The Liverpool Baby Breathing Study

The Cross-sectional and Longitudinal Assessment of Respiratory Symptoms and the Impact on Quality of Life in the First 22 Months of Life

A Birth Cohort Study

Errata

The following amendments have been made to this thesis in line with the recommendations made by examiners following Viva Voice examination on the 10th August 2017.

Section 1.1 Introduction to the Liverpool Baby Breathing Study- Addition of study aims as outlined by the study protocol and addition of objectives that were completed by the author. This helps the reader understand the expectations of the study as a whole and within this thesis and will help clarify if these aims were achieved later in the thesis. ***(Page 18)***

Section 1.2.1 Respiratory Disease and Symptoms - Table 1 was created from three separate tables. ***(Page 21)***

Section 1.5.2 The Liverpool Respiratory Symptom Questionnaire - Figures 1-4 were added. These figures show the Liverpool Respiratory Symptom Questionnaire. This has been moved from the appendix to make it more clear to the reader the questionnaire that has been used in the LBBS. ***(Pages 32-35)***

Section 1.6 Birth Cohort Studies- Previously this section contained a large amount of extraneous detail of the design and findings of previous birth cohort studies and other respiratory studies. This information has been condensed into a table and two summaries (section 1.6.1 and 1.6.2) discussing recruitment and attrition in previous cohort studies. The in depth analysis of the cohort studies has been moved to the appendix***. (Pages 30-40)***

Section 2.1 Section 1. LBBS Study Design and Development Summary - Previously this section contained a detailed description of work performed by previous MPhil students, and results of the Public Patient Involvement studies that they performed. This detailed description and the result was moved to the appendix and has been replaced with a short summary of this work. ***(Pages 45-47)***

Section 2.1.5 Modification of the Emailing Timeline to Reduce Attrition in the LBBS- This section was added. It describes how and why the author modified the questionnaire emailing timeline in the LBBS. This was not previously described and is an important part of the work carried out by the author in developing the study. ***(Pages 46-47)***

Section 2.2.2 Data Entry and Coding - This section was added. It provided a description of how the data was entered and coded for the use in the statistical packages. This was a significant proportion of work performed by the author that was not previously described in the thesis. ***(Pages 47-48)***

Section 2.2.8 Correction for Multiple Testing Analysis - A discussion on correction for multiple testing during analysis of the LBBS data was added. This discussion identifies why multiple testing is often performed, the benefits and disadvantages of using correction for multiple testing and why it was not used during analysis of the LBBS. ***(Page 51)***

2.2.9- Justification and Development of the Methods of Longitudinal Analysis in the LBBS- This section was added to the thesis to provide a more detailed description of how the longitudinal analysis methods used in the LBBS were developed. Prior to this modification this description was lacking detail. It now discusses in much detail how and why the method of multi-level mixed effects modelling was chosen and the advantages and disadvantages of its use. This section also

describes the exactly process that was used to develop the model and how the final results were obtained. *(Pages 52-53)*

Section 2.2.11 Presentation of the Analysis of the LBBS in this Thesis - This section was added. It provides a description of how the results of the LBBS will be presented in Chapter 3. Due to the large amount of results presented in the thesis it was difficult for the reader to follow previously. The addition of this section makes it easier for the reader to understand how and why the results will be presented in this thesis. This will make the thesis easier to read and follow as a whole. *(Pages 52-54)*

Section 3 Chapter 3- At the beginning of each subsection a description of what the results that follow show and how they relate to the study aims. This will add a narrative thread to the presentation of the results and help the reader follow the analysis. *(Pages 55-122)*

Section 3.5 Cross Sectional Analysis- Tables describing other health conditions were modified so that the types of underlying condition were in alphabetical order. Diseases within the condition type were rearranged so that they were in order of frequency in the cohort. *(Pages 69-117)*

Section 3.5 Cross Sectional Analysis- Tables describing the median, interquartile range, mean and mode score of each risk factor/exposure group was moved from the appendix to the main body of the text where the significant differences in LRSQ scores are described. This makes the presentation of the results of the cross sectional analysis more consistent throughout the 4 time points that are presented in this thesis. This will make the analysis easier to follow for the reader. The box and whisker diagrams of significant results only remains the same. *(Pages 69-117)*

Section 4.4 The Clinical Relevance of the LRSQ Score – This section was added. It describes what would be considered a clinically significant or parentally important difference in LRSQ score was adding. Although this has not been previously described the addition of this section gives the thesis more clinical relevance. *(Page 129)*

In addition to this, spelling, grammatical, and syntax errors have been corrected. Missing graph axis labels have been added.

Abstract

The Liverpool Baby Breathing Study- The cross-sectional and longitudinal assessment of respiratory symptoms and the impact on quality of life in the first 22 months of life by Joshua Stead.

Introduction. The Liverpool Baby Breathing Study (LBBS) is a longitudinal birth cohort study that investigates natural history of respiratory disease in preschool children in Merseyside. Merseyside has a high prevalence of risk factors for preschool respiratory disease. Preschool children in Liverpool have high rates of hospitalisation for asthma and bronchiolitis. Respiratory disease impacts on the quality of life (QoL) of infants and their families. The LBBS also assesses QoL impact on infants and their families, which makes the LBBS a novel study.

Study Aims. The aims of this thesis are: 1. To create a profile of the infants and mothers enrolled in the LBBS and compare this to the eligible population. 2. To describe respiratory symptoms in the cohort using the Liverpool Respiratory Symptom Questionnaire (LRSQ) from birth until 22 months of age. 3. To determine the differences in LRSQ scores in infants exposed to various risk factors. 4. To determine the change in the LRSQ score over time and the variability in this change with exposure. 5. To validate the LRSQ in a longitudinal study.

Methods. The LBBS uses the Liverpool Respiratory Symptom Questionnaire (LRSQ). Recruitment for the study was performed in the Liverpool Women's Hospital (LWH). Eligible births were those infants who lived in Liverpool postcodes L1-38, spoke sufficient English and were cared for by their parents. Questionnaires were sent to participants by post or through an automated online emailing system. Recruitment rates and response rates were described using descriptive statistics. Sensitivity analysis was performed, comparing the drop out population's exposure variables to the remaining cohort. The profile of the cohort was compared to the profile of eligible births in the LWH by χ^2 analysis. Cross-sectional analysis compared those exposed to risk factors using χ^2, Mann-Whitney U, Kruskal-Wallis analysis and Fisher's Exact Test. The cross-sectional analysis of the LBBS was weighted to ensure the index of multiple deprivations (IMD) decile distribution of the cohort was comparable to the eligible births in the LWH. The longitudinal analysis of the LBBS was done using multi-level mixed effects models. The internal consistency of the LRSQ was assessed using Cronbach alpha coefficients.

Results. 694 of the interested mothers (5.57% of all eligible births) consented to the study and completed the initial questionnaire. Attrition in the study was 44.0%, 60.4% and 63.0% at 10, 16 and 22 months. Mothers participating and retained in the LBBS were older, less deprived, more highly educated, breastfed more and smoked less in pregnancy than mothers of all eligible births. Infants were more likely to be of white or mixed ethnicity and born preterm than the eligible births. Cross-sectional analysis showed nursery attendance, being male, decreasing maternal age, decreasing maternal education, preterm birth, low birth weight, a family history of atopy and presence of other household children increased respiratory symptoms in the first 22 months of life. Breastfeeding and sharing a bedroom decreased respiratory symptoms. Longitudinally analysis found nursery attendance, being male, preterm birth, low birth weight, a family history of atopy and other household children increased respiratory symptoms over time. Breastfeeding, increasing gestational age and sharing a bedroom decreased respiratory symptoms over the first 22 months of life. Respiratory symptoms had a major impact on the QoL of both the infant and their families. There were unexpected and mixed results regarding the effect of smoke exposure on respiratory health in the LBBS. The LRSQ had acceptable to good internal consistency.

Conclusion. The LBBS deployed the LRSQ using contemporary technology, and has been accessible to mothers in Liverpool across all deciles between 2012 through 2017. LBBS has validated use of the LRSQ in a longitudinal birth cohort. Breastfeeding had the greatest protective effect with a positive duration dependent dose-effect on respiratory symptoms and QoL. Nursery school attendance had the greatest deleterious effect on respiratory symptoms and QoL.

Contents

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List of Abbreviations

A&E	Accident and Emergency
AFC®	Adobe Forms Central ®
ALSPAC	The Avon Longitudinal Study of Parents and Children
ATAQ	The Asthma Therapy Assessment Questionnaire
BiB	Born in Bradford
BMI	Body Mass Index
CAQ	Childhood Asthma Questionnaire
CAT	The COPD Assessment Test
CCQ	The Clinical COPD Questionnaire
CF	Cystic Fibrosis
COPD	Chronic Obstructive Pulmonary Disease
DNA	Deoxyribonucleic acid
ECRHS	The European Community Respiratory Health Survey
EISL-WQ	The International Study of Wheezing Infants Questionnaire
ELSPAC	The European Longitudinal Study of Pregnancy and Childhood
ETS	Environmental Tobacco Smoke
FEV1	Forced expiratory volume in one second
FH	Family History
FOT	Forced Oscillation Technique
FVC	Forced vital capacity
GI	Gastrointestinal
GP	General Practitioner
Ig	Immunoglobulin
IMD	Index of Multiple Deprivations
ISSAC	The International Study of Asthma and Allergy in Childhood
K-BILD	King's Brief Interstitial Lung Disease
LBBS	Liverpool Baby Breathing Study
LRSQ	Liverpool Respiratory Symptom Questionnaire
LRTI	Lower Respiratory Tract Infection
LWH	Liverpool Women's Hospital
MASS	Manchester Asthma and Allergy Study
MeDALL	The Mechanisms of development of Allergy
MRC	Medical Research Council
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
PAQLQ	Paediatric Asthma Quality of Life Questionnaire
PEACE	Pollution Effects on Asthmatic Children in Europe Study
PIAMA	The Prevention and Incidence of Asthma and Mite Allergy
PPI	Public Patient Involvement
QoL	Quality of Life
QOLLRIQ	The Quality of Life for Respiratory Illness Questionnaire
RIP	Respiratory Inductance Plethysmography
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Infection
SoB	Shortness of Breath
SPSS	Statistical Package for Social Sciences
SSN	SelectSurvey.NET
TRACK	Test for Respiratory and Asthma Control in Kids
UK	United Kingdom
WHO	The World Health Organisation
WYCAP	Wythenshawe Community Asthma Project

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The help and support of many different people over the last year has made the production of this thesis possible.

I would like to thank my supervisor, Dr Calum Semple. The work in producing this thesis would not have been possible in any way without him. His time and support through the year has made the production of this piece of work possible. Without his guidance, expertise, teaching and contacts, the production of this thesis would have been impossible. For all that, I am incredibly thankful.

I would like to thank Professor Ben Shaw for providing data from the LWH eligible births, without which a large proportion of this work would not have been possible.

I continue my thanks to Dr Semple and Professor Shaw and would like to thank Professor Paul McNamara, Professor Kevin Sothern and the previous MPhil Students, Rosanna Pickles, Bethan Griffith, Sanjay Patel and Jennifer Barclay for the initiation and running of the study before my involvement began. Without this previous work the study would not have existed for me to be involved with, and it is unlikely I would have found a project which would have enjoyed working on as much as this study.

I am extremely grateful to Dr Steven Lane from the University of Liverpool who has developed the methods for the longitudinal analysis of the study and helped me throughout the year with the analysis of the study. Without his help, teaching and knowledge, the analysis of this study would not have been possible. I cannot thank him enough for his time, help and input into the study.

I extend my thanks to the other MPhil Students this year for helping me through the year with a range of things from administration to providing conversations about how we are all getting on. I would particularly like to thank Pearl Ampha who has been based at Alder Hey Children's Hospital with myself; she has always been there to ask quick questions to and provided me with support I have needed through this year.

Finally I would like to thank my family and friends for their support over the last year whether that be financially, emotionally or socially. Without them this year would have been incredibly tough and much more difficult than it was. I cannot thank them enough.

Collaboration

The following work was completed either previous to my involvement in the LBBS or during my involvement in the study by other investigators described below.

The initiation of the Liverpool Baby Breathing Study and protocol development was conducted by Miss Rosanna Pickles, Miss Bethan Griffith, Dr Calum Semple, Professor Paul McNamara, Professor Kevin Sothern, and Professor Ben Shaw.

Development and initiation of the distribution of questionnaires to the study participants was conducted by Miss Rosanna Pickles, Bethan Griffith, Sanjay Patel and Jennifer Barclay.

Recruitment to the LBBS Study was conducted by Miss Rosanna Pickles, Miss Bethan Griffith, Mr Sanjay Patel and Miss Jennifer Barclay.

The collection and production of the demographic data of all the eligible births in the Liverpool Women's Hospital during the recruitment period was performed by Professor Ben Shaw in the LWH.

The development and validation of the LRSQ was conducted by Dr Ruth Trinick, Professor Kevin Southern, Professor Paul McNamara, Dr Colin Powell, Dr Arturo Solis and Professor Ben Shaw.

The development of the methods for the longitudinal analysis of the study was developed by Dr Steven Lane from the University of Liverpool.

Foreword

This thesis is comprised of five chapters.

Chapter one provides an introduction to the LBBS. It discusses background information respiratory disease in the preschool population. Recruitment and attrition in previous birth cohort studies are discussed. Measures of paediatric lung function are discussed along with analysis of previously used respiratory symptoms questionnaires and the in depth analysis of the Liverpool Respiratory Symptom Questionnaire. The health profile in Liverpool is discussed providing reasons why Liverpool is an ideal city to conduct a study of this nature.

Chapter two provided the details of the methods of the LBBS. Section one of this chapter is an outline of previous work that had been conducted; this describes the questionnaire development, initiation of the study and recruitment. Section two provides a detailed description of work performed by the author. It describes the methods of analysis of recruitment rates, dropout rates and the questionnaire responses.

Chapter three describes the results of the LBBS. This chapter is split into seven sections. Section one is the results of the analysis of recruitment and response rates in the LBBS. Section two describes attrition in the LBBS. This section provides a description of how the study accounted for the confounding effects created by the discrepancies between the drop out population and the population remaining in the study. Section three and four describe the profiles of the mothers and infants in the LBBS. In these sections there is a comparison of the LBBS profiles to the population of Liverpool and the eligible births in the LWH. Section five describes the results of the cross sessional analysis of each of the four questionnaires at four different time points in the first 22 months of life. Section six provides the results of the longitudinal analysis of the LBBS over the first 22 months of life. Section seven provides the results of the validation of the LRSQ when used in longitudinal studies.

Chapter four provides a discussion on the findings from the LBBS and how the current study's links to previous findings. The strengths and weaknesses of the LBBS and recommendations for future work are also discussed in chapter four.

Chapter five is a summary of the conclusions from the LBBS.

The Liverpool Baby Breathing Study

Chapter 1-Introduction

This chapter provides an introduction to the LBBS. It has a description of why the Liverpool Baby Breathing Study (LBBS) began, and why it is novel. It summarises the work done by previous students, prior to the author's involvement, and the work completed by the author leading to the production of this thesis. An overview of paediatric respiratory disease is given along with a discussion on the burden of respiratory disease in the paediatric population. Common risk factors previously identified for paediatric respiratory disease are discussed. Methods used to measure respiratory disease and lung function in the paediatric age group and the problems they possess are described. The recruitment methods and methods used to reduce attrition in previous birth cohort studies are described. Previously used respiratory symptom questionnaires are discussed, followed by an in depth description of the Liverpool Respiratory Symptom Questionnaire (LRSQ) that is used in the LBBS. The health profile of the Liverpool population and reasons why Liverpool is an ideal city to conduct a study of this nature is discussed.

1.1-Introduction to the Liverpool Baby Breathing Study

The Liverpool Baby Breathing Study (LBBS) was formerly known as 'The Liverpool Respiratory Birth Cohort Study'. It is a longitudinal birth cohort study that assesses the respiratory symptoms of preschool children from Liverpool. It assesses the impact of these symptoms on both the infant's and their family's quality of life (QoL). The aims of the study as outlined in the study protocol are;

- To create a profile of the infants and mothers enrolled in the LBBS and compare this to the population of Liverpool and those born in the LWH.
- To describe respiratory symptoms of preschool children in Liverpool using the LRSQ from birth until 5 years of age by biannual assessment.
- To determine the differences in LRSQ scores in the different populations at each questionnaire time point.
- To determine the change in the LRSQ scores over time and the variability in this change between different population groups in the LBBS.
- To validate the LRSQ in a longitudinal study.

The LBBS assesses infants biannually from four months to five years of age by means of a parent completed questionnaire; the Liverpool Respiratory Symptom Questionnaire (LRSQ). The LRSQ was developed by Powel et al. at Alder Hey Children's Hospital and Liverpool Women's Hospital (LWH). The LRSQ assesses a number of common respiratory symptoms, including cough, wheeze and shortness of breath (SoB), and the effect they have on the infant's and their family's QoL (1). In the LBBS the LRSQ has been used alongside a questionnaire assessing demographics and exposures developed by Rosanna Pickles and Bethan Griffith (2, 3). This questionnaire explored common risk factors associated with respiratory disease in preschool children such as deprivation (4), tobacco smoke exposure prenatally (5) and postnatally (6), breastfeeding (7) and prematurity (8). These questionnaires, along with assessment of healthcare service attendance allowed the study of the prevalence, the natural history and the impact of respiratory disease in preschool children from Liverpool. This study is now in its 4th year, with the whole cohort having completed the 5th questionnaire at 28 months of life. For the purpose of this thesis the first four questionnaires are discussed.

