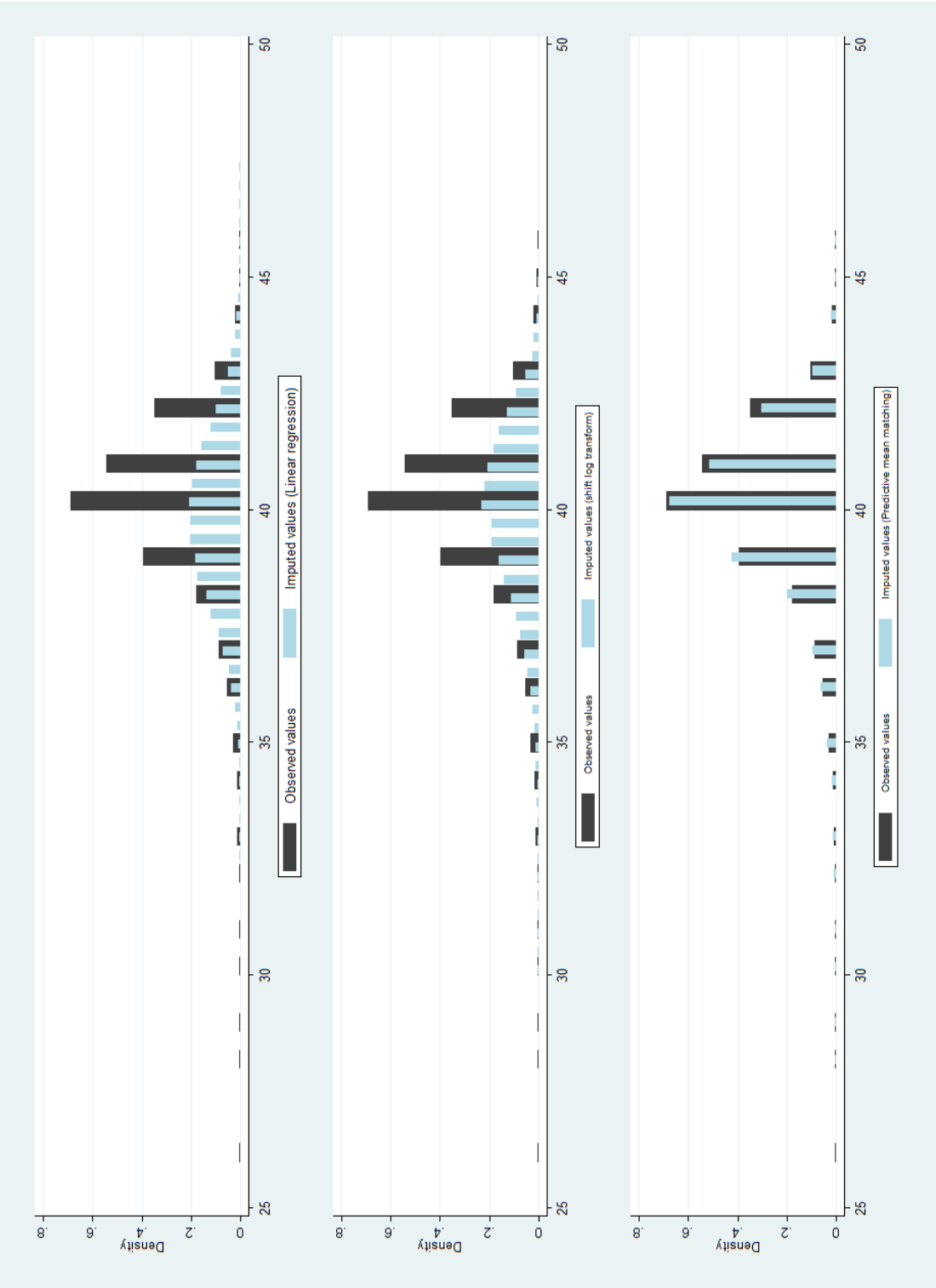


Figure B.4: *Three different strategies for imputation of gestational age. Top subfigure: imputation using linear regression; Middle subfigure: imputation using shifted log transformation; Bottom subfigure: imputation using predictive mean matching. Light blue bars represent the imputed values; dark gray bars represent the observed values.*

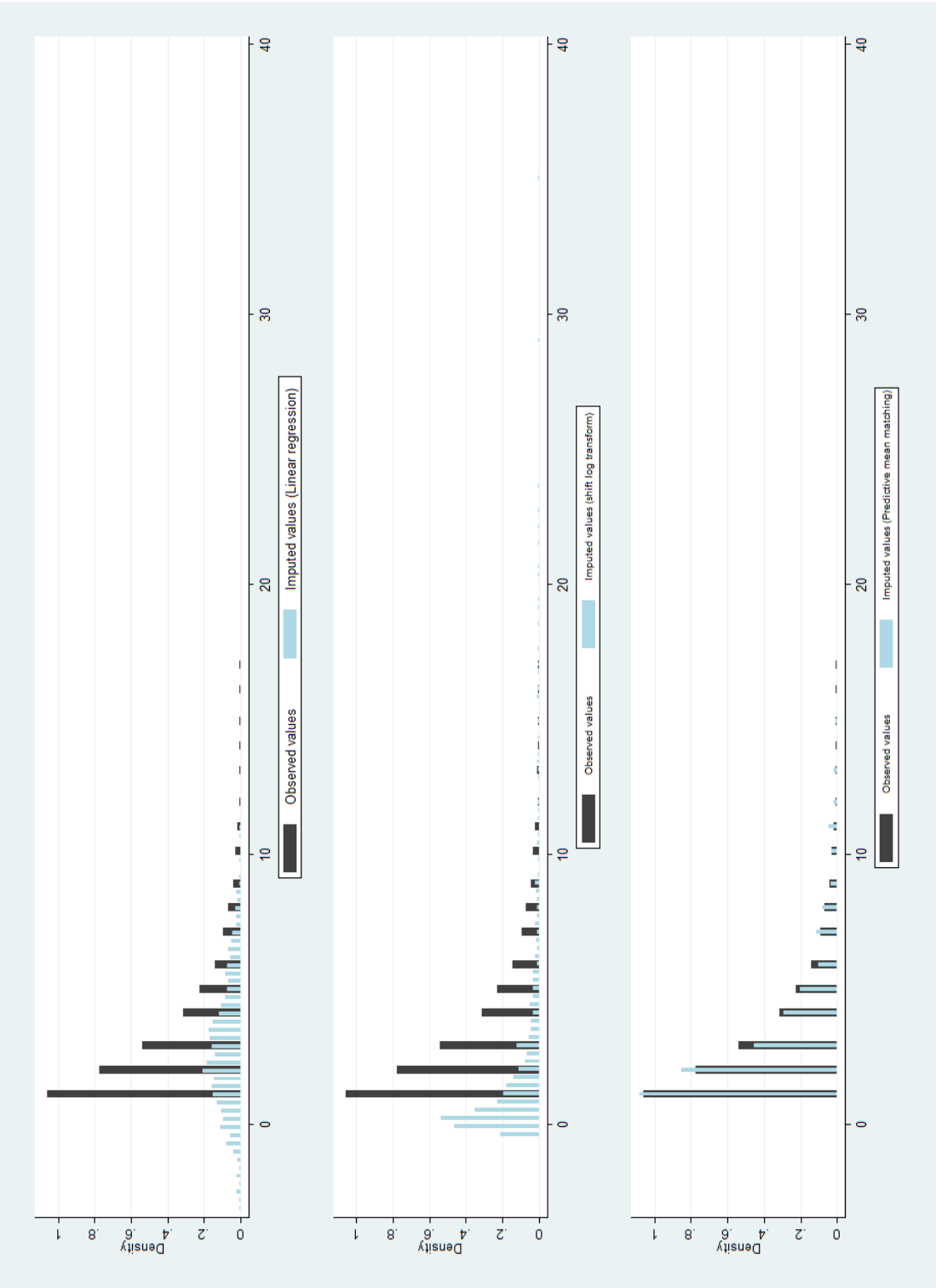


Figure B.5: *Three different strategies for imputation of parity. Top subfigure: imputation using linear regression; Middle subfigure: imputation using shifted log transformation; Bottom subfigure: imputation using predictive mean matching. Light blue bars represent the imputed values; dark gray bars represent the observed values.*

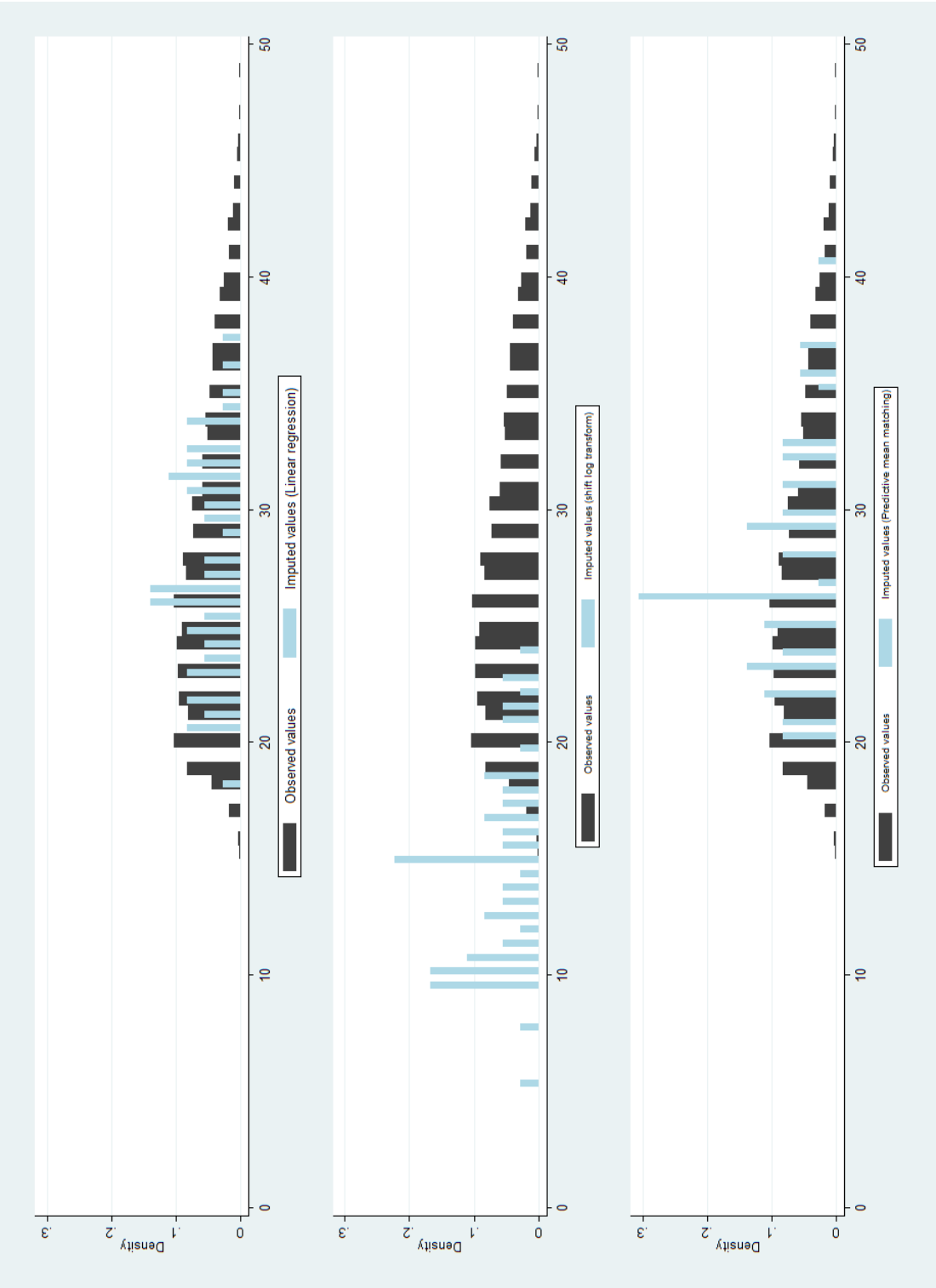


Figure B.6: *Three different strategies for imputation of maternal age at delivery. Top subfigure: imputation using linear regression; Middle subfigure: imputation using shifted log transformation; Bottom subfigure: imputation using predictive mean matching. Light blue bars represent the imputed values; dark gray bars represent the observed values.*

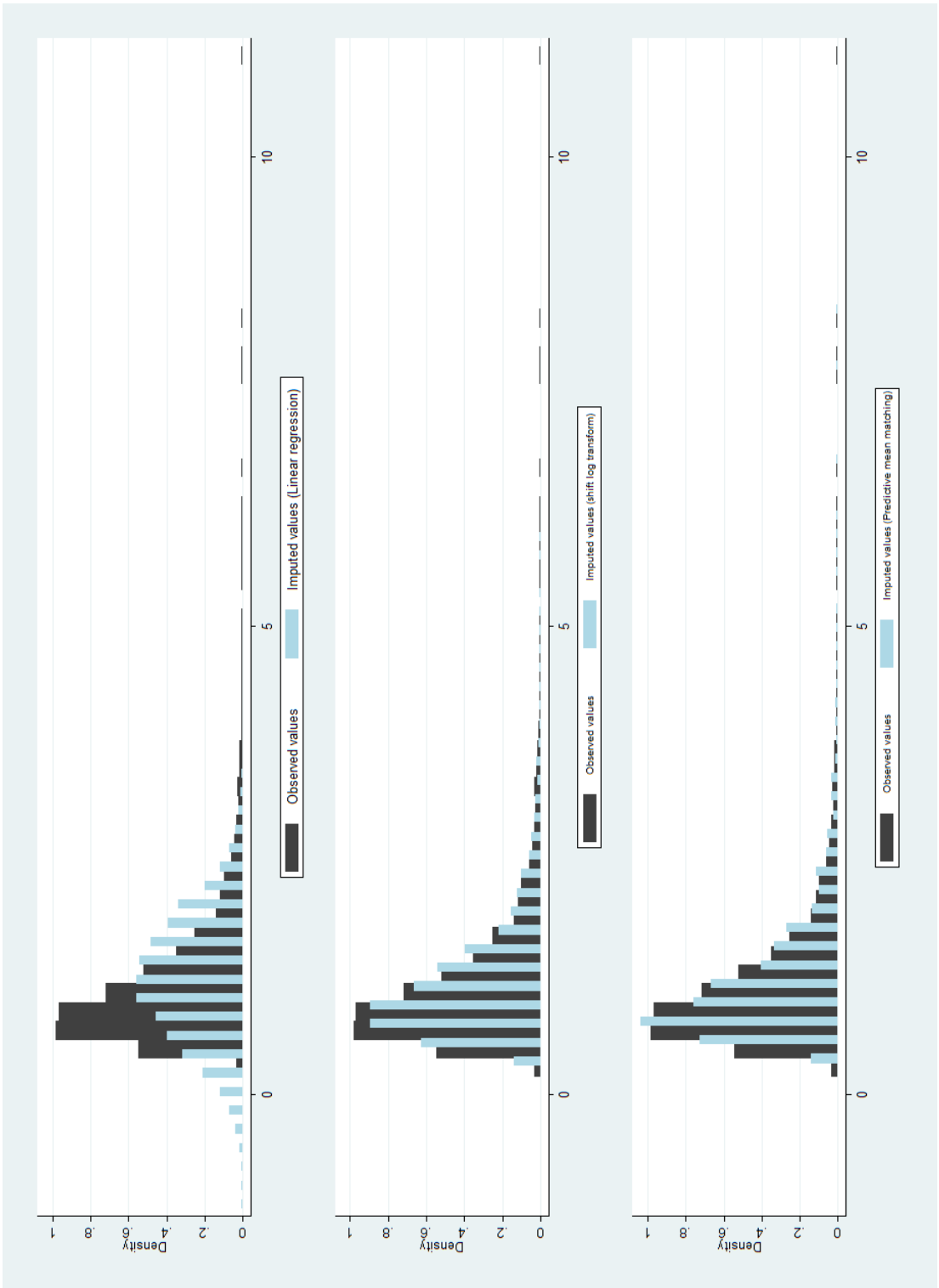


Figure B.7: *Three different strategies for imputation of triglyceride concentration. Top subfigure: imputation using linear regression; Middle subfigure: imputation using shifted log transformation; Bottom subfigure: imputation using predictive mean matching. Light blue bars represent the imputed values; dark gray bars represent the observed values.*

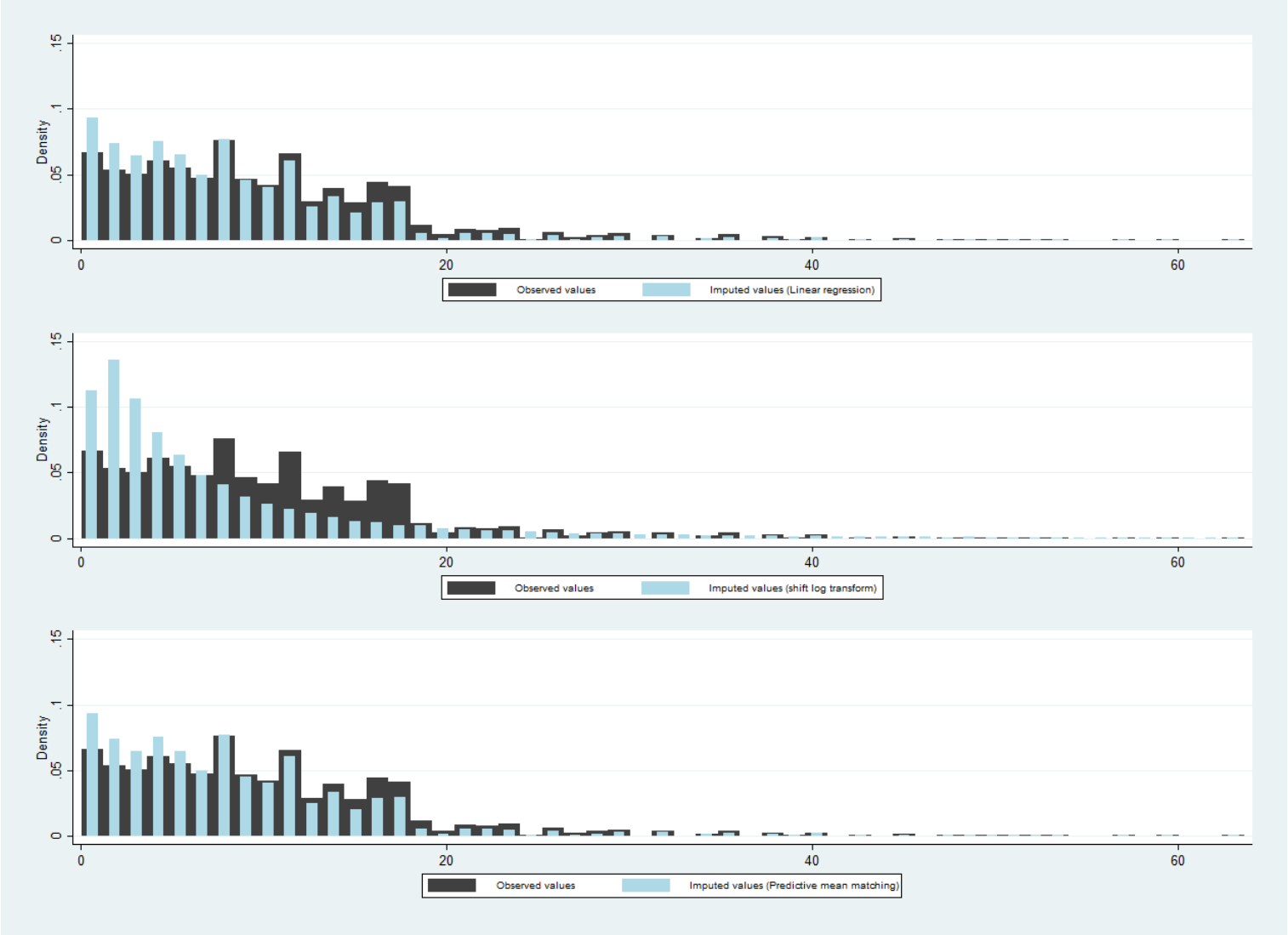


Figure B.8: *Three different strategies for imputation of pack-years. Top subfigure: imputation using linear regression; Middle subfigure: imputation using shifted log transformation; Bottom subfigure: imputation using predictive mean matching. Histogram does not show values at zero or, only for the shifted log transformation, if values are larger than 63. Light blue bars represent the imputed values; dark gray bars represent the observed values.*

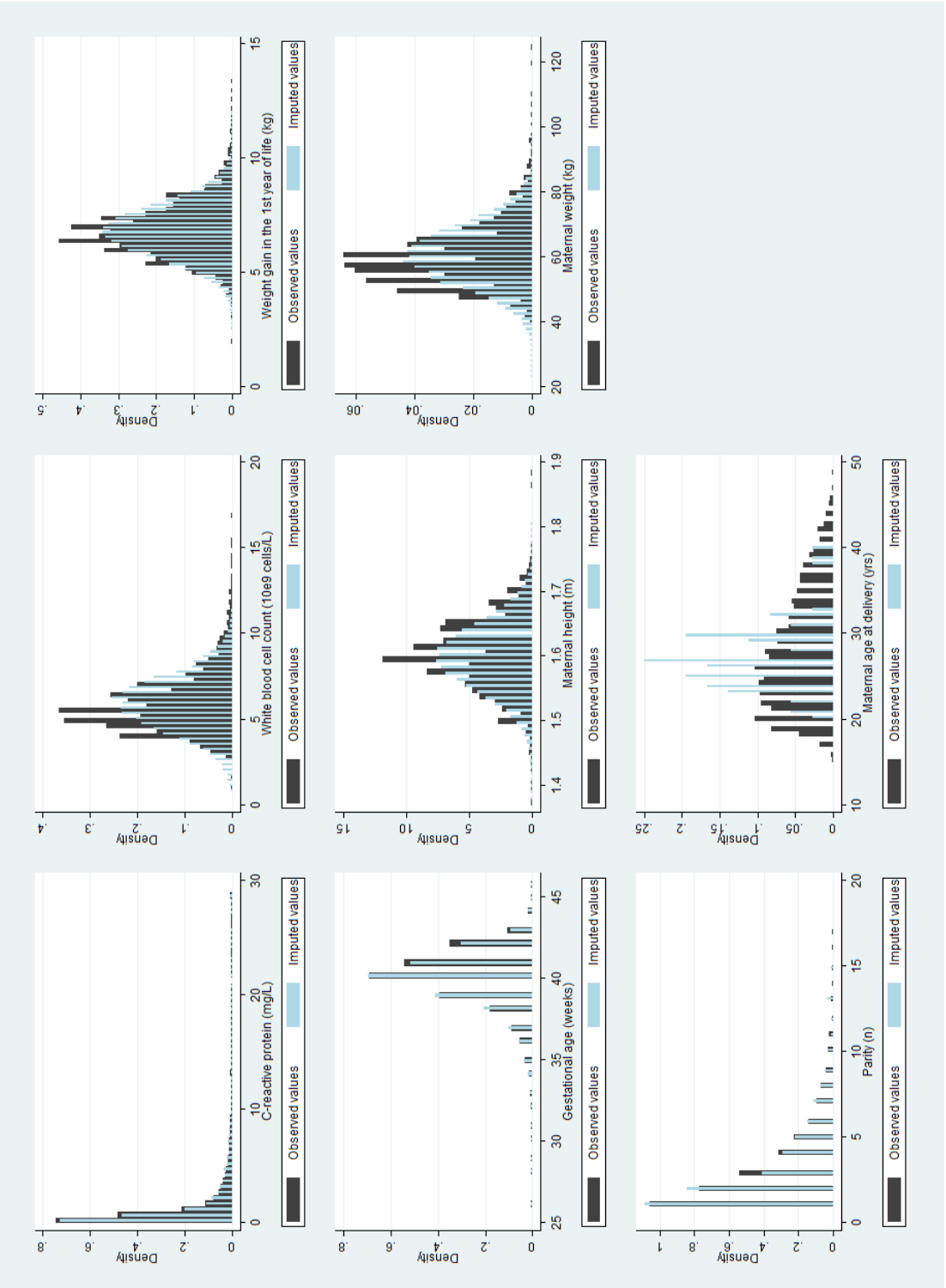


Figure B.9: *Comparison of imputed and original variables.* ***Continued on next page***

