THE ROLE OF FOETAL /INFANT GROWTH AND PHYSICAL ACTIVITY IN RESPIRATORY OUTCOMES OF PREMATURITY

A thesis submitted in fulfilment of the requirements for the degree of:

Doctor of Philosophy

By

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2017

DEDICATION

For Rachel and Jack

SUMMARY

This thesis uses data from three cohort studies in order to investigate the effects of foetal and infant growth on respiratory disease in preterm-born children, and the onward effects of this disease on measures of physical activity. Firstly, I investigated change in foetal growth using biometry obtained from antenatal ultrasounds scans, and related this to rates of respiratory symptoms obtained from the Respiratory and Neurological Outcomes of Children Born Preterm Study. I followed-up this work by reporting the effect of accelerated weight gain during infancy on the respiratory health of preterm-born children. The second half of my thesis then used measures of lung function, as well as data on respiratory symptoms, to investigate whether the decrements associated with preterm birth manifested as reduced participation in objectively measured physical activity. Data from the Avon Longitudinal Study of Parents and Children, and from the Millennium Cohort Study, were used in these analyses.

My results noted that change in foetal growth trajectory (acceleration or deceleration) between the trimesters of pregnancy was associated with increased respiratory symptoms in preterm-born children. Accelerated infant weight gain was also associated with increased odds of wheeze; this was in a dose-dependent manner across the spectrum of gestation, with the effect being the greatest at ≤32 weeks' gestation. Moreover, maternal smoking, as well as gestation, were noted to be a mediator of the relationship between infant weight gain and childhood respiratory health.

A reduction in moderate-to-vigorous physical activity at 7 years of age was noted in boys who were born at ≤32 weeks' gestation. This reduction remained after inclusion of other explanatory variables. No differences were noted at the ages of 11 and 15 years. The reduction in physical activity over the course of childhood may explain this observation.

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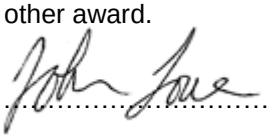
Signed  (candidate) Date 14/03/2017

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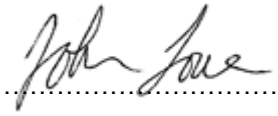
Signed  (candidate) Date 14/03/2017

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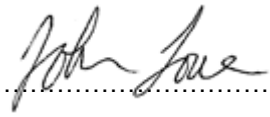
Signed  (candidate) Date 14/03/2017

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ACKNOWLEDGEMENTS

My sincere gratitude and thanks go to Professor Sailesh Kotecha for his support over the last 5 years in working towards the submission of this thesis. I would like to thank my fellow colleagues and PhD students, Sarah Kotecha and Martin Edwards, who were the main-stays in my office during this period. Martin and I shared many a therapeutic run (jog) around Heath Park which provided some catharsis during the more frustrating times balancing my PhD studies, day job, and family life. Sarah, I thank for her insights, experience and her positive attitude towards 'getting things done'. Special thanks are due to John Watkins for his statistical advice and support. He was, and still is, prepared to offer his help (and occasionally beer) even when his other commitments are pressing. Dr Colin Powell encouraged me pursue a PhD and provided a source of invaluable motivation and positivity. I must also thank Professor John Henderson for his erudite comments on my research proposals and when preparing manuscripts for journal publications.

I have also been exceptionally lucky to work with many other great people within the wider Child Health team during my studies, so I wish to thank members past-and present Kevin Poon, David Gallagher, Michael Cousins, Kylie Hart, Kim Rolfe, Rhian Thomas-Turner and Nicola Benallick for their mutual support in generating a positive working environment.

It would be remiss of me not to mention that following the arrival of our son, Jack, in April 2015, my wife Rachel and I endured a period of exceptional difficulty after he was born very unwell. Without the unconditional support of everyone named above (amongst many others), and of course, our family, I am confident I would not have made it to this point.

To Rachel, for her love, patience, and above all, her determination and belief in me (especially at the times when I had little in myself). Thank you. To Jack, thank you for fighting and smiling and keeping me in the moment when it was easier to dwell in the past or worry about the future.

Thank you to the wider family Lowe and family Breen. In particular, thanks to my brother Christopher Lowe, and Rachel, for their proof-reading of this thesis. To my parents, who have always supported me unreservedly, no cycle rides to Morecambe were undertaken during the writing of this thesis!

Finally, I must thank the children, families and researchers who took part in the ALSPAC< MCS and RANOPs studies, and for access to the data collected, which made this thesis possible.

LIST OF ABBREVIATIONS

ALSPAC	Avon Longitudinal Study of Parents and Children
BD	Biparietal diameter
BPD	Bronchopulmonary Dysplasia
BMI	Body mass index
BMR	Basal Metabolic rate
CI	Confidence interval
CLD	Chronic Lung disease of Prematurity
cpm	counts per minute
COPD	Chronic obstructive pulmonary disease
CRL	Crown-rump length
DCD	Developmental coordination disorder
DL_{CO}	Diffusing capacity of carbon monoxide
DLW	Doubly-labelled water
DXA	Dual-energy X-ray absorptiometry
ELBW	Extremely low birthweight
FEV_1	Forced expiratory volume at one second
$FEV_{0.4}$	Forced expiratory volume at 0.4 seconds
$FEV_{0.5}$	Forced expiratory volume at 0.5 seconds
FEF_{25-75}	Forced expiratory flow at 25-75% of FVC
FEF_{75}	Forced expiratory flow at 75% of FVC
FL	Femur length
FVC	Forced vital capacity
HC	Head circumference
LRTI	lower respiratory tract infection
MET	Metabolic equivalent task
MCS	Millennium Cohort Study
MVPA	Moderate-to-vigorous physical activity
NWIS	NHS Wales Informatics Service
OR	Odds ratio
PA	Physical activity
PPROM	Preterm premature rupture of membranes
RANOPS	Respiratory and neurological outcomes of children born preterm study
RSV	Respiratory syncytial virus
$V'max_{FRC}$	Maximal expiratory flows at functional residual capacity
VLB	Very low birthweight
$\dot{V}O_2$	Volume of oxygen consumption

LIST OF PUBLICATIONS

From this thesis

Lowe J, Kotecha SJ, Watkins WJ, Kotecha S. Role of early-life factors on the association between altered foetal and infant growth with respiratory outcomes in preterm-born children [submitted]

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Lowe J, Watkins WJ, Edwards MO, Spiller OB, Jacqz-Aigrain E, Kotecha SJ, Kotecha S. Association between pulmonary *Ureaplasma* colonisation and bronchopulmonary dysplasia in preterm infants: updated systematic review and meta-analysis. *Pead Infect Dis J* 2014;33(7):697-702

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Edwards MO, Kotecha SJ, **Lowe J**, Richards L, Watkins WJ, Kotecha S. Preterm birth and atopy as risk factors for childhood wheezing and inhaler treatment: a cross sectional population study. PLoS One. 2016;11(5):e0155695

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1 Introduction

1.1 Preface

The common theme within this thesis relates to preterm birth and its effect on the respiratory system. Thus, it is appropriate that this introduction begins with an outline of normal lung development and of neonatal lung disease. I will describe the 'state of the art' in terms of current literature on respiratory outcomes in childhood following preterm birth. I will also summarise the literature in relation to respiratory sequelae in adolescence and adulthood, which are important for contextualising the long-term impact.

My research is presented in four chapters, each of which were conducted as independent, but complementary studies. Chapters two and three investigate foetal, and then infant growth in preterm-born children and explored associations with respiratory outcomes in childhood. Therefore, this introduction presents background on low birthweight, intrauterine growth restriction, and the 'Developmental Origins of Health and Disease' hypothesis. It further summarises postnatal growth following preterm birth. The current literature in regards to respiratory outcomes are then presented in detail.

Chapters four and five investigate the levels of physical activity in preterm born children. In all cases, comparing data with 'term' (>37 weeks' gestation). The current literature on these topics will be detailed in this introduction to identify gaps in the evidence which guided my research aims. Lastly, the hypotheses generated from the review of the literature will be presented.

1.3 Organogenesis

1.3.1 Normal lung development

Lung development begins in the embryonic stages of growth with the appearance of the lung bud (respiratory diverticulum), derived from the endoderm, during the 4th week of gestation (Larsen, 1998). By week five, the bud has branched into both left and right main bronchi and formed secondary buds from which the bronchi will develop. The start of the pseudoglandular phase, at week seven, is characterised by further branching of the bronchi to produce tertiary structures under regulation of growth factors such as epithelial growth factor (EGF). The continuing expansion of the respiratory tree results in terminal bronchioles by the end of the seventeenth week (Kotecha, 2000). During the canalicular phase the surrounding mesodermal tissue becomes vascularised, and the supporting muscles and cartilage begin to develop from the same body cavity. The terminal bronchioles split in to respiratory bronchioles during the seventeenth to twenty-seventh week. The airway wall and epithelium are essentially in mature form; surfactant protein is detectable during the latter stages of this phase. The following saccular phase, between twenty-eight and thirty-sixth weeks, is characterised by growth of the peripheral airways and the final branching of the bronchioles and terminal branches. These will eventually be invested in a dense bed of capillaries thus forming nascent alveoli- terminal saccules, as well as thinning of the airway walls. The alveolar phase sees the continuing development of the terminal saccules and their maturation in to alveoli just prior to birth. After birth, alveolar fluid is absorbed and surfactant synthesis reduces the surface tension of the gas exchange interface. This facilitates the rapid expansion of the surface area available for gas exchange (Joshi and Kotecha, 2007).

1.3.2 Postnatal development of the lung

Following birth, airway calibre continues to improve. Alveolar development and multiplication continues rapidly after birth and in to childhood, with size and surface area continuing to increase longer still (Larsen, 1998, Joshi and Kotecha, 2007).

Historically, it has been assumed that as the lung grows and matures, the length and diameter of the airways increases proportionally with the lung parenchyma. This facilitates an improvement in gas exchange, mechanics and haemodynamic function. However, it is increasingly evident that the relationship between lung size and airflow is not consistent. This was first demonstrated by Green and colleagues who noted the variation in the forced expiratory volume in one second FEV_1 to forced vital capacity (FVC) ratio (FEV_1/FVC) comparing normal individuals with similar lung size (Green et al., 1974). The concept of disproportionate growth between lung size and airway calibre was termed 'dysanapsis', and debate still exists in regards to its clinical importance (Thompson, 2017). Preterm-born children are at heightened risk for dysregulated lung growth, both pre-and-postnatally (Merkus, 2003), and thus may be more susceptible to this developmental mismatch. For example, moderately preterm-born children (32-34 week's gestation) were noted to have no difference in FVC compared to term controls but had reduced forced expiratory flows and lower $FEV_{0.5}$/FVC ratios at two months of age (Friedrich et al., 2007). Accelerated weight gain (Den Dekker, et al. 2016) and subsequent overweight have recently been demonstrated to be associated with airway dysanapsis. Asthmatic children with dysanapsis also exhibited a greater number of exacerbations and daily bronchodilator use (Forno et al., 2017).

Recent hyperpolarised 3-helium MRI studies indicate that the alveolar surface area continues to increase at least in to adolescence (Narayanan et al., 2012), challenging the previously widely held view that alveolar development only continues up to 2 years of age. The lungs of preterm-born children are thought to contain fewer, larger alveoli, which

reduces the available surface area for gas exchange. Altered permeability of the alveolar membrane, which introduces a ventilation-perfusion mismatch, is identified by the decreased diffusing capacity of carbon monoxide (DL_{CO}) (Hakulinen et al., 1996). Historically, the data on alveoli size has been based on limited histological data of young children with fatal lung disease. However, recent innovations in hyperpolarised ^{3}He MRI scanning have provided novel insights into the lung structure of preterm-born children. A recent study by Flors and colleagues noted a higher apparent diffusion coefficient of inhaled ^{3}He, but same lung volumes, in children porn preterm aged between 4-15 years of age when compared to age-matched healthy controls (Flors et al., 2017). This indeed suggests that bronchopulmonary dysplasia (BPD) survivors have fewer, larger, alveoli. Moreover, the possibility now exists that the lungs of preterm-born children may exhibit a degree of 'catch-up' alveolarisation by adolescence and beyond (Narayanan et al., 2013).

Peak lung function is attained approximately at 21-22 years of age, by which time there has been a 30- fold increase in lung volume and a 20-fold increase in gas exchange surface since birth (Stocks and Sonnappa, 2013). From this plateau, both FEV_1 and FVC gradually decline as lung elasticity is lost (Quanjer et al., 2012).

1.4 Preterm birth

1.4.1 Definition

Preterm birth, defined as birth prior to 37 completed weeks of gestational age, accounts for 7-10% of all live births in the UK. This percentage is rising world-wide, especially in the later gestations (35-36 weeks' gestation) (Blencowe et al., 2012). There have been large-scale advances in the treatment of preterm birth in the last two decades and consequently many more of the most immature infants survive today with the limit of viability being around 23 weeks' gestation. Infants born at ≤28 weeks' gestation, often called 'extremely

preterm', now represent the group who are likely to require significant neonatal care immediately following birth, requiring hospital stays of weeks or months. Infants born at the limit of viability require substantial multidisciplinary follow-up post-discharge which places a significant burden on healthcare resources, and on families.

1.4.2 Risk factors for preterm birth

Spontaneous preterm labour, encompassing both premature preterm rupture of the membranes (PPROM) as well preterm labour with intact membranes, accounts for the majority of preterm births. The multifactorial aetiology leads to the exact causes being unknown in up to half of all cases, however, maternal, social and environment factors are associated with increased risk. Preterm birth is heavily linked to deprivation, which includes the domains of lower education and occupational status, and increased rates of obesity, tobacco smoking, diabetes and hypertension (Field et al., 2016). Maternal tobacco smoking is well recognised as a modifiable risk factor (Shah and Bracken, 2000) which also affects *in utero* lung growth. Nicotine is able to cross the placental boundary and is transferred to the foetus in proportionally higher concentrations than in the maternal serum (Luck et al., 1985). In animal models, lung hypoplasia was induced in rats exposed to cigarette smoke with fewer, more simple saccules observed (Collins et al., 1985). In lambs, nicotine exposure during the last trimester induced signs of proximal airway obstruction using a modified nitrogen washout technique (Sandberg et al., 2004). The exact causative mechanisms of tobacco smoke exposure in relation to preterm birth are not known, however both nicotine and carbon monoxide are potent vasoconstrictors, which may act upon the placenta to decrease blood flow to the foetus (Lo et al., 2015). Other complications relating to the placenta, including placenta praevia and placental abruption are also risk-factors for preterm birth. Previous history of preterm birth is also a strong risk factor, perhaps due to underlying or unresolved inflammation, especially if pregnancies are only separated by a short gestation.

A complex relationship exists between the risk of preterm birth and maternal body mass index (BMI), with associations being reported at both ends of the spectrum (Hendler et al., 2005). Proportionally, a larger percentage of preterm births in women of low BMI occur spontaneously, rather than as indicated deliveries. In contrast, higher BMI appears protective, although of the preterm births which occur, a higher percentage of these are medically indicated due to maternal factors secondary to increased BMI including gestational diabetes and pre-eclampsia (Figure 1-1). An increased risk for spontaneous preterm birth at low BMI may be explained by inadequate nutrient intake or placental insufficiency related to reduced blood flow (Neggers and Goldenberg, 2003). Pre-eclampsia itself is caused by dysregulated placental function and is also linked to reduced blood to the foetus as well as intrauterine growth restriction (IUGR). Preterm birth often results from pre-eclampsia, however, this is largely due to a medical decision to deliver early in order to reverse the condition (Steegers et al., 2010).

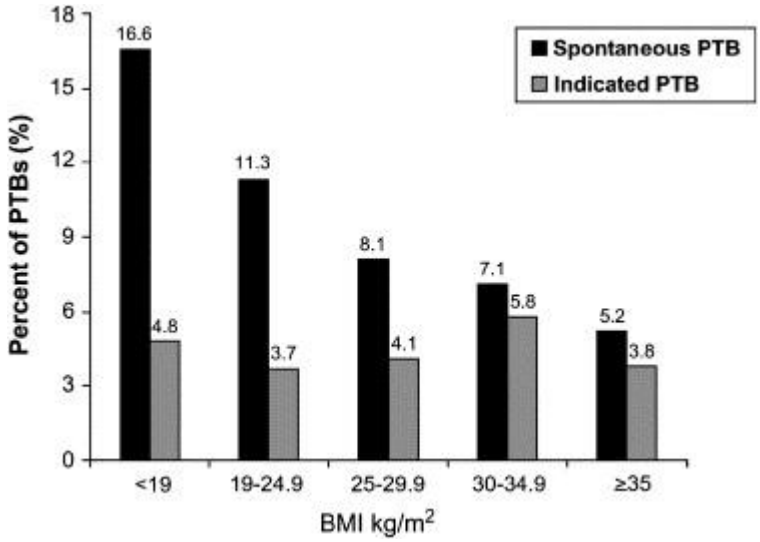


Figure 1-1: Proportion of preterm births (PTB) born via spontaneous or indicated means separated by BMI group. Reproduced with permission from Hendler et al. Am J Obstet Gynecol. 2005 Mar;192:882-6.

Intrauterine infection and inflammation are probably the best understood risk factors for preterm birth. Infections within the uterus can occur in multiple locations, and when the infection involves the foetal membranes, this is termed 'chorioamnionitis'. Infection may occur from a number of sources, however, ascension of bacteria from the vagina through the cervix is the most likely route for the organisms most frequently implicated. These include *Mycoplasma*, *Ureaplasma* and other anaerobic species (Maxwell et al., 2006). *Ureaplasma spp.* is the most common organism cultured from uterine samples and has been shown to be readily transferred from mother to foetus (Sanchez, 1993). Chorioamnionitis has been noted to increase with decreasing gestation (Hartling et al., 2012) and thus up to 80% of women delivering at <28 weeks' gestation have evidence of infection on histological examination, however, this often remains sub-clinical. Miralles et al. identified microbial genes in at least one tissue or fluid sample in 70% of deliveries after PPROM and in 80% of deliveries where the membranes remained intact (Miralles et al., 2005). Post-infection, preterm labour then occurs when presence of such bacteria promotes the releases of cytokines from maternal leukocytes which stimulate production of inflammatory molecules involved in cervical ripening, weakening of the membranes and uterine contractions (Goldenberg et al., 2000).

In summary, the risk factors for preterm birth may be separated in to broadly two groups, those associated with infection and inflammation (PPROM, chorioamnionitis, cervical insufficiency) and those associated with abnormal placentation (placenta praevia, placental abruption, pre-eclampsia and Intrauterine growth restriction).

1.4.3 Respiratory complications of the preterm neonate

The most common complications of preterm birth stem from interruption to the normal development of the respiratory system. The most immature of preterm-born neonates are

delivered at the canalicular or early saccular stages of lung development where the respiratory system provides an inadequate gas exchange surface as surfactant is not produced in sufficient amounts (Joshi and Kotecha, 2007). Consequently, respiratory support in the form of mechanical ventilation and supplementary oxygen is often required. Historically such intervention was associated with invasive intubation and high oxygen concentrations, which contributed to the severe pathophysiology of early lung disease. Modern neonatal care utilises more gentle forms of ventilation, exogenous surfactant replacement therapy and maternal antenatal corticosteroids, which can aid the maturation of the lungs prior to delivery. Nonetheless it may still take some time for the associated inflammation secondary to these interventions to resolve. Even if infants can be managed in room air, exposure to the relatively hyperoxic extrauterine environment on the immature lung may still alter development (Stocks, 2013).

Chronic Lung Disease of Prematurity (CLD) or BPD is the name given to ongoing respiratory insufficiency and inflammation. The definition has changed over time, latterly the need for supplemental oxygen at 28 days of life, or at 36 weeks' postmenstrual age. Notwithstanding, both are associated with increased respiratory sequelae in childhood. However, it is now those of the earliest gestations ('extremely preterm', ≤28 weeks' gestation) who constitute the majority of sufferers of BPD/CLD. The pathophysiology of their disease is different (Jobe and Bancalari, 2001, Jobe, 1999), with dysregulated development of the alveoli and microvasculature being the predominant features as opposed to smooth muscle hypertrophy, fibrosis, and thickening of capillary basement membranes in the historically affected more mature infants (Northway et al., 1967).

As well as patent ductus arteriosus and fluid overload, a dysregulated pulmonary inflammatory response (Chakraborty et al., 2010) and bacterial infection are often implicated as risk factors in the development of BPD/CLD (Maxwell et al., 2006, Maxwell et

al., 2009). Both may have antenatal origins, as described above, with increased inflammatory markers, such as tumour necrosis factor-α, present in the amniotic fluid of mothers who deliver prematurely (Watterberg et al., 1996). My recent systematic review and meta-analysis has noted that *Ureaplasma* infection continues to be associated with BPD/CLD both at 28 days of life (OR 3.04; 95% Confidence Interval[CI] 2.41, 3.83) and at 36 weeks' postmenstrual age (OR 2.22; 95% CI 1.42, 3.47) (Lowe et al., 2014). This association was robust to correction for differences in gestational ages between exposed and unexposed groups (Figure 1-2). Thus, preterm infants, especially those born ≤28 weeks' gestation are at risk of an initial 'hit' due to prenatal exposure to inflammation, which is then exacerbated by the adverse effects of the necessary neonatal care including ventilation pressures and supplemental oxygen. Moreover, the damage induced by both sets of insults may further modulate the immune system such that susceptibility to postnatal infections is increased (Kunzmann et al., 2013). Pro-inflammatory cytokines (Kotecha et al., 1996), chemokines (Kotecha et al., 1995), and neutrophils (Kotecha et al., 2003) persist in the lung following birth, along with microbes such as *Ureaplasma spp*. which colonise the lung after being acquired in the antenatal or perinatal period. Whether empirical or targeted treatment of *Ureaplasma* infections with antibiotics could reduce the incidence of lung disease in the preterm new-born is unknown (Turner et al., 2012).

Recent studies have also examined the role of pre-eclampsia in neonatal lung disease, however, the results have been inconclusive. The potential link relates to the exposure of the foetus to maternal anti-angiogenic factors associated with pre-eclampsia which contribute to dysregulated lung and vascular growth (Levine et al., 2004). This has been described as the 'vascular hypothesis' for BPD/CLD, which is characterised by loss of small arteries and capillary density (Thebaud and Lacaze-Masmonteil, 2010). This raises concern in regards to adverse cardiopulmonary outcomes in childhood and beyond (Poon et al.,

2013), although, a recent study noted only minor differences in systolic blood pressure and little evidence of endothelial dysfunction in preterm-born children (Edwards et al., 2014).

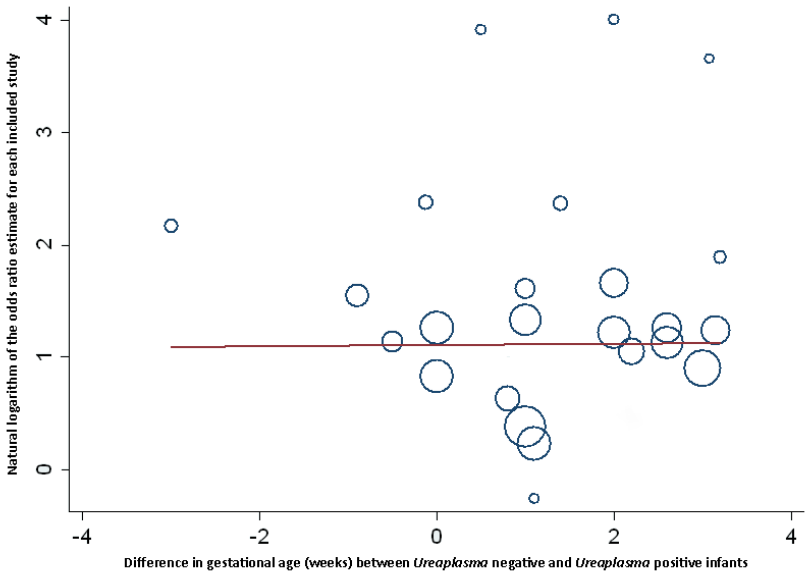


Figure 1-2: Meta-regression plot of association between *Ureaplasma* pulmonary colonisation and BPD/CLD at 28 days of life controlling for difference in gestational age between the colonised and non-colonised groups. There is little slope to regression line (p=0.96), indicating the risk of BPD/CLD attributed to *Ureaplasma* is not explained by lower gestational age. Reproduced with permission from Lowe et al. Pediatr Infect Dis J. 2014;33:697-702.

1.4.4 Respiratory outcomes in relation to preterm birth

1.4.4.1 Lung function and wheeze

Commensurate with the information presented above on risk factors is evidence that lung function in preterm-born children is already sub-optimal at birth. Studies using rapid thoracoabdominal compression have demonstrated reduced forced expiratory volume at 0.4 seconds, and decreased respiratory compliance in relation to low birthweight (Lucas et al., 2004). In healthy term-born children, Turner reported reduced maximal expiratory flow at functional residual capacity ($V'max_{FRC}$) at 1 month of age was associated with increased risk of asthma symptoms by age 3 (Turner et al., 2008). Friedrich et al. noted decreased

forced expiratory volume at 0.5 seconds ($FEV_{0.5}$), forced expiratory flows, but normal FVC in a small group of preterm infants at the age of two months. Moreover, this resulted in a reduced $FEV_{0.5}$/FVC ratio, indicating a mismatch between airway size and lung volume which tracked until longitudinal follow-up at the age of two years (Friedrich et al., 2007). These deficits are more pronounced in infants with a history of BPD/CLD. Thunquist and colleagues recently reported reduced indices of volume and flow compared to reference values both at 6 and 18 months of age which were exacerbated by active respiratory symptoms (Thunqvist et al., 2015). Similarly, Proietti reported a lower respiratory rate and increased tidal volume in preterm-born children at 44 weeks' postmenstrual age which may relate to an adapted breathing pattern secondary to ventilation-perfusion mismatch (Proietti et al., 2014).

The recent systematic review by Kotecha et al. noted decrements in lung function framed as reduction of approximately 7% in FEV_1 for individuals born <37 weeks' gestation when compared to term controls up to the age of 23 years (Figure 1-3) (Kotecha et al., 2013). Individuals with BPD/CLD had increased deficits of between approximately 16-19% when compared to controls. There is strong evidence that lung function tracks or deteriorates, but does not improve, through to the adult plateau which occurs between 20-25 years of age. For example, data from the Tuscon cohort indicates tracking of patterns of childhood wheezing and decrements in lung function in to adolescence (Morgan et al., 2005). Using the same cohort, Stern and colleagues noted that poor airway function in infancy framed as reduced $V'max_{FRC}$ correlated to reduced FEV_1/FVC ratio up to the age of 22 years (Stern et al., 2007).

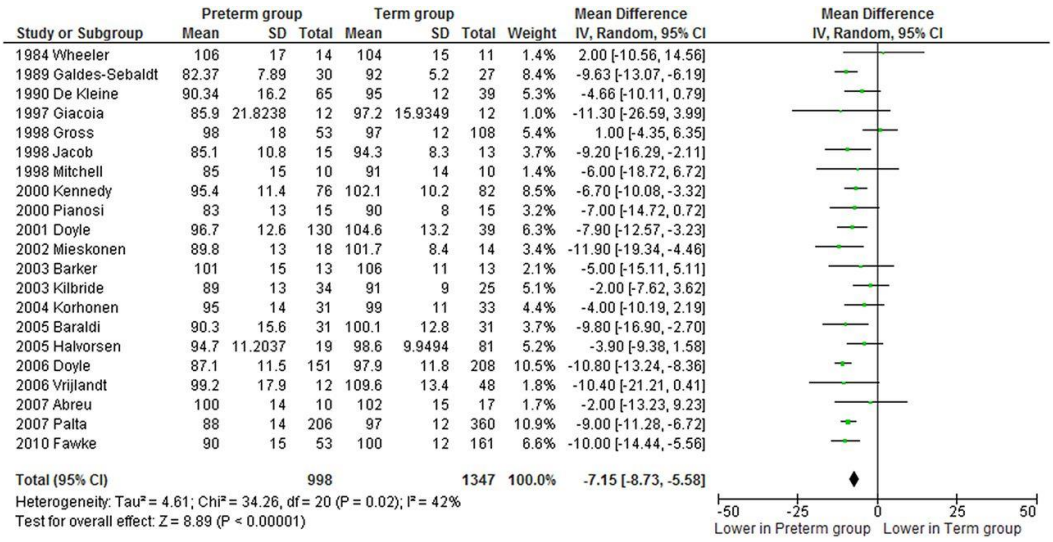


Figure 1-3 Forest plot representing the pooled mean difference in %FEV_1 between preterm born children and term-born controls. Reproduced with permission from Kotecha et al. Thorax 2013;68:760-6.

These data are supported by results from a cohort in New Zealand which reported persistent wheezing from childhood to 26 years of age was associated with continually reduced FEV_1/FVC ratio as well as increased bronchial hyper-responsiveness and sensitivity to house dust mite (Sears et al., 2003). Interestingly the slopes of FEV_1/FVC decline were similar in each of the wheeze phenotypes, indicating that the decrements in lung function had their origins in childhood (Teig et al., 2012).

These results are complementary to the review of childhood wheezing disorders described by Been and colleagues who noted increased risk of wheeze in preterm-born children (OR1.17; 95% CI 1.57-1.87) using a sample size of over 1.5 million subjects. Moreover, the authors also observed a strong dose-response effect of gestational age with a 6% decrease in risk of wheezing disorder for every additional week up until the fortieth week (Figure 1-4). Interestingly, substantial heterogeneity (up to I^2=80%) was also reported between the included studies which was somewhat explained by the variation in the age of the children included (Been et al., 2014). However, the strength of the association between preterm

birth and wheezing disorder was similar when analysis was stratified by age group. Thus, these results are consistent with the concept of tracking of poor respiratory outcome throughout childhood.

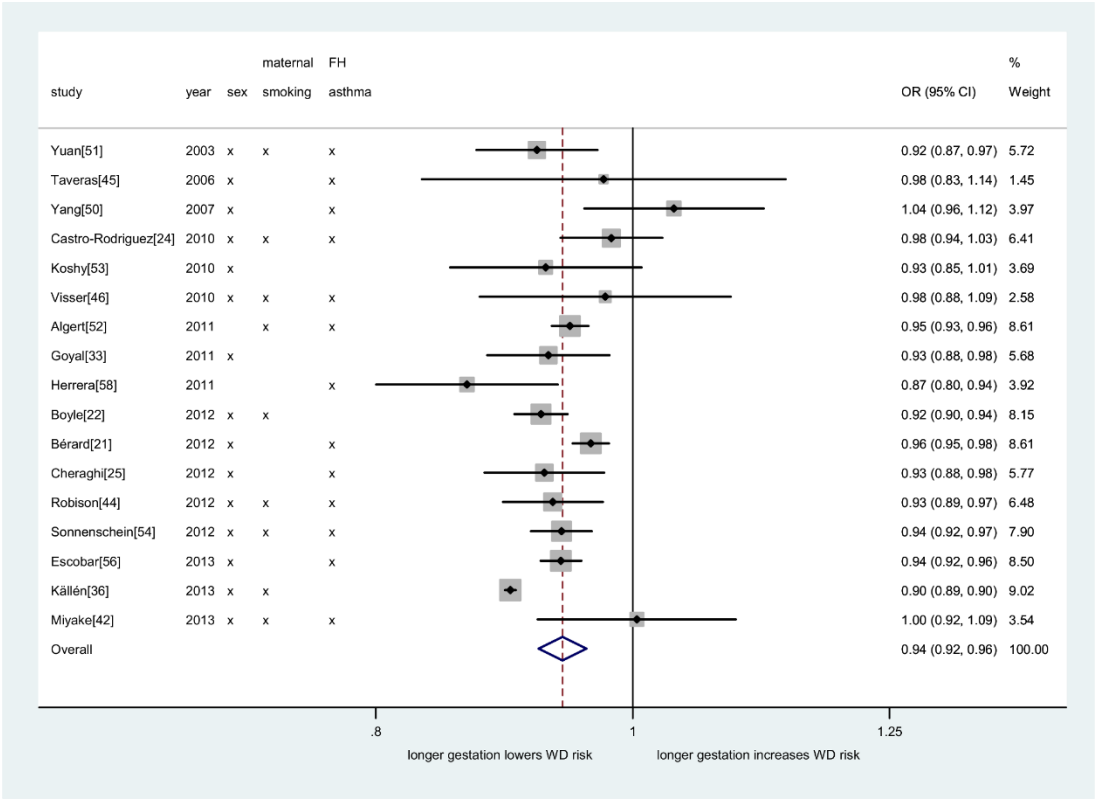


Figure 1-4 Forest plot representing a per-week dose-response effect of increasing gestation on the odds of wheezing disorders. The effect estimate is OR 0.94. Reproduced with permission from Been et al. PLOS Medicine 2014;11:e1001596 under Creative Commons Attribution (CC BY) licence.

These observations have recently been extended by studies within our department. The first study suggested that atopy does not play a role in the phenotype of wheezy disorder experienced by preterm-born children (Edwards et al., 2016). Rates of wheeze were noted to be similar in both preterm-born children with a family history of atopy (OR 2.0; 95% CI 1.6, 2.4) and those without a family history (OR 1.90; 95% CI 1.7, 2.1) when compared to term controls (Figure 1-5). The use of inhaled medication was also reported to be significantly higher in the preterm-born groups (especially ≤32 weeks' gestation), however, the efficacy of this treatment is not known. The second study reported that increased

respiratory symptoms could be demonstrated even up until 37-38 weeks' gestation; this has consequences as many elective caesarean sections are performed at this point of pregnancy (Edwards et al., 2015a). Often, preterm-born children are labelled as having asthma, however, there is growing evidence that the mechanisms and phenotypes of disease may be different. For example, preterm-born children have been shown to have airway inflammation which is mediated by neutrophils as oppose to eosinophils; furthermore, some studies do not show an increased risk for asthma (Astle et al., 2015) in preterm-born children when compared to those born at term.

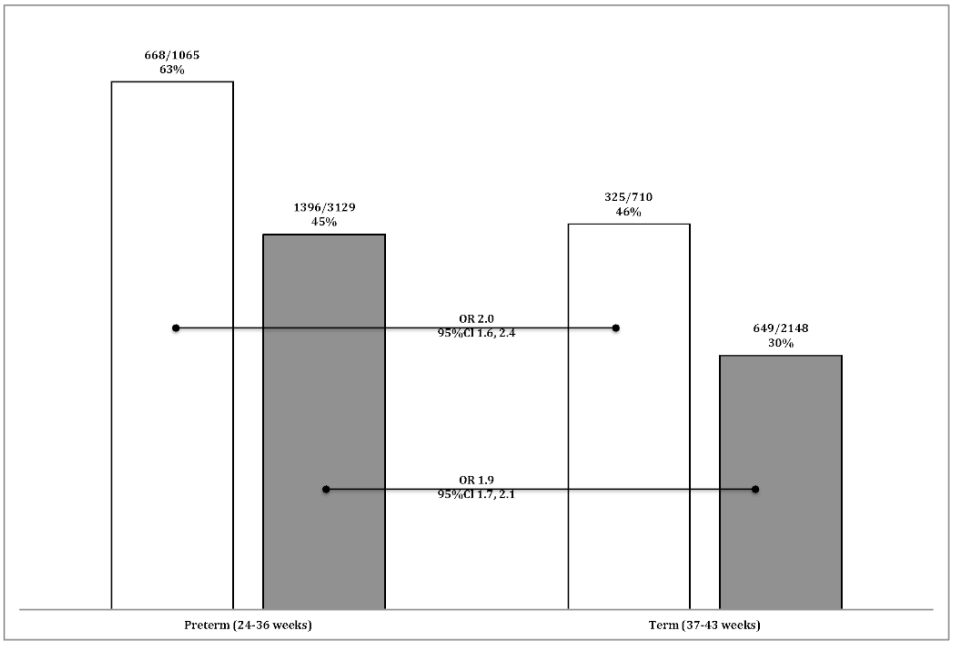


Figure 1-5: The prevalence of wheeze-ever within the RANOPS cohort for preterm-born children and term-born controls. The white bars denote family history of atopy and the grey bars denote no family history. The odds ratio for wheeze-ever is similar when comparing preterm-born children with, or without family history to term controls. Reproduced with permission from Edwards et al. PLOS One 2016;11:e0155695 under Creative Commons Attribution (CC BY) licence.

Taken together, these studies provide strong evidence that respiratory morbidity in adulthood has its origins early in life, and that these deficits track over time. The onset of age-related decline in lung function is not clinically relevant due to the large lung reserves available, however, preterm birth exacerbates these deficits, and imposes an additional burden which may further prevent attainment of peak lung function.

The longer-term impact of preterm birth on lung health is now starting to be realised as graduates of neonatal care from the 1970s onwards enter early adulthood. The recent systematic review by Gough and colleagues collated data from 8 eligible studies and reported evidence of increased respiratory symptoms and airflow obstruction in preterm-born adults, especially those with a history of BPD/CLD. This was accompanied by evidence of structural lung changes on radiological imaging which likely reflects lung injury during the neonatal period. (Gough et al., 2012).

Primary data collected by the same group also reported increased respiratory symptoms and medication use in BPD/CLD adults. FEV1 and FEF25-75 was also significantly lower than non-BPD preterms and term controls. These decrements were also accompanied by a lower EQ-5D score, potentially reflecting a perceived lower quality of life (Gough et al., 2014). Follow-up work by Caskey noted that adult survivors of BPD/CLD had increased rates of fixed airway obstruction, greater impairment in gas transfer, and reduced exercise capacity when compared to the term-born group. Lung clearance index as measured by multiple breath washout was also higher in the BPD/CLD compared to term-born controls (Caskey et al., 2016). These decrements may predispose preterm-born adults to an early and accelerated decline in pulmonary function later in life (Figure 1-6) and lead to early manifestation of chronic obstructive pulmonary disease (COPD) which impose restrictions on quality of life (Bush, 2008, Barker et al., 2013, Narang, 2010, Stocks, 2013); interventions have therefore been recommended to reduce the risk of chronic respiratory disease.

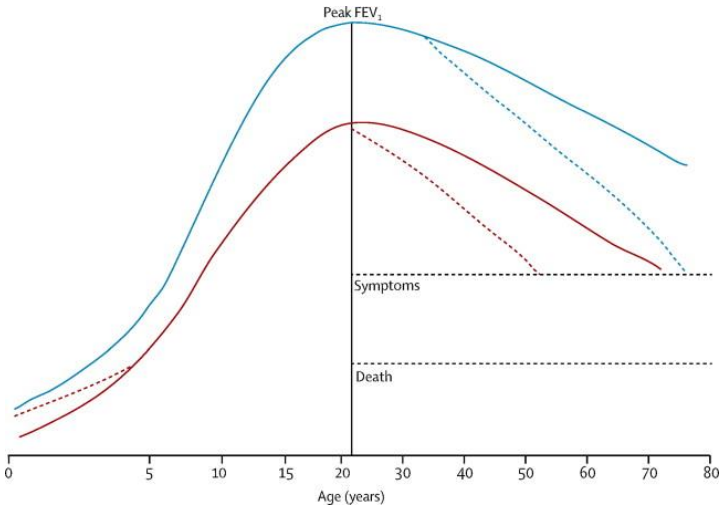


Figure 1-6 Diagrammatic representation of the potential early respiratory decline in individuals born with sub-optimal lung function. After failure to achieve peak FEV_1 in early adulthood in comparison with a normal trajectory (blue line), symptoms of disease may occur at a younger age (red line). The effect is exacerbated in the presence of other risk factors, e.g. tobacco smoking (dotted red line). Reproduced with permission from Stocks et al. Lancet Respir Med 2013 Nov;1(9):728-42.

1.4.4.2 Life course factors and the relationship between preterm birth and respiratory disease

It is necessary to briefly review other important determinants of respiratory sequelae in children, especially as many may act as important confounders or covariates when investigating the relationship between preterm birth and respiratory outcomes in childhood. In common with preterm birth, exposure to environmental tobacco smoke and other environmental pollutants, for example particulate matter, is strongly linked to reductions in lung function and increased symptoms such as wheeze (Dick et al., 2014), perhaps by promoting susceptibility to lower respiratory tract infections (LRTIs). Both tobacco smoking and preterm birth are intrinsically liked to lower socio-economic status. Moreover, preterm birth is a substantial risk factor for severe respiratory syncytial virus (RSV) infection and subsequent severe bronchiolitis, even in healthy moderately preterm-born children (Anderson et al., 2017). Historically, it has been difficult to assess the

direction of causality in terms of the effect of LRTIs and abnormal lung function. However, the ability to perform lung function testing in infancy has established that decrements in are present soon after birth, prior to infections such as RSV (Turner et al., 2008, Stern et al., 2007). Thus, poor lung function and propensity to gain respiratory infections may have origins in foetal life. Notwithstanding, RSV infection itself may increase susceptibility to later respiratory disease (Perez-Yarza et al., 2007) by persisting in a latent form and avoiding immune detection in privileged areas of the lung (Schwarze et al., 2004). A trial of RSV immunoprophylaxis indicated that prevention of infection was associated with decreased incidence of wheeze in the first year of life for healthy preterm-born infants. The authors suggest that early RSV infection leads to immunologic remodelling of the pulmonary system and to airway hyper-responsiveness and wheezing (Blanken et al., 2013)

1.5 Low birthweight and intrauterine growth restriction

1.5.1 Definitions

Low birthweight (LBW) is defined by the World Health Organisation (WHO) as <2500g, and is implicated in increased all-cause mortality in infancy and beyond (Watkins et al., 2016). However, it is important to realise that this definition may include infants who are born preterm at appropriate size for gestational age, or indeed, term-born infants with intrauterine growth restriction (IUGR) as gestation is not considered within the definition.

IUGR is most commonly defined as birth <10th centile for gestational age (World Health Organisation, 2002), and reflects failure to reach growth potential, either due to genetic disposition to be constitutionally small, or due to pathological reasons. The latter represents a substantial challenge to healthcare professionals during pregnancy and the perinatal period (Gardosi et al., 2013). Often IUGR is described as 'symmetrical', where the whole body is in proportion, or 'asymmetrical', in which the body is proportionally small in

relation to head size (Pike et al., 2012). The latter may reflect *in utero* adaptation by the foetus to preserve development of the brain and other essential organs. Symmetrical restriction of foetal growth is thought to originate in early in gestation, whereas asymmetrical restriction reflects the modified deposition of soft tissues (Lucas et al., 2004). Moreover, preterm birth is associated with increased risk for IUGR (Zeitlin et al., 2000).

1.5.2 The development origins of health and disease hypothesis

The concept that health outcomes throughout the life course may have their origins in foetal life (the 'foetal origins hypothesis') was established by Barker (Barker et al., 1989). This challenged the prevailing theory that the foetus existed in a 'privileged' environment which was protective against adverse exposures. In reality, disruption to the maternal environment during pregnancy from events such as exposure to noxious substances (tobacco smoke, alcohol) and under-nutrition (maternal diet or placental deficiency) can affect foetal development. In particular, the developmental origins of health and disease hypothesis encapsulates the paradigm of developmental plasticity (developmental programming) in which the foetus may make developmental adaptions in response to insults and adverse intrauterine conditions. The timing of the adverse exposure is critical in determining potential developmental effects on organ systems (Figure 1-7) (Gluckman et al., 2008); for example, in respect to the respiratory system, early growth faltering may influence the structural development of the respiratory tract such as the establishment of the trachea, main bronchi and airway epithelium. Such adaptations may be beneficial or detrimental in postnatal life depending on whether the postnatal environment is favourable or not, and may subsequently contribute to disease susceptibility (Pike et al., 2008).

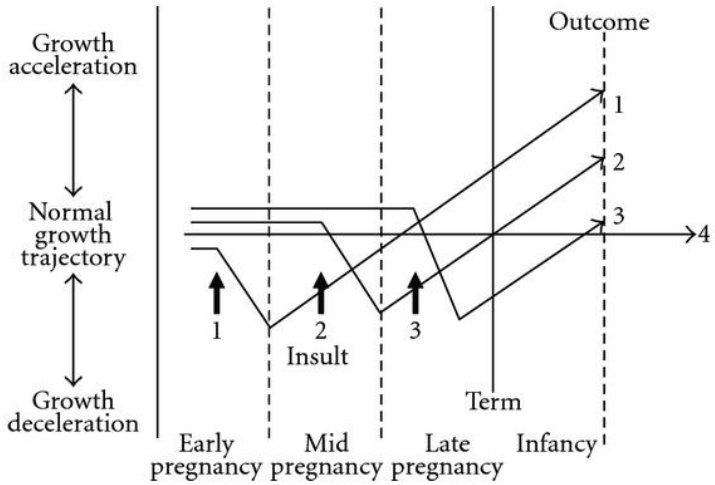


Figure 1-7: Example of timing of *in utero* insults and subsequent effects on foetal growth trajectory with impact upon birthweight at term, and beyond in to infancy. Reproduced from Turner S. Clin Dev Immunol. 2012;2012:962923 under the Creative Commons Attribution (CC BY) licence.

1.5.3 Risk factors for low birthweight and IUGR

Maternal hypertension and placental insufficiency are the key reasons for pathological low birthweight and IUGR. Thus, the important risk factors relate to those which cause impaired oxygen and nutrient exchange to the foetus secondary to dysregulated vascular development (Baschat, 2004). The extent to which this insufficiency affects the developing foetus depends upon the severity of the interference and the ability of the foetus to make an adaptive response. An example of metabolic adaptation is noted in sheep models where mild placental hypoglycaemia under hypoxaemia induces a compensatory increase in foetal glucose production (Jones et al., 1983). Early onset of this compromise may lead to permanent dysfunction or foetal demise, whereas late-onset may result in restricted growth velocity in the third trimester, but only sub-clinical metabolic effects.

Elegant studies using data from the Dutch Famine Birth Cohort Study (Lumey et al., 2007) have described the importance of maternal undernutrition during pregnancy on the health of their offspring in adult life, including an increased incidence of diabetes, cardiovascular

disease and obesity. In relation to respiratory disease, the study by Lopuhää noted that exposure to famine in mid-gestation was associated with increased prevalence of obstructive airway disease as diagnosed by a physician, but not reduced lung function or serum concentrations of immunoglobulin E (IgE). Lower ponderal index (representing 'thinness') was related to decrements in FEV_1 and FVC, but not FEV_1/FVC ratio, indicative of restrictive airway disease. Increased head circumference, reflecting growth faltering late in gestation, was related to increased IgE, which the authors speculate may promote an adverse Th2-mediated immune response and may predispose to atopy (Lopuhaä et al., 2000). The underlying mechanisms explaining the effect of undernutrition on the developing lung have been best observed in animals models, for example, studies in guinea-pigs which noted reductions in the available surface area for gas exchange (Lechner, 1985). Explanations for this include fewer alveolar attachment points (Elliot et al., 2003), fewer numbers of alveoli, which are increased in size, as well as thickened basement membrane. Moreover, numerous studies note reduced number and functionality of alveolar type-2 cells which are responsible for surfactant production (Pike et al., 2012).

Maternal exposure to noxious substances, including tobacco smoke, are also heavily implicated as determinants of IUGR. From a lung development perspective, nicotine has also been shown to decrease both alveolar surface area and capillary density (Maritz and Harding, 2011) as well as increased airway smooth muscle (Elliot et al., 1999).

1.5.4 Respiratory outcomes in relation to low birthweight

Increasing evidence demonstrates that low birthweight is associated with long term morbidities, including adverse respiratory outcomes, diabetes and cardiovascular disease. The first links between COPD and low birthweight in adults were reported over 25 years ago (Barker et al., 1991) and reductions in lung function have been confirmed in meta-analysis (Lawlor et al., 2005). However, confusion remains over the independent effects of

birthweight and gestational age, especially as preterm-born children are more likely to be small. Both low birthweight children (Kotecha et al., 2015) and those born at term but with IUGR (Kotecha et al., 2010) have been demonstrated to have decrements in lung function and increased respiratory symptoms (Mebrahtu et al., 2015a).

In exploring the foetal origins of health and disease hypothesis, authors investigating respiratory outcomes have historically used birthweight as a proxy for foetal growth. For example, Lucas and colleagues reported on foetal and early postnatal weight gain in term-born infants of 5-14 weeks of age and measures of lung function (Lucas et al., 2004). They observed reduction in forced expiratory volume in 0.4 seconds ($FEV_{0.4}$), total lung compliance and $V'max_{FRC}$ per standard deviation (SD) decrease in birthweight, head circumference and crown-heal length. They conclude that it is plausible that increases in adult respiratory morbidity are in part related to impaired lung development *in utero* and during the postnatal period. Reduced lung compliance as a result of growth restriction may imply a reduction of established elastic tissue which may predispose to earlier declines and early onset restrictive lung disease.

In an attempt to disentangle the relationship between preterm and IUGR birth, Kallen et al. investigated independent groups of children born preterm (with no IUGR) and term-born children with IUGR on rates of asthma as defined by inhaler prescription (Kallen et al., 2013). They reported that the association for use of inhalers decreased as gestation increased. Similarly, IUGR was noted to also predict increased inhaler use when examined in the term group, but to a less extent than reduced gestational age. Kurukulaaratchy investigated the effect of low birthweight in 10-year old children in relation to three wheezing phenotypes which had been established using longitudinal questionnaire data (Kurukulaaratchy et al., 2005). The population included appears to be largely born at term, however, as there were no specific data on gestational age this was not investigated as a

risk factor in statistical models. Low birthweight was reported to be an independent predictor of 'early transient wheeze', but not persistent wheeze.

In a term-born population, Caudri demonstrated increased respiratory symptoms as a result of the overall effect of decreased birthweight over a period of birth to five years of age which then attenuated over time (Caudri et al., 2007). The authors speculate that this may be due to the increase in lung size with age. However, there is still a possibility that smaller airways relative to lung size may result in suboptimal lung function and therefore increase the risk of a later onset respiratory disease. Further analysis was conducted to establish phenotypes from their longitudinal data on wheezing episodes, 'shorter pregnancy duration' was associated with transient early wheeze; birthweight was found to be an important perinatal factor for both transient early and intermediate-onset wheeze (Caudri et al., 2013).

Finally, in a recent study Barker and colleagues noted, in term-born adults, the odds of asthma were reduced with increasing birthweight in a dose-dependent fashion. Comparing the lowest birthweight category to the highest resulted in an odds ratio (OR) of 2.4 for the ≤2500g compared to >4000g group. These results were similar for length and head circumference and independent of gestation and preterm birth, concluding that asthma in adulthood was related to 'slow intrauterine growth' (Barker et al., 2013).

1.5.5 Respiratory outcomes in relation to foetal growth

To date, few cohort studies have reported on the foetal origins of childhood respiratory symptoms using foetal size and growth patterns as a risk factor for childhood asthma. One advantage of these studies is the use of foetal biometric measurements obtained from routine antenatal ultrasound scans as opposed to the proxy measure of birthweight. However, the results presented have been inconsistent. This is perhaps due to

methodological differences including comparisons of absolute foetal size versus measures of growth velocity, prospective and retrospective data collection of differing anthropometric measurements, varying age within the cohort studies at the time of outcome measurement, differing outcome measures and selection bias (Turner, 2012, Duijts, 2012).

The first study by Turner and colleagues demonstrated a 4% reduction in odds of wheezing ('ever wheeze'), and a 5% reduction in doctor-diagnosed asthma for each millimetre increase of crown-rump length (CRL) at age five years, with 2nd trimester measurements also associated with reductions (Turner et al., 2010). At age 10 years, increase in CRL was significantly associated with reduced odds of doctor-diagnosed asthma and wheeze in the last 12 months; CRL was also positively associated with increased lung function (6ml increase in FEV_1 per mm increase in CRL) (Turner et al., 2011). The effect of growth velocity between 1st and 2nd trimesters was measured by dichotomising the population around the median of each measurement. For example, below the median z-score for CRL in the 1st trimester and for biparietal diameter (BD) in the 2nd trimester was considered as persistent low growth. Below the median z-score for CRL and above for BD was defined as growth acceleration, whereas above the median for CRL and above for BD was defined as persistently high growth. At 5 years of age those exhibiting growth acceleration were found to have increased odds of asthma; at age 10 years, odds of doctor-diagnosed asthma were increased in the persistently 'low growth' group when compared to the persistently 'high growth' group.

The third study from the Southampton group found in 3-year old children that reduced growth in abdominal circumference during the 2nd trimester was associated with increased risk of atopy, whereas reduced growth during the 3rd trimester was associated with decreased risk. Atopic wheeze was similarly associated with 2nd trimester growth acceleration but with decelerated growth in the 3rd trimester. This was compared with non-atopic wheeze which was associated with early growth faltering of head circumference. This

suggests that factors restricting growth late in gestation influence development of atopy, whereas slow early growth may structurally affect the developing respiratory tract (Pike et al., 2010).

In contrast, the forth study by Sonnnenschien-Van der Voort et al. investigated the effect of foetal growth on a composite outcome derived from asthma symptoms collected longitudinally up to the age of 4 years. Growth restriction or acceleration was defined as a change of ±0.67 of foetal measurement z-score between first trimester CRL and second and third trimester head circumference (HC) femur length (FL) and abdominal circumference (AC) (Sonnenschein-van der Voort et al., 2012). They did not find any evidence of associations with foetal growth and asthma symptoms.