Liverpool has a high prevalence of risk factors for paediatric respiratory disease in its population such as deprivation (9), smoking (both in pregnancy (10) and postnatally (11)) and the low levels of breastfeeding (12). Liverpool has high rates of respiratory disease in both the adult and the paediatric population (13, 14); there are high levels of bronchiolitis and asthma hospitalisations in Liverpool compared to other areas of England (15). The LWH provides the mainstay of maternity care in Liverpool with around 8500 births per year. This has provided the research team with an ideal and valuable centre for recruitment and access to the majority of births in Liverpool.

The LRSQ has previously been validated for use in the preschool and infant population (1). It has been shown to distinguish well between those with Cystic Fibrosis (CF) from those without, and those who were unwell from those who were stable in both preschool children and in those 6-12 years old (16). It has successfully been used to examine the relationship between neurodisability and respiratory symptoms (17) and is being increasingly used in studies of respiratory disease in the preschool age group. This is the first time it has been used in a longitudinal study and on such a large population. LRSQ has allowed the researchers in the current study to explore the prevalence and patterns of respiratory symptoms and how these change over time in the preschool population of Liverpool.

My involvement in the LBBS began in September 2016 after previous work by Rosanna Pickles, Bethan Griffith, Sanjay Patel, and Jennifer Barclay under the supervision of Dr Calum Semple. At this point, the study protocol and supplementary documents had been finalised and ethical approval of the study had been granted in May 2012 by the East Midlands Research Ethics Committee, part of the NHS Research Authority (Reference: 12/EM/1904). Recruitment had finished, having occurred between October 2012 and November 2014 and data collection was into its fourth year. All the Participants had completed four questionnaires, and the fifth questionnaire was due to be fully completed in May 2017. My role within the LBBS research team was to analyse the data from the initial four questionnaires and continue with maintenance of the study. To achieve this, and to produce this thesis, the following objectives were completed:

- Perform a literature review on previous birth cohort studies and asses their design, recruitment strategies and ways in which attrition was reduced.
- Produce a systematic method of analysis of the LBBS data both (cross sectional and longitudinal) by having discussions with experts at the University of Liverpool.
- Modify the study to reduce attrition by inviting participants back into the study if they had not intended to leave.
- Code the raw data so that it could be analysed by the statistics packages used in the LBBS.
- Perform the analysis of the LBBS data, discuss the findings in line with previous findings, and investigate unexpected results.

1.2-Respiratory Disease in Preschool Children

1.2.1-Respiratory Disease and Symptoms

Cough is the most common problem managed by General Practitioners (GP's) and is most common in the preschool age group. Respiratory tract infection (RTI) and asthma are the leading causes of cough in the preschool age group (18). Two thirds of children will attend their GP with a RTI and three quarters of these will have a cough. Seventy five per cent of coughs will show improvement by one week however one in eight experience complications within two weeks of presentation (19). Very few children with recurrent cough go on to develop asthma with wheeze at four years (18). One in three children develop wheezing associated with a RTI in first three years of life but 60% of these will stop wheezing by six years (20).

There are many different phenotypes of wheeze described in literature, most commonly distinguished by their pattern (21), timing of onset (21) and the patient's atopic status(22). These are described in the tables below.

Table 1: The phenotypes of wheeze as described in literature

Pattern (20)	Episodic (viral) Wheeze	Wheezing during discrete time periods associated with viral cold. No wheeze in between episodes
	Multiple Trigger Wheeze	Discrete exacerbations with wheeze in between.
Timing (20)	Transient	Symptoms commence before three years. No symptoms by or after six years
	Persistent	Symptoms commence before three years and continue until and after six years
	Late-Onset	Symptoms start after three years
Atopy (21)	Atopic	Sensitized to one aeroallergen by age of six years, reaction to this allergen causes wheeze
	Non-Atopic	Wheeze with viral infections during years two and three of life

Those with transient early wheeze can be distinguished from other types of wheeze by a deficit in lung function which is evident shortly after birth, before any RTI (20). At birth, persistent wheezers have similar lung function to non-wheezers but had nearly 50% better lung function than transient wheezers. At six years however, persistent wheezers had significantly reduced lung function compared to other phenotypes of wheeze. Persistent wheezers have more frequent symptoms and more frequently have eczema, rhinitis and a family history (FH) of maternal asthma (20).

1.2.2-The Burden of Paediatric Respiratory Disease

In the United Kingdom (UK) across all age groups one in five deaths are due to respiratory disease, which is higher than ischemic heart disease. Only countries with poor health care systems and low funding having higher rates of respiratory disease in Europe. In 2006 respiratory disease was reported to cost the NHS around £6 billion and account for around one million hospital admissions (23).

Respiratory disease is the most common reported long term illness in children and babies with around one in five children and babies having a diagnosis of asthma in 2006 (23). Asthma alone costs the National Health Service (NHS) of around £672 million per year which accounts for between one per cent and two per cent of the NHS healthcare budget (23). In 2009 the estimated rate of asthma in the UK was 136.6/10,000 person years, and the 18-year prevalence was 22.9%(24). The Born in Bradford (BiB) cohort described the rate of wheezing disorders to be 40.3/1000 person years in the first five years of life and identified that one of five children will have been diagnosed with a wheezing disorder or rhinitis by five years of age (25). Respiratory Syncytial Virus (RSV) will effect one in five infants in first year of life; between two and three per cent of these will require hospital admission (26). In the UK RSV accounts for around 450,000 GP consultations, 29,000 hospitalizations and 83 deaths per year with the highest rates in those less than six months old (27). CF has an incidence of around one in 3,500 with a mortality rate between two and five per cent at two years of age, 10 to 30 per cent at five years and 35 per cent at 15 years. Children with CF will experience on average three exacerbations per year (28). The World Health Organization (WHO) reported that the biggest single cause of death globally in the first five years of life was acute respiratory illness such as pneumonia (29).

Respiratory disease impacts on the QoL of both the patients and their family. QoL was reported to be lower in infants aged between two months and five years of age with wheeze (30) and was lower in both children and their caregivers in diagnosed and undiagnosed asthma patients (31). Both patients diagnosed with CF and their families reported a lower QoL (16). A worse QoL in the infant and their caregivers was reported in those with severe asthma (compared to mind/moderate asthma) and those with poor control of their asthma (compared to those with good control) (32). It has been shown that QoL of children aged one to 14 years was improved with increased control of their asthma (33).

These figures show the burden of respiratory disease on both the population of the UK and the NHS and why investigation into the natural history of respiratory disease in preschool children is important.

1.3-Risk Factors for Paediatric Respiratory Disease

Many risk factors for paediatric respiratory disease have been described in the literature. However the significance of these risk factors and the natural history of respiratory disease is disputed in the preschool population. The commonly reported risk factors for paediatric

respiratory disease are discussed below and less reported risk factors are discussed later in this thesis.

1.3.1-Air Pollution

Coal Dust pollution was shown to be associated with increased respiratory symptoms in primary school children in both Merseyside (34) and elsewhere in the UK. In Nottingham it was shown that living within 90 meters of a road and therefore increased exposure to traffic air pollutants was associated with an increased prevalence of wheeze in children (35). In children already diagnosed with asthma, increased levels of air pollution was associated with an increase in symptoms and the use of bronchodilators (36). It was shown that hospital admissions due to respiratory symptoms and nitric oxide production in children's lungs were higher at times of higher air pollution levels; this may be due to inflammation of the airway epithelium (37, 38).

1.3.2-Breastfeeding

The evidence for the relationship of breastfeeding and wheeze over the ages of five is conflicting (39), however there is strong evidence supporting the benefit of breastfeeding on respiratory health before five years of age. Respiratory symptoms in the first six months of life decrease as breastfeeding time increased. Likewise a shorter breastfeeding time and none-exclusive breastfeeding was associated with increased risk of asthma symptoms (7). Breastfeeding for one month reduced the incidence of lower respiratory tract infection (LRTI) in the first six months of life (40). Breastfeeding for six months or more was associated with lower levels of wheezing, SoB, dry cough, and phlegm production during the first four years of life. The strongest association was in the first and second year of life (41). Breastfeeding may also reduce the negative effect of maternal smoking and premature birth on respiratory symptoms (7).

1.3.3-Smoke Exposure

There is a large evidence base supporting the hypothesis that smoking during pregnancy and postnatal environmental tobacco smoke (ETS) exposure is associated with a higher prevalence of respiratory symptoms in children. The effects of maternal and paternal smoking prenatally and postnatally is likely to be dependent on the individual and their environment. It may cause an adverse effect on the immune system, the structure and the function of the developing lung (42).

Maternal Smoking in Pregnancy

Maternal smoking in pregnancy has been shown to increase the incidence of wheeze in early childhood (43). Smoking in pregnancy, but not after, increased recurrent wheeze and the

diagnosis of asthma in the first 2 years of life (5). Meta-analysis of eight European cohort studies has shown that maternal smoking in pregnancy increased the risk of both wheeze and asthma between four and six years of age regardless of ETS after birth. Maternal smoking in pregnancy had a dose response relationship with the number of wheezing episodes, persistent wheezing and asthma diagnosis at 15 years of age (44).

Postnatal Smoking

Infants with a mother who smoked were shown to be three times more likely to have a LRTI in the first three years of life and had a younger age of first infection than those who did not have a mother who smoked. There was a dose response relationship shown between the number of cigarettes the mother smoked and the incidence of LRTI (45). Similarly in a Polish cohort study, three year olds who were exposed to ETS had more RTIs which required increased admissions to hospital and antibiotic treatment (6). Admissions to hospital with a LRTI in the first five years of life was higher in those infants with a smoking mother (46). ETS was associated with an increase incidence of wheeze in the first (47) and second year of life (5). In the first two years of life ETS was associated with new onset asthmatic and allergic symptoms and negatively associated with remission of symptoms between three and six years of age (48).

1.3.4-Prematurity

Preterm birth was associated with an increase prevalence of early remitting wheeze and persistent wheeze over the first seven years of life (49). In a Swiss cohort study, wheeze, inhalation therapy and hospitalisation in the first year of life were all associated with preterm birth (50). Babies born at less than 28 weeks are at risk of bronchopulmonary dysplasia (BPD) but there is mixed evidence on the difference in frequency of respiratory symptoms between premature babies with and without BPD (51).

1.3.5-Low Birth Weight

A meta-analysis study has shown that a low birth weight significantly increases the risk of developing asthma in childhood (52). A birthweight less than 1.5kg was a risk factor for diagnosis of asthma and hospitalisation due to asthma between birth and four years of age (53). A low birthweight was associated with reduced lung function at six weeks of age (54) and increased incidence of wheeze in the first three years of life (55).

1.3.6-Household Status

Poor housing increases respiratory disease in the first two years of life and a damp home environment increase cough and phlegm production at 10 years of age (56, 57). Household overcrowding may increase the risk of LRTI in children (58) however having siblings at home

was associated with decreased risk of asthma diagnosis between 4.5 and 14 years of life (59-61). Bed sharing at 24 months was shown to be a risk factor for wheeze between two and six years of age (62). Increased household humidity was associated with an increased prevalence of wheeze (63), however higher dust endotoxin levels were shown to be protective of asthma (64). Higher household income was associated with increased respiratory health, while children from poorer families had an increased risk of LRTI and asthma (56, 65, 66). Excessively clean environments were associated with increased wheezing in childhood (67). Many of these findings are in line with the hygiene hypothesis of asthma (68, 69).

The Hygiene Hypothesis of Allergy

It was suggested by Strachan in 1989 that infection in early childhood, due to the presences of older siblings may reduce the development of allergic illness (69). Rook developed this theory further by suggesting that the proper development of the immune system depended on microbes that were present during evolution. The absence of these microbes may lead to the development of allergic disease (68).

1.3.7-FH of Atopy

Having a mother with a history of atopy is associated with infant asthma between three and five years of age (70). Maternal asthma was a risk factor for wheeze in girls of two years old and above and for boys of five years old and above. Paternal asthma was a risk factor for boys between two and five years (71) . Children with mothers with asthma are more likely to have a diagnosis of asthma (72).

1.3.8-Other Risk Factors and Exposures

Wheeze during childhood is more common in boys than in girls (25). There is disagreement on the role of nursery attendance and its association with asthma and development of wheeze. Nursery attendance has been shown to be associated with an increased diagnosis of asthma between three and five years of age (70). In a different study however, it has been shown to reduce wheeze in the first five years of life (73). A further study showed nursery attendance to increase the symptoms of asthma during the first four years of life and be protective there after (74). A western diet with high levels of trans fatty acids may increase the risk of asthma, were as a Mediterranean diet with high fish, fruit and vegetables may be protective(75, 76). Sensitization to dogs, cats and dust mites were all associated with an increased risk of asthma (77, 78) and exposure to other furry pets was associated with increased early remitting and persistent wheeze(79).

1.4-Measures of Respiratory Disease in Preschool Children

There are many tests of lung function. The choice of test in preschool children is dependent on the intended outcome measure, the feasibility of the test, and cooperation of the child, and is often determined by their age. In 2007 the American Thoracic Society produced guidelines on the use of lung function tests in preschool children. Despite guidelines only 82.3% of children aged between four and five years can produced one acceptable spirometry result and only 54% can produce repeatable results (80).

Peak Expiratory flow rate is a simple and cheap assessment of airway obstruction which has produced acceptable measurements in preschool children (81). However, it is unreliable and has poor reproducibility so is only used as a screening tool (82).

A pneumotachometer and facemask can be used to measure tidal breathing, however it has not been tested for variability and the ability to detect disease in preschool children (80).

Respiratory Inductance Plethysmography (RIP) is performed by using volume signals monitored by bands placed around the chest and abdominal wall. In children between three and six years of age, RIP has successfully assessed changes in lung function and measured airflow obstruction (24, 83) however there is no data in infants younger than this. That being said, RIP is more successful than spirometry and the pneumotachometer system in very young children (84).

The Forced Oscillation Technique (FOT) is performed by exerting external pressure to the respiratory system and requires no breathing manoeuvres so little cooperation from the patient is required (85). FOT has been shown to be sensitive in assessing bronchodilation in children aged two to 18 years old and bronchial hyper-responsiveness in between five and 18 years old (86, 87).

The Interrupter Technique is the measure of the pressures produced during normal breathing after a sudden airflow interruption at the mouth (80). It is a feasible and repeatable measure of lung function and has been successfully used in those over three years for short term assessment of intervention response (80, 82).

The Multiple Breath Wash Out technique is as assessment of functional respiratory capacity and ventilation distribution which requires only passive breathing (80). Minimal cooperation is required and it has previously identified 73% of those with abnormal lung functions in CF patients between two and five years of age (88).

Bronchial responsiveness is assessed by the administration of histamine or methacholine to the lungs to cause airway narrowing (82). This has a high sensitivity and positive predictive value in asthma, and is useful to determine the effectiveness of interventions however carries the same problems as spirometry when used in preschool children (80).

Nitric Oxide is produced in the lungs by eosinophils during airway inflammation in allergic asthmatic patients (89). Nitric oxide measurements have successfully been used in a study in school children (37) however not in preschool children.

In conclusion pulmonary function testing in those younger than five years old is difficult due to the reduced ability to voluntarily perform the manoeuvres required and if testing is essential it is often performed whilst the child is asleep. Although children between two and five years of age, are usually more cooperative than those below two years old, they still have short attention and are unlikely to perform the test as well as children over five years (80, 82). There is no routine or simple measurement of function suitable for regular use in preschool children, especially in those under two years of age. Because of this, respiratory symptom questionnaires are often used to assess respiratory symptoms in preschool children. Respiratory symptoms questionnaires are discussed in section 1.5.

1.5- Respiratory Symptom Questionnaires

There are several adult, self-reporting respiratory questionnaires that have been validated for various uses in the adult population (see appendix 5). Although some adult questionnaires may have informed the design of paediatric questionnaires, they are often very different. The majority of questionnaires assessing the paediatric age group are completed by the subject's parents. Several questionnaires have been developed and validated for use in the paediatric population and specifically the preschool population. These are discussed below.

1.5.1-Paediatric Respiratory Symptoms Questionnaires

The Asthma Control Questionnaire for Children (ACQ)

The ACQ was developed to produce a reliable, valid and responsive questionnaire for clinical use, to assess asthma control in children aged six to 17 years old. It was developed without the need of a daily record of symptoms, medication use and airway calibre (90). It contains seven items assessing the previous seven days on a seven point scale; five symptom questions, a question assessing medication use and an FEV_1 measurement (90). It has been validated for use in children aged six to 10 years of age when administered by an interviewer (91). Cut off points have been determined dividing patients into 'well controlled' and 'inadequately controlled' asthma (92).