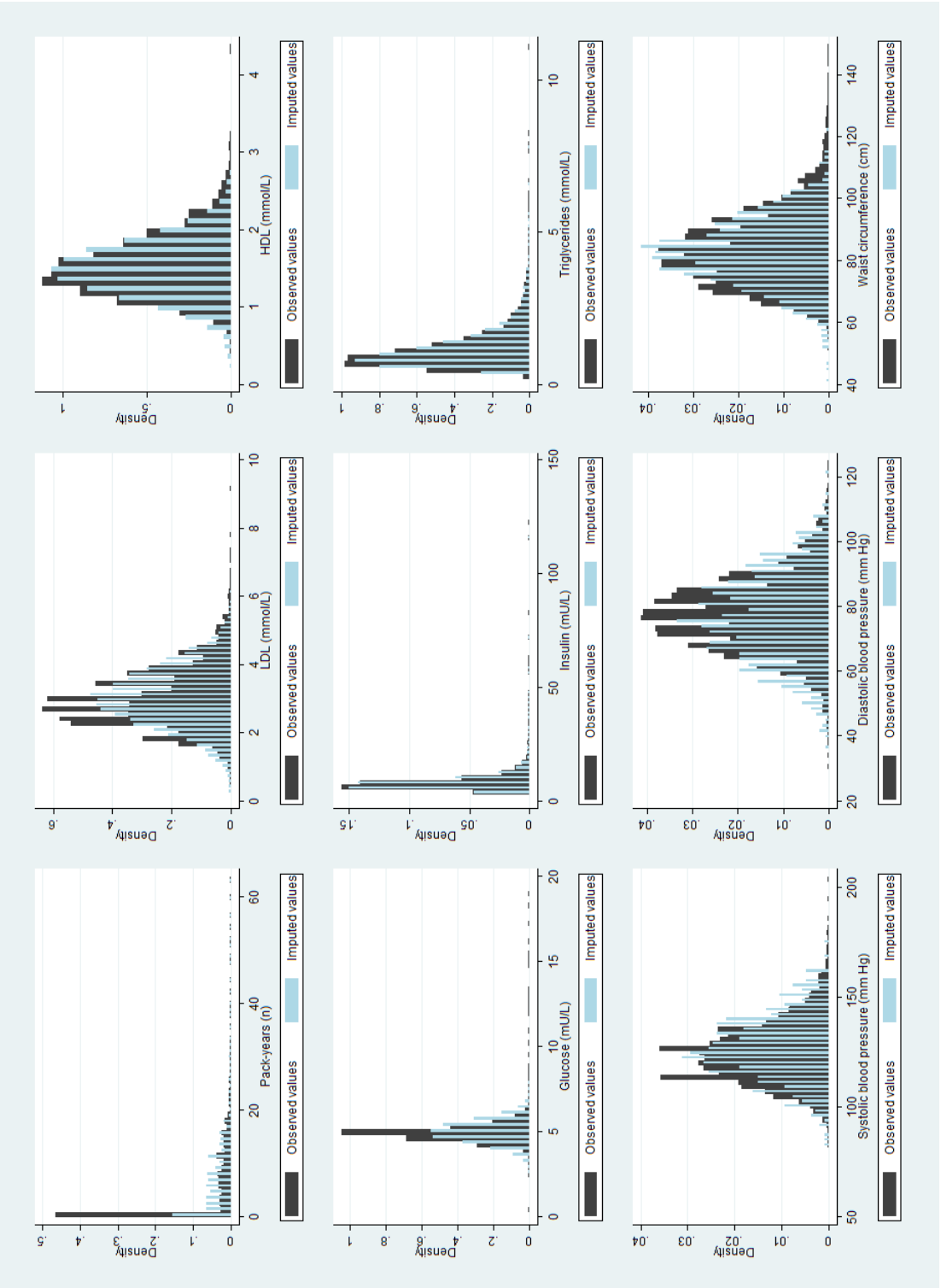


Figure B.9 – continued from previous page and continued on the next page

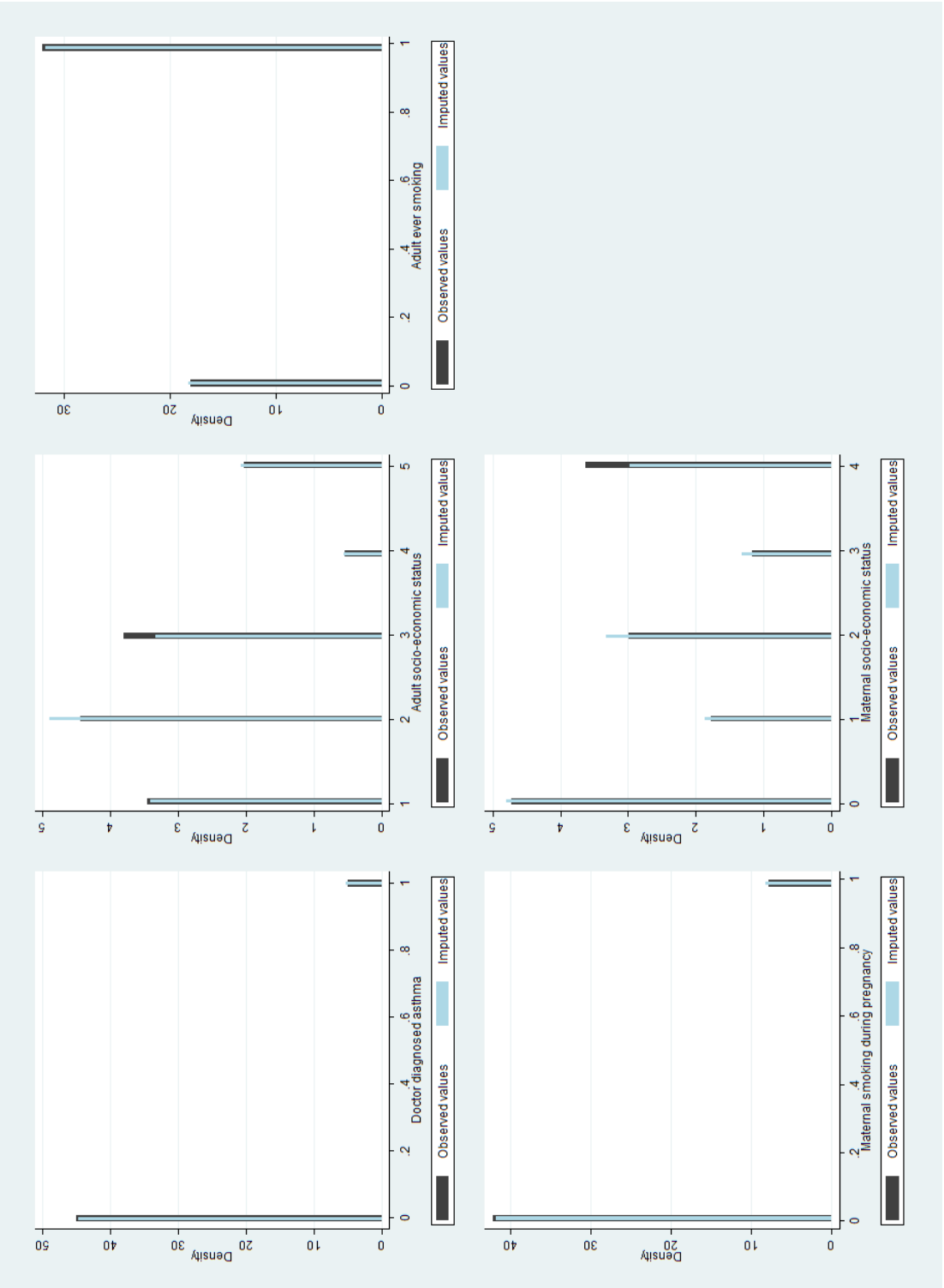


Figure B.9 – continued from previous page

B.2 Tables

Table B.1: *Missingness in total population and among men and women*

	Total population (N=5,453)	**Men (N=2,748)**	**Women (N=2,705)**
	Missing n (%)	**Missing n (%)**	**Missing n (%)**
Adult factors at 31 years			
Lung function and asthma			
FVC (L)	0 (0)	0 (0)	0 (0)
FEV_1 (L)	0 (0)	0 (0)	0 (0)
FEV_1/FVC (%)	0 (0)	0 (0)	0 (0)
Doctor diagnosed asthma (ref: Yes)	1,023 (18.8)	523 (19.1)	500 (18.5)
Anthropometry			
Height (m)	0 (0)	0 (0)	0 (0)
Weight (kg)	3 (1.0)	1 (0.04)	2 (0.1)
Hip circumference (cm)	24 (0.4)	13 (0.5)	11 (0.4)
Waist circumference (cm)	22 (0.4)	12 (0.4)	10 (0.4)
Socio-economic status	172 (3.2)	68 (2.5)	104 (3.84)
Smoking variables			
Ever smoking (ref: Yes)	85 (1.6)	54 (1.97)	31 (1.2)
Pack years (n)	1,235 (22.7)	574 (20.9)	661 (24.4)
Metabolic markers			
Cholesterol (mmol/L)	63 (1.2)	37 (1.4)	21 (1.0)
Low density lipoprotein (mmol/L)	79 (1.5)	46 (1.7)	33 (1.2)
High density lipoprotein (mmol/L)	63 (1.2)	37 (1.4)	26 (1.0)
Triglycerides (mmol/L)	64 (1.2)	38 (1.4)	26 (1.0)
Glucose (mmol/L)	101 (1.9)	59 (2.2)	42 (1.6)
Insulin (mU/L)	129 (2.4)	78 (2.8)	51 (1.9)
Systolic blood pressure (mm Hg)	8 (0.2)	5 (0.2)	3 (0.1)
Diastolic blood pressure (mm Hg)	15 (0.3)	5 (0.2)	10 (0.4)
Inflammatory markers			
C-reactive protein (mg/L)	130 (2.4)	63 (2.3)	67 (2.5)
White blood cell count (10^9 cells/L)	112 (2.1)	65 (2.4)	47 (1.7)
Weight in early life			
Birth weight (kg)	0 (0)	0 (0)	0 (0)
Weight gain in the first year (kg)	685 (12.5)	360 (13.1)	325 (12.0)
Gestational age (weeks)	183 (3.4)	86 (3.1)	97 (3.6)
Prenatal factors (during pregnancy)			
Parity	13 (0.2)	6 (0.2)	7 (0.3)
Maternal age at delivery (years)	1 (0.02)	1 (0.04)	0 (0)
Maternal height prior to pregnancy (m)	274 (5.0)	148 (5.4)	126 (4.7)
Maternal weight prior to pregnancy (kg)	281 (5.2)	154 (5.6)	127 (4.7)
Smoking during pregnancy (ref: Yes)	237 (4.4)	114 (4.2)	123 (4.6)
Maternal socio-economic status	85 (1.6)	41 (1.5)	44 (1.6)

Table B.2: *Pattern of missingness of data on variables groups in the Northern Finland 1966 Birth Cohort. A plus sign indicates that all variables in the group were observed; a minus sign indicates that at all variables in the group were missing. Variables were grouped into: (1) inflammatory markers (C-reactive protein and white blood cell count), (2) cardiometabolic markers (high density lipoprotein, low density lipoprotein, triglycerides, glucose and insulin concentration, systolic and diastolic blood pressure and waist circumference), (3) adult covariates (adult socio-economic status, adult smoking status and pack years), (4) weight in early life covariates (weight gain in the first year of life, birth weight) and (5) early life covariates (maternal height and weight before pregnancy, maternal age at delivery, maternal socio-economic status, maternal smoking during pregnancy and parity).*

Presence/absence of variable groups					
Adult covariates	**Inflammation covariates**	**Cardiometabolic markers**	**Weight in early life covariates**	**Early life covariates**	**Participants N (%)**
+	+	+	+	+	2976 (54.6)
-	+	+	+	+	953 (17.5)
+	+	+	+	-	421 (7.7)
+	+	+	-	+	398 (7.3)
-	+	+	+	-	169 (3.1)
-	+	+	-	+	133 (2.4)
+	+	+	-	-	89 (1.6)
+	+	-	+	+	68 (1.2)
+	-	+	+	+	57 (1.0)
+	-	-	+	+	47 (0.9)
-	+	+	-	-	26 (0.5)
+	-	-	-	+	13 (0.2)
-	+	-	+	+	12 (0.2)
+	-	+	+	.	12 (0.2)
-	-	+	+	+	12 (0.2)
-	-	-	+	+	12 (0.2)
+	+	-	+	-	11 (0.2)
+	-	-	+	-	11 (0.2)
+	+	-	-	+	8 (0.1)
+	-	+	-	+	8 (0.1)
-	+	-	+	-	4 (0.1)
+	+	-	-	-	3 (0.1)
-	+	-	-	+	2 (0.04)
-	-	+	-	+	2 (0.04)
-	-	-	+	-	2 (0.04)
+	-	+	-	-	1 (0.02)
-	-	+	+	-	1 (0.02)
-	+	-	-	-	1 (0.02)
-	-	-	-	+	1 (0.02)

Table B.3: *Distribution characteristics of the continuous variables with missing data in the NFBC 1966*

	Mean	SD	25th percentile	Median	75th percentile
Pack-years	5.4	7.8	0	0.8	9
Waist circumference	83.9	12	75	82.9	91
Low density lipoprotein	3	0.9	2.4	2.9	3.5
High density lipoprotein	1.5	0.4	1.3	1.5	1.8
Triglycerides	1.2	0.7	0.7	1	1.4
Glucose	5.1	0.7	4.7	5	5.3
Insulin	8.6	5.1	6.2	7.5	9.5
Systolic blood pressure	125	13.5	115	124	133
Diastolic blood pressure	77.6	11.2	70	77	85
C-reactive protein	1.9	3.7	0.4	0.7	1.7
White blood cell count	5.9	1.6	4.7	5.6	6.7
Weight gain in the first year	6.8	1.1	6.1	6.7	7.5
Gestational age	40	1.9	39	40	41
Parity	3	2.3	1	2	4
Maternal age at delivery	27.7	6.7	22	27	32
Maternal height prior to pregnancy	1.6	0.05	1.57	1.6	1.64
Maternal weight prior to pregnancy	59.8	8.9	53	59	65

Table B.4: *Distribution characteristics of non-normally distributed continuous variables in observed and imputed dataset, with different imputation strategies*

		Observed dataset	Imputed dataset		
			Linear regression	Transformation to normality	Predictive mean matching
C-reactive protein	Mean	1.9	1.9	1.9	1.9
	25th	0.4	0.3	0.3	0.3
	Median	0.7	0.7	0.7	0.7
	75th	1.7	1.8	1.7	1.7
	SD	3.7	3.7	3.7	3.7
	Min	0	-12.6	0	0
	Max	29	29	170	29
Insulin	Mean	8.6	8.6	8.6	8.6
	25th	6.2	6.2	6.2	6.2
	Median	7.5	7.5	7.5	7.5
	75th	9.5	9.5	9.5	9.5
	SD	5.1	5.1	5.1	5.1
	Min	2.9	-9	2.9	2.9
	Max	122.5	122.5	122.5	122.5
Gestational age	Mean	40	40	40	40
	25th	39	39	39	39
	Median	40	40	40	40
	75th	41	41	41	41
	SD	1.9	1.9	1.9	1.9
	Min	26	26	26	26
	Max	46	46	46	46
Parity	Mean	3	3	3	3
	25th	1	1	1	1
	Median	2	2	2	2
	75th	4	4	4	4
	SD	2.3	2.3	2.3	2.3
	Min	1	-2.8	-0.5	1
	Max	17	17	27.1	17
Maternal age at delivery	Mean	27.7	27.7	27.7	27.7
	25th	22	22	22	22
	Median	27	27	27	27
	75th	32	32	32	32
	SD	6.7	6.7	6.7	6.7
	Min	15	15	7.4	15
	Max	49	49	49	49
Pack-years	Mean	5.4	6.1	6.3	5.9
	25th	0	0	0	0
	Median	0.8	3.8	2.6	3
	75th	9	10.5	9.3	9.8
	SD	7.8	7.6	10.6	7.7
	Min	0	-20.4	0	0
	Max	63	63	632.7	63
Triglyceride	Mean	1.2	1.2	1.2	1.2
	25th	0.7	0.7	0.7	0.7
	Median	1	1	1	1
	75th	1.4	1.4	1.4	1.4
	SD	0.7	0.7	0.7	0.7
	Min	0.2	-1.3	0.2	0.2
	Max	11.1	11.1	11.1	11.1

Table B.5: *Identifying predictors for missingness of the five variables with the highest percentage of missingness. A plus sign indicates that the predictor was associated with the odds of the missingness; a minus sign indicates no statistically significant association.*

	Doctor-diagnosed asthma	Pack years	Weight gain in the 1st year of life	Maternal weight	Maternal height
Adult factors at 31 years					
FVC (L)	+	-	-	+	-
FEV_1/FVC	-	-	-	-	-
Doctor diagnosed asthma (ref: Yes)	NA	-	-	-	-
Gender (ref: Female)	+	-	-	-	-
Height (m)	-	+	-	-	-
Waist circumference (cm)	+	-	-	-	-
Socio-economic status	+	+	-	-	-
Ever smoking (ref: Yes)	-	-	-	-	-
Pack years (n)	-	NA	-	-	-
Low density lipoprotein (mmol/L)	+	-	-	-	-
High density lipoprotein (mmol/L)	-	-	-	-	-
Triglycerides (mmol/L)	-	+	-	-	-
Glucose (mmol/L)	-	-	-	-	+
Insulin (mU/L)	-	+	-	-	-
Systolic blood pressure (mm Hg)	-	+	-	+	-
Diastolic blood pressure (mm Hg)	+	-	-	+	-
C-reactive protein (mg/L)	-	-	-	-	-
White blood cell count (10^9 cells/L)	-	+	-	+	-
Weight in early life	-	-	-	-	-
Birth weight (kg)	-	-	-	-	-
Weight gain in the first year (kg)	-	-	NA	-	-
Gestational age (weeks)	-	-	-	-	-
Prenatal factors (during pregnancy)	-	-	-	-	-
Parity	+	-	+	-	-
Maternal age at delivery (years)	-	-	-	-	-
Maternal height prior to pregnancy (m)	-	+	+	NA	+
Maternal weight prior to pregnancy (kg)	-	-	-	-	NA
Smoking during pregnancy (ref: Yes)	-	+	-	-	-
Maternal socio-economic status	+	-	-	-	-

Table B.6: *Identifying variables associated with variables with missing data for the five variables with the highest percentage of missingness. A plus sign indicates that the predictor (variable in rows) was associated with the outcome (variable in column); a minus sign indicates no statistically significant association.*

	Doctor-diagnosed asthma	Pack years	Weight gain in the 1st year of life	Maternal weight	Maternal height
Adult factors at 31 years					
FVC (L)	-	+	+	-	-
FEV_1/FVC	+	+	-	-	-
Doctor diagnosed asthma (ref: Yes)	-	-	-	-	-
Gender (ref: Female)	-	+	+	-	+
Height (m)	-	-	+	-	+
Waist circumference (cm)	-	-	+	+	+
Socio-economic status	-	+	+	-	-
Ever smoking (ref: Yes)	-	+	-	-	-
Pack years (n)	-	-	-	-	-
Low density lipoprotein (mmol/L)	-	-	-	-	-
High density lipoprotein (mmol/L)	-	+	-	-	-
Triglycerides (mmol/L)	-	-	-	-	-
Glucose (mmol/L)	-	-	-	-	-
Insulin (mU/L)	-	-	-	-	-
Systolic blood pressure (mm Hg)	-	-	-	-	-
Diastolic blood pressure (mm Hg)	-	-	-	-	-
C-reactive protein (mg/L)	-	-	-	-	-
White blood cell count (10^9 cells/L)	-	+	-	-	-
Weight in early life					
Birth weight (kg)	-	-	+	+	-
Weight gain in the first year (kg)	-	-	-	+	-
Gestational age (weeks)	-	-	+	-	-
Prenatal factors (during pregnancy)					
Parity	-	-	-	-	+
Maternal age at delivery (years)	-	-	-	+	+
Maternal height prior to pregnancy (m)	-	-	-	+	-
Maternal weight prior to pregnancy (kg)	-	-	+	-	+
Smoking during pregnancy (ref: Yes)	-	+	+	+	-
Maternal socio-economic status	-	-	-	-	-
Maternal educational attainment	-	-	-	+	+

Table B.7: *Distribution characteristics of continuous variables with missing data in observed and imputed dataset*

	Dataset	Mean	SD	Minimum	25th percentile	Median	75th percentile	Maximum
Pack-years	Observed	5.4	7.8	0	0	0.8	9	63
	Imputed	5.9	7.7	0	0	3	9.8	63
Waist circumference	Observed	83.9	12	51	75	82.9	91	150
	Imputed	83.8	12	42	75	82.9	91	150
Low density lipoprotein	Observed	3	0.9	0.4	2.4	2.9	3.5	9.1
	Imputed	3	0.9	0.3	2.4	2.9	3.5	9.1
High density lipoprotein	Observed	1.5	0.4	0.4	1.3	1.5	1.8	4.3
	Imputed	1.5	0.4	0.1	1.3	1.5	1.8	4.3
Triglycerides	Observed	1.2	0.7	0.2	0.7	1	1.4	11.1
	Imputed	1.2	0.7	0.2	0.7	1	1.4	11.1
Glucose	Observed	5.1	0.7	0.3	4.7	5	5.3	19.1
	Imputed	5.1	0.7	0.3	4.7	5	5.3	19.1
Insulin	Observed	8.6	5.1	2.9	6.2	7.5	9.5	122.5
	Imputed	8.6	5.1	2.9	6.2	7.5	9.5	122.5
Systolic blood pressure	Observed	125	13.5	82	115	124	133	204
	Imputed	125	13.5	82	115	124	134	204
Diastolic blood pressure	Observed	77.6	11.2	30	70	77	85	124
	Imputed	77.6	11.2	30	70	77	85	128.6
C-reactive protein	Observed	1.9	3.7	0	0.4	0.7	1.7	29
	Imputed	1.9	3.7	0	0.4	0.7	1.7	29
White blood cell count	Observed	5.9	1.6	0.9	4.7	5.6	6.7	16.9
	Imputed	5.9	1.6	0.2	4.7	5.6	6.7	16.9
Weight gain in the first year	Observed	6.8	1.1	1.9	6.1	6.7	7.5	13.3
	Imputed	6.8	1.1	1.9	6.1	6.7	7.5	13.3
Gestational age	Observed	40	1.9	26	39	40	41	46
	Imputed	40	1.9	26	39	40	41	46
Parity	Observed	3	2.3	1	1	2	4	17
	Imputed	3	2.3	1	1	2	4	17
Maternal age at delivery	Observed	27.7	6.7	15	22	27	32	49
	Imputed	27.7	6.7	15	22	27	32	49
Maternal height prior to pregnancy	Observed	1.6	0.05	1.4	1.6	1.6	1.6	1.9
	Imputed	1.6	0.05	1.4	1.6	1.6	1.6	1.9
Maternal weight prior to pregnancy	Observed	59.8	8.9	39	53	59	65	125
	Imputed	59.8	9	14.8	53.7	59	65	125

Table B.8: Comparision of results in the complete dataset, among full term born participants and those with no diagnosis of asthma for the association of FVC (mL) with cardiometabolic markers in men. Waist circumference in cm , triglyceride concentration in mmol/L, low density lipoprotein in mmol/L, high density lipoprotein in mmol/L, glucose concentration in mmol/L, insulin concentration in mU/L, systolic blood pressure in mm Hg and diastolic blood pressure in mm Hg. Model 1: Mutually adjusted for other cardiometabolic markers; Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for C-reactive protein and white blood cell count; Model 5: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 6: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

	Imputed		**Gestational age [37,41]**		**No asthma**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Waist circumference						
Crude	2,748	-0.8 (-3.7;2.1)	2,083	-1 (-4.3;2.4)	2,484	-0.6 (-3.7;2.4)
Model 1	2,748	5.7 (2.2;9.3)	2,083	6.3 (2.1;10.4)	2,484	6.7 (2.8;10.5)
Model 2	2,748	-4.3 (-7.2;-1.4)	2,083	-4.2 (-7.7;-0.8)	2,484	-3.7 (-6.9;-0.6)
Model 3	2,748	-4.4 (-7.4;-1.5)	2,083	-4.4 (-7.9;-1)	2,484	-3.9 (-7.1;-0.7)
Model 4	2,748	-3.8 (-6.8;-0.9)	2,083	-3.7 (-7.1;-0.2)	2,484	-3.3 (-6.5;-0.1)
Model 5	2,748	-5.7 (-8.6;-2.7)	2,083	-5.8 (-9.2;-2.3)	2,484	-5.2 (-8.4;-2)
Model 6	2,748	-4.7 (-7.7;-1.7)	2,083	-4.7 (-8.2;-1.3)	2,484	-4.2 (-7.4;-1)
Triglyceride concentration						
Crude	2,748	-99.2 (-133.2;-65.2)	2,083	-99.7 (-137.8;-61.5)	2,484	-100 (-136.1;-63.8)
Model 1	2,748	-94.4 (-134.9;-53.9)	2,083	-97.7 (-143.4;-52)	2,484	-90.8 (-134.5;-47)
Model 2	2,748	-78.4 (-111.1;-45.7)	2,083	-78.9 (-115.9;-41.9)	2,484	-76.6 (-112;-41.2)
Model 3	2,748	-76.7 (-109.5;-43.8)	2,083	-78.9 (-116.1;-41.7)	2,484	-74.4 (-110.1;-38.8)
Model 4	2,748	-78.9 (-111.9;-46)	2,083	-83.1 (-120.3;-45.8)	2,484	-77.1 (-112.9;-41.4)
Model 5	2,748	-74 (-106.7;-41.2)	2,083	-75.6 (-112.7;-38.6)	2,484	-70.9 (-106.3;-35.4)
Model 6	2,748	-76.4 (-109.3;-43.5)	2,083	-77.8 (-115.1;-40.5)	2,484	-74 (-109.5;-38.4)
Low density lipoprotein						
Crude	2,748	-58.1 (-89.6;-26.6)	2,083	-64.6 (-100.8-28.4)	2,484	-65.9 (-98.9;-32.9)
Model 1	2,748	-44.1 (-76.6;-11.6)	2,083	-52.4 (-89.7;-15)	2,484	-51.1 (-85.2;-17.1)
Model 2	2,748	-9.9 (-36.3;16.4)	2,083	-9.6 (-39.9;20.7)	2,484	-15.2 (-42.9;12.4)
Model 3	2,748	-9 (-35.4;17.4)	2,083	-7.6 (-38;22.7)	2,484	-13.9 (-41.7;13.8)
Model 4	2,748	-11.1 (-37.5;15.3)	2,083	-10.3 (-40.6;20.1)	2,484	-16 (-43.7;11.8)
Model 5	2,748	-8.8 (-35.2;17.6)	2,083	-7.1 (-37.4;23.1)	2,484	-13.8 (-41.5;13.8)
Model 6	2,748	-9.9 (-36.4;16.6)	2,083	-8.2 (-38.8;22.3)	2,484	-14.5 (-42.3;13.3)
High density lipoprotein						
Crude	2,748	38.8 (-48.2;125.7)	2,083	34.2 (-67;135.3)	2,484	48 (-43.5;139.4)
Model 1	2,748	-60.1 (-156.9;36.6)	2,083	-76.2 (-189.9;37.5)	2,484	-51.8 (-153.7;50.1)
Model 2	2,748	-70.3 (-148.6;8)	2,083	-90.5 (-182.7;1.7)	2,484	-71.1 (-154;11.9)
Model 3	2,748	-73.2 (-151.6;5.3)	2,083	-98.6 (-190.9;-6.3)	2,484	-73.3 (-156.5;9.9)
Model 4	2,748	-84.6 (-163.2;-6)	2,083	-108.8 (-201.2;-16.4)	2,484	-85.1 (-168.6;-1.6)
Model 5	2,748	-78.8 (-156.9;-0.6)	2,083	-106.2 (-198;-14.3)	2,484	-79.7 (-162.7;3.2)
Model 6	2,748	-78.8 (-157.4;-0.2)	2,083	-103.5 (-195.9;-11.2)	2,484	-80.2 (-163.6;3.2)