1.6 Infant growth and weight gain

1.6.1 Growth in infancy

Growth can be seen as a progression in metrics against a recognised standard. Weight, head circumference and length (height) are the most common measurements obtained in children to assess growth. In infancy, the method of feeding is an important determinant of weight gain and influences early growth trajectory. Infants may lose weight within the first days of life, with a greater effect in those whom are breast-fed compared to those who are formula fed (Crossland et al., 2008). However, breast-fed infants can generally be expected to gain weight more rapidly in the first two months of life, then grow at a slower rate up to 12-18 months of age (Cole et al., 2002); velocity changes of various growth indices are common during this period (Mei et al., 2004), which may reflect regression to the mean and thus adjustment to a trajectory which represents an individual's genetic potential for growth. Growth following the first year of life is a non-linear process which is characterised by periods of relatively small changes followed by unpredictable 'spurts' (Thalange et al., 1996).

Promoting appropriate growth in preterm-born infants both on the neonatal intensive care unit, and post discharge, is challenging; the optimal rates are not known. Considerable efforts have recently been made to provide charts which are specific to lower gestations at birth (Villar et al., 2014), however, these have been limited by the relatively small number of uncomplicated pregnancies which result in birth at less than 33 weeks gestation' (Villar et al., 2016). Optimal nutrient intake during the neonatal stay can be limited due to the immaturity of the gastrointestinal system, the metabolic demands required to fight infections and combatting pulmonary insufficiency (Griffin et al., 2016). Although rates of growth failure have improved, a significant minority of infants are still <10th centile for weight at the time of discharge (Horbar et al., 2015). In particular, infants diagnosed with BPD/CLD have inadequate weight.

1.6.2 Catch-up growth

'Catch-up' growth describes the phenomenon of accelerated growth over a specified period of time, such that subjects regress towards the population mean for a given measure. In reference to birthweight, catch-up growth observed during childhood may be seen as re-establishment of the normal growth trajectory following release from unsatisfactory conditions *in utero* such as exposure to maternal smoking during pregnancy.

Preterm-born children are widely expected to catch-up in terms of weight, such that, by school age most are of similar size to their term-born peers. However, those born at the extremes of gestation, whilst exhibiting catch-up growth, remain smaller than term controls (Bracewell et al., 2008). Whilst weight may continue to improve, disparities in height may still be present and persist in to adolescence (Roberts and Cheong, 2014) and early adulthood (Euser et al., 2008). Of note in regard to the themes investigated in this thesis, BMI has been reported to be similar between preterm-born young adults and term born controls (Bracewell et al., 2008), indicating a more rapid trajectory of BMI in those

born preterm during childhood. This may place preterm-born children at an increased risk of adverse health outcomes due to the changes in metabolic profile associated with weight gain.

1.6.3 Infant growth and weight gain in relation to respiratory outcomes

A growing number of studies have investigated the influence of weight gain during infancy and the association with later respiratory health. Van der Gugten investigated the effect of weight gain on spirometric measures in the first 3 months of life (van der Gugten et al., 2012). Weight gain was calculated by difference between weight z-score at birth and at 3 months of age. Rapid weight gain was defined as a change of >0.67 difference in z-score whilst the control population was limited to -0.67 to 0.67 change in z-score. At 1 year of age, rapid weight gain was significantly associated with more days of wheezing symptoms. At age 5 years, rapid weight again was associated with higher rates of GP consultations for wheezing illness and significant decrements in FEV_1 and forced expiratory flow at 25-75% of vital capacity (FEF_{25-75}). Both measures appeared to be independent of birthweight as addition of this variable this to the statistical model did not affect the results. These data are supported by the studies from the Southampton Women's Study (Pike et al., 2010) and the Generation R cohort (Sonnenschein-van der Voort et al., 2012) who have also described that weight gain in infancy is associated with early childhood wheeze.

Exploring similar themes in early childhood, Magnus and colleagues recently reported on peak weight velocity within the first 36 months of life and asthma symptoms at the ages of 36 months and 7 years in their Norwegian cohort (Magnus et al., 2015). Peak weight velocity was noted to be associated with current asthma and increased lower respiratory tract infections at 36 months, and current asthma at 7 years. Flexeder et al. investigated peak weight velocity from birth to 24 months of age and reported that this was associated with asthma, but not wheeze at age 10 (Flexeder et al., 2012). In a follow-up study using

the same methodology for quantifying weight gain, lung function was noted to be negatively associated with peak weight velocity at 15 years of age (Claudia et al., 2015). Interestingly, the strongest associations were with lower measures of FEF_{25-75} as well as a reduction in the FEV_1/FVC ratio. The absence of significant bronchodilation (only 200µg of salbutamol were administered due to adverse reactions observed at higher doses), along with the lung function data presented, suggest that structural deficits accrued during foetal life and in the first years after birth may be a plausible mechanism. These results are in keeping with other studies who have reported similar decrements in lung function, such as that presented by Turner et al. who demonstrated an association between a relative reduction in lung growth between 1 to 12 months of age, increased postnatal weight gain and early transient wheeze at 3 years of age (Turner et al., 2008). Also, researchers using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) noted lower FEV_1/FVC ratio for children who exhibited rapid weight gain in infancy (Sonnenschein-van der Voort et al., 2015).

In the largest study to date, Sonnenschein-van der Voort conducted a meta-analysis of the influence of preterm birth and infant weight gain on the relationship with childhood asthma risk. Preterm birth was associated with increased respiratory symptoms in both the preschool wheezing and school-age asthma groups. Infant weight gain over the first year of life was also associated with increased respiratory symptoms (Sonnenschein-van der Voort et al., 2014). Both analyses were independent of birthweight, however, despite reporting odds ratios for preschool wheezing of 3.87 and school age asthma of 2.92 for ≤28 weeks' gestation when compared to those born at term, it was unclear how many children were born at the lower gestations. This work was taken forward by Den Dekker and colleagues who confirmed that significant reductions in FEV_1/FVC ratio, and increased respiratory symptoms, were associated with weight gain during infancy (den Dekker et al., 2016). FEV_1 was also reduced in preterm-born children and accompanied by reduction in forced

expiratory flow at 75% of vital capacity (FEF_{75}), suggesting that peripheral airway patency is implicated in their phenotype of lung disease; preterm-born children with low birthweight had the largest deficits in lung function. Importantly, it was noted that these associations were present across the full range of gestation and birthweight.

Popovic et al. also reported on infant weight trajectories and respiratory outcomes in term-born infants aged 18 months using data from the NINFEA cohort (Popovic et al., 2016). Using the superimposition by translation and rotation method of modelling growth, they noted that infant size and weight gain velocity were both independently associated with infant wheezing. The authors propose that both the mechanical effects of increased weight gain, as well as an adipogenic immune response and hormonal imbalance may dispose children to respiratory disease. In one of the few studies specifically focused on preterm-born children, researchers using data from the Infant Health and development programme in the US investigated both the effect of BMI gain in the first year of life, as well as linear growth, on doctor-diagnosed asthma at 8 years of age (Belfort et al., 2016). Each z-score gain in BMI was associated with increase of doctor-diagnosed asthma, with the effect being independent of linear growth. Possible explanations were noted to include epigenetic factors as well as diet, physical activity and inflammatory factors. Thus, promotion of excess weight gain, which does not match other variables of growth, may be detrimental to lung health in preterm-born children. Data from the 'Born in Bradford Cohort' which noted that rapid, or inconsistent growth after birth at low birthweight (adjusted for gestation) was associated with increased risk of wheezing disorders (Mebrahtu et al., 2015b), supports the notion that optimising postnatal growth may be beneficial in managing the risk of poor respiratory outcome in childhood.

In summary, there is evidence that both foetal growth trajectory, and accelerated infant weight gain are important determinants of respiratory health in childhood. However, there

is paucity of data specifically relating to outcomes in preterm-born children. Further investigation in to this vulnerable population is pertinent due to their additional pre-and-postnatal risk factors for respiratory sequelae.

1.7 Physical activity

Casperson describes physical activity (PA) as "any bodily movement produced by skeletal muscle that results in energy expenditure"(Caspersen CJ, 1985). There is little doubt PA is an important determinant of health and participation is associated with a broad range of health benefits including lower risk of all-cause mortality in adults. After tobacco, diet, and alcohol, inactivity is now recognised as one of the leading causes of non-communicable diseases by the World Health Organisation.

Indeed, *The Lancet* recently published a five-part series concerning physical activity. Branding the culture of inactivity a pandemic, the series sets the agenda for future research strategy and policy making (Das, 2012).

Thus it is unsurprising that promotion of PA amongst younger generations is a key public health message in order to advocate habit-forming behaviour, including avoiding obesity (Kohl et al., 2000). National guidelines recommend participation in 60 minutes of at least moderate activity per day for children to promote a wide range of health benefits (Department of Health, 2004, Strong et al., 2005). It is well recognised that participation in PA has been shown to be beneficial in attenuating risk factors for long term morbidities in adulthood with strong negative associations between PA, overweight, diabetes and some cancers. A recent meta-analysis showed that PA was beneficial in reducing the odds of obesity even in those genetically predisposed to being overweight (Kilpelainen, 2011). There is growing concern that such risk factors are present in young children and may lead

to early-onset chronic disease. Moreover, there is strong evidence that levels of PA decline through childhood and into adolescence. A clear gender effect also exists, with females less active than males across all domains of activity intensity, (Riddoch et al., 2004) Figure 1-8.

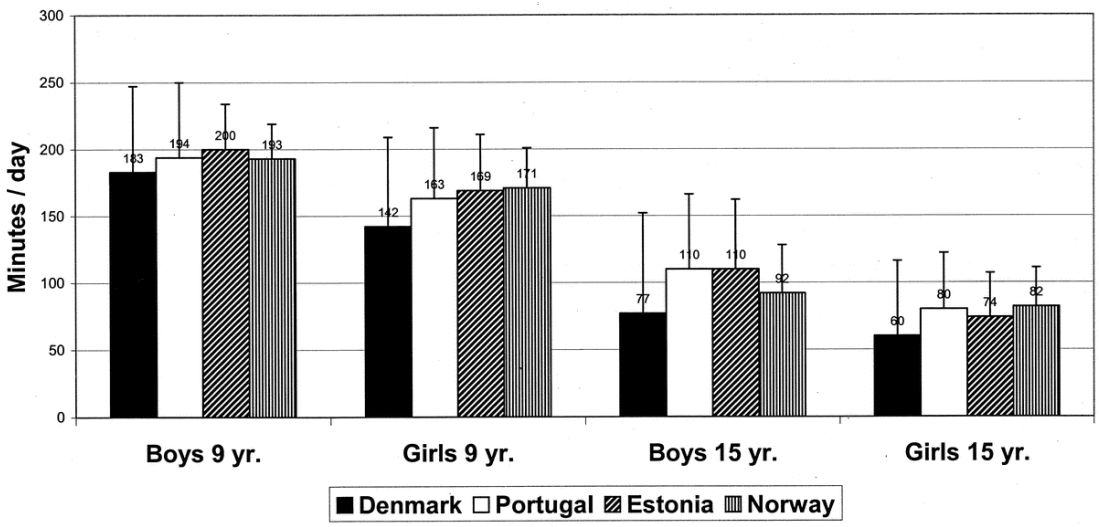


Figure 1-8 The age and gender distribution of time engaged in at least moderate-intensity physical activity in four European countries. The columns represent means and error bars represent standard deviation). A clear difference is demonstrated between males and females at both ages, with the decline evident between 9 and 15 years of age. Reproduced with permission from Riddoch et al. Med Sci Sports Exerc. 2004;36:86-92

Children born preterm may be at risk of reduced levels of PA as they have increased respiratory symptoms as well as decrements in lung function, muscle bulk and exercise capacity. The evidence presented earlier in this chapter indicates that the effects are prevalent across the whole range of gestational age. In this section, the current literature in regards to levels of PA in preterm-born children are presented, and I shall also explore PA in cohorts of young adults in order to contextualise the possible impact on long term risks to respiratory health. However I begin with a summary of the methodology in regards to PA measurement.

1.7.1 Measurement of physical activity

The objective measurement of physical activity under free-living conditions is challenging due to the need for ambulatory equipment which reliably and accurately records

movement. To ensure compliance with the protocol, it must be simple to use (for the technical staff and users) and well-tolerated outside of a clinical setting (so that sufficient duration of recording is obtained. As physical activity is defined in terms of energy expenditure (Caspersen CJ, 1985), data obtained from devices such as heart rate monitors and accelerometers (both popular for use in large cohort studies) must be validated to a corresponding physiological measure of energy expenditure to allow for interpretation of results. Three criterion standards are used to measure energy expenditure during physical activity: direct observation, doubly labelled water and indirect calorimetry (Sirad JR, 2001).

1.7.1.1 ***Criterion standards***

Methods of direct observation utilise questionnaire-based reports of exercise intensity completed by trained researchers, which can be burdensome. Estimates of energy expenditure are made from the results based on validation against a physiological measure, e.g. heart rate monitoring. These methods are suitable for widespread use and allow the researchers to contextualise facilitators and barriers to physical activity at group level as well as for individuals (McKenzie et al., 2000). Direct observation can also be suitable for children who are not able to accurately recall information (Anderssen et al., 1995). However, they still rely on subjective reporting (although inter-observer agreement is often high), do not capture activity outside of the sample environment (i.e. school, youth groups) and may be bias as children may alter their natural behaviour in lieu of participation. Moreover, children's activity varies on a daily basis thus repeatability of the results is a further limitation (Kohl et al., 2000).

Activity energy expenditure (AEE) can be quantified using Total Energy Expenditure (TEE) and basal metabolic rate (BMR) over a given period of time using the doubly labelled water (DLW) technique. This involves ingesting water containing heavy hydrogen and heavy oxygen ($^{2}H_{2}{}^{18}O$), and calculating CO_2 production by measuring the excretion of these

isotopes in urine over a 2-week period. ^{2}H is eliminated as water, whilst $^{18}0_2$ is eliminated as water and CO_2- the difference in elimination rates is proportional to energy expenditure (CO_2 production converted to TEE using food quotients from patient diaries). Basal metabolic rate is derived from gender, age, weight and height; AEE is then calculated as TEE minus BMR (Ekelund U, 2001, Livingstone et al., 1992). However, the procedure is expensive and therefore of limited use in large scale epidemiological studies.

The third standard, indirect calorimetry, has become more popular as a validation technique in recent years due to the development of portable equipment. Previously, participants in energy expenditure studies utilising this method of measurement may have been required to spend over 24 hours in an air-tight open-circuit chamber whilst performing a set routine of rest and exercise. The chamber is continuously ventilated by atmospheric air. A measure of CO_2 production versus O_2 consumption, the respiratory exchange ratio, is calculated periodically by extracting air through a flow meter which records the difference in gas concentrations between air entering and leaving the chamber (Bitar et al., 1996). The resulting value can then be used to calculate energy expenditure during different levels of activity. Modern equipment such as portable metabolic units now allow for similar measures to be recorded outside of a fixed laboratory setting, and these devices (which require a facemask and chest harness) have been used in accelerometer calibration studies (Mattocks et al., 2007)

Each criterion standard has its own limitations in terms obtaining optimal estimates of physical activity. Indeed, usage of these methods is limited to calibration studies involving a relatively small group of participants to validate other objective measures (Figure 1-9). Heart rate monitors and accelerometers are two such devices which have now found favour in large scale epidemiology studies. Both are minimally intrusive, simple to use, and accuracy has improved given advancements in technology.

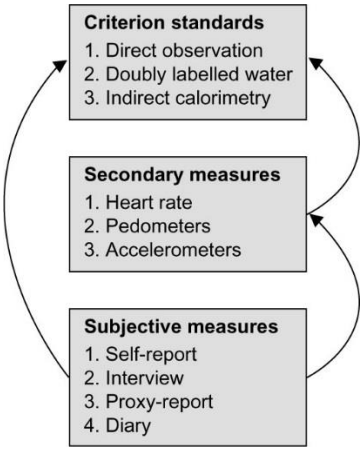


Figure 1-9 Validation of methods for recording physical activity against acceptable criterion standards. Reproduced with permission from Sirad & Pate. Sports Med. 2001;31:439.

*1.7.1.2 **Heart rate monitors***

Heart rate monitors have shown linear relationships with 0_2 consumption, however it can be difficult to control for factors such as cardiovascular fitness (lower resting heart rate) and obesity (higher resting heart rate, slower recovery to resting rate following exercise) (Maffeis et al., 1995). Furthermore, the relationship is confounded at sedentary and low levels of activity by physiological and environmental factors which may raise the resting heart rate (e.g. stress, medication) (Livingstone et al., 1992). The effect of these confounders can be reduced by establishing a threshold heart rate which can discriminate between resting and exercise values. During continuous recording, this allows periods to be assigned as resting energy expenditure (under threshold heart rate) and activity energy expenditure (over threshold heart rate). The limitation of this method is that heart rate must be calibrated against volume of oxygen consumption ($\dot{V}O_2$) at five levels of exercise intensity to produce a regression line for calculation of energy expenditure (Bitar et al., 1996).

1.7.1.3 ***Accelerometers***

Accelerometer technology can be seen as an evolution of pedometers. Whilst the former uses a mechanical component within the mechanism to register a 'count', the first accelerometers used a piezoelectric transducer to convert a detected motion in to an electric signal. Latterly, updated versions have used changes in capacitance which enable both static changes in g-force as well as those produced during motion to be recorded (John and Freedson, 2012). A number of accelerometers have been well validated against criterion standards, however strength of correlations with energy expenditure are variable due to differences in methodologies employed in the studies (e.g. placement of accelerometer, activities performed). The Actigraph 7164 accelerometer, used in ALSPAC, has been calibrated in both children and adolescents using indirect calorimetry. In a validation study designed to reflect free-living conditions, children were asked to perform 6 different activities for 5 minutes each whilst wearing the Actigraph to measure activity and a portable metabolic unit to measure $\dot{V}O_2$. Each activity represented an increased level of intensity as quantified by metabolic equivalent tasks (METs). A MET is defined as the energy cost of physical activity expressed as multiples of baseline $\dot{V}O_2$, with 1 MET equalling resting $\dot{V}O_2$ [mL kg^{-1} min^{-1}]. Regression equations were then produced (corrected for age and gender) to predict both energy expenditure and $\dot{V}O_2$ from activity counts. The number of accelerometer counts accumulated at 3, 4 and 6 METS was then used to establish cut-points for intensity of activity when adjusted for age and gender(Mattocks et al., 2007).

Worn on the right hip during waking hours (figure 1-10), the device recorded frequency and intensity of movement in a vertical plane; the signal from the Actigraph is sampled 10 times each second and movement counts summed over epochs of 1 minute (an epoch is defined as 'counts per unit time'). Ten hours (600mins) of data recoded on at least 3 of 7 days has

been show as sufficient to be valid for inclusion in analysis. A weekend day was found not to be mandatory (Mattocks et al., 2008).The total counts per minute are averaged over the period of a valid recording to provide a measure of total activity. The total activity count is then sub-divided into categories of activity (as per cut-points derived from the calibration study): Sedentary behaviour, light intensity PA, moderate intensity PA, and vigorous PA. The latter two categories are often combined in to moderate to vigorous physical activity (MVPA), as this is a definition commonly used in activity guidelines (e.g. children are encouraged to engage in at least 60mins MVPA per day (Department of Health, 2004)).

Figure 1-10 Position of accelerometer on the right hip.

Some limitations apply to use of the Actigraph 7164 accelerometer. Water-based activity cannot be recorded, and as the device records movement in the vertical plane only, activities where the torso remains stationary, namely cycling and upper-body activities, are not well captured. Secondly, in order to capture a full week of activity, 1 minute epochs are used (owing to the storage capacity of the device). This may lead to a certain under-estimation of activity levels. Finally, the upper limit of acceleration which can be detected is 2.5*g*. Since more strenuous activities such as jogging/running and jumping elicit accelerations well above this threshold, the device is limited in its ability to detect these higher-impact activities. Finally, the device was not calibrated to specifically measure sedentary behaviour.

The use of an updated version of the Actigraph accelerometer (GT1M) in the Millennium Cohort study solved some of these limitations. However, it still needs to be removed for water-based activities, and has the same constraints in measuring upper-body activities. Technological advances allowed increased battery life, and crucially data storage capacity which allows a higher sampling rate (15 second epochs). Moreover, calibration was also performed to define sedentary behaviour as well as light, moderate and vigorous activity, using indirect calorimetry and a range of free-living and self-paced routines, as similarly performed for ALSPAC (Pulsford et al., 2011).

1.7.2 Physical activity and exercise capacity in relation to preterm birth

Primary studies directly measuring PA in preterm-born children are relatively few, rather these data are often discussed as add-on elements to investigations of lung function, exercise capacity, neuromotor development, or a combination of these elements. Furthermore, most studies rely on subjective questionnaire data to quantify activity, whereas some secondary analyses of epidemiological data from longitudinal cohort studies have utilised objectively measured habitual PA from accelerometer recordings. One complication in comparing results is that some studies report associations based on birthweight rather than gestational age. Since such studies often include large numbers of preterm-born participants, all studies based on gestational age or birthweight are discussed below for completeness.

*1.7.2.1 **In children and adolescents***

In the youngest cohort of neurologically unimpaired preterm-born 5-7 year olds with and without BPD/CLD, habitual PA, expressed in hours per week, has been reported using a questionnaire comparing results to matched term controls (Kriemler, 2005). Lung function and exercise capacity were assessed as the primary endpoints of the study. The authors did

not find statistically significant differences in parent-reported PA between the three groups under study despite preterm-born children having reduced lung function (worst in the BPD/CLD group) and higher degrees of reported exercise-induced bronchoconstriction (decrease in FEV1 of ≥15% at any time up to 10 minutes' post-exercise) when compared to the term controls. Although there was no difference in maximal uptake of oxygen or exercise capacity, the oxygen cost of maximal power output was higher in the preterm-born children with BPD/CLD. These children also had increased respiratory rate, lower tidal volumes but similar minute ventilation compared to preterm-born children without history of BPD/CLD and term-born controls. Together these findings indicated that there may be a higher metabolic cost of exercise which may limit participation in prolonged activities. A further study using the same cohort examined anaerobic performance in children born preterm (<32 weeks' gestation)(Keller et al., 2000). Habitual PA was quantified using a self-administered questionnaire, although the focus of the study was on impaired anaerobic muscle performance which was noted to be reduced in extremely low birthweight (ELBW, <1000g) when compared to very low birthweight (VLBW, 1000-1500g) and normal birthweight (>2500g). Anaerobic muscle peak-power was assessed by cycle ergometer using a supramaximal test. The authors suggested that reduced levels of PA could be a contributing factor in the reduction of muscle performance, perhaps due to impaired exercise capacity and thus increased amount of time spent sedentary. However, they did not observe differences in levels of PA between the different birthweight groups and presented very limited data on the results. PA was measured using an adapted questionnaire which reported participation in recreational activities in excess of normal physical education classes.

In a further study, focusing on neurological outcomes, Wolcadlo investigated levels of PA in preterm-born 8 year old children both with and without Developmental Coordination Disorder (DCD)(Wocadlo and Rieger, 2008). The primary aim of the study was to assess

motor impairment and learning ability since other studies show deficits in ELBW and VLBW children. Measurement of PA was taken from verbal reports by the child and their parent of participation in after school sporting activities. Children with DCD scores of below the 15th centile were more likely to be motor impaired, have lower intellectual performance and participated in less sporting activity. The authors suggest that withdrawing from participation due to movement difficulties, or through exclusion by peers may explain the difference in activity levels.

Svien et al. investigated the 'health-related fitness' of a group of moderately preterm-born children (mean gestational age of 32 weeks', excluding those with history of BPD/CLD or other complications of preterm birth) and well-matched controls at approximately 9 years of age (Svien, 2003). PA data were reported using a questionnaire completed by the child and by their parents which captured information on the child's frequency of exercise or frequency of sports team participation in the past 7 days. Body fat was estimated using skinfold callipers, muscular strength and endurance measured by a battery of drills, and endurance measured via a treadmill protocol. The preterm group demonstrated deficits in muscle strength, endurance and coordination. However, no evidence of differences in cardiorespiratory endurance or in measures of PA (frequency of exercise or frequency of sports team participation in the past 7 days) were reported between those born preterm and those born at term. Of interest, a difference was noted in percentage body fat despite the groups being of similar weight, suggesting that the term controls had higher muscle mass contributing to higher cardiovascular endurance. There is a lack of detailed research relating to body composition in preterm-born children and results of available studies are conflicting. The study by Bott et al. reported that 4 to 8-year old children with BPD/CLD were smaller and leaner than healthy controls (Bott et al., 2007). Vardar-Yagli et al. compared a slightly older group of preterm-born children with BPD/CLD with term controls and reported fat-free mass was significantly lower in BPD/CLD children which correlated

with reduced distance covered on a six-minute walk test (Vardar-Yagli et al., 2015). In contrast, another study reported that fat mass, adjusted for height, is lower in preterm-born children at 8-12 years of age when compared to term-born children, but observed no differences in fat-free mass (Fewtrell et al., 2004).

Focusing on exercise capacity, Joshi et al. recently noted that preterm-born children with a history of BPD/CLD self-reported less time spent on PA when compared to preterm-born children without BPD/CLD and those born at term. The study team demonstrated exercised-induced bronchoconstriction, manifested as reduce (FEV_1), in preterm-born children with and without BPD/CLD after formal exercise (Joshi et al., 2013). This was reversible following administration of salbutamol in the BPD/CLD group. The study also showed that at peak exercise, preterm-born children have different breathing patterns, using increased ventilatory reserve to maintain similar oxygen uptake at maximal or peak exercise ($\dot{V}O_2$) as term-born children. Investigators from the EPICure study focussed on extremely preterm birth (<25 completed weeks' gestation) and associations with exercise capacity and PA using data from a national cohort of children at age 11 years (Welsh et al., 2010). In contrast to studies relying on questionnaire responses, a strength of this study was the use of accelerometers to collect objective measurements of PA. Exercise capacity, assessed using cycle ergometer, and spirometry were also performed. Extremely preterm-born children were noted to have reduced peak $\dot{V}O_2$, tidal volume, minute ventilation and used more of their ventilatory reserve. Despite these differences, there was only a weak correlation between peak $\dot{V}O_2$ and accelerometer counts (total activity or MVPA). Interestingly, those born extremely preterm had a self-perception of inferior exercise capability and reported increased difficulty in breathing during exercise when compared to term-born peers.

Kilbride et al. followed up a cohort of ELBW graduates of neonatal intensive care (mean gestational age 26 weeks' gestation at birth) between 9 and 15 years of age in order to assess exercise tolerance and lung function in this otherwise asymptomatic group of children, comparing them with a term-born control group (Kilbride et al., 2003). In terms of PA outcomes, parents perceived their ELBW children as less active physically than the term controls using a simple 5-point scale ('inactive' to 'very active'). Lung function was reported to be significantly reduced in the ELBW children, however, the majority of the difference was accounted for by ELBW children who had BPD/CLD in infancy. Additionally, ELBW children had reduced oxygen consumption (independent of BPD/CLD status) during exercise. This most likely reflected reduced fitness rather than cardiorespiratory dysfunction, but could represent other physiological limitations not yet described. Interestingly, a small proportion of BPD/CLD children were excluded from the exercise challenge analysis as their effort was considered sub-maximal. One possible reason for this diminished effort could be exercise-induced bronchoconstriction, which the authors acknowledged was not measured in their study.

One of the most well-characterised extremely preterm-born cohorts is that described by the Norwegian group who examined the exercise capacity of two cohorts of extremely preterm children aged 10 years (born in the 1990s) and 18 years (born in the 1980s) using an incremental treadmill test (Clemm et al., 2012). The study team did not find differences in peak $\dot{V}O_2$ or anaerobic threshold in spite of reduced FEV_1 in the preterm group although distance covered was on average 10% lower over the course of the test when compared to term controls. Conversely, leisure time PA reported via self-completed questionnaire was significantly reduced in the preterm-born group. When the 10 year old cohort was recently followed up at 18 years of age, there were small reductions in exercise capacity with decrements in mean peak $\dot{V}O_2$ and treadmill distance covered when compared to term controls (Clemm et al., 2015). However, these differences were largely explained by male

gender and individuals with minor disabilities. Lung function expressed as predicted FEV_1 was also lower in the extremely preterm group but this was interestingly not related to exercise capacity. The study also found that leisure-time physical exercise was lower in the preterm group when reported in hours per week. Higher levels of exercise correlated with higher peak $\dot{V}O_2$ in both the preterm and term groups suggesting that they both have similar training potential. Furthermore, longitudinal analysis demonstrated that capacity at 10 years of age was reported to predict capacity at age 18 years in terms of peak $\dot{V}O_2$ as well as treadmill distance covered suggesting tracking of exercise capacity over time. There was no changes in leisure time physical exercise, which remained lower in the preterm group.

Rogers and colleagues investigated differences in PA as well as aerobic capacity, flexibility and muscle strength in 17-year olds born with ELBW stating that "establishing early, adequate levels of fitness and activity may be particularly important in former tiny infants, who may be at risk of early onset adult disease" (Rogers et al., 2005). PA was measured using questionnaire-based data on sports and activity participation and aerobic fitness was measured using a graded stepping test. ELBW teenagers were noted to have reduced aerobic fitness capacity, participated in less sport and reported reduced levels of PA. The authors acknowledge that it is difficult to know if reduced exercise tolerance is a result of detraining through lack of activity or as a result of preterm birth (i.e. subclinical cardiorespiratory compromise) - an area that needs further evaluation. If the former, the authors speculate that this may be due to physical limitations, which may be physiological or perceived, and followed by a subsequent decision not to participate by the child themselves or through parental intervention. However, by 17 years of age, these individuals are likely to have freed themselves from obligatory participation (e.g. physical education lessons or other organised sport) and therefore may represent a lifestyle choice.

In summary, although some studies show only modest differences in exercise capacity in terms of peak volume of oxygen consumption ($\dot{V}O_2$), preterm-born children have different breathing patterns, using increased ventilatory reserve to maintain similar oxygen uptake at maximal or peak exercise ($\dot{V}O_2$) as term-born children. Furthermore, they exhibit increased rates of exercise-induced bronchoconstriction which are reversible following administration of salbutamol (Joshi et al., 2013). Other studies have shown a difference in peak $\dot{V}O_2$, as well as reduced anaerobic threshold, lower peak workload and increased residual volume in preterm-born children (Welsh et al., 2010, Kilbride et al., 2003, Smith et al., 2008) especially in those with BPD/CLD. Together these deficits suggest that airflow obstruction, reduced lung compliance, and gas trapping which may all be results of injury to the developing lung in the postnatal period. Moreover, the reduced DL_{CO} reported in some studies further indicates disruption in alveolar and pulmonary microvascular development in preterm-born children which may be secondary to neonatal lung injury.

1.7.2.2 ***In Adults***

Svedenkrans and colleagues recently reported on the exercise capacity of preterm-born adults aged between 18-26 years who enrolled for military service in Sweden (Svedenkrans et al., 2013) and noted reduced performance on cycle ergometry including after correction for birthweight. Indeed, the effect was dose-dependent with a decline in exercise capacity for each week of decrease in gestational age at birth (Figure 1-11). The authors suggest that fewer alveoli, reduced capillary density and smaller airways as sources of the deficit in exercise capacity but also cite cardiovascular, neurological and body composition limitations as possible contributing factors.

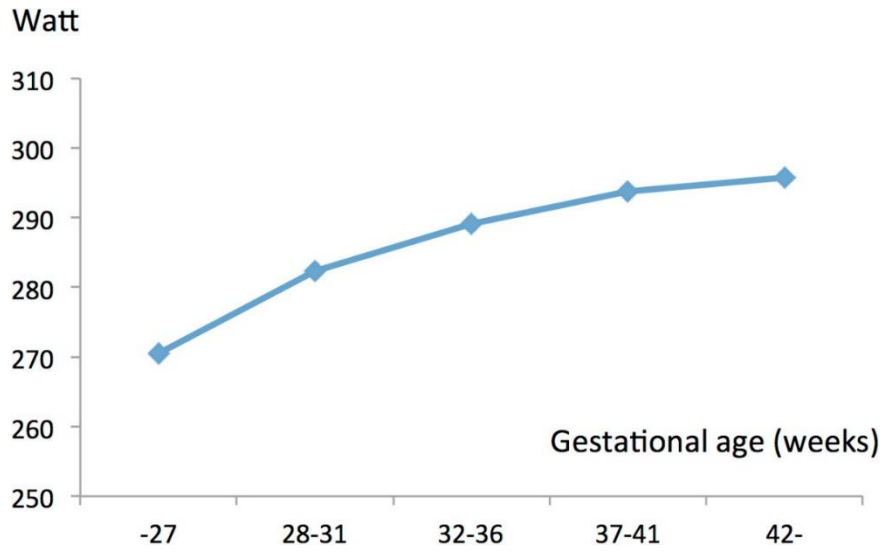


Figure 1-11 Adjusted results expressed as least squared means for maximal exercise capacity (Watt) in relation to gestational age. Reproduced from Svedenkrans et al. PLoS ONE. 2013:e80869 under the Creative Commons Attribution (CC BY) licence.

These findings correlate well with outcomes from other large cohort studies based in Scandinavia. Two previous studies have used data from the Helsinki study of VLBW adults established in the late 1970s which assessed frequency of conditioning leisure time PA using questionnaire-based data (Kajantie et al., 2010, Kaseva et al., 2012). Compared with term controls, VLBW adults participated in lower frequency, duration and intensity of conditioning PA (defined as exercise to maintain physical condition or competitive training) which was not explained by confounders including height, parental education, lean mass and percentage body fat. Notwithstanding, there is some evidence that body composition may be an additional factor. For example, in the study by Kaseva et al. VLBW participants had lower lean body mass. In contrast, in a study of young adults, there was no difference in lean body weight when preterm-born subjects with and without BPD/CLD, and term born subjects were compared (Landry et al., 2016). However, preterm-born subjects with BPD/CLD had reduced total active energy expenditure and spent more time sedentary; additionally, all preterm-born groups (irrespective of neonatal history) had increased

prevalence of bronchial hyper-responsiveness. Of note, follow up of the Helsinki cohort did not find evidence of differences in objective measures of total activity, MVPA, or time spent sedentary using accelerometry when compared to term controls (Kaseva et al., 2015).

A further Finnish cohort study demonstrated that extremely preterm-born 23-year olds perceived themselves to be less physically fit that term controls (Tikanmaki et al., 2016). This study excluded participants with cerebral palsy and other physical disabilities. The authors could not show any differences in cardiorespiratory fitness when measured by a submaximal step test and suggest that any associations are mediated through percentage body fat and PA. Instead the authors noted that reduced self-perceived fitness may be related to decrements in muscle strength. Saigal reported on a cohort of young adults also born in the 1970-80s (aged approximately 23 years) who were followed-up longitudinally after admission to the neonatal unit as a result of ELBW (Saigal et al., 2007). Information on PA and other measures (functional limitations, healthcare usage) were collected using questionnaires. ELBW young adults had significantly lower scores in measures of physical self-efficacy, perceived physical ability, and reported less participation in sports and strenuous activity when compared with term-born controls. They also reported higher rates of asthma and functional limitations including visual deficits and dexterity.

Another follow-up study of the Norwegian cohort by Clemm and colleagues reported that peak $\dot{V}O_2$ and distance completed during treadmill testing was reduced by 10% in those born extremely preterm when compared to term-born peers at 25 years of age. There were no differences between the groups in terms of self-reported leisure time PA although this did correlate with improved exercise performance (Clemm et al., 2014); furthermore, exercise capacity was not related to FEV_1 or a history of BPD/CLD. When combining results of this study with those from the previous analysis at 18 years of age, participants born

extremely preterm were less physically active, thus suggesting a detraining effect is responsible for reduced exercise capacity. This idea was shared by Vrijlandt and colleagues whose cohort of preterm-born young adults self-reported fewer hours of exercise per week at approximately 19 years of age (Vrijlandt et al., 2006).

Of note in regards to the studies presented in this section is the limited information of data presented on contemporary graduates of modern neonatal care. Preterm infants born in the late 1970s and 1980s were subject to prolonged invasive mechanical ventilation and high levels of oxygen supplementation. Commercially available exogenous surfactant, which significantly reduces the incidence of respiratory distress syndrome and allows rapid step-down to more gentle forms of ventilation, only become available in the 1990s following extensive clinical trials during the 1980s (Halliday, 2008). However, simultaneously, the survival rate at the extremes of viable gestation had markedly improved such that rates of BPD/CLD have remained largely the same (Costeloe et al., 2012). Thus, it would be of great interest to compare and contrast the respiratory outcomes, as they relate to levels of physical activity, in preterm-born children who were born in the early era and modern eras of surfactant use.

1.8 Summary of introduction

In this chapter, I have presented background information relating to foetal growth and development of the respiratory system; preterm birth and neonatal outcomes; low birthweight, and infant growth. The current evidence in regards to how these factors impact upon respiratory health in childhood, and beyond, have been reviewed. I have then presented the literature in relation to the impact of preterm birth on physical activity, a potential mediator of respiratory health through the life course.

In compiling the data included within this chapter, I have identified general paucity of data which specifically relates to preterm-born children, especially in regards to foetal and infant growth patterns and how these relate to later respiratory outcomes. There is growing evidence that the aetiology of lung disease in preterm-born children is different to those born at term, thus it is important to specifically investigate such factors and how they impact on the respiratory health in this vulnerable population. This is especially so given the rise in preterm birth rates worldwide. Chapters 2 and 3 of this thesis will address the effect of foetal growth, and then infant weight gain on later respiratory symptoms.

Physical activity is an important mediator of health and disease. Preterm-born children may be at risk of reduced PA secondary to decrements in lung function and impaired exercise capacity. The evidence presented in this introduction identifies a lack of data in regards to levels of physical activity in preterm-born children, especially those born in the surfactant era, and how this relates to markers of respiratory health; namely, lung function, and incidence of respiratory symptoms. Moreover, the majority of the existing studies do not focus on preterm birth as a primary exposure, and rely on questionnaire data as opposed to objective measures of PA such as accelerometers. Chapters 4 and 5 of this thesis will investigate the levels of objectively measured physical activity in preterm-born children. Below, I describe the cohort studies from which data for my analyses were obtained, before outlining the research questions and aims to address my specific hypotheses presented in each chapter.

1.9 Cohort studies

1.9.1 Respiratory and Neurological Outcomes of Preterms Study (RANOPS)

The RANOPS study was lead by Dr Martin Edwards and Professor Sailesh Kotecha from the Department of Child Heath at Cardiff University. The design of the study was a cross-

sectional questionnaire survey of children between 1-10 years of age with a history of preterm birth, and matched term-born controls (born in the same locality, gender, and day). Ethical approval for the survey was obtained from the Wales Research Ethics Committee (REC ref 13/WA/0155). In 2013, local principal investigators representing each of the health boards in Wales mailed out an invitation to participate on behalf of the research team in Cardiff (Appendix 1), along with the study questionnaire which included a section to obtain consent for use of the provided data. Optional consent was also obtained for database linkage, and to be contacted regarding queries/future research studies. The respiratory content of the questionnaire, which is the focus of this thesis, was based around the Liverpool Respiratory Questionnaire (Powell et al., 2002) for children <5 years of age (Appendix 2), and the ISAAC questionnaire (Asher et al., 1995) for children ≥5 years of age (Appendix 3). Both questionnaires are designed to be parent-completed. In total, 26,722 were mailed out with a final response rate of 7,149 (26.7%). Longitudinal follow-up of RANOPS in now under way.

1.9.2 Avon Longitudinal Study of Parents and Children (ALSPAC)

The ALSPAC cohort, branded for participants as 'Children of the 90s', was established by Professor Jean Golding at Bristol University as a response to the WHO call for longitudinal studies to determine the prevalence and antecedents of ill health (Golding et al., 2001). Initially focused on pregnant mothers, the primary aim was to collect observational data via self-completed questionnaires which could be linked to other information obtained from health records. Enrolment took place between 1990-1992 with the aim to recruit participants when they attended for their dating antenatal ultrasound scan (although enrolment was open throughout pregnancy and beyond). At the end of the pregnancy recruitment phase, 14,541 participants had been enrolled, with further numbers added during subsequent recruitment campaigns (Boyd et al., 2013). Over the first 6 years, follow-

up was based on postal questionnaires; however, a 10% sample of ALSPAC ('Child in Focus') were observed during frequent clinic visits, before the whole cohort at-large attended for their first clinic visit between 7-8 years of age. Follow-up has continued to this day with clinics completed at 11, 15, and 18 years of age, with data collection at the age 24 clinic currently ongoing.

1.9.3 Millennium Cohort Study (MCS)

The MCS was commissioned by the Economic and Social Research Council and administered by the Centre for Longitudinal Studies at University College London. Branded as 'Child of the New Century', the survey followed-up approximately 19,000 families of children born between 2000-2002. To improve the representativeness of the data in comparison to the UK's previous birth cohorts, MCS was designed to over-sample from geographic areas with high levels of child poverty, with high ethic minority populations, and from the devolved nations of the UK. This was particularly to investigate social and economic circumstances at birth and in early childhood, and the potential life disadvantages/advantages this may confer (Hansen K., 2012). The first 'sweep' was performed when children were aged approximately 9 months by a team of field workers and focused on the circumstances of pregnancy and birth. These data were linked to birth records to verify the information collected in the family's home. Further sweeps have been performed at the ages of 3, 5, 7 and 11. Data collection for the survey at 14 years of age has recently been completed and further follow-up at age 17 is planned.

1.10 Research questions and aims

1.10.1 Associations between foetal size, growth trajectory, and childhood respiratory symptoms in preterm-born and term-born children

In this first study, my principal question was:

‘Does foetal size, or growth trajectory, predict increased incidence of respiratory symptoms in preterm-born children?’

The specific aims of the study were to:

I. investigate whether anthropometric data obtained from first and second trimester foetal ultrasound scans were related to increased respiratory symptoms in childhood
II. investigate if altered growth trajectory, calculated from change in foetal biometric measurement between first and second trimester scans, and between second trimester scans and birthweight, are related to increased respiratory symptoms in childhood

Data for this study were obtained from the Respiratory and Neurological Outcomes of Preterms Study (RANOPS). Foetal ultrasound reports were obtained from the national radiology database via anonymous database linkage performed by the NHS Wales Informatics Service (NWIS).

1.10.2 Associations between weight gain and childhood respiratory symptoms in preterm-born and term-born children

The research question for my second study was:

‘Following preterm birth, is weight gain in infancy associated with increased respiratory symptoms later in childhood? What are the important factors mediating this relationship?’

My specific aims were:

I. To investigate if weight gain between birth and nine months of age was associated with increased respiratory symptoms in childhood.

II. To investigate if weight gain between birth and 24 months of age was associated with increased respiratory symptoms in childhood.

III. To investigate if degree of prematurity influenced the effect of weight gain on respiratory symptoms in childhood.

IV. To explore if early life factors mediate the relationship between infant weight gain and childhood respiratory symptoms.

Data for this study were obtained from the RANOPS cohort. Weight data were obtained from the national child health database via anonymous database linkage performed by NWIS.

1.10.3 Physical activity in preterm-born 11-year old children born in the 1990s

The research question for this study was:

'What are the levels of objectively measured physical activity in preterm-born children when compared to term-born controls? Are levels of physical activity related to the decrements in lung function observed in these children?'

The specific aims were:

I. To investigate the levels of total physical activity, moderate to vigorous physical activity, and sedentary behaviour in preterm-born children and compare these to term-born controls.

II. To investigate if measure of lung function are correlated to levels of physical activity.

Data were obtained from the Avon Longitudinal Study of Parents and Children (ALSPAC).

1.10.4 Physical activity and sedentary behaviour in preterm-born 7-year old children born in the 2000s

The research question for this final chapter was:

'What are the levels of objectively measured physical activity and sedentary behaviour in preterm-born children compared to those born at term? Do current respiratory symptoms and family history mediate these relationships?'

The specific aims were:

I. To compare the levels of physical activity and sedentary behaviour in preterm-born children to those of children born at term.
II. To investigate whether respiratory symptoms and family history of atopy mediate any observed relationships between preterm-birth and physical activity.

Data were obtained from the Millennium Cohort Study (MCS).

2 Association of foetal size and growth trajectory with respiratory symptoms in preterm-born and term-born children

2.1 Overview

Preterm-born children (<37 weeks' gestational age) are at an increased risk of respiratory symptoms, hospital admissions, and reduced lung function in childhood and beyond (Been et al., 2014, Kotecha et al., 2013, Edwards et al., 2016, Sonnenschein-van der Voort et al.,

2012). Increasing evidence suggests that these risks persist in to adulthood potentially developing in to early-onset COPD (Bush, 2008, Kotecha et al., 2013).

As presented in the Introduction to this thesis, there has been sustained interest in both antenatal and postnatal growth patterns in children, and how these relate to risk of childhood respiratory disease, most commonly asthma. Historically, birthweight has been used a proxy for foetal wellbeing and has been related to outcomes both in child and adulthood (Barker et al., 1991, Lawlor et al., 2005, Kotecha et al., 2015). However, it is increasingly recognised that birthweight is a result of many months of development during which the infant may be exposed to adverse intrauterine conditions including nutritional deficits, placental dysfunction, and maternal smoking (Duijts, 2012, Turner, 2012, Henderson and Warner, 2012). Foetal adaptations to this adversity may affect the development of organ systems (Gluckman et al., 2008), such as the respiratory system, which continues to develop throughout gestation (Kotecha, 2000). Dysregulation of lung growth may be further compounded by preterm birth (Joshi and Kotecha, 2007) and pulmonary inflammation associated with neonatal respiratory distress (Chakraborty et al., 2010). To date, the few studies investigating growth patterns in utero and their association with later childhood respiratory disease have reported inconsistent results (Pike et al., 2010, Turner et al., 2011, Turner et al., 2010, Sonnenschein-van der Voort et al., 2012). Moreover, none of these studies have been conducted in preterm-born children- a vulnerable population at-risk of long term respiratory morbidity. Little is known about the influence of foetal size and growth trajectory on the later risk of increased respiratory symptoms in the preterm-born population. Investigating this relationship may help to disentangle the interaction between foetal growth, birthweight, gestational age and risk of respiratory symptoms in childhood.

2.2 Aims and Hypothesis

The aim of this study was to (a) investigate whether differences in foetal size and growth trajectory are important factors in predicting increased respiratory symptoms in both preterm and term-born children; (b) investigate whether anthropometric data obtained from first and second trimester foetal ultrasound scans were related to increased respiratory symptoms in childhood; and (c) investigate if altered growth trajectory, calculated from change in foetal biometric measurement between first and second trimester scans, and between second trimester scans and birthweight, are related to increased respiratory symptoms in childhood.

The specific hypotheses are:

a) That reduced foetal size in the first or second trimester of pregnancy will be associated with increased respiratory symptoms in childhood
b) That changes in growth trajectory during gestation will be associated with increased respiratory symptoms. Specifically
    i. Growth faltering between the 1st trimester and 2nd trimester would be associated with increased respiratory symptoms
    ii. Growth faltering between the 2nd trimester and birth would be associated with increased respiratory symptoms

2.3 Methods

2.3.1 The Respiratory and Neurological Outcomes of Preterms Study (RANOPS)

Respiratory outcome data from RANOPS, a cross-sectional population study of preterm-born children, were used (Edwards et al., 2015a, Edwards et al., 2016). In 2013, our group sent Liverpool Respiratory Symptom Questionnaires (if <5 years of age) or a modified ISAAC Questionnaire (if over ≥5 years of age), to all identifiable live-born preterm (<37 weeks' gestation) surviving children born in Wales aged between 1 and 10 years, and term controls

(born same gender, day and locality), n=26,722. In total 7,149/26,722 (26.7%) were returned, of which 4283 were born preterm and 2,866 were born at term. Both questionnaires have been validated (Asher et al., 1995) (Powell et al., 2002) and use of such questionnaires is widely accepted in epidemiological studies. Ethical approval for the survey was obtained from the Research Ethics Committee and parents gave consent by returning completed questionnaires (REC ref 13/WA/0155).

2.3.2 Perinatal data

Demographic data, including gestation, birthweight, singleton or multiple birth and Wales index of multiple deprivation (WIMD, a measure of socio-economic status) were available from national healthcare databases via the NHS Wales Informatics Service (NWIS). Children were divided into four groups based on gestational age at birth: 25-32, 33-34, 35-36 weeks' gestation and term controls (37-43 weeks' gestation). This approach is similar to studies on lung function (Kotecha et al., 2012) and that of others as it represents specific stages in lung development (Joshi and Kotecha, 2007) and children most at risk of lung disease (Boyle et al., 2012, Greenough, 2012). Intrauterine growth restriction (IUGR) was defined as $<10^{th}$ centile for standardised birthweight corrected for gestation and gender using the LMS method (Medical Research Council, UK) as previously used in studies of growth and lung function (Ong, 2000, Kotecha et al., 2010). The LMS method uses a reference population to construct smoothed growth curves which can be applied to external datasets to derive percentiles and/or z-scores (Cole, 1990).

2.3.3 Foetal anthropometric data

Questionnaire responders had the option to give consent to healthcare database linkage for further study. Access to the national system for radiology imaging and reporting was possible for 4 of 7 Health Boards in Wales through NWIS (Aneurin Bevan, Abertawe, Hywel

Dda, Betsi Cadwalder). The remaining Health Boards (Cardiff and Vale, Powys, Cwm Taff) used differing systems which could not be linked. For each questionnaire responder giving consent for database linkage, a unique anonymous identifier originally generated for RANOPS by NWIS was returned to the information analyst. Using this ID the mother of the child was identified along with their date of birth, NHS number and Hospital number. The date of birth of the child, and the number born (i.e. singleton or multiple) were used to identify the correct pregnancy and extract the antenatal scan reports from the radiology database. All scan reports were anonymised using the RANOPS ID only prior to transmission back to the research team.

Scan reports were provided in a text-based format and therefore foetal measurements (crown rump length, head circumference, femur length) were extracted using C++ coding, which identified strings of characters following the name of the measurement (CRL, HC, FL and variants). C++ script was prepared by Dr W John Watkins. The extracted data file was checked in its entirety for accuracy against the original data file and cleaned where appropriate.

Gestation (in completed weeks) at the time of the scan was abstracted from the reports where possible, or, if missing, was calculated from the difference between gestation at birth and date of scan. The growth charts of Robinson (CRL) and Chitty (HC and FL) were used to create z-scores, adjusted for gestational age at the time of measurement, using the published equations (Loughna et al., 2009, Robinson and Fleming, 1975):

$$\mathrm{CRL\ z-score} = \frac{(\mathrm{GA} - 23.73)^2}{67.234}$$

$$\mathrm{HC\ z-score} = -109.7 + 15.16\mathrm{GA} - 0.002388\mathrm{GA}^3$$

$$\mathrm{FL\ z-score} = -32.43 + 3.416\mathrm{GA} - 0.0004791\mathrm{GA}^3$$

The CRL z-score for 1st trimester scans closest to 12 weeks' gestation (10-13 weeks' gestation inclusive, and within ±3.5SD of mean CRL measurement) was identified for each child. For second trimester scans, the HC and FL z-scores closest to 20 weeks' gestation (17-23 weeks' gestation inclusive, and within ±3.5SD of mean HC or FL measurement) were identified. The available data are presented graphically below (CRL, Figure 2-1; FL, Figure 2-2; and HC, Figure 2-3).

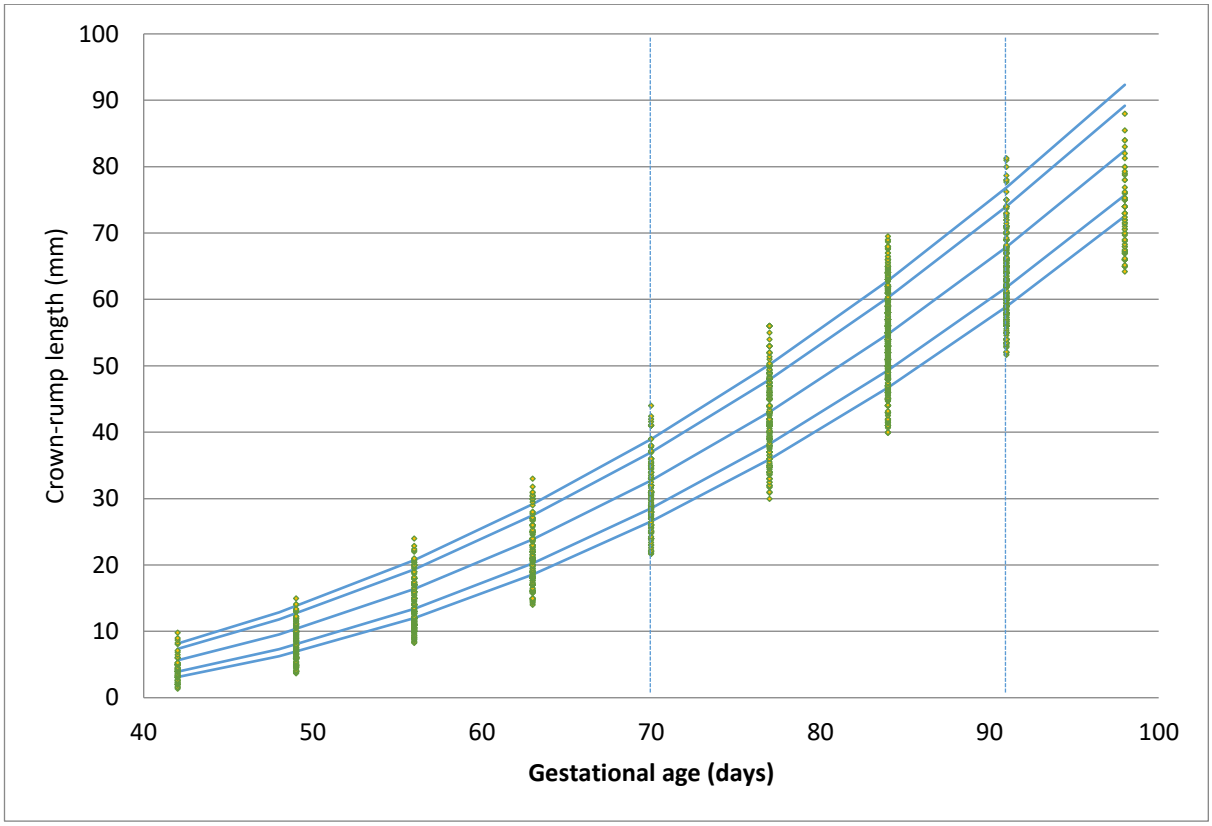


Figure 2-1 CRL data plotted according to Robinson & Fleming 1975. Lines represent the 97th, 90th, 50th, 10th, and 3rd centiles. A total of 2297/2581 CRL measurements are represented in the chart (284 were excluded for being greater than ±3.5SD from the mean CRL at a given gestational age). Measurements used in the analysis were limited to 10-13 weeks (70-91 days), as represented by the dotted lines. Use of CRL measurements are not recommended after 13 weeks of gestation as measurement error increases beyond this point.