The Asthma Therapy Assessment Questionnaire (ATAQ)

The ATAQ was developed to assist clinicians identify children and adolescents with asthma who are at risk of adverse outcomes. The questionnaire contains 20 items assessing symptom control, behaviours, attitude barriers, self-efficacy barriers and communication gaps. This questionnaire addresses issues that are not addressed by other questionnaires such as the ability to take medications. It is useful in identifying those in need of further management or medical attention in five to 17 year olds (93).

Breathmobile Case Identification Survey

The Breathmobile Case Identification Survey is a one-page survey that was developed as part of the Breathmobile programme. The Breathmobile programme aimed to detect cases of asthma in a large population aged less than 18 years of age (mean age 8.9) in reaction to a large increase in the incidence and prevalence of asthma (94). It contained seven questions to be completed by caregivers and was shown to have a sensitivity of 86.5% and a specificity of 83.6 per cent. It had a misclassification rate of 14.3 per cent. An inexpensive incentive to complete the questionnaire increased return rates from 35.3 to 65.0 per cent (95). It has been validated in a low socioeconomic, urban population to identify uncontrolled asthma with moderate to severe disease activity (94).

The Childhood Asthma Control Test

The Childhood Asthma Control Test was developed due to a lack of measure of asthma control in children under 12 years of age. Its development has provided a tool that provides the clinician with a quick overall picture of asthma control and aids communication between clinicians, caregivers and the child (96). It is a seven-item questionnaire with four child completed and three caregiver completed items. It is reliable and accurate in assessing asthma control in four to 11 year olds (96). A score of 19 or less indicates inadequate control (96) with a score of 12 showing the poorest control and increased risk of poor outcome (97).

Childhood Asthma Questionnaire (CAQ)

There are three versions of the CAQ; A, B and C which were each developed for a different age range (four to seven years, eight to 11 years and 12 to 16 years respectively). The questionnaires contain 14, 22 and 41 items respectively (98). These questionnaires assess the QoL of the respondent due to their diagnosis of asthma using pictorial scales of either increasing size bars or cartoon faces. The younger responders completed the questionnaires with the help of their parents (98, 99). The questionnaires had good test-test repeatability

and were shown to be good estimates of disease stability. Internal consistency of the questionnaires varied but was higher when used in older children (98).

Chronic Cough QoL Questionnaires

The Cough Specific QoL Questionnaire was originally developed in Brisbane due to the lack of a cough specific QoL measure in the paediatric population. It assesses parental feelings and worries towards their child's chronic chough (100). It is a 27-item questionnaire assessing physical, social and psychological domains of QoL. It is a reliable and valid outcome measure and is sensitive to change over time when assessing children under 14 years (100). Later, a 16-item child completed questionnaire was developed. That has been shown to be valid and reliable in seven to 17 year olds and is sensitive to change over time (101).

The International Study of Wheezing Infants Questionnaire (EISL-WQ)

The International Study of Wheezing Infants Questionnaire (EISL-WQ) contains 45 questions assessing demographics and risk factors for wheeze, respiratory symptoms, physician diagnosis of asthma and medication use. It was designed to be completed by parents (102). It has been validated in Spanish and Portuguese and shows agreement with clinical examination in infants aged 12 to 15 months old (103, 104). A shortened version containing 21 questions has been validated in Portuguese showing good reliability, reproducibility and internal consistency for children aged 12 to 36 months of age (102).

ISAAC Questionnaire

The ISAAC questionnaire was developed by experts using a consensus process at a workshop using previously validated questions. It contained 21 items assessing prevalence and severity of wheeze, eczema and rhinitis (105). The questionnaire was self-reported in 13 and 14 year olds, and parental reported in six to seven year olds (105). It has been successfully used in an international study (ISAAC) (105). The questionnaire has been produced in a variety of languages (105, 106) and an international video version of the questionnaire has also been validated (107).

The Leicester Respiratory Cohorts Questionnaire

The Leicester Respiratory Cohorts Questionnaire contains 51 questions assessing three domains; symptoms, environment and home factors, and family and social status (108, 109). The symptom domain assesses the nature of the respiratory history and specifically assesses wheeze, cough and doctor diagnosed asthma. If wheeze is reported an additional 10 questions assess the phenotype of the wheeze (109). It has been shown to have excellent repeatability (110).

The Mechanisms of Development of Allergy (MeDALL) Core Questionnaire

The MeDALL Core Questionnaire was developed to harmonize questionnaires that asses asthma and allergy used in birth cohort studies to allow comparison between studies (111). It is now in use in 11 birth cohort studies in eight different languages. It was developed by members of eight European birth cohorts to asses 14 to 18 year olds and their parents. It consists of eight sections with a total of 66 core questions with an additional 19 optional questions (111). There has been no formal validation of this questionnaire and it may not be suitable to younger populations.

The Paediatric Cough Questionnaire

The Paediatric Cough Questionnaire is a measure of the QoL of a child with a chronic cough completed by the caregiver. It contains five questions assessing frequency; sleep disturbance (of parent and child), severity, and 'bothersomeness' to the child on a 6-point Likert scale. It showed good test-test repeatability, internal consistency and validity (112).

Paediatric Asthma Quality of Life Questionnaire (PAQLQ)

The PAQLQ was designed to examine the burden of asthma experienced by children with the disease. It aimed to assess areas of function and physical and emotional wellbeing. It consisted of 23 items split into three domains; activity limitation, symptoms, and emotional function. The unique aspect of this is that the questionnaire is individualised; at the first time of completing the questionnaire the participants asked to identify three activities they enjoy doing. Questions are assessed on a 7-point Linkert scale (113). The PAQLQ was able to detect change in health status and differentiate from stable patients aged seven to 17 years. It was reproducible in stable patients (113). A pictorial version has been developed, however this had only been validated in those over five years of age (114).

Test for Respiratory and Asthma Control in Kids (TRACK)

The TRACK questionnaire is a five item questionnaire completed by parents which assesses symptoms, their frequency and their effect on activity, waking at night and medication use (115). It has been validated and is a reliable, easy to administer questionnaire. Cut off scores identifying those with respiratory control problems and a minimally important difference score have been determined (115, 116). The questionnaire is responsive to changes in symptoms over time (117).

Conclusion

There are many paediatric respiratory questionnaires some of which have been validated for use in the paediatric population. However the majority of these are not validated in those

less than five years of age. The majority of questionnaires are disease specific or assess QoL alone. The LRSQ questionnaire used in the LBBS is the only questionnaire that is validated in the preschool population, which assesses a range of respiratory symptoms under various conditions and combines the assessment of the QoL of the child and their caregiver with a respiratory questionnaire.

1.5.2-The Liverpool Respiratory Symptom Questionnaire
Development of the LRSQ

The Liverpool LRSQ was designed by respiratory consultants at the Liverpool Women's Hospital and Alder Hey Children's Hospital. It was designed using common reoccurring features and concepts from standard questionnaires already in use in older populations. It assesses wheeze, cough and breathlessness during both the day and night, and the impact of these symptoms on both the child's and family's quality of life over the previous three months. It is the assessment of the impact of these symptoms which makes the questionnaire unique. A 5-point Linkert scale is used ranging from no symptoms to symptoms every day (1). The original questionnaire contained 32 questions. A cohort of 242 babies was used to assess practicality, response rate, reliability, validity and criterion in comparison to expert opinion. (1).

Response rates to the questionnaire sent via post in an earlier study were 64% for the first questionnaire and 56% for the repeat questionnaire. Questionnaires completed in the outpatients department produced a response rate of 100%. Overall this led to 114 pairs of questionnaires for further analysis (1). The LRSQ showed moderate short term repeatability (Kappa score of 0.4 or more) in all bar one question which showed fair repeatability, and good internal consistency in all domains (1). Factor analysis showed four questions were responsible for a large proportion of the variance in responses so these were removed from the original questionnaire which was then rearranged into eight domains (table 2) (1). The questionnaire showed agreement with respiratory expert opinion. Those with asthma scored significantly higher in all domains. ROC analysis showed that all domains had a good sensitivity for identifying asthma patients, however some domains showed unacceptable specificity (1).

Overall the original development of the LRSQ has produced a practical, acceptable respiratory symptom questionnaire for the use in under five year olds, containing 28 questions over eight domains which produced good response rates and was valid, with good internal consistency (1). The questionnaire is shown in figures 1-4.

Name of Child   **Study Number**

1.   **This first question refers to at any time in your child's life:**

Has your child ever had wheezing (whistling noise coming from the chest) at <u>any time in the past</u>?	*Yes*	*No*

2. The next questions are specifically aimed at the <u>last three months</u>:

A) During the day (when awake) in the <u>last three months</u>:

i) My child has had wheezing (whistling noise coming from the chest):

Every day   *most days*   *some days*   *a few days*   *not at all*

ii) My child has had a cough:

Every day   *most days*   *some days*   *a few days*   *not at all*

iii) My child has had a rattly chest:

Every day   *most days*   *some days*   *a few days*   *not at all*

iv) My child has been short of breath:

Every day   *most days*   *some days*   *a few days*   *not at all*

B) During the night (when asleep) in the <u>last three months</u> :

i) My child has had wheezing (whistling noise coming from the chest):

Every night   *most nights*   *some nights*   *a few nights*   *not at all*

ii) My child has had a cough:

Every night   *most nights*   *some nights*   *a few nights*   *not at all*

iii) My child has had a rattly chest:

Every night   *most nights*   *some nights*   *a few nights*   *not at all*

iv) My child has been short of breath:

Every night   *most nights*   *some nights*   *a few nights*   *not at all*

v) My child has snored :

Every night   *most nights*   *some nights*   *a few nights*   *not at all*

Figure 1: Page 1 of the Liverpool Respiratory Symptom Questionnaire

C) How many colds has your child had in the last three months:

None   one   two   three   more than   always
                                    three   has a
                                                    cold

If the answer to the above question is 'none' continue to questions in section D:

When my child has had a COLD in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

Every cold   most colds   some colds   a few colds   not at all with colds

ii) My child has had a cough:

Every cold   most colds   some colds   a few colds   not at all with colds

iii) My child has had a rattly chest:

Every cold   most colds   some colds   a few colds   not at all with colds

iv) My child has been short of breath:

Every cold   most colds   some colds   a few colds   not at all with colds

---

D) When my child does NOT have a COLD, in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

Every day   most days   some days   a few days   not at all

ii) My child has had a cough:

Every day   most days   some days   a few days   not at all

iii) My child has had a rattly chest:

Every day   most days   some days   a few days   not at all

iv) My child has been short of breath:

Every day   most days   some days   a few days   not at all

Figure 2: Page 2 of the Liverpool Respiratory Symptom Questionnaire

E) When my child has been MORE ACTIVE (e.g. crawling, walking or when excited) in the <u>last three months</u>:

i) My child has had wheezing (whistling noise coming from the chest):

Every day   most days   some days   a few days   not at all

ii) My child has coughed:

Every day   most days   some days   a few days   not at all

iii) My child has had a rattly chest:

Every day   most days   some days   a few days   not at all

iv) My child has been short of breath:

Every day   most days   some days   a few days   not at all

F) These next three questions are about other problems your child may have had. Over the <u>last three months</u>:

i) My child has had noisy breathing that does not seem to come from the chest :

Every day   most days   some days   a few days   not at all

ii) My child has had fast breathing:

Every day   most days   some days   a few days   not at all

iii) My child has had noisy breathing that appears to come from the throat or back of the throat:

Every day   most days   some days   a few days   not at all

Figure 3: Page 3 of the Liverpool Respiratory Symptom Questionnaire

G) The next four questions are on how your child's chest symptoms actually affect HIM or HER over the <u>last three months</u>:

i) My child's chest symptoms have affected my child's feeding or eating:

Every day   most days   some days   a few days   not at all

ii) My child's chest symptoms have woken up my child:

Every night   most nights   some nights   a few nights   not at all

iii) My child's chest symptoms have reduced my child's activity:

Every day   most days   some days   a few days   not at all

iv) My child's chest symptoms have made my child unusually tired:

Every day   most days   some days   a few days   not at all

H) The next four questions are on how your child's chest symptoms actually affect YOU and YOUR family's life the <u>last three months</u>:

i) My child's chest symptoms have limited my activities:

Every day   most days   some days   a few days   not at all

ii) My child's chest symptoms have resulted in adjustments being made to our family life:

Every day   most days   some days   a few days   not at all

iii) My child's chest symptoms have disturbed our sleep:

Every night   most nights   some nights   a few nights   not at all

iv) I have been worried about my child's chest symptoms:

Every day   most days   some days   a few days   not at all

Figure 4: Page 4 of the Liverpool Respiratory Symptom Questionnaire

Previous Use of the LRSQ

Since its development the LRSQ has been further validated and has become a popular questionnaire in assessing respiratory symptoms in under five year olds.

The LRSQ can differentiate between those with CF and those without and between active and stable CF disease in both preschool infants and six to 12 year olds. It correlates well with other measures of respiratory disease. In the same study, analysis of the questionnaires showed all eight domains had good internal consistency in the preschool aged group. Removal of questions about snoring improved the internal consistency further (16).

The LRSQ has been increasingly used in studies that are independent of the original research team that are described below. The ADEM study used the LRSQ in the development of a new asthma diagnostic technique (118). The LRSQ was used as an outcome measure in premature infants without chronic lung disease to measure of lung function (119). Finally it was used in a study in preschool infants with wheeze to assess if the response to corticosteroids can be predicted by inflammatory response measures or by measuring the change in symptoms and lung function (120).

The LRSQ has been used in the 'Prevent Passive Smoke Exposure study' which assessed the benefit of motivational interviewing in preventing passive smoke exposure in those with a high asthma risk (121). It was used as a disease measure in a study assessing the impact of primary prevention programs on risk taking behaviour for allergic disease (122). A cross-sectional study showing preterm birth was associated with increased wheeze used the LRSQ to assess the respiratory symptoms in under five year olds (25, 46). It has also been used successfully to show that RSV associated wheeze was more likely to produce allergic sensitisation and lead to increase symptoms and steroid use compared to RSV Bronchiolitis (123).

Five studies investigating maternal and birth risk factors have used the LRSQ (124-128). Two studies assessing impact of maternal asthma control in pregnancy on preschool respiratory symptoms used the LRSQ (124, 125). They found that firstly, optimised control of maternal asthma may reduce the risk of infant bronchiolitis and possibly subsequent asthma in childhood (125). Secondly that exposure to maternal asthma may alter the infant's peripheral blood DNA methylation profile which is a possible risk factor for childhood asthma development (124) The LRSQ has been used to investigate the maternal acetate levels in pregnancy and showed that a higher levels and a high fibre diet may be associated with reduced preschool airway disease (127). Similarly the effects of amniotic protease on

childhood respiratory symptoms was assessed using the LRSQ but there was no association found (128). Lastly it was used to investigate the management of very early preterm premature rupture of membranes with amnion transfusion, but again no significant benefit was found with regards infant respiratory symptoms (126).

The LRSQ was used to assess the respiratory outcomes in children with neurodisability. It successfully concluded that children with neurodisability have higher respiratory symptom scores (17, 129). In infants who have undergone lobectomy due to congenital thoracic malformations the LRSQ was able to differentiate those who have ever had asthma compared to those who have not (130).

The LRSQ has been used in a variety of studies alongside the ISAAC questionnaire as a popular measure of baseline atopy. This combination of questionnaires has been used in studies assessing the use of skin prick testing and nitric oxide production measurement in the investigation of peanut allergies (131, 132). Likewise it has been used in a study to investigate the link between environmental smoke exposure, interleukin 4 and 13 gene polymorphisms and risk of infant wheeze. It was found those exposed to ETS with the interleukin 4 gene polymorphisms conferred at a tenfold increased risk of wheeze (133).

1.6- Birth Cohort Studies

Birth cohort studies have been commonly used to investigate risk factors for paediatric respiratory disease and to map the natural history of respiratory disease in children. A literature review of Birth Cohort Studies was performed to investigate their findings and study designs. The search terms used to identify cohort studies performed in both Britain and internationally, which follow both national and regional populations are shown in appendix 1. An in depth analysis of their main findings and their study design was performed and is shown in appendix 2; only those cohort studies with findings relevant to preschool respiratory disease and its risk factors, or those with novel and interesting study designs are discussed. During this literature review four large respiratory studies that did not follow a 'birth cohort study' design were identified. A detailed analysis of their study design and key findings is also included in appendix 3. The remaining cohort studies found in the literature review but that are not discussed in detail are shown in appendix 4. Table 2 shows a summary of the study design of the relevant cohort studies. A summary of recruitment strategies and methods to reduce attrition in previous cohort studies is given below.