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Table B.8 – continued from previous page

	Imputed		Gestational age [37,41]		No asthma	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Glucose concentration						
Crude	2,748	-52.3 (-91.4;-13.1)	2,083	-59.4 (-110.1;-8.6)	2,484	-46.5 (-89.2;-3.7)
Model 1	2,748	-29.2 (-69.7;11.3)	2,083	-32.9 (-86.5;20.7)	2,484	-16.5 (-61.1;28.1)
Model 2	2,748	-37.1 (-69.8;-4.3)	2,083	-23.3 (-66.8;20.2)	2,484	-35.4 (-71.7;1)
Model 3	2,748	-37.3 (-70.1;-4.4)	2,083	-24.6 (-68.3;19.1)	2,484	-35 (-71.5;1.4)
Model 4	2,748	-38.4 (-71.2;-5.6)	2,083	-26.3 (-69.9;17.4)	2,484	-36.2 (-72.7;0.2)
Model 5	2,748	-34.6 (-67.4;-1.9)	2,083	-18.9 (-62.4;24.6)	2,484	-32.2 (-68.4;4.1)
Model 6	2,748	-37.4 (-70.3;-4.5)	2,083	-23 (-66.9;20.9)	2,484	-36.1 (-72.5;0.4)
Insulin concentration						
Crude	2,748	-13.4 (-18.7;-8)	2,083	-13.3 (-19.1;-7.6)	2,484	-14.8 (-22.1;-7.5)
Model 1	2,748	-10.4 (-16.7;-4.2)	2,083	-10.5 (-17.4;-3.7)	2,484	-12.5 (-21.2;-3.8)
Model 2	2,748	-5.9 (-11;-0.9)	2,083	-6.2 (-11.6;-0.7)	2,484	-7.3 (-14.4;-0.2)
Model 3	2,748	-5.5 (-10.6;-0.5)	2,083	-5.6 (-11.1;-0.1)	2,484	-7 (-14.2;0.2)
Model 4	2,748	-4.8 (-9.9;0.2)	2,083	-4.9 (-10.4;0.6)	2,484	-6.4 (-13.5;0.8)
Model 5	2,748	-4.5 (-9.6;0.5)	2,083	-4.6 (-10.1;0.9)	2,484	-5.9 (-13;1.1)
Model 6	2,748	-5.5 (-10.6;-0.4)	2,083	-5.6 (-11.1;-0.1)	2,484	-7 (-14.1;0.1)
Systolic blood pressure						
Crude	2,748	-0.7 (-3;1.5)	2,083	-0.9 (-3.5;1.7)	2,484	-1.3 (-3.6;1.1)
Model 1	2,748	1.8 (-1;4.5)	2,083	1.9 (-1.3;5.1)	2,484	1.3 (-1.6;4.1)
Model 2	2,748	1 (-1.2;3.2)	2,083	0.6 (-1.9;3.2)	2,484	0.8 (-1.5;3.2)
Model 3	2,748	0.9 (-1.3;3.2)	2,083	0.6 (-2;3.2)	2,484	0.8 (-1.5;3.2)
Model 4	2,748	1 (-1.3;3.2)	2,083	0.6 (-2;3.2)	2,484	0.8 (-1.5;3.1)
Model 5	2,748	1.3 (-0.9;3.5)	2,083	1 (-1.6;3.6)	2,484	1.1 (-1.2;3.5)
Model 6	2,748	0.8 (-1.4;3.1)	2,083	0.4 (-2.2;3)	2,484	0.7 (-1.6;3.1)
Diastolic blood pressure						
Crude	2,748	-3.3 (-5.8;-0.8)	2,083	-3.6 (-6.5;-0.7)	2,484	-3.8 (-6.5;-1.2)
Model 1	2,748	-3.1 (-6.2;0)	2,083	-3.3 (-6.9;0.2)	2,484	-3.4 (-6.7;-0.2)
Model 2	2,748	-3.7 (-6.2;-1.2)	2,083	-3.7 (-6.6;-0.8)	2,484	-3.6 (-6.2;-1)
Model 3	2,748	-3.6 (-6.1;-1.1)	2,083	-3.6 (-6.5;-0.8)	2,484	-3.5 (-6.2;-0.9)
Model 4	2,748	-3.6 (-6.1;-1.1)	2,083	-3.6 (-6.5;-0.8)	2,484	-3.5 (-6.1;-0.8)
Model 5	2,748	-3.6 (-6.1;-1.1)	2,083	-3.7 (-6.5;-0.8)	2,484	-3.5 (-6.1;-0.8)
Model 6	2,748	-3.5 (-6;-1)	2,083	-3.4 (-6.2;-0.5)	2,484	-3.4 (-6;-0.8)

Table B.9: Comparision of results in the complete dataset, among full term born participants and those with no diagnosis of asthma for the association of FVC (mL) with cardiometabolic markers in women. Waist circumference in cm , triglyceride concentration in mmol/L, low density lipoprotein in mmol/L, high density lipoprotein in mmol/L, glucose concentration in mmol/L, insulin concentration in mU/L, systolic blood pressure in mm Hg and diastolic blood pressure in mm Hg. Model 1: Mutually adjusted for other cardiometabolic markers; Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for C-reactive protein and white blood cell count; Model 5: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 6: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

	Imputed		**Gestational age [37,41]**		**No asthma**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Waist circumference						
Crude	2,705	1.0 (-0.7;2.7)	2,035	0.8 (-1.2;2.8)	2,392	1.2 (-0.7;3)
Model 1	2,705	6.4 (4.3;8.5)	2,035	5.6 (3.2;8)	2,392	6.3 (4.1;8.6)
Model 2	2,705	1.8 (0;3.6)	2,035	1.2 (-0.8;3.2)	2,392	2.2 (0.3;4.1)
Model 3	2,705	1.7 (0;3.5)	2,035	1.1 (-0.9;3.1)	2,392	2.1 (0.2;4.1)
Model 4	2,705	2.6 (0.8;4.4)	2,035	1.9 (-0.2;3.9)	2,392	3.1 (1.1;5)
Model 5	2,705	1.2 (-0.6;3)	2,035	0.5 (-1.5;2.6)	2,392	1.6 (-0.4;3.5)
Model 6	2,705	1.4 (-0.4;3.3)	2,035	1 (-1.1;3)	2,392	1.9 (-0.1;3.8)
Triglyceride concentration						
Crude	2,705	-92.3 (-132.9;-51.6)	2,035	-78 (-125.3;-30.7)	2,392	-85.6 (-129.1;-42)
Model 1	2,705	-54.4 (-100.7;-8)	2,035	-36.4 (-90.6;17.7)	2,392	-50.2 (-99.7;-0.7)
Model 2	2,705	-24.5 (-62.9;13.9)	2,035	-11.4 (-56.2;33.3)	2,392	-19.4 (-60.5;21.7)
Model 3	2,705	-21.8 (-60.4;16.8)	2,035	-10.6 (-55.4;34.3)	2,392	-18 (-59.4;23.3)
Model 4	2,705	-6.2 (-45.3;32.8)	2,035	1.2 (-44.2;46.6)	2,392	-2.5 (-44.4;39.4)
Model 5	2,705	-17.4 (-55.9;21.1)	2,035	-5.9 (-50.6;38.9)	2,392	-13.4 (-54.6;27.9)
Model 6	2,705	-20.5 (-59.1;18)	2,035	-9.9 (-54.7;34.9)	2,392	-17.3 (-58.6;24)
Low density lipoprotein						
Crude	2,705	-46.6 (-73.1;-20.1)	2,035	-41.4 (-71.6;-11.2)	2,392	-38.1 (-66.4;-9.8)
Model 1	2,705	-44 (-71.4;-16.7)	2,035	-39.1 (-70.4;-7.9)	2,392	-38.7 (-68.2;-9.3)
Model 2	2,705	-4.7 (-27.5;18.1)	2,035	-4.6 (-30.5;21.3)	2,392	-3.4 (-28;21.2)
Model 3	2,705	-4.6 (-27.4;18.2)	2,035	-3.8 (-29.7;22.1)	2,392	-3 (-27.6;21.6)
Model 4	2,705	-8.6 (-31.3;14.2)	2,035	-7.5 (-33.4;18.4)	2,392	-6.9 (-31.6;17.7)
Model 5	2,705	-5.7 (-28.5;17)	2,035	-5.1 (-31;20.7)	2,392	-4.6 (-29.2;19.9)
Model 6	2,705	-4.7 (-27.5;18.1)	2,035	-3.6 (-29.6;22.4)	2,392	-3 (-27.6;21.6)
High density lipoprotein						
Crude	2,705	58.4 (2.3;114.5)	2,035	62.4 (-0.8;125.7)	2,392	40.2 (-20;100.3)
Model 1	2,705	53.2 (-6.5;112.9)	2,035	62.2 (-5.4;129.9)	2,392	38.2 (-25.7;102.1)
Model 2	2,705	-1.5 (-51.1;48)	2,035	9 (-46.9;64.9)	2,392	-8.3 (-61.4;44.8)
Model 3	2,705	-8.2 (-58.3;41.8)	2,035	2.5 (-53.8;58.8)	2,392	-13.4 (-67;40.2)
Model 4	2,705	-4.8 (-54.7;45)	2,035	4.7 (-51.5;60.9)	2,392	-9.1 (-62.5;44.3)
Model 5	2,705	-11.9 (-61.7;38)	2,035	-2.2 (-58.3;53.9)	2,392	-17.3 (-70.7;36.1)
Model 6	2,705	-4.8 (-55;45.3)	2,035	9.2 (-47.3;65.7)	2,392	-9.2 (-62.9;44.5)

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Table B.9 – continued from previous page

	Imputed		Gestational age [37,41]		No asthma	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Glucose concentration						
Crude	2,705	-63.6 (-94.3;-32.9)	2,035	-66.6 (-100.1;-33.1)	2,392	-74 (-106.9;-41)
Model 1	2,705	-44.9 (-77.2;-12.5)	2,035	-48.9 (-83.9;-13.9)	2,392	-58.3 (-93;-23.7)
Model 2	2,705	-18 (-44.9;8.9)	2,035	-19.6 (-48.6;9.4)	2,392	-29.1 (-58;-0.2)
Model 3	2,705	-16.9 (-43.9;10)	2,035	-18.5 (-47.5;10.6)	2,392	-28 (-56.9;0.9)
Model 4	2,705	-18.2 (-45;8.6)	2,035	-19.5 (-48.5;9.5)	2,392	-29.3 (-58.1;-0.5)
Model 5	2,705	-17.6 (-44.4;9.2)	2,035	-19.2 (-48.1;9.8)	2,392	-28.6 (-57.4;0.2)
Model 6	2,705	-18.2 (-45.1;8.7)	2,035	-19.6 (-48.6;9.5)	2,392	-29.9 (-58.8;-1)
Insulin concentration						
Crude	2,705	-11.7 (-16;-7.4)	2,035	-11.1 (-15.9;-6.3)	2,392	-11.2 (-15.8;-6.7)
Model 1	2,705	-11.8 (-17.1;-6.5)	2,035	-10.8 (-16.6;-4.9)	2,392	-11 (-16.5;-5.4)
Model 2	2,705	-8.6 (-13;-4.2)	2,035	-7.4 (-12.2;-2.6)	2,392	-8.6 (-13.2;-4)
Model 3	2,705	-8.7 (-13.1;-4.3)	2,035	-7.3 (-12.1;-2.5)	2,392	-8.6 (-13.2;-4)
Model 4	2,705	-8.2 (-12.6;-3.8)	2,035	-7 (-11.8;-2.2)	2,392	-8.2 (-12.8;-3.6)
Model 5	2,705	-8.3 (-12.6;-3.9)	2,035	-6.8 (-11.6;-2)	2,392	-8.2 (-12.8;-3.6)
Model 6	2,705	-8.3 (-12.7;-3.9)	2,035	-6.7 (-11.6;-1.9)	2,392	-8 (-12.6;-3.4)
Systolic blood pressure						
Crude	2,705	-1.1 (-2.8;0.6)	2,035	-0.9 (-2.9;1)	2,392	-1.5 (-3.3;0.3)
Model 1	2,705	1.6 (-0.6;3.8)	2,035	1.6 (-0.9;4.1)	2,392	1.2 (-1.1;3.5)
Model 2	2,705	0.8 (-1;2.6)	2,035	0.1 (-1.9;2.2)	2,392	0.7 (-1.2;2.6)
Model 3	2,705	0.7 (-1.1;2.5)	2,035	0.2 (-1.9;2.3)	2,392	0.7 (-1.2;2.6)
Model 4	2,705	0.9 (-0.9;2.7)	2,035	0.3 (-1.8;2.4)	2,392	0.9 (-1;2.8)
Model 5	2,705	0.7 (-1.1;2.5)	2,035	0.1 (-1.9;2.2)	2,392	0.7 (-1.3;2.6)
Model 6	2,705	0.5 (-1.3;2.4)	2,035	0 (-2.1;2.1)	2,392	0.5 (-1.5;2.4)
Diastolic blood pressure						
Crude	2,705	-3.5 (-5.5;-1.5)	2,035	-3 (-5.3;-0.8)	2,392	-3.6 (-5.7;-1.5)
Model 1	2,705	-4.2 (-6.8;-1.7)	2,035	-3.7 (-6.6;-0.8)	2,392	-4.1 (-6.8;-1.4)
Model 2	2,705	-4 (-6.2;-1.9)	2,035	-3.5 (-5.9;-1.1)	2,392	-4.3 (-6.6;-2)
Model 3	2,705	-4 (-6.1;-1.8)	2,035	-3.4 (-5.8;-1)	2,392	-4.2 (-6.5;-1.9)
Model 4	2,705	-4.1 (-6.3;-2)	2,035	-3.5 (-5.9;-1.1)	2,392	-4.4 (-6.6;-2.1)
Model 5	2,705	-3.9 (-6.1;-1.8)	2,035	-3.4 (-5.8;-1)	2,392	-4.2 (-6.5;-1.9)
Model 6	2,705	-3.7 (-5.8;-1.6)	2,035	-3.2 (-5.6;-0.8)	2,392	-3.9 (-6.2;-1.7)

Table B.10: Comparision of results in the complete dataset, among full term born participants and those with no diagnosis of asthma for the association of FEV_1/FVC (%) with cardiometabolic markers in men. Waist circumference in cm , triglyceride concentration in mmol/L, low density lipoprotein in mmol/L, high density lipoprotein in mmol/L, glucose concentration in mmol/L, insulin concentration in mU/L, systolic blood pressure in mm Hg and diastolic blood pressure in mm Hg. Model 1: Mutually adjusted for other cardiometabolic markers; Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for C-reactive protein and white blood cell count; Model 5: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 6: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

	Imputed		**Gestational age [37,41]**		**No asthma**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Waist circumference						
Crude	2,748	-0.0053 (-0.0270.016)	2,083	-0.0006 (-0.026;0.025)	2,484	-0.0095 (-0.0321;0.013)
Model 1	2,748	-0.0238 (-0.0505;0.003)	2,083	-0.0114 (-0.0428;0.02)	2,484	-0.0293 (-0.0572;-0.001)
Model 2	2,748	-0.0072 (-0.0341;0.02)	2,083	0.0062 (-0.0256;0.038)	2,484	-0.0107 (-0.0388;0.017)
Model 3	2,748	-0.0067 (-0.0336;0.02)	2,083	0.0069 (-0.0248;0.039)	2,484	-0.0099 (-0.0379;0.018)
Model 4	2,748	-0.0079 (-0.0349;0.019)	2,083	0.0059 (-0.026;0.038)	2,484	-0.0108 (-0.0391;0.017)
Model 5	2,748	-0.0036 (-0.0308;0.024)	2,083	0.0091 (-0.0229;0.041)	2,484	-0.0071 (-0.0356;0.021)
Model 6	2,748	-0.0024 (-0.0297;0.025)	2,083	0.0115 (-0.0206;0.044)	2,484	-0.0082 (-0.0368;0.02)
Triglyceride concentration						
Crude	2,748	0.0307 (-0.2268;0.288)	2,083	-0.0004 (-0.2902;0.289)	2,484	0.0568 (-0.2122;0.326)
Model 1	2,748	-0.0663 (-0.3736;0.241)	2,083	-0.0834 (-0.4314;0.265)	2,484	0.0165 (-0.3065;0.339)
Model 2	2,748	-0.093 (-0.3978;0.212)	2,083	-0.1147 (-0.4601;0.231)	2,484	-0.0089 (-0.3289;0.311)
Model 3	2,748	-0.0235 (-0.3291;0.282)	2,083	-0.0434 (-0.3898;0.303)	2,484	0.0585 (-0.2617;0.379)
Model 4	2,748	0.0119 (-0.2942;0.318)	2,083	-0.0168 (-0.3638;0.33)	2,484	0.0851 (-0.2358;0.406)
Model 5	2,748	-0.0214 (-0.3269;0.284)	2,083	-0.0483 (-0.3945;0.298)	2,484	0.0572 (-0.2631;0.378)
Model 6	2,748	0.0021 (-0.3037;0.308)	2,083	-0.0097 (-0.3572;0.338)	2,484	0.0838 (-0.2367;0.404)
Low density lipoprotein						
Crude	2,748	0.021 (-0.2155;0.258)	2,083	0.0504 (-0.2213;0.322)	2,484	-0.0354 (-0.2774;0.207)
Model 1	2,748	0.0226 (-0.2231;0.268)	2,083	0.0546 (-0.228;0.337)	2,484	-0.0372 (-0.289;0.215)
Model 2	2,748	-0.0342 (-0.2783;0.21)	2,083	-0.0167 (-0.2982;0.265)	2,484	-0.1015 (-0.3516;0.149)
Model 3	2,748	-0.0287 (-0.2725;0.215)	2,083	-0.0045 (-0.2848;0.276)	2,484	-0.0823 (-0.3318;0.167)
Model 4	2,748	-0.026 (-0.2696;0.218)	2,083	-0.0008 (-0.2812;0.28)	2,484	-0.0786 (-0.3282;0.171)
Model 5	2,748	-0.026 (-0.2695;0.217)	2,083	-0.0045 (-0.2845;0.275)	2,484	-0.0787 (-0.3277;0.17)
Model 6	2,748	-0.0637 (-0.3081;0.181)	2,083	-0.048 (-0.3299;0.234)	2,484	-0.1183 (-0.3685;0.132)
High density lipoprotein						
Crude	2,748	-0.1477 (-0.8005;0.505)	2,083	0.0348 (-0.7312;0.801)	2,484	0.0239 (-0.6535;0.701)
Model 1	2,748	-0.2014 (-0.9358;0.533)	2,083	0.0581 (-0.8123;0.929)	2,484	-0.0049 (-0.7729;0.763)
Model 2	2,748	-0.1846 (-0.9129;0.544)	2,083	0.0819 (-0.7811;0.945)	2,484	0.0296 (-0.7318;0.791)
Model 3	2,748	-0.2686 (-0.9958;0.459)	2,083	-0.004 (-0.8663;0.858)	2,484	-0.072 (-0.8274;0.683)
Model 4	2,748	-0.3189 (-1.0473;0.409)	2,083	-0.0557 (-0.9193;0.808)	2,484	-0.1179 (-0.8745;0.639)
Model 5	2,748	-0.2461 (-0.9726;0.48)	2,083	0.0103 (-0.8508;0.871)	2,484	-0.0524 (-0.8061;0.701)
Model 6	2,748	-0.2344 (-0.9619;0.493)	2,083	-0.0003 (-0.8639;0.863)	2,484	-0.0399 (-0.7974;0.718)

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Table B.10 – continued from previous page

	Imputed		Gestational age [37,41]		No asthma	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Glucose concentration						
Crude	2,748	-0.1265 (-0.4211;0.168)	2,083	-0.0334 (-0.4174;0.351)	2,484	-0.0465 (-0.3628;0.27)
Model 1	2,748	-0.2428 (-0.5505;0.065)	2,083	-0.1746 (-0.5851;0.236)	2,484	-0.1798 (-0.5117;0.152)
Model 2	2,748	-0.2296 (-0.535;0.076)	2,083	-0.1906 (-0.5978;0.217)	2,484	-0.146 (-0.4745;0.183)
Model 3	2,748	-0.1927 (-0.4976;0.112)	2,083	-0.1371 (-0.5443;0.27)	2,484	-0.1069 (-0.435;0.221)
Model 4	2,748	-0.1857 (-0.49;0.119)	2,083	-0.122 (-0.529;0.285)	2,484	-0.0956 (-0.4236;0.232)
Model 5	2,748	-0.202 (-0.5066;0.103)	2,083	-0.1484 (-0.5555;0.259)	2,484	-0.114 (-0.4417;0.214)
Model 6	2,748	-0.1791 (-0.4843;0.126)	2,083	-0.1091 (-0.5184;0.3)	2,484	-0.0999 (-0.4285;0.229)
Insulin concentration						
Crude	2,748	0.0443 (0.004;0.085)	2,083	0.0402 (-0.0032;0.084)	2,484	0.0472 (0.0044;0.09)
Model 1	2,748	0.0672 (0.0198;0.115)	2,083	0.0582 (0.0065;0.11)	2,484	0.0708 (0.0194;0.122)
Model 2	2,748	0.0596 (0.0126;0.107)	2,083	0.0509 (-0.0005;0.102)	2,484	0.0615 (0.0108;0.112)
Model 3	2,748	0.0575 (0.0106;0.104)	2,083	0.048 (-0.0032;0.099)	2,484	0.0576 (0.0068;0.108)
Model 4	2,748	0.0641 (0.0171;0.111)	2,083	0.0524 (0.001;0.104)	2,484	0.0617 (0.0111;0.112)
Model 5	2,748	0.0566 (0.0095;0.104)	2,083	0.0486 (-0.0028;0.1)	2,484	0.0573 (0.0064;0.108)
Model 6	2,748	0.0569 (0.0101;0.104)	2,083	0.0469 (-0.0043;0.098)	2,484	0.0586 (0.008;0.109)
Systolic blood pressure						
Crude	2,748	0.0072 (-0.0095;0.024)	2,083	0.0004 (-0.0194;0.02)	2,484	0.009 (-0.0082;0.026)
Model 1	2,748	0.0074 (-0.0133;0.028)	2,083	-0.0004 (-0.0247;0.024)	2,484	0.0088 (-0.0125;0.03)
Model 2	2,748	0.0087 (-0.0118;0.029)	2,083	0.0017 (-0.0225;0.026)	2,484	0.0096 (-0.0116;0.031)
Model 3	2,748	0.0071 (-0.0135;0.028)	2,083	-0.0014 (-0.02550.023)	2,484	0.008 (-0.0132;0.029)
Model 4	2,748	0.0089 (-0.0116;0.029)	2,083	0.0001 (-0.024;0.024)	2,484	0.0094 (-0.0117;0.03)
Model 5	2,748	0.0074 (-0.0131;0.028)	2,083	-0.0005 (-0.0246;0.024)	2,484	0.0087 (-0.0125;0.03)
Model 6	2,748	0.004 (-0.0166;0.025)	2,083	-0.0031 (-0.0272;0.021)	2,484	0.0052 (-0.0159;0.026)
Diastolic blood pressure						
Crude	2,748	0.0077 (-0.0111;0.026)	2,083	0.0024 (-0.0195;0.024)	2,484	0.0089 (-0.0105;0.028)
Model 1	2,748	0.0042 (-0.0192;0.028)	2,083	0.0015 (-0.0254;0.028)	2,484	0.005 (-0.019;0.029)
Model 2	2,748	0.0051 (-0.0181;0.028)	2,083	0.0021 (-0.0246;0.029)	2,484	0.0053 (-0.0184;0.029)
Model 3	2,748	0.0019 (-0.0213;0.025)	2,083	-0.0009 (-0.0276;0.026)	2,484	0.0022 (-0.0215;0.026)
Model 4	2,748	0.0008 (-0.0223;0.024)	2,083	-0.0018 (-0.0285;0.025)	2,484	0.0012 (-0.0225;0.025)
Model 5	2,748	0.0015 (-0.0217;0.025)	2,083	-0.0011 (-0.0278;0.026)	2,484	0.0015 (-0.0222:0.025)
Model 6	2,748	0.004 (-0.0192;0.027)	2,083	0.0013 (-0.0254;0.028)	2,484	0.0045 (-0.0193;0.028)