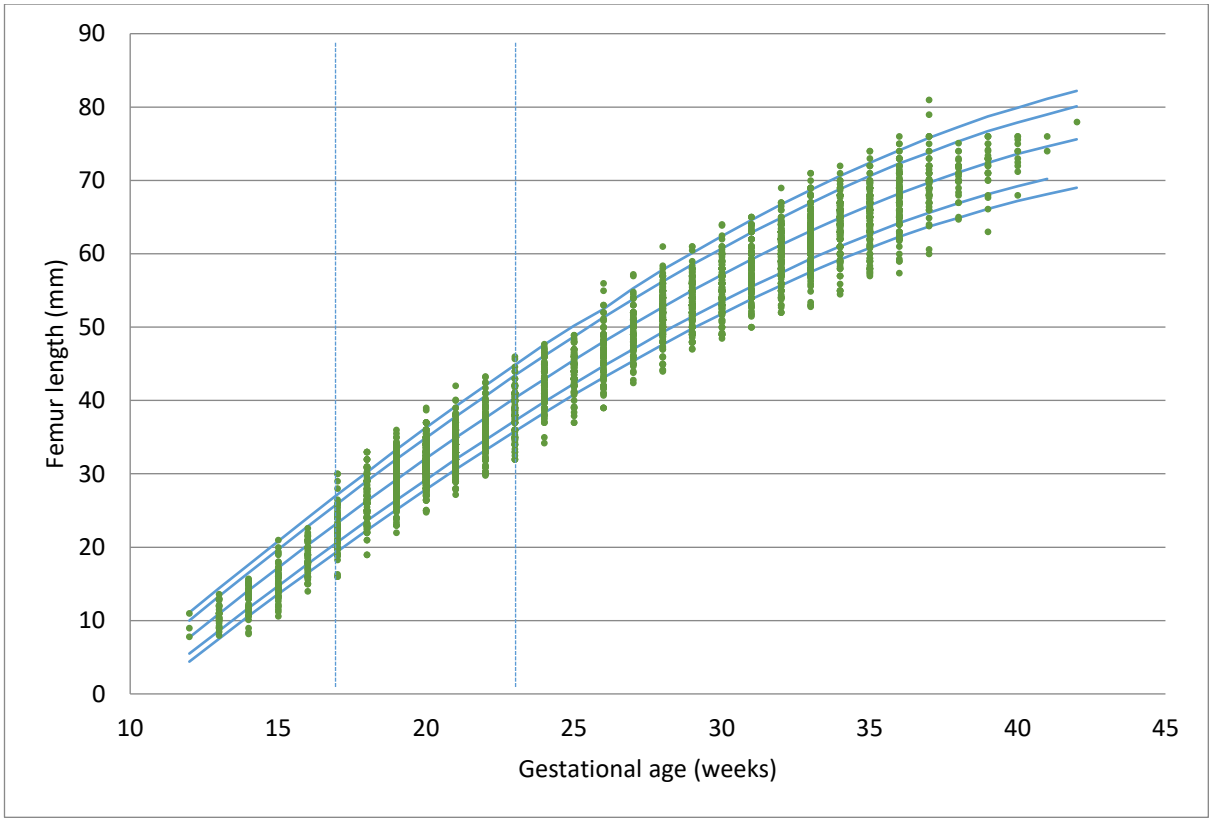


Figure 2-2 Femur length data plotted according to Chitty and Loughna et al. 2009. Lines represent the 97th, 90th, 50th, 10th, and 3rd centiles. A total of 5956/6230 FL measurements are represented in the chart (274 were excluded for being greater than ±3.5SD from the mean FL at a given gestational age). Measurements used in the analysis were limited to 17-23 weeks, as represented by the dotted lines.

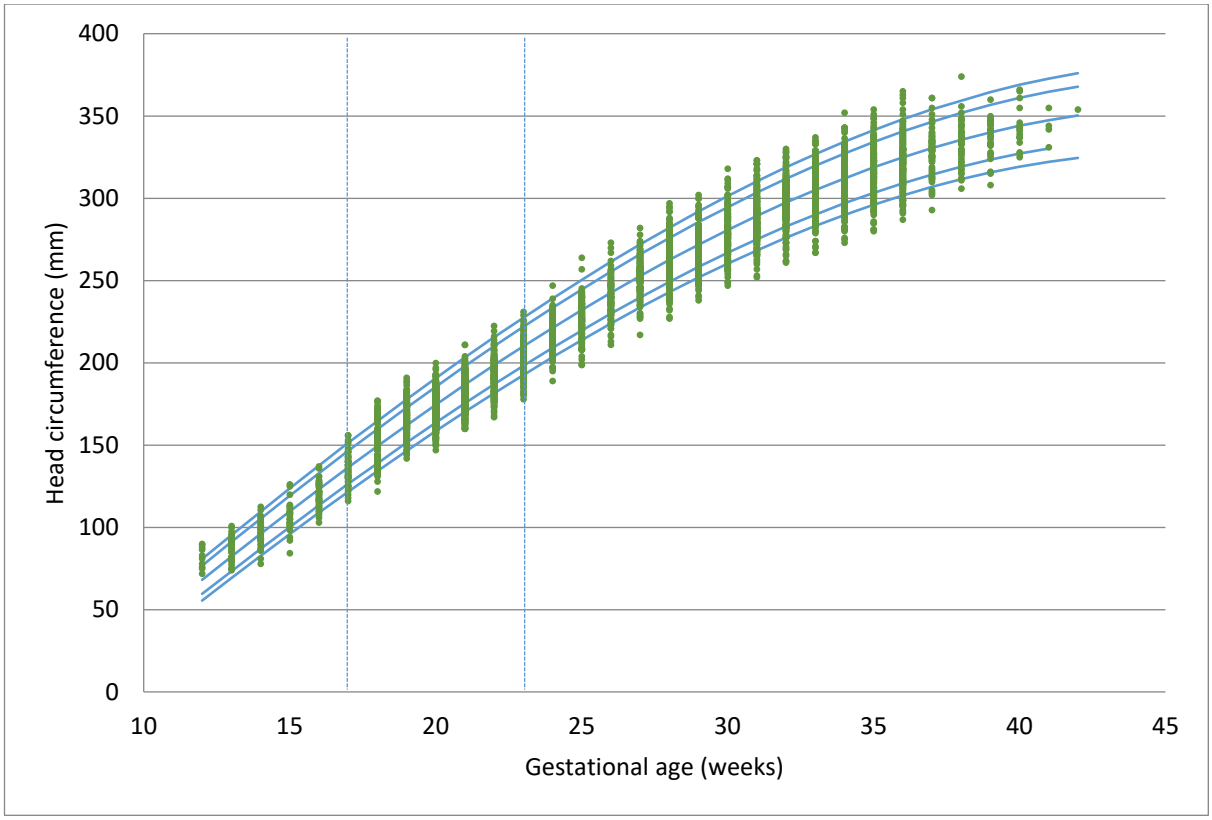


Figure 2-3 Head circumference plotted according to Chitty & Loughna et al. 2009. Lines represent the 97th, 90th, 50th, 10th, and 3rd centiles. A total of 6240/6402 HC measurements are represented in the chart (162 were excluded for being greater than ±3.5SD from the mean HC at a given gestational age). Measurements used in the analysis were limited to 17-23 weeks, as represented by the dotted lines.

Growth acceleration was defined as an increase in foetal measurement of >0.67SD and growth deceleration was defined as a decrease of >0.67SD between each time point (1st-2nd trimester and 2nd trimester to birthweight). A difference of 0.67 was chosen as this reflects the difference between centile lines drawn on the standard growth chart (e.g. 2nd, 9th, 25th, 50th, 75th, 91st and 98th centiles), is used clinically to assess growth change (Ong, 2000) and effects on later respiratory health (Kotecha et al., 2010).

2.3.4 Respiratory outcome data

Respiratory outcomes were taken from the RANOPS questionnaire data and included wheeze-ever, recent wheeze (last 3 months for <5 years of age; last 12 months for ≥5 years of age), use of inhalers, hospital admissions for chest-related problems, and doctor-diagnosed asthma (≥5 years of age only). All outcomes were dichotomous (Edwards et al., 2015a, Edwards et al., 2016).

2.4 Statistical Analysis

Not all cases had valid CRL, HC or FL measurements. Therefore, the number of participants included in each comparison of foetal measurement varied. In order to determine if this introduced selection bias, differences in demographics were compared to the whole dataset. Chi-squared tests were used to investigate the differences in categorical demographic data. Normality of continuous data was checked by visually inspecting Q-Q plots. Independent sample t-tests were used for continuous variables which were normally distributed.

Univariate logistic regression models were used to investigate the association between foetal size in the first trimester (CRL) and size in the 2nd trimester (HC and FL) with childhood respiratory outcomes. Further models were then used to investigate change in growth between (a) 1st and 2nd trimester (CRL to HC and CRL to FL); (b) between 1st trimester and birth (CRL to BW); (c) between 2nd trimester and birth (HC to BW and FL to BW), and risk of childhood respiratory outcomes. 'No change' was set as the reference category. Inclusion was limited to singletons as it was not possible to consistently ascertain from the scan reports the correct measurements in the case of multiple pregnancies. Furthermore, growth in multiple pregnancies may differ from that of singletons. The analyses were further stratified by age (<5 or ≥5 years) as some respiratory outcomes are reported differently in these two groups. Gestational age, birthweight, IUGR, gender, maternal smoking in pregnancy, current maternal smoking, family history of atopy,

caesarean delivery, breastfeeding, ethnicity and Welsh index of multiple deprivation were then included in adjusted multivariable models if they had a p-value <0.10 for 'wheeze-ever', which was the primary outcome for all analyses. A level of p<0.05 was set for statistical significance. All modelling was conducted independently for preterm-born and term-born participants using SPSS (version 20. SPSS Inc. Chicago, IL; US).

2.5 Results

2.5.1 Data availability

Figure 2-4 outlines the data available for this study. 4362/5012 (87%) questionnaire responders from the four LHBs consented to further healthcare database linkage. After removal of 13 duplicate IDs, sufficient information was available to identify 4295/4349 (99%) of mothers. After exclusion of multiple pregnancies (n=436), ultrasound scans for 3125 mothers were identified, of which 1486 infants were preterm-born (394 multiple pregnancies excluded) and 1203 were born at term (42 multiple pregnancies excluded). In total, 615 CRL, 1,196 HC and 1,326 FL measurements were available for analysis in the preterm group, 509 CRL, 1,141 HC and 1,326 FL measurements were available in the term group. When compared to the whole dataset, there were no differences in demographics when alternative foetal measurements were used in the analysis (Table 2-1). Therefore, additional selection bias was not introduced by using participants depending upon the availability of a particular biometric measurement.

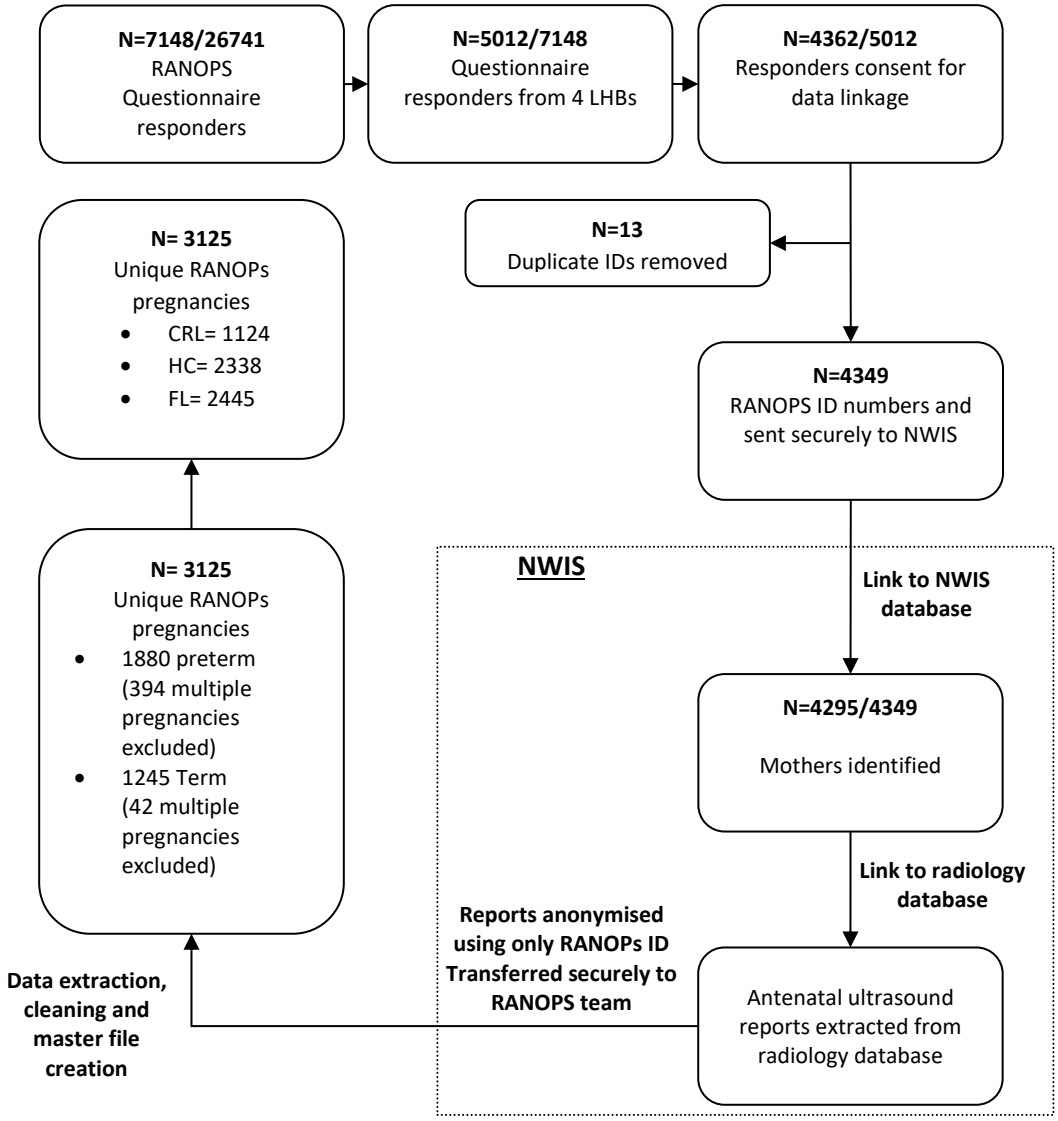


Figure 2-4 Process for acquisition of foetal anthropometric data

Table 2-1 Demographics of participants in RANOPS who had valid foetal anthropometry data

PRETERM	Before exclusions N=1880	CRL-BW analysis N=615	HC-BW analysis N=1196	FL-BW Analysis N=1326
Gestational age, weeks Mean (SD)	33.7 (2.77)	33.9 (2.62)	33.8 (2.72)	33.8 (2.72)
Birthweight, kg Mean (SD)	2.25 (0.70)	2.32 (0.70)	2.31 (0.72)	2.31 (0.72)
Male (%)	1,036/1880 (55)	332/615 (54)	672/1,196 (56)	753/1,326 (58)
WIMD rank median (IQR)	942 (936)	963 (822)	934 (819)	935 (819)
Age, years Mean (SD)	4.67 (2.89)	4.32 (2.65)	4.62 (2.74)	4.62 (2.75)
Mother smoke in pregnancy (%)	275/1880 (14.6)	91/615 (14.8)	181/1,196 (15.7)	209/1,326 (15.6)
Maternal age, years Mean (SD)	29.9/1880 (6.37)	29.7 (5.94)	29.5 (6.30)	29.5 (6.28)
≥5 years of age (%)	918/1880 (48.8)	347/615 (43.6)	514/1,196 (43.0)	689/1,326 (52.0)
IUGR (%)	222/1880 (11.8)	53/717 (8.6)	117/1,196 (9.8)	129/1,326 (9.7)
Family history of atopy	512/1880 (27.2)	173/615 (28.1)	351/1196 (29.3)	376/1326 (28.4)

TERM	Before exclusions N=1245	CRL-BW analysis N=509	HC-BW analysis N=1141	FL-BW Analysis N=1118
Gestational age, weeks Mean (SD)	39.6 (1.28)	39.6 (1.23)	39.6 (1.24)	39.7 (1.21)
Birthweight, kg Mean (SD)	3.45 (0.50)	3.47 (0.49)	3.48 (0.48)	3.48 (0.48)
Male (%)	692/1245 (55.6)	275/509 (54.0)	627/1141 (55.0)	612/1118 (54.7)
WIMD rank median (IQR)	1009 (825)	988 (814)	1006 (493)	1000 (812)
Age, years	4.74	4.41	4.6	4.62

Mean (SD)	(2.82)	(2.74)	(2.78)	(2.79)
Mother smoke in pregnancy (%)	165/1245 (13.3)	62/509 (12.2)	149/1092 (13.1)	146/1118 (0.34)
Maternal age, years Mean (SD)	30.3 (5.7)	30.3 (5.7)	30.2 (5.7)	30.2 (5.74)
≥5 years of age (%)	634/1245 (50.9)	238/509 (46.8)	560/1141 (49.1)	553/1118 (49.5)
IUGR (%)	73/1245 (5.9)	24/509 (4.7)	62/1141 (5.4)	57/1118 (5.1)
Family history of atopy	327/1245 (26.3)	133/509 (26.1)	307/1141 (26.9)	301/1118 (26.9)

2.5.2 Results: Preterm-born children

First trimester CRL size at 12 weeks' and 2nd trimester HC or FL at 20 weeks' gestation were not associated with later respiratory outcomes including wheeze-ever, recent wheeze, hospital admission for respiratory problems, inhaler use or doctor-diagnosed asthma. The results were unchanged when preschool and school-aged children were analysed separately (Table 2-2). Gestational age, gender, current maternal smoking, family history of asthma/atopy, breastfeeding, WIMD and whether the child was aged <5 or ≥5 years were all significantly associated with wheeze-ever in univariate analysis as shown in Table 2-3. These covariates were thus included in the adjusted models. When a change of ±0.67 of z-score was used to define growth trajectory, both accelerated and decelerated growth from 1st trimester CRL to birthweight was associated with increased odds of wheeze-ever (Acceleration: OR 1.82; 95% CI 1.16, 2.86; deceleration: OR 1.27; 95% CI 0.87, 1.86) when compared to those with unchanged trajectory. However, only growth acceleration was statistically significant (Table 2-4). In the adjusted model, the odds of wheeze-ever increased to 2.21 (95% CI 1.25, 2.32) for growth acceleration and 1.32 (95% CI 0.89, 1.94) for deceleration, with the latter noted to not be statistically significant.

Table 2-2 Association between foetal size variables and respiratory outcomes in preterm-born childhood. Data are Odds ratios (95% confidence intervals)

Size variables		Wheeze-ever	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All							
Crown-rump length	N=615	0.97 (0.87, 1.08)	-	-	1.02 (0.89, 1.16)	1.12 (0.92, 1.36)	-
Head circumference	N=1196	0.95 (0.85, 1.05)	-	-	1.03 (0.91, 1.17)	1.05 (0.88, 1.27)	-
Femur length	N=1327	0.96 (0.87, 1.07)	-	-	1.05 (0.92, 1.18)	1.04 (0.87, 1.24)	-
Under 5							
Crown-rump length	N=347	1.02 (0.87, 1.20)	-	1.09 (0.92, 1.30)	0.99 (0.83, 1.19)	1.10 (0.87, 1.39)	-
Head circumference	N=680	0.99 (0.86, 1.15)	-	1.03 (0.88, 1.19)	1.04 (0.88, 1.22)	1.09 (0.89, 1.34)	-
Femur length	N=688	0.96 (0.83, 1.12)	-	1.02 (0.88, 1.20)	1.08 (0.91, 1.28)	0.98 (0.78, 1.21)	-
Over 5							
Crown-rump length	N=268	0.93 (0.80, 1.08)	0.86 (0.73, 1.03)	-	1.05 (0.87, 1.27)	1.50 (0.88, 2.56)	1.04 (0.87, 1.24)
Head circumference	N=516	0.91 (0.77, 1.08)	1.04 (0.86, 1.26)	-	1.05 (0.85, 1.29)	1.10 (0.69, 1.74)	0.90 (0.74, 1.11)
Femur length	N=638	0.93 (0.81, 1.08)	1.03 (0.87, 1.21)	-	0.99 (0.82, 1.19)	1.07 (0.72, 1.57)	0.96 (0.81, 1.15)

Table 2-3 Univariate associations between potential confounders of the association between foetal growth trajectory and respiratory outcomes in preterm-born children.

	Wheeze-ever	Recent Wheeze	Wheeze last 12 months§	Wheeze last 3 months†	Inhaler use	Hospital admission	Doctor-diagnosed asthma§
Gestational age							
≤32 weeks	**2.12****	**1.69****	**1.54***	**1.79****	**2.03****	**2.41****	**1.59***
	(1.69, 2.65)	**(1.33, 2.13)**	**(1.08, 2.19)**	**(1.31, 2.47)**	**(1.58, 2.61)**	**(1.67, 3.48)**	**(1.10, 2.31)**
33-34 weeks	1.21	1.13	1.15	1.09	0.93	1.25	0.81
	(0.94, 1.52)	(0.87, 1.45)	(0.79, 1.69)	(0.77, 1.53)	(0.70, 1.25)	(0.81, 1.94)	(0.52, 1.26)
35-36 weeks	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SD Birthweight	0.96	0.95	0.88	1.02	0.91*	0.98	0.91
	(0.89, 1.04)	(0.87, 1.04	(0.78, 1.00)	(0.91, 1.14)	(0.83, 1.00)	(0.85, 1.13)	(0.80, 1.04)
IUGR (<10th centile for SD birthweight)							
Yes	1.20	1.15	1.47	0.94	1.05	0.65	1.13
	(0.91, 1.60)	(0.85, 1.56	(0.95, 2.26)	(0.61, 1.42)	(0.75, 1.48)	(0.52, 1.49)	(0.70, 1.84)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Gender							
Male	1.19	1.19	1.28	1.15	1.14	**1.62***	**1.41***
	(1.00, 1.43)	(0.98, 1.46)	(0.95, 1.74)	(0.88, 1.51)	(0.92, 1.43)	**(1.15, 2.27)**	**(1.01, 1.96)**
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Maternal smoking - pregnancy							
Yes	1.08	1.14	1.26	1.06	1.00	1.03	1.10
	(0.83, 1.30)	(0.86, 1.49)	(0.85, 1.87)	(0.72, 1.60)	(0.74, 1.37)	(0.67, 1.63)	(0.71, 1.69)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref

Maternal smoking-current							
Yes	**1.34***	**1.40***	1.27	1.58	1.25	1.37	1.25
	(1.07, 1.69)	**(1.10, 1.79)**	(0.89, 1.82)	(1.13, 2.21)	(0.95, 1.63)	(0.94, 2.01)	(0.85, 1.84)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Family history of asthma/atopy							
Yes	**2.01****	**2.44****	**2.77****	**2.12****	2.01	**1.84****	2.10
	(1.63, 2.47)	**1.97, 3.02)**	**(2.00, 3.84**	**(1.59, 2.81)**	(0.60, 2.54)	**(1.32, 2.57)**	(1.48, 2.99)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Delivery by caesarean section							
Yes	1.03	1.01	1.03	0.96	1.05	0.94	0.98
	(0.81, 1.31)	(0.78, 1.32)	(0.68, 1.57)	(0.68, 1.37)	(0.79, 1.41)	(0.62, 1.43)	(0.63, 1.51)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Breastfeeding							
Yes	**1.24***	1.27	1.19	1.40*	**1.30***	1.36	0.90
	(1.04, 1.49)	(1.04, 1.54)	(0.88, 1.60)	(1.07, 1.83)	**(1.04, 1.62)**	(0.98, 1.89)	(0.65, 1.24)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Ethnicity							
Non-white	0.72	0.66	1.40	**0.36***	0.66	0.88	0.66
	(0.46, 1.15)	(0.38, 1.13)	(0.63, 3.15)	**(0.17, 0.79)**	(0.35, 1.23)	(0.38, 2.07)	(0.23, 1.92)
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref
WIMD quintile							
1-lowest	**1.52***	**1.52***	1.48	1.51	1.27	**1.83***	0.78
	(1.11, 2.07)	**(1.08, 2.14)**	(0.89, 2.45)	(0.95, 2.40)	(0.87, 1.84)	**(1.04, 3.22)**	(0.45, 1.35)
2	1.10	1.25	1.36	1.14	0.96	1.35	1.08

	(0.82, 1.47)	(0.90, 1.72)	(0.85, 2.19)	(0.73, 1.78)	(0.67, 1.68)	(0.77, 2.36)	(0.67, 1.74)
3	1.27	1.08	1.00	1.06	1.12	1.57	0.67
	(0.96, 1.70)	(0.78, 1.49)	(0.61, 1.67)	(0.69, 1.63)	(0.79, 1.59)	(0.91, 2.69)	(0.40, 1.14)
4	1.07	1.15	1.29	1.03	1.11	0.97	0.86
	(0.79, 1.44)	(0.82, 1.60)	(0.80, 2.09)	(0.65, 1.64)	(0.77, 1.59)	(0.53, 1.78)	(0.52, 1.42)
5-highest	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Age <5/≥5 years							
>5	**0.56****	**0.69****	-	-	**0.65****	**0.23****	-
	(0.50, 0.68)	**(0.56, 0.84)**			**(0.52, 0.81)**	**(0.15, 0.34)**	
≤5	Ref	Ref	-	-	Ref	Ref	-

*p<0.05; **p<0.001; §children >5 years of age only; †children ≤5 years of age only
SD= standard deviation IUGR= intrauterine growth restriction WIMD=Wales index of multiple deprivation

Table 2-4 Association between 1st trimester to birthweight growth trajectory and respiratory symptoms in preterm-born children. Data are Odds ratios (95% confidence intervals)

1st Trimester CRL to birthweight		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All measurements N=615	Deceleration N= 306	1.27 (0.87, 1.86)	1.01 (0.67, 1.54)	-	-	0.70 (0.45, 1.11)	0.75 (0.37, 1.49)	-
	Acceleration N=142	**1.82* (1.16, 2.86)**	1.35 (0.83, 2.18)	-	-	1.29 (0.78, 2.14)	1.29 (0.61, 2.71)	-
	No change N=167	Ref	Ref	-	-	Ref	Ref	-
All measurements N=615 (adjusted)††	Deceleration N= 306	1.32 (0.89, 1.94)	1.00 (0.65, 1.54)	-	-	0.71 (0.45, 1.13)	0.80 (0.39, 1.64)	-
	Acceleration N=142	**2.21* (1.25, 2.32)**	1.42 (0.86, 2.34)	-	-	1.35 (0.81, 2.26)	1.70 (0.78, 3.70)	-
	No change N=167	Ref	Ref	-	-	Ref	Ref	-
Under 5 N=347	Deceleration N=176	1.45 (0.89, 2.38)	-	-	0.95 (0.56, 1.61)	0.67 (0.38, 1.18)	0.87 (0.41, 1.83)	-
	Acceleration N=70	**2.58* (1.35, 4.90)**	-	-	1.60 (0.85, 3.02)	1.28 (0.66, 2.47)	1.54 (0.67, 3.57)	-
	No change N=101	Ref	-	-	Ref	Ref	Ref	-
Under 5 N=347 (adjusted)††	Deceleration N=176	1.53 (0.92, 2.53)	-	-	0.95 (0.55, 1.64)	0.67 (0.37, 1.21)	0.92 (0.43, 1.96)	-
	Acceleration N=70	**2.80* (1.45, 5.46)**	-	-	1.72 (0.89, 3.32)	1.39 (0.70, 2.77)	1.68 (0.71, 3.98)	-
	No change N=101	Ref	-	-	Ref	Ref	Ref	-

Over 5 N=268	Deceleration N=130	1.09 (0.60, 2.00)	-	1.15 (0.58, 2.28)	-	0.79 (0.37, 1.69)	0.25 (0.02, 2.79)	1.35 (0.64, 2.85)
	Acceleration N=72	1.50 (0.74, 2.86)	-	1.20 (0.56, 2.58)	-	1.46 (0.66, 3.26)	1.39 (0.23, 8.60)	1.85 (0.83, 4.15)
	No change N=66	Ref	-	Ref	-	Ref	Ref	Ref
Over 5 N=268 (adjusted) ‡	Deceleration N=130	1.06 (0.57, 1.97)	-	1.08 (0.54, 2.20)	-	0.74 (0.34, 1.61)	0.25 (0.02, 2.88)	1.25 (0.58, 2.67)
	Acceleration N=72	1.35 (0.68, 2.71)	-	1.09 (0.49, 2.40)	-	1.34 (0.59, 3.03)	1.26 (0.19, 8.27)	1.66 (0.73, 3.78)
	No change N=66	Ref	-	Ref	-	Ref	Ref	Ref

*p<0.05

†adjusted for gestational age, gender, current maternal smoking, family history of atopy, breastfeeding, WIMD and child ≤5 or >5 years of age

‡adjusted for gestational age, gender, current maternal smoking, family history of atopy, breastfeeding and WIMD

First trimester CRL to second trimester HC growth deceleration was associated with increased odds of wheeze-ever (OR 1.43; 95% CI 0.92, 2.22), inhaler use (OR 1.47; 95% CI 0.88, 2.45), and hospital admission (OR 2.79; 95% CI 1.18, 6.62) but only hospital admission reached statistical significance (Table 2-5). In the adjusted model the odds of wheeze-ever (OR 1.59; 95%CI 1.01, 2.51), inhaler use (OR 1.60; 95% CI 0.94, 2.70) and hospital admission (OR 3.84; 95% CI 1.56, 9.51) all increased, with wheeze-ever and hospital admission, but not inhaler use, being statistically significant. There were no associations with 1st Trimester CRL to 2nd trimester FL growth (Table 2-6).

When a change of ±0.67 of z-score was used to define growth trajectory, accelerated growth from 2nd Trimester HC to birthweight was associated with increased odds of wheeze-ever (OR 1.49; 95% CI 1.09, 2.04). This increased in the adjusted model to an OR of 1.60 (95%CI 1.15, 2.22). Growth deceleration was also associated with increased odds of wheeze-ever, but this was not statistically significant in the adjusted model (OR 1.24; 95% CI 0.95, 1.62); these results appeared to be attributable to the <5 years age group where both deceleration and acceleration were significant for wheeze-ever (OR 1.55; 95%CI 1.09, 2.21 and OR 2.00; 95%CI 1.27, 3.15 respectively in the adjusted model).

In the ≥5 years age group, growth deceleration was significantly associated with decreased odds of doctor-diagnosed asthma (OR 0.59; 95% CI 0.35, 0.97). However, this was in the absence of association with any other outcome and was not statistically significant in the adjusted model. The odds of hospital admission also appeared to be associated with growth acceleration (OR 4.22 95% CI 1.02, 17.52), but the wide range of the upper confidence interval suggests this finding may be spurious (Table 2-7). Both growth deceleration (OR 1.38; 95% CI 0.97, 1.95) and acceleration (OR 1.37; 95% CI 0.88, 2.12) between 2nd Trimester FL and birthweight tended to be associated with wheeze-ever but were not statistically significant (Table 2-8).

Table 2-5 Association between 1st trimester (CRL) to 2nd Trimester (HC) growth trajectory and respiratory symptoms in preterm-born children. Data are Odds ratios (95% confidence intervals)

1st Trimester CRL to 2nd trimester HC		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All measurements N= 527	Deceleration N= 151	1.43 (0.92, 2.22)	1.22 (0.76, 1.95)	-	-	1.47 (0.88, 2.45)	**2.79* (1.18, 6.62)**	-
	Acceleration N= 203	1.14 (0.76, 1.72)	1.04 (0.66, 1.62)	-	-	1.05 (0.64, 1.73)	**2.38* (1.03, 5.52)**	-
	No change N= 173	Ref	Ref	-	-	Ref	Ref	-
All measurements N= 527 (adjusted)†	Deceleration N= 151	**1.59* (1.01, 2.51)**	1.29 (0.79, 2.11)	-	-	1.60 (0.94, 2.70)	**3.84* (1.56, 9.51)**	-
	Acceleration N= 203	1.07 (0.70, 1.62)	0.94 (0.59, 1.50)	-	-	1.00 (0.60, 1.66)	**2.57* (1.08, 6.09)**	-
	No change N= 173	Ref	Ref	-	-	Ref	Ref	-
Under 5 N= 327	Deceleration N=85	1.46 (0.52, 2.60)	-	-	1.43 (0.78, 2.60)	1.52 (0.80, 2.89)	**2.53* (1.01, 6.37)**	-
	Acceleration N=131	1.11 (0.67, 1.84)	-	-	1.04 (0.60, 1.80)	1.10 (0.58, 1.94)	2.32 (0.98, 5.50)	-
	No change N=111	Ref	-	-	Ref	Ref	Ref	-
Under 5 N= 327 (adjusted) ‡	Deceleration N=85	1.61 (0.88, 2.93)	-	-	1.53 (0.82, 2.85)	1.65 (0.84, 3.23)	**2.97* (1.15, 7.71)**	-
	Acceleration N=131	1.09 (0.64, 1.83)	-	-	1.01 (0.57, 1.78)	1.04 (0.57, 1.98)	**2.51* (1.04, 6.06)**	-
	No change N=111	Ref	-	-	Ref	Ref	Ref	-

Over 5 N= 200	Deceleration N=66	1.60 (0.79, 3.23)	-	1.00 (0.45, 2.20)	-	1.48 (0.63, 3.51)	Not computed	1.87 (0.81, 4.35)
	Acceleration N=72	1.21 (0.60, 2.43)	-	1.03 (0.48, 2.23	-	1.02 (0.42, 2.48)	Not computed	1.12 (0.47, 2.68)
	No change N=62	Ref	-	Ref	-	Ref	Ref	Ref
Over 5 N= 200 (adjusted) ‡	Deceleration N=66	1.65 (0.80, 3.40)	-	0.91 (0.40, 2.11)	-	1.46 (0.61, 3.53)	Not computed	1.82 (0.77, 4.34)
	Acceleration N=72	1.10 (0.53, 2.27)	-	0.82 (0.36, 1.90)	-	0.85 (0.34, 2.13)	Not computed	0.95 (0.38, 2.38)
	No change N=62	Ref	-	Ref	-	Ref	Ref	Ref

*p<0.05

†adjusted for gestational age, gender, current maternal smoking, family history of atopy, breastfeeding, WIMD and child ≤5 or >5 years of age

‡adjusted for gestational age, gender, current maternal smoking, family history of atopy, breastfeeding and WIMD

Table 2-6 Association between 1st trimester (CRL) to 2nd trimester (FL) growth trajectory and respiratory symptoms in preterm-born children. Data are Odds ratios (95% confidence intervals)

1st Trimester CRL to 2nd trimester FL		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All measurements N= 582	Deceleration N= 154	1.10 (0.72, 1.67)	0.88 (0.56, 1.39)	-	-	0.76 (0.47, 1.25)	1.18 (0.56, 2.50)	-
	Acceleration N= 223	1.27 (0.87, 1.86)	1.01 (0.67, 1.52)	-	-	0.79 (0.51, 1.23)	1.23 (0.62, 2.42)	-
	No change N= 205	Ref	Ref	-	-	Ref	Ref	-
All measurements N= 582 (adjusted)†	Deceleration N= 154	1.24 (0.80, 1.82)	0.97 (0.60, 1.55)	-	-	0.83 (0.50, 1.39)	1.74 (0.78, 3.88)	-
	Acceleration N= 223	1.34 (0.91, 1.98)	1.06 (0.70, 1.61)	-	-	0.82 (0.52, 1.29)	1.39 (0.69, 2.81)	-
	No change N= 205	Ref	Ref	-	-	Ref	Ref	-
Under 5 N= 334	Deceleration N=76	1.27 (0.71, 2.26)	-	-	1.13 (0.62, 2.05)	0.83 (0.43, 1.59)	1.28 (0.55, 2.94)	-
	Acceleration N=130	1.06 (0.65, 1.73)	-	-	0.91 (0.54, 1.54)	0.87 (0.50, 1.51)	1.29 (0.62, 2.67)	-
	No change N=128	Ref	-	-	Ref	Ref	Ref	-
Under 5 N= 334 (adjusted) ‡	Deceleration N=76	1.37 (0.75, 2.50)	-	-	1.24 (0.66, 2.32)	1.01 (0.50, 2.01)	1.56 (0.64, 3.76)	-
	Acceleration N=130	1.11 (0.67, 1.84)	-	-	0.99 (0.58, 1.70)	0.95 (0.54, 1.70)	1.40 (0.67, 2.94)	-
	No change N=128	Ref	-	-	Ref	Ref	Ref	-

Over 5 N=248	Deceleration N=78	1.15 (0.60, 2.20)	-	0.70 (0.34, 1.45)	-	0.73 (0.34, 1.56)	3.04 (0.31, 30)	0.98 (0.47, 2.07)
	Acceleration N=93	1.77 (0.96, 3.27)	-	1.19 (0.62, 2.30)	-	0.68 (0.33, 1.43)	1.67 (0.15, 18.8)	1.21 (0.60, 2.42)
	No change N=77	Ref	-	Ref	-	Ref	Ref	Ref
Over 5 N=248 (adjusted) ‡	Deceleration N=78	1.13 (0.58, 2.19)	-	0.71 (0.34, 1.52)	-	0.73 (0.33, 1.60)	3.57 (0.35, 37.0)	0.98 (0.46, 2.10)
	Acceleration N=93	1.76 (0.94, 2.30)	-	1.20 (0.61, 2.36)	-	0.67 (0.32, 1.42)	1.74 (0.15, 20.2)	1.21 (0.59, 2.47)
	No change N=77	Ref	-	Ref	-	Ref	Ref	Ref

*p<0.05

†adjusted for gestational age, gender, current maternal smoking, family history of atopy, breastfeeding, WIMD and child ≤5 or >5 years of age

‡adjusted for gestational age, gender, current maternal smoking, family history of atopy, breastfeeding and WIMD

Table 2-7 Association between 2nd trimester (HC) to birthweight growth trajectory and respiratory symptoms in preterm-born children. Data are Odds ratios (95% confidence intervals)

2nd Trimester HC to birthweight		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All measurements N=1196	Deceleration N=486	1.12 (0.87, 1.45)	0.89 (0.68, 1.18)	-	-	0.88 (0.65. 1.19)	0.85 (0.55, 1.33)	-
	Acceleration N=238	**1.49* (1.09, 2.04)**	1.30 (0.94, 1.80)	-	-	1.15 (0.80, 1.64)	1.27 (0.77, 2.09)	-
	No change N=472	Ref	Ref	-	-	Ref	Ref	-
All measurements N=1196 (adjusted)†	Deceleration N=486	1.24 (0.95, 1.62)	0.94 (0.74, 1.26)	-	-	0.95 (0.70, 1.31)	0.92 (0.58, 1.46)	-
	Acceleration N=238	**1.60* (1.15, 2.22)**	1.39 (0.99, 1.96)	-	-	1.22 (0.84, 1.77)	1.39 (0.23, 2.34)	-
	No change N=472	Ref	Ref	-	-	Ref	Ref	-
Under 5 N=682	Deceleration N=282	**1.41* (1.01, 1.98)**	-	-	1.03 (0.73, 1.48)	1.02 (0.69, 1.50)	0.72 (0.44, 1.17)	-
	Acceleration N =130	**1.99* (1.28, 3.09)**	-	-	1.42 (0.92, 2.19)	1.27 (0.80, 2.03)	1.11 (0.63, 1.94)	-
	No change N=270	Ref	-	-	Ref	Ref	Ref	-
Under 5 N=682 (adjusted) ‡	Deceleration N=282	**1.55* (1.09, 2.21)**	-	-	1.07 (0.74, 1.55)	1.12 (0.75, 1.66)	0.79 (0.48, 1.30)	-
	Acceleration N =130	**2.00* (1.27, 3.15)**	-	-	1.43 (0.92, 2.24)	1.35 (0.84, 2.17)	1.16 (0.65, 2.06)	-
	No change N=270	Ref	-	-	Ref	Ref	Ref	-

Over 5 N=514	Deceleration N=204	0.82 (0.55, 1.22)	-	0.70 (0.45, 1.10)	-	0.66 (0.40, 1.10)	2.36 (0.60, 9.25)	**0.59* (0.35, 0.97)**
	Acceleration N=108	1.11 (0.70, 1.77)	-	1.17 (0.70, 1.94)	-	1.00 (0.57, 1.77)	3.90 (0.96, 15.9)	1.19 (0.69, 2.04)
	No change N=202	Ref	-	Ref	-	Ref	Ref	Ref
Over 5 N=514 (adjusted) ‡	Deceleration N=204	0.92 (0.61, 1.39)	-	0.78 (0.48, 1.25)	-	0.75 (0.44, 1.28)	2.51 (0.63, 9.97)	0.63 (0.37, 1.06)
	Acceleration N=108	1.17 (0.72, 1.91)	-	1.31 (0.76, 2.25)	-	1.04 (0.57, 1.90)	**4.22* (1.02, 17.51)**	1.28 (0.73, 2.25)
	No change N=202	Ref	-	Ref	-	Ref	Ref	Ref

*p<0.05

†adjusted for gestational age, gender, current maternal smoking, family history of atopy, breastfeeding, WIMD and child ≤5 or >5 years of age

‡adjusted for gestational age, gender, current maternal smoking, family history of atopy, breastfeeding and WIMD

Table 2-8 Association between 2nd trimester (FL) to birthweight growth trajectory and respiratory symptoms in preterm-born children. Data are Odds ratios (95% confidence intervals)

2nd Trimester FL to birthweight		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All measurements N=1326	Deceleration N=594	0.97 (0.77, 1.24)	0.83 (0.64, 1.08)	-	-	0.78 (0.58, 1.03)	1.00 (0.66, 1.53)	-
	Acceleration N=228	1.17 (0.86, 1.61)	1.28 (0.92, 1.77)	-	-	1.28 (0.90, 1.81)	1.46 (0.89, 2.42)	-
	No change N=504	Ref	Ref	-	-	Ref	Ref	-
All measurements N=1326 (adjusted)†	Deceleration N=594	1.06 (0.82, 1.35)	0.86 (0.66, 1.13)	-	-	0.83 (0.62, 1.11)	1.17 (0.76, 1.81)	
	Acceleration N=228	1.17 (0.84, 1.61)	1.32 (0.94, 1.84)	-	-	1.30 (0.91, 1.87)	1.46 (0.87, 2.44)	
	No change N=504	Ref	Ref	-	-	Ref	Ref	-
Under 5 N=689	Deceleration N=286	1.25 (0.89, 1.75)	-	-	1.02 (0.72, 1.44)	0.86 (0.59, 1.26)	0.95 (0.59, 1.54)	-
	Acceleration N=129	1.35 (0.88, 2.08)	-	-	1.34 (0.87, 2.06)	1.17 (0.74, 1.86)	1.31 (0.74, 2.30)	-
	No change N=274	Ref	-	-	Ref	Ref	Ref	-
Under 5 N=689 (adjusted) ‡	Deceleration N=286	1.38 (0.97, 1.95)	-	-	1.08 (0.75, 1.56)	0.94 (0.64, 1.40)	1.04 (0.64, 1.69)	-
	Acceleration N=129	1.37 (0.88, 2.12)	-	-	1.41 (0.90, 2.19)	1.24 (0.78, 1.99)	1.34 (0.76, 2.38)	-
	No change N=274	Ref	-	-	Ref	Ref	Ref	-

Over 5 N=637	Deceleration N=308	0.80 (0.57, 1.13)	-	0.69 (0.47, 1.01)	-	0.71 (0.46, 1.10)	1.98 (0.70, 5.64)	0.67 (0.45, 1.10)
	Acceleration N=99	0.97 (0.61, 1.55)	-	1.20 (0.72, 1.97)	-	1.42 (0.83, 2.43)	2.39 (0.68, 8.46)	1.06 (0.63, 1.81)
	No change N=230	Ref	-	Ref	-	Ref	Ref	Ref
Over 5 N=637 (adjusted)‡	Deceleration N=308	0.81 (0.57, 1.16)	-	0.64* (0.45, 0.99)	-	0.67 (0.43, 1.05)	0.70 (0.45, 1.10)	0.63 (0.37, 1.06)
	Acceleration N=99	0.92 (0.59, 1.56)	-	1.21 (0.72, 2.04)	-	1.34 (0.77, 2.34)	1.41 (0.81, 2.45)	1.28 (0.73, 2.25)
	No change N=230	Ref	-	Ref	-	Ref	Ref	Ref

*p<0.05

†adjusted for gestational age, gender, current maternal smoking, family history of atopy, breastfeeding, WIMD and child ≤5 or >5 years of age

‡adjusted for gestational age, gender, current maternal smoking, family history of atopy, breastfeeding and WIMD

2.5.3 Outcomes in term-born children

In common with the results from the preterm-born group, there were no associations between foetal size variables and childhood respiratory outcomes in term-born children (Table 2-9). Results of the univariate modelling to identify potential confounders are shown in Table 2-10. Gestational age, gender, family history of asthma/atopy and delivery by caesarean section were significant independent variables and were thus included in the adjusted model.

When a change of ±0.67SD of z-score was used to define growth trajectory between 1st trimester CRL and BW, growth acceleration was significantly associated with increased inhaler usage (OR 2.13; 95% CI 1.02, 4.70) but not with wheeze-ever or recent wheeze. In the <5 years age group, acceleration was significantly associated with wheeze in the last 3 months (OR 2.38; 95% CI 1.06, 5.36), whereas deceleration was associated with inhaler use only (OR 2.51; 95% CI 1.03, 6.14). These results were not robust to the inclusion of covariates in the adjusted model as the effect size was attenuated and was no longer statistically significant. In the ≥5 years group, deceleration was negatively associated with wheeze-ever (OR 0.48 95%CI 0.24, 0.94), however this was not significant in the adjusted model (Table 2-11).

First trimester CRL to 2nd trimester HC growth did not appear to be associated with any respiratory outcome (Table 2-12). On the other hand, 1st Trimester CRL to 2nd trimester FL growth deceleration was associated with increased odds ratios for wheeze-ever (OR 2.56; 95%CI 1.23, 5.33) and inhaler use (OR 4.89; 95% CI 1.48, 16.1) in the ≥5 age group. This was supported by a (non-significant) association of growth deceleration with wheeze in the last 12 months (OR 2.23, 95%CI 0.90, 5.51) (Table 2-13).

Regarding 2nd to 3rd trimester growth change (HC to BW), there were no consistent associations aside from decreased odds of inhaler use for growth deceleration in the over 5

age group (OR 0.50; 95% CI 0.27, 0.95) (Table 2-14). Similarly, there were no associations when FL was used as the measure of 2nd trimester growth (Table 2-15).

Table 2-9 Association between foetal size variables and respiratory outcomes in term-born childhood. Data are Odds ratios (95% confidence intervals)

Size variables		Wheeze-ever	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All							
Crown-rump length	N= 509	0.99 (0.88, 1.12)	-	-	1.04 (0.88, 1.23)	1.10 (0.83, 1.44)	-
Head circumference	N= 1007	1.07 (0.95, 1.21)	-	-	0.94 (0.80, 1.13)	1.07 (0.79, 1.45)	-
Femur length	N= 1118	1.00 (0.88, 1.13)	-	-	0.92 (0.77, 1.09)	0.91 (0.67, 1.22)	-
Under 5							
Crown-rump length	N= 271	0.98 (0.83, 1.16)	-		1.03 (0.82, 1.29)	1.18 (0.86, 1.60)	-
Head circumference	N= 561	1.05 (0.89, 1.24)	-	0.99 (0.80, 1.21)	0.86 (0.67, 1.10)	1.12 (0.78, 1.90)	-
Femur length	N=565	0.94 (0.79, 1.12)	-	0.93 (0.74, 1.15)	0.79 (0.61, 1.03)	0.85 (0.59, 1.25)	-
Over 5							
Crown-rump length	N= 238	1.02 (0.86, 1.22)	0.99 (0.80, 1.22)	-	1.07 (0.84, 1.36)	0.89 (0.43, 1.84)	0.96 (0.77, 1.19)
Head circumference	N= 446	1.08 (0.90, 1.31)	1.17 (0.93, 1.46)	-	1.05 (0.80, 1.37)	0.88 (0.48, 1.60)	1.01 (0.80, 1.27)
Femur length	N= 553	1.02 (0.85, 1.21)	1.07 (0.87, 1.32)	-	1.03 (0.81, 1.32)	0.90 (0.52, 1.55)	1.00 (0.80, 1.24)

Table 2-10 Univariate associations between potential confounders of the association between foetal growth trajectory and respiratory outcomes in term-born children.