Table 2: Birth cohort studies identified by literature review

Cohort	Year	Cohort Size	Recruitment Rate	Attrition
1946 British Cohort Study (134)	1946	13,600	82%	12.6% (4 years) 19.9% (15 years)
1958 British Cohort Study (135)	1958	17,400	99%	0.7% (7 years)
1970 British Cohort Study (136)	1970	16,600	96%	21.1% (5 years)
The Millennium Cohort Study (137)	2000	18,800	88%	17.2% (3 years) 17.8 (5 years)
Aberdeen Children of the 1950's Cohort Study (138)	1950	12,000	85%	36% (50 years)
Avon Children of the 90's Study (139)	1991	14,541	95%	2.6% (2 years) 15.6% (5 years)
Born in Bradford (49)	2007	13,776	64%	25% (1 year) 30% (2 years)
Isle of Man Cohort Study (140)	1992	1,314	95%	21.2% (15 years)
The Newcastle Thousand Family Study (141)	1947	1,146	84%	26.1% (5 years)
The Southampton Women's Cohort (142)	1998	12,583	75%	5% (1 year) 7% (2 years)
Manchester Asthma and Allergy Study (143)	1995	1,500	41%	6.9% (1 year) 8.3% (3 years)
The Prevention and Incidence of Asthma and Mite Allergy (144)	1996	4,000	50%	8% (8 years)
The Tucson Children's Respiratory Study (45)	1980	1,200	78%	13% (5 years)

1.6.1- Summary of Recruitment in Birth Cohort Studies

Recruitment strategies in previous birth cohort studies have led to recruitment rates between 41% and 99% of the eligible population (135, 143); regional cohort studies report recruitment rates between 95% and 41% (139, 143). Recruitment has been from GP practices (142), prenatal clinics (144), during postnatal care (134-136) or using electronic records after

birth (137, 138). Recruitment has been performed by either midwives, other members of the study team (136, 141, 143) or by participants self-registering (142). The length of recruitment has varied from one week in some studies (134-136) to over a year in others (72, 74, 75); the use of all year round recruitment has reduced the seasonal variability in characteristics of birth and diseases. The use of advertisement before the study in the Isle of Man cohort study lead to very high participation rates (140). The Avon Children of the 90's study and the Isle of Man Cohort study were the two regional cohort studies with the most successful recruitment strategies. They both recruited for over a year using midwives to recruit mothers during their prenatal care (139, 140).

The profile of the infants and their families recruited into the cohort studies were often not representative of the population eligible for recruitment particularly in smaller regional birth cohort studies. For example in the Avon Children of the 90's study (ALSPAC), mothers were more likely to be white, own a home and car, be married, have a higher socioeconomic status and live in an overcrowded home that the population eligible for recruitment (139). The BiB cohort contained older, more educated mothers (49) and the mothers in the Prevention and Incidence of Asthma and Mite Allergy study (PIAMA) were more highly educated and more likely to breastfeed than the population of the Netherlands (144). Likewise infants of the minor ethnicities were under represented in the 1958 British Birth cohort (135).

1.6.2- Summary of Attrition in Birth Cohort Studies

It is clear from previous cohort studies that attrition is an unavoidable phenomenon in cohort studies due to a variety of causes. These include death, withdrawal of consent, emigration and loss of contact. The 1958 British cohort had the lowest attrition rate; it was still able to trace 99.3% of its participants at 7 years (135). Of the smaller regional cohorts the PIAMA study had the lowest attrition rates with only 8% of the cohort being lost over the first 8 years of the study (144). The BiB 1000 sub-study had the highest rates of attrition with 30% of the cohort being lost over the first 2 years (49).

Measures have been taken to increase response rates and reduce attrition in previous cohort studies. Methods used are regular contact with participants through the use of newsletters, birthday cards (49), phone calls (142) and study websites (49). School registers and links to medical or government records have been used to reduce the proportion of participants who are lost due to a change in their contact details (134-136). It is clear that studies that have more resources (such as access to school/medical/government records and a team designated to improving follow up) had reduced attrition rates in comparison to smaller studies with fewer resources.

1.7-Merseyside Health Profile and Respiratory Studies

1.7.1-Merseyside Health Profile

In 2015 Liverpool was ranked the 4th most deprived city in the UK with 8.7% of its population being in the most deprived 1% of the UK population (145). Over 32% of children in Liverpool live in low income families (13) . Life expectancy is lower than the national average for both males and females and this is most pronounced in more deprived areas (13). Liverpool has high levels of preschool respiratory disease compared to the average in the UK. The Chief Medical Officer's report of 2012 stated that Liverpool has a higher rate of hospital admissions due to bronchiolitis and the duration of stay in hospital is longer than the average in England (15). The hospital admission rate due to LRTI's is similar to that of the average in England however the length of stay in hospital is longer than the average in England (15). The prevalence of asthma in Liverpool is increasing and the number of emergency admissions due to asthma in both children and adults is higher (304.7 compared to 216.1 per 10000 patients), and the average duration of stay in hospital is longer again indicating inadequate control (14, 146). The rate of death due to respiratory conditions at all ages is higher in Liverpool than the average in England (14). Liverpool has high rates of smoking compared to the average in England and smoking related deaths are more common, accounting for 928 deaths a year (13).

Children in Liverpool tend to be less educated than the average children in England, and they are more likely not to be in education at 16-18 years old and more likely to be living in poverty at 16 years of age (146). Liverpool has higher rates of child Accident and Emergency (A&E) attendances compared to England, higher levels of children with decayed teeth and a higher rate of admissions due to dental caries (146). In school year 6, 23% of children are classified as obese, which is higher than the national average (13).

In 2015 mothers in Liverpool were more likely to be teenagers, less likely to initiated breastfeeding, less likely to vaccinate their children and are more likely to be smoking at the time of delivery (16.1% compared to 10.6%) than the average mother in England (13).

All this together makes the Liverpool population a good cohort for respiratory epidemiological studies due to the higher prevalence of risk factors for respiratory disease that they express.

1.7.2-Merseyside Respiratory Studies

In 2006, 61.4% of children in Liverpool lived in household with at least one smoker, compared to 53% in the rest of the UK. This exposure to tobacco smoke was shown to give the children

a higher average saliva cotinine concentration than the average in England (1.6+/-0.4 ng/ml compared to 0.5ng/ml) (147). Risk factors for an increased ETS exposure was maternal (rather than paternal) smoking, age less than seven years of age, being male and a lower socioeconomic status (147).

Two studies investigated the effect of dust air pollution on respiratory symptoms in school children in Liverpool. Liverpool was an ideal place for this study due to the Bootle dock yard situated within a large residential area (36, 148). Studies found that exposure to the coal dust increased risk of respiratory symptoms and absence from school. Those expose to coal dust were also more likely to be low birth weight and their parents were more likely to be unemployed and smoke (34). It was shown that living within two kilometres of the docks made the children twice as likely have excess cough, breathlessness, be absent form school and have a doctor diagnosis of asthma compared to those over two kilometres from the docks (148).

Two cross-sectional studies distributed questionnaires based on Clifford et al. (149) across 15 schools on Merseyside to investigate the effect of parental asthma on premature birth and subsequent respiratory disease (150, 151). It was found that maternal smoking and maternal asthma were risk factors for preterm birth which was associated with respiratory disease in school children (150).

Between 1991 and 1998 maternal asthma and hospital admissions due to asthma had nearly doubled in Liverpool. Wheezing had increased in school children but the diagnosis of asthma (defined by the triad of symptoms of cough, SoB and wheeze) had remained stable. Higher deprivation, male sex, allergy, obesity and parental asthma were all shown to be associated with higher risk of asthma (151).

A study, that assessed lung infection in adults from Liverpool, showed that opportunistic mycobacterial infections accounted for 3.9% of pulmonary infections. This was higher than a similar study in Wales at a similar time (2.9%). The high smoking rates in Liverpool may have accounted for this difference (152).

1.8-Conclusion

The LBBS is a longitudinal birth cohort study now running into its 6th year. It uses the LRSQ, a popular, validated measure of respiratory disease in preschool children, to assess the respiratory symptoms of the cohort biannually from four months to five years. The study aims to map the natural history of respiratory disease in Merseyside. Birth cohort studies have been used to assess respiratory disease for many years and have produced many novel

findings with regards paediatric respiratory disease. Common risk factors for respiratory disease discussed in the literature are parental smoking pre and postnatally, air pollution, premature birth, low birth weight and deprivation. Breastfeeding has been shown to be protective of respiratory disease in early life. Merseyside is an ideal area for a respiratory cohort study due to its high prevalence of risk factors of respiratory disease in children, including high maternal smoking, low breastfeeding rates and high air pollution. Liverpool has a high rate of hospitalisation of asthma and bronchiolitis compared to the population of the UK. A questionnaire was chosen to assess respiratory disease rather than formal measures of lung function as they are unreliable in the preschool population. The LRSQ has been chosen as a measure of respiratory disease in the current study due to its previous development and validation on the preschool population of Liverpool. It also incorporates assessment of the QoL of infants and their families into the questionnaires. This is an important factor to consider when assessing respiratory disease as shown by previous studies. Attrition is an inevitable phenomenon in cohort studies for a variety of reasons including death, emigration, loss of interest and loss of contact. A good relationship with the cohort is imperative for reducing attrition; this has previously been done in some studies with the use of birthday cards, newsletters and social media. Well supported studies with team members dedicated to reducing attrition by contacting participants, and studies with access to school or hospital records have the lowest attrition rates.

Chapter 2 -Methods

There are two distinct phases in the methodology of the LBBS; the methods of the study design and the methods of analysis of the data of the study. The study design and development were conducted by previous investigators and published in their MPhil theses (2, 3). A short summary of this is presented in section one of this chapter. The second phase of work was the analysis of the LBBS conducted by the author. The methods used to analysis the data are described in detail in section two of this chapter.

The LBBS is 'a prospective, longitudinal birth cohort study' that uses the LRSQ 'to conduct biannual assessment of the respiratory symptoms in preschool children born in Liverpool from birth until the age of five years'. The design of the LBBS and questionnaire development began in 2012 and has undergone five phases outlined in table 3.

Table 3: Phases of the LBBS

	Phase	Investigator (s)	Dates
1	Protocol Completion and Ethical Approval	Miss Rosanna Pickles Miss Bethan Griffith Dr Calum Semple Prof Paul McNamara Prof Kevin Southern Prof Ben Shaw	May 2012
2	Questionnaire Development Redevelopment	Miss Rosanna Pickles Miss Bethan Griffith Mr Sanjay Patel	September 2012- January 2013 June 2015
3	Recruitment	Miss Rosanna Pickles Miss Bethan Griffith Mr Sanjay Patel Miss Jennifer Barclay	January 2013 - November 2014
4	Distribution	Miss Jennifer Barclay	September 2014 - August 2015
5	Analysis	Mr Joshua Stead	September 2016 – June 2017

2.1-Section 1. LBBS Study Design and Development Summary

2.1.1-Aims

The aims of this section of the study were to:

- Develop the study protocol and obtain ethical approval for the study.

- Develop study materials and the questionnaire to be used in the study using expert knowledge, Public Patient Involvement (PPI) sessions and pilot studies.

- To determine and initiate a method of creating an automated online system for the distribution and completion of questionnaires.

2.1.2-Protocol Development

Protocol development finished and ethical approval was granted in May 2012 (Research Ethics Committee Ref: 12/EM/1904). The study protocol was developed by Miss Rosanna Pickles, Dr MG (Calum) Semple, Prof Paul S McNamara, Prof Kevin W Southern and Professor NJ (Ben) Shaw. The study protocol is shown in appendix 6.

2.1.3-Questionnaire and Study Material Development

Rossana Pickles and Bethan Griffith developed the questionnaires through the use of PPI sessions based at the LWH. This work has been described previously by MPhil students in their own work (2, 3). A summary of this is given in appendix 7. The final design of the questionnaire and other materials used in the LBBS are shown in appendix 10- 13.

2.1.4-Recruitment

The recruitment phase was carried out by Rossana Pickles, Bethan Griffith, Sanjay Patel and Jennifer Barclay and occurred between January 2013 and November 2014. Eligible Infants were recruited after birth from the LWH. Inclusion and exclusion criteria are shown in figure 5. Initially if interested in the study, parents (usually mothers) would complete a postcard with

> **INCLUSION**
>
> - Born at LWH
> - Parents lived in postcodes L1-L38
> - Spoke sufficient English to consent to the study and complete questionnaire
>
> **EXCLUSION**
>
> - Infants in local authority care
> - Infants with futile prognosis as identified by clinical team

Figure 5: Inclusion and Exclusion criteria in the LBBS

contact details and leave it with the research team after their discharge from hospital. Later parents would complete an app-based form on a tablet offered by members of the research team. The research team or automated email process would then contact the participants when their child reached four months of age with the consent form and questionnaire one via post or email respectively.

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A four-week pilot study of recruitment of infants into the LBBS was performed by Rosanna Pickles and Bethan Griffith. The results of this pilot study are shown in appendix 8. Discussions within the research team took into account the results of the pilot study and it was decided that four days a week (Monday, Tuesday, Thursday and Friday) would be a more suitable strategy. This was trialled for one week producing response rates of 69% and was therefore deemed effective (2, 3).

2.1.5- Questionnaire Distribution

Questionnaire distribution began in May 2013, is ongoing, and due to finish in October 2019. A consent form and questionnaire one was sent to the cohort when the infant was four months of age. Infants are assessed every six months until 10 questionnaires have been completed at four years and 10 months of age. The cohort has currently received four questionnaires. The PPI sessions showed that the questionnaire would be most acceptable to the public if available online. Therefore the development of an online questionnaire that was automatically sent to participants was required; this work was done by Bethan Griffith and Roseanna Pickles and is shown in appendix 9. It was decided that questionnaires would be completed using Adobe FormsCentral® (AFC®) (Adobe Systems Inc. California, USA). The email platform that would be used to send the questionnaire link to the participants was MailChimp® (The Rocket Science Group, Atlanta, USA). In June 2015 AFC® was suspended to allow development as a future premium product with charges. This forced the study team to change to use JotForm® (JotForm Inc. San Francisco, USA) for questionnaire completion and response storage.

Modification of the Emailing Timeline to Reduce Attrition in the LBBS

During the early analysis of the data it was apparent that a significant proportion of the drop out in the LBBS was due to participants not being invited back into the study if they did not complete the previous questionnaire. This was because the study protocol intended to analysis the longitudinal data of the LBBS using multivariate regressions that do not allow for missing data. The use of multi-level mixed effect models allowed participants to miss questionnaires and still be included in the analysis. Therefore it was decided to send participants the next questionnaire regardless of them completing the previous questionnaire providing they had not intentionally left the study. This was done by modifying the automation instructions in MailChimp® so that sending the next questionnaire to a participant was no longer dependant on opening the previous questionnaire. This modification was completed by the author. Participants could still intentionally leave the

study by unsubscribing from the emailing list themselves and by emailing the study team directly.

2.1.6- Batch Testing

Due to ethical approval requirements in 2012, the study needed a method of identifying deceased infants throughout the study so as to avoid contact with bereaved parents that could cause distress. This process was performed by the IT department at Alder Hey Children's Hospital through batch testing the list of infants in the study on a monthly basis. Transfer of information between institutions for batch testing was done using encrypted files.

2.2-Section 2. Methods Used in the Statistical Analysis of the LBBS

2.2.1-Aims

The aims of this phase of the study were to;

- To create a profile of the infants and mothers enrolled in the LBBS and make a comparison with the population of Liverpool and those born in the LWH.
- To describe respiratory symptoms of preschool children using the LRSQ from birth until 22 months of age.
- To determine the differences in LRSQ scores in the different populations at each questionnaire time point.
- To determine the change in the LRSQ scores over time and the variability in this change between different population groups in the LBBS.
- To validate the LRSQ in a longitudinal study.

These aims were achieved by analysing each of the following individually; 1. The response rates and drop out from the LBBS, 2. The profile of the infants their mothers and families, 3.The LBBS data at each time point individually (cross-sectional), 4. The LBBS data from all time points together (longitudinal) and 5.the internal validity of the questionnaire.

2.2.2- Data Entry and Coding

Questionnaire responses were downloaded from JotForm (and previously AFC) to Microsoft Excel (Microsoft Excel, 2016, Washington, United States). At this point data was in a non-coded form with responses matching that of the questionnaire format. Data was coded using the find and replace function to give each variable response a numerical number which could be used in the statistical packages used for data analysis in the LBBS. The codes used in the LBBS are shown in appendix 15. The table in the appendix shows the variable code and the response code used in the statistical packages. Birth weights that were given in 'pounds and ounces' were converted to grams for the purpose of this analysis. Postcodes were converted

to IMD decile as described in section 2.2.6 of this thesis. Descriptions of underlying health conditions were converted to health conditions were possible by the author. Where this was not possible the description given by the mother was given in the results section of this thesis.

2.2.3- Statistical Packages Used During Analysis

Social Sciences (SPSS) version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and STATA version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) were used during the analysis of the study. SPSS was used during analysis of recruitment and response rates, the infant and mother profiles in the LBBS and the cross-sectional analysis of the LBBS. STATA was used for the longitudinal analysis of the LBBS and the validation of the LRSQ.

2.2.4-Recruitment

Recruitment and response rates were determined from denominator data given by Professor Ben Shaw from LWH for all the eligible births in the LWH during the recruitment period. Numerator data were the number of mothers considered to be interested in the study who returned a post card to the study team, signed up to the study via the quick response code or via the tablet used by the research team. Only those mothers who completed the consent form and responded to questionnaire one when their infant was four months of age were labelled as enrolled in the study. Descriptive statistics were used to describe the recruitment and response rates in the LBBS.