Table B.11: Comparision of results in the complete dataset, among full term born participants and those with no diagnosis of asthma for the association of FEV_1/FVC (%) with cardiometabolic markers in women. Waist circumference in cm , triglyceride concentration in mmol/L, low density lipoprotein in mmol/L, high density lipoprotein in mmol/L, glucose concentration in mmol/L, insulin concentration in mU/L, systolic blood pressure in mm Hg and diastolic blood pressure in mm Hg. Model 1: Mutually adjusted for other cardiometabolic markers; Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for C-reactive protein and white blood cell count; Model 5: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 6: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

	Imputed		**Gestational age[37,41]**		**No asthma**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Waist circumference						
Crude	2,705	-0.0353 (-0.0535;-0.017)	2,035	-0.0462 (-0.0669;-0.026)	2,392	-0.0367 (-0.0562;-0.017)
Model 1	2,705	-0.0419 (-0.0645;-0.019)	2,035	-0.053 (-0.0783;-0.028)	2,392	0.1876 (0.1634;0.212)
Model 2	2,705	-0.0349 (-0.0577;-0.012)	2,035	-0.0456 (-0.071;-0.020)	2,392	-0.0332 (-0.0576;-0.009)
Model 3	2,705	-0.0325 (-0.0554;-0.012)	2,035	-0.0434 (-0.069;-0.018)	2,392	-0.0314 (-0.0558;-0.007)
Model 4	2,705	-0.0298 (-0.0531;-0.006)	2,035	-0.0411 (-0.0672;-0.015)	2,392	-0.029 (-0.0539;-0.004)
Model 5	2,705	-0.0323 (-0.0554;-0.009)	2,035	-0.043 (-0.0688;-0.015)	2,392	-0.0308 (-0.0555;-0.006)
Model 6	2,705	-0.0305 (-0.0538;-0.007)	2,035	-0.0423 (-0.0682;-0.016)	2,392	-0.0286 (-0.0535;-0.004)
Triglyceride concentration						
Crude	2,705	-0.4199 (-0.8529;0.013)	2,035	-0.6167 (-1.117;-0.116)	2,392	-0.5259 (-0.9914;-0.060)
Model 1	2,705	-0.2859 (-0.7824;0.211)	2,035	-0.5088 (-1.0828;0.065)	2,392	-0.4089 (-0.9419;0.124)
Model 2	2,705	-0.331 (-0.8265;0.165)	2,035	-0.5511 (-1.1232;0.021)	2,392	-0.4639 (-0.9954;0.068)
Model 3	2,705	-0.2776 (-0.775;0.220)	2,035	-0.4854 (-1.0599;0.089)	2,392	-0.4158 (-0.9504;0.119)
Model 4	2,705	-0.1758 (-0.6832;0.332)	2,035	-0.398 (-0.9829;0.187)	2,392	-0.3061 (-0.8514;0.239)
Model 5	2,705	-0.2782 (-0.7758;0.219)	2,035	-0.4776 (-1.0527;0.097)	2,392	-0.4262 (-0.9615;0.109)
Model 6	2,705	-0.2584 (-0.7549;0.238)	2,035	-0.4653 (-1.0394;0.109)	2,392	-0.3945 (-0.9288;0.140)
Low density lipoprotein						
Crude	2,705	-0.1644 (-0.4458;0.117)	2,035	-0.2661 (-0.5842;0.052)	2,392	-0.2423 (-0.5455;0.061)
Model 1	2,705	0.0056 (-0.2876;0.299)	2,035	-0.0576 (-0.3871;0.272)	2,392	-0.0568 (-0.3748;0.261)
Model 2	2,705	-0.0539 (-0.3476;0.240)	2,035	-0.1161 (-0.4455;0.213)	2,392	-0.1198 (-0.4378;0.198)
Model 3	2,705	-0.069 (-0.3635;0.225)	2,035	-0.1339 (-0.4637;0.196)	2,392	-0.1297 (-0.4489;0.189)
Model 4	2,705	-0.0817 (-0.3766;0.213)	2,035	-0.1471 (-0.4781;0.184)	2,392	-0.1438 (-0.46340.176)
Model 5	2,705	-0.0683 (-0.3628;0.226)	2,035	-0.1383 (-0.4684;0.192)	2,392	-0.1274 (-0.4464;0.192)
Model 6	2,705	-0.0846 (-0.3789;0.210)	2,035	-0.15 (-0.4806;0.181)	2,392	-0.1492 (-0.468;0.170)
High density lipoprotein						
Crude	2,705	1.2414 (0.6475;1.835)	2,035	1.1141 (0.4514;1.777)	2,392	1.4966 (0.8572;2.136)
Model 1	2,705	0.905 (0.2663;1.544)	2,035	0.5991 (-0.1122;1.310)	2,392	1.1475 (0.4614;1.834)
Model 2	2,705	0.9879 (0.3497;1.626)	2,035	0.6893 (-0.0207;1.399)	2,392	1.2303 (0.5457;1.915)
Model 3	2,705	0.8695 (0.2269;1.512)	2,035	0.5736 (-0.1409;1.288)	2,392	1.1317 (0.4436;1.820)
Model 4	2,705	0.8395 (0.1965;1.483)	2,035	0.5531 (-0.1616;1.268)	2,392	1.0925 (0.4036;1.781)
Model 5	2,705	0.8508 (0.2078;1.494)	2,035	0.5649 (-0.1503;1.280)	2,392	1.1106 (0.4223;1.799)
Model 6	2,705	0.8429 (0.1999;1.486)	2,035	0.5872 (-0.1289;1.303)	2,392	1.0988 (0.4098;1.788)

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Table B.11 – continued from previous page

	Imputed		Gestational age[37,41]		No asthma	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Glucose concentration						
Crude	2,705	0.0816 (-0.2449;0.408)	2,035	0.2245 (-0.1292;0.578)	2,392	0.1131 (-0.237;0.463)
Model 1	2,705	0.0847 (-0.2604;0.430)	2,035	0.2365 (-0.1339;0.607)	2,392	0.1157 (-0.2524;0.484)
Model 2	2,705	0.044 (-0.3008;0.389)	2,035	0.1869 (-0.183;0.557)	2,392	0.0635 (-0.3039;0.431)
Model 3	2,705	0.0485 (-0.2965;0.393)	2,035	0.1932 (-0.1764;0.563)	2,392	0.0687 (-0.2994;0.437)
Model 4	2,705	0.0302 (-0.3147;0.375)	2,035	0.18 (-0.18970.550)	2,392	0.0553 (-0.3125;0.423)
Model 5	2,705	0.059 (-0.2859;0.404)	2,035	0.2013 (-0.1683;0.571)	2,392	0.0843 (-0.2837;0.452)
Model 6	2,705	0.031 (-0.3135;0.376)	2,035	0.1741 (-0.1953;0.544)	2,392	0.0548 (-0.3128;0.423)
Insulin concentration						
Crude	2,705	0.0046 (-0.0412;0.050)	2,035	0.0063 (-0.0443;0.057)	2,392	0.012 (-0.0365:0.061)
Model 1	2,705	0.0609 (0.0042;0.118)	2,035	0.0696 (0.008;0.131)	2,392	0.0708 (0.0115;0.130)
Model 2	2,705	0.0561 (-0.0005;0.113)	2,035	0.0638 (0.0024;0.125)	2,392	0.0666 (0.0075;0.126)
Model 3	2,705	0.0541 (-0.0024;0.111)	2,035	0.0604 (-0.0009;0.122)	2,392	0.065 (0.0059;0.124)
Model 4	2,705	0.0589 (0.0022;0.116)	2,035	0.0658 (0.0042;0.128)	2,392	0.0695 (0.0103;0.129)
Model 5	2,705	0.0549 (-0.0016;0.111)	2,035	0.0606 (-0.0008;0.122)	2,392	0.0658 (0.0068;0.125)
Model 6	2,705	0.0577 (0.0011;0.114)	2,035	0.0669 (0.0054;0.128)	2,392	0.069 (0.0099;0.128)
Systolic blood pressure						
Crude	2,705	0.0176 (-0.0003;0.035)	2,035	0.0176 (-0.0027;0.038)	2,392	0.0204 (0.0014;0.039)
Model 1	2,705	0.0262 (0.003;0.049)	2,035	0.0304 (0.0043;0.057)	2,392	0.0262 (0.0017;0.051)
Model 2	2,705	0.0274 (0.0043;0.051)	2,035	0.0329 (0.0068;0.059)	2,392	0.0271 (0.0027;0.052)
Model 3	2,705	0.0292 (0.0059;0.053)	2,035	0.0334 (0.0072;0.060)	2,392	0.0292 (0.0045;0.054)
Model 4	2,705	0.0317 (0.0083;0.055)	2,035	0.0357 (0.0094;0.062)	2,392	0.032 (0.0073;0.057)
Model 5	2,705	0.0303 (0.007;0.054)	2,035	0.0342 (0.0079;0.060)	2,392	0.0307 (0.0061;0.055)
Model 6	2,705	0.0256 (0.0022;0.049)	2,035	0.0288 (0.0025;0.055)	2,392	0.0265 (0.0018;0.051)
Diastolic blood pressure						
Crude	2,705	0.0077 (-0.0132;0.029)	2,035	0.0017 (-0.0218;0.025)	2,392	0.0121 (-0.0104;0.035)
Model 1	2,705	-0.0001 (-0.0275;0.027)	2,035	-0.0054 (-0.0357;0.025)	2,392	0.0045 (-0.0247;0.034)
Model 2	2,705	-0.0004 (-0.0277;0.027)	2,035	-0.0057 (-0.0359;0.025)	2,392	0.0049 (-0.0242;0.034)
Model 3	2,705	-0.0054 (-0.0328;0.022)	2,035	-0.0103 (-0.0407;0.020)	2,392	0.0002 (-0.029;0.029)
Model 4	2,705	-0.0073 (-0.0348;0.020)	2,035	-0.0122 (-0.0426;0.018)	2,392	-0.0022 (-0.03140.027)
Model 5	2,705	-0.0056 (-0.033;0.022)	2,035	-0.0109 (-0.0413;0.020)	2,392	-0.0001 (-0.0293;0.029)
Model 6	2,705	-0.0024 (-0.0299;0.025)	2,035	-0.0072 (-0.0376;0.023)	2,392	0.0018 (-0.0274;0.031)

Table B.12: Comparision of results in the complete dataset, among full term born participants and those with no diagnosis of asthma for the association of FVC (mL) with C-reactive protein (mg/L) and white blood cell count (10^9 cells/L) in men and women. Model 1: Adjusted for other inflammatory marker (i.e. either CRP or WBC); Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socioeconomic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 5: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

Men						
	Imputed		**Gestational age [37,41]**		**No asthma**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
C-reactive protein						
Crude	2,748	-20.4 (-29.3;-11.4)	2,083	-23.6 (-33.9;-13.2)	2,484	-19.5 (-28.5;-10.4)
Model 1	2,748	-16.9 (-26.1;-7.7)	2,083	-20.5 (-31.2;-9.9)	2,484	-16.4 (-25.7;-7)
Model 2	2,748	-13.1 (-20.6;-5.6)	2,083	-17.1 (-25.8;-8.4)	2,484	-13.1 (-20.7;-5.4)
Model 3	2,748	-13.1 (-20.6;-5.6)	2,083	-17 (-25.7;-8.2)	2,484	-13 (-20.7;-5.4)
Model 4	2,748	-13.5 (-21;-6)	2,083	-17.2 (-25.9;-8.5)	2,484	-13.5 (-21.1;-5.8)
Model 5	2,748	-12.7 (-20.3;-5.2)	2,083	-16.9 (-25.6;-8.2)	2,484	-12.6 (-20.2;-4.9)
White blood cell count						
Crude	2,748	-35.7 (-52.8;-18.6)	2,083	-34.3 (-53.9;-14.6)	2,484	-33.4 (-51.2;-15.5)
Model 1	2,748	-28 (-45.6;-10.4)	2,083	-25.5 (-45.6;-5.3)	2,484	-25.8 (-44.1;-7.4)
Model 2	2,748	-19.1 (-33.4;-4.7)	2,083	-13 (-29.4;3.4)	2,484	-17.3 (-32.3;-2.2)
Model 3	2,748	-17.7 (-33;-2.5)	2,083	-10.3 (-27.8;7.1)	2,484	-15.6 (-31.7;0.5)
Model 4	2,748	-16.3 (-31.5;-1.1)	2,083	-8.8 (-26.2;8.7)	2,484	-14.1 (-30.1;2)
Model 5	2,748	-18.4 (-33.7;-3.1)	2,083	-11 (-28.5;6.5)	2,484	-16.3 (-32.3;-0.2)
Women						
	Imputed		**Gestational age [37,41]**		**No asthma**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
C-reactive protein						
Crude	2,705	-17.2 (-22.4;-12.1)	2,035	-16.9 (-23;-10.7)	2,392	-16.5 (-21.9;-11.1)
Model 1	2,705	-15 (-20.4;-9.7)	2,035	-14.5 (-20.9;-8.1)	2,392	-14.5 (-20.1;-8.9)
Model 2	2,705	-12.2 (-16.7;-7.8)	2,035	-10.8 (-16.1;-5.5)	2,392	-11.8 (-16.5;-7.1)
Model 3	2,705	-12.2 (-16.6;-7.7)	2,035	-10.5 (-15.8;-5.2)	2,392	-11.6 (-16.3;-6.9)
Model 4	2,705	-12.1 (-16.6;-7.7)	2,035	-10.4 (-15.7;-5.1)	2,392	-11.6 (-16.2;-6.9)
Model 5	2,705	-12 (-16.4;-7.5)	2,035	-10.4 (-15.7;-5.1)	2,392	-11.3 (-16;-6.7)
White blood cell count						
Crude	2,705	-30.2 (-43.2;-17.2)	2,035	-30.5 (-45.5;-15.4)	2,392	-28.4 (-42.2;-14.5)
Model 1	2,705	-19.2 (-32.8;-5.7)	2,035	-20.2 (-35.9;-4.5)	2,392	-17.8 (-32.2;-3.4)
Model 2	2,705	-6.1 (-17.3;5.1)	2,035	-5.4 (-18.4;7.5)	2,392	-4.1 (-16.1;7.8)
Model 3	2,705	-4.2 (-15.8;7.5)	2,035	-3 (-16.5;10.5)	2,392	-2.9 (-15.4;9.6)
Model 4	2,705	-3.3 (-15;8.3)	2,035	-2.6 (-16.1;10.8)	2,392	-2.1 (-14.5;10.4)
Model 5	2,705	-4.4 (-16.1;7.3)	2,035	-4 (-17.5;9.5)	2,392	-2.8 (-15.3;9.7)

Table B.13: Comparision of results in the complete dataset, among full term born participants and those with no diagnosis of asthma for the association of FEV_1/FVC (%) with C-reactive protein (mg/L) and white blood cell count (10^9 cells/L) in men and women. Model 1: Adjusted for other inflammatory marker (i.e. either CRP or WBC); Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socioeconomic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 5: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy

Men						
	Imputed		**Gestational age [37,41]**		**No asthma**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
C-reactive protein						
Crude	2,748	0.02 (-0.05;0.08)	2,083	0.03 (-0.05;0.1)	2,484	0.01 (-0.05;0.08)
Model 1	2,748	0.05 (-0.02;0.12)	2,083	0.05 (0.03;0.14)	2,484	0.04 (-0.03;0.11)
Model 2	2,748	0.05 (-0.02;0.11)	2,083	0.05 (-0.03;0.13)	2,484	0.04 (-0.03;0.1)
Model 3	2,748	0.04 (-0.02;0.11)	2,083	0.05 (-0.03;0.13)	2,484	0.04 (-0.03;0.1)
Model 4	2,748	0.05 (-0.02;0.11)	2,083	0.05 (-0.03;0.13)	2,484	0.04 (-0.03;0.11)
Model 5	2,748	0.04 (-0.03;0.11)	2,083	0.05 (-0.03;0.13)	2,484	0.03 (-0.04;0.1)
White blood cell count						
Crude	2,748	-0.25 (-0.38;-0.12)	2,083	-0.22 (-0.37;-0.07)	2,484	-0.21 (-0.35;-0.08)
Model 1	2,748	-0.28 (-0.41;-0.14)	2,083	-0.24 (-0.39;-0.09)	2,484	-0.23 (-0.37;-0.1)
Model 2	2,748	-0.29 (-0.42;-0.16)	2,083	-0.26 (-0.41;-0.11)	2,484	-0.25 (-0.38;-0.11)
Model 3	2,748	-0.21 (-0.35;-0.07)	2,083	-0.18 (-0.34;-0.02)	2,484	-0.15 (-0.29;-0.01)
Model 4	2,748	-0.21 (-0.35;-0.07)	2,083	-0.18 (-0.34;-0.02)	2,484	-0.15 (-0.3;-0.01)
Model 5	2,748	-0.2 (-0.34;-0.06)	2,083	-0.17 (-0.33;-0.01)	2,484	-0.15 (-0.29;-0.01)
Women						
	Imputed		**Gestational age [37,41]**		**No asthma**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
C-reactive protein						
Crude	2,705	-0.04 (-0.09;0.02)	2,035	-0.05 (-0.11;0.02)	2,392	-0.04 (-0.09;0.02)
Model 1	2,705	-0.01 (-0.07;0.04)	2,035	-0.02 (-0.09;0.04)	2,392	-0.01 (-0.07;0.05)
Model 2	2,705	-0.02 (-0.08;0.04)	2,035	-0.03 (-0.1;0.04)	2,392	-0.01 (-0.07;0.05)
Model 3	2,705	-0.02 (-0.08;0.03)	2,035	-0.03 (-0.1;0.03)	2,392	-0.02 (-0.08;0.04)
Model 4	2,705	-0.02 (-0.08;0.04)	2,035	-0.03 (-0.1;0.03)	2,392	-0.02 (-0.08;0.04)
Model 5	2,705	-0.02 (-0.080.04)	2,035	-0.03 (-0.1;0.03)	2,392	-0.02 (-0.08;0.04)
White blood cell count						
Crude	2,705	-0.23 (-0.37;-0.1)	2,035	-0.22 (-0.38;-0.06)	2,392	-0.24 (-0.39;-0.1)
Model 1	2,705	-0.22 (-0.37;-0.08)	2,035	-0.2 (-0.37;-0.04)	2,392	-0.24 (-0.39;-0.08)
Model 2	2,705	-0.24 (-0.39;-0.1)	2,035	-0.23 (-0.39;-0.06)	2,392	-0.26 (-0.41;-0.11)
Model 3	2,705	-0.18 (-0.33;-0.03)	2,035	-0.17 (-0.34;0)	2,392	-0.21 (-0.37;-0.05)
Model 4	2,705	-0.18 (-0.33;-0.03)	2,035	-0.16 (-0.34;0.01)	2,392	-0.2 (-0.36;-0.04)
Model 5	2,705	-0.16 (-0.31;-0.01)	2,035	-0.15 (-0.32;0.02)	2,392	-0.19 (-0.35;-0.03)

Table B.14: Comparision of results in the complete dataset, using a more limited imputation strategy and with complete case analyses for the association of FVC (mL) with cardiometabolic markers in men. Waist circumference in cm , triglyceride concentration in mmol/L, low density lipoprotein in mmol/L, high density lipoprotein in mmol/L, glucose concentration in mmol/L, insulin concentration in mU/L, systolic blood pressure in mm Hg and diastolic blood pressure in mm Hg. Model 1: Mutually adjusted for other cardiometabolic markers; Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for C-reactive protein and white blood cell count; Model 5: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 6: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

	Imputed		**Limited imputed**		**Complete case**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Waist circumference						
Crude	2,748	-0.8 (-3.7;2.1)	2,736	-0.8 (-3.7;2.1)	2,736	-0.8 (-3.7;2.1)
Model 1	2,748	5.7 (2.2;9.3)	2,639	5.5 (1.9;9.1)	2,639	5.5 (1.9;9.1)
Model 2	2,748	-4.3 (-7.2;-1.4	2,639	-4.3 (-7.2;-1.4)	2,639	-4.3 (-7.2;-1.4)
Model 3	2,748	-4.4 (-7.4;-1.5	2,639	-4.4 (-7.4;-1.5)	2,042	-4.7 (-8;-1.4)
Model 4	2,748	-3.8 (-6.8;-0.9)	2,639	-3.8 (-6.7;-0.8)	2,005	-4 (-7.4;-0.7)
Model 5	2,748	-5.7 (-8.6;-2.7)	2,639	-5.7 (-8.7;-2.7)	1,778	-6 (-9.7;-2.4)
Model 6	2,748	-4.7 (-7.7;-1.7)	2,639	-4.6 (-7.6;-1.6)	1,772	-4.3 (-7.8;-0.7)
Triglyceride concentration						
Crude	2,748	-99.2 (-133.2;-65.2)	2,710	-99.8 (-133.8;-65.8)	2,710	-99.8 (-133.8;-65.8)
Model 1	2,748	-94.4 (-134.9;-53.9)	2,639	-93.1 (-133.9;-52.4)	2,639	-93.1 (-133.9;-52.4)
Model 2	2,748	-78.4 (-111.1;-45.7)	2,639	-76.4 (-109.3;-43.5)	2,639	-76.4 (-109.3;-43.5)
Model 3	2,748	-76.7 (-109.5;-43.8)	2,639	-74.6 (-107.7;-41.4)	2,042	-73.4 (-109.8;-36.9)
Model 4	2,748	-78.9 (-111.9;-46)	2,639	-77.1 (-110.3;-43.9)	2,005	-82.1 (-119.2;-45)
Model 5	2,748	-74 (-106.7;-41.2)	2,639	-71.8 (-104.9;-38.8)	1,778	-83.2 (-121.2;-45.2)
Model 6	2,748	-76.4 (-109.3;-43.5)	2,639	-73.8 (-107;-40.6)	1,772	-83.5 (-122.5;-44.5)
Low density lipoprotein						
Crude	2,748	-58.1 (-89.6;-26.6)	2,702	-58.6 (-90;-27.2)	2,702	-58.6 (-90;-27.2)
Model 1	2,748	-44.1 (-76.6;-11.6)	2,639	-42.9 (-75.6;-10.2)	2,639	-42.9 (-75.6;-10.2)
Model 2	2,748	-9.9 (-36.3;16.4)	2,639	-8.2 (-34.7;18.2)	2,639	-8.2 (-34.7;18.2)
Model 3	2,748	-9 (-35.4;17.4)	2,639	-7.3 (-33.9;19.2)	2,042	-13.7 (-43.8;16.4)
Model 4	2,748	-11.1 (-37.5;15.3)	2,639	-9.2 (-35.7;17.3)	2,005	-11.1 (-41.4;19.3)
Model 5	2,748	-8.8 (-35.2;17.6)	2,639	-7.3 (-33.8;19.1)	1,778	-13.7 (-45.8;18.5)
Model 6	2,748	-9.9 (-36.4;16.6)	2,639	-8.3 (-34.9;18.4)	1,772	-16.2 (-48.7;16.3)
High density lipoprotein						
Crude	2,748	38.8 (-48.2;125.7)	2,711	42.8 (-44;129.7)	2,711	42.8 (-44;129.7)
Model 1	2,748	-60.1 (-156.9;36.6)	2,639	-55.3 (-153.7;43.1)	2,639	-55.3 (-153.7;43.1)
Model 2	2,748	-70.3 (-148.6;8)	2,639	-65.4 (-144.8;14.1)	2,639	-65.4 (-144.8;14.1)
Model 3	2,748	-73.2 (-151.6;5.3)	2,639	-68.2 (-147.8;11.3)	2,042	-27.4 (-119.2;64.4)
Model 4	2,748	-84.6 (-163.2;-6)	2,639	-79.3 (-158.9;0.4)	2,005	-37.8 (-130.4;54.8)
Model 5	2,748	-78.8 (-156.9;-0.6)	2,639	-75.3 (-154.6;4.1)	1,778	-55.8 (-156.4;44.8)
Model 6	2,748	-78.8 (-157.4;-0.2)	2,639	-73.1 (-152.9;6.6)	1,772	-44.6 (-144.1;54.8)