	Wheeze-ever	Recent wheeze	Wheeze last 12 months§	Wheeze last 3 months†	Inhaler use	Hospital admission	Doctor-diagnosed asthma§
Gestational age	**0.85 * (0.78, 0.93)**	**0.89* (0.77, 0.96)**	**0.82* (0.70, 0.96)**	**0.89 (0.78, 1.04)**	**0.83* (0.73, 0.94)**	**0.92 (0.74, 1.15)**	**0.82* (0.69, 0.97)**
SD Birthweight	0.99 (0.89, 1.12)	1.00 (0.87, 1.16)	0.60 (0.69, 1.07)	1.16 (0.94, 1.42)	0.94 (0.79, 1.12)	0.77 (0.57, 1.06)	0.88 (0.70, 1.11)
IUGR (<10th centile for SD BW)							
Yes	1.29 (0.80, 2.09)	**1.72* (1.01, 2.93)**	**3.17* (1.54, 6.55)**	0.89 (0.38, 2.07)	1.69 (0.92, 3.11)	1.93 (0.74, 5.03)	2.24* (1.12, 5.24)
No	Re	**Ref**	**Re**	Ref	Ref	Re	Re
Gender							
Male	**1.39* (1.10, 1.76)**	**1.38* (1.03, 1.85)**	**1.59* (1.04, 2.43)**	1.24 (0.80, 1.81)	1.36 (0.96, 1.91)	1.63 (0.88, 3.00)	**1.61* (1.03, 2.52)**
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Maternal smoking - pregnancy							
Yes	1.37 (0.98, 1.91)	1.67* (1.14, 2.45)	1.34 (0.77, 2.33)	**2.11* (1.24, 3.59)**	**1.74* (1.13, 2.68)**	1.33 (0.61, 2.88)	1.24 (0.69, 2.23)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Maternal smoking-current							
Yes	1.31 (0.95, 1.79)	1.60 (1.09,	1.16 (0.67, 2.01)	2.07* (1.26, 3.41)	1.18 (0.75, 1.84)	0.95 (0.42, 2.12)	0.81 (0.43, 1.52)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Family history of asthma/atopy							
Yes	**2.29** (1.78, 2.96)**	**2.41** (1.79, 3.25)**	**3.47** (2.25, 5.33)**	**1.70* (1.12, 2.59)**	**2.42** (1.71, 3.41)**	**1.72 (0.95, 3.14)**	**3.51** (2.24, 5.50)**

No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Delivery by Caesarean section							
Yes	**1.54***	1.27	**1.87***	0.89	1.48	1.58	**1.98***
	(1.11, 2.13)	(0.86, 1.88)	**(1.06, 2.28)**	(0.52, 1.54)	(0.96, 2.26)	(0.73, 3.43)	**(1.09, 3.59)**
No	**Ref**	Ref	**Ref**	Ref	Ref	Ref	Ref
Breastfeeding							
Yes	1.10	0.98	0.76	1.26	1.15	1.69	1.15
	(0.87, 1.40)	(0.73, 1.30)	(0.50, 1.15)	(0.85, 1.89)	(0.82, 1.61)	(0.94, 3.02)	(0.75, 1.77)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Ethnicity							
Non-white	1.27	1.82	**3.10***	0.97	0.55	**2.73***	1.00
	(0.72, 2.24)	(0.98, 3.38)	**(1.37, 7.04)**	(0.36, 2.63)	(0.20, 1.54)	**(1.03, 7.22)**	(0.34, 2.97)
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref
WIMD quintile							
1	1.09	1.18	0.84	1.51	1.01	0.77	0.77
	(0.72, 1.63)	(0.70, 1.97)	(0.39, 1.82)	(0.73, 3.12)	(0.57, 1.79)	(0.34, 1.74)	(0.34, 1.74)
2	1.16	1.31	1.30	1.32	0.92	1.64	1.64
	(0.79, 1.69)	(0.82, 2.11)	(0.67, 2.53)	(0.67, 2.63)	(0.54, 1.57)	(0.84, 3.21)	(0.84, 3.21)
3	1.18	1.63	1.59	1.67	1.14	1.48	1.48
	(0.82, 1.69)	(1.04, 2.54)	(0.88, 2.88)	(0.85, 3.27)	(0.70, 1.88)	(0.80, 2.77)	(0.80, 2.77)
4	0.83	0.83	0.44	0.89	0.66	0.58	0.58
	(0.57, 1.21)	(0.51, 1.34)	(0.40, 1.49)	(0.43, 1.84)	(0.38, 1.14)	(0.78, 1.21)	(0.28, 1.21)
5	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Age <5/≥ 5 years							
>5	**0.56****	0.87	-	-	0.88	0.38	-
	(0.44, 0.70)	(0.65, 1.16)			(0.63, 1.23)	(0.20, 0.72)	
<5	Ref	Ref	-	-	Ref	Ref	-

*p<0.05; **p<0.001; §children > 5 years of age only; †children ≤5 years of age only

SD= standard deviation IUGR=intrauterine growth restriction WIMD=Welsh index of multiple deprivation

Table 2-11 Association between 1st trimester to birthweight growth trajectory and respiratory symptoms in term-born children. Data are Odds ratios (95% confidence intervals)

1st Trimester CRL to birthweight		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All measurements N=509	Deceleration N= 240	0.79 (0.52, 1.22)	1.35 (0.78, 2.35)	-	-	1.70 (0.87, 3.32)	1.46 (0.45, 4.74)	-
	Acceleration N=131	0.80 (0.49, 1.31)	1.70 (0.93)	-	-	2.05 (0.99, 4.24)	2.47 (0.74, 8.23)	-
	No change N=138	Ref	Ref	-	-	Ref	Ref	-
All measurements N=509 (adjusted)†	Deceleration N= 240	0.87 (0.56, 1.35)	1.15 (0.61, 2.16)	-	-	1.85 (0.94, 3.66)	1.56 (0.47, 5.18)	-
	Acceleration N=131	0.86 (0.52, 1.43)	1.36 (0.67, 2.78)	-	-	**2.13* (1.02, 4.70)**	2.74 (0.80, 9.43)	-
	No change N=138	Ref	Ref	-	-	Ref	Ref	-
Under 5 N=271	Deceleration N=125	1.21 (0.69, 2.12)	-	-	1.90 (0.91, 4.0)	**2.51* (1.03, 6.14)**	2.26 (0.60, 8.48)	-
	Acceleration N=65	0.96 (0.50, 1.85)	-	-	**2.38* (1.06, 5.36)**	2.39 (0.88, 6.48)	3.14 (0.78, 12.7)	-
	No change N=81	Ref	-	-	Ref	Ref	Ref	-
Under 5 N=271 (adjusted) ‡	Deceleration N=125	1.18 (0.67, 2.10)	-	-	1.96 (0.93, 4.15)	2.47 (1.00, 6.12)	2.20 (0.58, 8.40)	-
	Acceleration N=65	0.89 (0.45, 1.75)	-	-	2.26 (0.99, 5.18)	2.22 (0.80, 6.12)	2.96 (0.72, 12.2)	-
	No change N=81	Ref	-	-	Ref	Ref	Ref	-

Over 5 N=238	Deceleration N=115	**0.48*** **(0.24, 0.94)**	-	0.87 (0.37, 2.04)	-	0.99 (0.35, 2.79)	Not computed	0.68 (0.29, 1.57)
	Acceleration N=66	0.69 (0.33, 1.15)	-	1.15 (0.46, 2.87)	-	1.70 (0.59, 4.93)	1.75 (0.16, 19.8)	0.84 (0.33, 2.11)
	No change N=57	Ref	-	Ref	-	Ref	Ref	Ref
Over 5 N=238 (adjusted) ‡	Deceleration N=115	0.54 (0.27, 1.09)	-	1.03 (0.42, 2.50)	-	1.05 (0.36, 3.04)	Not computed	0.76 (0.32, 1.81)
	Acceleration N=66	0.75 (0.35, 1.63)	-	1.20 (0.45, 3.16)	-	1.74 (0.58, 5.23)	1.54 (0.13, 18.4)	0.95 (0.37, 2.48)
	No change N=57	Ref	-	Ref	-	Ref	Ref	Ref

*p<0.05

†Adjusted for gestational age, gender, family history of atopy and delivery by caesarean section, ≤5 or >5 years of age

‡Adjusted for gestational age, gender, family history of atopy and delivery by caesarean section

Table 2-12 Association between 1st trimester to 2nd Trimester (HC) growth trajectory and respiratory symptoms in term-born children. Data are Odds ratios (95% confidence intervals)

1st Trimester CRL to 2nd trimester HC		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All measurements N= 442	Deceleration N= 116	0.89 (0.55, 1.42)	1.02 (0.59, 1.77)	-	-	1.40 (0.74, 2.63)	0.51 (0.14, 1.94)	-
	Acceleration N= 143	1.03 (0.66, 1.60)	0.71 (0.41, 1.24)	-	-	0.91 (0.48, 1.74)	1.30 (0.50, 3.36)	-
	No change N= 183	Ref	Ref	-	-	Ref	Ref	-
All measurements N= 442 (adjusted)†	Deceleration N= 116	0.84 (0.51, 1.37)	0.83 (0.42, 1.62)	-	-	1.34 (0.71, 2.55)	0.48 (0.12, 1.87)	-
	Acceleration N= 143	0.98 (0.62, 1.55)	0.57 (0.30, 1.11)	-	-	0.87 (0.45, 1.69)	1.24 (0.47, 3.30)	-
	No change N= 183	Ref	Ref	-	-	Ref	Ref	-
Under 5 N= 262	Deceleration N=64	0.66 (0.35, 1.23)	-	-	1.06 (0.53, 2.14)	1.26 (0.56, 2.85)	0.36 (0.08, 1.73)	-
	Acceleration N=88	0.92 (0.53, 1.61)	-	-	0.60 (0.30, 1.21)	0.86 (0.39, 1.92)	0.97 (0.35, 2.72)	-
	No change N=110	Ref	-	-	Ref	Ref	Ref	-
Under 5 N= 262 (adjusted) ‡	Deceleration N=64	0.54 (0.28, 1.04)	-	-	0.94 (0.46, 1.93)	1.07 (0.46, 2.46)	0.30 (0.06, 1.51)	-
	Acceleration N=88	0.88 (0.49, 1.57)	-	-	0.59 (0.29, 1.20)	0.83 (0.37, 1.87)	0.92 (0.32, 2.66)	-
	No change N=110	Ref	-	-	Ref	Ref	Ref	-

Over 5 N= 180	Deceleration N=52	1.45 (0.69, 3.07)	-	1.03 (0.41, 2.48)	-	1.70 (0.61, 4.75)	Not computed	1.53 (0.62, 3.73)
	Acceleration N=55	1.22 (0.58, 2.58)	-	0.94 (0.38, 2.30)	-	1.00 (0.32, 3.05)	Not computed	1.00 (0.39, 2.56)
	No change N=73	Ref	-	Ref	-	Ref	Ref	Ref
Over 5 N= 180 (adjusted) ‡	Deceleration N=52	1.48 (0.68, 3.20)	-	0.96 (0.37, 2.49)	-	1.67 (0.59, 4.83)	Not computed	1.71 (0.68, 4.29)
	Acceleration N=55	1.17 (0.54, 2.51)	-	0.81 (0.32, 2.09)	-	0.93 (0.30, 2.91)	Not computed	0.98 (0.37, 2.56)
	No change N=73	Ref	-	Ref	-	Ref	Ref	Ref

†Adjusted for gestational age, gender, family history of atopy and delivery by caesarean section, ≤5 or >5 years of age
‡Adjusted for gestational age, gender, family history of atopy and delivery by caesarean section

Table 2-13 Association between 1st trimester to 2nd trimester (FL) growth trajectory and respiratory symptoms in term-born children. Data are Odds ratios (95% confidence intervals)

1st Trimester CRL to 2nd trimester FL		Wheeze-ever	Recent wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All measurements N= 499	Deceleration N= 136	1.18 (0.75, 1.84)	**1.72* (1.01, 2.93)**	-	-	**1.95* (1.04, 3.67)**	0.81 (0.29, 2.28)	-
	Acceleration N= 178	0.93 (0.61, 1.41)	0.97 (0.57, 1.67)	-	-	1.29 (0.68, 2.42)	0.72 (0.27, 1.93)	-
	No change N= 185	Ref	Ref	-	-	Ref	Ref	-
All measurements N= 499 (adjusted)†	Deceleration N= 136	1.31 (0.81, 2.10)	1.62 (0.85, 3.09)	-	-	**2.14* (1.12, 4.09)**	0.89 (0.30, 2.60)	-
	Acceleration N= 178	1.02 (0.66, 1.59)	0.93 (0.49, 1.74)	-	-	1.41 (0.74, 2.69)	0.78 (0.28, 2.17)	-
	No change N= 185	Ref	Ref	-	-	Ref	Ref	-
Under 5 N= 265	Catch down N=66	0.74 (0.40, 1.38)	-	-		1.35 (0.60, 3.02)	0.87 (0.28, 2.70)	-
	Acceleration N=95	0.74 (0.42, 1.29)	-	-		0.87 (0.40, 1.92)	0.71 (0.24, 2.08)	-
	No change N=104	Ref	-	-	Ref	Ref	Ref	-
Under 5 N= 265 (adjusted) ‡	Catch down N=66	0.76 (0.40, 1.44)	-	-	1.74 (0.85, 3.54)	1.43 (0.62, 3.28)	0.83 (0.26, 2.67)	-
	Acceleration N=95	0.86 (0.48, 1.53)	-	-	0.86 (0.42, 1.77)	1.06 (0.47, 2.41)	0.76 (0.25, 2.30)	-
	No change N=104	Ref	-	-	Ref	Ref	Ref	-

Over 5 N=234	Deceleration N=70	**2.48*** **(1.12, 5.02)**	-	2.10 (0.89, 5.00)	-	**4.39*** **(1.36, 14.17)**	1.16 (0.07, 18.89)	0.46 (0.19, 1.13)
	Acceleration N=83	1.42 (0.70, 2.89)	-	1.44 (0.60, 3.46)	-	2.94 (0.90, 9.65)	0.98 (0.06, 15.87)	0.67 (0.27, 1.67)
	No change N=81	Ref	-	Ref	-	Ref	Ref	Ref
Over 5 N=234 (adjusted) ‡	Deceleration N=70	**2.56*** **(1.23, 5.33)**	-	2.23 (0.90, 5.51)	-	**4.89*** **(1.48, 16.1)**	1.24 (0.08, 20.7)	2.42 (0.96, 6.09)
	Acceleration N=83	1.37 (0.66, 2.84)	-	1.36 (0.55, 3.40)	-	3.05 (0.91, 10.2)	1.06 (0.06, 17.8)	1.48 (0.58, 3.75)
	No change N=81	Ref	-	Ref	-	Ref	Ref	Ref

†Adjusted for gestational age, gender, family history of atopy and delivery by caesarean section, ≤5 or >5 years of age
‡Adjusted for gestational age, gender, family history of atopy and delivery by caesarean section

Table 2-14 Association between 2nd trimester (HC) to birthweight growth trajectory and respiratory symptoms in term-born children. Data are Odds ratios (95% confidence intervals)

2nd Trimester HC to birthweight		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All measurements N=1141	Deceleration N=378	0.96 (0.73, 1.26)	0.98 (0.70, 1.37)	-	-	0.86 (0.59, 1.27)	0.96 (0.49, 1.90)	-
	Acceleration N=192	1.16 (0.83, 1.62)	1.12 (0.74, 1.69)	-	-	0.81 (0.49, 1.33)	1.37 (0.64, 2.95)	-
	No change N=571	Ref	Ref	-	-	Ref	Ref	-
All measurements N=1141 (adjusted)†	Deceleration N=378	0.95 (0.72, 1.51)	0.84 (0.54, 1.31)	-	-	0.86 (0.58, 1.27)	0.90 (0.45, 1.80)	-
	Acceleration N=192	1.06 (0.75, 1.51)	0.67 (0.38, 1.21)	-	-	0.73 (0.44, 1.23)	1.26 (0.58, 2.74)	-
	No change N=571	Ref	Ref	-	-	Ref	Ref	-
Under 5 N=581	Deceleration N=200	0.97 (0.67, 1.40)	-	-	1.11 (0.71, 1.74)	1.23 (0.73, 2.07)	0.81 (0.36, 1.80)	-
	Acceleration N=103	0.96 (0.61, 1.51)	-	-	0.80 (0.44, 1.46)	0.80 (0.39, 1.65)	1.12 (0.45, 2.78)	-
	No change N=278	Ref	-	-	Ref	Ref	Ref	-
Under 5 N=581 (adjusted) ‡	Deceleration N=200	1.01 (0.69, 1.46)	-	-		1.29 (0.76, 2.20)	0.78 (0.35, 1.75)	-
	Acceleration N=103	0.96 (0.60, 1.53)	-	-		0.79 (0.38, 1.64)	1.11 (0.44, 2.78)	-
	No change N=278	Ref	-	-	Ref	Ref	Ref	-

Over 5 N=560	Deceleration N=178	0.90 (0.60, 1.36)	-	0.81 (0.49, 1.36)	-	0.54 (0.29, 1.00)	1.32 (0.36, 5.00)	0.83 (0.50, 1.39)
	Acceleration N=89	1.40 (0.85, 2.30)	-	1.56 (0.88, 2.75)	-	0.82 (0.40, 1.67)	2.01 (0.47, 8.60)	0.91 (0.48, 1.73)
	No change N=293	Ref	-	Ref	-	Ref	Ref	Ref
Over 5 N=560 (adjusted) ‡	Deceleration N=178	0.87 (0.57, 1.34)	-	0.80 (0.47, 1.36)	-	0.50* (0.27, 0.95)	1.34 (0.35, 5.14)	0.77 (0.45, 1.33)
	Acceleration N=89	1.17 (0.70, 1.97)	-	1.38 (0.76, 2.51)	-	0.66 (0.32, 1.40)	1.77 (0.40, 7.89)	0.73 (0.36, 1.44)
	No change N=293	Ref	-	Ref	-	Ref	Ref	Ref

*p<0.05

†Adjusted for gestational age, gender, family history of atopy and delivery by caesarean section, ≤5 or >5 years of age

‡Adjusted for gestational age, gender, family history of atopy and delivery by caesarean section

Table 2-15 Association between 2nd trimester (FL) to birthweight growth trajectory and respiratory symptoms in term-born children. Data are Odds ratios (95% confidence intervals)

2nd Trimester FL to birthweight		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
All measurements N= 1118	Deceleration N= 466	0.95 (0.73, 1.24)	1.15 (0.82, 1.60)	-	-	1.10 (0.75, 1.61)	1.00 (0.51, 1.94)	-
	Acceleration N= 188	0.94 (0.66, 1.34)	1.20 (0.78, 1.84)	-	-	1.05 (0.63, 1.74)	1.25 (0.55, 2.83)	-
	No change N= 464	Ref	Ref	-	-	Ref	Ref	-
All measurements N= 1118 (adjusted)†	Deceleration N= 466	1.03 (0.78, 1.36)	1.16 (0.75, 1.80)	-	-	1.19 (0.80, 1.77)	1.07 (0.54, 2.10)	-
	Acceleration N= 188	0.96 (0.66, 1.37)	1.07 (0.60, 1.90)	-	-	1.10 (0.65, 1.83)	1.28 (0.56, 2.95)	-
	No change N= 464	Ref	Ref	-	-	Ref	Ref	-
Under 5 N= 565	Deceleration N=221	0.97 (0.67, 1.40)	-	-	1.19 (0.76, 1.87)	1.12 (0.67, 1.89)	1.03 (0.47, 2.24)	-
	Acceleration N=100	0.70 (0.43, 1.13)	-	-	0.86 (0.47, 1.58)	0.63 (0.29, 1.38)	1.05 (0.39, 2.81)	-
	No change N=244	Ref	-	-	Ref	Ref	Ref	-
Under 5 N= 565 (adjusted) ‡	Deceleration N=221	0.98 (0.68, 1.43)	-	-	1.25 (0.79, 1.97)	1.15 (0.68, 1.96)	1.03 (0.47, 2.25)	-
	Acceleration N=100	0.70 (0.43, 1.14)	-	-	0.86 (0.45, 1.56)	0.67 (0.29, 1.40)	1.09 (0.40, 2.97)	-
	No change N=244	Ref	-	-	Ref	Ref	Ref	-

Over 5 N=553	Deceleration N=245	0.99 (0.67, 1.48)	-	1.13 (0.69, 1.86)	-	1.10 (0.62, 1.95)	1.13 (0.30, 4.24)	0.75 (0.46, 1.23)
	Acceleration N=88	1.36 (0.81, 2.30)	-	1.72 (0.93, 3.16)	-	1.68 (0.83, 3.38)	1.91 (0.42, 8.70)	0.85 (0.44, 1.66)
	No change N=220	Ref	-	Ref	-	Ref	Ref	Ref
Over 5 N=553 (adjusted) ‡	Deceleration N=245	1.12 (0.74, 1.70)	-	1.29 (0.77, 2.17)	-	1.24 (0.69, 2.25)	1.27 (0.33, 4.88)	0.82 (0.49, 1.38)
	Acceleration N=88	1.40 (0.82, 2.41)	-	1.82 (0.96, 3.44)	-	1.77 (0.86, 3.63)	1.96 (0.43, 9.01)	0.87 (0.43, 1.74)
	No change N=220	Ref	-	Ref	-	Ref	Ref	Ref

†Adjusted for gestational age, gender, family history of atopy and delivery by caesarean section, ≤5 or >5 years of age
‡Adjusted for gestational age, gender, family history of atopy and delivery by caesarean section

2.6 Discussion

In this chapter, I have suggested that foetal growth patterns are potentially important factors in predicting the risk of increased wheeze in preterm and term born children. Previous studies in term-born cohorts have used birthweight as proxy for foetal growth, and examined associations with respiratory symptoms and lung function, with mixed results in children and adults (Kotecha et al., 2015, Lawlor et al., 2005). By assessing growth over specific periods of gestation, I have attempted to define the impact of growth trajectory in during key periods of development. In contrast to my hypotheses, I noted that both growth acceleration, and deceleration, were associated with increased risk of respiratory symptoms in preterm-born, and term-born children. The results are summarised in Table 2-16 and Table 2-17 below which indicate the direction of growth change for a given period of gestation and the OR associated with the outcome:

Table 2-16: Summary of results in relation to growth change during foetal life and associations with increased respiratory symptoms in preterm-born children (p<0.05)

Preterm-born children		Wheeze-ever	Hospital admission
1st trimester- birth CRL-BW (Table 2-4)	Whole group	↑OR 2.21	n/s
	<5 years of age	↑OR 2.80	n/s
	≥5 years of age	n/s	n/s
1st-2nd trimester CRL-HC (Table 2-5)	Whole group	↓OR 1.59	↑OR2.57; ↓OR3.84
	<5 years of age	n/s	↑OR2.51; ↓OR2.97
	≥5 years of age	n/s	Not computed
1st-2nd trimester CRL-FL (Table 2-6)	Whole group	n/s	n/s
	<5 years of age	n/s	n/s
	≥5 years of age	n/s	n/s
2nd trimester- birth HC-BW (Table 2-7)	Whole group	↑ OR1.60	n/s
	<5 years of age	↑OR2.00 ↓OR1.55	n/s
	≥5 years of age	n/s	↑OR4.22
2nd trimester- birth FL-BW (Table 2-8)	Whole group	n/s	n/s
	<5 years of age	n/s	n/s
	≥5 years of age	n/s	n/s

↑= growth acceleration significantly associated with respiratory outcome
↓= growth deceleration significantly associated with respiratory outcome
n/s= not statistically significant

Table 2-17 Summary of results in relation to growth change during foetal life and associations with increased respiratory symptoms in term-born children (p<0.05)

Term-born children		Wheeze-ever	Inhaler use
1st trimester- birth CRL-BW (Table 2-11)	Whole group	n/s	↑ OR2.13
	<5 years of age	n/s	n/s
	≥5 years of age	n/s	n/s
1st-2nd trimester CRL-HC (Table 2-12)	Whole group	n/s	n/s
	<5 years of age	n/s	n/s
	≥5 years of age	n/s	n/s
1st-2nd trimester CRL-FL (Table 2-13)	Whole group	n/s	n/s
	<5 years of age	n/s	n/s
	≥5 years of age	↓OR2.56	↓OR4.89
2nd trimester- birth HC-BW (Table 2-14)	Whole group	n/s	n/s
	<5 years of age	n/s	n/s
	≥5 years of age	n/s	n/s
2nd trimester- birth FL-BW (Table 2-15)	Whole group	n/s	n/s
	<5 years of age	n/s	n/s
	≥5 years of age	n/s	n/s

↑= growth acceleration significantly associated with respiratory outcome
↓= growth deceleration significantly associated with respiratory outcome
n/s= not statistically significant

To date, three other groups have investigated similar hypotheses to this study- all of which were conducted in term-born cohorts, and present varying results. In common with my study, investigators from the Generation R cohort did not identify any association with measures of foetal size and childhood respiratory outcomes at four years of age (Sonnenschein-van der Voort et al., 2012). In contrast, Turner and colleagues reported a 4% decrease in the odds of wheeze-ever and 5% decrease in asthma ever per millimetre increase in CRL in 5-year old children. Increases in BD and FL were associated with decreases in doctor-confirmed asthma of 12% and 10% respectively (Turner et al., 2010). Furthermore, improvements in lung function were also identified for increases in first trimester CRL and BD. Although asthma is difficult to diagnose in children under 5 years of age as wheezy symptoms can be transient in this age group, when the cohort was followed up at age 10, increases in first trimester CRL and second trimester BD were still associated with a 6% and 13% reduction in risk of recent and active wheeze respectively and increased CRL and BD was also associated with increased FEV_1 (Turner et al., 2011).

Although it was not possible to classify children by atopic status in my study, the data presented in this chapter somewhat complement that of Pike et al. who reported that a reduction in the relative risk of non-atopic wheeze was related to an increase in head circumference only (RR 0.90 95% CI 0.81, 0.90 per SD increase in HC growth velocity) between the 1st and 2nd trimesters in 3-year old children (Pike et al., 2010). I similarly observed that growth faltering between approximately 10-20 weeks' gestation was associated with increased odds of wheeze-ever, recent wheeze, inhaler use and hospital admission (OR 1.59, 1.29, 1.60 and 3.84 respectively) in preterm-born children (acknowledging that recent wheeze, nor inhaler use, met the criteria for statistical significance). Further observations from the Southampton group suggested that foetal abdominal growth acceleration between the 1st and 2nd trimesters was associated with an increase in atopy (RR 1.46; 95% CI 1.11, 1.93 per SD of increase in growth velocity) and atopic wheeze (RR 1.32 95% CI 0.94, 1.85); an increase in growth velocity during the 2nd to 3rd trimester (19-34 weeks) was associated with a decreased risk of atopy (RR 0.80; 95%CI 0.68 0.95) and atopic wheeze (RR 0.8; 95% CI 0.65, 1.00).

In my study, when growth trajectories for both between the 1st trimester to birth and between the 2nd trimester and birth were investigated, both growth acceleration and deceleration were associated with increased odds of wheeze-ever, predominantly in preterm-born children aged less than five years. One can speculate that when compared to a normal pattern of growth, both growth acceleration and deceleration may have deleterious effects on early respiratory health. This concept is supported by the recent systematic review presented by Alkandari and colleagues who noted that accelerated growth was associated with both advantageous and disadvantageous effects on respiratory outcomes (Alkandari et al., 2015).

The mechanisms of how change in growth rate impacts upon the developing organs are not yet known. However, timing of insults which prompt growth change are likely to be of significant importance. The main structures of the respiratory system are established in the first and early second trimester, whereas the majority of differentiation and maturation occurs between the 2nd trimester and birth (Larsen, 1998). One possibility is that structural and mechanical deficits are established early in gestation that later manifest as airway obstruction due to smaller airways. For example, the data presented by Turner in term-born children demonstrated increased respiratory symptoms for children with persistently low 1st-2nd trimester growth (wheeze-ever OR 3.31; 1.82, 6.02) (Turner et al., 2010). My data in term-born children similarly noted increased odds ratios for wheeze-ever, wheeze in the last 12 months, and inhaler use in children ≥5 years of age when growth deceleration was expressed as a >0.67SD decrease between 1st trimester CRL and 2nd trimester FL z-scores.

In the Southampton cohort, early growth faltering was associated with non-atopic wheeze, and atopic wheeze was related to growth faltering in the 3rd trimester (Pike et al., 2010). The authors suggest that the latter may be an effect of altered immunological status. These associations are consistent with the "developmental origins of health and disease" and that of a predictive adaptive response, where adverse intrauterine conditions induce a developmental mismatch with the postnatal environment (Pike et al., 2008). In contrast, co-workers from the Generation R cohort did not find any associations between 2nd to 3rd trimester growth trajectory and asthma symptoms over the first four years of life (Sonnenschein-van der Voort et al., 2012) in term-born children.

Finally, an interesting contribution from my data noted that the effect of growth trajectory change was most evident in children aged under five. Thus, this could represent part of an 'early wheeze' phenotype which may in part may be due to altered response to infections

as a result of dysregulated lung growth (Barker et al., 2013). These finding may be especially pertinent to the RANOPS preterm-born cohort as the risk of both chronic airway obstruction and inflammation are substantially increased due to the immaturity of the airways, trauma caused by perinatal respiratory disease, and propensity to being born small for gestational age.

2.7 Strengths and limitations

The main strength of this study is the use of contemporary cohort of preterm-born children which was specifically designed to investigate associations with respiratory symptoms in childhood. Validated questionnaires were used, allowing comparison with other studies. Moreover, I was able to link to national databases to obtain additional information on birth outcomes and socio-economic status.

Database access also facilitated collection of antenatal ultrasound data for the majority of the cohort and allowed investigations of foetal growth measures rather than using birthweight as a proxy for foetal wellbeing. Although the data were obtained retrospectively and each scan was performed by a qualified ultrasonographer, it is acknowledged that prospective data obtained as part of a research protocol may have improved the accuracy of the results (Royston and Altman, 1995); however, some findings were comparable with other studies. Unfortunately, under the standard scanning protocols within units in Wales, no single measurement is performed both in the first and second trimester scans. Third trimester scans are not routine, therefore abdominal circumference, which is used to assess *in utero* growth restriction, was only available in a minority of cases. The available measurements were compared under the assumption that they reflect similar levels of growth. Also, data on head circumference and length at birth were not available,

as a nationwide neonatal database did not exist at that time; thus, birthweight was used as a measure of 3rd trimester growth to compare with antenatal measurements.

Finally, in common with all cohort studies, residual confounding by unmeasured covariates cannot be ruled out. In the cohort at large, non-responders to the questionnaire were of lower socio-economic status (Edwards et al., 2016). However, given that infants born into such conditions are more likely to be born preterm, IUGR and have been exposed to a less favourable intrauterine growth environment (e.g. tobacco smoke) one would expect inclusion of these children to strengthen rather than weaken the associations I have presented.

2.8 Summary and conclusions

In this chapter I have presented data on foetal growth trajectory and potential associations with respiratory health in preterm-born children and demonstrated that change in trajectory may be a determinant of later lung disease. Mine is the first study to specifically assess this in children born preterm. Consistent with the "Developmental Origins of Health and Disease" hypothesis, the timing of growth change is likely to be an important factor in terms of influencing lung development. Future prospective studies might focus on the collection on serial measurements of the foetus during pregnancy to allow more detailed comparisons of anthropometry and the relationship with birth outcomes such as prematurity and IUGR, and with later health outcomes in childhood and beyond. Initiatives such as the GROW software, which builds in maternal parameters such as height and weight to produce and 'individualised' foetal growth trajectory, provide valuable tools to assess foetal wellbeing and timing of growth change (Figueras and Gardosi, 2011).

3 Associations between infant weight gain and childhood respiratory symptoms in preterm-born and term-born children

3.1 Overview

In the previous chapter, potential links between foetal growth and respiratory health in childhood were identified, especially in preterm-born children. However, data are not consistent between studies, and in addition, some data suggest that postnatal growth, commonly weight gain, results in increased respiratory symptoms in childhood and beyond. Recent studies have focused on the term-born population (Claudia et al., 2015, Magnus et al., 2015, Popovic et al., 2016, van der Gugten et al., 2012, Flexeder et al., 2012). A meta-analysis of 147,000 children included 7,384 preterm-born children from several European cohorts, and noted an association between greater weight gain in infancy and increased childhood asthma (Sonnenschein-van der Voort et al., 2014). A further exploration of 24,938 children, 2,053 of whom were born preterm, noted an association between gestational age, infant weight gain in the first year of life, and measures of lung function (den Dekker et al., 2016). However, both studies included preterm-born subjects who were recruited in largely term-born cohorts, suggesting selection bias. Moreover, previous studies have reported only associations and have not explored the important early-life factors that may influence the effect of foetal growth trajectories and postnatal weight gain on respiratory outcomes. In this chapter I use data from the RANOPS cohort which was specifically designed to investigate preterm-born children and key factors associated with their respiratory disease.

3.2 Aims and Hypothesis

In this study, I investigated postnatal weight gain and the association with the risk of respiratory symptoms in preterm and term-born children. Furthermore, multiple regression analysis and mediation analysis were conducted to establish if early-life factors may be important in the association between infant weight gain and childhood respiratory symptoms.

My hypotheses were:

- Infant weight gain was associated with increased respiratory symptoms in preterm- and term-born children.
- There would be a 'dose dependent' effect of gestational age on the association between rapid infant weight gain and later respiratory outcomes.
- The effect of weight gain on respiratory health would be mediated by gestational age; other important factors may be identified.

3.3 Methods

3.3.1 The Respiratory and Neurological Outcomes of Preterms Study (RANOPS)

Respiratory outcome data from RANOPS, a cross-sectional population study of preterm-born children, were used. In 2013, all identifiable live-born preterm (<37 weeks' gestation) surviving children born in Wales aged between 1 and 10 years, and term controls (born same gender, day and locality) were sent the Liverpool Respiratory Symptom Questionnaire (if <5 years of age) or a modified ISAAC Questionnaire (if ≥5 years of age), n=13,361. (Edwards et al., 2015a, Edwards et al., 2016). Both questionnaires have been validated previously (Asher et al., 1995) (Powell et al., 2002) and use of such questionnaires is widely accepted in epidemiological studies. Ethical approval for the survey was obtained from the

Research Ethics Committee and parents gave consent by virtue of returning completed questionnaires.

3.3.2 Perinatal data

Demographic data, including gestation, birthweight, singleton or multiple birth and Wales index of multiple deprivation (WIMD, a measure of socio-economic status) were available from NWIS. For the preterm analysis, children were divided into four groups based on gestational age at birth: 25-32, 33-34, 35-36 weeks' gestation. This approach is similar to studies on lung function (Kotecha et al., 2012) and that of others as it represents specific stages in lung development (Joshi and Kotecha, 2007) and children most at risk of lung disease (Boyle et al., 2012, Greenough, 2012). Gestational age in term-born children was defined as 'early-term' (37-38 weeks' gestation) and Term (≥39 weeks), as early-term children have also been noted to have increased respiratory symptoms (Edwards et al., 2015a). Intrauterine growth restriction (IUGR) was defined as <10th centile for standardised birthweight corrected for gestation and gender using the LMS method (Medical Research Council, UK) (Ong, 2000, Kotecha et al., 2010).

3.3.3 Infant weight data

Postnatal weight data obtained from clinic and community appointments were provided by NWIS. The closest available weight measurement to 9 months (limited to a range of 6 to 12 months) and 24 months of age (limited to a range of 18 to 28 months) was identified for each participant. Birthweight, weight at 9 months and weight at 24 months of age were then standardised for gestational age (birthweight), age at time of measurement (postnatal weight) and gender using the LMS method (Medical Research Council, UK) to produce z-scores. Participants with birthweight or postnatal weight outside ±3.5 SD or with unknown gestational age were excluded.

Infant weight gain between birth and 9 months of age, and between birth and 24 months of age was defined by dichotomising the population into those who demonstrated an increase of >0.67SD in weight and those who did not. A change of >0.67 was chosen as this reflects the difference between centile lines drawn on the standard growth chart (e.g. 2nd, 9th, 25th, 50th, 75th, 91st and 98th centiles) and is used clinically to assess growth (Ong, 2000). However, the use of 'centile crossing' as measure of change in growth velocity in longitudinal data is sometimes criticised. In order to validate my results, the method of Royston was used to calculate measures of conditional growth velocity between birth and nine months of age (Royston, 1995). With this method, the measures of growth velocity are independent from initial size and are corrected for regression to the mean (Royston and Altman, 1995) (Figure 3-1).

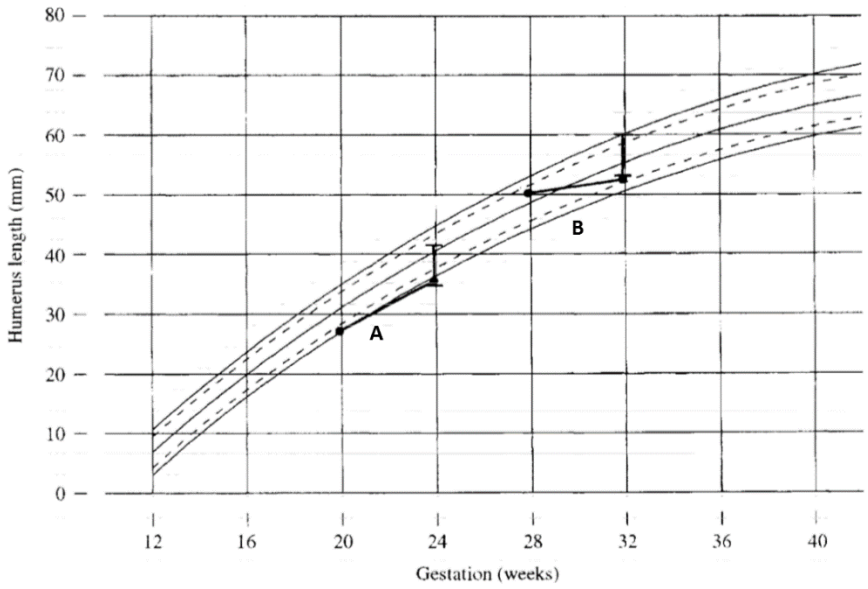


Figure 3-1: Example of conditional measures of humerus length in two foetuses. The reference curves represent the 3rd, 10th, 50th, 90th and 97th centiles. Foetus 'A' is on the 3rd cross-sectional centile for humerus length at 20 weeks of gestation, and grows to be on the 1st cross-sectional centile at 24 weeks. The foetus is small at both timepoints, however, conditional to the measurement of length at 20 weeks, is placed on the conditional 8th centile which reflects adequate growth. Foetus 'B' is on the 75th cross-sectional centile for length at 28 weeks, and 13th centile at 32 weeks. Obtaining the measure of conditional growth notes this foetus is on the 1st conditional centile, which may indicate more concern in regards to growth trajectory than the crossing of cross-sectional centiles. Reproduced with permission from Royston and Altman. Ultrasound Obstet Gynecol. 1995 Nov;6(5):307-12.

Multilevel models using all available weight data for preterm-born (n= 11,581) and term-born children (n= 9,163) were used to derive regression equations to predict expected weight at 9 months (Figure 3-2). Multilevel models are advantageous as they allow consideration to be given to within-subject regression slopes whilst taking in to account missing data in longitudinal data sets (Rabe-Hesketh and Skrondal, 2012). Level one of the hierarchical model used all available weight data, and level two consisted of each individual's study ID. Multilevel modelling was performed in Stata (Version 12, StataCorp, Texas USA). The resulting regression equation and constants from the model were applied to the dataset to calculate the conditional growth velocity using Royston's published equations. A separate model was run for the preterm group and for the term group due to the difference in growth patterns of preterm-born children.

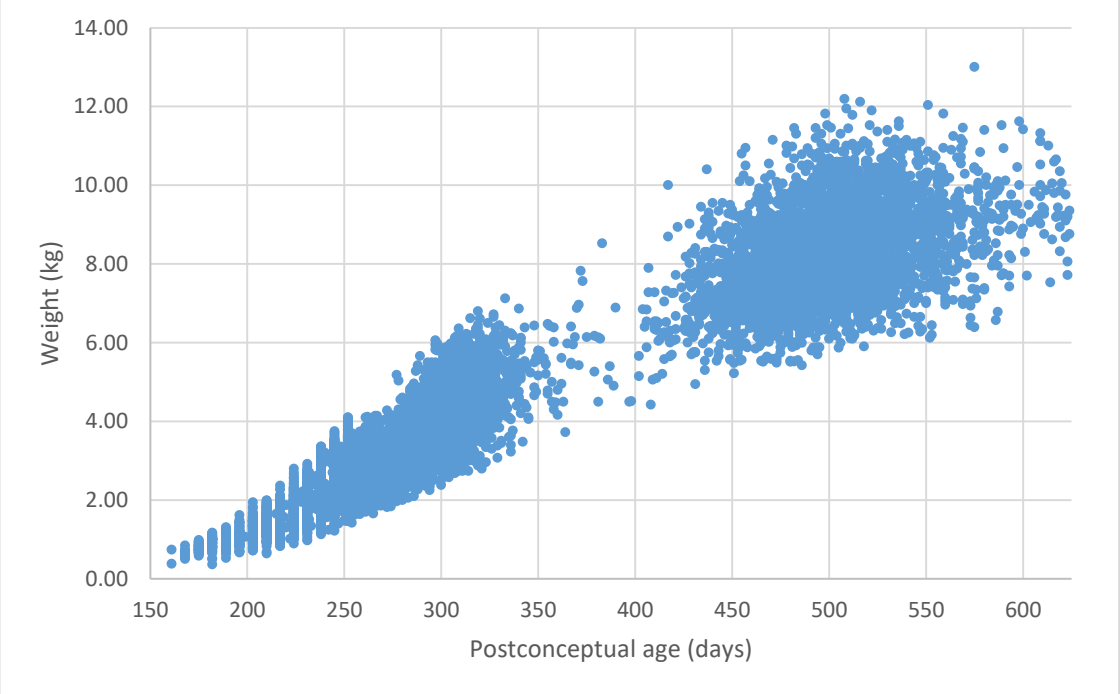


Figure 3-2 Example of available weight data in preterm-born children for use in multilevel modelling

3.3.4 Respiratory outcomes

Respiratory outcomes were extracted from the RANOPS questionnaire which included wheeze-ever, recent wheeze (last 3 months for <5 years of age; last 12 months for ≥5 years of age), use of inhalers, hospital admissions for chest-related reasons, and doctor-diagnosed asthma (≥5 years of age only). All outcomes were dichotomous (Edwards et al., 2015a, Edwards et al., 2016).

3.4 Statistical analysis

Chi-squared tests were used to investigate the differences in categorical demographic data between weight gain groups (>0.67SD weight gain or not). Normality of continuous data was checked by visually inspecting Q-Q plots. Independent sample t-tests were used for continuous variables which were normally distributed. WIMD score was subsequently converted into quintiles for use in statistical models.

First, univariate logistic regression models were used to investigate the association between infant weight gain at both 9 months and 2 years of age with childhood respiratory outcomes. 'No change' was set as the reference category. Confounders were then included in adjusted multivariable models if they had a p-value <0.10 for associations with 'wheeze-ever', which was the primary outcome for all analyses. Both the univariate and multivariable models were initially conducted using all available data (<5 and ≥5 years of age combined). The 'Recent Wheeze' outcome was a combined outcome of 'wheeze in the last 3 months' (<5 years of age) and 'wheeze in the last year' (≥5 years of age). Modelling was then conducted with the data separated into the <5 and ≥5 years age groups. In order to validate the results, the analyses were repeated using the measure of conditional growth at 9 months of age.

Second, to assess if the relationship between weight gain and 'wheeze-ever' was mediated via gestational age and or via significant covariates, mediation analysis was performed using structural equation modelling (Mplus version 7, Muthen and Muthen, Los Angeles, California USA). Mediation analysis explores how the relationship between an exposure and an outcome can be explained by their relationship with a third variable (or more). Mediation is said to occur if inclusion of the mediating variable(s) reduces the strength of the relationship (direct effect) between the exposure and outcome (Figure 3-3). However, use of bootstrapping to produce robust 95% confidence intervals for the indirect effect of the mediator is the favoured way to interpret if mediation has occurred, as the distribution of the indirect effect is often not close to normal (Field, 2013). Bootstrapping is a technique that does not rely on assumptions of normality (it is non-parametric) and repeatedly samples from within the dataset (1000 samples in my analysis) in order to derive confidence intervals for the indirect effect (Muthen et al., 2016). All potential mediators were entered in parallel (Muthen et al., 2016). Modelling was conducted independently for both the preterm and term-born groups.

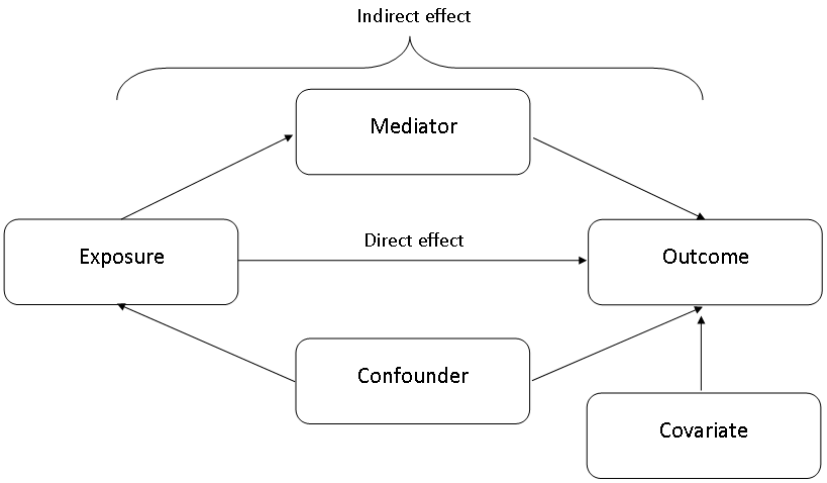


Figure 3-3 Diagram representing the relationship between a mediating variable and the exposure and outcome of interest, for comparison with relationships with confounders and covariates. The direct effect is the effect of the exposure on the outcome, adjusted for the mediator (and any other variables in the model, as per a standard regression). The indirect effect is the effect of the exposure on the outcome *via* the mediating variable.

Finally, I considered the cohort as a whole study population (including preterm and term groups) and used interaction terms to investigate the combined effects of gestation groups and infant weight gain when defined as >0.67SD increase between birthweight and weight at 9 months using logistic regression. Term-born children with 'no change' for weight gain were used as the control category. Both univariate, and multivariable modelling including covariates with a p-value <0.10 as described above, were performed. This was then repeated to include 'early term' as an additional gestational group. All modelling was performed using SPSS (version 20, IBM, Chicago IL, USA). Statistical significance was set at $p<0.05$ for all analyses described above.

3.5 Results

3.5.1 Data availability

Following exclusions for missing birthweight (n=193), missing weight at 9 months, and weight z-score ±3.5 SD (n=1,132), 5,824/7,149 (81%) participants had valid data; 3,425 participants were born preterm and 2,399 were born at term. At 24 months of age, 3,094/7,149 (43%) participants had valid data following exclusions for missing weight data, or weight z-score ±3.5 SD; 1,819 were born preterm and 1,275 born at term.

3.5.2 Demographics

Demographics of preterm and term-born children with, and without, >0.67SD weight gain at 9 months of age and at 24 months of age are presented in Table 3-1 and Table 3-2, respectively. In the preterm-born group, children of lower birthweight, whose mothers smoked during pregnancy, were of the lowest WIMD quintile, and whose mothers currently smoke, were more likely to exhibit weight gain of >0.67SD between birth and 9 months of age. Children born IUGR, by caesarean section, and as one of a multiple birth were also

significantly more likely to have infant weight gain. In term-born children, lower birthweight, maternal smoking in pregnancy and current maternal smoking, multiple birth, and IUGR were associated with infant weight gain at 9 months.

Table 3-1 Demographics of participants included in the infant weight gain analysis at 9 months of age

Postnatal weight data at age 9 months		Preterm N = 3425		Term N= 2399	
		No change N=2,661	>0.67SD N=764	No change N=1765	>0.67SD N=634
Birthweight, kg**‡ Mean (SD)		2.30 (0.66)	2.11 (2.11)	3.55 (0.48)	3.21 (0.45)
Gender (%) †	Male	1,447 (54.4)	436 (57.1)	909 (51.5)	366 (57.7)
	Female	1,214 (45.6)	328 (42.9)	856 (48.5)	268 (42.3)
WIMD quintiles (%)*	1(most)	454 (17.1)	151 (19.8)	256 (14.5)	105 (16.6)
	2	533 (20.0)	165 (21.6)	323 (18.3)	127 (20.0)
	3	560 (21.0)	171 (22.4)	377 (21.4)	142 (22.4)
	4	556 (20.9)	126 (16.5)	373 (21.1)	134 (21.1)
	5 (least)	558 (21.0)	151 (19.8)	436 (24.7)	126 (19.9)
Maternal smoking: pregnancy (%) **‡	Yes	307 (11.5)	146 (19.1)	159 (9.0)	95 (15.0)
	No	2,354 (88.5)	618 (80.9)	1606 (91.0)	539 (85.0)
Maternal smoking: Current (%) **‡	Yes	411 (15.4)	179 (23.4)	181 (10.3)	119 (18.8)
	No	2,250 (84.6)	585 (76.6)	1584 (89.7)	515 (81.2)
Maternal age, years Mean (SD)		30.4 (5.9)	29.6 (6.0)	30.6 (5.6)	29.9 (5.7)

Singletons (%)*†	Multiple	558 (21.0)	119 (26.0)	18 (1.00)	15 (2.4)
	Singleton	2,103 (79.0)	565 (74.0)	1747 (99.0)	619 (97.6)
Caesarean delivery (%)*	Yes	1,204/3,232 (48.0)	390/3,232 (53.8)	440/2250 (26.6)	169/2250 (28.4)
	No	1,303/3,232 (52.0)	335/3,232 (46.2)	1214/2250 (73.4)	427/2250 (71.6)
IUGR (%) **‡	Yes	183 (6.9)	193 (25.3)	57 (3.2)	97 (15.3)
	No	2,478 (93.1)	571 (74.7)	1708 (96.8)	537 (84.7)
Breastfeeding	Yes	1,415 (53.2)	376 (49.2)	1093 (61.9)	376 (59.3)
	No	1,246 (46.8)	388 (50.8)	672 (38.1)	258 (40.7)
Family history of asthma/atopy	Yes	675 (25.4)	215 (28.1)	457 (25.9)	145 (22.9)
	No	1,986 (74.6)	549 (71.9)	1308 (74.1)	489 (77.1)
Weight at 9m, kg Mean (SD) **‡		7.97 (1.14)	9.04 (1.19)	8.53 (1.05)	9.61 (1.34)

Preterm *p<0.05, **p<0.001; Term †p<0.05, ‡p<0.001
Denominators are given for categorical variables with missing data

At 24 months of age in the preterm-born group, children of lower birthweight, whose mothers smoked during pregnancy, of lowest WIMD quintile, and whose mothers currently smoke, were more likely to exhibit weight gain >0.67SD between birth and 24 months of age (Table 3-2). Children born IUGR, by caesarean section, and as one of a multiple birth were also significantly more likely to have infant weight gain. In term-born children, lower birthweight, gender, maternal smoking in pregnancy, current maternal smoking, and IUGR were associated with infant weight gain at 24 months of age.

Table 3-2 Demographics of participants included in the infant weight gain analysis at 24 months of age

Postnatal weight data at age 24 months		Preterm N = 1819		Term N= 1275	
		No change N=1253	>0.67SD N=566	No change N=871	>0.67SD N=404
Birthweight, kg**‡ Mean (SD)		2.29 (0.66)	2.09 (0.55)	3.54 (0.47)	3.28 (0.47)
Gender (%) †	Male	684 (54.6)	298 (52.7)	446 (51.2)	228 (56.4)
	Female	569 (45.4)	268 (47.3)	425 (48.8)	176 (43.6)
WIMD quintiles (%)	1(most)	171 (13.6)	92 (16.3)	98 (11.3)	51 (12.6)
	2	238 (19.0)	120 (21.2)	145 (16.6)	72 (17.8)
	3	274 (21.9)	128 (22.6)	208 (23.9)	89 (22.0)
	4	288 (23.0)	97 (17.1)	207 (23.8)	85 (21.0)
	5 (least)	282 (22.5)	129 (22.8)	213 (24.5)	107 (26.5)
Maternal smoking: pregnancy (%)*†	Yes	140 (11.2)	94 (16.6)	76 (8.7)	54 (13.4)
	No	1113 (88.8)	472 (83.4)	795 (91.3)	350 (86.6)
Maternal smoking: Current (%)*†	Yes	184 (14.7)	121 (21.4)	90 (10.3)	61 (15.1)
	No	1069 (85.3)	445 (78.6)	781 (89.7)	343 (84.9)
Maternal age, years Mean (SD)		30.6 (5.80)	30.1 (5.78)	31.1 (5.51)	30.2 (5.75)
Singletons (%)*	Multiple	268 (21.4)	148 (26.1)	12 (1.4)	9 (2.2)
	Singleton	985 (78.6)	418 (73.9)	859 (98.6)	395 (97.8)
Caesarean delivery (%)*	Yes	543/1,693 (46.6)	278/1,693 (52.7)	242/1,195 (29.7)	98/1,195 (25.7)
	No	622/1,693 (53.4)	250/1,693 (47.3)	572/1,195 (70.3)	283/1,195 (74.3)
IUGR (%) **‡	Yes	76	132	23	59

		(6.1)	(23.3)	(2.6)	(14.6)
	No	1177 (93.9)	434 (76.7)	848 (97.4)	345 (85.4)
Breastfeeding	Yes	691 (55.1)	310 (54.8)	575 (66.0)	261 (64.6)
	No	562 (44.9)	256 (45.2)	296 (34.0)	143 (35.4)
Family history of asthma/atopy	Yes	314 (25.1)	132 (23.3)	217 (24.9)	105 (26.0)
	No	939 (74.9)	434 (76.7)	654 (75.1)	299 (74.0)
Weight at 24m, kg**‡ Mean (SD)		11.60 (1.48)	13.03 (1.64)	12.1 (1.35)	13.70 (1.58)

Preterm *p<0.05, **p<0.001; Term †p<0.05, ‡p<0.001
Denominators are given for categorical variables with missing data

3.5.3 Outcomes in preterm-born children

*3.5.3.1 **Univariate analysis***

Results of the univariate analyses are shown in Table 3-3. Lower gestation, male gender, maternal smoking in pregnancy, current maternal smoking, family history of asthma/atopy and lower WIMD quintile were associated with increased wheeze-ever at p<0.10 (of which all were significant at p<0.05 aside from maternal smoking in pregnancy. Breastfeeding, non-white ethnicity and being ≥5 years of age were significantly associated with decreased wheeze-ever (all p<0.10 and thus entered in to the fully adjusted model).

*3.5.3.2 **Using >0.67SD change in weight as primary exposure***

A >0.67SD increase in weight between birth and 9 months of age was significantly associated with wheeze-ever in preterm-born children (OR 1.21; 95% CI 1.03, 1.42). In the fully adjusted model, the association remained after inclusion of covariates (which had p<0.10 in univariate analysis). When the cohort was split into those aged <5 years and those aged over 5, wheeze-ever was significant in the fully adjusted model in the ≥5 years

age group only (OR 1.37; 95% CI 1.06, 1.77); wheeze in the last 12 months showed a similar but non-significant effect (OR 1.25; 95% CI 0.93, 1.68), Table 3-4.

When weight gain was defined as >0.67SDS change between birthweight and 24 months of age, there were no significant associations with later respiratory symptoms. However, the largest effect was in the ≥5 years age group (wheeze-ever OR 1.27; 95% CI 0.96, 1.67); this attenuated in the fully adjusted model (OR 1.13; 95% CI 0.83, 1.55), Table 3-5.