2.2.5-Response Rates and Attrition

Response rates to each questionnaire were described by descriptive statistics. Those who intentionally removed themselves from the mailing list or emailed the recruitment team to be removed from the study were described as having left the study. MailChimp® gave statistics on emails that had 'bounced' indicating an incorrect email and these participants were subsequently described as email bounces. Babies that had died since mothers declared their interest to the study or were enrolled were identified by batch tracing using records at Alder Hey Children's Hospital on a monthly basis. Participants that did not respond to the questionnaire were declared lost to follow up.

The demographics and exposures of the drop out population and remaining population at each questionnaire was described using summary statistics to evaluate the change in the cohort characteristics as attrition occurred. This was used to account for the uneven drop out from exposure groups throughout the study.

2.2.6-Profiles of Mothers in the LBBS

The profile of the mothers in the LBBS will be described by descriptive and summary statistics. Where appropriate the profile of mothers in the LBBS will be compared to the mothers of all the eligible births from the LWH during the recruitment period, and that of the population of Liverpool and England using χ^2 analysis. A significant result was indicated by p≤0.05. The profile of the mothers of the eligible births in LWH was obtained from Professor Ben Shaw at the LWH. Data regarding maternal age group and education was obtained from the Office of National Statistics(153). Deprivation data was obtained from the UK Government Official Statistics (154). The postcodes of all the eligible births from the LWH and the postcodes of the mothers enrolled in the LBBS were converted to IMD decile using The Department of Communities and Local Governments Postcode Converter (155). Participants in IMD decile onehad the highest level of deprivation. Cigarette smoking and breastfeeding rates in Liverpool and England were obtained from the NHS Statistical Release for a similar time period of recruitment (12, 156).

2.2.7-Profile of Infants in the LBBS

The profile of the infants enrolled in the LBBS will be described by descriptive statistics. Where appropriate the profile of the infants in the LBBS will be compared to that of all the eligible births from the LWH during the recruitment period, and that of the population of Liverpool and England using χ^2 analysis. A significant result was indicated by p≤0.05. The profile of the eligible infants born in the LWH was obtained from Professor Ben Shaw at the LWH. Data regarding sex and ethnicity was obtained from the Official Labour Market National Statistics (157). Data regarding multiple births in England was obtained from the Office of National Statistics (153). Data regarding gestational age and birth weight was obtained from the NHS Digital Monthly Maternity Services Statistics (158).

2.2.8-Cross-sectional Analysis

Cross-sectional analysis in the LBBS study was split into five sections and was carried out using data from each of the four questionnaires individually; 1. Risk factor exposure analysis, 2. LRSQ total and domain score analysis, 3. Symptom prevalence analysis, 4 .Health care attendance analysis and 5. Analysis of the impact on the Child's and their Family's QoL.

Demographics, Risk Factors and Exposures Used During Cross-sectional Analysis

The factors used to group the cohort during analysis are shown in figure 6. Due to drop out in the study, and the particularly low levels of non-white ethnicities the decision was made to analyse ethnicity using two groups; white and other ethnicities.

Sex (Male/Female)

Birth number (Single/Multiple)

Infant Ethnicity (White/Other)

IMD decile (1-10)

Maternal age at birth (<20/ 20-24/ 25-29/ 30-34/ 35-39/ 40-44/ ≥45)

Highest maternal qualification attained, (Degree or Higher/ Higher Education/ A-Level/ GCSE/ Other/ None)

Preterm birth (Preterm/Term)

Low birth weight (Low Birth Weight/ Normal Birth Weight)

Breastfeeding (Breastfed/ Not Breastfed)

Breastfeeding time up to 4 months (Not Breastfed/ <1 Month/ ≥1- <4 Months/ ≤4 months)

FH of atopy (Yes/ No)

Other household children (Yes/ No)

Number of other household children (1-4, 5+)

Sharing a Bedroom (Yes/ No)

Sharing a Bedroom with Who (Parents/ another Child/ Other)

Figure 6: Risk factors and exposures assessed in the LBBS

Exposure Analysis

Descriptive statistics of the infant's exposures to risk factors in the previous three months were presented. Exposures include nursery attendance, other household children, sharing a bedroom and ETS exposure. Households with smoking were compared to the prevalence of smoking in Liverpool in 2012 and 2015 (11, 157) using χ^2 analysis; a significant result was indicated by $p \leq 0.05$. A description of the co-morbid health conditions in the LBBS cohort was given.

LRSQ Scores

Descriptive statistics of the total and domain LRSQ scores were presented. The Mann-Whitney U test and Kruskal-Wallis H Test were used to compare questionnaire scores in exposed groups and non-exposed groups; a significant result was indicated by $p \leq 0.05$. The Mann-Whitney U test was used to compare scores of variables with only two groups whereas

the Kruskal-Wallis H test was used to compare variables when there was more than two groups. Post hoc testing using Dunn's Test was performed to identify differences between pairs of groups when the Kruskal-Wallis test indicated significant variance between groups. During comparison of exposed and non-exposed groups within the cohort, the cohort was weighted so that it represented the deprivation of the eligible births in the LWH using factor weighting. The weighting factors used are shown in the appendix.

Correction for Multiple Testing Analysis

Post hoc analysis of 'maternal age', 'maternal education', 'IMD decile' and 'breastfeeding time' caused multiple testing. Multiple testing increases the chance of finding a significant result by chance (159). Because of this, the significance value cut off is usually adjusted to account for this. One commonly used method is the Bonferroni adjustment. Bonferonni adjustment states that a significant p value = p/n where n is the number of tests that have been performed (159). In the analysis of this thesis is was decided not to correct the analysis for multiple testing. The reason for this is that for the purpose of this thesis the LBBS is interested in trends in scores with changing variables (for example with increasing maternal age or increasing education or increasing breastfeeding time). Bonferroni adjustment is often over conservative (159), and therefore these trends may be missed if used. Likewise finding a significant result when using Bonferrioni adjustment is proportional to the number of tests done (159); in the LBBS the extremes of maternal age are lost and therefore less tests are done. This changes the adjusted significant p vale which may mean changes in the difference in score that is significant. This being said, any results produced in this thesis where multiple testing has occurred must be approached with this in mind.

Symptom Prevalence and Health Care Attendance

Symptom prevalence and health care service attendance in exposed and non-exposed groups was compared by χ^2 analysis and Fisher's Exact Test where appropriate. Fisher's Exact Test was indicated where expected values were deemed to be less than 10. During comparison of exposed and no exposed groups within the cohort, the cohort was weighted so that it represented the deprivation of the eligible births in the LWH using factor weighting. The weighting factors used are shown in the appendix.

The Impact on the Child's and their Family's Quality of Life

Domains seven and eight in the LRSQ are quality of life domains for the infant and their families respectively. Analysis of these domains was identical to other domains in the LRSQ

as described in the 'LRSQ scores' section above. The prevalence of the individual impacts on the QoL of both the infant and these were shown graphically at each time point.

2.2.9-Longitudinal Analysis

Longitudinal analysis of the change in LRSQ score over time and domain scores over time was analysed using multilevel mixed-effects modelling and compared exposed groups to non-exposed groups. The final multi-Level model used in the analysis of the LBBS therefore consisted of three levels; 1.IMD decile at birth, 2.highest maternal qualification obtained and 3.questionnaire number. Exposures and risk factors deemed to significantly effect LRSQ scores over time if p≤0.1.

Justification and Development of the Methods of Longitudinal Analysis in the LBBS

The LBBS required a method of longitudinal analysis that allowed for the reduction of confounding variables and could assess multiple variable simultaneously. This could be done by either multivariate regression analysis or using multi-level mixed effects models. The LBBS needed a method of analysis that could allow for a large amount of missing data due to many participants completing some questionnaires and not others. Multi-level mixed effects models coped with missing data more effectively than the multivariate regression method of analysis. For this reasons multi-level mixed effects models were chosen as the method for longitudinal analysis in the LBBS. The multi-level model originally consisted of only two levels; 1.IMD decile at birth and 2.questionnaire number which allowed for both the under representation of the more deprived population of Liverpool and participants who had not completed every questionnaire.

To develop the longitudinal models, risk factors of respiratory disease were firstly added to the model individually. Individual exposures and risk factors deemed to change LRSQ scores over time significantly if p≤0.1. Once risk factors and exposures were deemed to have a significant impact on LRSQ scores over time they were added into the model one at a time, beginning with the exposure or risk factor with the smallest p value. Risk factors and exposers with a p value that remained ≤0.1 once multiple variables had been added to the model remained in the final model. If p values of variables became larger than 0.1 as more variables were added to the model, they were removed from the model. If the addition of a variable caused multiple variables' p value become greater than 0.1 the variable with the largest p value was removed first.

During the longitudinal analysis of the LBBS data it became apparent that the category 'Highest maternal qualification' was causing a confounding effect of the results of the LBBS. It consistently removed many risk factors and exposures from the models when it was added

to the model. For this reason it was decided by the research team to add 'highest attained maternal qualification' as a level in the multi-level mixed effects model. The final model used in the LBBS therefore consisted of three levels; 1.IMD decile at birth, 2.highest maternal qualification obtained and 3.questionnaire number. The longitudinal analysis was then performed again using the methods previously described.

2.2.10-Questionnaire Validation

The internal validity of the domains within the LRSQ was tested using Cronbach alpha test to validate the LRSQ in a longitudinal study. An α score of >0.7 was deemed to show acceptable internal constancy, α >0.8 was deemed to show good internal consistency and α >0.9 was excellent internal constancy. Below α =0.7 was deemed as unacceptable internal consistency (1).

2.2.11-Presentation of the Analysis of the LBBS in this Thesis

There is a large amount of data analysis from the LBBS to be presented in this thesis. The presentation of the results will be split into seven sections:

1. Analysis of recruitment,

2. Analysis of the attrition in the LBBS,

3. Analysis of the profile of the mothers in the LBBS,

4. Analysis of the profile of the infants in the LBBS

5. Results of the cross sectional analysis,

6. Results of the longitudinal analysis,

7. Results of the validation of the LRSQ.

Recruitment

The recruitment and response rates in the LBBS will be described using descriptive statistics. The reasons for participants not being recruited will also be discussed. This will also be shown pictorially in a flow diagram.

Attrition

Attrition in the LBBS will be described. A flow diagram will be used to describe the reasons for attrition. Following this analysis of the drop out population will be show. This will be described and shown graphically to show the difference between the drop out population and the remaining cohort. A table will be presented to show the difference in total LRSQ scores in the drop out population and the remaining population. This will show the impact of the difference in the characteristics of the drop out population and the remaining cohort on symptom scores. Following this there will be a description of the ways in which this uneven

attrition was accounted for during the analysis. This will be justified using graphs to show the reduction in the confounding effects of the uneven drop out after adjustment.

Profile of the Mothers in the LBBS

The characteristics of the mothers in the LBBS cohort will be presented. The characteristics will be described and compared to LWH births, or the population of England or Liverpool were appropriate. These comparisons will be presented graphically or in tables.

Profile of the Infants in the LBBS

The characteristics of the infants in the LBBS cohort will be presented. The characteristics will be described and compared to LWH births, or the population of England or Liverpool were appropriate. These comparisons will be presented graphically or in tables.

Cross Sectional Analysis

For the presentation of the cross sectional analysis each questionnaire will be presented individually in chronological order. For each questionnaire, firstly the summary statistics of the LRSQ scores will be presented alongside a histogram of the LRSQ scores to show the spread of scores in the cohort. Secondly the comparison of total LRSQ scores between infants exposed and not exposed to risk factors will be presented. A table that shows the comparison of LRSQ scores between those exposed and unexposed to risk factors will be presented; this table shows the median, the interquartile range, the mean and the mode score for each exposure/risk factor group. Results that show a statistically significant score between those exposed and not exposed to risk factors will be described in detail and a box and whisker diagram of these results will be shown. This will be followed by an analysis of each of the domain scores in the LBBS. A table will be presented with the minimum and maximum score, the median, mean and the standard deviation of each of the domain. This table shows which domains scored highest and lowest and allows the comparison of domains. Differences in domain scores between exposed and non-exposed groups will be described; only significant results will be described. Following this, the prevalence of specific respiratory symptoms in the previous 3 months will be presented. This will be presented graphically per 100 infants. A comparison of symptom prevalence in the previous 3 months in those exposed and not exposed to risk factors and exposure will be made. Only exposures with significant difference will be described. The use of health care services by infants in the previous 3 months will be presented. The difference in health care attendance n exposed and non-exposed groups will be described. Only significant results will be described. Health care attendance to infants born to mothers of different maternal ages and with different levels of education will be presented graphically. The effect of respiratory symptoms of QoL of the infants and their

families will then be presented. A description of how the QoL of the infants and their families was affected by respiratory disease will be shown graphically. This will be followed by a description of differences in the effect of respiratory symptoms on QoL in those exposed and not exposed to risk factors and exposures. Finally a correlation between the QoL scores and respiratory symptom scores will be made.

Longitudinal Analysis

The longitudinal analysis of the LBBS will be presented as final multi-level mixed effects models. The coefficient, standard deviations and p values of risk factors and exposures that have a significant effect on the LRSQ scores over time will be presented. The total LRSQ score model will be presented first, followed by a model for each of the domains in the LBBS.

Questionnaire Validation

The Coronach alpha coefficients and a corresponding description of the domains internal consistency of each of the domains in the LBBS will be presented in a table.

Chapter 3- Results of the LBBS

This section presents the results of the LBBS. This presentation has 7 sections and will be presented as discussed in section 2.2.10. At the beginning of each section there will be a description of what the results that follow show and how this relates to the study aims.

3.1-Recruitment

This section outlines the recruitment rates in the LBBS. It shows the reasons for non-recruitment. The reasoning behind these results and their significance is discussed in chapter four.

Recruitment led to 18.84% (n=2,346) of all the eligible births in the LWH (n=12,454) declaring their interest in taking part in the study. Recruitment analysis is shown in figure 7. Of all the births in the LWH between 23/01-2013 and 03/11/2014, 6.99% births occurred during breaks in recruitment. Of the births during active recruitment 11.94% were ineligible due to their postcode, 0.71% were ineligible due to speaking insufficient English, 0.52% were ineligible due to infants being taken directly into care of social services and 0.46% were not suitable to recruit as the infant had a futile prognosis. This led to 12,454 eligible births in the LWH during active recruitment. It was documented that 0.55% (n=68) of these actively declined to be a part of the study. 80.61% (n=10,040) of the eligible births could not be labelled either declined or interested in the study so therefore these births are assumed to have not shown interest in the study.

All interested families (n=2,346) were sent a consent form and questionnaire one when their child was four months of age by post or email according to their expressed preference. 18.84% (n=694) of the interested parents (684 Mothers and 10 Fathers), equating to 5.57% of all the eligible births, consented to the study and completed the initial questionnaire. See table 4. For the purpose of this thesis the parents of the infants will be referred to as mothers due to the negligible proportion of fathers.