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Table B.14 – continued from previous page

	Imputed		Limited imputed		Complete case	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Glucose concentration						
Crude	2,748	-52.3 (-91.4;-13.1)	2,689	-51.9 (-91.2;-12.7)	2,689	-51.9 (-91.2;-12.7)
Model 1	2,748	-29.2 (-69.7;11.3)	2,639	-29.7 (-70.5;11)	2,639	-29.7 (-70.5;11)
Model 2	2,748	-37.1 (-69.8;-4.3)	2,639	-37.7 (-70.6;-4.8)	2,639	-37.7 (-70.6;-4.8)
Model 3	2,748	-37.3 (-70.1;-4.4)	2,639	-38 (-70.9;-5)	2,042	-58.7 (-99.6;-17.9)
Model 4	2,748	-38.4 (-71.2;-5.6)	2,639	-39.3 (-72.2;-6.3)	2,005	-56.8 (-97.8;-15.8)
Model 5	2,748	-34.6 (-67.4;-1.9)	2,639	-35.6 (-68.5;-2.8)	1,778	-49.6 (-92;-7.2)
Model 6	2,748	-37.4 (-70.3;-4.5)	2,639	-37.9 (-71;-4.9)	1,772	-72.8 (-118.5;-27)
Insulin concentration						
Crude	2,748	-13.4 (-18.7;-8)	2,670	-13.4 (-18.7;-8)	2,670	-13.4 (-18.7;-8)
Model 1	2,748	-10.4 (-16.7;-4.2)	2,639	-10 (-16.3;-3.8)	2,639	-10 (-16.3;-3.8)
Model 2	2,748	-5.9 (-11;-0.9)	2,639	-5.8 (-10.9;-0.8)	2,639	-5.8 (-10.9;-0.8)
Model 3	2,748	-5.5 (-10.6;-0.5)	2,639	-5.5 (-10.5;-0.4)	2,042	-3.8 (-9.2;1.6)
Model 4	2,748	-4.8 (-9.9;0.2)	2,639	-4.8 (-9.9;0.3)	2,005	-3.5 (-8.9;1.9)
Model 5	2,748	-4.5 (-9.6;0.5)	2,639	-4.5 (-9.5;0.6)	1,778	-2.7 (-8.2;2.9)
Model 6	2,748	-5.5 (-10.6;-0.4)	2,639	-5.5 (-10.6;-0.4)	1,772	-3.4 (-9;2.2)
Systolic blood pressure						
Crude	2,748	-0.7 (-3;1.5)	2,743	-0.7 (-2.9;1.5)	2,743	-0.7 (-2.9;1.5)
Model 1	2,748	1.8 (-1;4.5)	2,639	1.9 (-0.9;4.7)	2,639	1.9 (-0.9;4.7)
Model 2	2,748	1 (-1.2;3.2)	2,639	1.2 (-1.1;3.4)	2,639	1.2 (-1.1;3.4)
Model 3	2,748	0.9 (-1.3;3.2)	2,639	1.1 (-1.1;3.4)	2,042	0.8 (-1.8;3.4)
Model 4	2,748	1 (-1.3;3.2)	2,639	1.1 (-1.1;3.4)	2,005	0.8 (-1.8;3.4)
Model 5	2,748	1.3 (-0.9;3.5)	2,639	1.5 (-0.8;3.7)	1,778	0.2 (-2.6;3)
Model 6	2,748	0.8 (-1.4;3.1)	2,639	1 (-1.3;3.3)	1,772	1.3 (-1.5;4.1)
Diastolic blood pressure						
Crude	2,748	-3.3 (-5.8;-0.8)	2,743	-3.3 (-5.8;-0.8)	2,743	-3.3 (-5.8;-0.8)
Model 1	2,748	-3.1 (-6.2;0)	2,639	-3.2 (-6.3;-0.1)	2,639	-3.2 (-6.3;-0.1)
Model 2	2,748	-3.7 (-6.2;-1.2)	2,639	-3.7 (-6.2;-1.1)	2,639	-3.7 (-6.2;-1.1)
Model 3	2,748	-3.6 (-6.1;-1.1)	2,639	-3.6 (-6.2;-1.1)	2,042	-3.4 (-6.3;-0.4)
Model 4	2,748	-3.6 (-6.1;-1.1)	2,639	-3.6 (-6.1;-1.1)	2,005	-3.2 (-6.1;-0.3)
Model 5	2,748	-3.6 (-6.1;-1.1)	2,639	-3.6 (-6.1;-1.1)	1,778	-2.8 (-5.9;0.4)
Model 6	2,748	-3.5 (-6;-1)	2,639	-3.4 (-6;-0.9)	1,772	-3.4 (-6.6;-0.3)

Table B.15: Comparision of results in the complete dataset, using a more limited imputation strategy and with complete case analyses for the association of FVC (mL) with cardiometabolic markers in women. Waist circumference in cm , triglyceride concentration in mmol/L, low density lipoprotein in mmol/L, high density lipoprotein in mmol/L, glucose concentration in mmol/L, insulin concentration in mU/L, systolic blood pressure in mm Hg and diastolic blood pressure in mm Hg. Model 1: Mutually adjusted for other cardiometabolic markers; Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for C-reactive protein and white blood cell count; Model 5: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 6: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

	Imputed		**Limited imputed**		**Complete case**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Waist circumference						
Crude	2,705	1 (-0.7;2.7)	2,695	1 (-0.7;2.8)	2,695	1 (-0.7;2.8)
Model 1	2,705	6.4 (4.3;8.5)	2,619	6.2 (4.1;8.3)	2,619	6.2 (4.1;8.3)
Model 2	2,705	1.8 (0;3.6)	2,619	1.5 (-0.3;3.3)	2,619	1.5 (-0.3;3.3)
Model 3	2,705	1.7 (0;3.5)	2,619	1.5 (-0.3;3.3)	1,920	1 (-1;3.1)
Model 4	2,705	2.6 (0.8;4.4)	2,619	2.4 (0.6;4.2)	1,879	2.3 (0.2;4.5)
Model 5	2,705	1.2 (-0.6;3)	2,619	0.9 (-0.9;2.7)	1,688	0.7 (-1.5;2.9)
Model 6	2,705	1.4 (-0.4;3.3)	2,619	1.2 (-0.6;3.1)	1,685	0.8 (-1.5;3)
Triglyceride concentration						
Crude	2,705	-92.3 (-132.9;-51.6)	2,679	-94.9 (-135.3;-54.5)	2,679	-94.9 (-135.3;-54.5)
Model 1	2,705	-54.4 (-100.7;-8)	2,619	-53.1 (-100.1;-6.2)	2,619	-53.1 (-100.1;-6.2)
Model 2	2,705	-24.5 (-62.9;13.9)	2,619	-28.8 (-67.5;10)	2,619	-28.8 (-67.5;10)
Model 3	2,705	-21.8 (-60.4;16.8)	2,619	-25.8 (-64.7;13.1)	1,920	-29.2 (-75.1;16.8)
Model 4	2,705	-6.2 (-45.3;32.8)	2,619	-9 (-48.4;30.4)	1,879	-15.4 (-62.4;31.6)
Model 5	2,705	-17.4 (-55.9;21.1)	2,619	-21.3 (-60.1;17.5)	1,688	-28.7 (-78.5;21)
Model 6	2,705	-20.5 (-59.1;18)	2,619	-24.5 (-63.3;14.4)	1,685	-23.9 (-72.2;24.4)
Low density lipoprotein						
Crude	2,705	-46.6 (-73.1;-20.1)	2,672	-47.6 (-74;-21.1)	2,672	-47.6 (-74;-21.1)
Model 1	2,705	-44 (-71.4;-16.7)	2,619	-43.1 (-70.6;-15.6)	2,619	-43.1 (-70.6;-15.6)
Model 2	2,705	-4.7 (-27.5;18.1)	2,619	-3.8 (-26.6;19)	2,619	-3.8 (-26.6;19)
Model 3	2,705	-4.6 (-27.4;18.2)	2,619	-3.8 (-26.7;19.1)	1,920	-1.2 (-28.1;25.8)
Model 4	2,705	-8.6 (-31.3;14.2)	2,619	-8 (-30.8;14.8)	1,879	-9.3 (-36.5;18)
Model 5	2,705	-5.7 (-28.5;17)	2,619	-5 (-27.8;17.8)	1,688	-7 (-35.3;21.2)
Model 6	2,705	-4.7 (-27.5;18.1)	2,619	-4 (-26.8;18.9)	1,685	-3.2 (-32.3;25.9)
High density lipoprotein						
Crude	2,705	58.4 (2.3;114.5)	2,679	61.6 (5.6;117.6)	2,679	61.6 (5.6;117.6)
Model 1	2,705	53.2 (-6.5;112.9)	2,619	50.4 (-10.1;111)	2,619	50.4 (-10.1;111)
Model 2	2,705	-1.5 (-51.1;48)	2,619	-4.9 (-54.9;45.2)	2,619	-4.9 (-54.9;45.2)
Model 3	2,705	-8.2 (-58.3;41.8)	2,619	-12.4 (-62.9;38)	1,920	-29.8 (-88.9;29.3)
Model 4	2,705	-4.8 (-54.7;45)	2,619	-8.3 (-58.6;42)	1,879	-34.2 (-93.9;25.6)
Model 5	2,705	-11.9 (-61.7;38)	2,619	-15.5 (-65.8;34.8)	1,688	-53.3 (-115.8;9.3)
Model 6	2,705	-4.8 (-55;45.3)	2,619	-8.6 (-59.2;41.9)	1,685	-18.5 (-81.1;44.1)

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Table B.15 – continued from previous page

	Imputed		Limited imputed		Complete case	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Glucose concentration						
Crude	2,705	-63.6 (-94.3;-32.9)	2,679	-64.7 (-95.5;-33.9)	2,663	-64.7 (-95.5;-33.9)
Model 1	2,705	-44.9 (-77.2;-12.5)	2,619	-44.2 (-76.7;-11.7)	2,619	-44.2 (-76.7;-11.7)
Model 2	2,705	-18 (-44.9;8.9)	2,619	-16.8 (-43.7;10)	2,619	-16.8 (-43.7;10)
Model 3	2,705	-16.9 (-43.9;10)	2,619	-15.8 (-42.7;11.1)	1,920	-23.6 (-53;5.7)
Model 4	2,705	-18.2 (-45;8.6)	2,619	-17 (-43.8;9.7)	1,879	-24.2 (-53.6;5.2)
Model 5	2,705	-17.6 (-44.4;9.2)	2,619	-16.5 (-43.3;10.3)	1,688	-28 (-57.6;1.6)
Model 6	2,705	-18.2 (-45.1;8.7)	2,619	-17 (-43.9;9.9)	1,685	-31.2 (-69.2;6.8)
Insulin concentration						
Crude	2,705	-11.7 (-16;-7.4)	2,654	-12 (-16.3;-7.7)	2,654	-12 (-16.3;-7.7)
Model 1	2,705	-11.8 (-17.1;-6.5)	2,619	-11.9 (-17.2;-6.6)	2,619	-11.9 (-17.2;-6.6)
Model 2	2,705	-8.6 (-13;-4.2)	2,619	-8.3 (-12.7;-3.9)	2,619	-8.3 (-12.7;-3.9)
Model 3	2,705	-8.7 (-13.1;-4.3)	2,619	-8.4 (-12.7;-4)	1,920	-9.3 (-14.2;-4.4)
Model 4	2,705	-8.2 (-12.6;-3.8)	2,619	-7.9 (-12.2;-3.5)	1,879	-10.5 (-15.6;-5.5)
Model 5	2,705	-8.3 (-12.6;-3.9)	2,619	-8 (-12.4;-3.6)	1,688	-9.6 (-14.7;-4.4)
Model 6	2,705	-8.3 (-12.7;-3.8)	2,619	-8 (-12.4;-3.6)	1,685	-9 (-14.1;-3.9)
Systolic blood pressure						
Crude	2,705	-1.1 (-2.8;0.6)	2,702	-1.1 (-2.8;0.6)	2,702	-1.1 (-2.8;0.6)
Model 1	2,705	1.6 (-0.6;3.8)	2,619	1.9 (-0.3;4.2)	2,619	1.9 (-0.3;4.2)
Model 2	2,705	0.8 (-1;2.6)	2,619	1.1 (-0.8;2.9)	2,619	1.1 (-0.8;2.9)
Model 3	2,705	0.7 (-1.1;2.5)	2,619	1 (-0.9;2.9)	1,920	0.4 (-1.7;2.6)
Model 4	2,705	0.9 (-0.9;2.7)	2,619	1.2 (-0.7;3.1)	1,879	1 (-1.1;3.2)
Model 5	2,705	0.7 (-1.1;2.5)	2,619	1 (-0.9;2.8)	1,688	0.1 (-2.1;2.4)
Model 6	2,705	0.5 (-1.3;2.4)	2,619	0.8 (-1;2.7)	1,685	0.6 (-1.7;2.9)
Diastolic blood pressure						
Crude	2,705	-3.5 (-5.5;-1.5)	2,695	-3.4 (-5.4;-1.4)	2,695	-3.4 (-5.4;-1.4)
Model 1	2,705	-4.2 (-6.8;-1.7)	2,619	-4.6 (-7.2;-2)	2,619	-4.6 (-7.2;-2)
Model 2	2,705	-4 (-6.2;-1.9)	2,619	-4.2 (-6.4;-2.1)	2,619	-4.2 (-6.4;-2.1)
Model 3	2,705	-4 (-6.1;-1.8)	2,619	-4.2 (-6.3;-2)	1,920	-3 (-5.5;-0.4)
Model 4	2,705	-4.1 (-6.3;-2)	2,619	-4.3 (-6.5;-2.2)	1,879	-3.5 (-6.1;-0.9)
Model 5	2,705	-3.9 (-6.1;-1.8)	2,619	-4.1 (-6.3;-2)	1,688	-2.7 (-5.3;0)
Model 6	2,705	-3.7 (-5.8;-1.6)	2,619	-3.9 (-6.1;-1.8)	1,685	-3 (-5.7;-0.3)

Table B.16: Comparision of results in the complete dataset, using a more limited imputation strategy and with complete case analyses for the association of FEV_1/FVC (%) with cardiometabolic markers in men. Waist circumference in cm , triglyceride concentration in mmol/L, low density lipoprotein in mmol/L, high density lipoprotein in mmol/L, glucose concentration in mmol/L, insulin concentration in mU/L, systolic blood pressure in mm Hg and diastolic blood pressure in mm Hg. Model 1: Mutually adjusted for other cardiometabolic markers; Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for C-reactive protein and white blood cell count; Model 5: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 6: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

	Imputed		**Limited imputed**		**Complete case**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Waist circumference						
Crude	2,748	-0.005 (-0.027;0.016)	2,736	-0.005 (-0.027;0.017)	2,736	-0.005 (-0.027;0.017)
Model 1	2,748	-0.024 (-0.051;0.003)	2,639	-0.026 (-0.053;0.002)	2,639	-0.026 (-0.053;0.002)
Model 2	2,748	-0.007 (-0.034;0.02)	2,639	-0.01 (-0.037;0.017)	2,639	-0.01 (-0.037;0.017)
Model 3	2,748	-0.007 (-0.034;0.02)	2,639	-0.01 (-0.037;0.017)	2,042	-0.005 (-0.036;0.025)
Model 4	2,748	-0.008 (-0.035;0.019)	2,639	-0.011 (-0.039;0.016)	2,005	-0.009 (-0.04;0.023)
Model 5	2,748	-0.004 (-0.031;0.024)	2,639	-0.006 (-0.034;0.021)	1,778	-0.002 (-0.037;0.032)
Model 6	2,748	-0.002 (-0.03;0.025)	2,639	-0.006 (-0.034;0.021)	1,772	0.005 (-0.028;0.037)
Triglyceride concentration						
Crude	2,748	0.031 (-0.227;0.288)	2,710	0.038 (-0.218;0.295)	2,710	0.038 (-0.218;0.295)
Model 1	2,748	-0.066 (-0.374;0.241)	2,639	-0.013 (-0.322;0.296)	2,639	-0.013 (-0.322;0.296)
Model 2	2,748	-0.093 (-0.398;0.212)	2,639	-0.04 (-0.347;0.266)	2,639	-0.04 (-0.347;0.266)
Model 3	2,748	-0.023 (-0.329;0.282)	2,639	0.035 (-0.272;0.342)	2,042	0.076 (-0.261;0.414)
Model 4	2,748	0.012 (-0.294;0.318)	2,639	0.069 (-0.238;0.377)	2,005	0.123 (-0.223;0.468)
Model 5	2,748	-0.021 (-0.327;0.284)	2,639	0.037 (-0.269;0.344)	1,778	0.073 (-0.284;0.431)
Model 6	2,748	0.002 (-0.304;0.308)	2,639	0.069 (-0.238;0.376)	1,772	0.057 (-0.301;0.415)
Low density lipoprotein						
Crude	2,748	0.021 (-0.216;0.258)	2,702	0.03 (-0.206;0.266)	2,702	0.03 (-0.206;0.266)
Model 1	2,748	0.023 (-0.223;0.268)	2,639	-0.016 (-0.264;0.232)	2,639	-0.016 (-0.264;0.232)
Model 2	2,748	-0.034 (-0.278;0.21)	2,639	-0.072 (-0.318;0.175)	2,639	-0.072 (-0.318;0.175)
Model 3	2,748	-0.029 (-0.273;0.215)	2,639	-0.067 (-0.313;0.179)	2,042	-0.119 (-0.398;0.16)
Model 4	2,748	-0.026 (-0.27;0.218)	2,639	-0.064 (-0.31;0.182)	2,005	-0.151 (-0.433;0.132)
Model 5	2,748	-0.026 (-0.269;0.217)	2,639	-0.063 (-0.309;0.182)	1,778	-0.066 (-0.368;0.236)
Model 6	2,748	-0.064 (-0.308;0.181)	2,639	-0.107 (-0.354;0.139)	1,772	-0.157 (-0.455;0.142)
High density lipoprotein						
Crude	2,748	-0.148 (-0.801;0.505)	2,689	-0.167 (-0.819;0.485)	2,711	-0.167 (-0.819;0.485)
Model 1	2,748	-0.201 (-0.936;0.533)	2,639	-0.129 (-0.875;0.616)	2,639	-0.129 (-0.875;0.616)
Model 2	2,748	-0.185 (-0.913;0.544)	2,639	-0.113 (-0.853;0.627)	2,639	-0.113 (-0.853;0.627)
Model 3	2,748	-0.269 (-0.996;0.459)	2,639	-0.193 (-0.931;0.545)	2,042	-0.237 (-1.087;0.613)
Model 4	2,748	-0.319 (-1.047;0.409)	2,639	-0.24 (-0.979;0.499)	2,005	-0.189 (-1.052;0.673)
Model 5	2,748	-0.246 (-0.973;0.48)	2,639	-0.162 (-0.899;0.575)	1,778	-0.238 (-1.184;0.708)
Model 6	2,748	-0.234 (-0.962;0.493)	2,639	-0.159 (-0.897;0.579)	1,772	-0.217 (-1.129;0.695)

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Table B.16 – continued from previous page

	Imputed		Limited imputed		Complete case	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Glucose concentration						
Crude	2,748	-0.126 (-0.421;0.168)	2,670	-0.121 (-0.415;0.173)	2,689	-0.121 (-0.415;0.173)
Model 1	2,748	-0.243 (-0.551;0.065)	2,639	-0.231 (-0.54;0.078)	2,639	-0.231 (-0.54;0.078)
Model 2	2,748	-0.23 (-0.535;0.076)	2,639	-0.218 (-0.525;0.088)	2,639	-0.218 (-0.525;0.088)
Model 3	2,748	-0.193 (-0.498;0.112)	2,639	-0.18 (-0.486;0.126)	2,042	0.015 (-0.364;0.393)
Model 4	2,748	-0.186 (-0.49;0.119)	2,639	-0.173 (-0.479;0.133)	2,005	0.018 (-0.364;0.4)
Model 5	2,748	-0.202 (-0.507;0.103)	2,639	-0.19 (-0.496;0.116)	1,778	-0.075 (-0.473;0.324)
Model 6	2,748	-0.179 (-0.484;0.126)	2,639	-0.17 (-0.476;0.136)	1,772	0.012 (-0.408;0.432)
Insulin concentration						
Crude	2,748	0.044 (0.004;0.085)	2,670	0.045 (0.004;0.085)	2,670	0.045 (0.004;0.085)
Model 1	2,748	0.067 (0.02;0.115)	2,639	0.068 (0.02;0.115)	2,639	0.068 (0.02;0.115)
Model 2	2,748	0.06 (0.013;0.107)	2,639	0.061 (0.014;0.108)	2,639	0.061 (0.014;0.108)
Model 3	2,748	0.058 (0.011;0.104)	2,639	0.059 (0.012;0.106)	2,042	0.047 (-0.003;0.097)
Model 4	2,748	0.064 (0.017;0.111)	2,639	0.065 (0.018;0.112)	2,005	0.052 (0.002;0.102)
Model 5	2,748	0.057 (0.01;0.104)	2,639	0.058 (0.011;0.105)	1,778	0.044 (-0.008;0.097)
Model 6	2,748	0.057 (0.01;0.104)	2,639	0.058 (0.011;0.105)	1,772	0.037 (-0.014;0.089)
Systolic blood pressure						
Crude	2,748	0.007 (-0.01;0.024)	2,743	0.007 (-0.01;0.024)	2,743	0.007 (-0.01;0.024)
Model 1	2,748	0.007 (-0.013;0.028)	2,639	0.008 (-0.013;0.029)	2,639	0.008 (-0.013;0.029)
Model 2	2,748	0.009 (-0.012;0.029)	2,639	0.009 (-0.012;0.03)	2,639	0.009 (-0.012;0.03)
Model 3	2,748	0.007 (-0.013;0.028)	2,639	0.008 (-0.013;0.029)	2,042	0.002 (-0.022;0.026)
Model 4	2,748	0.009 (-0.012;0.029)	2,639	0.009 (-0.012;0.03)	2,005	0.005 (-0.019;0.029)
Model 5	2,748	0.007 (-0.013;0.028)	2,639	0.008 (-0.013;0.029)	1,778	0.002 (-0.024;0.029)
Model 6	2,748	0.004 (-0.017;0.025)	2,639	0.004 (-0.017;0.025)	1,772	-0.007 (-0.033;0.018)
Diastolic blood pressure						
Crude	2,748	0.008 (-0.011;0.026)	2,743	0.008 (-0.011;0.026)	2,743	0.008 (-0.011;0.026)
Model 1	2,748	0.004 (-0.019;0.028)	2,639	0.006 (-0.018;0.029)	2,639	0.006 (-0.018;0.029)
Model 2	2,748	0.005 (-0.018;0.028)	2,639	0.006 (-0.017;0.03)	2,639	0.006 (-0.017;0.03)
Model 3	2,748	0.002 (-0.021;0.025)	2,639	0.003 (-0.02;0.027)	2,042	0.005 (-0.022;0.032)
Model 4	2,748	0.001 (-0.022;0.024)	2,639	0.002 (-0.021;0.026)	2,005	0.003 (-0.024;0.03)
Model 5	2,748	0.001 (-0.022;0.025)	2,639	0.003 (-0.021;0.026)	1,778	0 (-0.03;0.029)
Model 6	2,748	0.004 (-0.019;0.027)	2,639	0.005 (-0.018;0.029)	1,772	-0.001 (-0.029;0.028)

Table B.17: Comparision of results in the complete dataset, using a more limited imputation strategy and with complete case analyses for the association of FEV_1/FVC (%) with cardiometabolic markers in women. Waist circumference in cm , triglyceride concentration in mmol/L, low density lipoprotein in mmol/L, high density lipoprotein in mmol/L, glucose concentration in mmol/L, insulin concentration in mU/L, systolic blood pressure in mm Hg and diastolic blood pressure in mm Hg. Model 1: Mutually adjusted for other cardiometabolic markers; Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for C-reactive protein and white blood cell count; Model 5: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 6: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