Table 3-3 Univariate associations between potential confounders with weight gain and respiratory outcomes in preterm-born children

Preterm only	Wheeze-ever	Recent Wheeze	Wheeze last 12 months§	Wheeze last 3 months†	Inhaler use	Hospital admission	Doctor-diagnosed asthma§
Gestation							
≤32 weeks	**1.83****	**1.56****	**1.52****	**1.57****	**1.79****	**2.03****	**1.70****
	(1.54, 2.18)	**(1.30, 1.87)**	**(1.16, 2.00)**	**(1.22, 2.01)**	**(1.46, 2.19)**	**(1.50, 2.74)**	**(1.28, 2.25)**
33-34 weeks	**1.20***	1.15	1.02	1.24	1.03	1.41*	0.97
	(1.01, 1.42)	(0.95, 1.39)	(0.77, 1.36)	(0.96, 1.60)	(0.83, 1.28)	(1.02, 1.96)	(0.91, 1.31)
35-36 weeks	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Birthweight SDS							
	0.97	0.97	0.96	0.98	0.97	0.93	0.97
	(0.93, 1.02)	(0.92, 1.02)	(0.88, 1.03)	(0.91, 1.04)	(0.92, 1.03)	(0.85, 1.01)	(0.90, 1.06)
IUGR							
Yes	1.02	1.08	1.22	0.97	0.98	1.11	1.04
	(0.82, 1.26)	(0.85, 1.37)	(0.86, 1.73)	(0.70, 1.34)	(0.75, 1.29)	(0.75, 1.65)	(0.72, 1.52)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Gender							
Male	**1.38****	**1.32****	**1.37***	**1.32***	**1.34****	**1.38***	**1.33***
	(1.22, 1.56)	**(1.15, 1.52)**	**(1.11, 1.69)**	**(1.10, 1.59)**	**(1.14, 1.57)**	**(1.10, 1.74)**	**(1.06, 1.67)**
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Maternal smoking - pregnancy							
Yes	**1.17‡**	**1.25***	**1.43***	1.17	1.08	0.85	1.14
	(0.98, 1.40)	**(1.03, 1.51)**	**(1.09, 1.89)**	(0.89, 1.54)	(0.86, 1.35)	(0.60, 1.20)	(0.85, 1.55)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Maternal smoking-current							
Yes	**1.26***	**1.20***	1.02	**1.44***	1.14	1.05	1.08
	(1.08, 1.48)	**(1.20, 1.43)**	(0.78, 1.33)	**(1.13, 1.82)**	(0.94, 1.40)	(0.78, 1.40)	(0.82, 1.43)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Family history of Asthma/ Atopy							

	Yes	**2.07****	**2.24****	**2.33****	**2.07****	**2.09****	**1.76****	**3.03****
		(1.79, 2.40)	**(1.93, 2.60)**	**(1.85, 2.93)**	**(1.70, 2.52)**	**(1.78, 2.47)**	**(1.36, 2.19)**	**(2.38, 3.86)**
	No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Delivery by C/S								
	Yes	1.12	1.15	1.08	1.56	1.12	1.43*	1.09
		(0.98, 1.27)	(0.99, 1.32)	(0.87, 1.34)	(0.96, 1.40)	(0.94, 1.30)	(1.13, 1.80)	(0.87, 1.38)
	No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Breastfeeding								
	Yes	**0.83***	**0.81***	0.85	**0.74***	**0.76***	**0.80***	0.98
		(0.73, 0.94)	**(0.71, 0.93)**	(0.69, 1.04)	**(0.62, 0.89)**	**(0.65, 0.89)**	**(0.63, 1.00)**	(0.79, 1.23)
	No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Ethnicity								
	Non-white	**0.71***	0.91	1.57	**0.59***	0.72	0.94	1.29
		(0.54, 0.94)	(0.67, 1.24)	(0.99, 2.47)	**(0.39, 0.90)**	(0.49, 1.04)	(0.57, 1.55)	(0.79, 2.11)
	White	Ref	Ref	Ref	Ref	Ref	Ref	Ref
WIMD quintile								
	lowest- 1	**1.44****	**1.74****	**2.06****	**1.46***	**1.44***	1.42	1.46
		(1.18, 1.75)	**(1.39, 2.16)**	**(1.46, 2.92)**	**(1.09, 1.95)**	**(1.13, 1.84)**	(0.99, 2.03)	(1.01, 2.09)
	2	1.16	**1.30***	**1.72***	1.03	1.08	1.30	**1.57***
		(0.96, 1.41)	**(1.04, 1.61)**	**(1.23, 2.40)**	(0.77, 1.38)	(0.85, 1.40)	(0.92, 1.86)	**(1.11, 2.20)**
	3	**1.23***	**1.36****	**1.59***	1.17	1.23	1.09	1.13
		(1.02, 1.49)	**(1.09, 1.69)**	**(1.13, 2.34)**	(0.88, 1.57)	(0.96, 1.56)	(0.76, 1.58)	(0.79, 1.62)
	4	1.17	**1.30***	**1.53***	1.18	1.16	1.13	1.29
		(0.97, 1.42)	**(1.04, 1.63)**	**(1.09, 2.15)**	(0.87, 1.59)	(0.91, 1.49)	(0.78, 1.64)	(0.91, 1.83)
	highest- 5	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Age <5/≥5 years								
	>5	**0.60****	**0.59****	-	-	**0.65****	**0.18****	-
		(0.53, 0.68)	**(0.51, 0.68)**			**(0.55, 0.76)**	**(0.13, 0.24)**	
	<5	Ref	Ref	-	-	Ref	Ref	-

§Children ≥5 years of age only; †children <5 years of age only
‡p<0.10, *p<0.05; **p<0.001

Table 3-4 Associations between rapid weight gain from birth to 9 months of age and respiratory outcomes in preterm-born children

All		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
Univariate								
>0.67	N=764	**1.21***	1.19	-	-	1.08	1.03	-
		(1.03, 1.42)	(0.99, 1.42)			(0.88, 1.32)	(0.76, 1.40)	
No change	N= 2661	Ref	Ref	-	-	Ref	Ref	-
Fully adjusted†								
>0.67	N= 684	**1.22***	1.15	-	-	1.07	1.01	-
		(1.02, 1.45)	(0.95, 1.40)			(0.86, 1.33)	(0.79, 1.53)	
No change	N= 2358	Ref	Ref	-	-	Ref	Ref	-
<5								
Univariate								
>0.67	N= 378	1.10	-	-	1.11	1.06	1.07	-
		(0.87, 1.38)			(0.87, 1.42)	(0.81, 1.39)	(0.76, 1.51)	
No change	N= 1314	Ref	-	-	Ref	Ref	Ref	-
Fully adjusted‡								
>0.67	N= 353	1.11	-	-	1.11	1.11	1.13	-
		(0.86, 1.42)			(0.85, 1.44)	(0.83, 1.49)	(0.79, 1.62)	
No change	N= 1231	Ref	-	-	Ref	Ref	Ref	-
≥5								
Univariate								
>0.67	N= 386	**1.33***	-	1.28	-	1.10	0.87	1.24
		(1.06, 1.67)		(0.99, 1.67)		(0.81, 1.48)	(0.38, 1.82)	(0.94, 1.63)
No change	N= 1347	Ref	-	Ref	-	Ref	Ref	Ref
Fully adjusted‡								
>0.67	N= 331	**1.37***	-	1.25	-	1.03	1.01	1.21
		(1.06, 1.77)		(0.93, 1.68)		(0.74, 1.44)	(0.45, 2.29)	(0.89, 1.64)
No change	N= 1127	Ref	-	Ref	-	Ref	Ref	Ref

†Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, breastfeeding at birth, ethnicity, WIMD, <5/≥5 years of age
†Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, breastfeeding at birth, ethnicity, WIMD

Table 3-5 Associations between weight gain from birth to 24 months of age and respiratory outcomes in preterm-born children

All		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
Univariate								
>0.67	N=566	1.14 (0.94, 1.39)	1.09 (0.87, 1.36)	-	-	1.08 (0.85, 1.39)	1.18 (0.80, 1.73)	-
No change	N= 1253	Ref	Ref	-	-	Ref	Ref	-
Fully adjusted†								
>0.67	N= 501	1.12 (0.89, 1.39)	1.16 (0.91, 1.48)	-	-	1.14 (0.87, 1.50)	1.14 (0.87, 1.50)	-
No change	N= 1080	Ref	Ref	-	-	Ref	Ref	-
<5								
Univariate								
>0.67	N= 258	1.05 (0.78, 1.41)	-	-	1.10 (0.81, 1.49)	1.07 (0.76, 1.50)	1.24 (0.79, 1.92)	-
No change	N= 603	Ref	-	-	Ref	Ref	Ref	-
Fully adjusted‡								
>0.67	N= 240	1.12 (0.81, 1.54)	-	-	1.19 (0.85, 1.66)	1.19 (0.81, 1.73)	1.34 (0.84, 2.15)	-
No change	N= 551	Ref	-	-	Ref	Ref	Ref	-
≥5								
Univariate								
>0.67	N= 308	1.27 (0.96, 1.67)	-	1.12 (0.81, 1.56)	-	1.13 (0.79, 1.62)	1.21 (0.50, 2.92)	1.19 (0.85, 1.66)
No change	N= 650	Ref	-	Ref	-	Ref	Ref	Ref
Fully adjusted‡								
>0.67	N= 261	1.13 (0.83, 1.55)	-	1.11 (0.76, 1.61)	-	1.09 (0.73, 1.63)	1.09 (0.40, 2.99)	1.14 (0.78, 1.65)
No change	N=529	Ref	-	Ref	-	Ref	Ref	Ref

†Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, breastfeeding at birth, ethnicity, WIMD, <5/≥5 years of age
†Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, breastfeeding at birth, ethnicity, WIMD

3.5.3.3 ***Using conditional growth change in weight as primary exposure***

Using the continuous measure of conditional growth, weight gain between birth and 9 months of age was associated with increased odds of wheeze-ever (OR 1.30; 95% CI 1.14, 1.49), recent wheeze (OR 1.21; 95% CI 1.05, 1.41) and inhaler use (OR 1.27; 95% CI 1.08, 1.51) in the univariate model. Adjusting for covariates attenuated these results however wheeze-ever still remained statistically significant (OR 1.17; 95% CI 1.01, 1.37) and was similar to the result when weight gain was defined as >0.67SD change (OR1.22; 95% CI 1.02, 1.45). Considering the <5 years age group, weight gain was associated with increased wheeze in the last 3 months (OR 1.24; 95% CI 1.01, 1.53) and inhaler use (OR 1.32; 95% CI 1.05, 1.66) in the univariate model, however both effects attenuated in the adjusted model (OR 1.15; 95% CI 0.92, 1.45 and OR 1.13; 95% CI 0.87, 1.45 for wheeze in the last 3 months and inhaler use, respectively). In the ≥5 years age group, weight gain was significantly associated with wheeze-ever (OR 1.50; 95% CI 1.24, 1.82) and doctor-diagnosed asthma (OR 1.44; 95% CI 1.14, 1.82); after adjustment, both remained statistically significant (wheeze-ever OR 1.26; 95% CI 1.02, 1.57. Doctor-diagnosed asthma OR 1.33 95% CI 1.02, 1.75) (Table 3-6).

Table 3-6 Associations between conditional weight gain from birth to 9 months of age and respiratory outcomes in preterm-born children

All		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
Univariate	Conditional growth N= 3425	**1.30** (1.14, 1.49)**	**1.21* (1.05, 1.41)**	-	-	**1.27* (1.08, 1.51)**	1.11 (0.86, 1.43)	-
Fully adjusted†	Conditional growth N=3042	**1.17* (1.01, 1.37)**	1.09 (0.93, 1.29)	-	-	1.12 (0.93, 1.36)	0.98 (0.73, 1.31)	-
Age <5 years								
Univariate	Conditional growth N= 1692	1.08 (0.97, 1.33)	-	-	**1.24* (1.01, 1.53)**	**1.32* (1.05, 1.66)**	1.20 (0.90, 1.60)	-
Fully adjusted‡	Conditional growth N=1584	1.08 (0.87, 1.33)	-	-	1.15 (0.92, 1.45)	1.13 (0.87, 1.45)	1.10 (0.81, 1.49)	-
Age ≥5 years								
Univariate	Conditional growth N=1733	**1.50** (1.24, 1.82)**	-	1.22 (0.98, 1.53)	-	1.25 (0.98, 1.61)	0.98 (0.52, 1.84)	**1.44* (1.14, 1.82)**
Fully adjusted‡	Conditional growth N= 1458	**1.26* (1.02, 1.57)**	-	1.08 (0.83, 1.39)	-	1.10 (0.83, 1.47)	0.84 (0.42, 1.66)	**1.33* (1.02, 1.75)**

*p<0.05; **p<0.001

†Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, breastfeeding at birth, ethnicity, WIMD, <5/≥5

‡ Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, breastfeeding at birth, ethnicity, WIMD

3.5.3.4 ***Mediation analysis***

Results of the mediation analysis for preterm-born children are summarised in Table 3-7 and Figure 3-4. Gestational age, maternal smoking in pregnancy, current maternal smoking and breastfeeding all had significant univariate associations with weight gain whereas male gender, being ≥5 years of age, ethnicity and family history of asthma/atopy did not; all of these factors were significant predictors ($p<0.05$) of wheeze-ever except for maternal smoking in pregnancy. Of the above covariates, bootstrapped confidence intervals for specific indirect effects did not include zero for gestational age and current maternal smoking, indicating strong evidence that weight gain influenced wheeze-ever via gestational age and current maternal smoking. Moreover, the size of the direct effect (B=0.07, p=0.22) diminished relative to the adjusted regression model presented in Table 3-4 (B=0.19, p=0.03), further indicating the mediating effect of these two factors.

Table 3-7 Results of mediation analysis on the effect of infant weight gain from birth to 9 months of age on wheeze-ever in preterm-born children

>0.67SDS weight gain	**b**	**SE**	**95% CI**	**p**
Univariate associations				
Gestation on weight gain	-0.22	0.05	-0.31, -0.13	<0.001
Maternal smoking on weight gain	0.29	0.06	0.17, 0.41	<0.001
*Direct effect**				
Wheeze-ever on Weight gain	0.07	0.06	-0.04, 0.18	0.22
Specific indirect effects				
Wheeze-ever on weight gain via gestation	-0.04	0.01	-0.06, -0.02†	‡<0.001
Wheeze-ever on weight gain via current maternal smoking	0.03	0.01	0.01, 0.18†	‡0.02

*adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, breastfeeding, ethnicity, WIMD, age under/over 5 years
†bootstrapped confidence intervals (1000 samples)
‡normal theory (sobel) test

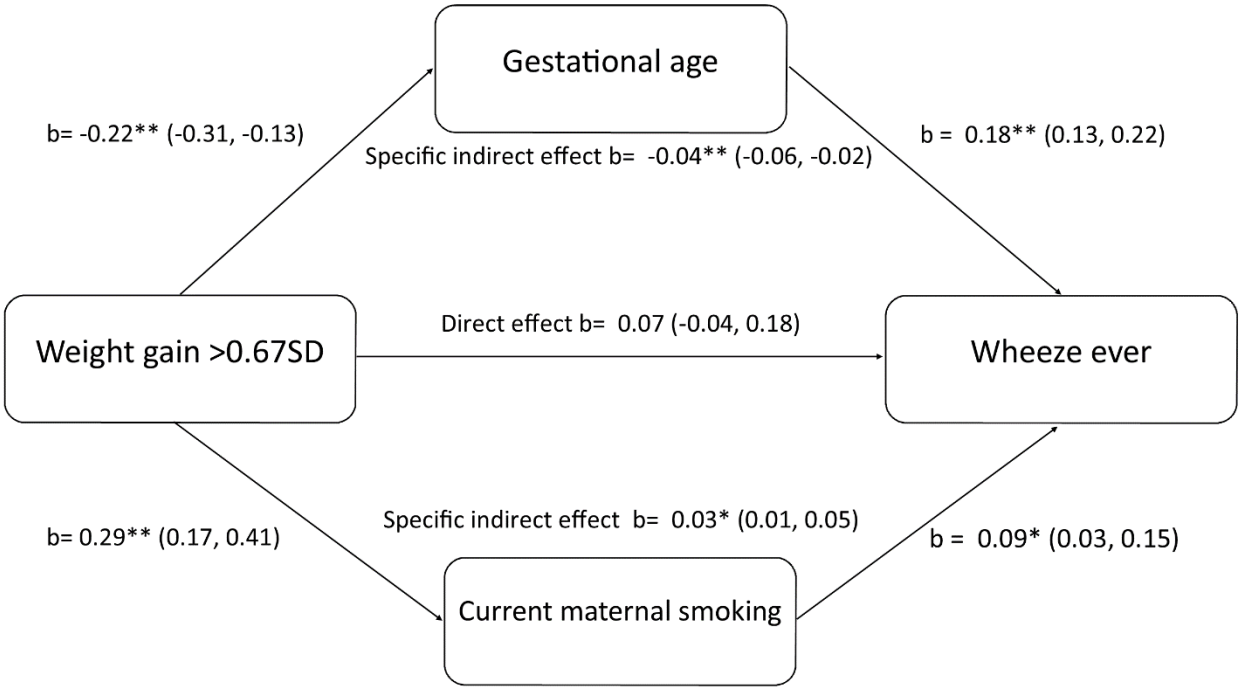


Figure 3-4 Diagrammatic representation of mediation analysis results in preterm-born children (>0.67SD weight gain). Both the indirect effects of gestational age and current maternal smoking mediate the direct effect of rapid weight gain on wheeze-ever in preterm born children.

3.5.4 Outcomes in term-born children

*3.5.4.1 **Univariate analysis***

Results of univariate analyses in term-born children are shown in Table 3-8. Gestation, male gender, current maternal smoking, family history of asthma/atopy and lower WIMD quintile were associated with increased odds of wheeze-ever at the p<0.10 level. Being ≥5 years of age was associated with decreased odds of wheeze-ever. These covariates were therefore included in the adjusted model.

Table 3-8 Univariate associations between potential confounders and respiratory outcomes in term-born children

	Wheeze-ever	Recent Wheeze	Wheeze last 12 months§	Wheeze last 3 months†	Inhaler use	Hospital admission	Doctor-diagnosed asthma§
Gestational age	0.88** (0.83, 0.93)	0.87** (0.80, 0.94)	0.88* (0.78, 0.98)	0.86* (0.78, 0.96)	0.81** (0.74, 0.89)	0.85* (0.73, 0.998)	0.87* (0.77, 0.98)
Gestation							
37-38 weeks	**1.51** (1.23, 1.87)**	**1.71** (1.32, 2.20)**	**1.77* (1.22, 2.55)**	**1.66* (1.17, 2.35)**	**1.92** (1.44, 2.55)**	0.94 (0.51, 1.72)	**1.71* (1.15, 2.52)**
≥39 weeks	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SDS Birthweight	0.97 (0.89, 1.05)	0.98 (0.89, 1.09)	0.94 (0.81, 1.09)	1.02 (0.89, 1.17)	0.95 (0.84, 1.07)	0.90 (0.73, 1.11)	1.00 (0.85, 1.17)
IUGR (<10th centile for SD BW)							
Yes	1.10 (0.80, 1.48)	1.34 (0.93, 1.94)	1.66 (0.99, 2.80)	1.09 (0.67, 1.84)	1.34 (0.88, 2.05)	0.92 (0.40, 2.13)	1.67 (0.96, 2.90)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Gender							
Male	**1.45** (1.24, 1.70)**	**1.39* (1.14, 1.70)**	1.35 (1.01, 1.81)	**1.43* (1.09, 1.88)**	**1.45* (1.15, 1.84)**	**1.95* (1.27, 3.01)**	**1.56* (1.13, 2.16)**
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Maternal smoking - pregnancy							
Yes	1.15 (0.90, 1.46)	**1.34* (1.001, 1.80)**	1.08 (0.71, 1.66)	**1.75* (1.16, 2.64)**	1.31 (0.93, 1.84)	1.01 (0.53, 1.91)	1.12 (0.71, 1.77)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Maternal smoking-current							
Yes	**1.27* (1.02, 1.59)**	**1.38** (1.05, 1.81)**	1.07 (0.71, 1.62)	**1.75* (1.2, 2.53)**	1.00 (0.71, 1.42)	1.12 (0.63, 1.99)	0.81 (0.50, 1.32)
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Family history of Atopy							

	Yes	**1.94***	**2.15****	**2.32****	**1.98****	**2.13****	**1.78***	**2.75****
		(1.63, 2.31)	**(1.75, 2.65)**	**(1.70, 3.16)**	**(1.49, 2.63)**	**1.67, 2.71)**	**(1.17, 2.71)**	**(1.98, 3.81)**
	No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Delivery by C/S								
	Yes	**1.23***	1.21	1.28	1.15	1.13	0.88	1.22
		(1.01, 1.49)	(0.97, 1.51)	(0.91, 1.79)	(0.85, 1.55)	(0.87, 1.48)	(0.54, 1.42)	(0.85, 1.75)
	No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Breastfeeding								
	Yes	0.87	0.90	1.06	**0.75***	0.80	0.65*	0.81
		(0.74, 1.02)	(0.74, 1.10)	(0.79, 1.42)	**(0.57, 0.99)**	(0.63, 1.01)	(0.44, 0.98)	(0.59, 1.11)
	No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Ethnicity								
	Non-white	1.06	1.46	**1.99***	1.14	1.18	2.19*	1.28
		(0.74, 1.49)	(0.98, 2.17)	**(1.09, 3.64)**	(0.67, 1.92)	(0.72, 1.91)	(1.44, 4.20)	(0.62, 2.65)
	White	Ref	Ref	Ref	Ref	Ref	Ref	Ref
WIMD quintile								
	lowest- 1	**1.29***	1.28	1.42	1.13	**1.75***	1.68	**1.83***
		(1.00, 1.66)	(0.92, 1.78)	(0.88, 2.30)	(0.71, 1.78)	**(0.21, 2.54)**	(0.88, 3.18)	**(1.11, 3.03)**
	2	1.23	1.43*	**1.76***	1.15	1.36	1.60	**1.96***
		(0.97, 1.57)	(1.05, 1.95)	**(1.12, 2.77)**	(0.75, 1.76)	(1.03, 2.08)	(0.86, 2.96)	**(1.20, 3.20)**
	3	1.26	1.61*	**1.74***	1.44	**1.46***	1.24	**1.73***
		(1.002, 1.60)	(1.20, 2.16)	**(1.14, 2.67)**	(0.61, 1.48)	**(1.03, 2.08)**	(0.66, 2.33)	**(1.08, 2.77)**
	4	1.04	1.001	1.03	0.95	0.99	0.90	0.94
		(0.82, 1.32)	(0.73, 1.38)	(0.65, 1.64)	(0.61, 1.48)	(0.68, 1.47)	(0.46, 1.79)	(0.55, 1.58)
	highest- 5	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Age <5/≥ 5 years of age								
	≥5	**0.55****	0.77*	-	-	0.91	**0.27****	-
		(0.47, 0.65)	(0.63, 0.94)			(0.72, 1.15)	**(0.17, 0.44)**	
	<5	Ref	Ref	-	-	Ref	Ref	-

§Children ≥5 years of age only; †children <5 years of age only
‡p<0.10, *p<0.05; **p<0.001

3.5.4.2 ***Using >0.67SD change in weight as primary exposure***

Within the term-born group wheeze-ever (OR 1.37; 95%CI 1.13. 1.65), recent wheeze (OR 1.28; 95%CI 1.01. 1.63) and inhaler use (OR 1.45; 95%CI 1.10. 1.89) were all significantly increased in children with weight gain >0.67 SDS between birth and 9 months of age (Table 3-9). These associations were strengthened in the final model after adjustment for covariates: wheeze-ever (OR 1.43; 95%CI 1.17, 1.74), recent wheeze (OR 1.31; 95% CI 1.03, 1.67) and inhaler use (OR 1.51; 95% CI 1.15, 2.00). Results were similar when the data were separated into the <5 years and ≥5 years age groups, however, the associations tended to be stronger in the ≥5 years age group (wheeze-ever OR 1.55; 95% CI 1.16, 2.06), in keeping with the analyses in preterm-born children described earlier. Doctor-diagnosed asthma was also strongly related to weight gain in the ≥5 group (OR 2.00; 1.39, 2.92) in the fully adjusted model.

When investigating the effect of >0.67 SD weight gain between birthweight and 24 months of age, results showed increased respiratory symptoms, hospital admissions and doctor-diagnosed asthma for the whole preterm-born group (Table 3-10). However, few associations remained statistically significant in the adjusted model: inhaler use in the whole term-born population (OR 1.63, 95%CI 1.13, 2.35), and between weight gain and wheeze-ever in the ≥5 years age group (OR 1.58; 95% CI 1.10, 2.30). There were no significant associations noted in the <5 years age group.

3.5.4.3 ***Using conditional growth change in weight as primary exposure***

The alternative analyses of using a measure of conditional growth largely corroborated the results described above: weight gain between birth and 9 months of age was associated with increased odds of wheeze-ever, recent wheeze, inhaler use and hospital admission for chest-related reasons in univariate analysis (Table 3-11). When covariates were included in the model, wheeze-ever (OR 1.25 95% CI 1.05, 1.50) and inhaler use (OR 1.58; 1.22, 2.05) remained statistically significant. In the ≥5 years age group, wheeze-ever was of borderline

significance (OR 1.31 95% CI 0.99, 1.72), whereas inhaler use (OR 1.62 95% CI 1.12, 2.37) and doctor-diagnosed asthma (OR 1.65 95% CI 1.15, 2.36) remained significant. Results in the <5 years age group showed similar results; particularly, increased weight gain was associated with increased hospital admission (OR 1.82 95% CI 1.12, 2.93), although this was not statistically significant in the adjusted model (OR 1.59; 95% CI 0.94, 2.69).

Table 3-9 Associations between rapid weight gain from birth to 9 months of age and respiratory outcomes in term-born children

All		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
Univariate								
>0.67	N=634	**1.37*** **(1.13, 1.65)**	**1.28*** **(1.01, 1.63)**	-	-	**1.45*** **(1.10, 1.89)**	1.47 (0.90, 2.40)	-
No change	N= 1765	Ref	Ref	-	-	**Ref**	Ref	-
Fully adjusted†								
>0.67	N=596	**1.38**** **(1.13, 1.69)**	1.28 (0.97, 1.65)	-	-	**1.53*** **(1.15, 2.04)**	1.46 (0.87, 2.45)	-
No change	N= 1654	Ref	Ref	-	-	Ref	Ref	-
<5								
Univariate								
>0.67	N= 299	**1.32*** **(1.03, 1.75)**	-	-	1.23 (0.88, 1.71)	1.34 (0.91, 1.97)	1.45 (0.86, 2.70)	-
No change	N= 872	**Ref**	-	-	Ref	Ref	Ref	-
Fully adjusted‡								
>0.67	N=290	**1.32*** **(1.00, 1.74)**	-	-	1.19 (0.85, 1.68)	1.39 (0.93, 2.07)	1.52 (0.84, 2.75)	-
No change	N= 849	Ref	-	-	Ref	Ref	Ref	-
≥5								
Univariate								
>0.67	N= 335	**1.45*** **(1.11, 1.91)**	-	1.36 (0.96, 1.91)	-	**1.56*** **(1.07, 2.29)**	1.45 (0.54, 3.98)	**1.78*** **(1.25, 2.53)**
No change	N= 893	**Ref**	-	Ref	-	**Ref**	Ref	**Ref**
Fully adjusted‡								
>0.67	N= 306	**1.48*** **(1.10, 2.01)**	-	1.43* (0.98, 2.07)	-	**1.73*** **(1.15, 2.61)**	1.26 (0.54, 3.84)	**2.02**** **(1.37, 2.98)**
No change	N= 805	Ref	-	Ref	-	Ref	Ref	Ref

†Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, WIMD, caesarean section,<5/≥5 years of age
‡Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, WIMD, caesarean section,<5/≥5 years of age

Table 3-10 Associations between rapid weight gain from birth to 24 months of age and respiratory outcomes in term-born children

All		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
Univariate								
>0.67	N=404	1.17 (0.92, 1.50)	0.94 (0.69, 1.29)	-	-	1.50* (1.06, 2.14)	1.43 (0.77, 2.66)	-
No change	N= 871	Ref	Ref	-	-	Ref	Ref	-
Fully adjusted†								
>0.67	N=404	1.26 (0.97, 1.63)	0.99 (0.71, 1.36)	-	-	1.63* (1.13, 2.35)	1.49 (0.78, 2.85)	-
No change	N= 871	Ref	Ref	-	-	Ref	Ref	-
<5								
Univariate								
>0.67	N= 189	1.03 (0.73, 1.46)	-	-	0.98 (0.64, 1.56)	1.52 (0.91, 2.51)	1.29 (0.61, 2.75)	-
No change	N= 437	Ref	-	-	Ref	Ref	Ref	-
Fully adjusted‡								
>0.67	N= 189	1.06 (0.74, 1.52)	-	-	0.96 (0.61, 1.51)	1.61 (0.95, 2.74)	1.33 (0.60, 2.90)	-
No change	N= 437	Ref	-	-	Ref	Ref	Ref	-
≥5								
Univariate								
>0.67	N= 215	1.41 (0.99, 2.01)	-	0.99 (0.64, 1.56)	-	1.49 (0.91, 2.44)	2.05 (0.65, 6.43)	1.48 (0.92, 2.37)
No change	N= 434	Ref	-	Ref	-	Ref	Ref	Ref
Fully adjusted‡								
>0.67	N= 215	1.58* (1.10, 2.30)	-	1.05 (0.66, 1.67)	-	1.67 (1.00, 2.78)	1.68 (0.51, 5.12)	1.63 (1.00, 2.67)
No change	N= 434	Ref	-	Ref	-	Ref	Ref	Ref

†Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, WIMD, caesarean section,<5/≥5 years of age
‡Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, WIMD, caesarean section

Table 3-11 Associations between conditional weight gain from birth to 9 months of age and respiratory outcomes in term-born children

All		Wheeze-ever	Recent Wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor-diagnosed asthma
Univariate	Conditional growth N= 2250	**1.41** (1.20, 1.65)**	**1.33* (1.09, 1.63)**	-	-	**1.68** (1.33, 2.11)**	**1.56* (1.03, 2.39)**	-
Fully adjusted†	Conditional growth N=2399	**1.25* (1.05, 1.50)**	1.20 (0.96, 1.51)	-	-	**1.58** (1.22, 2.05)**	1.46 (0.91, 2.34)	-
Age <5 years								
Univariate	Conditional growth N=1171	**1.41* (1.13, 1.75)**	-	-	**1.37* (1.04, 1.80)**	**1.69* (1.21, 2.23)**	**1.82* (1.12, 2.93)**	-
Fully adjusted‡	Conditional growth N=1139	1.21 (0.95, 1.54)	-	-	1.16 (0.86, 1.57)	**1.55* (1.09, 2.20)**	**1.59 (0.94, 2.69)**	-
Age ≥5 years								
Univariate	Conditional growth N=1228	**1.43* (1.13, 1.82)**	-	1.29 (0.96, 1.74)	-	**1.67* (1.20, 2.32)**	0.95 (0.38, 2.40)	**1.76* (1.23, 2.51)**
Fully adjusted‡	Conditional growth N= 1228	1.31 (0.99, 1.72)	-	1.26 (0.90, 1.77)	-	**1.62* (1.12, 2.37)**	1.02 (0.34, 3.04)	**1.65* (1.15, 2.36)**

*p<0.05; **p<0.001

†Adjusted for gestation, gender, current maternal smoking, family history of asthma/atopy, WIMD, caesarean section, <5/≥5 years of age

‡Adjusted for gestation, gender, current maternal smoking, family history of asthma/atopy, WIMD, caesarean section

3.5.4.4 ***Mediation analysis***

The results of the mediation analysis for term-born children are presented in Table 3-12 and Figure 3-5. Gestational age, gender, maternal smoking, and WIMD all had significant univariate associations with weight gain whereas being aged <5 or ≥5 years, family history of asthma/atopy and birth by caesarean section did not. All of these factors were significant predictors of wheeze ($p<0.05$) with the exception of current maternal smoking and WIMD. Of the above covariates, bootstrapped confidence intervals did not include zero for male gender only, but did for the remaining variables entered in to the model. Therefore, gender was a significant mediator of the relationship between rapid infant weight gain and childhood wheeze. Early-term birth was not statistically significant as a mediator in the model ($p=0.07$). The direct effect of weight gain was reduced when compared to the final logistic regression model presented in Table 3-9 (B= 0.32 and B= 0.20 respectively) indicating the mediating effect of gender.

Table 3-12 Summary of mediation analysis in term-born children

>0.67SDS weight gain	**b**	**SE**	**95% CI**	**p**
Univariate associations				
Gender on weight gain	0.16	0.06	0.04, 0.27	0.03
*Direct effect**				
Wheeze-ever on Weight gain	0.20	0.06	0.07, 0.32	0.002
Specific indirect effects				
Wheeze-ever on weight gain via gestation	0.02	0.01	-0.05, -0.004†	0.07‡
Wheeze-ever on weight gain via gender	0.02	0.01	0.01, 0.05†	0.02‡

*adjusted for gestation, gender, maternal smoking (current), family history of asthma/atopy, WIMD, caesarean section, age </≥ 5 years
†bootstrapped confidence intervals (1000 samples)
‡normal theory (sobel) test

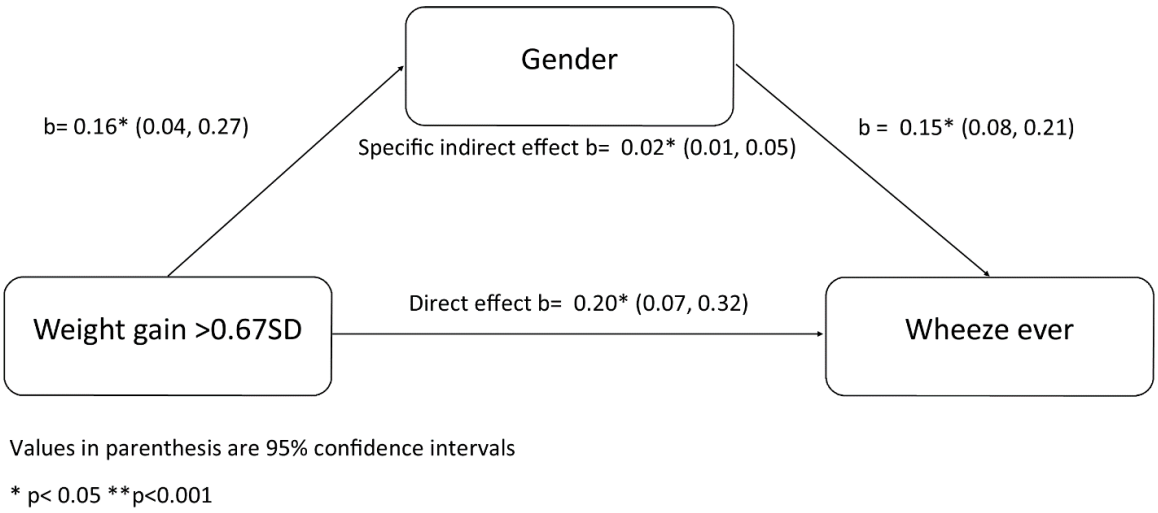


Figure 3-5 Diagrammatic representation of mediation analysis result in term-born children

3.5.5 Outcome of combined analysis

The results of the interaction analysis using data from the whole population are shown below in Table 3-13. Compared to term-born children who did not demonstrate weight gain of >0.67SD between birth and the age of 9 months, children born ≤32 weeks' gestational age with infant weight gain >0.67SD had significantly increased odds of wheeze-ever (OR 4.92; 95%CI 3.34, 7.27). Including significant covariates in the adjusted model increased the strength of the association (OR 5.04; 95% CI 3.36, 7.54); Figure 3-6 demonstrates a clear trend of the effect of infant weight gain and gestation on the odds of wheeze-ever.

When the term-born group was further subdivided, early-term birth with subsequent rapid postnatal weight gain was associated with increased odds of wheeze-ever when compared to the term born group without rapid weight gain (OR 2.25; 95% CI 1.48, 3.43). Of note, the magnitude of this effect was greater than the late preterm group, and marginally greater than the moderate preterm group (ORs 1.84, 2.20, respectively, Table 3-14 and Figure 3-7).

Table 3-13 Results of interaction analysis for odds of wheeze-ever. Each interaction term is compared with the reference group of term-born, no weight gain (OR 1.0). Including >0.67SD in the interaction with each gestational age group resulted in an increase in the odds ratio for wheeze-ever. The highest odds ratio for wheeze-ever was noted to be in the very preterm group who exhibited weight gain >0.67SD when compared to the reference group.

Interaction (univariate)	OR	95% CI	p
>0.67SD* Very preterm	4.92	3.34, 7.27	<0.001
No weight gain* Very preterm	2.90	2.41, 3.50	<0.001
>0.67SD* Moderate preterm	2.94	2.12, 4.07	<0.001
No weight gain *Moderate preterm	1.89	1.56, 2.28	<0.001
>0.67SD*Late preterm	1.83	1.49, 2.25	<0.001
No weight gain *Late preterm	1.69	1.46, 1.96	<0.001
>0.67SD*Term	1.37	1.13, 1.65	0.001
No weight gain *Term	1.0		

Interaction (adjusted†)			
>0.67SD* Very preterm	5.04	3.36, 7.54	<0.001
No weight gain * Very preterm	2.95	2.42, 3.58	<0.001
>0.67SD* Moderate preterm	2.83	2.01, 2.98	<0.001
No weight gain *Moderate preterm	2.01	1.65, 2.44	<0.001
>0.67SD*Late preterm	1.70	1.37, 2.11	<0.001
No weight gain *Late preterm	1.68	1.44, 1.95	<0.001
>0.67SD*Term	1.36	1.11, 1.65	0.002
No weight gain *Term	1.0		

†Adjusted for Gender, maternal smoking, family history of asthma, WIMD, aged >5 or ≥5 years

Table 3-14 Results of interaction analysis for odds of wheeze-ever, including the additional 'early term group'. Each interaction term is compared with the reference group of term-born, no weight gain (OR 1.0). The additional interaction between early-term birth and >0.67SD weight gain was noted to be highly significant when compared to the reference group.

Interaction (univariate)	OR	95% CI	p
>0.67SDS* Very preterm	5.38	3.63, 7.97	<0.001
No weight gain * Very preterm	3.17	2.613, 3.85	<0.001
>0.67SDS* Moderate preterm	3.21	2.31, 4.47	<0.001
No weight gain *Moderate preterm	2.06	1.70, 2.50	<0.001
>0.67SDS*Late preterm	2.00	1.61, 2.47	<0.001
No weight gain *Late preterm	1.85	1.58, 2.16	<0.001
>0.67SDS*Early term	2.22	1.48, 3.33	<0.001
No weight gain *Early term	1.52	1.19, 1.94	0.001
>0.67SDS*Term	1.38	1.12, 1.70	0.003
No weight gain *Term	1.0		

Interaction (adjusted†)			
>0.67SDS* Very preterm	5.52	3.67, 8.30	<0.001
No weight gain * Very preterm	3.22	2.63, 3.95	<0.001
>0.67SDS* Moderate preterm	3.10	2.20, 4.38	<0.001
No weight gain *Moderate preterm	2.20	1.79, 2.70	<0.001
>0.67SDS*Late preterm	1.87	1.49, 2.33	<0.001
No weight gain *Late preterm	1.84	1.56, 2.16	<0.001
>0.67SDS*Early term	2.25	1.48, 3.43	<0.001
No weight gain *Early term	1.54	1.20, 1.98	0.001
>0.67SDS*Term	1.37	1.10, 1.70	0.005
No weight gain *Term	1.0		

†Adjusted for Gender, maternal smoking (current), family history of asthma, WIMD, aged >5 or ≥5 years

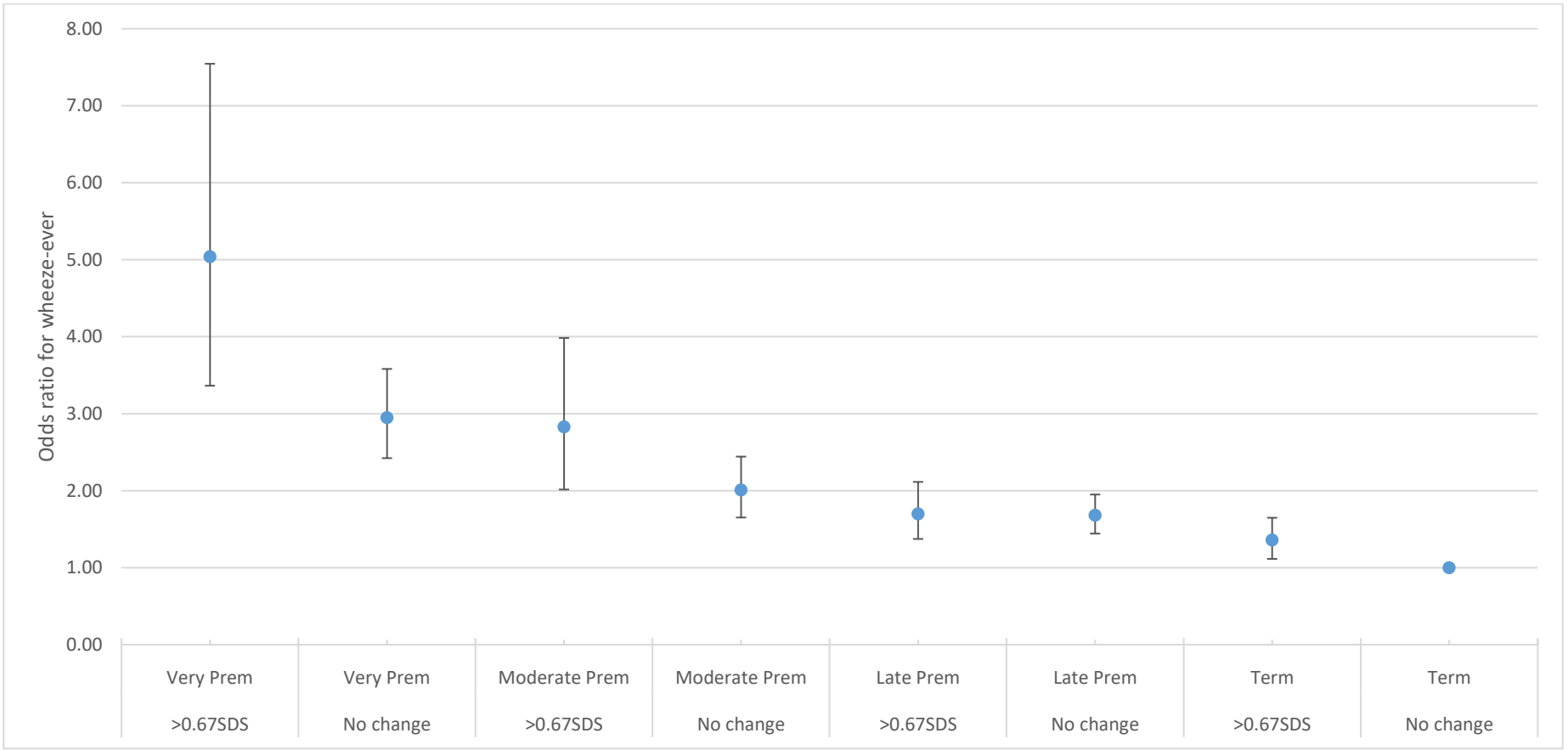


Figure 3-6 Graphical representation of interaction analysis (adjusted) presented in table 3-13. All ORs for wheeze-ever are compared to the reference category of Term-born, no change in weight gain between birth and 9 months of age. Error bars represent 95% confidence intervals for ORs.

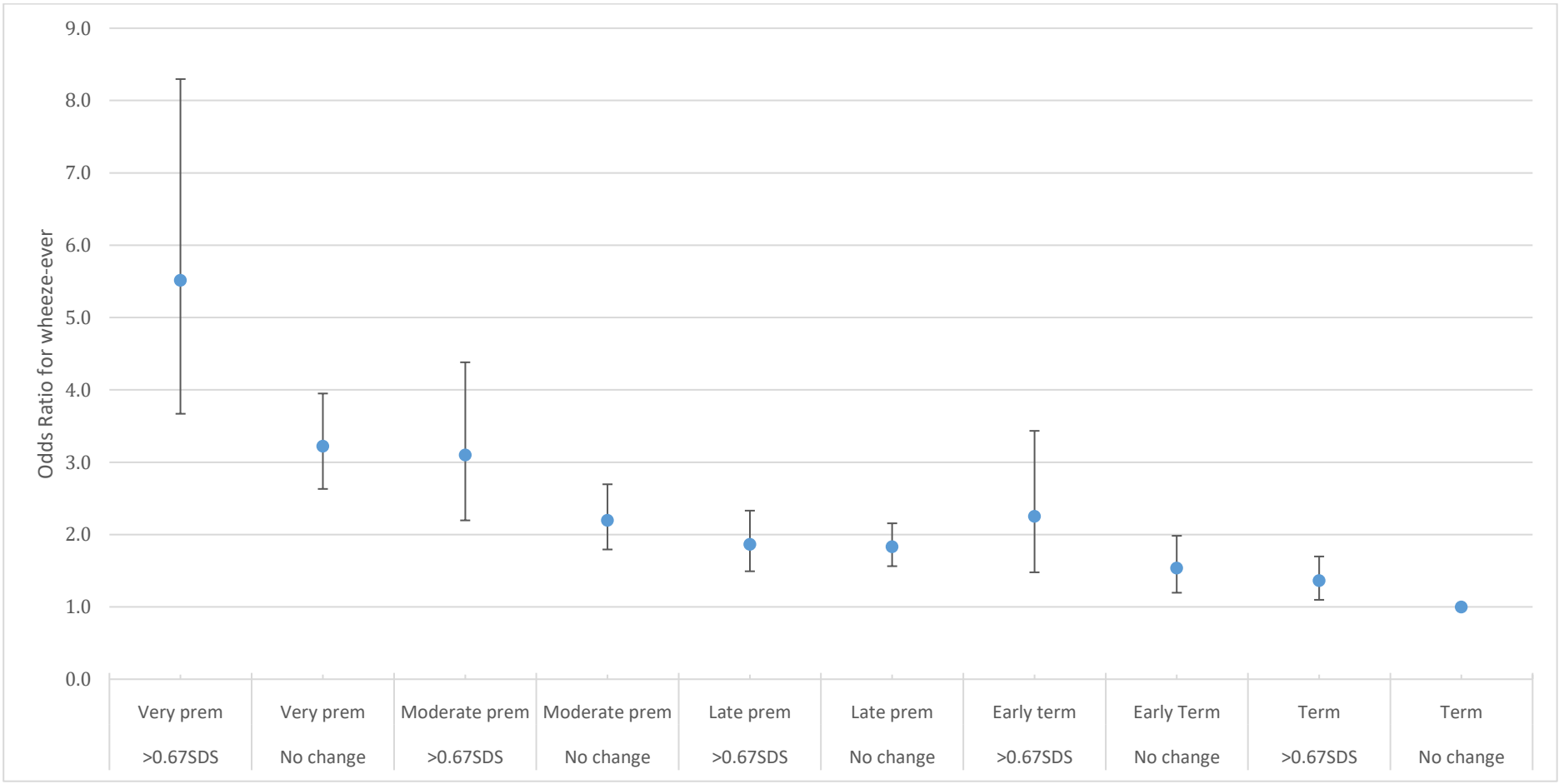


Figure 3-7 Graphical representation of interaction analysis (adjusted), including the early-term group, presented in table 3-14. All ORs for wheeze-ever are compared to the reference category of Term-born, no change in weight gain between birth and 9 months of age. Error bars represent 95% confidence intervals for ORs.

3.6 Discussion

In this chapter, I have reported increased wheeze-ever in childhood because of rapid weight gain, defined as >0.67SD change in the first year of life, after adjusting for confounding factors, in both preterm-born and term-born children. The odds ratios were 1.22 (95% CI 1.02, 1.45) and 1.38 (95% CI 1.13, 1.69) respectively. Using the alternative method of conditional growth change yielded similar results (OR1.17 for preterm-born and 1.25 for term-born children). Investigating rapid weight gain up until 2 years of age and the association with respiratory symptoms yielded results which were not statistically significant. The interaction between birth at the extremes of prematurity (≤32 weeks' gestation) and postnatal weight gain resulted in the poorest respiratory outcome when compared to the reference group of term-born children who did not exhibit rapid weight gain (OR 5.04; 95%CI 3.36, 7.5). The combination of early-term birth and rapid weight gain was also noted to be associated with increased wheeze-ever (OR 2.25; 95% CI 1.48, 3.43) compared to the reference group.

Furthermore, using mediation analysis, I have identified important and modifiable factors influencing the relationship between weight gain and respiratory symptoms in preterm-born children. Although the majority of preterm births are spontaneous and not modifiable *per se*, the risk factors implicated in preterm birth (see introduction section 1.4.2) certainly are. Moreover, I also noted that current maternal smoking was another significant mediating factor indicating the continuing deleterious effects of environmental tobacco smoke on respiratory health in childhood. In term-born children, male gender was identified as a mediator of the association between rapid weight gain and increased respiratory symptoms.

A growing number of studies, but few in preterm-born cohorts, have investigated the association between early weight gain in infancy and respiratory health in childhood and adolescence, using variable definitions of weight gain and time at which the outcome is measured. The recent study of the NINFEA cohort demonstrated that rapid growth, in terms of body size and growth velocity, was a significant predictor of increased wheeze during the first 18 months of life in term-born infants; these associations were independent, thus suggesting that the effects of being large and showing rapid growth potentially act through different mechanisms or have independent effects (Popovic et al., 2016). Using the same measure of weight gain (>0.67SD) as presented in this chapter, two recent studies reported decrements in lung function and increased respiratory symptoms at age 5 when rapid postnatal growth was observed between birth and 3 months of age, the latter of which was independent of foetal growth (van der Gugten et al., 2012, Sonnenschein-van der Voort et al., 2012). Both the Southampton and Aberdeen groups noted that early childhood wheeze at age 3 was associated with excessive weight gain throughout the first year of life (Pike et al., 2010) (Turner et al., 2008).

Other studies in term-born cohorts have investigated longer periods over which weight gain was defined. In a recent report, peak weight velocity in infancy between birth and 36 months resulted in increased rates of asthma and recurrent lower respiratory tract infections at 3 years of age, and increased asthma at 7 years of age (Magnus et al., 2015). Similarly, Flexeder and colleagues investigated peak weight gain from birth to 24 months of age and reported increased risk of asthma at age 10 years of age (Flexeder et al., 2012) and a negative association with lung function, especially measures of flow, in adolescents (Claudia et al., 2015). Interestingly, lung function was not affected following administration of bronchodilator suggesting that the weight gain resulted in structural rather than functional changes to the airways (the salbutamol dose was limited to 200mcg due to side effects, thus larger doses may have been effective). Using data from eight European

cohorts, the study by Rzehak noted that risk of asthma at 6 years of age was increased in children with rapid weight gain up to 2 years; the population was characterised by increased incidence of low birthweight (Rzehak et al., 2013).

These studies, along with my data, support the concept that rate of weight gain is an important factor in influencing later respiratory health, possibly because growth and development of the respiratory system does not match somatic growth. Thus, the airways may be small in comparison to lung capacity (dysanapsis). Further data on lung function complement this hypothesis, for example, term-born infants with decreased flow and respiratory compliance at birth were reported to have an increased risk of asthma at the age of 10 years (Haland et al., 2006). Results from the ALSPAC cohort demonstrated increased FVC and forced FEV_1, but lower FEV_1/FVC ratio for children who exhibited rapid weight gain in infancy (Sonnenschein-van der Voort et al., 2015). When I performed a repeat analysis using the available weight data at 24 months, lesser associations with respiratory symptoms were noted. Methodological differences in calculating measures of weight gain may be responsible for differences in these results. However, one possibility is that the deleterious effects of early weight gain on respiratory health may be mitigated if 'catch-up growth' occurs over a longer period of time, such as previous data suggesting that deficits in FEV_1 present in IUGR term-born children are ameliorated by catch up growth by eight years of age (Kotecha et al., 2010).

Similar to others (Sonnenschein-van der Voort et al., 2014), I observed an incremental increase in odds of wheeze-ever with decreasing gestational age with infant weight gain, when compared to a term-born control growth without weight gain (OR 5.04). An additional finding from my data presented evidence that birth at 'early-term', followed by rapid weight gain from birth to 9 months of age was also associated with increased odd of wheeze. I extended my investigation by identifying current maternal smoking, as well as

gestation, as mediators of the relationship between weight gain and wheeze in preterm-born children. Passive smoking is associated with increased incidence of viral respiratory infections in early childhood and has long-term impacts on lung health (Narang and Bush, 2012).

Maternal smoking can be considered a proxy of socio-economic status and may represent higher rates of formula feeding (McAndrew et al., 2012). A recent study using data from the Millennium Cohort Study observed that increased prevalence of early transient and persistent/relapsing wheeze is socially patterned. Furthermore, the authors noted a dose-dependent effect of smoking during pregnancy, which increased risk of wheezing, and breastfeeding, with ameliorated the risk (Taylor-Robinson et al., 2016). Although it was not identified as a significant mediator, lack of breastfeeding promoted weight gain, whereas breastfeeding was protective of childhood wheeze in my logistic regression analysis. Thus, nutrition may be key in balancing the beneficial effects of growth versus potential harm of excess weight gain in preterm-born infants. Exclusive breastfeeding ameliorated the association between postnatal weight gain and increased early transient wheeze in term-born children in the study by Turner et al. (Turner et al., 2008). The recent report by Belfort and colleagues noted an association between asthma at the age of 8 years and postnatal growth in preterm infants when defined by increase in BMI up to 12 months of age (Belfort et al., 2016). This was not compensated for by increased linear growth, further indicating the potential developmental mismatch between somatic and organ growth which may promote later obesity and lung disease, possibly through the pro-inflammatory immunological effects of excess adipose tissue (Gishti et al., 2014).

3.7 Strengths and limitations

The main strength of my study is the use of contemporary cohort of preterm-born children that was specifically designed to investigate associations with respiratory symptoms in childhood. The use of validated respiratory questionnaires in the original RANOPS study, which are widely used in clinical epidemiology, allows comparison with other studies. Moreover, I was able to link to national databases to obtain additional information on birth and infant outcomes and socio-economic status.

The postnatal weight data used were taken from the national child health databases; these originated from multiple sources including hospital clinics, community appointments and GP surgeries. There will be some variation due to differences between equipment and use by the operator (Bryant et al., 2015). However, the strength of these data are the number of points available, which allowed the use of multilevel modelling to construct "individualised" conditional growth standards which correct for regression to the mean. This more complex method resulted in similar results when compared to the primary analysis of >0.67 change in standard deviation score for weight, a well-established and parsimonious method for quantifying growth change in the clinical environment.