Of the 2,364 infants whose mothers had declared their interest in the study 1.5% (n=36) did not consent to the study, 2.1% (n=49) gave a wrong postal address and could not be traced, 8.7% (n=204) gave a non-valid email and could not be traced and 0.2% (n=5) infants died in the first four months of life. 58.7% (n=1,358) of the infants whose mothers had declared their interest in the LBBS shortly after delivery were not enrolled four months later.
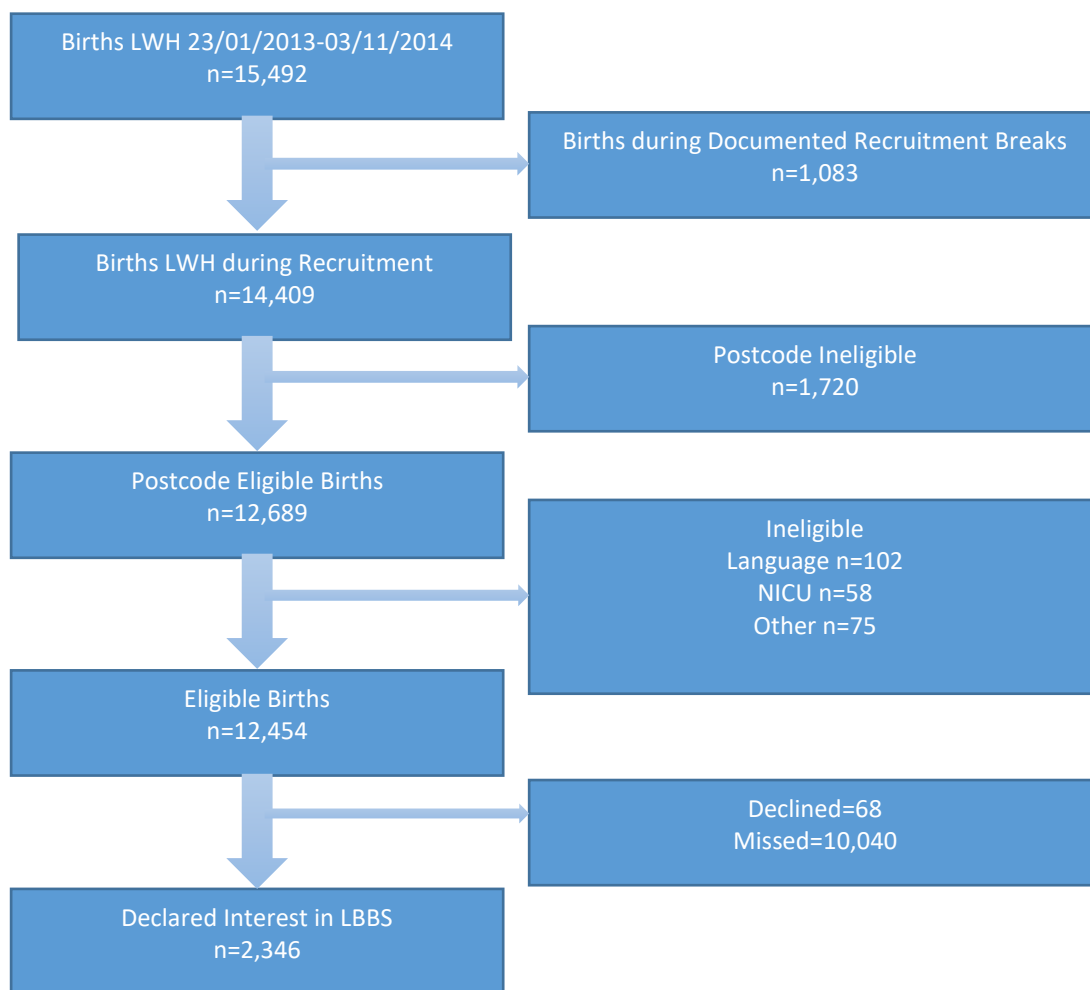
Figure 7: Flow diagram of the recruitment in the LBBS

Table 4: Recruitment rates in the LBBS

Recruitment Stage	Eligible Births	Interested	Consented and Completed Q1
Response	12,454	2,346	694
% of Eligible LWH Births	100%	18.84%	5.57%

3.2-Drop Out

Attrition in the LBBS is described in this section. The cause of attrition in the study is described. The profile of the drop out population is compared to the remaining cohort. The difference in these profiles forms the basis for the choice of analysis methods in the LBBS. The justification of the analysis methods is also described in this chapter; these methods of analysis have allowed the LBBS to successfully complete the following aims of the current thesis;

- To describe respiratory symptoms of preschool children using the LRSQ from birth until 22 months of age.
- To determine the differences in LRSQ scores in the different populations at each questionnaire time point, using univariate and multivariate analysis.
- To determine the change in the LRSQ scores over time and the variability in this change between different population groups in the LBBS.

3.2.1-Summary

Of the 694 mothers that were enrolled and completed questionnaire 1, 54.0% (n=375) completed questionnaire 2, 39.6% (n=275) completed questionnaire three and 37.0% (n=257) completed questionnaire 4. The analysis of dropout in the LBBS is shown in table 5 and figure 8.

Table 5: Attrition in the LBBS

Questionnaire	Q1- 4 Months	Q2- 10 Months	Q3-16 Months	Q4-22 Months
Response	694	375	275	257
% of Q1 Cohort	100%	54.0%	39.6%	37.0%
% Dropout from Previous Questionnaire		46.0%	26.7%	6.55%
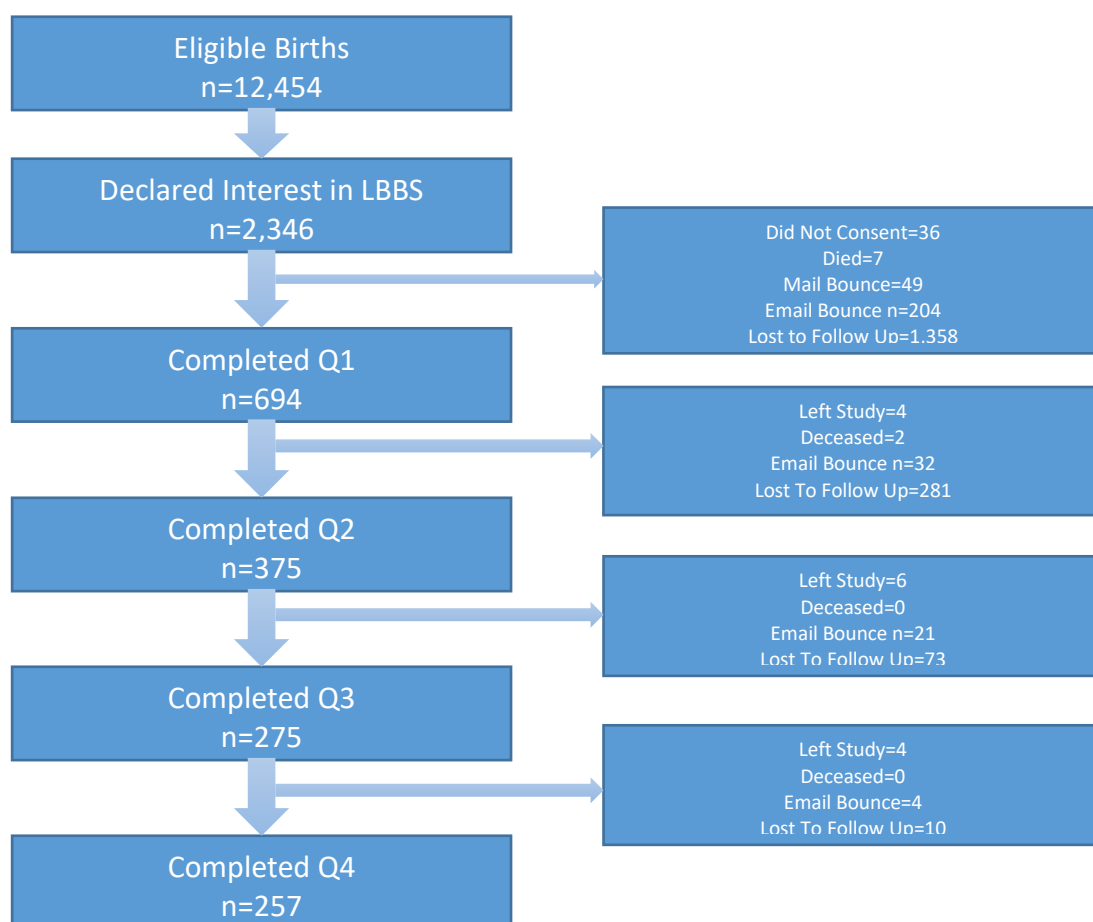
Figure 8: Flow diagram of attrition in the LBBS

3.2.2-Recognition of Drop Out and Bias

During the early analysis of the cohort, it was noted that that drop out occurred more often in participants from more deprived postcodes. In the two most deprived deciles (IMD deciles one and two), drop out after four questionnaires was 73.3% and 65.0% respectively compared to 53.3% drop out and 60% drop out in the two least deprived deciles (IMD deciles nine and 10). This is shown in figure 9. Initial analysis showed that maternal education groups had unequal drop out. Mothers who were more highly educated dropped out less frequently than those who had a lower level education. This is shown in figure 10. Maternal age also had an uneven distribution of drop out as the study went on; older mothers were more likely to remain in the study. The mean age of the mothers in the cohort was 32 years at four months, 32 years and three months at 10 months, 32 years and 10 months at 16 months and 33 years and five months at 22 months. Figure 11 shows that younger mothers are more likely to drop out of the study than older mothers. This uneven drop out from the study produced a confounding effect within the study; infants who had been exposed to smoking pre and postnatally and had not been breastfed were more likely to drop out of the study;

see figure 12 and 13. Table 10 shows the total LRSQ score for the cohort and the drop out population for the previous questionnaire. The drop out population scored higher in the previous LRSQ than the population that remain in the cohort. This clearly shows that the uneven drop out in the study population has created a confounding effect in the study and this drop out needed to be adjusted for in the analysis of the study.
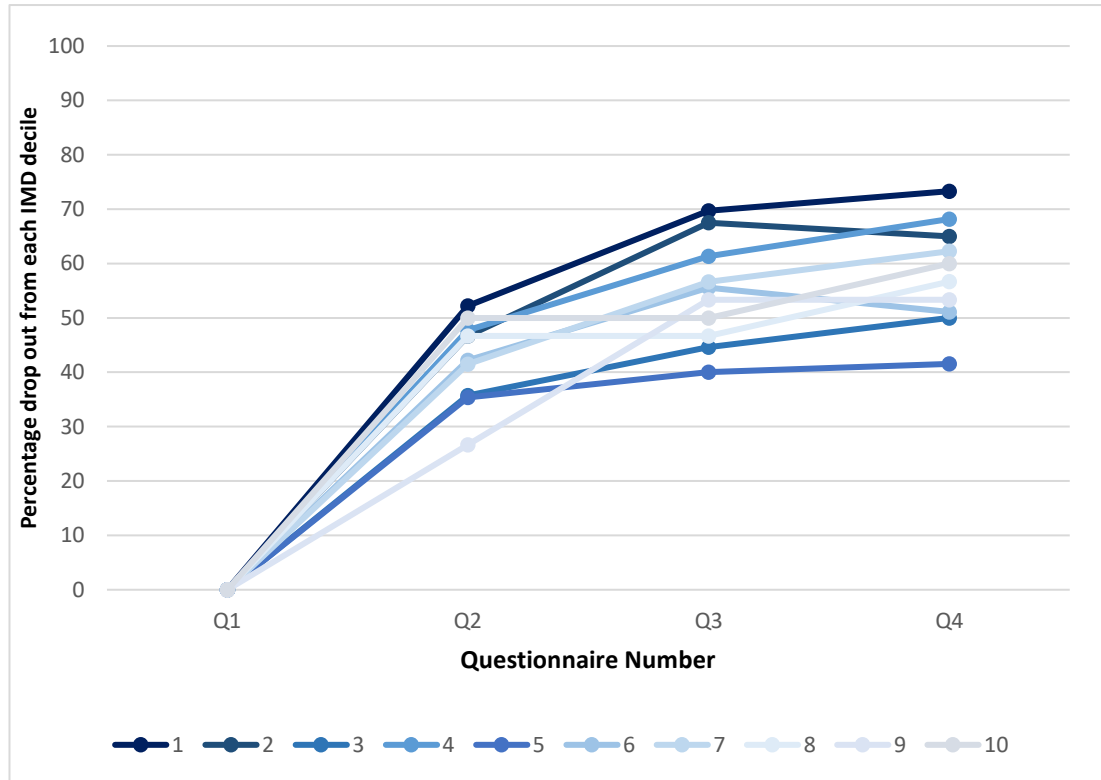
Figure 9: Accumulative percentage drop out in the LBBS in each IMD decile at each questionnaire
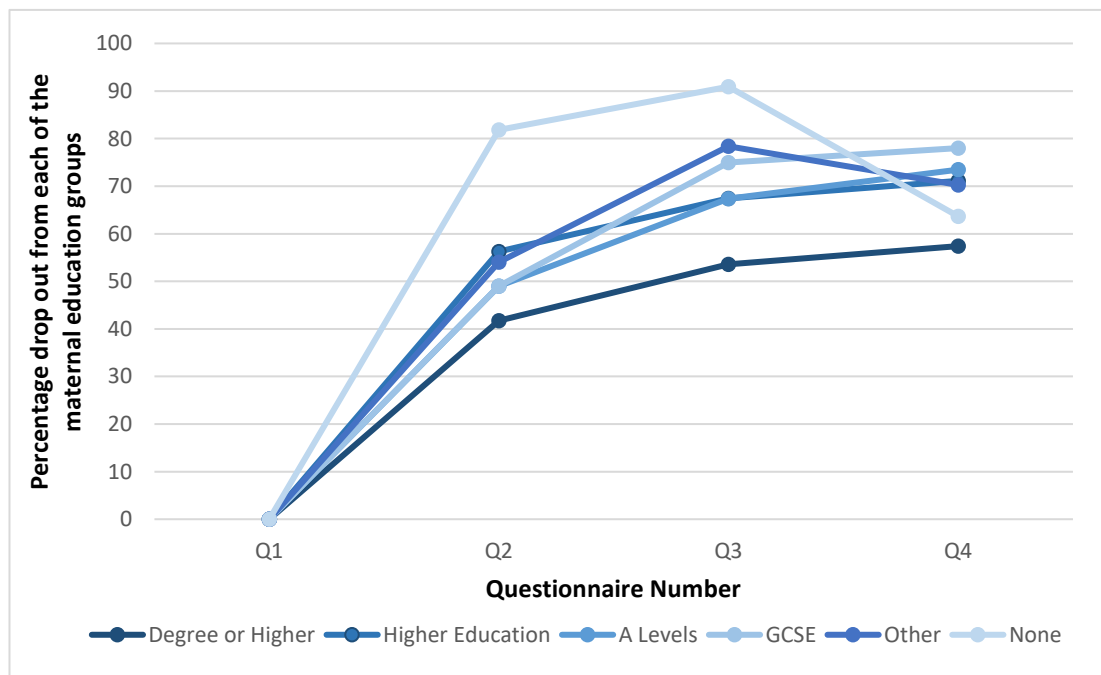
Figure 10: Accumulative percentage drop out in the LBBS by mother's highest qualification attained
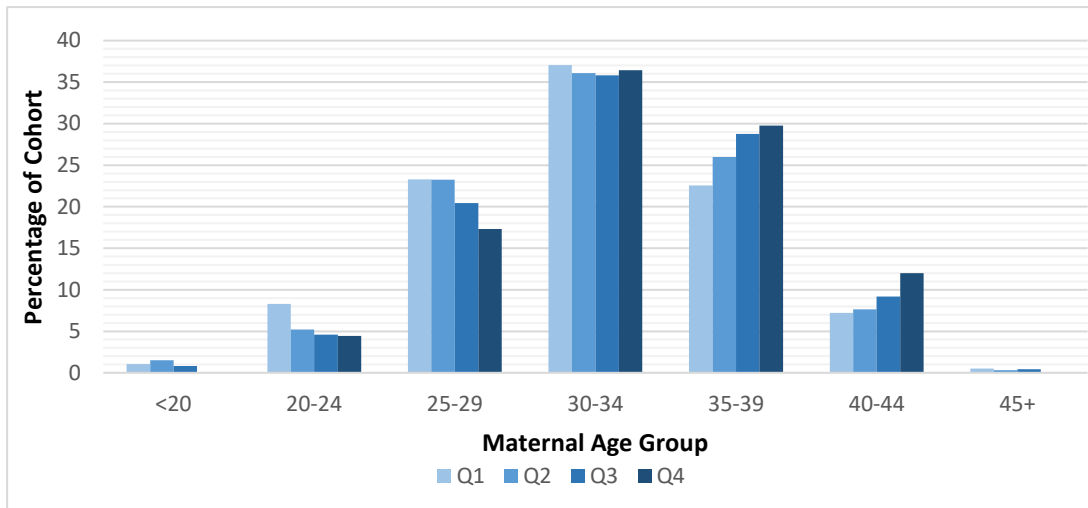
Figure 11: Percentage of the cohort with mothers in each age category at each questionnaire in the LBBS
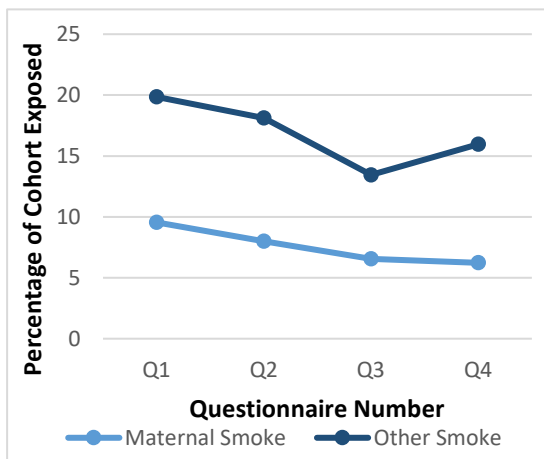
Figure 12: Percentage of the cohort exposed to tobacco smoke at each questionnaire in the LBBS
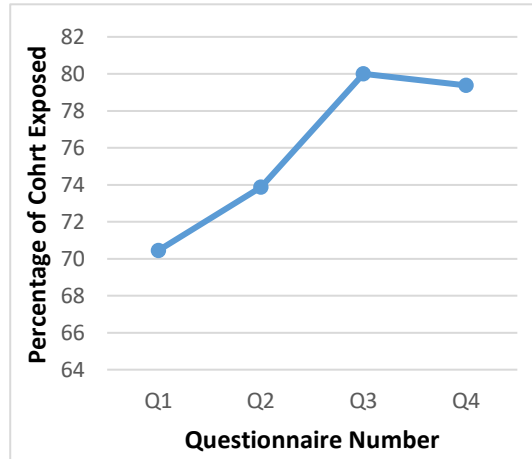
Figure 13: Percentage of the cohort that were breastfed at each questionnaire in the LBBS

Table 6: Previous questionnaire total LRSQ score comparing the drop out population to the remaining LBBS cohort

		Cohort Q1	Cohort Q2	Drop Out	Cohort Q3	Drop Out	Cohort Q4	Drop Out
T Score	Mean	9.9	9.4	10.5	9.1	10.5	9.7	10.1
	Median	5	5	6	5	6	5	5
	Mean		13.4	-	13.6	13.3	12.8	14.2
	Median		9	-	9	8.5	8	9
	Mean				15.3	-	14.7	17.1
	Median				10	-	9	13

3.2.3-Choice of Analysis to Mitigate for Drop Out Bias

After discussions with Dr Steve Lane at the University of Liverpool, it was decided that cross-sectional analysis would be weighted using factor weighting to ensure the cohort at each time point was representative of the eligible births in the LWH. It was decided that the data should be weighted so that the IMD decile of the cohort was representative of that of all the eligible births in the LWH. Weighting factors for IMD decile at each questionnaire is shown in the appendix. A multilevel, mixed effects linear model would be used for the longitudinal analysis of the data. The model would have three levels: 1. IMD decile, 2. Highest maternal qualification and 3. Questionnaire number. This would account for the unequal drop out from each of the IMD Deciles and the maternal qualification groups. It also allowed for inclusion of data where one of a series of questionnaires for an individual in the cohort was missing.