	Imputed		**Limited imputed**		**Complete case**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Waist circumference						
Crude	2,705	-0.035 (-0.053;-0.017)	2,695	-0.036 (-0.054;-0.017)	2,695	-0.036 (-0.054;-0.017)
Model 1	2,705	-0.042 (-0.065;-0.019)	2,619	-0.038 (-0.06;-0.015)	2,619	-0.038 (-0.06;-0.015)
Model 2	2,705	-0.035 (-0.058;-0.012)	2,619	-0.031 (-0.054;-0.008)	2,619	-0.031 (-0.054;-0.008)
Model 3	2,705	-0.032 (-0.055;-0.01)	2,619	-0.028 (-0.051;-0.005)	1,920	-0.019 (-0.045;0.007)
Model 4	2,705	-0.03 (-0.053;-0.006)	2,619	-0.026 (-0.049;-0.002)	1,879	-0.017 (-0.044;0.009)
Model 5	2,705	-0.032 (-0.055;-0.009)	2,619	-0.028 (-0.051;-0.005)	1,688	-0.024 (-0.051;0.004)
Model 6	2,705	-0.03 (-0.054;-0.007)	2,619	-0.027 (-0.051;-0.004)	1,685	-0.016 (-0.044;0.012)
Triglyceride concentration						
Crude	2,705	-0.42 (-0.853;0.013)	2,679	-0.394 (-0.818;0.031)	2,679	-0.394 (-0.818;0.031)
Model 1	2,705	-0.286 (-0.782;0.211)	2,619	-0.223 (-0.718;0.272)	2,619	-0.223 (-0.718;0.272)
Model 2	2,705	-0.331 (-0.827;0.165)	2,619	-0.259 (-0.752;0.235)	2,619	-0.259 (-0.752;0.235)
Model 3	2,705	-0.278 (-0.775;0.22)	2,619	-0.211 (-0.706;0.284)	1,920	-0.52 (-1.087;0.048)
Model 4	2,705	-0.176 (-0.683;0.332)	2,619	-0.109 (-0.613;0.395)	1,879	-0.437 (-1.018;0.144)
Model 5	2,705	-0.278 (-0.776;0.219)	2,619	-0.218 (-0.713;0.278)	1,688	-0.717 (-1.335;-0.098)
Model 6	2,705	-0.258 (-0.755;0.238)	2,619	-0.191 (-0.685;0.303)	1,685	-0.426 (-1.029;0.176)
Low density lipoprotein						
Crude	2,705	-0.164 (-0.446;0.117)	2,672	-0.151 (-0.428;0.126)	2,672	-0.151 (-0.428;0.126)
Model 1	2,705	0.006 (-0.288;0.299)	2,619	-0.003 (-0.293;0.287)	2,619	-0.003 (-0.293;0.287)
Model 2	2,705	-0.054 (-0.348;0.24)	2,619	-0.061 (-0.352;0.23)	2,619	-0.061 (-0.352;0.23)
Model 3	2,705	-0.069 (-0.363;0.225)	2,619	-0.075 (-0.367;0.216)	1,920	0.023 (-0.31;0.356)
Model 4	2,705	-0.082 (-0.377;0.213)	2,619	-0.088 (-0.38;0.203)	1,879	-0.026 (-0.363;0.311)
Model 5	2,705	-0.068 (-0.363;0.226)	2,619	-0.074 (-0.365;0.217)	1,688	0.144 (-0.207;0.496)
Model 6	2,705	-0.085 (-0.379;0.21)	2,619	-0.09 (-0.38;0.201)	1,685	0.079 (-0.284;0.442)
High density lipoprotein						
Crude	2,705	1.241 (0.647;1.835)	2,679	1.204 (0.619;1.79)	2,679	1.204 (0.619;1.79)
Model 1	2,705	0.905 (0.266;1.544)	2,619	0.953 (0.315;1.592)	2,619	0.953 (0.315;1.592)
Model 2	2,705	0.988 (0.35;1.626)	2,619	1.035 (0.397;1.672)	2,619	1.035 (0.397;1.672)
Model 3	2,705	0.87 (0.227;1.512)	2,619	0.931 (0.288;1.574)	1,920	1.023 (0.293;1.754)
Model 4	2,705	0.84 (0.197;1.483)	2,619	0.901 (0.258;1.545)	1,879	1.166 (0.427;1.905)
Model 5	2,705	0.851 (0.208;1.494)	2,619	0.913 (0.27;1.556)	1,688	1.117 (0.339;1.894)
Model 6	2,705	0.843 (0.2;1.486)	2,619	0.907 (0.264;1.55)	1,685	1.017 (0.236;1.798)

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Table B.17 – continued from previous page

	Imputed		Limited imputed		Complete case	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
Glucose concentration						
Crude	2,705	0.082 (-0.245;0.408)	2,663	0.086 (-0.237;0.409)	2,663	0.086 (-0.237;0.409)
Model 1	2,705	0.085 (-0.26;0.43)	2,619	0.072 (-0.27;0.415)	2,619	0.072 (-0.27;0.415)
Model 2	2,705	0.044 (-0.301;0.389)	2,619	0.032 (-0.31;0.374)	2,619	0.032 (-0.31;0.374)
Model 3	2,705	0.048 (-0.297;0.393)	2,619	0.035 (-0.308;0.377)	1,920	-0.004 (-0.367;0.359)
Model 4	2,705	0.03 (-0.315;0.375)	2,619	0.018 (-0.324;0.36)	1,879	-0.019 (-0.382;0.345)
Model 5	2,705	0.059 (-0.286;0.404)	2,619	0.047 (-0.295;0.389)	1,688	0.051 (-0.317;0.418)
Model 6	2,705	0.031 (-0.314;0.376)	2,619	0.018 (-0.324;0.359)	1,685	0.04 (-0.434;0.515)
Insulin concentration						
Crude	2,705	0.005 (-0.041;0.05)	2,654	0.006 (-0.039;0.051)	2,654	0.006 (-0.039;0.051)
Model 1	2,705	0.061 (0.004;0.118)	2,619	0.059 (0.003;0.115)	2,619	0.059 (0.003;0.115)
Model 2	2,705	0.056 (0;0.113)	2,619	0.053 (-0.002;0.109)	2,619	0.053 (-0.002;0.109)
Model 3	2,705	0.054 (-0.002;0.111)	2,619	0.052 (-0.004;0.108)	1,920	0.067 (0.006;0.127)
Model 4	2,705	0.059 (0.002;0.116)	2,619	0.057 (0.001;0.113)	1,879	0.085 (0.022;0.147)
Model 5	2,705	0.055 (-0.002;0.111)	2,619	0.053 (-0.003;0.109)	1,688	0.085 (0.02;0.149)
Model 6	2,705	0.058 (0.001;0.114)	2,619	0.056 (0;0.112)	1,685	0.055 (-0.009;0.119)
Systolic blood pressure						
Crude	2,705	0.018 (0;0.035)	2,702	0.018 (0;0.035)	2,702	0.018 (0;0.035)
Model 1	2,705	0.026 (0.003;0.049)	2,619	0.018 (-0.006;0.041)	2,619	0.018 (-0.006;0.041)
Model 2	2,705	0.027 (0.004;0.05)	2,619	0.019 (-0.004;0.042)	2,619	0.019 (-0.004;0.042)
Model 3	2,705	0.029 (0.006;0.053)	2,619	0.021 (-0.003;0.045)	1,920	0.024 (-0.003;0.051)
Model 4	2,705	0.032 (0.008;0.055)	2,619	0.023 (0;0.047)	1,879	0.025 (-0.002;0.052)
Model 5	2,705	0.03 (0.007;0.054)	2,619	0.022 (-0.002;0.046)	1,688	0.027 (-0.002;0.055)
Model 6	2,705	0.026 (0.002;0.049)	2,619	0.017 (-0.007;0.041)	1,685	0.021 (-0.008;0.049)
Diastolic blood pressure						
Crude	2,705	0.008 (-0.013;0.029)	2,695	0.006 (-0.014;0.027)	2,695	0.006 (-0.014;0.027)
Model 1	2,705	0 (-0.027;0.027)	2,619	0.002 (-0.025;0.029)	2,619	0.002 (-0.025;0.029)
Model 2	2,705	0 (-0.028;0.027)	2,619	0.002 (-0.026;0.029)	2,619	0.002 (-0.026;0.029)
Model 3	2,705	-0.005 (-0.033;0.022)	2,619	-0.003 (-0.031;0.024)	1,920	-0.007 (-0.039;0.024)
Model 4	2,705	-0.007 (-0.035;0.02)	2,619	-0.005 (-0.033;0.022)	1,879	-0.01 (-0.042;0.022)
Model 5	2,705	-0.006 (-0.033;0.022)	2,619	-0.003 (-0.031;0.024)	1,688	-0.008 (-0.041;0.022)
Model 6	2,705	-0.002 (-0.03;0.025)	2,619	0 (-0.027;0.028)	1,685	0 (-0.034;0.034)

Table B.18: Comparision of results in the complete dataset, using a more limited imputation strategy and with complete case analyses for the association of FVC (mL) with C-reactive protein (mg/L) and white blood cell count (10^9 cells/L) in men and women. Model 1: Adjusted for other inflammatory marker (i.e. either CRP or WBC); Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socio-economic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 5: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

Men						
	Imputed		**Limited imputed**		**Complete case**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
C-reactive protein						
Crude	2,748	-20.4 (-29.3;-11.4)	2,685	-20.4 (-29.2;-11.5)	2,685	-20.4 (-29.2;-11.5)
Model 1	2,748	-16.9 (-26.1;-7.7)	2,656	-16.8 (-25.9;-7.7)	2,656	-16.8 (-25.9;-7.7)
Model 2	2,748	-13.1 (-20.6;-5.6)	2,656	-13.0 (-20.4;-5.5)	2,656	-13.0 (-20.4;-5.5)
Model 3	2,748	-13.1 (-20.6;-5.6)	2,656	-13.0 (-20.5;-5.6)	2,060	-13.1 (-21.3;-4.9)
Model 4	2,748	-13.5 (-21;-6.0)	2,656	-13.4 (-20.8;-6.0)	1,794	-11.0 (-19.7;-2.3)
Model 5	2,748	-12.7 (-20.3;-5.2)	2,656	-12.7 (-20.1;-5.2)	1,789	-13.7 (-22.6;-4.8)
White blood cell count						
Crude	2,748	-35.7 (-52.8;-18.6)	2,683	-36.4 (-53.5;-19.2)	2,656	-36.4 (-53.5;-19.2)
Model 1	2,748	-28.0 (-45.6;-10.4)	2,656	-28.7 (-46.3;-11.0)	2,656	-28.7 (-46.3;-11.0)
Model 2	2,748	-19.1 (-33.4;-4.7)	2,656	-19.4 (-33.8;-5.0)	2,656	-19.4 (-33.8;-5.0)
Model 3	2,748	-17.7 (-33;-2.5)	2,656	-16.1 (-31.4;-0.7)	2,060	-4.5 (-21.9;12.9)
Model 4	2,748	-16.3 (-31.5;-1.1)	2,656	-14.6 (-29.9;0.7)	1,794	-5.4 (-24;13.1)
Model 5	2,748	-18.4 (-33.7;-3.1)	2,656	-16.7 (-32.1;-1.4)	1,789	-5.9 (-24.5;12.6)
Women						
	Imputed		**Limited imputed**		**Complete case**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
C-reactive protein						
Crude	2,705	-17.2 (-22.4;-12.1)	2,638	-17.7 (-22.9;-12.6)	2,638	-17.7 (-22.9;-12.6)
Model 1	2,705	-15.0 (-20.4;-9.7)	2,618	-15.4 (-20.7;-10.0)	2,618	-15.4 (-20.7;-10.0)
Model 2	2,705	-12.2 (-16.7;-7.8)	2,618	-12.7 (-17.1;-8.2)	2,618	-12.7 (-17.1;-8.2)
Model 3	2,705	-12.2 (-16.6-7.7)	2,618	-12.6 (-17;-8.1)	1,914	-14.9 (-20.1;-9.6)
Model 4	2,705	-12.1 (-16.6;-7.7)	2,618	-12.5 (-16.9;-8.1)	1,682	-15.1 (-20.8;-9.5)
Model 5	2,705	-12.0 (-16.4;-7.5)	2,618	-12.4 (-16.8;-7.9)	1,677	-15.3 (-20.8;-9.8)
White blood cell count						
Crude	2,705	-30.2 (-43.2;-17.2)	2,658	-31.3 (-44.3;-18.3)	2,658	-31.3 (-44.3;-18.3)
Model 1	2,705	-19.2 (-32.8;-5.7)	2,618	-21.7 (-35.3;-8.0)	2,618	-21.7 (-35.3;-8.0)
Model 2	2,705	-6.1 (-17.3;5.1)	2,618	-7.2 (-18.4;4.1)	2,618	-7.2 (-18.4;4.1)
Model 3	2,705	-4.2 (-15.8;7.5)	2,618	-5.5 (-17.2;6.2)	1,914	-2.5 (-15.9;10.9)
Model 4	2,705	-3.3 (-15;8.3)	2,618	-4.8 (-16.4;6.9)	1,682	-2.8 (-17;11.5)
Model 5	2,705	-4.4 (-16.1;7.3)	2,618	-5.8 (-17.6;5.9)	1,677	0.8 (-13.5;15.1)

Table B.19: Comparision of results in the complete dataset, using a more limited imputation strategy and with complete case analyses for the association of FEV_1/FVC (%) with C-reactive protein (mg/L) and white blood cell count (10^9 cells/L) in men and women. Model 1: Adjusted for other inflammatory marker (i.e. either CRP or WBC); Model 2: Model 1 further adjusted for adult height; Model 3: Model 2 further adjusted adult socioeconomic status, pack-years and ever smoking status; Model 4: Model 3 further adjusted for birth weight and weight gain in the first year of life; Model 5: Model 3 further adjusted for maternal factors: parity, age at delivery, height and weight prior to pregnancy, smoking in pregnancy and socio-economic status during pregnancy.

Men						
	Imputed		**Limited imputed**		**Complete case**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
C-reactive protein						
Crude	2,748	0.02 (-0.05;0.08)	2,685	0.02 (-0.05;0.09)	2,685	0.02 (-0.05;0.09)
Model 1	2,748	0.05 (-0.02;0.12)	2,656	0.05 (-0.02;0.12)	2,656	0.05 (-0.02;0.12)
Model 2	2,748	0.05 (-0.02;0.11)	2,656	0.04 (-0.02;0.11)	2,656	0.04 (-0.02;0.11)
Model 3	2,748	0.04 (-0.02;0.11)	2,656	0.04 (-0.02;0.11)	2,060	0.06 (-0.01;0.14)
Model 4	2,748	0.05 (-0.02;0.11)	2,656	0.05 (-0.02;0.11)	1,794	0.05 (-0.03;0.13)
Model 5	2,748	0.04 (-0.03;0.11)	2,656	0.04 (-0.03;0.11)	1,789	0.08 (0;0.16)
White blood cell count						
Crude	2,748	-0.25 (-0.38;-0.12)	2,683	-0.25 (-0.38;-0.12)	2,683	-0.25 (-0.38;-0.12)
Model 1	2,748	-0.28 (-0.41;-0.14)	2,656	-0.27 (-0.4;-0.14)	2,656	-0.27 (-0.4;-0.14)
Model 2	2,748	-0.29 (-0.42;-0.16)	2,656	-0.29 (-0.42;-0.15)	2,656	-0.29 (-0.42;-0.15)
Model 3	2,748	-0.21 (-0.35;-0.07)	2,656	-0.21 (-0.35;-0.07)	2,060	-0.19 (-0.35;-0.03)
Model 4	2,748	-0.21 (-0.35;-0.07)	2,656	-0.21 (-0.35;-0.07)	1,794	-0.19 (-0.36;-0.02)
Model 5	2,748	-0.2 (-0.34;-0.06)	2,656	-0.2 (-0.34;-0.06)	1,789	-0.24 (-0.41;-0.08)
Women						
	Imputed		**Limited imputed**		**Complete case**	
	N	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**	**N**	**Beta (95 % CI)**
C-reactive protein						
Crude	2,705	-0.04 (-0.09;0.02)	2,638	-0.04 (-0.09;0.02)	2,638	-0.04 (-0.09;0.02)
Model 1	2,705	-0.01 (-0.07;0.04)	2,618	-0.02 (-0.07;0.04)	2,618	-0.02 (-0.07;0.04)
Model 2	2,705	-0.02 (-0.08;0.04)	2,618	-0.02 (-0.08;0.04)	2,618	-0.02 (-0.08;0.04)
Model 3	2,705	-0.02 (-0.08;0.03)	2,618	-0.02 (-0.08;0.03)	1,914	-0.02 (-0.09;0.04)
Model 4	2,705	-0.02 (-0.08;0.04)	2,618	-0.02 (-0.08;0.03)	1,682	0 (-0.07;0.07)
Model 5	2,705	-0.02 (-0.08;0.04)	2,618	-0.02 (-0.08;0.03)	1,677	0 (-0.07;0.07)
White blood cell count						
Crude	2,705	-0.23 (-0.37;-0.1)	2,658	-0.22 (-0.36;-0.09)	2,658	-0.22 (-0.36;-0.09)
Model 1	2,705	-0.22 (-0.37;-0.08)	2,618	-0.2 (-0.34;-0.05)	2,618	-0.02 (-0.34;-0.05)
Model 2	2,705	-0.24 (-0.39;-0.1)	2,618	-0.22 (-0.36;-0.08)	2,618	-0.22 (-0.36;-0.08)
Model 3	2,705	-0.18 (-0.33;-0.03)	2,618	-0.15 (-0.3;0)	1,914	-0.14 (-0.3;0.03)
Model 4	2,705	-0.18 (-0.33;-0.03)	2,618	-0.15 (-0.3;0)	1,682	-0.18 (-0.35;0)
Model 5	2,705	-0.16 (-0.31;-0.01)	2,618	-0.13 (-0.28;0.02)	1,677	-0.11 (-0.29;0.07)

APPENDIX C

THE DIVERSITY IN ETHNICITY, LUNG FUNCTION AND BIRTH WEIGHT AMONG YOUNG ADULTS (DELBYA) STUDY: A PILOT STUDY

C.1 Adverts and website

DELBYA

Diversity in **E**thnicity, **L**ung function and **B**irth weight in **Y**oung **A**dults

STUDY

Are you interested in learning how healthy your lungs are and helping medical research?



We are looking for **healthy 18-23 year old VOLUNTEERS** for a study of Lung Function at Imperial College London.

We will give you a contribution of £15 for the 1 hour that your participation takes.

If you were born in the UK and you define yourself as White or South Asian ethnicity, please get in touch through the following website:
www1.imperial.ac.uk/delbyastudy

For questions you can contact DELBYA Study Coordinator on:
delbya.study@imperial.ac.uk or 0207 594 7592

The study has the approval of the Imperial College Medical Education Ethics Committee (Ref: MEEC1314-07). Version 3.1 – 29 Sept 2014

Figure C.1: *Study advert*

Royal Brompton & Harefield NHS
NHS Foundation Trust

DELBYA
Diversity in Ethnicity, Lung function and Birth weight in Young Adults
STUDY

Imperial College London

The study has the approval of the Imperial College Medical Education Ethics Committee (Ref: MEEC1314-07)
Version 3.1 – 29 Sept 2014

Are you interested in learning how healthy your lungs are and helping medical research?



We are looking for **healthy 18-23 year old VOLUNTEERS** for a study of Lung Function at Imperial College London.

We will give you a contribution of £15 for the 1 hour that your participation takes.

If you were born in the UK and you define yourself as White or South Asian ethnicity, please get in touch through the following website:
www1.imperial.ac.uk/delbyastudy

For questions you can contact the DELBYA Study Coordinator on:
delbya.study@imperial.ac.uk or 0207 594 7592

DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T:0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
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DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952
DELBYA Study E:delbya.study@ic.ac.uk T: 0207 594 7952

Figure C.2: *Study advert with tear-off slips*

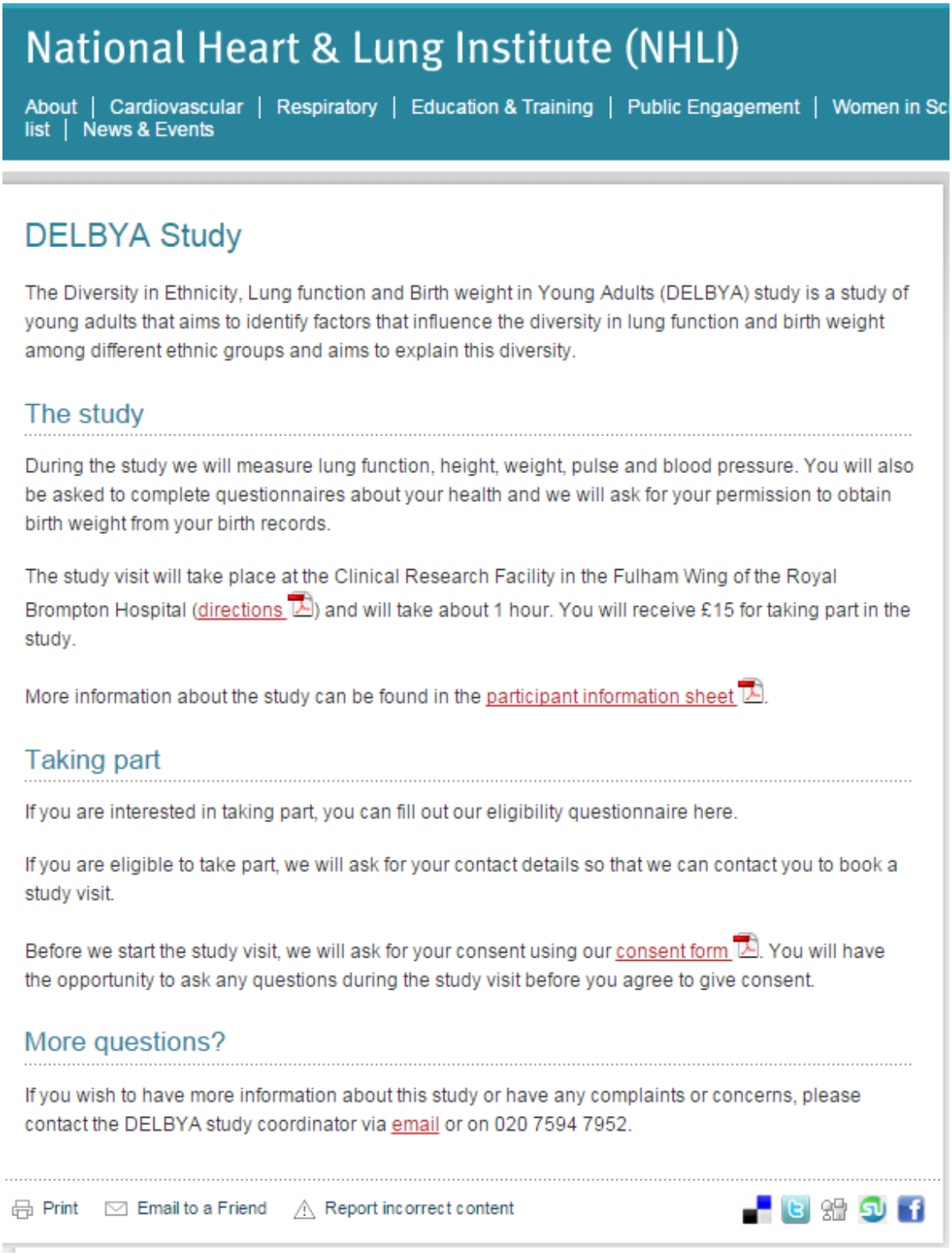


Figure C.3: *Screenshot of study website*

C.2 Questionnaires

This section contains the following questionnaires:

1. An online registration questionnaire prior to the study visit, which assessed the inclusion/exclusion criteria and obtained participants' contact details to book the study visit

2. A safety questionnaire during the study visit, which reassessed the exclusion criteria

3. A measurement questionnaire during the study visit, which was used to record the results from the anthropometric and cardiovascular measurements and the compliance of, or adverse events to, spirometry

4. A core questionnaire during the study visit, which recorded information on respiratory symptoms, smoking, parental and grandparental socio-economic status and educational attainment, and parental and grandparental upbringing and place of birth

5. An online feedback questionnaire after the study visit, which collected feedback on the study conduct and procedures

ELIGIBILITY QUESTIONNAIRE

(STAGE 1)

Instructions

The inclusion questionnaire will be designed using Qualtrics, which is an online survey system offered by Imperial College London. The inclusion questionnaire will be completed online by the participants and will be available to the participants via the website.

*If participants answer **Yes** to Questions 1.1 and 1.2, if they are between 18 and 23 years of age and if they consider themselves as White or South Asian ethnicity (i.e. English/Welsh/Scottish/Northern Irish/British, Irish, Gypsy or Irish Traveller, Any other White background, White and Asian, Indian, Pakistani, Bangladeshi, Any other Asian background) and answer **Yes** to Question 1.5 then they are eligible to participate in the study and the safety questions will be asked (Questions 2.1 to 2.7). If participants are eligible and it is safe for them to participate then the contact details (Questions 3.1 to 3.5) will be asked. Eligible participants will be informed that they will be contacted by email or phone to book a study visit.*

No safety questions will be asked or contact details will be collected from the participants if they are not eligible to participate. The obtained information would not allow us to track the non-eligible participant and the answers to the questions do not contain any sensitive information.

1. Demographic information

1.1.Are you a student at Imperial College London?

Yes ❑
No ❑

1.2.Are you born in the United Kingdom (England, Scotland, Wales, Northern Ireland)?

Yes ❑
No ❑

1.3. What is your age range?

<18yrs ❑
18-23 ❑
24-27 ❑
>27yrs ❑

1.4. To which of the ethnic group do you consider that you belong?
(Choose one option that best describes your ethnic group or background)

White

English / Welsh / Scottish / Northern Irish / British ❑
Irish ❑
Gypsy or Irish Traveller ❑
Any other White background, please describe: ❑

_____

Mixed / Multiple ethnic groups

White and Black Caribbean ❑
White and Black African ❑
White and Asian ❑
Any other Mixed / Multiple ethnic background, please describe: ❑

_____

Asian / Asian British

Indian ❑
Pakistani ❑
Bangladeshi ❑
Chinese ❑
Any other Asian background, please describe: ❑

_____

Black / African / Caribbean / Black British

Caribbean ❑
African ❑
Any other Black / African / Caribbean background, please describe: ❑

_____

Other ethnic group

Arab ❑
Any other ethnic group, please describe: ❑

_____

1.5.Were at least three of your grandparents born in United Kingdom, Western-Europe, South-Asia (Pakistan, India, Nepal, Bangladesh, Bhutan, Sri Lanka) or East-Africa (Kenya, Tanzania, Uganda)?