Finally, in common with all cohort studies, residual confounding of the data by unmeasured covariates cannot be ruled out. In the cohort at-large, non-responders to the questionnaire were of lower socio-economic status (Edwards et al., 2016). However, given that infants born into such conditions are more likely to be born preterm, IUGR and have been exposed to a less favourable intrauterine growth environment (e.g. tobacco smoke), inclusion of these children would be expected to strengthen rather than weaken the associations I have presented.

3.8 Summary and conclusions

I have demonstrated that postnatal growth rates are important for future respiratory health in preterm-born and term-born children. In the preterm-born population, the factors noted to mediate the relationship between rapid postnatal weight gain and later wheeze were modifiable. Since preterm-born children are unlikely to have the same aetiology of lung disease as their term-born peers, it is important to consider strategies for ensuring appropriate growth. Optimising nutrition and diminishing exposure to tobacco smoke during pregnancy and beyond are potential interventions which are possible in the wider context of reducing the social inequalities related to preterm birth. My additional analysis, which reports a similar effect of weight gain on respiratory outcomes of children born 'early term' is relevant in regards to the debate on the categorisation of gestational age and 'term pregnancy'(ACOG, 2013a), and on timing of such deliveries (ACOG., 2013b). Although I have speculated that dysanapsis may be important, we need to study the mechanisms whereby accelerated somatic growth results in increased respiratory symptoms in childhood.

4 Physical activity in preterm-born 11-year old children born in the 1990's

4.1 Overview

There is strong evidence that children born preterm have decreased lung function (Kotecha et al., 2012, Kotecha et al., 2013), increased respiratory symptoms, admissions to hospital for respiratory problems and increased inhaler medication use (Been et al., 2014, Paranjothy et al., 2013, Edwards et al., 2016). These effects appear to be inversely incremental across a wide range of gestational age including those born 'near term' (Edwards et al., 2015a). In the previous chapter, it was described that early infant weight gain in the first year of life was also associated with increased respiratory symptoms in preterm-born school-age children. Consistent with the developmental origins of health and disease hypothesis, it is conceivable that such weight gain reflects dysregulated growth patterns secondary to developmental adaptations which may induce dysanapsis between somatic and respiratory system development.

In keeping with these concepts is the finding that exercise capacity may also be sub-normal in preterm-born children, possibly due to respiratory factors including airway obstruction, restricted lungs and associated inflammation but also due to altered cardiometabolic processes and neurodevelopmental sequelae (Ridgway et al., 2009). Moreover there is evidence that preterm-born children appear to make adaptations during exercise, such as increased use of their ventilatory reserve, in order to maintain similar levels of intensity when compared to term-born children; they may also suffer from increased rates of exercise-induced bronchoconstriction especially if they suffered from BPD/CLD during infancy (Joshi et al., 2013).

PA is an important lifestyle choice which helps to ameliorate the risk of chronic disease. However, studies have shown that few children meet the recommended levels of PA (Chief

Medical Officers of England, 2011), with a steep decline occurring during adolescence. Preterm-born adults report reduced conditioning leisure time PA and reduced exercise capacity compared to those born at term (Kaseva et al., 2012, Svedenkrans et al., 2013, Lovering et al., 2014). Since respiratory morbidities track from childhood in to adulthood (Bolton et al., 2015), investigating habitual PA participation in childhood with a view to introducing activity programmes might be of great importance for preterm-born children.

What is unclear is if increased respiratory symptoms, reduced lung function and reduced exercise capacity are associated with decreased levels of objectively measured PA. One possible reason for reduced levels of PA in preterm-born compared with term-born subjects could be airway obstruction and associated impaired gas exchange on exertion, and the subsequent unpleasant sensations such as fatigue and breathlessness which may follow. There have been few such epidemiological studies investigating the levels of objectively measured PA in children who were born preterm and who have had lung function measurements. A recent systematic review has synthesized the literature (Dahan-Oliel et al., 2012), but most studies rely on questionnaire data to quantify activity and relate mainly to exercise capacity (Clemm et al., 2012, Joshi et al., 2013), or focus on those born with extremely low birthweight and who suffered from BPD/CLD (Welsh et al., 2010).

4.2 Aims and hypothesis

The aims of this study were to investigate objectively measured levels of PA, MVPA, and sedentary behaviour in preterm-born children and compare these to term controls. Also, I planned to investigate if measures of lung function are correlated to levels of physical activity.

The specific hypotheses were:

a) That preterm-born children would participate in significantly less Total PA, less MVPA, and would spend more time in sedentary behaviour.

b) That decrements in lung function, particularly $FEV_{1,}$ would correlate with reduced levels of total PA and MVPA.

4.3 Methods

4.3.1 Avon Longitudinal Study of Parents and Children

Data from ALSPAC were used (Boyd et al., 2013). 14,541 pregnant women with an expected delivery date of 1st April 1991 to 31st December 1992 were enrolled. There were 14,062 live born infants (13,988 alive at one year) who were subsequently followed up by means of questionnaire and clinical assessments. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

4.3.2 Physical activity

Children attending the ALSPAC clinic were invited by the ALSPAC team to wear an accelerometer (MTI Actigraph) for a 7-day period during waking hours. The device recorded a sample at 1 minute intervals (epochs), which was a compromise between duration of epochs and data storage capacity. The Actigraph has been validated against the criterion standard of indirect caliometry and for use in free-living conditions. Children participated in an exercise session where they performed 6 activities of increasing intensity whilst wearing a portable metabolic unit to measure rate of O_2 production and energy expenditure. Cut-points for accelerometer counts, representative of different levels of intensity were then derived using a prediction equation (Mattocks et al., 2007, Mattocks et al., 2008). Three outcomes were used for analyses: average 'counts per minute' (cpm) over the period of the valid recording, time (in minutes per day) spent at ≥3600cpm (MVPA), and time (in minutes

per day) spent at <200cpm (sedentary behaviour). MVPA was used to provide a measure of intensity because guidelines for levels of PA in children present recommendations in terms of MVPA (Department of Health, 2004). Sedentary time was used because it is possible for an individual to spend increased amounts of time sedentary even if they meet guidelines for MVPA (Mitchell et al., 2012), and because it has been independently associated with risk factors for chronic disease (Mitchell et al., 2009). Inclusion of only participants with valid accelerometer data excluded children with severe cognitive or physical impairments.

4.3.3 Gestation Groups

All children with valid PA data were divided into four groups based on gestational age: 25-32 weeks, 33-34 weeks, 35-36 weeks and 37-43 weeks (term control). Gestational age was based on maternal reporting of the last menstrual period and paediatric assessment at birth for the majority of the cohort, with antenatal ultrasounds scans only being available in a minority of cases in the early 1990s (Lawlor et al., 2008).

4.3.4 Lung Function

Spirometry was performed by the ALSPAC team at the clinic visit according to established international guidelines when the children were approximately 7-9 years of age (ATS, 1995). Measurements of FEV_1, FVC and FEF_{25-75} were converted into z-scores adjusted for age, sex and height (Kotecha et al., 2012).

4.3.5 Demographics

Prior to birth the mother completed an antenatal questionnaire which asked her to record information regarding smoking habits and her highest level of education which was categorised into none, Certificate of secondary education or vocational, O-level, A-level, or university degree. Social status was based on the father's occupation from the same questionnaire. Perinatal data on respiratory management were extracted from hospital records.

4.4 Statistical analysis

To assess the representativeness of the data available, demographic information was compared between participants who attended clinic and provided valid accelerometer data and those who did not attend using χ^2 tests. This analysis was repeated with participants who attended clinic and provided valid data and those attended but did not provide valid data. Characteristics of the gestation groups were compared using independent sample t-tests for normally distributed data and Mann-Witney *U* Tests were used for non-normal data. Prior to conducting statistical tests, the assumption of normality was tested for all outcome variables. At age 11, both variables were found to be significantly positively skewed on visual assessment of Q-Q plots. Log_e transformation of Total PA and $e^{2/5}$ transformation of MVPA resulted in normal distributions as shown on the following Q-Q plots (Figure 4-1). Sedentary behaviour was normally distributed. At age 15 years, both Total PA and MVPA variables were positively skewed. Total PA was normalised by log_e and MVPA by square-root transformation. Sedentary behaviour was normally distributed. Z-scores were also created for each PA variable in order to perform correlations with lung function values.

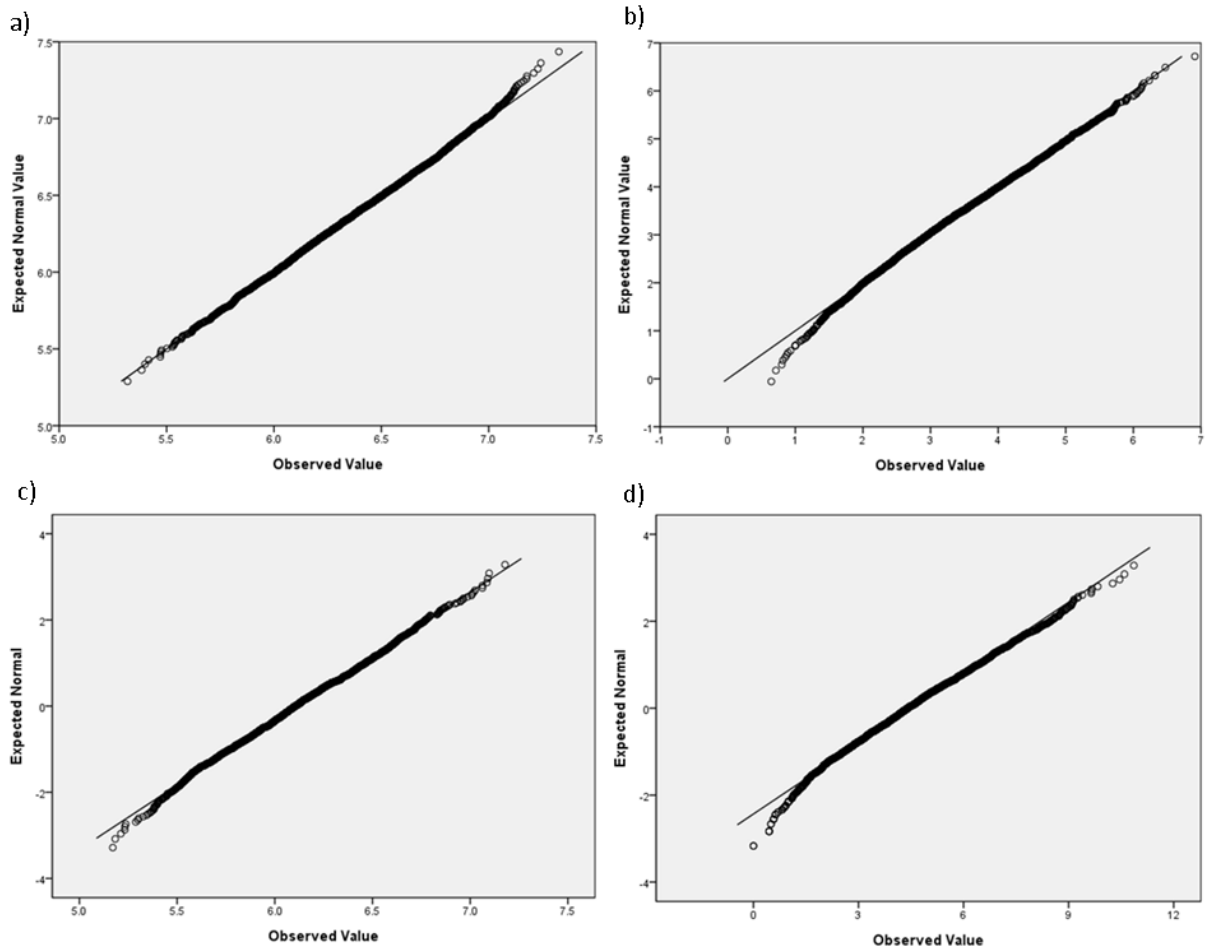


Figure 4-1: Q-Q plots of transformed variables a) Total PA age 11, b) MVPA age 11, c) Total PA age 15 and d) MVPA age 15. Normality is observed when data points largely follow the line of best fit

One-way ANOVA (with post-hoc multiple comparisons using Bonferroni correction) was used to investigate differences in PA between the gestation groups. Levene's test was conducted to assess homogeneity of variance. All analyses were stratified by gender as previous studies using this cohort have shown significant differences in PA between boys and girls (Riddoch et al., 2007).

Since low birthweight and obesity have been previously identified as risk factors for reduced levels of PA, the analysis was repeated excluding term-born individuals with a z-score of less than 10th centile or greater than 80th centile for birthweight (World Health Organisation,

2002). Children born between the 20th and 80th centiles were therefore selected as control subjects in this secondary sensitivity analysis.

4.5 Results

Valid PA data at age 11 were available for 5,327 children. 5,025 were term-born (≥37 weeks' gestation); 48 were born at 25-32 weeks, 57 were born at 33-34 weeks, and 197 were born at 35-36 weeks' gestation. Children born between 25-32 weeks' gestation had significantly increased rates of doctor-diagnosed asthma when compared to the term-born controls. At age 15, valid PA data were available for 1,947 children of which 1,829 were term; 24 were born at 25-32 weeks, 32 were born at 33-34 weeks, and 62 were born at 35-36 weeks' gestational age (Table 4-1). The maximum duration of ventilation during the perinatal period for children with valid accelerometer data was 624 hours (approximately 26 days); of those children admitted to the neonatal unit, few were receiving supplemental oxygen for 5 days or more (Table 4-2).

Table 4-1: Characteristics of participants included in the PA analysis

	25-32w	33-34w	35-36w	Term
Total Liveborn	185	169	522	13,164
Survivors at 1 year	161	166	520	13,133
Had PA data @11	48	57	197	5,025
Median age, years (IQR)	11.6	11.5	11.6	11.5
	(11.4-11.7)	(11.4-11.6)	(11.4-11.7)	(11.4-11.7)
Mean Height, cm (SD)	148.3	148.7	151.2	150.7
	(8.4)	(5.8)	(8.4)	(7.3)
Mean Weight, kg (SD)	41.5	40.5	43.2	43.5
	(12.0)	(7.2)	(9.6)	(9.8)
Had Lung function data @8	38	50	158	4169
Current asthma @7.6 (%) †*	7/25	8/38	15/118	454/3,343
	(28)	(21)	(13)	(14)
Had PA data @15	24	32	62	1,829
Median age, years	15.4	15.4	15.4	15.4
	15.3-15.5)	(15.3-15.6)	(15.3-15.6)	(15.3-15.5)
Mean Height, cm (SD)	168.4	167.3	169.2	168.8
	(9.5)	(8.7)	(7.6)	(8.3)
Median Weight, kg (IQR)	59.8	61.2	58.6	59.2
	(51.5-64.7)	(49.1-67.4)	(54.4-66.2)	(53.4-66.6)

*$p<0.05$

†based on reported doctor-diagnosed asthma ever with symptoms and/or treatment in previous 12 months. Those with both PA and lung function measurements; denominators are given as this variable had missing data.

Table 4-2: Neonatal characteristics for children with PA measurements at 11

	25-32w	33-34w	35-36w	Term
Mean Birthweight, g (SD)	1,471 (453)	2,246 (427)	2,682 (425)	3,469 (476)
Oxygen at any time (%)*	37 (77)	21 (36)	9 (4.5)	36 (0.7)
Numbers (%) receiving oxygen treatment for:*				
Less than 1 day	14 (29)	10 (18)	5 (2.5)	26 (0.6)
2-4 days	5 (4)	7 (12)	4 (2.0)	7 (0.1)
≥5 days*	18 (38)	4 (7.0)	0 (0)	3 (0.1)
Ever ventilated (%)*	31 (65)	9 (16)	2 (1.0)	9 (0.2)
Mean (range) duration of ventilation (h)*	120 (1-624)	76 (9-105)	45 (8-82)	53 (1-576)
Surfactant (%)	15 (31)	5 (9.0)	0 (0)	1 (0.02)

*It was assumed the answer was no for children who did not have a neonatal admissions questionnaire completed, hence percentages are calculated based on the total number in the group who had valid PA data, not the number who had neonatal admissions questionnaires completed.

Children who provided valid accelerometry data were more likely to be girls, white, have non-smoking mothers with a higher level of education, and be of higher socio-economic status when compared with children who did not attend the clinic (Table 4-3). A similar pattern was seen in comparison with children who took part in activity monitoring but failed to provide valid data (no differences in sex and ethnicity). These results are consistent with previous findings in this cohort (Riddoch et al., 2007) and were similar at age 15.

In all gestation groups, females were more sedentary and were significantly less active than males. The median levels of MVPA were substantially lower than the recommended levels of 60 minutes per day (Preterm females 16.2, males 26.6 $min \cdot day^{-1}$; Term females 15.6, males 25.5 $min \cdot day^{-1}$). There was no strong evidence of differences in Total PA, MVPA or sedentary behaviour between children born preterm and those born at term at age 11 years (Figure 4-2 and Table 4-4).

Table 4-3: Demographics of children participating in accelerometry

	Attended age 11 clinic visit		Attended age 15 clinic visit	
	Valid PA data N= 5327	Did not attend N= 8166	Valid PA data N= 1947	Did not attend N= 8726
Sex[§*]				
Male	2547 (48%)	4428 (54%)	868 (45%)	4742 (54%)
Female	2780 (52%)	3736 (46%)	1079 (55%)	3984 (46%)
Maternal smoking[§*]				
Smoking	942 (18%)	2355 (32%)	287 (15%)	2539 (32%)
Non-smoking	4295 (82%)	5093(68%)	1631 (85%)	5483 (68%)
Socio-economic status[§*]				
Manual	1893 (38%)	2921 (48%)	636 (35%)	3247 (49%)
Non-Manual	3047 (62%)	3217 (52%)	1206 (66%)	3405 (51%)
Ethnicity[§*]				
Other	195 (4%)	397 (6%) [§]	68 (4%)	396 (6%)
White	4887(96%)	6155 (94%)	1807 (96%)	6699 (94%)
Mother's education[§*]				
CSE	660 (13%)	1767 (26%)	188 (10%)	1916 (26%)
Vocational	428 (8%)	743 (11%)	119 (6%)	826 (11%)
O Level	1840 (36%)	2286 (34%)	660 (35%)	2534 (35%)
A Level	1386 (27%)	1308 (19%)	553 (29%)	1369 (19%)
Degree	843 (16%)	697 (10%)	384 (20%)	704 (10%)
Gestational age				
Term	5025 (94%)	7660 (94%)	1829 (94%)	8168 (94%)
35-36	197 (4%)	303 (4%)	62 (1%)	355 (1%)
33-34	57 (1%)	102 (1%)	32 (2%)	103 (1%)
25-32	48 (1%)	101 (1%)	24 (3%)	102 (4%)

[§] Age 11 Attendees with valid data Vs. non-attendees: χ^2 test, $p<0.05$

*Age 15 Attendees with valid data Vs. non-attendees: χ^2 test, $p<0.05$

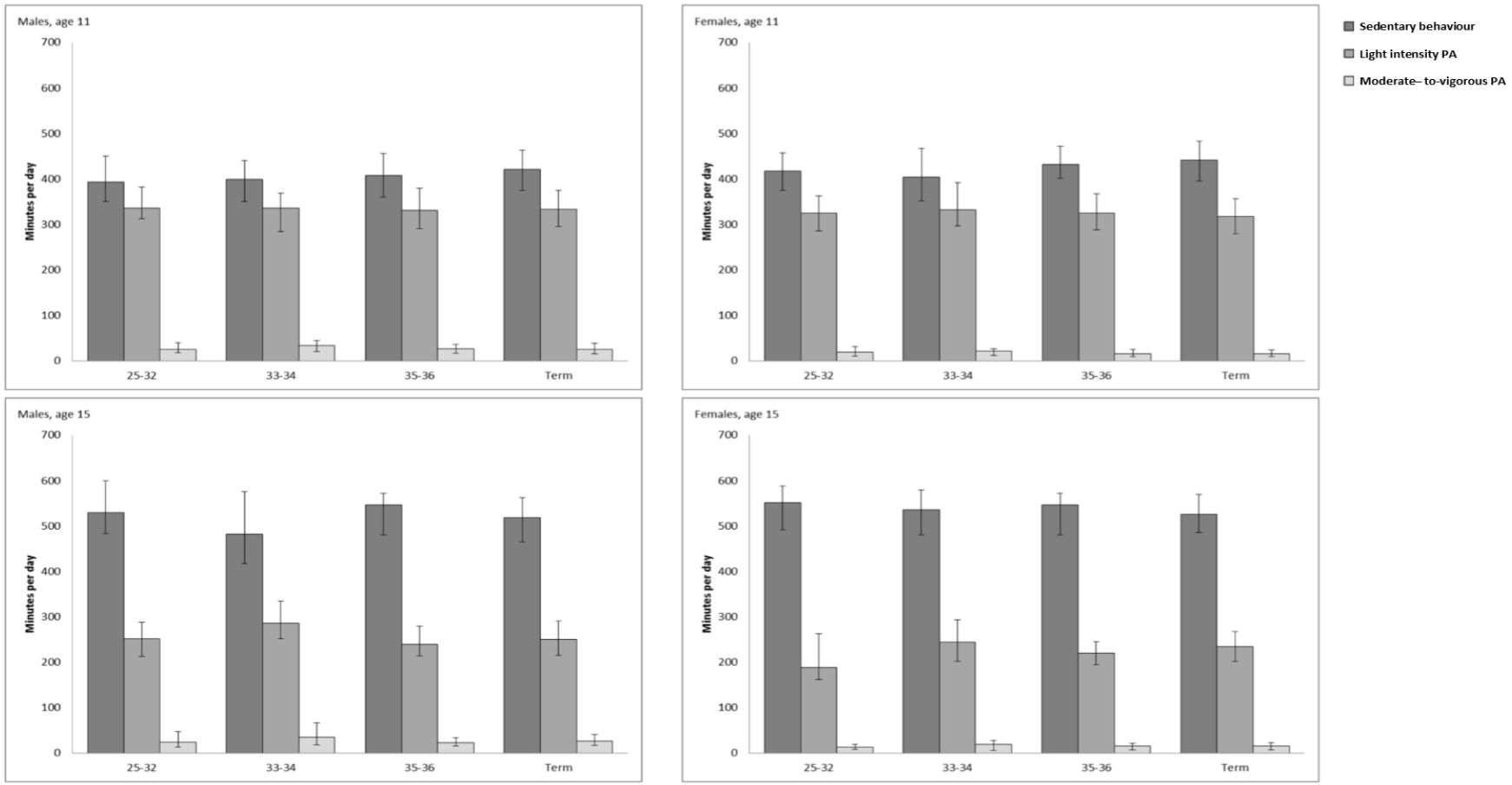


Figure 4-2 Levels of sedentary, light and MVPA (mins day^{-1}) in males and females at age 11 (top) and age 15 (bottom). Levels of MVPA are noted to make up a small proportion of the average minutes per day spent active. Levels of PA decline significantly from age 11 to age 15 years with sedentary behaviour increasing at the expense of light-intensity PA. There are no differences in the levels of PA or sedentary behaviour between groups of gestational age.

Table 4-4: Levels of physical activity by gestation group

Age 11		25-32w N= 48	33-34w N=57	35-36w N=197	All Preterm 302	Term N=5025	Term (20-80th centile for BW) N= 2803
Total PA (cpm)	M	649 (551-875)	733 (541-877)	636 (537-771)	658 (540-826)	645 (528-772)	647 (535-771)
	F	567 (501-689)	590 (476-709)	529 (442-617)	544 (459-653)	527 (443-636)	530 (442-630)
Sedentary (min·day^{-1})	M	393 (350-450)	399 (350-440)	407 (360-456)	404 (353-451)	421 (374-464)	419 (375-463)
	F	417 (374-457)	404 (351-467)	432 (401-472)	422 (392-470)	442 (395-483)	441 (394-483)
Light (min·day^{-1})	M	335 (312-382)	336 (284-368)	331 (291-380)	332 (294-380)	333 (295-375)	334 (296-376)
	F	325 (286-362)	332 (296-392)	325 (288-367)	328 (291-367)	317 (280-356)	318 (279-357)
MVPA (min·day^{-1})	M	25.1 (18.2-39.2)	33.5 (20.7-44.7)	25.8 (16.3-36.1)	26.6 (17.0-39.0)	25.5 (15.7-37.9)	25.6 (15.9-38)
	F	19.4 (10.6-30.5)	21.6 (11.4-26.2)	15.2 (9.5-25.3)	16.2 (9.7-25.8)	15.6 (15.6-24.3)	15.9 (9.7-24.3)
Age 15		25-32w N=24	33-34w N=32	35-36w N=62	All Preterm N=118	Term N=1829	Term (20-80th centile for BW) N= 992
Total PA (cpm)	M	445 (389-615)	601 (515-839)	462 (402-574)	516 (411-692)	511 (407-644)	510 (405-641)
	F	352 (283-480)	394 (308-507)	381 (331-474)	379 (321-475)	412 (337-502)	411 (337-497)
Sedentary (min·day^{-1})	M	529 (483-600)	482 (417-575)	526 (490-548)	526 (458-573)	518 (465-562)	519 (468-561)
	F	551 (491-588)	535 (480-579)	546 (481-572)	541 (484-573)	529 (486-569)	533 (492-569)
Light (min·day^{-1})	M	251 (212-288)	286 (252-334)	239 (214-280)	256 (220-297)	250 (215-290)	244 (213-287)
	F	188 (161-262)	244 (201-293)	220 (194-246)	223 (189-252)	234 (202-267)	234 (202-268)
MVPA (min·day^{-1})	M	24 (13.0-46.4)	35.2 (18.0-66.8)	22 (15.6-33.0)	25.2 (14.7-39.4)	26.0 (16.7-41.4)	26.0 (17.0-40.3)
	F	12.5 (7.8-19.0)	18.7 (5.0-27.3)	15.8 (6.7-21.3)	15.4 (7.1-22.0)	14.7 (7.5-25.4)	14.8 (8.0-25.4)

Data are medians (IQRs)

Lung function values for each gestation group compared to term are shown in Table 4-5. Children born at 25-32 weeks and at 33-34 weeks' gestation had statistically significant decrements in standardised FEV_1: mean difference -0.54 ($p<0.05$, 95%CI -0.98, -0.11) and -0.59 ($p<0.05$ 95% CI-0.98, -0.20) and in FEF_{25-75}: mean difference -0.61 ($p<0.05$ 95%CI -1.05, -0.18) and -0.53 ($p<0.05$ 95%CI -0.91, -0.15), respectively, when compared to term controls. Values in the late preterm group (35-36 weeks) were similar to those born at term. When spirometry measures were plotted against values of PA, there were no significant correlations; the best model fit was between Total PA and FEV_1 in the 25-32 weeks' gestation group ($R^2=0.1$, $p=0.06$), but numbers in the sub-group were small (38 individuals with both measurements).

Table 4-5: Difference in standardised lung function measurements in preterm groups compared to terms

	25-32 weeks	N=38	Term	N=4169	
	Mean	SD	Mean	SD	Difference
FEV_1	-0.54	0.78	0.0017	1.00	-0.54 (-0.98, -0.11)*
FVC	-0.25	0.88	-0.0002	0.995	-0.24 (-0.68, 0.19)
FEF_{25-75}	-0.61	1.04	0.0032	1.00	-0.64 (-1.12, -0.15)*
	33-34 weeks	N=50	Term	N=4169	
	Mean	SD	Mean	SD	Difference
FEV_1	-0.59	1.13	0.0017	1.00	-0.59 (-0.98, -0.20)*
FVC	-0.34	1.11	-0.0002	0.995	-0.34 (-0.72, 0.03)
FEF_{25-75}	-0.53	1.16	0.0032	1.00	-0.56 (-0.99, -0.12)*
	35-36 weeks	N=158	Term	N=4169	
	Mean	SD	Mean	SD	Difference
FEV_1	0.05	0.90	0.0017	1.00	0.05 (-0.17, 0.27)
FVC	0.047	0.94	-0.0002	0.995	0.05 (-0.17, 0.26)
FEF_{25-75}	0.029	0.91	0.0032	1.00	0.026 (-0.19, 0.24)

*p<0.05

At 15 years of age levels of MVPA were similar to those at age 11 (Preterm females 15.4, males 25.2 min·day^{-1}; Term females 14.7, males 26.0 min·day^{-1}), although Total PA was significantly reduced and sedentary behaviour increased in both boys and girls. There was no evidence of differences in PA between preterm-born children and term controls (Figure 4-2, Table 4-4)

4.6 Discussion

The results of this study show that objectively measured levels of PA, in terms of both frequency and intensity, were remarkably similar in both preterm and term-born children despite documented deficits in lung function in the former group. No relationship between lung function and PA measures was noted in this general population sample.

Previous studies have shown, using questionnaire based methods, that preterm-born children self-report reduced PA when compared with term-born peers (Welsh et al., 2010, Joshi et al., 2013). Although these reports are based on subjective measures, they indicate at least a perception of reduced capacity for PA that could perpetuate a cycle of self-limitation which persists into adulthood. Welsh et al. noted that children born extremely preterm (≤25 week's gestation) self-reported lower exercise capability and employed increased breathing and lower tidal volumes during peak exercise when compared with matched term controls (Welsh et al., 2010), but these observations did not correlate with objectively measured accelerometer activity where reductions were not noted between the preterm-born and term-born groups. In a recent study, self-reported PA (hours per week), was significantly lower in preterm-born children who had suffered from BPD/CLD when compared to those did not, and when compared to term-born controls (Joshi et al., 2013). Similarly, a study by Clemm and colleagues showed reduced self-reported frequency and duration of PA in both extremely preterm-born children and young adults when compared with well-matched term controls (Clemm et al., 2012). The disparity

between questionnaire data and accelerometer data may be explained by the difficulties in recording PA in children. Periods of activity are sporadic and short in duration resulting in poor recall by participants; self-reporting using questionnaires do not correlate well with directly observed measurements (Riddoch et al., 2004)

If decrements in lung function were to manifest as reduced PA, this would likely be under the scenario in which children choose not to take part due to the symptoms associated with exercise limitation (e.g. breathlessness), perhaps in combination with psychosocial pressures of being unable to perform. Given the results of my study it is likely that few children are regularly undertaking activity of the intensity required to provoke such adverse response. Indeed, in comparison to terms, the preterm group as a whole (<37 weeks' gestation) appear to take part in more MVPA at 11 years of age, raising the possibility that low activity levels in term-born children may mask the effect of any differences in lung function. Airway obstruction did not appear to hinder exercise performance in the studies by Clemm, but incidence of exercise-induced bronchoconstriction and reversibility were not reported. It has been recently demonstrated that exercised-induced bronchoconstriction, manifested as reduced FEV_1, in preterm-born children with and without BPD/CLD. This was reversible following administration of salbutamol in the BPD/CLD group. The same study also showed that at peak exercise, preterm-born children have different breathing patterns, using increased ventilatory reserve to maintain similar oxygen uptake at maximal or peak exercise ($\dot{V}O_2$) as term-born children (Joshi et al., 2013).

Other studies have shown a difference in peak volume of oxygen consumption ($\dot{V}O_2$), as well as reduced anaerobic threshold, lower peak workload and increased residual volume in preterm-born children (Welsh et al., 2010, Kilbride et al., 2003, Smith et al., 2008) especially in those with BPD/CLD. Together these deficits suggest airflow obstruction, reduced lung compliance, and gas trapping which may all be results of injury to the

developing lung in the postnatal period. Moreover, the reduced DL_{CO} reported in some studies would further indicate disruption in the alveolar and pulmonary microvascular development in preterm-born children. Emerging studies using hyperpolarised ^{3}He Magnetic Resonance Imaging to investigate alveolar size and number in preterm-born children should help to elucidate the influence of acinar development, which appears to continue in to childhood and beyond (Narayanan et al., 2012, Narayanan et al., 2013), well beyond the currently accepted dogma of lung growth being completed by 2 years of age.

My population sample included few children with a history of ventilation ≥5 days or supplemental oxygen, few children born extremely preterm in the ≤32 weeks' gestation group, and did not note differences between the groups for 'doctor-diagnosed asthma'. These factors may in part explain the similar levels of activity. Additionally, given the inherent selection bias in cohort studies (selecting those who attended the clinic, those with valid accelerometer data, and those with valid lung function measurements) it is likely that those with severe cognitive or physical impairments have been excluded, although those with degrees of developmental coordination disorder (DCD) may have been. In a previous study, boys with probable DCD (between 5th and 15th centile for coordination score) were found to have significantly reduced levels of MVPA, but the differences were small and levels were similar to those reported in this study (Green et al., 2011).

It is difficult to disentangle the relative influence of birthweight and gestational age, two different developmental constructs, when comparing my results with other studies. Ridgway et al. reported no association between PA measured by accelerometer and birthweight in a meta-analysis of 4 studies in children (Ridgway et al., 2011). However, children most likely to have been born preterm (<1500g birthweight) were excluded from the analysis as gestational age was not universally available. In contrast, a meta-analysis by Andersen et al. synthesized the results from 13 cohorts of adolescents and adults and

showed reduced leisure time PA in participants born with very low or very high birthweight (Andersen et al., 2009). The association was strengthened when gestational age was included in the model but this analysis was limited by missing data. In a recent study, 12-year old children born with high birthweight (>4000g) participated in an additional 1 hour per week of outdoor PA than very low birthweight (<2000g) peers, independent of gestational age (Gopinath, 2013). When I performed a repeat analysis to remove the influence of low birthweight and emerging obesity from the term control group by excluding children <20th centile and >80th centile for birthweight, my results remained unchanged.

Kaseva and colleagues reported that very low birthweight preterm-born adults participated in significantly less 'conditioning leisure time PA' than matched controls who were born at term, and extremely low birthweight-born young adults perceive themselves as less physically able suggesting that inactivity may track in to adulthood (Kajantie and Hovi, 2014). Contrastingly, despite markedly reduced lung function, Burns et al. (Burns et al., 2009), reported no association between reduced FEV_1 and cardiorespiratory endurance in extremely low birthweight 12-year olds, further indicating that at least during childhood, the cardiopulmonary system is able to compensate for airflow limitation.

Interestingly, although there was no change in levels of MVPA between the ages of 11 and 15 years, Total PA decreased and sedentary behaviour increased. Previous studies in the ALSPAC cohort have shown the increase in sedentary behaviour to be at the expense of light intensity PA (Mitchell et al., 2012). Although sedentary behaviour has evolved to be considered a separate construct independent from MVPA, a recent meta-analysis demonstrated that increased MVPA was associated with reduced cardiometabolic risk factors regardless of levels of sedentary behaviour. A modest increase in 20 minutes per

day was required to move from the bottom to the top tertile of MVPA (Ekelund et al., 2013), which given the result of this study is achievable for all preterm-born children.

4.7 Strengths and limitations

The main strength of this study is the use of objectively measured PA data collected in the 'free living' environment (Mattocks et al., 2008) using a device validated against criterion standards (Mattocks et al., 2007). Data were taken from participants in a large cohort study which is representative of the UK population.

In common with other long term observational studies, there was considerable loss to follow-up of participants with valid accelerometry data at ages 11 and by 15 years. None of the preterm-born children had both valid accelerometer data and lung function data at age 15. Additionally, the children who attended the clinic visits and recorded valid accelerometer data were more likely to come from families of higher socio-economic backgrounds compared with those who did not attend. However this is unlikely to introduce major bias as lower socio-economic status was weakly associated with marginally increased PA in the cohort as a whole (Riddoch et al., 2007).

As levels of PA were low in both term and preterm-born children, the sensitivity of the accelerometer may not be sufficient to identify subtle differences between groups. The length of epoch used (1 minute) may underestimate the amounts of MVPA as movement in children is often sporadic, although any such differences which are missed due to measurement error would be of questionable utility. Investigation of vigorous PA only (VPA, > 6000 cpm) showed no differences between groups; however, the contribution of VPA formed only a small part of MVPA. One possible reason for this is the upper range of acceleration which can be measured by the Actigraph is 2.5*g*. Since more strenuous activities such as dancing, jogging/running and jumping can elicit accelerations well above this threshold, the Actigraph device was limited in its ability to detect these higher-impact

activities. Such activities are more likely to challenge the cardiorespiratory system and thus provoke adverse symptoms which may lead to decreased participation in activity. This may account for the disparity between questionnaire studies, where children were more likely to recall participation in organized activities (such as physical education lessons, attending sports clubs), and accelerometry which records mainly habitual activity.

Lastly, qualitative data on participation in activities such as swimming (as the device was removed for water-based activity) and cycling (which is poorly captured by the Actigraph device) was not available. However, previous studies have shown repeating analyses in children who did not take part in these activities did not affect the results (Ness et al., 2007).

4.8 Summary and conclusions

I did not observe a difference in objectively measured habitual PA in children born preterm compared with term-born children. Given that capacity for exercise is equal to their term-born peers and appears both safe and beneficial, PA should be encouraged thus forming habits persisting in to adulthood. PA has the potential to improve cardiopulmonary health and ameliorate the increased risk of chronic lung disease later in life in this vulnerable group. This deserves attention and future studies should take advantage of technological developments to allow monitoring of participants over the complete range of activity.

5 Physical activity and sedentary behaviour in preterm-born 7-year old children

5.1 Overview

In the previous chapter, I investigated the levels of objectively measured levels of habitual PA in 11 and 15-year old children born preterm in the 1990s using data from ALSPAC and found no evidence of differences compared to children born at term. However, there were some methodological limitations including a possible underestimation in levels of Moderate to Vigorous Physical Activity (MVPA) due to the longer accelerometer epoch time which may not capture the sporadic PA commonly observed in children. Overall levels of PA were also low and this may have masked the effect of preterm birth; thus, it may be better to study a younger cohort of children. In this chapter, I now describe an investigation into objectively measured levels of physical activity and sedentary behaviour from 7-year old preterm children who participated in the Millennium Cohort Study (MCS). This cohort reflects the modern era of neonatal care including innovations such as the routine use of exogenous surfactant, routine maternal antenatal corticosteroid administration and more gentle forms of ventilation. In comparison to the ALSPAC cohort, who were born in the early 1990s, these interventions are likely to have improved the respiratory outcomes of preterm birth. However, during this time rates of BPD/CLD have stayed largely the same, largely due to increased survival at the extremes of viable gestational age (Costeloe et al., 2012). Additionally, the MCS was designed to disproportionally sample from areas of lower socio-economic status and may be a more representative of the preterm population than that studied in the previous chapter.

5.2 Aims and Hypothesis

The aims of this study were to compare the levels of physical activity and sedentary behaviour in preterm-born children to those of children born at term, and to further investigate whether respiratory symptoms and family history of atopy mediate any observed relationships between preterm-birth and physical activity.

My specific hypotheses were:

I. That preterm-born children would participate in reduced levels of total PA and MVPA; and that levels of sedentary behaviour would be increased when compared to term-born controls.
II. That current respiratory symptoms would mediate the observed associations between preterm birth and physical activity outcomes.

5.3 Methods

5.3.1 Millennium Cohort Study

I used data from the MCS, a UK-based geographically representative cohort which disproportionally sampled areas of ethnic minorities and lower socio-economic status in England as well as the devolved nations of the UK (Wales, Scotland and Northern Ireland) (Hansen, 2012). The cohort recruited, 18,818 children and families between the years of 2000-2002 and performed follow-up from the age of nine months and subsequently at 3, 5 and 7 years of age with data collection ongoing. At the age 7 follow-up, 14,043 of 18,818 families participated in the home interview where 12,781 of 14,043 participants (91%) agreed to wear the activity monitor (University of London, 2008). Valid PA data (at least 10 hours on at least 2 days) were available for 6,675 participants representing 52% of the children included at 7 years of age. After removing those with missing gestational age at birth (n=253), 6,422/12,781 (50%) children were included (Figure 5-1). Written informed

consent was obtained prior to data collection from the child's caregiver. Ethics approval was given by the Northern and Yorkshire research ethics committee. I used the downloadable data which does not contain personal identifiable information.

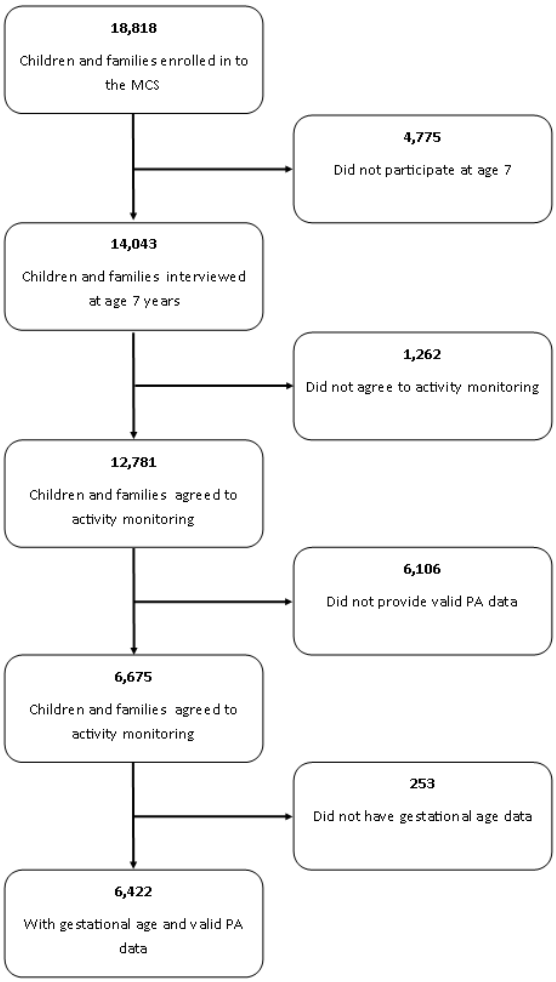


Figure 5-1 Flow diagram of MCS participants with available PA and gestational age data at age 7

5.3.2 Physical activity

Children were provided with a uniaxial accelerometer (Actigraph GT1M, Pensacola, Florida, USA) to wear around the waist during waking hours for seven consecutive days. The device has been validated against criterion standards and the methods for data recording, processing and establishing activity 'cut-point' thresholds are described in my introduction.

(Pulsford et al., 2011). Valid data were considered to be a recording of a minimum of 10 or more hours on 2 or more days of recording (Rich et al., 2013b, Pulsford et al., 2011). Three outcomes were used in the analysis: Total PA, the average number counts per minute over the period of the valid recording; MVPA, defined as average time in minutes per day spent at >2241cpm over the period of the valid recording; and sedentary behaviour, average time in minutes per day spent at <100cpm. Total PA was used as it provides a summary measure of activity and is the variable used for comparison in calibration studies (Pulsford et al., 2011). MVPA was used because national guidelines recommend at least 60 minutes of MVPA per day (Chief Medical Officers of England, 2011). Sedentary behaviour was investigated as it has been described as an risk factor for poor health outcomes, independent of MVPA (Mitchell et al., 2009).

5.3.3 Perinatal data

Perinatal data on birthweight, admission to the neonatal intensive care unit and length of hospital stay were extracted from hospital records by the MCS team (University of London, 2008). Gestational age was derived from maternal report of the expected due date during the 9-month interview, which was based on the date of the last menstrual period and results of the antenatal ultrasound scan. These data have been shown to provide an accurate estimation when compared to linked hospital database records (Poulsen et al., 2011). Children with valid accelerometry data were divided into four groups based on gestational age at birth: 25-32, 33-34, 35-36 and 37-43 weeks' gestation (term control).This approach is similar to our other studies on lung function (Kotecha et al., 2012), will allow comparison to the previous chapter and that of others as it represents specific stages in lung development and children most at risk of lung disease (Boyle et al., 2012, Greenough, 2012).

5.3.4 Respiratory outcomes

Rates of wheeze and atopy in the last 12 months were derived from interviews conducted by the MCS study team during the home visit at 7 years of age. Use of such data for assessing respiratory outcomes, using a modified ISAAC questionnaire, is well-established and extensively validated (Asher et al., 1995).

5.3.5 Demographics

Information on gender, ethnicity, mother's smoking habits during pregnancy and educational qualifications were collected at the home-based interview conducted after 9 months of age (University of London, 2003). Highest level of education was categorized into none, other, GCSE, A-level, or university degrees. At the 7 years of age home visit data on the child's age, weight and height were measured, from which BMI was calculated. Social class was based on the 5-category UK Office for National Statistics Socio-economic Classification (NS-SEC) which relates to maternal employment (last known job) at the age 7 years visit.

5.3.6 Statistical analysis

Firstly, in order to assess the representativeness of the available data, χ^2 tests were used to compare demographics between participants who provided valid PA data and those who did not.

Secondly, I compared birth characteristics of the four groups of gestational age using ANOVA for normally distributed data, and used Kruskal-Wallis Tests for non-normal data. Since total accelerometer wear time was not consistent across all participants, the methods of Griffiths were used to standardise the measures of MVPA and sedentary behaviour (Griffiths et al., 2013). This was achieved by introducing a standard day of equal duration (735 minutes) for all children which is equal to the mean wear time across all valid days of recording. A weighting variable is then computed for each measure of intensity and

multiplied with the total time spent at a given intensity. Finally, the weighted total time is divided by the value of the standard day to give a weighted mean time spent at an activity intensity across the valid days of recording. This procedure was performed using Stata (Version 12, StataCorp, Texas USA), applying the syntax provided in the MCS technical report on processing of accelerometry data (Griffiths, 2013) . Each PA variable was then tested for normality using P-P plots; MVPA was found to have a positively skewed distribution and was therefore square-root transformed prior to analysis (Figure 5-2). Total PA and sedentary behaviour did not require transformation.

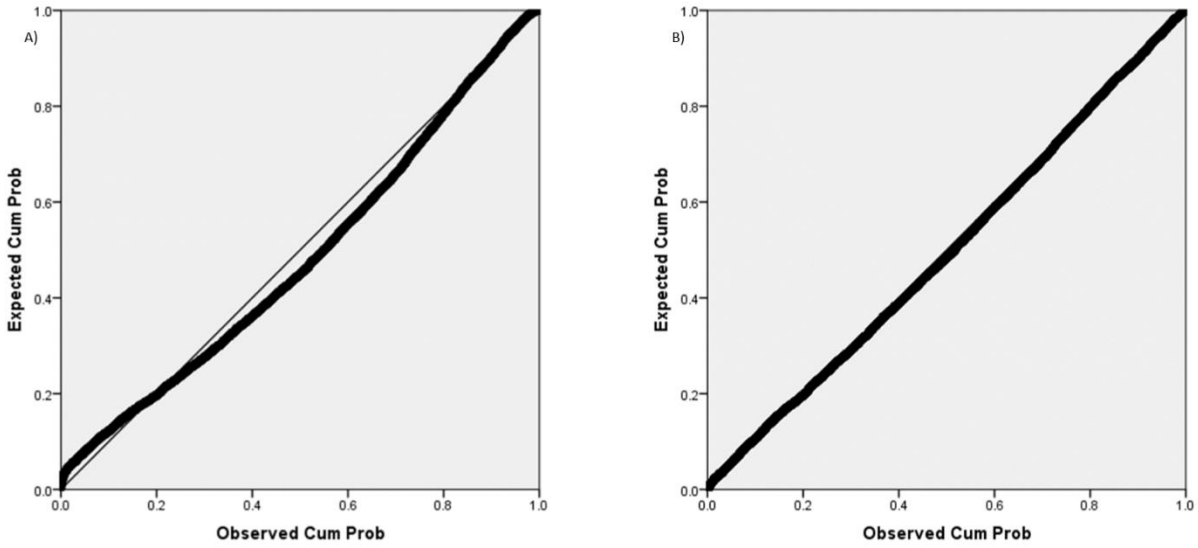


Figure 5-2: P-P plots of A) MVPA raw data showing deviation from the line of best fit indicative of a positive skew, and B) MVPA transformed data

In order to investigate the effect of gestational age on measures of activity (Total, MVPA or sedentary behaviour), I opted to use a series of general linear models. Since results in the previous chapter showed a significant difference between levels of activity in males and females, the association between gestation group and PA was tested for an interaction with gender. As expected there was significant evidence ($p<0.001$) of an interaction hence all analyses were stratified by gender. In model 1 (adjusted for birth factors only), gestation

group, single or multiple births, intrauterine growth restriction status (IUGR, defined as <10th centile for standardised birthweight [LMS Grow Program; Medical Research Council, UK]), admission to the neonatal unit and maternal smoking in pregnancy were included; model 2 adjusted for the variables in model 1 plus age, body mass index (BMI) and season of accelerometry data collection at the 7-year visit; model 3 adjusted for the variables in models 1 and 2 plus social factors at the 7-year visit: ethnicity, maternal education and social class; model 4 adjusted for the variables in models 1, 2 and 3 plus respiratory symptoms: current wheeze and atopy. General linear modelling was performed using SPSS Statistics (version 20, IBM, Chicago, IL., USA).

In order to further investigate the mediation of respiratory symptoms (current wheeze and atopy) on the association between gestational age and measures of PA, I conducted mediation analysis. This enables distinction between the direct effect, which is the relationship of the independent variable on the dependent variable, adjusting for the mediating variable, and the indirect effect, which is the effect of the independent variable on the dependent variable through the mediating variable. Mediation is said to occur if the strength of the relationship between the predictor and the outcome is diminished by including a mediator (Field, 2013). Mediation analysis was performed with Mplus using structural equation modelling (version 7, Muthen and Muthen, Los Angeles, California USA). For all analyses $p<0.05$ was considered statistically significant.

5.4 Results

After excluding participants without valid accelerometry and gestational age data, 79 children were born at 24-32 weeks', 119 were born at 33-34 weeks', and 275 were born at 35-36 weeks' gestation. The control population consisted of 5949 children born at term (37-43 weeks' gestation), Table 5-1. Children born at ≤32 weeks' gestational age were noted to have a significantly lower BMI and had increased incidence of recent wheeze and

asthma when compared to those born at term. Rates of atopy were similar between gestation groups. Preterm-born children were more likely to be born to mothers who smoked during pregnancy; however, there were no significant differences in socio-economic status when measured by maternal employment or maternal education.

Table 5-1 Characteristics of participants included who had valid PA data and gestational age data

	25-32w	**33-34w**	**35-36w**	**Term**
Total Cohort	253	373	876	17063
Had PA data at age 7	79	119	275	5949
Gender, M (%)	37/79 (46.8)	57/119 (47.9)	135/275 (49.1)	2901/5949 (48.8)
Mean age, years (SD)	7.3 (0.3)	7.2 (0.2)	7.2 (0.2)	7.2 (0.2)
Mean Height, cm (SD)	122 (5.9)	122 (5.6)	123 (5.8)	124 (5.4)
Mean Weight, kg (SD)[§]	23.3 (4.4)	24.3 (4.2)	25.2 (5.1)	25.2 (4.5)
Mean BMI (SD) [§]	15.5 (1.96)	16.2 (1.9)	16.5 (2.4)	16.4 (2.4)
Wheeze at 7 (%) [§]	17/79 (21.5)	12/119 (10.1)	34/274 (12.4)	661/5941 (11)
Asthma at 7 (%) [§]	19/79 (24.1)	24/118 (20.3)	47/272 (17.3)	878/5936 (14.8)
Atopy at 7 (%)	35/79 (44.3)	49/119 (41.2)	125/274 (45.6)	2446/5943 (41.4)
Neonatal characteristics	**25-32w**	**33-34w**	**35-36w**	**Term**
Mean Birthweight, g (SD) [§]	1619 (614)	2147 (507)	2683 (503)	3452 (495)
IUGR[§]	9/79 (11.4)	22/119 (18.5)	25/274 (9.1)	522/5944 (8.8)
Caesarean section (%) [§]	44/79 (55.7)	60/119 (50.4)	102/275 (37.1)	1244/5922 (21.0)

Admitted to Neonatal unit (%) §	69	87	91	351
	(87.3)	(73.1)	(33.1)	(5.9)
Length of stay after	44	19	8	3
birth, days (SD) §	(27.6)	(20.3)	(8.4)	(6.0)
Breastfeeding (%) §	58/79	81/119	187275	4454/5949
	(73.4)	(68.1)	(68.0)	(74.9)
Socio-economic characteristics	**25-32w**	**33-34w**	**35-36w**	**Term**
Maternal smoking in pregnancy (%) §				
Smoking	24/78	42/119	91/275	1636/5944
	(30.8)	(35.3)	(34.2)	(27.5)
Non-smoking	54/78	77/119	181/275	4308/5944
	(69.2)	(64.7)	(65.8)	(72.5)
Employment status (%)				
Management/Professional	28/76	33/110	86/259	2119/5703
	(36.8)	(30.0)	(33.2)	(37.2)
Intermediate	12/76	22/110	64/259	1115/5703
	(15.8)	(20.0)	(24.7)	(19.6)
Self employed	7/76	11/110	15/259	446/5703
	(9.2)	(10.0)	(5.5)	(7.8)
Supervisory/Technical	5/76	8/110	12/259	260/5703
	(6.6)	(7.3)	(4.6)	(4.6)
Semi routine/routine	24/76	36/110	82/259	1763/5703
	(31.6)	(32.7)	(31.7)	(30.9)
Ethnicity (%)				
White	68/79	105/119	247/275	5261/5938
	(86.1)	(88.2)	(89.8)	(88.6)
Other	11/79	14/119	28/275	677/5938
	(13.9)	(11.8)	(10.2)	(11.4)
Mother's education (%)				
None of these	13/79	12/119	36/275	640/6418
	(16.5)	(10.1)	(13.1)	(10.8)
Other academic	0	0/119	1/275	133/6418
	(0.0)	(0.0)	(0.4)	(2.2)
GCSE grades D-G	6/79	15/119	23/275	520/6418
	(7.6)	(12.6)	(8.4)	(8.7)

GCSE grades (A-C)	27/79	41/119	107/275	1916/6418
	(34.2)	(34.5)	(38.9)	(32.2)
A or AS levels	5/79	10/119	22/275	676/6418
	(6.3)	(8.4)	(8.0)	(11.4)
Diplomas in College	8/79	17/119	29/275	648/6418
	(10.1)	(14.3)	(10.5)	(10.9)
First Degree	16/79	22/119	51/275	1118/6418
	(20.3)	(18.5)	(18.5)	(18.8)
Higher degree	4/79	2/119	6/27	297/6418
	(5.1)	(2.2)	(2.2)	(5.0)

§ $p<0.05$

In terms of neonatal history, children born at ≤32 weeks' gestation had a significantly lower birthweight, were more likely to be born IUGR, more likely to be born by caesarean section, were more likely to be admitted to the neonatal unit, and more likely to have an increased length of hospital stay when compared to the term control group (Table 5-1).