3.2.4-Justification of Weighting Data –The Effect on Variables in the Cohort
Breastfeeding in the LBBS

Over time the proportion of breastfed infants in the LBBS cohort increased due to the higher drop out of mothers who did not breastfeed. Weighting of the data reduced this change in the breastfeeding population somewhat. See figure 14. Although weighting reduced the drop out of the non-breastfed infants the proportion of breastfed infants was still significantly higher in the LBBS when compared to all the eligible births at LWH at four months (χ^2=73.3 p<0.05), 10 months (χ^2=65.7 p<0.05), 16 months (χ^2=82.8 p<0.05) and 22 months (χ^2=66.8 p<0.05).
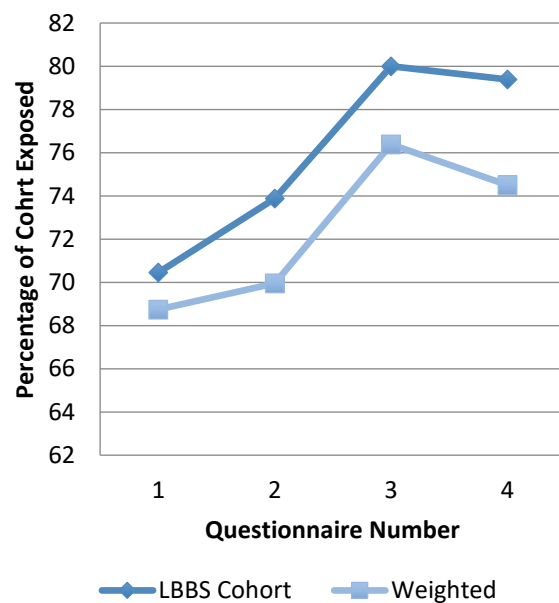
Figure 14: Percentage of the cohort breastfed in the LBBS before and after weighting by IMD decile

Smoking in the LBBS

Over time the proportion of the cohort that had been exposed to smoking in pregnancy and since birth reduced. Although weighting of the analysis reduced this decline somewhat, the proportion exposed to tobacco smoke during pregnancy and since birth was still lower than the eligible births at the LWH and the population of Liverpool. See figures 15-18 below.
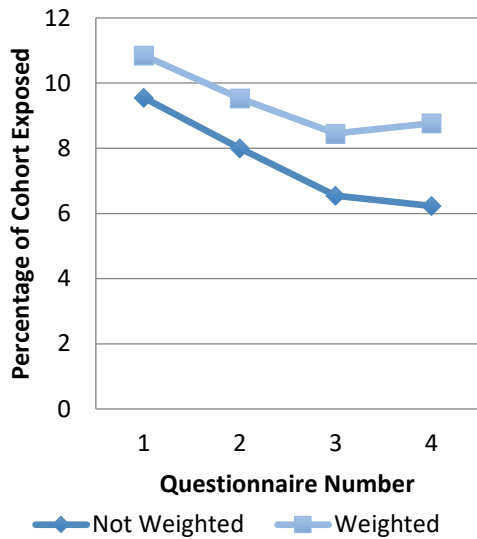
Figure 15: Percentage of the cohort in the LBBS exposed to maternal smoking in pregnancy before and after weighting by IMD decile
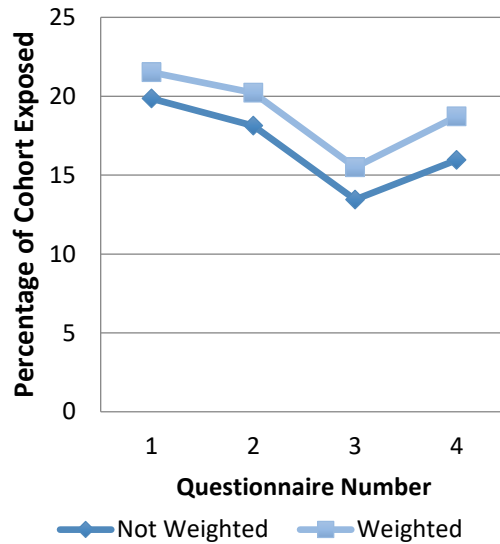
Figure 16: Percentage of the cohort in the LBBS exposed to ETS in pregnancy from other household smokers before and after weighting by IMD decile
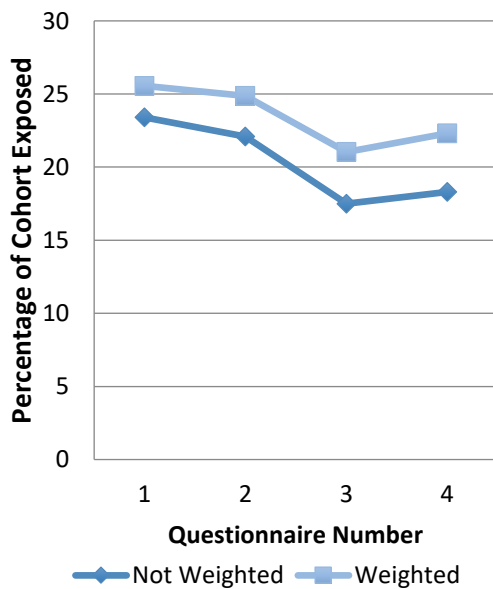
Figure 17: Percentage of LBBS cohort exposed to any smoking in pregnancy before and after weighting by IMD decile
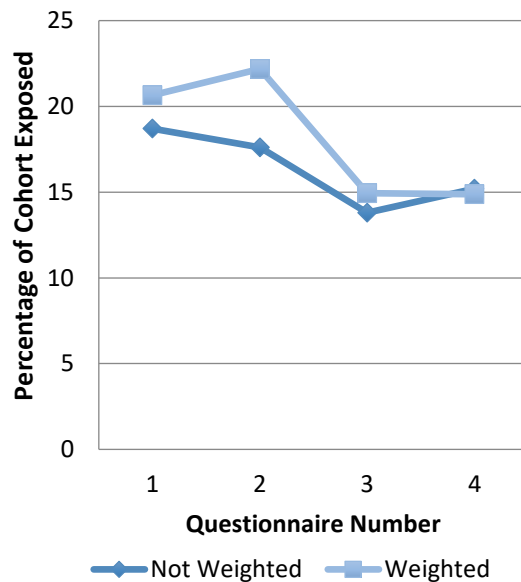
Figure 18: Percentage of the cohort in the LBBS exposed to household smoking postnatally before and after weighting by IMD decile

The proportion of the cohort exposed to smoking, both during pregnancy and after birth are shown in table 11. Although weighting reduced the drop out of the infants exposed to tobacco smoke, the proportion of the cohort exposed to maternal smoking during pregnancy was still significantly smaller than the proportion of all the eligible births from the LWH at four months (χ^2 =21.5 p<0.05), 10 months (χ^2=16.8 p<0.05), 16 months (χ^2=16.0 p<0.05) and

22 months (χ^2=13.8 p<0.05). Those infants exposed to ETS after birth was significantly smaller in the LBBS cohort than to population of Liverpool that smoked at four months (χ^2=4.6 p<0.05) 16 months (χ^2=12.3 p<0.05), and 22 months (χ^2=11.7 p<0.05) when compared to 2012 data and was lower in the LBBS cohort at 16 months (χ^2 =9.5 p<0.05) and 22 months (χ^2=9.1 p<0.05) when compared to 2015 data.

Table 7: The effect of weighting of the cohort by IMD decile on smoking exposures in the LBBS

			Q1	%	Q2	%	Q3	%	Q4	%
Maternal Smoke	LBBS Cohort	No	606.0	90.5	345.0	92.0	257.0	93.5	241.0	93.8
		Yes	64.0	9.6	30.0	8.0	18.0	6.6	16.0	6.2
	Weighted	No	600.0	89.2	332.0	90.5	249.0	91.5	229.0	91.2
		Yes	73.0	10.8	35.0	9.5	23.0	8.5	22.0	8.8
Other Smoke	LBBS Cohort	No	537.0	80.2	307.0	81.9	238.0	86.6	216.0	84.1
		Yes	133.0	19.9	68.0	18.1	37.0	13.5	41.0	16.0
	Weighted	No	529.0	78.5	292.0	79.8	229.0	84.5	204.0	81.3
		Yes	145.0	21.5	74.0	20.2	42.0	15.5	47.0	18.7
Any Smoking In Pregnancy	LBBS Cohort	No	513.0	76.6	292.0	77.9	227.0	82.5	210.0	81.7
		Yes	157.0	23.4	83.0	22.1	48.0	17.5	47.0	18.3
	Weighted	No	501.0	74.4	275.0	75.1	214.0	79.0	195.0	77.7
		Yes	172.0	25.6	91.0	24.9	57.0	21.0	56.0	22.3
Home Smoke	LBBS Cohort	No	545.0	81.3	309.0	82.4	237.0	86.2	218.0	84.8
		Yes	125.0	18.7	66.0	17.6	38.0	13.8	39.0	15.2
	Weighted	No	534.0	79.3	228.0	77.8	222.0	85.1	206.0	85.1
		Yes	139.0	20.7	65.0	22.2	39.0	14.9	36.0	14.9

3.3-Profiles of Mothers and Families in the Liverpool Baby Breathing Study

This section describes the profiles of the mothers and families enrolled in the LBBS. It also compares the profile in the LBBS to the population of Liverpool and the mothers and families of the eligible births in the LWH. This description and comparison has allowed the following aim of this thesis to be partially achieved;

- To create a profile of the infants and mothers enrolled in the LBBS and make a comparison with the population of Liverpool and those born in the LWH.

3.3.1-Deprivation

Deprivation decile was calculated by using an online postcode converter (155). Participants in IMD decile one had the highest level of multiple deprivations. The distribution of IMD decile by postcode in the LBBS is shown below in comparisons to all the eligible births in the LWH and the population of Liverpool. The LBBS had a lower proportion of the cohort in IMD decile one (36.4%) compared to all the eligible births in the LWH (51.7%) and the population of Liverpool (45.0%) and had more in IMD decile 10 (1.6%) than the LWH eligible births (0.53%) and the Liverpool population (0.34%). See figure 19.
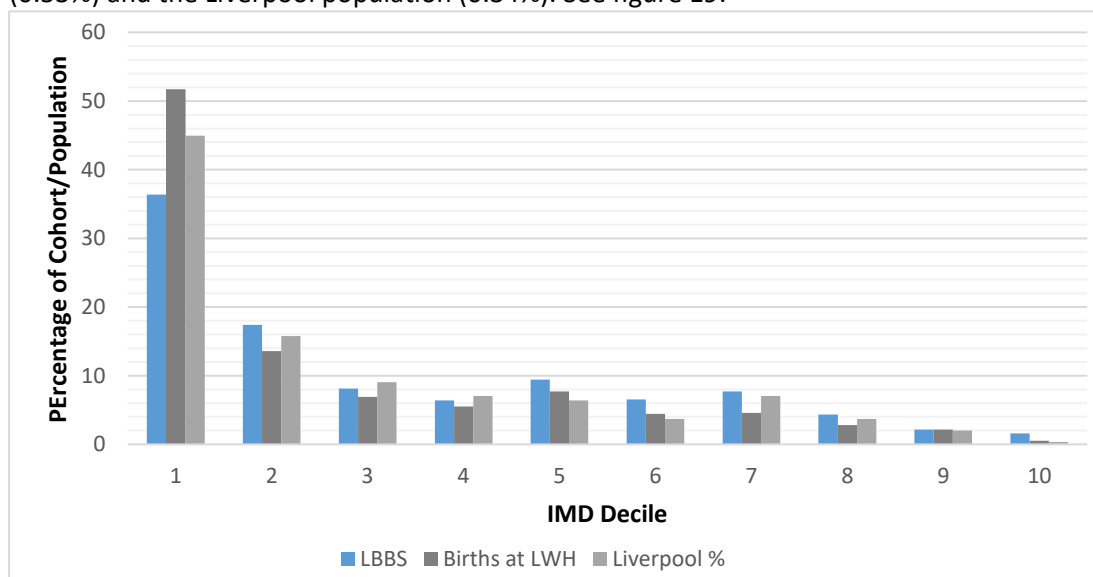
Figure 19: Percentage of the LBBS cohort in each IMD decile in comparison to LWH births and the Liverpool population

3.3.2-Maternal Age

The question regarding maternal age was added to the study after the pilot study, therefore only 567 mothers gave their age. The mean age of the mothers in the study was 31 years and 9 months. The youngest mother was 16 and he oldest 47 years of age giving a range of 31 years. Comparisons for the maternal ages in the LBBS were made to that of all the eligible births in the LWH and the births in Liverpool and England in the year of 2015. This showed

than the mothers in the LBBS are more likely to be older than those born in LWH, Liverpool and England. See figure 20.
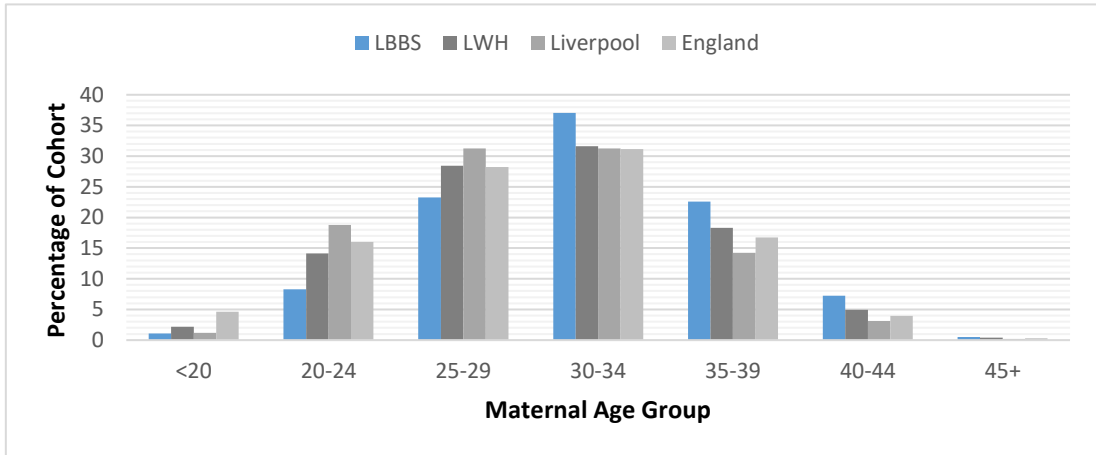
Figure 20: Percentage of mothers in the LBBS cohort in age group in comparison to LWH, Liverpool and England births

3.3.3-Maternal Education

The cohort in the LBBS had 50.41% mothers with a degree or a post graduate degree, 20.0% of the cohort only attended higher education, 7.49% had A-Levels and 15.13% had GCSE's. 1.73% of the population had no qualifications. The remaining 5.48% had 'other' qualifications. When compared to the population of Merseyside and England, the LBBS cohort was more highly educated. The LBBS had higher a proportion of the people with a degree or postgraduate degree or who attended higher education and fewer people with A-levels, GCSE's, 'other' qualifications or no qualifications. See figure 21.