Yes ❑
No ❑

2. Safety Questions

2.1.In the past three months have you had any surgery on your chest or abdomen? Yes ❑ No ❑

2.2. Have you had a heart attack within the past three months? Yes❑ No ❑

2.3.Do you have a detached retina or have you had eye surgery within the past three months? Yes ❑ No ❑

2.4.Have you been hospitalized for any other heart problem within the past month? Yes ❑ No ❑

2.5.Are you in the last trimester of pregnancy? Yes ❑ No ❑

2.6.Are you currently taking medication for tuberculosis? Yes ❑ No ❑

2.7.Have you had a pneumothorax within the past three months? Yes ❑ No ❑

3. Contact details

3.1. What is your Surname? _____

3.2. What is your Name? _____

3.3. What is your date of birth?

____ ____/____ ____/____ ____ ____ ____
d d m m y y y y

3.4. What is your Phone number? _____

3.5. What is your Imperial College London email address? _____

3.6. When would it suit you to have the study visit?

	Morning (8-11am)	Lunch time (11am-2pm)	Afternoon (2-5pm)
Monday	❑	❑	❑
Tuesday	❑	❑	❑
Wednesday	❑	❑	❑
Thursday	❑	❑	❑
Friday	❑	❑	❑

ID _____ _____ _____ _____ _____ _____

Date:____ ____/____ ____/_____ _____ _____ _____
d d m m y y y y

ELIGIBILITY QUESTIONAIRE (STAGE 2)

Instructions
*The Eligibility questionnaire (stage 2) contains questions which are necessary to assess whether it is safe for the participant to perform spirometry. If any of the Questions 1.1 through 1.9 is **Yes** then it is not safe for the participant to perform the lung function testing. Therefore, the participant will be excluded from the study.*

Safety Questions

1. I just want to check the safety questions that you answered when you volunteered and check that nothing has changed.

1.1. Have you had any surgery on your chest or abdomen?
Yes ❑
No ❑

1.2. Have you had a heart attack within the past three months?
Yes ❑
No ❑

1.3. Do you have a detached retina or have you had eye surgery within the past three months?
Yes ❑
No ❑

1.4. Have you been hospitalized for any other heart problem within the past month?
Yes ❑
No ❑

1.5. Are you in the last trimester of pregnancy?
Yes ❑
No ❑

1.6. Does the participant have a resting pulse of greater than 120 beats per minute?
Yes ❑
No ❑

1.7. Are you currently taking medication for tuberculosis?
Yes ❑
No ❑

1.8. Have you had a pneumothorax within the past three months?
Yes ❑
No ❑

1.9. *Is there some other reason why this participant should not perform the spirometry maneuver?* If ***yes,*** record reason.
Yes ❑
No ❑

_____
_____

If the answer to any of Questions 1.2. through 1.9. is "Yes", then the participant will be excluded from the study.

2. Researcher ID ____ ____ ___

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

MEASUREMENT QUESTIONNAIRE

Instructions
The Measurements questionnaire contains questions related to respiratory disease and/or symptoms and will record the results of the anthropometric and cardiovascular measurement and lung function testing.

1. Demography

1.1. What is the participant's sex?

Male ❑
Female ❑

2. Respiratory infection

2.1 Have you had a respiratory infection (cold) in the last three weeks? Yes ❑
No ❑

3. Medications for breathing

3.1. Have you taken any medications for breathing in the last 24 hours? Yes ❑
No ❑

*If **yes**, record name/type of medication(s used.*

_____

_____

If Question 3.1 is yes and the medication used includes any of the types below, go to question 3.2. If no, go to question 4

TYPE OF MEDICATION	EXAMPLES	
Short-acting beta-2 agonist	albuterol, salbutamol	6 hours prior to clinic visit
Anticholinergic inhaler	Atrovent, ipratropium	6 hours prior to clinic visit
Long-acting beta-2 agonist (including combination preparations that contain a LABA)	Serevent, Advair, formoterol, Symbicort	12 hours prior to clinic visit
Oral beta-2 agonist	Albuterol	12 hours prior to clinic visit
Oral theophylline	Theodur	12-24 hours prior to clinic visit, depending upon preparation
Long-acting anticholinergic	Spiriva, tiotropium	24 hours prior to clinic visit

3.2. Did you use a short acting beta agonist or anticholinergic inhaler, either alone or in combination with some other product, in the last six hours? Yes ❑
No ❑

3.3 Did you use a long acting beta agonist or oral beta 2 agonist, either alone or in combination with some other product, in the last 12 hours? Yes ❑
No ❑

3.4. Did you use an oral theophyllin/ long acting anticholinergic, either alone or in combination with some other product, in the last 24 hours? Yes ❑
No ❑

4. Smoking

4.1. When did you last smoke? i) ____ ____ ____hrs ago
ii) ____ ____days ago

Enter 999 if non smoker or ex smoker (has not smoked in the last month)

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

5. Cardiovascular measurements

5.1.A. Pulse	___ ____ ____ **bpm**
5.1.B. Pulse	___ ____ ____ **bpm**
5.1.C. Pulse	___ ____ ____ **bpm**
5.2.A. Blood pressure (Syst/Dia)	___ ___ ___/___ ___ __ **mm Hg**
5.2.B. Blood pressure (Syst/Dia)	___ ___ ___/___ ___ __ **mm Hg**
5.2.C. Blood pressure (Syst/Dia)	___ ___ ___/___ ___ __ **mm Hg**

6. Anthropometric measurements

6.1. Height	____ ____ ____**cm**
6.2. Weight	____ ____ ____.____**kg**
6.3.A Long bone length (ulna)	____ ____ ____**cm**
6.3.B Long bone length (ulna)	____ ____ ____**cm**
6.4.A Long bone length (demispan)	____ ____ ____**cm**
6.4.B Long bone length (demispan)	____ ____ ____**cm**

7. Measurements Compliance – Prebronchodilator Spirometry

7.1. Acceptable pre-bronchodilator test completed?
Yes ❑
No ❑

7.2. Unable to obtain satisfactory spirometry (check one)?
The participant did not understand the instructions ❑
The participant was unable to physically cooperate ❑
refused ❑
not applicable ❑

7.3. Were any adverse events related to the spirometry maneuver observed by the evaluator?
Yes ❑
No ❑

If yes, please describe the event
_____
_____

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

7.4. If the participant had a condition that would affect the result of their spirometry test (e.g., kyphosis, missing limbs, etc) note that condition here

_____
_____

8. Measurement Compliance - Bronchodilator

8.1. Bronchodilator administered?

Yes ❑
No ❑

9. Measurements Compliance – Postbronchodilator Spirometry

9.1. Acceptable post-bronchodilator test completed?

Yes ❑
No ❑

9.2. Unable to obtain satisfactory spirometry (check one)?

The participant did not understand the instructions ❑
The participant was unable to physically cooperate ❑
refused ❑
not applicable ❑

9.3. Were any adverse events related to the spirometry maneuver observed by the evaluator?

Yes ❑
No ❑

If yes, please describe the event

_____
_____

9.4. If the participant had a condition that would affect the result of their spirometry test (e.g., kyphosis, missing limbs, etc) note that condition here

_____
_____

10. Cardiovascular measurements before completing study visit

10.1.A. Pulse ___ ____ ____ **bpm**

10.1.B. Pulse ___ ____ ____ **bpm**

10.2.A. Blood pressure (Syst/Dia) ___ ___ ___/___ ___ __ **mm Hg**

10.2.B. Blood pressure (Syst/Dia) ___ ___ ___/___ ___ __ **mm Hg**

11. Researcher ID

____ ____ ____ ____

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____

d d m m y y y y

CORE QUESTIONNAIRE

PART A – Respiratory Symptoms, disorders and comorbidities

These questions pertain mainly to your chest. Please answer yes or no if possible. If you are in doubt about whether your answer is yes or no, please answer no.

Cough

1. Do you usually cough when you don't have a cold? Yes ❑
*[If **yes**, continue with Question 1A; If **no**, skip to Question 2]* No ❑

1A. Are there months in which you cough on most days? Yes ❑
*[If **yes**, ask both Questions 1B & 1C; If **no**, skip to Question 1]* No ❑

1B. Do you cough on most days for as much as three months each year? Yes ❑
No ❑

1C. For how many years have you had this cough? Less than 2 years ❑
2-5 years ❑
More than 5 years ❑

Phlegm

2. Do you usually bring up phlegm from your chest, or do you usually have phlegm in your chest that is difficult to bring up when you don't have a cold? Yes ❑
No ❑
*[If **yes**, continue with Question 2A; If **no**, skip to Question 3]*

2A. Are there months in which you have this phlegm on most days? Yes ❑
*[If **yes**, ask both Questions 2B & 2C; If **no**, skip to Question 3]* No ❑

2B. Do you bring up this phlegm on most days for as much as three months each year? Yes ❑
No ❑

2C. For how many years have you had this phlegm? Less than 2 years ❑
2-5 years ❑
More than 5 years ❑

Wheezing/Whistling

3. Have you had wheezing or whistling in your chest at any time in the last 12 months? Yes ❑
No ❑
*[If **yes**, ask both Questions 3A & 3B; If **no**, skip to Question 4]*

3A. In the last 12 months, have you had this wheezing or whistling only when you have a cold? Yes ❑
No ❑

3B. In the last 12 months, have you ever had an attack of wheezing or whistling that has made you feel short of breath? Yes ❑
No ❑

ID _____ _____ _____ _____ _____ _____
Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

Breathlessness

4. Are you unable to walk due to a condition other than shortness of breath? Yes ❑ No ❑
[*If **yes** to Question 4, please describe this condition on the line below and then skip to Question 5. If **no*** or unsure*, go directly to Question 20.]*

Nature of condition(s): _____

5. Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill? Yes ❑ No ❑
*[If **yes**, ask Question 5A through 5D; If **no**, skip to Question 6]*

5A. Do you have to walk slower than people of your age on level ground because of shortness of breath? Yes ❑ No ❑ Does not apply ❑

5B. Do you ever have to stop for breath when walking at your own pace on level ground? Yes ❑ No ❑ Does not apply ❑

5C. Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on level ground? Yes ❑ No ❑ Does not apply ❑

5D. Are you too short of breath to leave the house or short of breath on dressing or undressing? Yes ❑ No ❑ Does not apply ❑

Diagnosed lung disease

6. Has a doctor or other health care provider ever told you that you have asthma, asthmatic bronchitis or allergic bronchitis? Yes ❑ No ❑
*[If **yes**, ask Question 6A. If **no**, skip to Question 7]*

6A. Do you still have asthma, asthmatic bronchitis or allergic bronchitis? Yes ❑ No ❑

7. Has a doctor or other health care provider ever told you that you have chronic bronchitis? Yes ❑ No ❑
*[If **yes**, ask Question 7A. If **no**, skip to Question 8]*
7A. Do you still have chronic bronchitis? Yes ❑ No ❑

Exacerbations

8. Have you ever had a period when you had breathing problems that got so bad that they interfered with your usual daily activities or caused you to miss work? *[If **yes**, ask Question 8A. If **no**, skip to Question 9]* Yes ❑ No ❑

8A. How many such episodes have you had in the past 12 months?
[If 25A >0, ask Questions 8B and 8C, else skip to Question 9] ____ ____ episodes

8B. For how many of these episodes did you need to see a doctor or other health care provider in the

ID _____ _____ _____ _____ _____ _____
Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

past 12 months? ____ ____ episodes

8C. For how many of these episodes were you hospitalized overnight in the past 12 months?
[If 8C >0, ask Question 8C1, else skip to Question 9] _____ _____ episodes

8C1. All together, for how many total days were you hospitalized overnight for breathing problems in the past 12 months? ____ ____ ____ days

Comorbidities

9. Has a doctor or other health care provide ever told you that you had:

	Yes	No
A. Hypertension	❑	❑
B. Diabetes	❑	❑
C. Tuberculosis	❑	❑

*[If **yes** to 9C, then ask 9C1; otherwise, skip to Question 10]*

9C1. Are you currently taking medicine for tuberculosis? Yes ❑
*[If **no** to 9C1, then ask 9C2; otherwise, skip to Question 10]* No ❑

9C2. Have you ever taken medicine for tuberculosis? Yes ❑
No ❑

10. Have you ever had an operation on your chest in which a part of your lung was removed?
Yes ❑
No ❑

11. Were you hospitalized as a child for breathing problems <u>prior to</u> the age of 10?
Yes ❑
No ❑
Don't Know ❑

12. Has a doctor or other health care professional told your father, mother, sister or brother that they had a diagnosis of emphysema, chronic bronchitis or COPD? Yes ❑
No ❑

ID _____ _____ _____ _____ _____ _____
Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

PART B - Quality of life

13. In general, would you say your health is: *(Check one)*

Excellent	❑
Very good	❑
Good	❑
Fair	❑
Poor	❑

14. The following questions are about activities you might do during a typical day. Does ***your health now limit*** you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	Not limited at all
14a. ***Moderate activities,*** such as moving a table, pushing a vacuum cleaner, bowling or playing golf	❑	❑	❑
14b.Climbing **several** flights of stairs	❑	❑	❑

15. **During *the past 4 weeks*,** have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	No, none of the time	Yes, a little of the time	Yes, some of the time	Yes, most of the time	Yes, all the time
15a. Accomplished **less** than you would like	❑	❑	❑	❑	❑
15b. Were limited in the **kind** of work or other activities	❑	❑	❑	❑	❑

16. **During *the past 4 weeks***, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	No, none of the time	Yes, a little of the time	Yes, some of the time	Yes, most of the time	Yes, all the time
16a. **Accomplished less** than you would like	❑	❑	❑	❑	❑
16b. Didn't do work or other activities as **carefully** as usually	❑	❑	❑	❑	❑

17. **During the *past 4 weeks*,** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all	❑
Slightly	❑
Moderately	❑
Quite a bit	❑
Extremely	❑

ID _____ _____ _____ _____ _____ _____
Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

18. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
18a.Have you felt calm and peaceful?	❑	❑	❑	❑	❑	❑
18b.Did you have a lot of energy?	❑	❑	❑	❑	❑	❑
18c.Have you felt downhearted and blue?	❑	❑	❑	❑	❑	❑

19. **During the *past 4 weeks***, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

All the time ❑
Most of the time ❑
Some of the time ❑
A little of the time ❑
None of the time ❑

20. Now we'd like to ask you some questions about how your health may have changed. Compared to one year ago,

	Much better	Slightly better	About the same	Slightly worse	Much worse
20a.How would you rate your **physical health** in general now?	❑	❑	❑	❑	❑
20b.How would you rate your **emotional problems** (such as feeling anxious, depressed or irritable) **now** ?	❑	❑	❑	❑	❑

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

PART C - Management Section

Now I am going to ask you about medicines that you may be taking to help with your breathing. I want to know about medicines that you take on a regular basis and medicines that you may take only for the relief of symptoms. I would like you to tell me each medicine that you take, what form do you take it in, and how often you take it each month.

21. In the past 12 months, have you taken any medications for your breathing (including medications for nasal congestion)? Yes ❑

If participant does not take any medications to help their breathing, skip to Question 27. No ❑

21.A. Medication Name (not entered)				
21.B. Medication Code	__ __ __	__ __ __	__ __ __	__ __ __
21.C. Formulation	Pills ❑ Inhaler ❑ Nebulizer ❑ Liquid ❑ Suppository ❑ Injection ❑ Other ❑	Pills ❑ Inhaler ❑ Nebulizer ❑ Liquid ❑ Suppository ❑ Injection ❑ Other ❑	Pills ❑ Inhaler ❑ Nebulizer ❑ Liquid ❑ Suppository ❑ Injection ❑ Other ❑	Pills ❑ Inhaler ❑ Nebulizer ❑ Liquid ❑ Suppository ❑ Injection ❑ Other ❑
21.D. Is the medicine taken on most days or just when you have symptoms or both? *(If 'most day ask Q26E if both ask 'both' 26E and Q26F)*	Most days ❑ Symptoms ❑ Both ❑ Other ❑	Most days ❑ Symptoms ❑ Both ❑ Other ❑	Most days ❑ Symptoms ❑ Both ❑ Other ❑	Most days ❑ Symptoms ❑ Both ❑ Other ❑
21.E. When you are taking the medication how many days a week do you take it?	__ days/week	__ days/week	__ days/week	__ days/week
21.F. When you are taking the medication, how many months in the past 12 months have you taken it?	0-3 ❑ 4-6 ❑ 7-9 ❑ 10-12 ❑	0-3 ❑ 4-6 ❑ 7-9 ❑ 10-12 ❑	0-3 ❑ 4-6 ❑ 7-9 ❑ 10-12 ❑	0-3 ❑ 4-6 ❑ 7-9 ❑ 10-12 ❑

22. Please tell me about any other products that you take or things you do to help your breathing that you have not already told me about.

Medicine or Activity	**Code**
	___ ___ ___
	___ ___ ___
	___ ___ ___
	___ ___ ___

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____

d d m m y y y y

PART D - Smoking

Now I am going to ask you about smoking. First I will ask about cigarettes, including hand rolled cigarettes, and then I will ask about other items that are smoked.

23.1. Have you ever smoked **cigarettes**? Yes ❑ No ❑

("Yes," means more than 20 packs of cigarettes in a lifetime or more than 1 cigarette each day for a year)
*[if **yes**, ask questions 23.2 through 23.5; otherwise, skip to Question 24.1)*

23.2. How old were you when you first started regular cigarette smoking? ____ _____ years old

23.3. If you have stopped smoking, how old were you when you last stopped? _____ years old
(If the participant has not stopped smoking, record as code '999'.)

23.4. On average over the entire time that you smoke(d), about how many cigarettes per day/per week do (did) you smoke? i)____ ____ ____ cigarettes/day
ii)___ ____ ____ cigarettes/week

23.5. On average over the entire time that you smoke(d), do (did) you primarily smoke manufactured or hand-rolled cigarettes? Manufactured ❑ Hand-rolled ❑

24.1. Have you ever smoked a **water pipe**? Yes ❑ No ❑

("Yes," means more than 1 water pipe per week for one year at any time in your life)
*[if **yes**, ask questions 24.2 through 24.4; otherwise, skip to Question 25.1)*

24.2. How old were you when you first started regular water pipe smoking? ____ _____ years old

24.3. If you have stopped smoking, how old were you when you last stopped? _____ ____ years old
(If the participant has not stopped smoking, record as code '999'.)

24.4. On average over the entire time that you smoke(d), about how many water pipe per day/per week do (did) you smoke? i)___ ____ ____ water pipes /day
ii)___ ____ ____water pipes /week

Second hand smoke exposure

25.1. Not counting yourself, how many people in your household smoke regularly? ___ ___

25.2. Do people smoke regularly in the room where you work? Yes ❑ No ❑ Don't work ❑

25.3. How many hours per day, are you exposed to other people's tobacco smoke in the following locations?
25.3.1. At home __ __hours
25.3.2. In workplace __ __hours
25.3.3. Bars, restaurants, cinemas or similar social settings __ __hours
25.3.4. Elsewhere __ __hours

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

PART E – Family history

Family Composition

26. How many siblings do you have? _____

If the answer to Question 26 is >0 then ask Question 27 to 28, otherwise skip to Question 29.1.

27. How many older siblings do you have? _____

28. How many older brothers do you have? _____

Family history – Education

29.1 What is the highest level of schooling your mother has completed?

Primary School	❑
Middle School	❑
High School	❑
Some College (Trade/Professional/Community)	❑
Four Year College/University	❑
None	❑
Unknown	❑

29.2 What is the highest level of schooling your maternal grandmother has completed?

Primary School	❑
Middle School	❑
High School	❑
Some College (Trade/Professional/Community)	❑
Four Year College/University	❑
None	❑
Unknown	❑

29.3 What is the highest level of schooling your maternal grandfather has completed?

Primary School	❑
Middle School	❑
High School	❑
Some College (Trade/Professional/Community)	❑
Four Year College/University	❑
None	❑
Unknown	❑

29.4 What is the highest level of schooling your father has completed?

Primary School	❑
Middle School	❑
High School	❑
Some College (Trade/Professional/Community)	❑
Four Year College/University	❑
None	❑
Unknown	❑

29.5 What is the highest level of schooling your paternal grandmother has completed?

Primary School	❑
Middle School	❑
High School	❑
Some College (Trade/Professional/Community)	❑
Four Year College/University	❑
None	❑

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____

d d m m y y y y

Unknown ❑

29.6 What is the highest level of schooling your paternal grandfather has completed?

Primary School ❑
Middle School ❑
High School ❑
Some College (Trade/Professional/Community) ❑
Four Year College/University ❑
None ❑
Unknown ❑

Family history – Occupation

30.1. What has been your father's usual occupation or job? _____
If the he has never worked then enter "never worked" and go to question 31.1

30.2. What does/did he actually do in his work (describe) _____
_____

30.3. What industry does he work in? _____
If father unemployed put 999

30.4. For how many years has your father worked at this job? _____ _____ years

30.5. Is your father:

A manager working for an employer? ❑
A foreman or supervisor working for an employer? ❑
Working for an employer, but neither a manager, supervisor or foreman? ❑
Self-employed? ❑

30.6. Enter ISCO code here: __ __ __ __

31.1. What has been your paternal grandfather's usual occupation or job?_____
If the he has never worked then enter "never worked" and go to question 32.1

31.2. What does/did he actually do in his work (describe) _____
_____

31.3. What industry did he work in? _____
If grandfather unemployed put 999

31.4. For how many years has your paternal grandfather worked at this job?_____ _____ years

31.5. Has your paternal grandfather been a farmer?
If yes go to Question 31.6., otherwise skip to Question 31.7.

Yes ❑
No ❑

31.6. Has your paternal grandfather been:
If Question 31.6. is being completed then skip to 32.1.

An owner, but didn't work on the farm ❑
An owner, but worked on the farm ❑

ID _____ _____ _____ _____ _____ _____
Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

A tenant, worked on the farmer but didn't own the farm ❑
Employed on the farm but not a tenant or owner ❑

31.7. Was your paternal grandfather:
A manager working for an employer? ❑
A foreman or supervisor working for an employer? ❑
Working for an employer, but neither a manager, supervisor or foreman? ❑
Self-employed? ❑
31.8. Enter ISCO code here: __ __ __ __

32.1. Did your paternal grandmother work outside the home?
Yes ❑
No ❑
*If Question 32.1 is **Yes** then go to Question 32.2 to 32.9, otherwise skip to Question 33.1*

32.2. What was your paternal grandmother's usual occupation or job? _____

32.3. What does/did she actually do in her work (describe) _____
_____

32.4. What industry did she work in? _____
If grandmother unemployed put 999

32.5. For how many years has your paternal grandmother worked at this job?_____ _____
years

32.6. Has your paternal grandmother been a farmer?
If yes go to 32.7. else skip to 32.8.
Yes ❑
No ❑
32.7. Has your paternal grandmother been:
If Question 32.7. is being completed then skip to 33.1.
An owner, but didn't work on the farm ❑
An owner, but worked on the farm ❑
A tenant, worked on the farmer but didn't own the farm ❑
Employed on the farm but not a tenant or owner ❑
32.8. Was your paternal grandmother:
A manager working for an employer? ❑
A foreman or supervisor working for an employer? ❑
Working for an employer, but neither a manager, supervisor or foreman? ❑
Self-employed? ❑
32.9. Enter ISCO code here: __ __ __ __

33.1. Has or does your mother work outside the home?
*If Question 33.1. is **Yes** then go to Question 33.2 to 33.7,*
otherwise skip to Question 34.1
Yes ❑
No ❑

33.2. What has been your mother's usual occupation or job? _____

33.3. What does/did she actually do in her work (describe) _____
_____

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

33.4. What industry does she work in? _____

If mother unemployed put 999

33.5. For how many years has your mother worked at this job? _____ _____ years

33.6. Is your mother:

A manager working for an employer? ❑
A foreman or supervisor working for an employer? ❑
Working for an employer, but neither a manager, supervisor or foreman? ❑
Self-employed? ❑

33.7. Enter ISCO code here: __ __ __ __

34.1. What has been your maternal grandfather's usual occupation or job?_____

If the he has never worked then enter "never worked" and go to question 35.1

34.2. What does/did he actually do in his work (describe) _____
_____

34.3. What industry did he work in? _____

If grandfather unemployed put 999

34.4. For how many years has your maternal grandfather worked at this job?_____ _____ years

34.5. Has your maternal grandfather been a farmer?

If yes go to Question 34.6., otherwise skip to Question 34.7.