There were some small but statistically significant differences between children and families who participated in the accelerometry study, and those who did not. Participants with valid data were more likely to be female, white, and born at term. Mothers were more likely to have achieved a higher educational qualification, have not smoked during pregnancy and be of higher socio-economic status (Table 5-2). A previous study investigating the demography of non-consent to participate in the accelerometer study found consent was less likely for children with limiting illness or disability, those who reported exercise less than once per week, and a number of social factors related to increased levels of deprivation (Rich et al., 2013a).

Table 5-2 Demographics of children participating in accelerometry

	Participants N= 6422	Non-participants N= 12842
Sex (%)*		
Male	3130/6422 (48.7)	6489/12,336 (52.6)
Female	3292/6422 (51.3)	5847/12,336 (47.4)
Maternal smoking in pregnancy (%) §		
Smoking	1796/6416 (28.0)	4726/12,294 (38.4)
Non-smoking	4662/6416 (72.0)	7568/12,294 (61.6)
Employment status (%) §		
Management/Professional	2337/6012 (38.9)	2565/10,546 (24.3)
Intermediate	1172/6012 (19.5)	1965/10,546 (18.6)
Self employed	274/6012 (4.6)	384/10,546 (3.6)
Supervisory/Technical	352/6012 (5.9)	654/10,546 (6.2)
Semi routine/routine	1877/6012 (31.2)	4978/10,546 (47.2)
Ethnicity (%) §		
White	5681/6411 (88.6)	9800/12,300 (79.7)
Other	730/6411 (11.4)	2500/12,300 (20.3)
Mother's education (%) §		
None of these	701/6418 (10.9)	2941/12,272 (24.0)
Other academic	134/6418 (2.1)	399/12,272 (3.3)
GCSE grades D-G	564/6418 (8.8)	1424/12,272 (11.6)
GCSE grades (A-C)	2091/6418 (32.6)	4166/12,272 (33.9)
A or AS levels	713/6418 (11.1)	1024/12,272 (8.3)
Diplomas in College	702/6418 (10.9)	885/12,272 (7.2)
First Degree	1204/6418 (18.8)	1117/12,272 (9.1)
Higher degree	309/6418 (4.8)	316/12,272 (2.6)
Gestational age (%)*		
Term	5949 (92.6)	11114/12,143 (91.5)
35-36	275 (4.3)	601/12,143 (5.0)
33-34	119 (1.9)	245/12,143 (2.0)
25-32	79 (1.2)	183/12,143 (1.5)

* $\chi^2 < 0.05$; § $\chi^2 = <0.001$

Table 5-3 shows levels of PA by gestation group, presented separately for males and females. Females participated in significantly less PA and spent more time in sedentary behaviour. The mean levels of MVPA were close to or exceeded the recommended guidelines of 60 minutes per day (Preterm females 55, males 66 min·day^{-1}; Term females 55, males 69 min·day^{-1}). 63% of term-born boys participated in greater or equal to 60 minutes of MVPA compared to 55% of those born preterm. In females, 34% of those born preterm participated in greater or equal to 60 minutes of MVPA compared to 36% of those born at term.

Table 5-3 Levels of physical activity by gestation groups adjusted for wear time

		25-32w N= 79	33-34w N= 119	35-36w N= 275	All Preterm N= 473	Term N=5949	Whole cohort N=6422
Total PA	M	576 (145)	640 (175)	630 (161)	624 (143)	640 (154)	639 (155)
(cpm)	F	534 (159)	527 (163)	581 (152)	559 (157)	568 (142)	567 (144)
Sedentary	M	404 (45)	385 (48)	383 (50)	386 (49)	384 (49)	384 (49)
(min·day^{-1})	F	417 (51)	416 (52)	401 (53)	407 (53)	400 (53)	400 (50)
Light	M	271 (32)	281 (33)	285 (38)	282 (36)	282 (38)	282 (38)
(min·day^{-1})	F	265 (38)	269 (39)	276 (41)	272 (40)	280 (39)	279 (39)
MVPA	M	61 (23)	69 (25)	67 (24)	66 (24)	69 (23)	69 (23)
(min·day^{-1})	F	52 (21)	51 (22)	58 (20)	54 (21)	55 (19)	55 (19)

Data are means (SD)

The results of the univariate analyses and the general linear modelling analyses for males are presented in Table 5-4 and Table 5-5, respectively. In the minimally adjusted model (model 1), gestational age in boys was significantly associated with reduced levels of MVPA in the ≤32 weeks' gestation group when compared to term but not for the 33-34 and 35-36 week groups. After addition of further sets of variables, this relationship remained statistically significant in the fully adjusted model (model 4) (Table 5-5). Although the effect

size of gestational age group and contribution to the model fit as a whole were both small; when the regression equation derived from model 4 was used to calculate the mean predicted values it equated to a difference of approximately 9 minutes per day of MVPA between boys born at term (mean predicted MVPA 67.7 min·day-[1]) and those born ≤32 weeks' gestation (mean predicted MVPA 58.9 min·day^{-1}) representing over 1 hour of decreased MVPA per week. Total PA was also noted to be lower in the ≤32 weeks' gestation group when compared to term in model 1; however, these associations attenuated as further variables were added to the model. There was also a significant association between gestational age (≤ 32 weeks' gestation) and increased levels of sedentary behaviour for model 1 when compared to term-born controls; this again attenuated in models 2 to 4 mainly due to the strong influence of non-white ethnicity and higher socio-economic status, both of which were significantly associated with increased levels of sedentary behaviour.

Results from univariate analyses, general linear modelling analyses for females are presented in Table 5-6 and Table 5-7, respectively. There were no significant associations between gestation groups for Total PA, MVPA or sedentary behaviour in the minimally or maximally adjusted models.

Table 5-4 Univariate analysis of confounders and their association with levels of physical activity (males)

	Total PA			MVPA			Sedentary		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
SDS Birthweight	-2.78	-8.13, 2.62	0.32	0.03	-0.08, 0.02	0.24	-0.31	-2.02, 1.40	0.72
IUGR									
<10th Centile	10.5	-9.00, 30.0	0.29	0.03	-0.14, 0.20	0.75	-4.77	-11.0, 1.41	0.13
≥10th Centile	Ref			Ref			Ref		
Singleton									
Singleton	3.08	-31.3, 37.5	0.86	0.06	-0.25, 0.36	0.71	0.24	-10.7, 11.2	0.97
Multiple	Ref						Ref		
NNU Admission									
Yes	-16.29	-34.2, 1.63	0.08	-0.14	-0.30, 0.02	0.08	5.40	-0.30, 11.10	0.06
No	Ref			Ref			Ref		
Maternal Smoking									
Yes	21.4	9.27, 33.5	0.01	**0.17**	**0.06, 0.28**	**0.002**	-2.99	-6.83, 0.86	0.13
No	Ref			Ref			Ref		
Social Class (Mothers last employment)									
Manage & Prof	**-19.5**	**-32.9, -6.03**	**0.005**	**-0.15**	**-0.27, -0.03**	**0.01**	4.99	**0.74, 9.24**	**0.02**
Intermediate	-9.67	-25.6, 6.24	0.23	-0.11	-0.25, 0.03	0.13	3.21	-1.82, 8.23	0.21
Small emp/self em	**-33.8**	**-55.9, -11.8**	**0.003**	**-0.30**	**-0.49, -0.10**	**0.003**	4.91	-2.06, 11.9	0.17
Lo sup/technical	-7.23	-34.9, 20.5	0.67	0.00	-0.25, 0.24	1.00	2.39	-6.36, 11.1	0.59
Routine	Ref			Ref			Ref		
Ethnicity									

White	**23.1**	**6.15, 40.1**	**0.008**	0.03	-1.20, 0.18	0.69	-2.30	-7.70, 3.10	0.40
Other	Ref			Ref			Ref		
Age	-5.16	-27.0, 16.7	0.64	0.05	-0.15, 0.24	0.64	**10.4**	**3.44, 17.3**	**0.003**
Wheeze at 7									
Yes	-7.22	-23.1, 8.69	0.37	-0.10	-0.24, 0.04	0.18	0.19	-4.87, 5.25	0.94
No	Ref			Ref			Ref		
BMI at 7	**-7.95**	**-8.50, -3.40**	**<0.001**	**-0.08**	**-0.10, 0.05**	**<0.001**	-0.25	-1.06, 0.57	0.55
Season of accelerometry									
Winter	**-103**	**-124, -82.1**	**<0.001**	**-0.80**	**-0.99, -0.61**	**<0.001**	**30.0**	**23.2, 36.6**	**<0.001**
Autumn	**-84.4**	**-103, -66.2**	**<0.001**	**-0.61**	**-0.77, -0.44**	**<0.001**	**25.8**	**20.0, 31.6**	**<0.001**
Summer	**-38.0**	**-54.7, -19.5**	**<0.001**	**-0.32**	**-0.48, -0.17**	**<0.001**	**7.90**	**2.32, 13.47**	**0.006**
Spring	Ref			Ref			Ref		
Mothers Education									
None	27.6	-2.35, 57.6	0.07	0.14	-0.12, 0.41	0.30	**-14.9**	**-24.4, -5.37**	**0.002**
Other	-14.5	-62.4, 33.5	0.55	-0.17	-0.59, 0.25	0.43	7.60	-7.65, 22.8	0.33
GCSE G-D	26.6	-4.40,57.5	0.09	0.08	-0.20, 0.35	0.59	-9.04	-18.9, 0.80	0.07
GCSE A-C	7.20	-19.5, 34.0	0.60	-0.09	-0.33, 0.15	0.46	-6.22	-14.7, 2.28	0.15
A/AS level	6.69	-23.2, 36.5	0.66	-0.09	-0.35, 0.18	0.52	-4.27	-13.8, 5.22	0.38
Higher diploma	-0.07	-29.7, 29.6	1.00	-0.14	-0.41, 0.20	0.28	-5.11	-14.5, 4.32	0.29
First Degree	-10.2	-38.2, 17.8	0.48	-0.18	-0.43, 0.07	0.16	-0.12	-8.99, 8.76	0.98
Higher degree	Ref			Ref			Ref		

Table 5-5 Results of general linear models regressing activity variables on gestation groups adjusting for confounders (males)

MALES			Total PA			MVPA*			Sedentary		
		n	ß	95% CI	p-value	ß	95% CI	p-value	ß	95% CI	p-value
Model 1	≤32	29	**-67.2**	**-128, -5.91**	**0.03**	**-0.59**	**-1.13, -0.05**	**0.03**	**20.1**	**0.62, 39.5**	**0.04**
	33-34	44	-1.92	-53.0, 49.1	0.94	-0.08	-0.53, 0.37	0.72	2.03	-14.2, 18.2	0.81
	35-36	104	-13.9	-46.0, 18.3	0.40	-0.19	-0.48, 0.09	0.19	0.73	-9.49, 11.0	0.89
	Term	2377	Ref			Ref			Ref		
Model 2	≤32	29	**-61.6**	**-122, -1.37**	**0.05**	**-0.58**	**-1.12, -0.05**	**0.03**	15.58	-3.57, 34.7	0.11
	33-34	44	-1.12	-51.1, 48.9	0.97	-0.09	-0.53, 0.36	0.70	1.22	-14.7, 17.13	0.88
	35-36	103	-13.2	-44.8, 18.5	0.41	-0.20	-0.48, 0.08	0.16	-0.31	-10.4, 9.77	0.95
	Term	2366	Ref			Ref			Ref		
Model 3	≤32	28	-59.8	-121, 1.58	0.06	-0.60	-1.15, -0.06	0.03	14.39	-5.01, 33.8	0.15
	33-34	43	7.06	-44.0, 58.1	0.79	-0.04	-0.49, 0.42	0.88	-0.25	-16.4, 15.9	0.98
	35-36	99	-13.7	-45.9, 18.5	0.41	-0.20	-0.49, 0.08	0.16	-0.23	-10.4, 10.0	0.96
	Term	2263				Ref			Ref		
Model 4	≤32	28	-58.7	-120, 2.81	0.06	**-0.58**	**-1.12, -0.03**	**0.04**	14.60	-4.85, 34.0	0.14
	33-34	43	6.93	-44.1, 58.0	0.79	-0.04	-0.49, 0.41	0.87	-0.36	-16.5, 15.8	0.97
	35-36	98	-13.9	-46.2, 18.5	0.40	-0.20	-0.49, 0.08	0.16	0.05	-10.2, 10.3	0.99
	Term	2261	Ref			Ref			Ref		

Model 1: adjusted for single or multiple births, intrauterine growth restriction status, admission to the neonatal unit and maternal smoking in pregnancy
Model 2: as model 1 but additionally adjusted for body mass index, and season of accelerometry data collection
Model 3: as model 2 but additionally adjusted for ethnicity, maternal education and socio-economic status (mother's last known employment)
Model 4: as model 3 but additionally adjusted for current wheeze, atopy
*MVPA beta values are square root transformed

Table 5-6 Univariate analysis of confounders and their association with levels of physical activity (females)

	Total PA			MVPA			Sedentary		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
SDS Birthweight	1.38	-3.21, 5.98	0.56	0.004	-0.04, 0.05	0.85	-1.56	-3.15, 0.03	0.06
IUGR									
<10th Centile	-15.6	-33.1, 1.86	0.08	-0.09	-0.25, 0.06	0.23	5.33	-0.66, 11.3	0.08
≥10th Centile	Ref			Ref			Ref		
Singleton									
Singleton	24.9	-5.12, 55.3	0.11	0.13	-0.14, 0.40	0.34	**-11.8**	**-22.4, -1.33**	**0.03**
Multiple	Ref			Ref			Ref		
NNU Admission									
Yes	-15.0	-32.5, 2.53	0.09	**-0.17**	**-0.33, -0.02**	**0.03**	5.30	-0.78, 11.4	0.09
No	Ref			Ref			Ref		
Maternal Smoking									
Yes	**18.0**	**7.14, 29.0**	**0.001**	**0.12**	**0.02, 0.21**	**0.02**	**-4.38**	**-8.13, -0.63**	**0.02**
No	Ref			Ref			Ref		
Social Class (Mothers last employment)									
Manage & Prof	**-20.7**	**-32.8, -8.69**	**0.001**	**-0.15**	**-0.25, -0.04**	**0.008**	**9.41**	**5.22, 13.6**	**<0.001**
Intermediate	-7.92	-22.2, 6.32	0.28	-0.08	-0.21, 0.05	0.23	4.23	-0.71, 9.18	0.09
Small emp/self em	-4.49	-24.3, 15.4	0.66	-0.05	-0.22, 0.13	0.61	0.67	-6.22, 7.56	0.85
Lo sup/technical	-4.24	-28.7, 20.2	0.73	-0.05	-0.27, 0.16	0.63	1.86	-6.62, 10.3	0.67
Routine	Ref			Ref			Ref		

Ethnicity									
White	**36.2**	**21.1, 51.4**	**0.001**	0.11	-0.02, 0.25	0.11	**-6.90**	**-12.2, -1.64**	**0.01**
Other	Ref			Ref			Ref		
Age	**-37.6**	**-57.5, -17.7**	**0.001**	**-0.25**	**-0.43, -0.08**	**0.005**	**13.7**	**6.84, 20.6**	**0.001**
Wheeze at 7									
Yes	7.50	-9.32, 24.31	0.38	0.06	-0.09, 0.21	0.45	-4.05	-9.87, 1.77	0.17
No	Ref			Ref			Ref		
BMI at 7	**-3.03**	**-5.30, -0.76**	**0.009**	**-0.04**	**-0.06, -0.02**	**<0.001**	-0.41	-1.20, 0.38	0.31
Season of accelerometry									
Winter	-96.7	-116, -77.4	**<0.001**	-0.82	-0.10, -0.65	**<0.001**	**26.4**	**19.7, 33.2**	**<0.001**
Autumn	-90.1	-107, -73.6	**<0.001**	-0.70	-0.85, -0.55	**<0.001**	**28.3**	**22.5, 34.0**	**<0.001**
Summer	-27.8	-43.9, -11.8	**<0.001**	-0.29	-0.43, -0.14	**<0.001**	5.54	-0.03, 11.1	0.05
Spring	Ref			Ref			Ref		
Mothers Education									
None	25.7	-0.44, 52.0	0.05	0.21	-0.03, 0.44	0.08	**-18.9**	**-27.9, -9.82**	**<0.001**
Other	-30.3	-68.4, 7.86	0.12	-0.20	-0.54, 0.14	0.25	-1.30	-14.5, 11.7	0.85
GCSE G-D	19.7	-7.59, 47.0	1.16	0.12	-0.12, 0.36	0.32	**-14.7**	**-24.1, -5.27**	**0.002**
GCSE A-C	18.78	-4.76, 42.3	0.12	0.08	-0.12, 0.29	0.43	**-15.3**	**-23.4, -7.16**	**<0.001**
A/AS level	-10.7	-37.1, 15.6	0.42	-0.14	-0.37, 0.10	0.25	-4.37	-13.5, 4.73	0.35
Higher diploma	7.78	-18.9, 34.4	0.57	-0.01	-0.24, 0.23	0.96	-8.36	-17.6, 0.84	0.08
First Degree	5.64	-19.1, 30.3	0.65	0.02	-0.20, 0.24	0.87	-8.14	-16.7, 3.39	0.06
Higher degree	Ref			Ref			Ref		

Table 5-7 Results of general linear models regressing activity variables on gestation groups adjusting for confounders (females)

FEMALES	n		Total PA			MVPA*			Sedentary		
			ß	95% CI	p-value	ß	95% CI	p-value	ß	95% CI	p-value
Model 1	≤32	27	-39.4	-98.5, 19.7	0.19	-0.27	-0.80, 0.24	0.30	18.01	-2.27, 38.3	0.08
	33-34	47	-26.0	-72.3, 20.4	0.27	-0.24	-0.65, 0.17	0.26	11.77	4.12, 27.6	0.15
	35-36	101	16.7	-13.3, 46.7	0.27	0.21	-0.05, 0.48	0.11	-2.18	-12.5, 8.10	0.68
	Term	2456	Ref			Ref			Ref		
Model 2	≤32	27	-43.2	-100, 14.0	0.14	-0.32	-0.83, 0.19	0.21	18.0	-1.47, 37.7	0.07
	33-34	47	-25.5	-70.3, 19.2	0.26	-0.24	-0.64, 0.16	0.24	11.2	-4.27, 26.6	0.16
	35-36	101	17.9	-11.1, 46.8	0.23	0.22	-0.04, 0.48	0.09	-2.62	-12.6, 7.37	0.61
	Term	2453	Ref			Ref			Ref		
Model 3	≤32	26	-35.6	-93.3, 22.1	0.23	-0.29	-0.81, 0.22	0.27	16.7	-3.16, 36.9	0.10
	33-34	40	0.83	-46.7,48.3	0.98	0.01	-0.42, 0.43	0.98	5.11	-11.3, 21.5	0.54
	35-36	92	7.73	-22.4,37.9	0.62	0.13	-0.14, 0.40	0.36	0.19	-10.2, 10.6	0.97
	Term	2323	Ref			Ref			Ref		
Model 4	≤32	26	-35.2	-92.9, 22.6	0.23	-0.29	-0.81, 0.23	0.27	16.9	-3.11, 36.9	0.10
	33-34	40	0.38	-47.2, 47.9	0.99	0.002	-0.43, 0.43	0.99	6.36	-10.1, 22.8	0.45
	35-36	92	8.00	-22.1, 38.1	0.60	0.13	-0.14, 0.40	0.36	0.40	-10.1, 10.9	0.94
	Term	2320	Ref			Ref			Ref		

Model 1: adjusted for single or multiple births, intrauterine growth restriction status, admission to the neonatal unit and maternal smoking in pregnancy

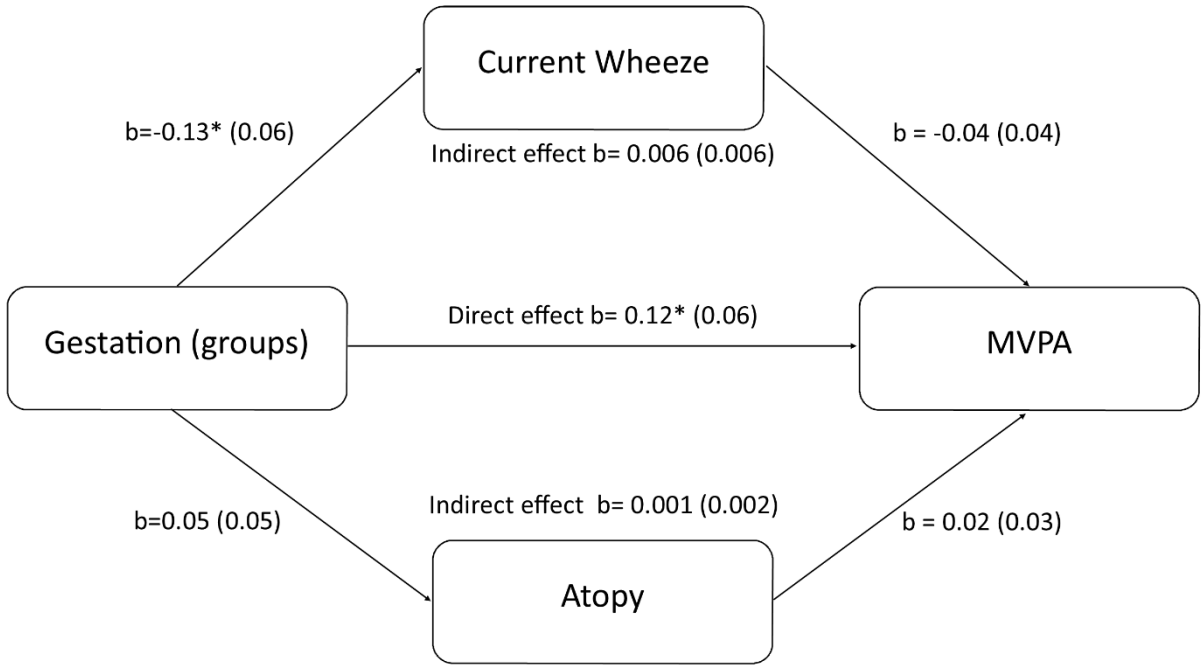
Model 2: as model 1 but additionally adjusted for body mass index, and season of accelerometry data collection

Model 3: as model 2 but additionally adjusted for ethnicity, maternal education and socio-economic status (mother's last known employment)

Model 4: as model 3 but additionally adjusted for current wheeze, atopy

*MVPA beta values are square root transformed

The results of the mediation analyses confirm the outcome of the general linear modelling presented above. Although gestational age was found to be a significant predictor of increased wheeze in boys, there was no evidence that wheeze or atopy mediated the association between gestational age and MVPA (indirect effect for wheeze ß= 0.006 p=0.3; indirect effect for atopy ß= 0.001 p=0.7: Figure 5-3). The mediation analyses for both males and females on both MVPA and sedentary behaviour are shown in Figure 5-4, Figure 5-5, and Figure 5-6).



Values in parenthesis are standard errors

* p< 0.05

Figure 5-3 Mediation analysis of the effects of wheeze and atopy on the association between gestational age at birth and levels of MVPA in 7-year old boys. The direct effect of gestational age on MVPA was significant, however, current wheeze, nor atopy mediated this relationship.

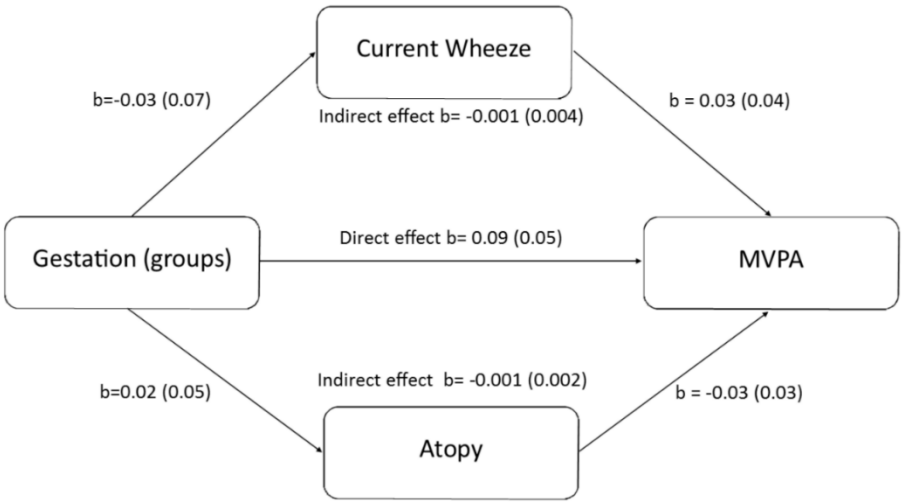


Figure 5-4 Mediation analysis of the effects of wheeze and atopy on the association between gestational age at birth and levels of MVPA in 7-year old girls. The direct effect of gestational age on MVPA was not statistically significant, commensurate with the results of the general linear model (Table 5-7). There was no evidence of mediation through current wheeze and atopy.

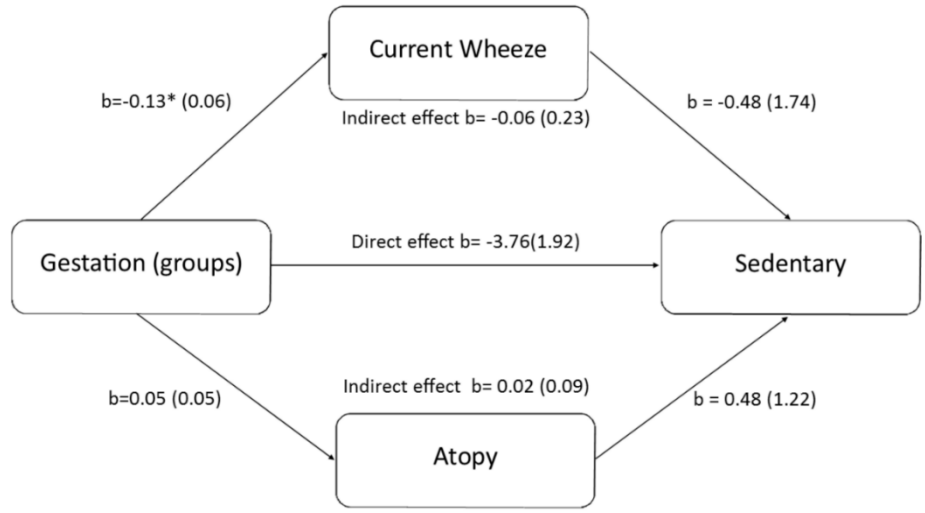


Figure 5-5 Mediation analysis of the effects of wheeze and atopy on the association between gestational age at birth and levels of sedentary behaviour in 7-year old boys. Gestational age was not significantly associated with sedentary behaviour (direct effect), are per results of the general linear model (Table 5-5). There was no evidence of mediation through current wheeze and atopy.

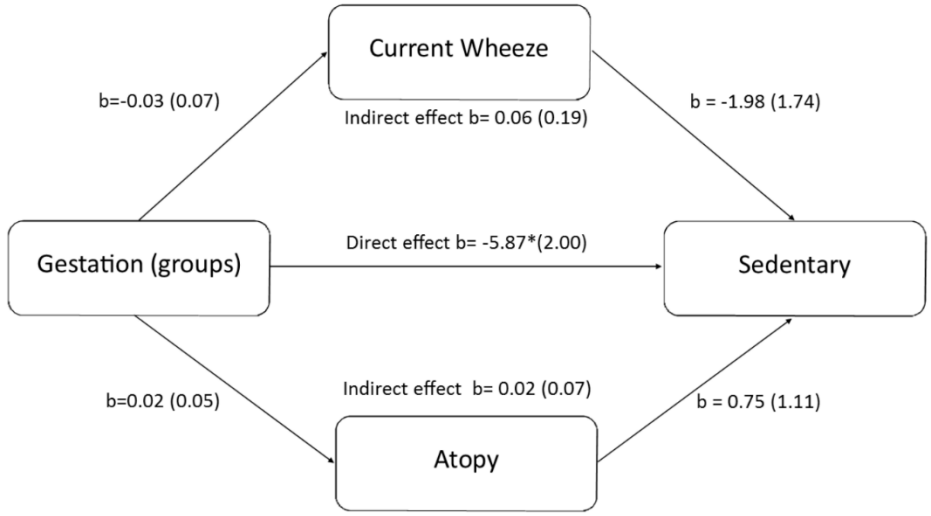


Figure 5-6 Mediation analysis of the effects of wheeze and atopy on the association between gestational age at birth and levels of sedentary behaviour in 7-year old girls. The direct effect, which represents the association between decreasing gestational age on levels sedentary behaviour, adjusted for current wheeze and atopy, was statistically significant. However, there was no evidence of mediation by current wheeze and atopy (both indirect effects non-significant).

5.5 Discussion

Using data from a large cohort study of children born during the surfactant era, I have shown that birth at ≤32 weeks' gestation is a statistically significant factor in predicting reduced levels of MVPA in 7-year old boys after adjustment for birth, growth and socio-economic factors. This equated to approximately a one-hour difference in MVPA over the course of a week between boys born at ≤32 weeks' gestation when compared to those born at term. There was also some association between decreased levels of total physical activity and increased levels of sedentary behaviour in boys born at ≤32 weeks' gestation when compared to those born at term; these were not statistically significant in the fully adjusted models. None of the above findings were replicated in females.

In the previous chapter, the analysis using data from the ALSPAC study showed no differences in Total PA, MVPA or sedentary behaviour in 11-15 year-old preterm-born children when compared to term controls. The decrements in lung function previously observed in preterm-born children within ALSPAC were also not correlated with reduced activity. However, overall levels of activity were low. In contrast, children participating in the MCS showed significantly higher levels of MVPA, meeting or exceeding the recommended guidelines. In comparison, another UK-based cohort of 7 year old children conducted by Basterfield et al. showed that only 10% of boys and 3% of girls met the national guidelines for MVPA when the cut-point was set at 3,200cpm (Basterfield et al., 2011).

There are a number of possible reasons for these differences. Firstly, the 15 second data collection epoch used in the current study is more likely to detect MVPA, which occurs in short, sporadic bursts in young children (Riddoch et al., 2004). This may be reflected in the differences in proportions of vigorous activity making up MVPA (32% of MVPA in MCS and 7% in ALSPAC). Secondly, the cut-point used to derive the MVPA variable are lower (>2241cpm) in the MCS, possibly leading to an over-estimation. When the thresholds used by Basterfield were applied to the MCS data, the proportion of boys and girls meeting MVPA guidelines decreased from 63% and 38% to 14% and 0.4% respectively (Griffiths et al., 2013). Longitudinal data from Basterfield et al. also demonstrated a significant decrease in MVPA and a rise in sedentary behaviour between the ages of 7 and 9 years. One possible explanation for these differences is that younger children are more likely to spend time in habitual 'free-living' play activities than 9 or 11 year olds who are undergoing a transition to middle/high school education with formalised physical education lessons, heightened social pressures, and increased exposure to screen-based activities.

Similarly, differences in sedentary behaviour between cohorts are difficult to compare due to variation in the accelerometer cut-point used, for example: <100cpm in the MCS, <200cpm in ALSPAC and <1100 in the Gateshead Millennium Study (Basterfield et al., 2011), the latter of which captures a proportion of light intensity PA as defined in the MCS or ALSPAC. Although I also did show that the ≤32 weeks' gestation group had increased levels of sedentary behaviour compared to term-born boys, this association was not robust to the addition of other explanatory variables in terms of maintaining statistical significance. However, this still does equate to over 14 minutes of additional sedentary time per day for the ≤32 weeks' gestation group compared to term-born controls. This could reflect a preference for this group of children to choose to spend less time active.

It is interesting that markers of lower socio-economic status (maternal smoking history) were associated with less time spent in sedentary behaviour and increases in total PA and MVPA. In contrast, markers of higher status (mother's last known employment, higher level of maternal education) where associated with decreased Total PA, decreased MVPA, and increased sedentary time. Children of non-white ethnicity was also significantly associated with lower Total PA and more time spent sedentary. The observed differences between socio-economic groups were small and without a clear trend, consistent with previous studies (Riddoch et al., 2007). Sedentary behaviour is not merely the absence of PA, but reflects a specific engagement in activities of low energy expenditure (Reilly et al., 2008), and may be highly dependent upon the context of the activity. For example, having a parent with higher levels of education has been associated with increased sedentary behaviour during school hours, whereas increased MVPA during the same period has been associated with children from families of lower socio-economic status (Pulsford et al., 2013). More research is warranted in this area to determine the reasons for differences in PA between socio-economic and ethnic groups.

In a recent study by our group, increased rates of exercise-induced bronchoconstriction and reduced levels of PA in preterm-born children were observed using data from a self-completed questionnaire (Joshi et al., 2013). This led me to propose the hypothesis in this thesis that experiencing such symptoms of airway obstruction on exertion is a conceivable pathway to reduced levels of activity. A previous study described that children with asthma may exercise less to avoid the unpleasantness of these sensations (Glazebrook et al., 2006). Other questionnaire-based studies also support the hypothesis that preterm-born children consider themselves less active. Clemm et al. and Welsh et al. both demonstrated reduced levels of self-reported PA; however, both these studies included only children with ≤28 weeks' and <26 weeks' gestation, respectively (Clemm et al., 2012, Welsh et al., 2010). Furthermore, in the latter study, questionnaire responses did not correlate with accelerometry which may be attributed to the differing types of activity recorded when using subjective or objective methods (Riddoch et al., 2004).

Somewhat surprisingly, my findings suggest that despite preterm-born children demonstrating significantly increased rates of current wheeze, this was not a mediating factor in the relationship between gestational age and levels of physical activity. It is likely that the reporting of respiratory symptoms at the time of assessment was accurate as the questionnaire used in the MCS is well validated and collected during a home visit where answers could be clarified. Although it is difficult to compare my study with those focusing on low birthweight, such studies often contain a significant proportion of participants who were born preterm, especially in the very low birthweight and extremely low birthweight groups (<1500g and <1000g birthweight, respectively). A summary of these studies showed that reductions in exercise capacity were present from an early age - consistent with the modest differences found in our recent systematic review (Edwards et al., 2015b). This may

reflect the ability of the cardio-respiratory system to compensate for any airway obstruction during exertion, especially due to the availability of ventilatory reserve (Joshi et al., 2013); however, this is accompanied with a diminished ability to perform tests of motor function and strength-based tasks, with differences in habitual physical activity only manifesting from adolescence onwards (Siebel et al., 2012). Other potential mediators of PA in preterm-born children, therefore, may include differences in body composition such as muscle mass and fat mass (Bott et al., 2007), and limitations imposed by neurodevelopmental sequelae of preterm birth (Rogers et al., 2005, Burns et al., 2009). Similar reasons could possibly help to explain why in my results, lower levels of MVPA in preterm-born boys born at ≤32 weeks' gestation but not in girls. Peacock et al. suggested that respiratory and neurological outcomes following preterm birth may be worse in males than in females, especially at the extremes of gestation (Peacock et al., 2012). Also, sex-typed behaviour emerges early in childhood and 'male typical' activities have been linked to increased levels PA by late childhood (Mattocks et al., 2010); it is conceivable that preterm-born boys with milder forms of developmental coordination disorder, which has been linked to decreased MVPA, spend less time in male typical activities due to reduced self-perception of abilities and difficulties with keeping up with their peers (Green et al., 2011).

Notwithstanding, since PA has the potential to improve cardio-respiratory health, preterm-born children should be encouraged to participate in adequate levels in order to develop positive attitudes towards exercise. Although the 9-minute difference in MVPA per day in boys of ≤32 weeks' gestation was small, this equated to over 1 hour a week and this may have some clinical utility. An increase of 9 minutes would improve the proportion of preterm-born boys meeting daily MVPA recommendations from 55% to approximately 73%. Achieving such improvements may be of heightened importance given the clear

evidence of a steep decline in PA which has been observed during adolescence and consistent reporting of decrements in exercise capacity and PA in preterm-born adults. Both point towards detraining of the cardio-respiratory system which may have implications for the development of early-onset chronic respiratory disease and thus deserves further surveillance. The benefit of introducing active plans to promote PA in preterm-born children also needs evaluation.

5.6 Strengths and limitations

The main strengths of the work presented in this chapter are the use of recent data from a large contemporary cohort which sampled from the whole of the UK and from a diverse range of socio-economic backgrounds. The Actigraph device used has been well validated and in contrast to other studies (including that in chapter 4) used a shorter sampling epoch thus allowing for capture of shorter periods of MVPA. One limitation is the accelerometer required removing for contact sports or water-based activities, and does not capture bicycle riding adequately. However, the age of children in this study makes participation in contact sports less likely than those conducted in older cohorts. In any case, these data reflect habitual activity rather than sports participation. Additionally, the sample was taken from a proportion of the MCS who participated in the home visit and provided valid accelerometry data; the study by Rich et al. showed that non-consent rates were higher in children with a limiting illness or disability (Rich et al., 2013a). Such selection bias reduces the possibility of including children with severe physical or cognitive impairments. In common with many longitudinal studies, there is some attrition over time and my analyses are limited by the data available. Other data on socio-economic status such as the Index of Multiple Deprivation were available but this is calculated differently in the four devolved nations of the UK. Although the participants included in my analyses were of higher socio-economic status it is reasonable to consider that the results are generalisable as lower

socio-economic status was associated with increases in physical activity (Griffiths et al., 2013). Finally, although banding of gestation into categories will result in a small degree of misclassification, treating of the data in this manor is reflective distinct stages of lung development and allows comparison with other studies.

5.7 Summary and conclusions

In conclusion, I have shown small but important differences in objectively measured physical activity in 7-year old boys who were born very preterm when compared to term-born controls. Children born in the MCS reflect the more immature graduates of modern neonatal care including gentler ventilation, maternal antenatal corticosteroid administration and exogenous surfactant therapy. The difference in cut-points for levels of activity make comparisons of similar studies difficult; however, it appears that preterm-born children are capable of participating in adequate levels of habitual physical activity. This requires surveillance due to the declines in PA and increased sedentary behaviour that have been shown to occur throughout childhood and adolescence.

6 General Discussion

The aim in this final chapter is, firstly, to summarise results from each of my studies and detail my key contributions. Secondly, I shall contextualise these within the scope of the current literature. After considering the strengths and limitations of my work, I will discuss the clinical relevance of my results on the management of preterm-born children and suggest areas of future study. The sections on strengths and limitations, and clinical relevance are combined for Chapters 2 & 3, and 4 & 5, as they present complementary data. I shall conclude with a brief thesis summary.

6.1 Chapter 2: Association of foetal size and growth trajectory with respiratory symptoms in preterm-born and term-born children

6.1.1 Overview and principal findings

In this first study, my principal question was: *"Does foetal size, or growth trajectory, predict increased incidence of respiratory symptoms in preterm-born children?"* The rationale for this question was based upon the 'developmental origins of health and disease hypothesis', which describes that adverse insults *in utero*, and the timing of these events, have a profound impact on the developing foetus. Moreover, the foetus makes developmental adaptations to mitigate this adversity in order to protect developing organs and systems. Such programming of development may be detrimental to future health if conditions after birth do not match those during gestation. Historically, studies investigating foetal origins of disease have used birthweight as a proxy for foetal growth. More recently, foetal biometry, obtained from antenatal ultrasound scans, has found favour as a research tool to study the association with later health outcomes. The results of these studies in relation to the respiratory system, the focus of this thesis, have been mixed; however, two studies noted that foetal growth restraint between the first and second, or second and third trimesters were related to poorer

respiratory outcomes in childhood. Preterm-born children undoubtedly have increased respiratory sequelae in childhood and are more likely to be born small for gestational age, an indication of poor growth during foetal life. Thus, I decided to investigate if foetal size and growth trajectory, particularly growth faltering (deceleration) in preterm-born children would impact on the incidence of respiratory symptoms including wheeze, use of inhaled medication, and hospital admissions for chest-related problems. Contrary to this hypothesis, I noted that both growth acceleration and deceleration were associated with increased respiratory morbidity in preterm born children. Specifically, accelerated growth (>0.67 SD increase in foetal measurement) from the first trimester until birth was associated with increased wheeze-ever (OR 2.21 95%CI 1.25, 2.32). When growth patterns between trimesters were investigated, growth deceleration between the 1st and 2nd trimester was associated with increased wheeze-ever (OR 1.59 95% CI 1.01, 2.51). Increased risk for wheeze-ever was noted when growth was accelerated between the 2nd and 3rd trimester (OR 1.60 95% CI 1.15, 2.22).

6.1.1.1 ***Comparison with other studies***

The mechanisms behind the observed associations between foetal growth and respiratory outcomes in epidemiological studies are not known. However, maternal smoking during pregnancy is strongly associated with IUGR birth. Both epidemiological and animal models point to the adverse influence of nicotine on the developing respiratory system, with the effects on respiratory health persisting into childhood and beyond (Maritz and Harding, 2011). Researchers from the Generation R study identified that continued maternal smoking during pregnancy was associated with increased risk of wheezing in early childhood (Duijts et al., 2012).

Data from large cohort studies have recently provided proof-of-concept that the use of foetal biometry is valid as a research method in assessing the impact of growth on later health

outcomes. However, mine is the first to specifically assess foetal growth patterns in preterm-born children and thus difficult to compare with the existing literature. In common with the Aberdeen cohort, my study relied upon routinely collected data; unfortunately, due to the limitations of the available databases, I was unable to obtain ultrasound reports for all participants. Moreover, the standard scanning protocols dictated that different measurements were available in each of the 1st trimester and 2nd trimester scans. This limited the application of a more statistically sophisticated measure of growth change such as that proposed by Royston (Royston, 1995), since the multilevel modelling required uses raw data as oppose to standardised scores. Therefore, I opted to use the same method of assessing growth change as the Generation R cohort (>0.67 SD change) under the assumption that z-scores (adjusted for gestation and gender) of crown-rump length, head circumference or femur length, and birthweight are compatible measures of growth. Foetal biometry was collected prospectively in all three trimesters in both the Rotterdam and Southampton cohorts under a research protocol. Third trimester scans are not routine in standard antenatal care. In any case, in reference to the preterm-born population included in the RANOPS study, the mean gestation of those with foetal biometry was 34 weeks' (Table 2-1), the same gestation at which 3rd trimester scans were performed in the Southampton study. Thus, a future study investigating the associations of preterm birth, foetal growth and later health outcomes would necessarily have to have an adapted protocol such that serial scans are performed earlier in pregnancy, perhaps at approximately 30 weeks' gestation. An interesting finding within the Southampton cohort was that growth faltering in the first to second trimester was linked to non-atopic wheeze, whereas faltering in the second to third trimester was associated with atopic wheeze. This is consistent with my results which noted that growth deceleration between the 1st and 2nd trimester was similarly associated with increased wheeze-ever. Both acceleration and deceleration from the 2nd to 3rd trimester were associated with wheeze-ever. To date, the RANOPS cohort does not have any direct data on atopic status (i.e. results of skin prick

testing), however family history of atopy was abstracted from the questionnaire. Although this was strongly related to respiratory outcomes in univariate analysis (Table 2-3), family history of atopy was not significant in the statistical analysis performed when modelling with measures of foetal growth change. This is in keeping with the primary analysis of the RANOPS cohort which established that 'prematurity-associated wheeze' phenotype is unlikely to include atopy as one of its determinants (Edwards et al., 2016).

Nutrition is another key determinant of foetal growth (Lumey et al., 2007) and may be sub-optimal due to a combination of maternal stature (underweight/overweight), dietary intake, and placental insufficiently. Animal models note that extreme restriction of nutrients significantly affects lung growth and development (Lechner, 1985). The role of specific food groups in benefiting *in utero* respiratory development is not defined, however, a varied diet with limited amount of processed foods, but high in fish and vegetables including antioxidants, may be optimal (Netting et al., 2014). The study of the Aberdeen cohort noted that maternal serum levels of the micronutrient vitamin E in the lowest quartile was associated with decreased CRL in the first trimester when compared to vitamin E levels in the highest quartile (Turner et al., 2010). The same group had previously demonstrated that deficits in maternal vitamin E intake was associated with increased incidence of wheeze-ever at 5 years of age (Devereux et al., 2007). A possible mechanism may include removal of oxidant species, such as those found in tobacco smoke. For example, pre-and-post natal antioxidant-rich dietary supplementation prevented nicotine-related lung damage in rat models (Maritz et al., 2011).

6.2 Chapter 3: Associations between infant weight gain and childhood respiratory symptoms in preterm-born and term-born children

6.2.1 Overview and principal findings

The research question for my second study was*: "Following preterm birth, is weight gain in infancy associated with increased respiratory symptoms later in childhood? What are the*

important factors mediating this relationship?" These investigations were based upon the growing evidence base regarding the influence of postnatal weight gain during infancy on respiratory health in childhood and beyond. The management of growth of preterm infants both on the neonatal unit and post-discharge is challenging to health professionals and the optimal rates of growth are not known; thus, investigating the effect of rapid weight gain specifically in a preterm-born cohort of children would answer an important question. The results of my study were in line with the stated hypothesis, that infant weight gain between birth and 9 months of age was indeed associated with increased respiratory symptoms. Specifically, a >0.67 SD gain in weight between birth and 9 months of age was associated with increased wheeze-ever (OR 1.22; 95% CI 1.02, 1.45) in preterm-born children. The association appeared to be greatest in the ≥5 years of age group. Furthermore, the combination of birth at the extremes of gestation (≤32 weeks' gestation) and rapid weight gain resulted in the poorest respiratory outcome when compare to term-born controls (OR 5.04; 95% CI 3.36, 7.54). This trend was present across the continuum of gestational age.

To compare my results with other studies, I conducted similar analysis with the available data in term-born children and noted that >0.67 SD weight gain was significantly associated wheeze-ever (OR 1.38; 95% CI 1.13, 1.69). The combination of 'early term' birth (37-38 weeks' gestation) and rapid infant weight gain also resulted in a poorer respiratory outcome, with an OR of 2.25 (95% CI 1.48, 3.48) for wheeze-ever compared to children born at term.

Finally, by conducing mediation analysis, I identified gestational age at birth and current maternal smoking as modifiable factors through which the association between rapid infant weight gain and increased wheeze in preterm-born children may, in part, be explained.

6.2.2 Comparison with other studies

My results are in keeping with the other studies investigating the association between accelerated infant weight gain and respiratory health in childhood. However, the majority of studies did not focus on preterm-born children, with the exception of the meta-analysis performed by Sonnenschein-Van der Voort et al. (Sonnenschein-van der Voort et al., 2014). I opted to measure weight gain between birth and approximately 9 months of age, a period of rapid growth. The analyses were repeated using weight gain between birth and 24 months as lung development in terms of alveolar number increases rapidly during this period (Lucas et al., 2004). Moreover, the majority of catch-up growth has occurred by two years of age (Taal et al., 2013, den Dekker et al., 2016) and performing this analysis would allow for comparison to other studies who monitored a similar period of growth (Flexeder et al., 2012, Claudia et al., 2016, Magnus et al., 2015). In my analysis, a difference of >0.67SD in weight z-score was used to quantify accelerated weight gain, a parsimonious and easily interpretable measurement which is used clinically to monitor growth change. However, since more statistically complex methods have been recently used, I opted to use a multilevel modelling approach as described by Royston to validate my results. This allowed the use of all the available weight data, but also allowed the inclusion of each participant regardless of the number of datapoints available, in contrast to other recently employed methods.

My results indicated that accelerated weight gain up to 9 months of age was associated with respiratory symptoms in both preterm and term-born children after adjustment for potential confounders. When weight gain between birth and 24 months was used as the primary exposure variable, few outcomes were statistically significant. However, it is worthy of note that a number of associations were of a similar magnitude to the results presented at 9 months of age. Fewer participants were included in the analysis at 24 months (e.g. n=3425 at 9 months and n=1819 at 24 months), therefore, the sample size may have been insufficient and reduced the precision of the effect estimates. Another possibility is that the majority of lung

growth may have occurred during the first 9-12 months of life, thus associations with increased respiratory symptoms were stronger than those observed when weight gain was defined over a period of 24 months. Comparing studies is complicated by the variation in the period over which weight gain is measured. Notwithstanding, my results are consistent with studies where the respiratory outcome, manifesting as increased symptoms or reduced lung function, is measured in early childhood (van der Gugten et al., 2012, Magnus et al., 2015, Pike et al., 2010), at school age (Magnus et al., 2015, Popovic et al., 2016, Flexeder et al., 2012, Belfort et al., 2016), and in adolescence (Claudia et al., 2016). Thus, there appears to be tracking of the effect of rapid infant weight gain on respiratory health at least until the age of 15 years, and potentially beyond. With the exception of the study by Belfort, all were conducted in term-born children only. This study noted that rapid BMI gain in the first year of life, but not linear growth, was associated with higher odds of asthma at four years of age (Belfort et al., 2016). These results suggest that gain in somatic mass may be impacting upon the developing respiratory system. Furthermore, a study using data from the Generation R cohort reported that accelerated weight gain in the neonatal period, between birth and term-equivalent gestational age, was associated with markers of cardiovascular disease and diabetes in preterm-born young adults (Kerkhof et al., 2012). Similar results were noted with weight gain in the first year of life, which was associated with increased percentage body fat and higher serum triglyceride levels.

An emerging theme from the results of my work and others is the potential role of accelerated weight gain in defining phenotypes of lung disease. Phenotypes have been well defined within the term-born population (Henderson et al., 2008), however data are lacking describing patterns of symptoms in preterm-born children. Within this context, my results raise the question of whether rapid weight gain within the first year of life predisposes to a particular wheeze phenotype, whereas a similar magnitude of weight gain over a longer period (e.g. two years), does not. Interestingly, the cross-sectional data from the RANOPS cohort used in my

analysis identified a stronger effect of weight gain on 'wheeze-ever' in preterm-born children ≥5 years of age compared to those <5 years of age. A similar effect was observed in the term born population, however, the magnitude of the difference between the two age groups was smaller. In both instances, the odds of doctor-diagnosed asthma in children aged ≥5 years tended to be related to weight gain in the preterm group (OR 1.21; 95% CI 0.89, 1.64, Table 3-4) and was significantly related in the term-born group (OR 2.02; 95%CI 1.37, 2.98, Table 3-9). Thus, one possible explanation of the increased effect size in children aged ≥5 years could be an emerging 'asthma-related' phenotype of which accelerated infant weight gain is one potential determinant.

To date, degree of prematurity is not included in methods of predicting later asthma (Castro-Rodriguez, 2010), whereas paediatricians consider this information crucial in assessing the nature of early (Bush and Nagakumar, 2016) and late respiratory disease (Bolton et al., 2015). My results demonstrate that lower gestational age impacted on the effect of weight gain on childhood respiratory health across the spectrum, including in children born 'early term' (37-38 weeks'). This finding is pertinent due to the rising number of births during this period, especially due to increased rates of caesarean section and growing evidence to suggest that relative immaturity, as opposed to caesarean section delivery, explains the increased respiratory symptoms in such children (Edwards et al., 2015a).

Another theme relates to the mechanisms whereby accelerated weight gain may impact on childhood respiratory health. Infants with reduced lung function in the first weeks and months of life have poorer respiratory outcomes in childhood (Turner et al., 2008, Haland et al., 2006), especially those born at low birthweight (Lucas et al., 2004). The decrements appear to track into adolescence and early adulthood (Stern et al., 2007, Mullane et al., 2013). Since these deficits are present from birth, there is strong evidence that lung growth during foetal life predisposes to adverse respiratory outcomes. Moreover, preterm birth may further

exacerbate the effects of growth restriction due to pulmonary inflammation associated with neonatal respiratory distress and subsequent dysregulated lung growth (Kallen et al., 2013). One explanation is the concept of dysanapsis whereby somatic growth occurs at a faster rate than growth of the airways. As a result the airways are smaller in comparison to lung volume. For example, moderately preterm-born children (32-34 week's gestation) were noted to have no difference in FVC compared to term controls but had reduced forced expiratory flows and lower $FEV_{0.5}$/FVC ratios at two months of age (Friedrich et al., 2007). When these measurements were repeated at 24 months, similar differences were present between the preterm and term-born groups, however, longitudinal analysis revealed tracking of lung size with somatic growth but no catch-up in terms of respiratory function. These data are complemented by other large cohort studies which also identified a disparity between lung volume, airway calibre and poorer respiratory outcomes in childhood (Sonnenschein-van der Voort et al., 2015), including an early wheeze phenotype (Turner et al., 2008). Rapid weight gain in infancy may, therefore, reflect excessive somatic growth which promotes dysanapsis and contributes to the observed decrements in lung function and increased rates of symptoms.

Within the preterm-born population of the RANOPS cohort, the results of my analysis identified current maternal smoking, rather than antenatal smoking, as a mediator of the association between weight gain and increased rates of wheeze. Antenatal smoking was noted to be related to wheeze in univariate analysis ($p<0.10$), but was not significant in the multivariable models. Underestimation of the prevalence of antenatal smoking may explain this lack of effect (Shipton et al., 2009), moreover, women's smoking habits tend not to change such that those who smoke during pregnancy continue to do so postnatally (Le Souef, 2000). Thus, it is difficult to assess these effects independently. Notwithstanding, the deleterious effect of exposure to tobacco smoke on lung health is consistent with other studies in preterm-born (Hoo et al., 1998) and low birthweight children (Caudri et al., 2007). The effects of

nicotine exposure on the developing foetus *in utero* is well described. In relation to lung development, evidence from animal models demonstrates lung hypoplasia, including fewer and larger saccules thus reducing the overall surface for gas exchange (Collins et al., 1985). Also, the structural and functional development of the small airways may be affected (Elliot et al., 2003) leading to poor lung function which is evident soon after birth (Stick et al., 1996). A recent study noted that maternal smoking in pregnancy, and hypertension, were associated with increased rates of BPD/CLD at 36 weeks' postmenstrual age and respiratory disease within the first two years of life (Morrow et al., 2017).

Postnatally, exposure to environmental tobacco smoke has been noted to increase the risk of early wheeze and respiratory tract infections (Tager et al., 1993). Reports from longitudinal analysis of children exposed to parental smoking indicate deficits in lung function, especially in children with wheeze (Sherrill et al., 1992). The mechanisms of how postnatal tobacco smoke exposure affects lung function and increases the propensity for wheezy illness in childhood are not known. However, one possibility with regards to structural development is thickening of the large airway wall, which increases airway resistance (Elliot et al., 1999). Other potential explanations include increased bronchial hyper-responsiveness and increased sensitivity to allergens (Martinez et al., 1992).

As described above, dysanapsis relates to a mismatch between somatic growth (including the lungs), and growth of the respiratory tract. This raises the question, what is the composition of the body mass gained during a period of accelerated weight gain? A recurring theory in the literature is that such weight gain relates to the deposition of excess adipose tissue (Popovic et al., 2016, Claudia et al., 2016, Flexeder et al., 2012, Kerkhof et al., 2012). In the recent study by Gishti, weight gain in infancy was associated with increased total body and abdominal fat mass (Gishti et al., 2014). This may impose an additional deleterious effect on lung health by increasing the mechanical pressure on the lungs and diaphragm, thus decreasing functional

residual capacity and increasing the inspiratory effort required to achieve normal tidal volumes (Vijayakanthi et al., 2016).

A more complex notion is the modulation of immune pathways through release of pro-inflammatory agents, such as leptin, from adipocytes (Guler et al., 2004). This may increase susceptibility to early infections such as respiratory syncytial virus (RSV), which are implicated in childhood respiratory disease, especially in those with a history of preterm birth (Gijtenbeek et al., 2015). For preterm-born children, who already have an increased risk of infection (Greenough et al., 2004), this is highly pertinent. The effect of preterm birth on the development of body composition are not widely known, and current results are conflicting. A study by Bott and colleagues reporting on differences in energy expenditure in preterm-born children with BPD/CLD noted reduced fat mass in participants with severe airway obstruction when compared to BPD/CLD children with health controls. In contrast, a study by Vardar-Yagli noted fat-free mass was reduced in children with BPD/CLD but found no differences in fat mass (Bott et al., 2007, Fewtrell et al., 2004, Vardar-Yagli et al., 2015). However, there is strong evidence that excess infant weight gain predisposes to later obesity (Ong and Loos, 2006), which in turn is a risk-factor for respiratory disease. Data from the Isle of Wight birth cohort demonstrated that an early trajectory of obesity from infancy was associated with increased risk of developing asthma in late adolescence (Ziyab et al., 2014). This is possibly in part due to leptin-mediated, systemic low-grade inflammation associated with increased fat mass and an altered metabolic profile (Vijayakanthi et al., 2016). Systemic inflammation has been noted to correlate with reductions in pulmonary function (Rastogi et al., 2012) and increased bronchial hyper-responsiveness (Baek et al., 2011).

6.3 Chapters 2 & 3: Strengths and limitations

The main strengths of my studies presented in Chapters 2 and 3 is the use of data from a large cohort of preterm-born children (RANOPS). This cohort was specifically designed to investigate the respiratory symptomology of such children using validated parent-reported questionnaires. The availability of demographic data from NWIS also allowed for the adjustment of numerous confounders within the statistical analyses I applied. Notwithstanding, no epidemiological study can rule out residual confounding due to unmeasured covariates. For example, particularly relating to foetal growth, it would have been interesting to have data on incidence of maternal complications of pregnancy and labour (e.g. hypertension, pre-eclampsia, chorioamnionitis). However, I was able to include IUGR as a confounder in my analysis and did not note strong associations with respiratory outcomes. The RANOPS cohort sampled the preterm-born population across an age range of 1-11 years, which allowed assessment of my research questions during early childhood and at school-age. This may give some insight in to the differential effects of the exposures I have studied (foetal growth, infant weight gain) on respiratory outcomes at different stages of life. However, it is noted that the data used were cross-sectional rather than longitudinal, thus, separating the cohort in to children aged ≤5 and >5 years of age used different participants in each analysis. This will have limited my ability to accurately study change in effects over time. Despite this limitation, I observed some hypotheses-generating differences between age-groups which warrant further study. Specifically, if foetal growth or infant weight again are associated with a particular phenotype of respiratory disease. Again, longitudinal data are required to explore this question in more detail.

The problems of non-response and loss to follow-up are ubiquitous in cohort studies. The availability of demographic data for the whole cohort (including non-responders to the questionnaire survey) allowed assessment of the generalisability of my results. Within the RANOPS cohort, questionnaire return was linked to higher levels of socio-economic status. The

overall response rate was also noted to be relatively low (27%) and it is possible that responders were families whose children suffer from a relatively increased prevalence or severity of respiratory symptoms. Thus, there is inherent selection bias which may affect my results. However, the incidence of intrauterine growth restriction and preterm birth are higher in mothers of lower socioeconomic status, secondary to alcohol and tobacco smoke exposure, and poor nutrition. Postnatally, infants would also be more likely to be exposed to environmental tobacco smoke, and be more likely to be formula fed. Therefore, one would expect that inclusion of families from disadvantaged backgrounds would strengthen my results rather than weaken them.

My analyses in Chapter 2 used retrospective foetal biometry data which was limited to the routine data collected at antenatal ultrasound clinics. Unfortunately, availability of the data for the whole population of RANOPs questionnaire responders was constrained by restrictions to data access and linkage. No single measurement was available for both scans. Therefore, I opted to standardise each for gestational age and gender, using the difference in z-scores between measurements to calculate growth change. This was under the assumption that each standardised measurement reflected a similar level of growth. It must also be noted that the references growth charts (Altman and Chitty, 1994) used are based upon data collected in England during the late 1980s and early 1990s and may not reflect the population I have studied. However, the same charts are widely used clinically to assess foetal growth, including in Wales, despite reservations by methodologists (Royston, 1995). The availability of serial measurements of a single parameter would have enabled calculation of conditional growth as I later implemented in chapter 3 and as used in the Southampton Women's study (Pike et al., 2010). Similarly, it would have been optimal to investigate change in foetal abdominal circumference and calculate estimate foetal weight to assess IUGR during gestation as well as at birth. A recent study noted that suspected foetal growth restriction, combined with IUGR at birth, was associated with increased rates of BPD/CLD when compared to infants born IUGR

with no evidence of foetal growth restriction, or controls of normal birthweight (Monier et al., 2017). Moreover, I was not able to assess the symmetry or asymmetry of IUGR using, for example, ponderal index ([weight/length^3]*100), as data on birth length was not available. However, it has been noted that birthweight is a better predictor of body asymmetry than ponderal index (Haggarty et al., 2004).

A key strength of my study in Chapter 3 was the volume of measurements which were available for use in modelling weight gain. The large majority of the population included had at least 2 measurements (birthweight, and weight at approximately 9 months of age) to allow calculation of change in weight by comparing z-scores at these timepoints. These z-scores were produced using the UK 1990 reference population which was compiled from a composite of anthropometric studies conducted between the late 1970s and mid 1990s (Cole et al., 1998). Consequentially, these standards may not be appropriate as a reference source for growth in contemporary cohorts of preterm-born infants and children who have undergone a very different neonatal course. However, the UK 1990 population is still favoured for use for monitoring of birthweight and early weight gain in preterm infants as the recently adopted WHO reference charts do not include data from preterm-born children (Wright et al., 2008). The WHO charts are then favoured up to 2 years of age (Standards, 2007). A further strength of my work is calculating the measures of conditional growth change, which avoids the use of reference charts and uses the available data as an internal standard to produce z-scores. The associations observed in this secondary analysis were similar to the parsimonious method of classifying rapid weight gain as >0.67 SD change in weight, which adds validity to my results.

Finally, a further limitation of cohort studies is the ability to only demonstrate association, not causation, due to the effect of measured or unmeasured variables, and due for the possibility of reverse causation. By using mediation analysis, which imposes a system of causal inference between the included variables (Hayes, 2013), I have attempted to ascertain the factors

through which a potential causal relationship between rapid weight gain during infancy and respiratory outcomes in preterm-born children may be explained.

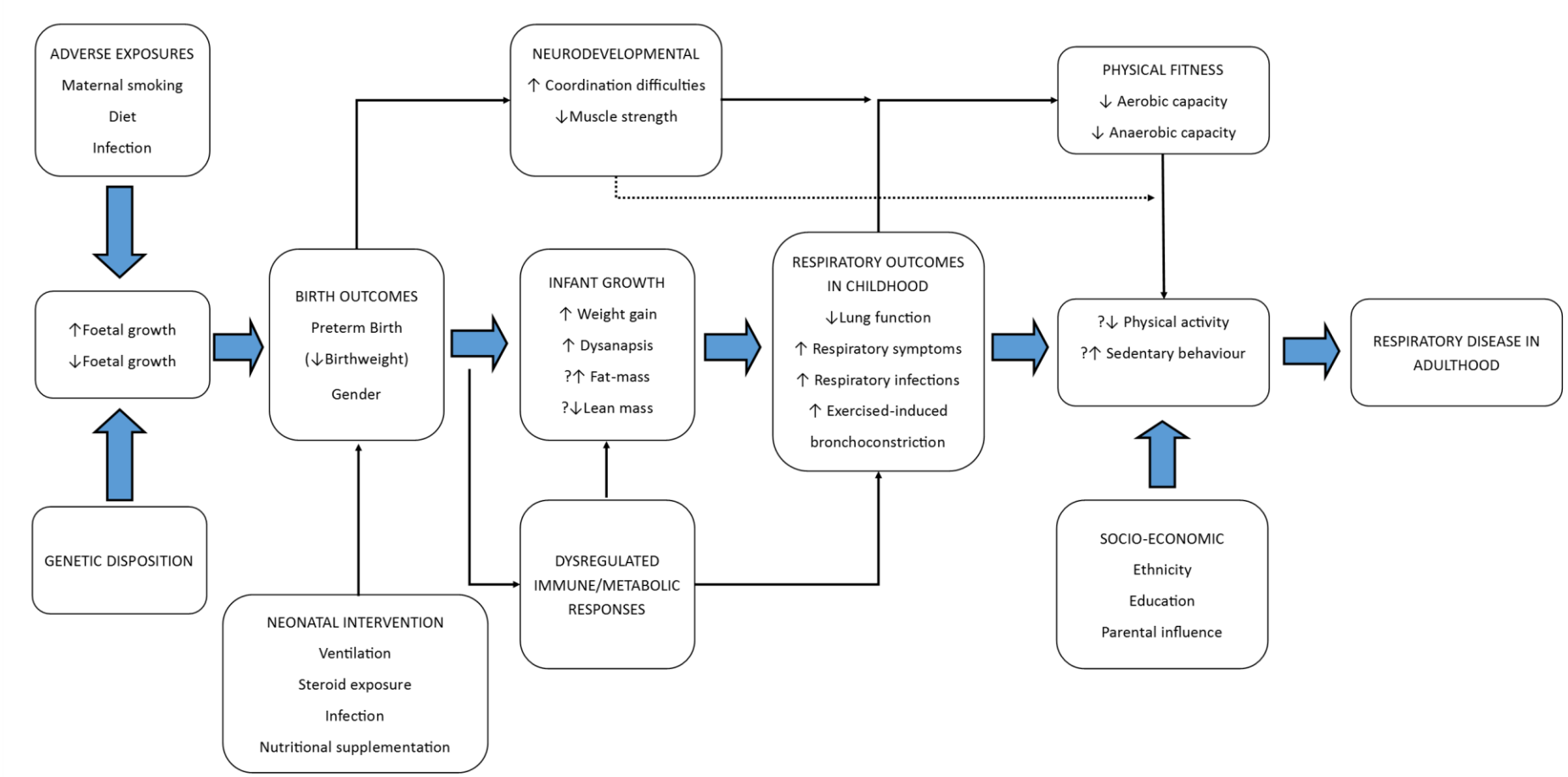


Figure 6-1 Summary of potential factors involved in determining the respiratory health of preterm-born children and later effects on physical activity

6.4 Chapters 2 & 3: Clinical relevance and future work

Within the first half of my thesis, I established the importance of altered foetal growth trajectory, and infant weight gain on respiratory health outcomes in children. My results highlight the additional burden preterm birth imposes on both these measures of development. A conceptual diagram, Figure 6-1, outlines the role of foetal growth and the contribution of known risk factors for adverse birth outcomes, including both prematurity and IUGR, consistent with the "developmental origins of health and disease hypothesis", and that of a "predictive adaptive response". *In utero* modifications to the structural development and maturation of the respiratory system adversely affects respiratory health, with the adverse effects on lung function being evident soon after birth. A 'second hit' occurs if the infant is born preterm and suffers from the associated pulmonary inflammation and respiratory insufficiency, as well as the deleterious effects of the necessary neonatal care. Dysregulated immunological and metabolic processes may contribute to rapid gain in weight early in life, which is coupled to dysanaptic lung growth as well as an increased susceptibility to respiratory infections. These processes culminate in the poor respiratory outcomes observed in preterm-born children which are present across the continuum of gestational age.

Optimising foetal growth by minimising antenatal exposure to noxious substances such as tobacco smoke, and by improving the quality of maternal nutrition, would serve to improve outcomes for many pregnancies where there is an increased risk of preterm birth (McCowan et al., 2009). However, it is acknowledged that reducing the rates of maternal smoking in pregnancy is complex, and is closely linked to levels of social deprivation (Shipton et al., 2009). Initiatives such as the 'Gestation Related Optimal Weight' (GROW) software, developed by the Perinatal Institute Gestation Network, provide valuable tools to assess foetal wellbeing and timing of growth change (Figueras and Gardosi, 2011) which are

customised to the individual foetus. Thus, surveillance strategies which aid in identifying risk factors and markers of poor foetal growth, such as intrauterine growth restriction, are best placed to provide guidance to families and support health professionals (RCOG, 2013). Moreover, this increased surveillance may serve to decrease the risk of preterm birth, especially in late gestation by means of elective caesarean section.

Establishing a feeding regimen in preterm-born infants which represents the rate of *in utero* growth (15g/kg/day) is challenging in the neonatal period. This may be due to the immaturity of the gut and the requirement to rely on parenteral nutrition, and also increased caloric requirements (Agostoni et al., 2010). Once enteral feeds are tolerated, the emphasis is placed upon maximising intake in order to promote growth, however, nutritional deficits are still prevalent (Embleton et al., 2001). Moreover, at term-equivalent age, preterm-born children have been shown to have increased body fat percentage which is largely explained by reductions in fat-free mass (Johnson et al., 2012). Post-discharge, the optimal growth rate for preterm infants is not known (Kleinman, 2009), however, data from the MCS cohort indicate that preterm-born children remain disproportionally shorter and lighter when compared to term-born controls at the ages of three and five years (Boyle et al., 2012) . My results support the notion that carefully balancing the nutritional intake of preterm-born infants to achieve maximal growth, but avoiding disproportionate gain in weight compared to length, may help avoid the potentially deleterious effects of accelerated weight gain whilst supporting overall development (Singhal et al., 2003, Kerkhof et al., 2012). Encouraging, or extending the use of breast milk could support this strategy, especially given the protective effects noted on early respiratory health (Elliott et al., 2008, Dogaru et al., 2012).

Finally, within the literature presented and used for comparison against my results in Chapters 2 and 3, most studies use lung function, or a definition of asthma as the primary

outcome for investigating the effect of foetal growth trajectory and infant weight gain. Asthma is a multi-factorial disease, the symptoms of which may change markedly with age, thus, several phenotypes have been proposed, each of which may have different risk factors (Henderson et al., 2008). Data from the RANOPS cohort (used in the first half of this thesis), and others, have challenged the notion that respiratory symptoms, such as wheeze, in preterm-born children have the same aetiology as asthma (Edwards et al., 2016). For example, preterm-born children have bronchial lability and reversible airway obstruction commonly found in asthma, but do not exhibit eosinophilic airway inflammation (Baraldi et al., 2005). Thus, a future epidemiological study might use longitudinal data to define wheeze phenotypes existing within the preterm-born population and to explore the role of foetal growth and accelerated infant weight gain amongst other risk factors. Doing so may help guide the longer-term management of preterm-born children, including identifying the most appropriate strategy for optimal growth in preterm infants. A future clinical study might focus on longitudinal measures of weight, length and body composition in infancy and beyond, in combination with pulmonary function testing. Use of novel modes of testing such as the forced oscillation technique, and inert gas multiple-breath washout, may be effective in detecting deficits in both distal and peripheral airway function (Gray et al., 2016, Udomittipong et al., 2008). This may delineate the role of nutrient intake and tissue accretion on later respiratory health. Use of duel-energy X-ray absorptiometry or air displacement plethysmography, rather than other techniques such bioelectric impedance, would be advantageous to obtain accurate measures of fat mass and lean mass (Bott et al., 2006).

6.5 Chapter 4: Physical activity in preterm-born 11-year old children born in the 1990's

6.5.1 Overview and principal findings

The research question for this study was: *"What are the levels of objectively measured PA in preterm-born children when compared to term-born controls. Are levels of physical activity related to the decrements in lung function observed in these children?"* The hypothesis for this study based upon the reduced lung function and increased respiratory symptoms observed in previous studies within our research group (Kotecha et al., 2013, Kotecha et al., 2012). Moreover, exercise testing within a population of preterm-born children with, and without BPD/CLD had established evidence of exercise-induced bronchoconstriction and increased use of ventilatory reserve (Joshi et al., 2013). The same study noted reduced levels of physical activity in preterm-born children (reported via questionnaire) when compared to term-born controls, which was consistent with the limited literature available. However, there was a paucity of evidence on whether these respiratory sequelae translated to reduced levels of objectively measured PA in preterm-born children. Contrary to my hypotheses, I did not observe any differences between preterm-born children and those born at term in the ALSPAC cohort, even at the extremes of gestation. Boys born ≤32 weeks' gestation were participating in an average of 24 minutes per day of MVPA compared with 26 minutes in term-born children at 11 years of age. Further to this, there was no correlation with measures of lung function. As a result of these observations, I opted not to proceed with further analysis (for example multivariable regression). However, it was noted that there was a significant gender difference within the whole study population, with girls participating in significantly less PA. Furthermore, there was a decline in activity levels (and a rise in sedentary behaviour) between 11 and 15 years of age. At both ages, average levels of MVPA were considerably lower than the recommendation of at least 60 minutes per day.

6.5.2 Comparison with other studies

As noted above, there was a significant difference between boys and girls at both 11 and 15 years of age. The influence of gender on rates of PA may have its origins in early childhood (Mattocks et al., 2010) with the divergence continuing through to school age and beyond (Golombok et al., 2008). The decline in total PA, and the rise of sedentary behaviour at the expense of light intensity PA over the period of early adolescence into early adulthood has also been described in the ALSPAC cohort (Riddoch et al., 2007, Mitchell et al., 2012). Thus, the overall low rates of PA may be one explanation for my findings. However, in contrast, questionnaire studies have consistently observed reduced PA in low birthweight and preterm-born children (Joshi et al., 2013, Welsh et al., 2010). It is possible that self-reported questionnaires capture different domains of PA, such as high-intensity exercise or sports participation, which do not correlate well with accelerometer data (Riddoch et al., 2004). Moreover, the majority of previous studies in children have relied on proxy reports of activity completed by parents (Keller et al., 2000, Kriemler, 2005, Wocadlo and Rieger, 2008, Svien, 2003, Kilbride et al., 2003). It is not clear, therefore, whether parent's perceptions of their child's physical ability is affected by their history of preterm-birth (Kilbride et al., 2003) or indeed whether they restrict activity based on perceptions of disability or adverse responses to exercise (Keller et al., 2000).

Since ALSPAC is comprised of a general sample of the population, the numbers of preterm-born children included are relatively low compared to a specifically-designed preterm-born cohort. This may be a further explanation for the lack of observed associations, however, researchers from the EPIcure study similarly did not report any differences in PA as measured by accelerometer, despite comparing the most immature preterm-born children against term-born controls (Welsh et al., 2010).

If decrements in lung function are not a determinant of PA in preterm-born children, other factors may be more important. Within the ALSPAC cohort at-large, reduced PA has been associated with increased fat mass (Ness et al., 2007, Riddoch et al., 2009). In contrast, vigorous PA was beneficial to measures of bone quality (Tobias et al., 2006, Sayers et al., 2011) whereas duration, rather than intensity of PA may be more important for cardiovascular health (Leary et al., 2008). Developmental coordination disorder (Green et al., 2011) and myopia (Deere et al., 2009) were also associated with reductions in PA. Contextually this could be important as preterm-born children are more likely to have neuromotor problems which could socially limit participation in more vigorous types of activity, such as organised sports, which correlate with higher rates of MVPA (Koorts et al., 2011).

As mentioned earlier in this chapter, body composition has not been widely studied in preterm-born children; however, of note for continuity with the first half of my thesis, van Deutekom and colleagues recently assessed the influence of accelerated infant weight gain in term-born low birthweight children and physical fitness at approximately 9 years of age (van Deutekom et al., 2015). This study noted that low birthweight, followed by accelerated weight gain was associated with lower scores on the Léger multistage fitness test when compared to children of normal birthweight and normal infant weight gain. This was not mediated by fat-free mass, or objectively measured MVPA or sedentary behaviour. Decreased handgrip strength was also associated with low birthweight, and this effect was substantially mediated by fat-free mass but not MVPA or sedentary behaviour, indicating deficits in neuromuscular fitness.

Increased rates of neurodevelopmental deficits in preterm-born children are well recognised, even in those born at the moderate gestations (Odd et al., 2013). For example, the study by Burns and colleagues noted lower scores in tests of motor coordination, which

was a more potent predictor of maximal $\dot{V}O_2$ than respiratory function in 13-year old children (Burns et al., 2009). Similar associations appear to persist into adolescence (Rogers et al., 2005) and adulthood (Ridgway et al., 2009). Thus, neuromotor sequelae of preterm birth including reduced coordination and muscle strength appear to be at least equally important as respiratory function in imposing limitations, perceived or otherwise, on the ability of preterm-born children to actively participate in life-functional activities and are present from mid-childhood. Over time, these limitations may impose a detraining effect which impacts upon exercise capacity in late adolescence and early adulthood- around the time when differences in habitual PA appear (at least in questionnaire-based studies). This may have consequences for the long-term risk of respiratory disease as evidence suggests that decrements in lung function and exercise capacity remain significant, even in relatively unimpaired preterm-born individuals.

6.6 Chapter 5: Physical activity and sedentary behaviour in preterm-born 7-year old children

6.6.1 Overview and principal findings

The research question for this final chapter was: *"What are the levels of objectively measured physical activity and sedentary behaviour in 7-year old preterm-born children compared to those born at term. Do current respiratory symptoms and family history of atopy mediate these relationships?"* My hypotheses were similar to those presented in chapter four, however, using data from the more recent Millennium Cohort Study provided an opportunity to examine these associations earlier in childhood, prior to the steep decline in activity which occurs during adolescence. Moreover, the MCS recruited participants at the turn of the century, with children born preterm more likely to have benefited from advances in neonatal care when compared to participants in the ALSPAC cohort. Additionally, the accelerometer used in MCS captured data in 15-second epochs,

making it a more sensitive tool to measure the short bursts of activity observed in younger children.

In line with my hypothesis, I noted that boys born ≤32 weeks' gestation participated in 7 minutes less MVPA per day when compared to term controls. This equated to over 1 hour per week, and the results were robust to adjustment for a number of potential confounders. In contrast, current wheeze or atopy were not identified as significant mediators, indicating that poor respiratory health is not on the causal pathway between preterm birth and levels of objectively measured PA in young children.

6.6.2 Comparison with other studies

In comparison with the results of my study in chapter 4 which used data from the ALSPAC cohort, I noted that both males and females met, or exceeded the national guideline for participation in MVPA in the MCS study. These observations need to be interpreted with caution, as the cut-points used to define intensity of PA vary between studies due to the utilisation of different calibration protocols (Mattocks et al., 2007, Pulsford et al., 2011). However, there was still a significant gender gap thus indicating that disparities in levels of PA are already established by the age of 7 years.

In keeping with the potential mechanisms of adiposity gain and associated inflammation as a result of rapid infant weight gain discussed earlier in this chapter, it is interesting to note that increased BMI was univariately associated with reductions in total PA and MVPA, but not sedentary behaviour. In multivariable analysis, BMI explained the highest proportion of unique variance in the model compared to any of the other independent variable, except for season of accelerometry data collection (winter). Thus, one limitation of the available data is lack of information on body composition. Investigating whether the association between preterm birth and PA was mediated via fat-mass, or fat-free mass would be interesting to study. BMI has limitations as a proxy for specific measures of body

composition as increased activity is positively associated with lean mass (Ness et al., 2007). Notwithstanding, it is reasonable to speculate that emerging obesity may be an important factor in predicting reduced PA. The absence of an association between BMI and sedentary behaviour might be explained by the relative importance of MVPA in promoting loss of fat mass (Mitchell et al., 2009). In interpreting these observations, one must be wary of reverse causality (i.e. that reduced PA promotes obesity) (Riddoch et al., 2009). A study using data from the Southampton Women's Study reported that time spent in vigorous PA was independently and inversely associated with total body adiposity, measured by dual x-ray absorptiometry (DXA), in 4-year old children (Collings et al., 2013). Lower intensity PA was not associated with fat mass and, moreover, sedentary behaviour was not associated with adiposity.

The largest associations with increased sedentary behaviour were the season of accelerometry data collection (winter), non-white ethnicity and higher socio-economic status. The study by Brodersen noted that school-age children of Asian descent were less physically active, whereas children of black ethnicity were more sedentary than white peers, but had similar amounts of MVPA (Brodersen et al., 2007). These data, along with my results, indicate that PA and sedentary behaviour have different socio-economic determinants.

It was surprising that wheeze was not noted to be a significant mediator of the observed association between preterm birth and measures of PA. The rates of wheeze reported from the MCS are lower at age 7 than in earlier studies using this cohort at age 5 (Boyle et al., 2012) and in other cohorts (Vrijlandt et al., 2013). One possibility is that respiratory function of preterm-born children may have improved by age 7 such that unpleasant symptoms such as wheeze do not impair participation in PA. A study of term-born IUGR children within our research group noted that 'catch up' growth, defined as >0.67 SD

increase in weight between birth and 8 years of age, was associated with an improvement of lung function deficits compared to those without catch-up, albeit still reduced compared to non-IUGR children (Kotecha et al., 2010). This is supported by the notion of continued lung growth and repair in childhood (Narayanan et al., 2012). As recommended earlier in this chapter, defining wheeze phenotypes in preterm-born children may elucidate particular groups who are at risk of reduced PA.

6.7 Chapters 4 & 5: Strengths and limitations

The key strength of the two studies undertaken in the second half of this thesis relate to the objective measurement of PA, and to the availability of this data within large longitudinal cohorts.

As with all large-scale cohort studies, there was attrition in the number of participants who remained involved across the follow-up period in both cohorts. Availability of PA data was limited to only a proportion of ALSPAC (38% at 11 years of age) and MCS (52% at 7 years of age) who were initially enrolled. I noted that in both instances, there was a clear socio-economic trend, with valid data more likely to be available from girls, participants of white ethnicity, and families whose mothers had received higher levels of education and who were non-smokers.

Since the incidence of preterm birth is closely linked to deprivation, a limitation of my work could be the potential under-representation of the group under study. Children born ≤32 weeks' gestation comprised 0.9% of the participants with valid accelerometry data in ALSPAC, and 1.2% in MCS. These numbers are broadly representative of the cohorts at large, where the incidence of preterm birth ≤32 weeks' gestation are 1.1% and 1.6% in ALSPAC and MCS, respectively. Moreover, they are representative of the national rates of

preterm birth in England and Wales, with 11,400/693,169 (1.6%) being born a with a valid record of gestation age in 2015 (McLaren, 2016).

The other key limitation in interpreting my results is the differences between calibration protocols applied by the ALSPAC and MCS teams to derive cut-points for various intensities of activity. The most closely-allied study to mine, in relation to investigation of the effect of gestational age on later levels of PA, was performed in the EPIcure cohort. This study used the same accelerometer count cut-off for MVPA as described in the calibration study performed by the ALSPAC team, but used the same device as provided to families in the MCS cohort. The EPIcure team reported only 8 minutes per day of MVPA in 11-year old children born at <25 weeks' gestation compared to 11 minutes in term-born controls (Welsh et al., 2010). The epoch length was not noted, however these levels are lower than my report in Chapter 4 (19 minutes in girls born ≤32 weeks' gestation and 16 in term-born controls). In both calibration studies, cut-points were defined by metabolic equivalent values assigned to a battery of self-paced activities. Differences in defining the additional variables required to calculate energy expenditure, including basal metabolic rate, may therefore, be responsible for the higher cut- points for MVPA in ALSPAC (and EPIcure) thus underestimating the true volume of MVPA within these cohorts (Pulsford et al., 2011).

Choice of epoch length is also a consideration, and more contemporary studies favour the use of short epochs in children to capture more intermittent periods of activity. Longer epochs are thought to be disadvantageous as the average count over the epoch is the value recorded. Thus, short bursts of high intensity activity may be 'averaged out' by relative inactivity over the rest of the period, leading to an underestimation of vigorous PA. The study by Reilly noted that recalculation of their accelerometry data into epoch lengths of 15 and 60 seconds resulted in a statistically significant reduction in MVPA from 28 minutes to 17 minutes per day, respectively, in 4 to 5-year old children (Reilly et al., 2008). The

authors question the clinical value of these differences, however it is worthy to note this equates to over an hour a week, which does not seem insignificant given the overall low levels observed in my two studies.

Finally, a further limitation of accelerometry is the failure to accurately capture activities where the trunk remains stable, such as cycling, as well as water-based activities and contact sports. However, direct observation studies have noted that the majority of free-living activities which children choose to participate in are largely locomotor in boys and girls aged between 5 and 11 years of age (Sleap and Warburton, 1996).

6.8 Chapters 4 & 5: Clinical relevance and future work

Although there is much subjectively reported PA data, there is a relative paucity of data on objectively measured PA in preterm-born children. My studies have added to this limited evidence-base and noted small differences in objectively measured MVPA in 7-year-old boys born ≤32 weeks' gestation, but not at 11 years of age. Other reports in older children (Welsh et al., 2010), and adults (Kaseva et al., 2015), have presented similar results. Notwithstanding, existing questionnaire-based studies, which rely on self-reporting, appear to demonstrate that reductions in habitual PA manifest in adolescence and early adulthood. Moreover, at an age when physical fitness generally peaks, a large study of preterm-born 18 to 25-year olds noted reductions in exercise capacity (Svedenkrans et al., 2013). This is clinically relevant as peak lung function is attained at a similar time (Burrows et al., 1977). The conceptual diagram, Figure 6-1, outlines the potential pathways linking preterm birth with reduced participation in PA during childhood. Aside from respiratory function, these pathways may also include alterations in body composition (increased fat mass, and/or decreased fat-free mass) which may be related to lower muscle strength. Neuromotor sequelae of preterm-birth could lead to poorer physical fitness if this limits participation in certain types of vigorous activity. Social factors, including exclusion from

activity by peers, or by concerned parents may also contribute to a gradual detraining effect that manifests as lower self-perception of ability by early adulthood.

Encouragingly, longitudinal follow-up studies note positive associations between exercise habits and peak $\dot{V}O_2$ in 18-year olds born extremely preterm, indicating a similar training potential as term-born controls (Clemm et al., 2015). Interventions in the form of training programmes are challenging but beneficial for cardiopulmonary rehabilitation after severe COPD exacerbations (Man et al., 2015), but few studies have assessed whether similar interventions in children may improve lung function and reduce symptoms. A systematic review noted an overall increased peak $\dot{V}O_2$, but not respiratory function, in asthmatics of varying severity, using methods as diverse as swimming, ball sports, and group aerobic activities. The interpretation of lung function data were complicated by the lack of studies including data on the derivation of predicted values and on inhaled medication use (Crosbie, 2012). A study by Varray and colleagues conducted in 12-year old atopic children with reversible airway obstruction noted some of the challenges involved in designing a training programme. They reported on an individualised swimming protocol (6 months duration: 3 months aerobic, followed by 3 months high intensity) and looked to observe improvements in physical conditioning relative to baseline exercise capacity. Compared to the control group, maximal $\dot{V}O_2$ was significantly improved in the training group, specifically after the aerobic portion of the intervention. In contrast, no improvements in lung function were observed (Varray et al., 1991). This resulted in reduced subjective reports of intensity of wheezing, and reduced anxiety in regards to control of exacerbations. The authors suggest that the potential mechanism, in the absence of improvements in respiratory function, is that frequent exercise trains ventilatory adaption which maximises the individual's ability for gas exchange. This hypothesis is supported by exercise data in preterm-born children which noted similar adaptation including increased use of ventilatory reserve (Joshi et al., 2013) and of respiratory rate (Kriemler, 2005) to

maintain peak $\dot{V}O_2$. In contrast, the authors are cautious in promoting high-intensity training which did not demonstrate improvements in exercise capacity, and which may provoke exercise-induced exacerbations.

Thus, future studies could investigate the efficacy of similar aerobic programmes in optimising the longer-term outcomes of preterm-born children who have increased risk factors for respiratory disease (Caskey et al., 2016). This could be coupled to trials of inhaled bronchodilators to reduce the incidence of exercise-induced bronchoconstriction, however, more data in regards to the mechanisms of respiratory disease and response to treatment in this vulnerable group of children are required first. One must also consider that whilst exercise capacity is a function of physiology and symptom limitation, being physically active can be viewed as a behaviour (Singh, 2014). The effect of pulmonary rehabilitation on increasing PA in adult patients has been limited (Cindy Ng et al., 2012). Thus, a successful study would benefit from an intervention to promote behavioural change in in addition to an exercise programme (Cruz et al., 2014). In children, an opportunity exists to instigate behavioural change early in childhood, prior to the declines in PA I have observed in my studies. Novel strategies are required early in life to increase levels of activity with respiratory problems and researchers should include families as well as healthcare professionals in designing future studies (Jago et al., 2017).

6.10 Thesis Summary

My thesis brings together data from three independent cohorts to describe the impact of foetal growth trajectory and infant weight gain on the respiratory symptoms of preterm-born children. It then investigates the influence of these symptoms on measures of physical activity in childhood through into adolescence. My results have demonstrated that deviations from the 'normal' foetal growth trajectory are important in defining later respiratory health, possibly due to developmental programming *in utero*. Thus, optimising the management and monitoring of growth during pregnancy may serve to reduce the adverse outcomes associated with preterm birth, especially being small for gestational age. My second study, using data from the same cohort, highlighted the influence of accelerated weight gain during infancy on adverse respiratory outcomes in childhood. In particular, the mediating effects of gestational age and maternal smoking were identified. The 'dose-dependent' effect of gestation was noted to be present across the whole range, and adds weight to the growing evidence-base for the re-classification of 'term' delivery. Moreover, these results implicated tobacco smoking as a key modifiable factor which is also highly relevant to the discussion presented on foetal growth. The second half of my thesis takes forward the respiratory sequelae of preterm birth and investigates if deficits in lung function and increased symptoms are associated with decreased levels of physical activity. My results indicated that decrements in moderate-to-vigorous PA exist in 7-year old boys who were born at ≤32 weeks' gestation. In contrast, levels of PA at the ages of 11 and 15 were remarkably similar in both the preterm and term-born groups, perhaps due to the overall low levels of PA at this age. An intervention to improve participation in PA would therefore be required early in life and would need to consider the complex social factors involved.

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9 APPENDICES

9.1 Appendix 1: RANOPS participant information

Parent Information Sheet:

RANOPs

Project title: Respiratory and neurological outcomes in children born preterm study

Principal Investigator: Professor Sailesh Kotecha.

Thank you for reading this information sheet about the RANOPs study.

We would like to invite you and your child to take part in our research study based at the Department of Child Health at Cardiff University. Before you and your child decide whether to take part by completing the questionnaire, it is important for you to understand why the study is being performed and what it involves. Please take time to read the following information and if you have any questions, please feel free to contact us with any questions. Thank you for taking the time to read this leaflet.

What is the purpose of this study?

We already know that some babies who are born very prematurely (i.e. more than 10 weeks prematurely) sometimes develop breathing and developmental problems as a baby and as a child. However, it is not clear if babies who are born only slightly prematurely (4 – 8 weeks prematurely) are also at risk of developing breathing and developmental problems. We would like to further study the symptoms of children who were born prematurely and compare their symptoms to those of children who were born on time. This will establish if children born only slightly prematurely need to be followed up closely during childhood.

Why have you been chosen to take part?

You have been invited to take part in our study because your child was born between 1st September 2003 and 31st August 2011. We are inviting families with children who were born prematurely and also families with children who were born on time - a total 24,000 children from Wales between the ages of 1 and 9 years are being invited to take part in this study.

Do I have to take part?

It is entirely your own and your child's decision whether you want to complete and return the questionnaire. If you decide to take part we would be delighted if you can complete the enclosed questionnaire. If possible and only if you agree, we would like to contact you to clarify any answers you give and also to invite you to future similar studies. If, at any time, you change your mind, you are free to withdraw any information you have given about your child and do not need to give a reason why. A decision to withdraw at any time, or a decision not to take part, will not affect the care that you or your child receives.

What will I be asked to do if I decide to take part?

If you decide to take part, please complete the enclosed questionnaire and return it to us in

the pre-paid envelope.

The questionnaire should only take you 15 – 20 minutes to complete but please do not hesitate to contact Dr Martin Edwards on telephone 02920 743927 or by email (edwardsmo@cardiff.ac.uk) if you have *any* queries.

With your permission we would like to (i) contact you to clarify any questions that you may have answered, or (ii) to send questionnaires or invite you to future studies, and (iii) ask you if we may access information about your child specifically from the health database records here in Wales. These form part of the questionnaire and please do let us know if we may or may not contact you in the future.

What will happen to the information I provide?

From the information we collect, our primary aim is to compare symptoms between children who were born prematurely with symptoms of children who were born on time especially from a breathing and development point of view. The information will help guide future planning of health care services for children born prematurely.

What are the possible disadvantages and risks of taking part?

We do not anticipate any disadvantages in taking part but please do not hesitate to contact us if you have any concerns or questions.

What are the possible benefits of taking part?

There are no direct benefits to your child for taking part. The information you provide may help us establish the best way of monitoring prematurely born children in the future.

Will my taking part in this study be kept confidential?

The information collected in this study will be kept strictly confidential. The questionnaire only contains the date of birth of your child and a study number. Only if you give us permission, shall we be allowed other information including your child's medical history. Any information will only be accessible by members of the research team. No individual names or details that can identify any children will be included in any future study reports or publications.

What will happen to the results of the study?

The results will be written up as medical papers for publication in medical journals and for presentations at medical meetings.

Who is organising and funding the research?

This study is being organised and funded by the Department of Child Health at Cardiff University. We have also applied for research funding to medical charities.

Who has reviewed the study?

The study has been reviewed and approved by the South East Wales Research Ethics Committee (REC).

What should I do if I have any concerns about the study?

If you have any questions about the study, please contact Professor Sailesh Kotecha or Dr Martin Edwards. If you remain unhappy and wish to complain formally, you can do this through NHS Complaints Procedure.

Dr Martin Edwards

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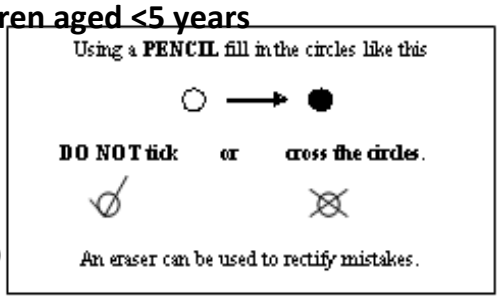
What do I do now?

Thank you for reading our Information Pack and we would be delighted if you complete the questionnaire and return it in the pre-paid envelope.

9.2 Appendix 2: RANOPS questionnaire for children aged <5 years



Study No: xxxxx

Health questionnaire for preschool children (<5 years old)

Today's date: _____2013

Person completing the questionnaire: Mother (M)

Father (F)

Other (O)

1. Has your child ever had wheezing or whistling in their chest at any time in their life?

Yes (Y) No (N) Unsure (U)

IF YOU HAVE ANSWERED "NO" PLEASE GO TO QUESTION 4.

2. In the last three months , during the day time (i.e. when awake) does your child:

	Not at all	a few days	some days	most days	every day
a. Wheeze:	(N)	(F)	(S)	(M)	(E)
b. Cough:	(N)	(F)	(S)	(M)	(E)
c. Short of breath:	(N)	(F)	(S)	(M)	(E)
d. Rattly chest:	(N)	(F)	(S)	(M)	(E)
e. Snuffly:	(N)	(F)	(S)	(M)	(E)

3. In the last three months , during the night time (i.e. when asleep) does your child:

	Not at all	a few nights	some nights	most nights	every night
a. Wheeze:	(N)	(F)	(S)	(M)	(E)
b. Cough:	(N)	(F)	(S)	(M)	(E)
c. Short of breath:	(N)	(F)	(S)	(M)	(E)
d. Rattly chest:	(N)	(F)	(S)	(M)	(E)
e. Snore:	(N)	(F)	(S)	(M)	(E)

4. How many colds has your child had in the last three months?

None (N) 1 to 3 (1) more than 3 (3) always has a cold (A)

IF YOU HAVE ANSWERED "None" PLEASE GO TO QUESTION 6.

5. When my child has had a cold in the last three months, s/he has a:

	Not at all	a few colds	some colds	most colds	every cold
a. Wheeze:	(N)	(F)	(S)	(M)	(E)

b. Cough:	(N)	(F)	(S)	(M)	(E)
c. Short of breath:	(N)	(F)	(S)	(M)	(E)
d. Rattly chest:	(N)	(F)	(S)	(M)	(E)
e. Snuffly:	(N)	(F)	(S)	(M)	(E)

6. When my child does NOT have a cold, in the last three months, s/he has a:

	Not at all	a few days	some days	most days	every day
a. Wheeze:	(N)	(F)	(S)	(M)	(E)
b. Cough:	(N)	(F)	(S)	(M)	(E)
c. Short of breath:	(N)	(F)	(S)	(M)	(E)
d. Rattly chest:	(N)	(F)	(S)	(M)	(E)
e. Snuffly:	(N)	(F)	(S)	(M)	(E)

7. When my child has been more active (e.g. crawling, walking or when excited), in the last three months, s/he has a:

	Not at all	a few days	some days	most days	every day
a. Wheeze:	(N)	(F)	(S)	(M)	(E)
b. Cough:	(N)	(F)	(S)	(M)	(E)
c. Short of breath:	(N)	(F)	(S)	(M)	(E)
d. Rattly chest:	(N)	(F)	(S)	(M)	(E)
e. Snuffly:	(N)	(F)	(S)	(M)	(E)

8. Has your child ever been diagnosed with asthma by a doctor?

Yes (Y) No (N) Unsure (U)

9. Is there a family history of:

	Yes	No
a. Asthma	(Y)	(N)
b. Eczema	(Y)	(N)
c. Hayfever	(Y)	(N)
d. Allergies	(Y)	(N)

10. In the last 12 months, has your child ever used any regular asthma inhalers (pumps) or medicines?

Yes (Y) No (N) Unsure (U)

If yes, please provide the name (or colour of the pump) with details of how often used:

_____

11. In the last 12 months, has your child had any chest infections?

Yes (Y) No (N) Unsure (U)

12. In the last 12 months, how many chest infections has your child had?

None (N) 1 to 3 (1) 4 to 10 (4) More than 10 (>)

13.In the last 12 months, how many courses of antibiotics has your child had?

None (N) 1 to 3 (1) 4 to 10 (4) More than 10 (>)

14.In the last 12 months, how many admissions (overnight or longer) has your child had to hospital for breathing problems?

None (N) 1 to 3 (1) 4 to 10 (4) More than 10 (>)

15.Does the child's mother smoke cigarettes?

Yes (Y) No (N) Unsure (U)

If yes, how many per day?

1 to 10 (1) 11 to 20 (2) More than 20 (>)

If the child's mother smokes did she smoke during the pregnancy?

Yes (Y) No (N) Unsure (U)

16.Does the child's father smoke cigarettes?

Yes (Y) No (N) Unsure (U)

If yes, how many per day?

1 to 10 (1) 11 to 20 (2) More than 20 (>)

17.Do any other house members smoke cigarettes?

Yes (Y) No (N) Unsure (U)

If yes, how many per day for the whole household?
(please add up all the cigarettes which are smoked by everyone living in the same household

1 to 10 (1) 11 to 20 (2) More than 20 (>)

18.Who else lives at the same household as the child?

Mother (M) Father (F) Brother/s (B) Sister/s (S) Other (O)

19.Has your child ever been diagnosed with any breathing problems (e.g. asthma, CF, TB etc.)?

Yes (Y) No (N) Unsure (U)

If yes, please provide some details:

_____

20.Has your child ever been diagnosed with any other conditions (e.g. diabetes, epilepsy etc.)?

Yes (Y) No (N) Unsure (U)

If yes, please provide some details:

_____

21.Does your child have any problems with moving (crawling, walking, running etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

22.Does your child have any problems with using their hands (holding, throwing, catching, writing etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

23.Does your child have any problems with their speech (delayed, limited, impediment etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

24.Does your child have any problems with their vision (partially sighted, registered blind etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

25.Does your child have any problems with their hearing (partially hearing, wears hearing aids etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

26.Does your child have any problems with their behaviour (hyperactive, disruptive, aggressive etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

27.Does your child have any learning difficulties (developmental delay)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

Thank you for filling in the form. The following section asks how you are happy for us to use the data or to contact:

A. If we need to clarify some of your answers, would you be willing to be contacted?

Yes Ⓨ No Ⓝ Please initial the box here ☐

Address, Telephone number &/or email:

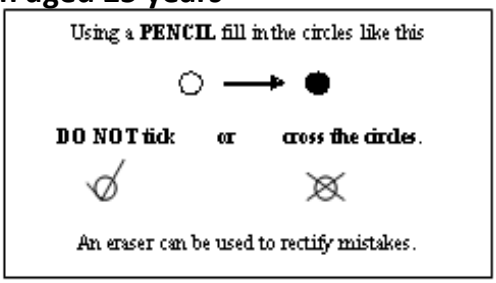
B. Most admissions and GP visits in Wales are stored in computer database. As part of this study, we would also like to study how children in Wales have used their GPs or have had admission to hospitals. Would you be happy for us to use your son's or daughter's records on these databases?

Yes (Y) No (N) Please initial the box here ☐

C. We may plan similar studies in the future, would you be willing to be contacted in the future?

Yes (Y) No (N) Please initial the box here ☐

9.3 Appendix 3: RANOPS questionnaire for children aged ≥5 years



Study No: xxxxx

Health questionnaire for school age children (>5 years old)

Today's date: _____2013

Person completing the questionnaire:

Mother (M)

Father (F)

Other (O)

28.Has your child ever had wheezing or whistling in their chest at <u>any time</u> in the past?

Yes (Y) No (N) Unsure (U)

IF YOU HAVE ANSWERED "NO" PLEASE GO TO <u>QUESTION 10</u>.

29.Has your child had wheezing or whistling in the chest <u>in the last 12 months</u>?

Yes (Y) No (N) Unsure (U)

IF YOU HAVE ANSWERED "NO" PLEASE GO TO <u>QUESTION 10</u>.

30.How many attacks of wheezing has your child had <u>in the last 12 months</u>?

None (N) 1 to 3 (1) 4 to 12 (4) More than 12 (>)

31.<u>In the last 12 months</u>, how often, on average, has your child's sleep been disturbed due to wheezing?

a. Never woken with wheezing (Y)

b. Less than one night per week (Y)

c. One or more nights per week (Y)

32.<u>In the last 12 months</u>, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

Yes (Y) No (N) Unsure (U)

33.Has a doctor ever told you that your child has asthma?

Yes (Y) No (N) Unsure (U)

34.<u>In the last 12 months</u>, has your child's chest sounded wheezy during or after exercise?

Yes (Y) No (N) Unsure (U)

35.<u>In the last 12 months</u>, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?

Yes (Y) No (N) Unsure (U)

36.<u>In the last 12 months</u>, has your child ever used any regular asthma inhalers (pumps) or medicines?

Yes (Y) No (N) Unsure (U)

If yes, please provide the name (or colour of the pump) with details of how often used:

_____

37. Is there a family history of:

	Yes	No
a. Asthma	(Y)	(N)
b. Eczema	(Y)	(N)
c. Hayfever	(Y)	(N)
d. Allergies	(Y)	(N)

38. In the last 12 months, has your child had any chest infections?

Yes (Y) No (N) Unsure (U)

39. In the last 12 months, how many chest infections has your child had?

None (N) 1 to 3 (1) 4 to 10 (4) More than 10 (>)

40. In the last 12 months, how many courses of antibiotics has your child had?

None (N) 1 to 3 (1) 4 to 10 (4) More than 10 (>)

41. In the last 12 months, how many admissions (overnight or longer) has your child had to hospital for breathing problems?

None (N) 1 to 3 (1) 4 to 10 (4) More than 10 (>)

42. Does the child's mother smoke cigarettes?

Yes (Y) No (N) Unsure (U)

If yes, how many per day?

1 to 10 (1) 11 to 20 (2) More than 20 (>)

If the child's mother smokes did she smoke during the pregnancy?

Yes (Y) No (N) Unsure (U)

43. Does the child's father smoke cigarettes?

Yes (Y) No (N) Unsure (U)

If yes, how many per day?

1 to 10 (1) 11 to 20 (2) More than 20 (>)

44. Do any other house members smoke cigarettes?

Yes (Y) No (N) Unsure (U)

If yes, how many per day for the whole household?
(Please add up all the cigarettes which are smoked by everyone living in the same household)

1 to 10 ① 11 to 20 ② More than 20 >

45. Who else lives at the same household as the child?

Mother Ⓜ Father Ⓕ Brother/s Ⓑ Sister/s Ⓢ Other Ⓞ

46. Has your child ever been diagnosed with any breathing problems (e.g. asthma, cystic fibrosis, BPD, etc.)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

47. Has your child ever been diagnosed with any other conditions (e.g. diabetes, epilepsy etc.)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

48. Is your child on any medication?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

49. Does your child take part in any physical activity such as cycling, swimming or dancing?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details of how often and for how long:

_____

50. Does your child have any learning problems?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

51. Does your child have any problems with their behaviour (hyperactive, disruptive, aggressive etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

52. Does your child have an educational statement?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

_____

53. Does your child have any problems with moving (difficulty running, use of a wheelchair etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

54. Does your child have any problems with using their hands (difficulty writing, poor ball skills etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

55. Does your child have any problems with their speech (delayed, limited, impediment etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

56. Does your child have any problems with their vision (partially sighted, registered blind etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

57. Does your child have any problems with feeding (needs help cutting up food, has a gastrostomy etc…)?

Yes Ⓨ No Ⓝ Unsure Ⓤ

If yes, please provide some details:

Thank you very much for filling in the form.

The following section asks how you are happy for us to use the data or to contact you:

D. If we need to clarify some of your answers, may we contact you?

Yes Ⓨ No Ⓝ Please initial the box here ☐

Address, Telephone number &/or email:

E. Most admissions and GP visits in Wales are stored in computer databases. As part of this study, we would also like to study how children in Wales have used their GPs or have had admission to hospitals. Would you be happy for us to use your son's or daughter's records on these databases?

Yes Ⓨ No Ⓝ Please initial the box here ☐

F. We may plan similar studies in the future, would you be willing to be contacted in the future?

Yes Ⓨ No Ⓝ Please initial the box here ☐

9.5 Appendix 4: Published manuscripts

9.5.1 Lowe J, Watkins WJ, Edwards MO, Kotecha SJ, Henderson AJ, Kotecha S. Levels of physical activity in preterm born school-age children. J Pediatr 2015;166 :877-83

9.5.2 Lowe J, Watkins WJ, Kotecha SJ, Kotecha S. Physical activity and sedentary behaviour in preterm-born 7-year old children. PLoS One 2016;11:e0155229

9.5.3 Lowe J, Cousins M, Kotecha SJ, Kotecha S. Physical activity outcomes following preterm birth. Paediatric Respiratory Reviews. 2017;22:76-82