Yes ❑
No ❑

34.6. Has your maternal grandfather been:

If Question 34.6. is being completed then skip to 35.1

An owner, but didn't work on the farm ❑
An owner, but worked on the farm ❑
A tenant, worked on the farmer but didn't own the farm ❑
Employed on the farm but not a tenant or owner ❑

34.7. Was your maternal grandfather:

A manager working for an employer? ❑
A foreman or supervisor working for an employer? ❑
Working for an employer, but neither a manager, supervisor or foreman? ❑
Self-employed? ❑

34.8. Enter ISCO code here: __ __ __ __

35.1. Did your maternal grandmother work outside the home?

Yes ❑
No ❑

*If Question 35.1 is **Yes** then go to Question 35.2 to 35.9, otherwise skip to Question 36.1*

35.2. What was your maternal grandmother's usual occupation or job? _____

35.3. What does/did she actually do in her work (describe) _____
_____

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

35.4. What industry did she work in? _____

If grandmother unemployed put 999

35.5. For how many years has your maternal grandmother worked at this job?_____ _____ years

35.6. Has your maternal grandmother been a farmer?

If yes go to 35.6. else skip to 35.8.

Yes ❑
No ❑

35.7. Has your maternal grandmother been:

If Question 35.7. is being completed then skip to 36.1.

An owner, but didn't work on the farm ❑
An owner, but worked on the farm ❑
A tenant, worked on the farmer but didn't own the farm ❑
Employed on the farm but not a tenant or owner ❑

35.8. Was your maternal grandmother:

A manager working for an employer? ❑
A foreman or supervisor working for an employer? ❑
Working for an employer, but neither a manager, supervisor or foreman? ❑
Self-employed? ❑

35.9. Enter ISCO code here: __ __ __ __

Family history – Place of birth

36.1. Where was your mother born? City/region:_____ Country:_____

36.2. Where was your maternal grandmother born? City/region:_____ Country:_____

36.3. Where was your maternal grandfather born? City/region:_____ Country:_____

36.4. Where was your father born? City/region:_____ Country:_____

36.5. Where was your paternal grandmother born? City/region:_____ Country:_____

36.6. Where was your paternal grandfather born? City/region:_____ Country:_____

Family history – Place of childhood

37.1. What term best describes the place your mother lived most of the time during her childhood?

Farm ❑
Village in rural area ❑
Small town ❑
Suburb or a city ❑
Don't know ❑

37. 2. What term best describes the place your maternal grandmother lived most of the time during her childhood?

Farm ❑

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

Village in rural area ❑
Small town ❑
Suburb or a city ❑
Don't know ❑

Don't know ❑37. 3. What term best describes the place your <u>maternal grandfather</u> lived most of the time during his childhood?

Farm ❑
Village in rural area ❑
Small town ❑
Suburb or a city ❑
Don't know ❑

37. 4. What term best describes the place your <u>father</u> lived most of the time during his childhood?

Farm ❑
Village in rural area ❑
Small town ❑
Suburb or a city ❑
Don't know ❑

37. 5. What term best describes the place your <u>paternal grandmother</u> lived most of the time during her childhood?

Farm ❑
Village in rural area ❑
Small town ❑
Suburb or a city ❑
Don't know ❑

37. 6. What term best describes the place your <u>paternal grandfather</u> lived most of the time during his childhood?

Farm ❑
Village in rural area ❑
Small town ❑
Suburb or a city ❑
Don't know ❑

Family history – Smoking

38.1. Did your <u>mother</u> smoke regularly before your pregnancy?

Yes ❑
No ❑
Don't know ❑

38.2. Did your <u>father</u> smoke regularly before your pregnancy?

Yes ❑
No ❑
Don't know ❑

38.3. Did your <u>mother</u> smoke regularly during your pregnancy?

Yes ❑
No ❑
Don't know ❑

38.4. Did your <u>father</u> smoke regularly during your pregnancy?

Yes ❑
No ❑
Don't know ❑

ID _____ _____ _____ _____ _____ _____

Date:_____ _____/_____ _____/_____ _____ _____ _____
d d m m y y y y

38.5. Did your mother smoke regularly during your childhood?

Yes ❑
No ❑
Don't know ❑

38.6. Did your father smoke regularly during your childhood?

Yes ❑
No ❑
Don't know ❑

38.7. Does your mother smoke regularly nowadays?

Yes ❑
No ❑
Don't know ❑

38.8. Does your father smoke regularly nowadays?

Yes ❑
No ❑
Don't know ❑

PART F - Birth linkage, GP and withdrawal details

Birth linkage

This section will only be completed if the participant consents to accessing birth weight information (See consent form).

39. Is your birth name different from your current name? Yes ❑ No ❑

If the answer to Questions 39 is "Yes", then proceed with Questions 39.1.and 39.2. If the answer to Question 39 is ***No*** *then skip to Question 40.*

39.1. What was your Birth Surname? _____

39.2. What was your Birth Name? _____

40. What is your NHS number? ___ ___ ___/___ ___ ___/___ ___ ___ ___

General practice contact details

This section will only be completed if the participant consents to sending the results of the lung function testing to their GP (See consent form).

41.1. What is the name of your GP practice?

_____

41.2. What is the contact address of your GP practice?

_____

_____

Withdrawal

42. Define the circumstance under which the participant withdrew if the participant withdrew

_____

_____

_____

53. Researcher ID ___ ___ ___ ___

Feedback questionnaire

Instructions

The feedback questionnaire will be designed using Qualtrics, which is an online survey system offered by Imperial College London. The feedback questionnaire will be completed online and will be sent by email to the participants who attended the study visit and to those who expressed an interest in participating but did not attend a study visit. The results from this questionnaire will be used to evaluate the conduct of the current study and to improve future studies.

Feedback questionnaire for the Diversity in Ethnicity, Lung function and Birth weight in Young Adults (DELBYA) study

This questionnaire should take about 3 minutes to complete.

Participating in this questionnaire is optional and not required as part of the study.

We are grateful for any feedback you will give.

Study recruitment and motivation

1. How did you learn about the DELBYA study?

- ❑ Flyer on College noticeboard
- ❑ Facebook or twitter
- ❑ Email from Imperial College Club or Society
- ❑ Shout-out during lecture
- ❑ Word of mouth from friends
- ❑ Other: _____

2. Was the study information in the participant information sheet adequate?

Yes ❑
No ❑

3. Why did you want to participate in the study?

- ❑ Interested in helping medical research
- ❑ Interested in knowing my lung function
- ❑ For the reimbursement
- ❑ Other: _____

4. Did you attend the study visit?

Yes ❑
No ❑

If no, go to Q14

Study visit and procedures

5. Was traveling to the hospital for the study visit difficult for you?

Yes ❑
No ❑

If yes, go to Q6 otherwise go the Q7

6. Why was traveling to the hospital difficult for you?

- ❑ Got lost
- ❑ Travel time too long
- ❑ Cost of travelling
- ❑ Other: _____

7. How comfortable were you with the following procedures of the study visit?

	Very comfortable	Somewhat comfortable	Not comfortable
Blood pressure and pulse measurement	❑	❑	❑
Height and Weight measurement	❑	❑	❑
Lung function measurement	❑	❑	❑
Questionnaire	❑	❑	❑

If at least one procedure was not comfortable, please go to Q8, otherwise go to Q9

8. If you were not comfortable with at least one procedure, please let us know why and how this could be improved.

_____

_____

9. Did the study visit last longer than you expected?

Yes ❑
No ❑

10. How did you find the reimbursement (£15) for participating?
If too little, go to Q10.a otherwise go the Q11

❑ About right
❑ Too little
❑ Too much

10.a. How much do you think the reimbursement should have been? _____

Study perception

11. Overall, how would you rate your experience of the study visit?

❑ Very good
❑ Fair
❑ Poor

12. Did you recommend the study to your friends?

Yes ❑
No ❑

13. Would you attend similar studies in the future?

Yes ❑
No ❑

Go to Q15, skip Q14

Reasons for not attending study visit

14. Why did you no longer want to attend the study visit?

❑ No longer interested
❑ No time for the study visit
❑ Did not want to travel to the hospital
❑ Reimbursement (£15) not enough, would have liked _____
❑ Other: _____

Name and comment

15. What is your surname and first name? (Optional) _____

16. Please let us know if you have any other recommendations or comments (Optional)

_____

_____

C.3 Ethical approval, consent form and participant information sheet

This section contains the following documents:

1. Ethical approval from the Imperial College Research Ethics Committee
2. Ethical approval from the Medical Education Ethics Committee
3. Consent form
4. Participant information sheet

Imperial College London

Imperial College Research Ethics Committee

Imperial College London
Room 5L10D, 5th Floor, Lab Block
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF

Tel: +44 (0)203 331 0208 Fax: +44 (0) 203 311 0203

researchethicscommittee@imperial.ac.uk

Professor Peter Burney
NHLI
Imperial College London
London
SW3 6LR

11 December 2014

Dear Professor Burney,

Study Title: Diversity in Ethnicity, Lung function and Birth-weight in Young Adults (DELBYA).

ICREC reference: ICREC_13_6_16.

The above study was approved by your Head of Department on 5th November 2013 and by the Joint Research Compliance Office on the 9th December 2014.

Under the Imperial College Research Ethics Committee process, a study that has been reviewed by the Joint Research Compliance Office and Head of Division/Department (or Principal), where no significant ethical issues have been identified in the protocol or ethics application, can be approved without requiring it to go to full committee.

Documents
The documents reviewed were:

- ICREC Application form
- Participant Information Sheet (V4.4 09/12/14)
- Core Questionnaire (V1.4 29/09/14)
- Eligibility Questionnaire stage 1 (V3.3 10/10/14)
- Eligibility Questionnaire stage 2 (V1.2 29/09/14)
- Consent Form (V4.3 29/09/14)
- Protocol (V5.4 29/09/14)
- Risk Assessment (V2.1 11/12/14)
- Appendix 1: Flow chart (V4.1 29/09/14)
- GP Letter (V1.4 10/10/14)
- Recruitment poster (online) (V3.1 29/09/14)
- Recruitment poster (noticeboard) (V3.1 29/09/14)

Yours sincerely,



Gary Roper,
Head of Regulatory Compliance,
Imperial College London

Imperial College London

Royal Brompton & Harefield NHS
NHS Foundation Trust

ID Study Number: _____

CONSENT FORM

Diversity in Ethnicity, Lung function and Birth weight in Young Adults (DELBYA) Study

Principal Investigator: Professor Peter GJ Burney

Please Initial the boxes you agree with
Leave blank boxes you don't agree with

1. I confirm that I have read and understand the information sheet Version 4.4 dated 09 Dec 2014 for the above study and have had the opportunity ask questions and have them answered satisfactorily ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or my legal rights being affected. ☐
3. I understand that the information held and maintained by The Health and Social Care Information Centre and the NHS Central Register may be used to help contact me or provide information about my health status. In particular regarding birth weight information for the purpose of the research as detailed in the information sheet. ☐
4. I agree for the results of my tests to being made available to me as per Information Sheet. ☐
5. I agree for the results of the clinical tests performed during this research to being sent to my GP ☐
6. I agree for a summary of the study findings to being made available to me as per Information Sheet. ☐
7. I understand that data collected during the study and any relevant sections of my medical notes may be looked at by responsible individuals from Imperial College, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
8. I agree to take part in the above research ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Researcher taking consent	Date	Signature

When completed, 1 for researcher file; 1 for volunteer;

The study has the approval of the Imperial College Medical Education Ethics Committee (Ref: MEEC1314-07)
Version 4.4 - 16 December 2014

Imperial College London

School of Medicine
Imperial College London

Room 101, Sir Alexander Fleming Building
South Kensington Campus, London SW7 2AZ, UK
Tel: +44 (0)20 7594 1298

m.schachter@imperial.ac.uk
http://www1.imperial.ac.uk/medicine/

Dr Mike Schachter
Chair, Medical Education Ethics Committee

10 November 2014

Department of Surgery and Cancer
Sir Alexander Fleming Building
Imperial College London
Imperial College Road
London SW7 2AZ

Dear Mr Saad,

Thank-you for submitting your application entitled "Diversity in Ethnicity, Lung function and Birth weight in Young Adults (DELBYA) study" to the Medical Education Ethics Committee for review. Your application number is MEEC1314-07. The committee first reviewed and approved your application in November 2013. Since this time, you have submitted amended documentation as a result in changes to your study protocol, the most recent incidence being on 10 October 2014. This letter is to confirm that your documentation has been reviewed and approved.

Yours faithfully

Mike Schachter
Chair, Medical Education Ethics Committee

Imperial College London

Royal Brompton & Harefield NHS
NHS Foundation Trust

NATIONAL HEART AND LUNG INSTITUTE

Diversity in Ethnicity, Lung function and Birth weight in Young Adults (DELBYA) study

Information sheet

You are being invited to take part in a research study looking at the diversity in ethnicity, lung function and birth weight in young adults. Before you decide to participate it is important for you to understand the aim of the research and what it will involve. Please read the following information carefully and discuss it with others if you wish. Feel free to ask any questions you may have.

What is the "Diversity in Ethnicity, Lung function and Birth weight in Young Adults (DELBYA) study"?
The DELBYA is a study of young adults that aims to identify factors that influence the diversity in lung function and birth weight among different ethnic groups and aims to explain this diversity. The study will therefore measure lung function, height, weight, pulse and blood pressure. Information on birth weight will be obtained, after consent, via the Health and Social Care Information Centre.

What is involved?
You will be contacted with an appointment for a study visit. During the study visit, you will complete a questionnaire and a clinical examination will take place. For the clinical examination we will measure your height, weight, will test your lungs and will measure your pulse and blood pressure.

Testing lung function involves blowing into a machine (a spirometer) that measures how much air can be blown out of the lungs, and how fast. We will ask you to inhale two puffs of a medicine that may expand the airways (a "bronchodilator" called salbutamol or Ventolin). This medicine is commonly used by patients with asthma or other breathing problems and its part of a standard test to measure lung health at any hospital.

Blood pressure will be measured at your upper arm, using a cuff and air will be pumped into the cuff attached to your arm.

All these tests are routinely carried out in hospitals and are safe to perform.

Where will the study visit take place and how long will it take?
The study visit will take place at the Royal Brompton Hospital and will take about 1 hour.

Will I be reimbursed for taking part?
Yes, you will receive £15 for taking part in the study.

Why are you asking to obtain birth weight information?
We know that birth weights are lower among individuals from ethnic minorities and also among those who have a low lung volume. We are interested in the diversity in birth weight among different ethnic groups. Therefore, would like to get an accurate measure of birth weight. Because not everyone will know their birth weight we would like to contact the Health and Social Care Information Centre to obtain birth weight information from your birth records data.

Why are you asking about my ethnicity?
Lung function and birth weight differ among different ethnic groups. The DELBYA study aims to identify factors that influence and explain this diversity. Therefore, we are recruiting participants from two ethnic groups.

Do I have to take part?
No. This study is entirely voluntary and you can decide whether you want to take part. Even if you take part, you can withdraw at any point during the study.

Will this research be beneficial to me and others?
We would like to understand the diversity in lung function and birth weight among different ethnic groups. There will be no immediate benefits for you if you agree to participate, apart from knowing the status of your lung function. We will send you the results from the lung function test and the blood pressure by email. If you do not want to know your results, simply cross the appropriate box in the consent form. If you wish, we will send your results to your GP and can provide you with a summary of the study findings by email once the study is completed.

Imperial College
London

Are there any disadvantages and risks of taking part?
Some people may feel a bit light headed when they blow hard into the machine that measures the lung's health, but you will be sitting securely in a chair when you do the test and the research staff is trained to look out for this. The lung function tests are safe, but we will not ask you to blow if you recently had any major conditions that may affect your ability to do the test.

The puffer (salbutamol) can make your heart beat a little faster and can cause some jitterness for a short time but this is rare with the low dose you will be given and wears off within half an hour.

Very rarely, the puffer might give you a headache, hives, a fine tremor, some nervous tension, muscle cramp, a drop in blood pressure which may result in fainting, might disturb you behaviour and sleep due to agitation and might give you an allergic reaction which causes temporary swelling around the lips and eyes.

In extremely rare cases, and unlikely given the low dose, salbutamol might give you a unexpected narrowing of the airways causing wheezing, abnormal heart rhythm, reduced blood supply to the heart and dilation of blood vessels in the skin.

Is there anyone who should not take part?
Some people may be excluded from performing the lung function tests due to reasons such as chest or abdominal surgery in the last 3 months; a heart attack in the last 3 months; a detached retina or eye surgery in the past 3 month; hospitalisation for any other cardiovascular reason in the past month; being in the last three months of a pregnancy; having had a pneumothorax within the past three months; a resting pulse over 120 beats per minute and currently taking medication for tuberculosis.

Will my taking part in the study be kept confidential?
If you consent to take part in the research your name will not be disclosed outside the research group. Under no circumstances will your personal details, nor information that identifies you be disclosed to anyone. Your answers to the questionnaire will not be stored with your name on them. The questionnaire will be stored in a locked cabinet and the cabinet placed in a room to which only members of the research group have access. Data of the study will be used and stored only on Imperial College London owned computers which are password protected. Data will be released to your GP only if we have signed consent from you. As part of the study, we will be asking you about your quality of life, which includes questions about your emotional health status. In the case of extreme answers, we might contact you and ask you for permission to refer you to a College tutor or to your GP.

The results of this research are likely to be published but will contain no identifiable personal information.

Who to contact for more information or complaints?
If you wish to have more information about this study or have any complaints or concerns, please contact Mr Neil Saad at the National Heart & Lung Institute, Imperial College London, Manresa Road, SW3 6LR London on 020 7594 7952.

If you are not satisfied with the response you may contact:

Royal Brompton Hospital Patient Advice and Liaison Service (PALS)
Telephone: 020 7349 7715; Email: pals@rbht.nhs.uk

Joint Research Compliance Office (JRCO), Imperial College London
Email: jrco@imperial.ac.uk

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.
If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Professor Peter Burney, at the National Heart & Lung Institute, Imperial College London, Manresa Road, SW3 6LR London on 0207 564 7941). The normal National Health Service complaint complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Research Ethics Committee (ICREC).

Thank you for reading this information sheet

The study has the approval of the Imperial College Medical Education Ethics Committee (Ref: MEEC1314-07)
Version 4.4 - 09 Dec 2014

C.4 Tables

Table C.1: Smoking status of participants' mother and father across the life course

	White (N=68)	**South Asian British (N=22)**	
	N (%)	**N (%)**	**P-value**
Paternal smoking, before pregnancy	18 (26.5)	4 (18.2)	0.57
Maternal smoking, before pregnancy	11 (16.2)	1 (4.5)	0.28
Paternal smoking, during pregnancy	7 (10.3)	0 (0.0)	0.39
Maternal smoking, during pregnancy	1 (1.5)	0 (0.0)	1.00
Paternal smoking, during childhood*	7 (10.3)	2 (9.1)	1.00
Maternal smoking, during childhood	4 (5.9)	1 (4.5)	1.00
Paternal smoking, nowadays	5 (7.4)	1 (4.5)	1.00
Maternal smoking, nowadays	2 (2.9)	1 (4.5)	1.00

*Smoking during pregnancy of one father of a White participants as unknown

Table C.2: Overview of maternal and maternal grandparents' occupational status

	Mother		Maternal grandmother		Maternal grandfather	
	White (N=67)	**South Asian British (N=22)**	**White (N=62)**	**South Asian British (N=22)**	**White (N=60)**	**South Asian British (N=18)**
ISCO-88 Major Groups	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Armed forces	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.4)	0 (0.0)
Legislators, senior officials and managers	11 (16.2)	3 (13.6)	9 (13.2)	0 (0.0)	17 (25.0)	6 (27.3)
Professionals	35 (51.5)	8 (36.4)	16 (23.5)	3 (13.6)	17 (25.0)	6 (27.3)
Technicians and associate professionals	8 (11.8)	2 (9.1)	1 (1.5)	1 (4.5)	2 (2.9)	0 (0.0)
Clerks	6 (8.8)	6(27.3)	14 (20.6)	0 (0.0)	3 (4.4)	1 (4.5)
Service workers and shop and market sales workers	3 (4.4)	1(4.5)	3 (4.4)	0 (0.0)	1 (1.5)	0 (0.0)
Skilled agricultural and fishery workers	1 (1.5)	0 (0.0)	2 (2.9)	1 (4.5)	4 (5.9)	0 (0.0)
Craft and related trade workers	0 (0.0)	0 (0.0)	1 (1.5)	1 (4.5)	4 (5.9)	1 (4.5)
Plant and machine operators and assemblers	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (7.4)	2 (9.1)
Elementary occupations	1 (1.5)	0 (0.0)	1 (1.5)	1 (4.5)	4 (5.9)	2 (9.1)
Did not work	2 (2.9)	2 (9.1)	15 (22.1)	15 (72.0)	0 (0.0)	0 (0.0)
P-value	0.26		0.001		0.58	

Table C.3: Overview of father's and paternal grandparents' occupational status

	Father		Paternal grandmother		Paternal grandfather	
	White (N=68)	South Asian British (N=22)	White (N=57)	South Asian British (N=22)	White (N=50)	South Asian British (N=19)
ISCO-88 Major Groups	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Armed forces	1 (1.5)	0 (0.0)	1 (1.5)	0 (0.0)	2 (2.9)	0 (0.0)
Legislators, senior officials and managers	33 (48.5)	7 (28.0)	5 (7.4)	2 (9.1)	12 (17.6)	6 (27.3)
Professionals	23 (33.8)	10 (48.0)	13 (19.1)	1 (4.5)	13 (19.1)	3 (13.6)
Technicians and associate professionals	6 (8.8)	1 (4.0)	4 (5.9)	0 (0.0)	2 (2.9)	1 (4.5)
Clerks	1 (1.5)	1 (4.0)	12 (17.6)	1 (4.5)	4 (5.9)	2 (9.1)
Service workers and shop and market sales workers	2 (2.9)	0 (0.0)	2 (2.9)	0 (0.0)	5 (7.4)	1 (4.5)
Skilled agricultural and fishery workers	1 (1.5)	0 (0.0)	0 (0.0)	1 (4.5)	2 (2.9)	3 (13.6)
Craft and related trade workers	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (11.8)	0 (0.0)
Plant and machine operators and assemblers	0 (0.0)	3 (16.0)	0 (0.0)	0 (0.0)	1 (1.5)	2 (9.1)
Elementary occupations	0 (0.0)	0 (0.0)	2 (2.9)	1 (4.5)	1 (1.5)	1 (4.5)
Did not work	0 (0.0)	0 (0.0)	20 (29.4)	16 (72.7)	0 (0.0)	0 (0.0)
P-value	0.53		0.001		0.42	

Table C.4: Overview of number and percentage of missing data in the DELBYA study

	White (N=68)	**South Asian British (N=22)**
	N (%)	**N (%)**
Smoking		
Father smoking, during pregnancy	1 (1.5)	0 (0.0)
Upbringing		
Upbringing, Maternal grandmother	9 (13.2)	3 (13.6)
Upbringing, Maternal grandfather	16 (23.5)	3 (13.6)
Upbringing, Paternal grandmother	12 (17.6)	2 (9.1)
Upbringing, Paternal grandfather	16 (23.5)	2 (9.1)
Educational attainment		
Educational attainment, maternal grandmother	12 (17.6)	7 (31.8)
Educational attainment, maternal grandfather	15 (22.1)	5 (22.7)
Educational attainment, paternal grandmother	15 (22.1)	8 (36.4)
Educational attainment, paternal grandfather	18 (26.5)	5 (22.7)
Occupation		
Occupation, Mother	1 (1.5)	0 (0.0)
Occupation, maternal grandmother	6 (8.8)	0 (0.0)
Occupation, maternal grandfather	8 (11.8)	4 (18.2)
Occupation, paternal grandmother	11 (16.2)	0 (0.0)
Occupation, paternal grandfather	18 (26.5)	3 (13.6)
Farming, maternal grandmother	5 (7.4)	2 (9.1)
Farming		
Farming, maternal grandfather	5 (7.4)	2 (9.1)
Farming, Paternal grandmother	2 (2.9)	0 (0.0)
Farming, Paternal grandfather	7 (10.3)	2 (9.1)

Table C.5: Ventilatory function reversibility in the DELBYA study. Ventilatory function reversibility defined as the percentage difference in ventilatory function (FVC, FEV_1 or FEV_1/FVC) and was calculated by obtaining the ratio of the difference in pre- to post-bronchodilator ventilatory function to the post-bronchodilator ventilatory function times hundred. Mean, standard deviation (SD), mininium (Min) and maximum (Max) were obtained in the total population and among White and South Asian British participants seperately.

	Total population				**White**				**South Asian British**			
	N	**Mean (SD)**	**Min**	**Max**	**N**	**Mean (SD)**	**Min**	**Max**	**N**	**Mean (SD)**	**Min**	**Max**
FVC	87	-0.4 (2.6)	-8.7	7.3	65	-0.6 (2.6)	-8.7	7.3	22	-0.1 (2.6)	-4.0	6.0
FEV_1	88	-2.6 (4.1)	-9.1	23.3	67	-3.0 (2.7)	-9.1	3.2	21	-1.6 (6.9)	-8.2	23.3
FEV_1/FVC	85	-2.1 (3.2)	-7.4	19.7	64	-2.4 (1.9)	-7.4	3.1	21	-1.4 (5.5)	-7.1	19.7

% diff= (pre-post)/post*100