3.3.4-Smoking

Smoke exposure during pregnancy was explored through two questions. One assessing maternal smoking at any time
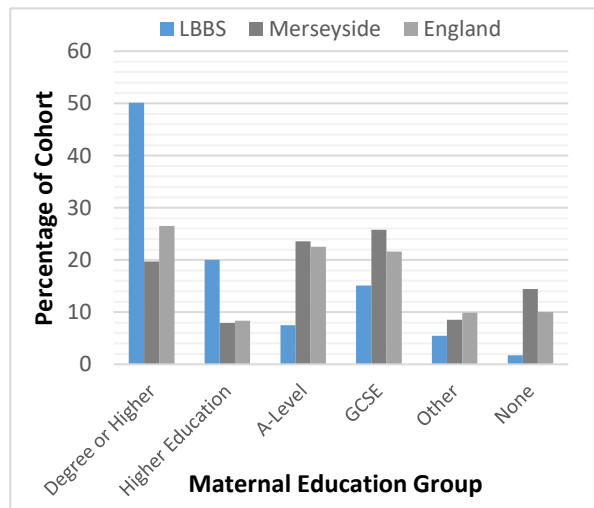
Figure 21: Percentage of the cohort by highest qualification attained in the LBBS in comparison to the population of Merseyside and England
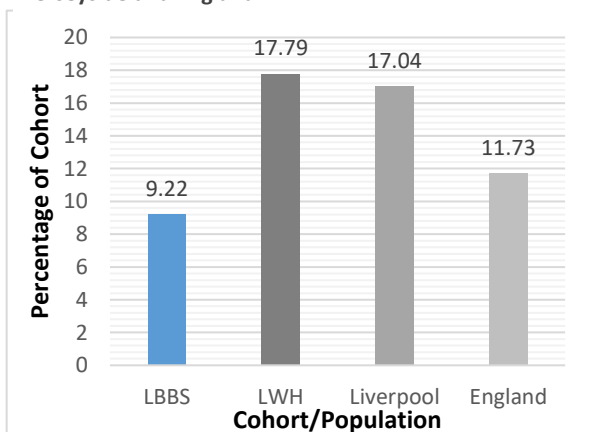
Figure 22: Percentage of mothers that smoked during pregnancy in the LBBS in comparison to LWH, Liverpool and England births

during pregnancy, and one assessing maternal exposure to tobacco smoke (passive smoking) in the household during pregnancy. Of the 694 respondents 9.22% (n=64) of mothers smoked during pregnancy. This was compared to data from all eligible births from the LWH and the population of Liverpool and England. χ^2 analysis has shown these be significantly higher than the LBBS cohort (χ^2=33.8 p<0.05 DoF=1, χ^2 =28.9 p<0.05 DoF=1, χ^2 =4.2 p<0.05 DoF=1 respectively). See figure 22.

19.45% (n=13) of the cohort was exposed to other smoking in the household in pregnancy. The location of smoking by these other household smokers is shown in figure 23. Overall 22.91% (n=159) of the cohort was exposed to tobacco smoke of any kind in pregnancy.

3.3.5-Breastfeeding

In the LBBS 70.5% (n=489) of the cohort were breastfed. This was compared to the proportion of the eligible births from the LWH that were breastfed and all the births in Liverpool and England. The study cohort had a significantly higher proportion of breastfed infants than LWH births and all the births in Liverpool (χ^2=127.7 p<0.05 DoF=1, χ^2=78.2 p<0.05 DoF=1,). The proportion of breastfed infants in the LBBS was significantly lower than that of England (χ^2 =4.5 p<0.05 DoF=1). See figure 24. At four months 241 of the mothers were still breastfeeding, 98 had breastfed for greater than one month but
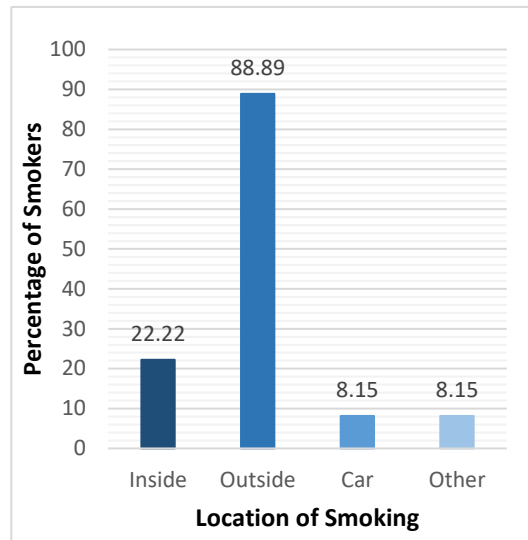
Figure 23: The location of smoking of household smokers during pregnancy in the LBBS
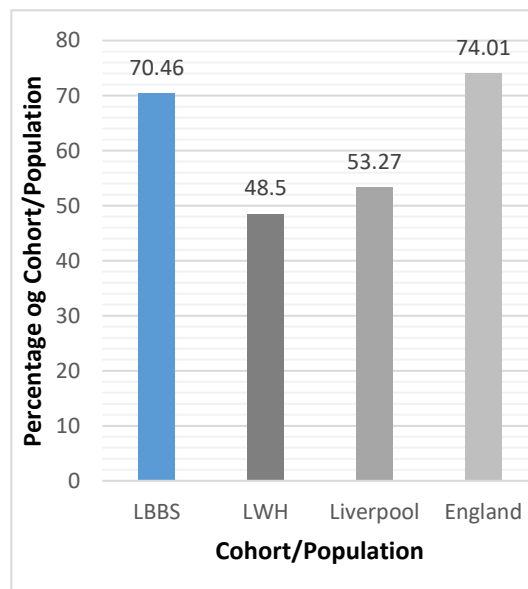
Figure 24: Percentage of breastfed infants in the LBBS in comparison to the rates of breastfeeding in LWH, Liverpool and England
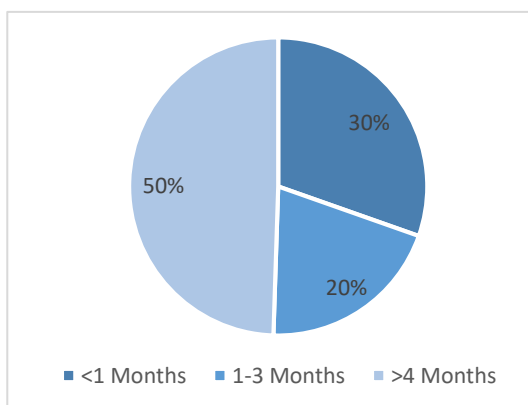
Figure 25: Duration of breastfeeding in breastfed infants in the LBBS

were no longer breastfeeding at four months and 148 breastfed for less than one month. This is shown in figure 25.

3.3.6-Family History of Atopy

59.8% (n=415) of the cohort had a family history of atopy in at least one first degree sibling. 61.7% (n=256) of the cohort infants had a mother with atopy, 52.0% (n=216) had a father with atopy and 26.0% (n=108) had a brother or sister with atopy. Of the family members with atopy: 56.4% (n=234) had asthma, 77.8% (n=323) had eczema, and 64.1% (n=266) had hay fever. The overlap of atopic disease in the LBBS cohort is shown in figure 26.
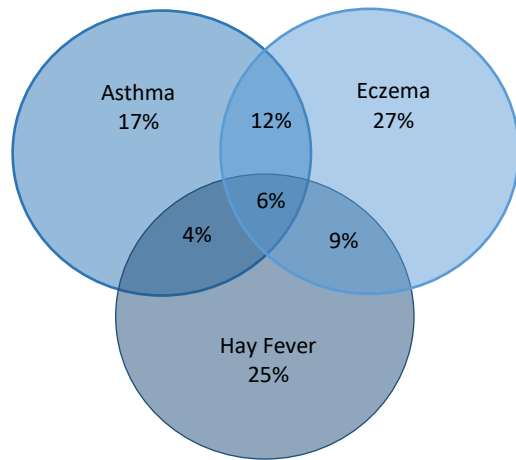
Figure 26: Combinations of atopic disease in first degree relatives in the LBBS

3.4-Profile of Infants in the Liverpool Baby Breathing Study

This section describes the profiles of the infants enrolled in the LBBS. It also compares the profile in the LBBS to the population of Liverpool and the eligible births in the LWH. This description and comparison has allowed the following aim of this thesis to be completed;

- To create a profile of the infants and mothers enrolled in the LBBS and make a comparison with the population of Liverpool and those born in the LWH.

3.4.1-Sex

Of the 694 infants in the cohort, 49.7% (n=345) were male, and 50.3% (n=349) were female. This was not significantly different to all the births in Liverpool, the North West or Great Britain for a year in the recruitment period (p>0.05). See figure 27.

3.4.2-Multiple Births

The LBBS cohort contained 680 singletons and seven sets of twins. There were no triplets in the study. This was not
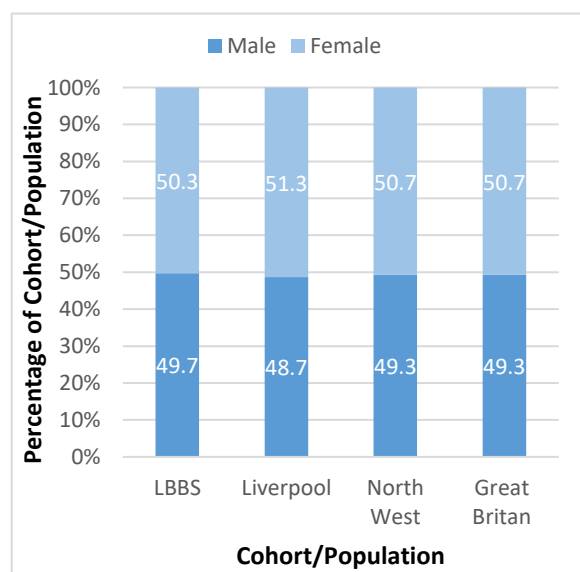
Figure 27: Proportion of males and females in the LBBS in comparison to the population of Liverpool, the North West and Great Britain

significantly different (p>0.05) to all the eligible births in the LWH and all the births in England.

3.4.3-Ethnicity

99.7% of the cohort gave information on their ethnicity. 90.6 of the cohort were white, 6.1% were mixed ethnicity, 0.7% were Asian, 1.4% were black and 0.3% were 'other' ethnicities. The cohort had a higher proportion of white and mixed ethnicity infants and lower proportions of Asian, black and other ethnicities when compared to the births at LWH and the population of Liverpool. See table 12.

Table 8: Ethnicity in the LBBS in comparison to LWH and Liverpool Births

Ethnicity	LBBS	LWH	Liverpool
White	90.63%	87.69%	88.91%
Mixed	6.05%	0.94%	2.52%
Asian	0.72%	5.29%	4.16%
Black	1.44%	3.59%	2.46%
Other	0.86%	2.49%	1.77%

3.4.4-Gestation

Gestational age of the infants enrolled in the LBBS and all the eligible births in the LWH are shown in figure 28. Preterm birth was defined as birth before 37 full weeks of pregnancy, indicated by the blue dotted line (160). 12.7% of the infants enrolled in the LBBS study were born preterm. This is significantly higher than the eligible births in the LWH (9.8%- χ^2 =6.00 p<0.05 DoF=1) and births in England (7.8%- χ^2 =22.6 p<0.05 DoF=1).
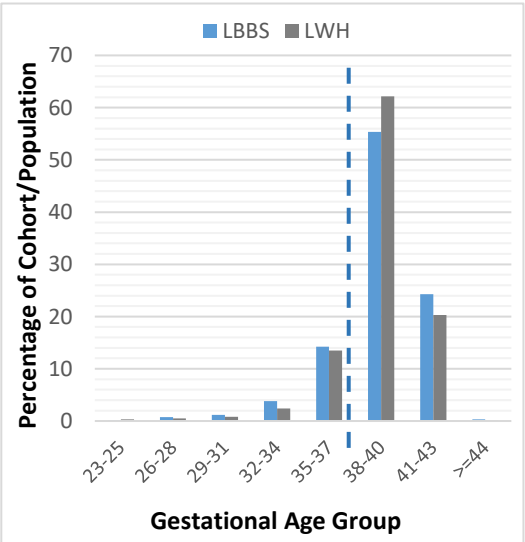
Figure 28: Gestational age of the LBBS cohort in comparison the LWH births

3.4.5-Birth Weight

The distribution of birth weights of babies in the LBBS, as well as the births in the LWH, the North West and England are shown in figure 29. Low birth weight was defined as birth under 2500 grams (161) and is indicated by the blue dotted line. 8.93% (n=62) of the births in the LBBS were low birth weight. This was not significantly different to that of the eligible births in the LWH (8.7% p>0.05), however was significantly higher than the births in England (6.5%- χ^2 =6.9 p<0.05 DoF=1).
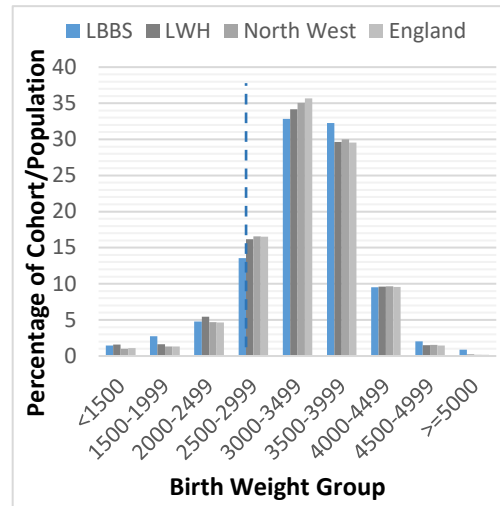
Figure 29: Birth weight of the LBBS cohort in comparison the LWH, North West and England births

3.5-Cross-sectional Analysis

The cross sectional analysis of the LBBS data is split into 4 sections; one for each of the four time points that the infants were assessed for the current thesis. The presentation of each of the individual time points is described in section 2.2.10. The presentation of each other the time points individually in chronological order in the layout described earlier has allowed the following aims of this thesis to be achieved;

- To describe respiratory symptoms of preschool children using the LRSQ from birth until 22 months of age.
- To determine the differences in LRSQ scores in the different populations at each questionnaire time point.

3.5.1-Questionnaire 1- 4 Months

Cohort Profile, Exposures and Risk Factors at 4 Months

Nursery Attendance, Other Household Children and Sharing a Bedroom

4.19% (n=28) of the cohort attended nursery in the first four months. 68.91% (n=416) of the cohort shared a bedroom. 97.41% (n=452) of these shared a bedroom with their parents, 4.4% (n=20) of which shared with their parents and another child. 1.94% (n=9) shared with another child but not their parents and 0.65% (n=3) shared their bedroom with another family member. 36.17% (n=242) of the cohort lived in a household with at least one other child. The number of other children in these households is shown in figure 30.
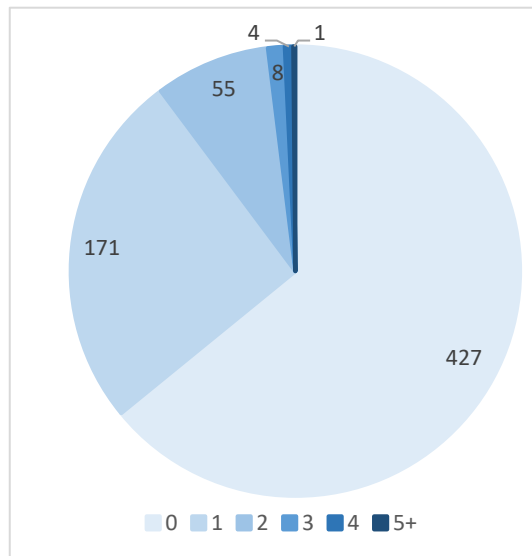
Figure 30: The number of other household children in the LBBS households at 4 months of age.

Household Smoking

18.66% (n=125) of the cohort was exposed to ETS; see figure 31. Thirteen infants were exposed to tobacco smoke inside the house, 120 stated they smoked outside, four smoked in the car and eight smoked elsewhere. The reported household smoking was significantly lower than the smoking rate for Liverpool in both 2012 (χ^2 =9.83 p<0.05 DF=1) and 2015 (χ^2 =6.27 p=0.036 DF=1).
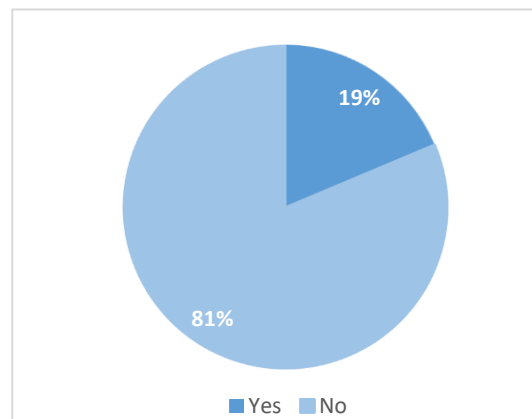
Figure 31: Percentage of households with smokers at 4 months in the LBBS

Underlying Medical Conditions

At four months of age 8.50% (n=59) of the cohort had at least one underlying medical condition. The underlying medical conditions in the cohort at four months are shown in table 13.

Table 9: Underlying medical conditions in the LBBS cohort at 4 months

Type of Underlying Condition	Underlying Condition	Frequency
Cardiac (7)	Congenital Heart Disease	6
	Heart Murmur	1
Gastrointestinal (15)	Reflux	8
	Milk Intolerance	5
	Blood in the Stools	1
	Gastroenteritis	1
Neurological (3)	'Bleed on the Brain'	1
	Hydrocephalous	1
	Sagittal Craniosynostosis	1
Other (27)	Eczema	17
	Allergies	5
	Hip Dysplasia	2
	Cleft Pallet	1
	Hypospadias	1
	Trisomy 21	1
Respiratory (9)	Cystic Fibrosis	2
	Floppy Larynx	2
	Bronchitis	1
	Chronic Lung Disease of Prematurity	1
	Lung Collapse	1
	Oxygen Therapy (Reason not defined)	1
	Recurrent Bronchiolitis	1
Urinary (2)	Vesico-ureteric Reflux	1
	Duplex Kidney	1

Total LRSQ Score

The total LRSQ score was calculated for each participant out a maximum of 132. The lowest total score was 0 and the highest score was 109. The mean score was 10.44, the median was 6 and the mode was 1. The distribution of the Total LRSQ scores at four months is shown in figure 32.
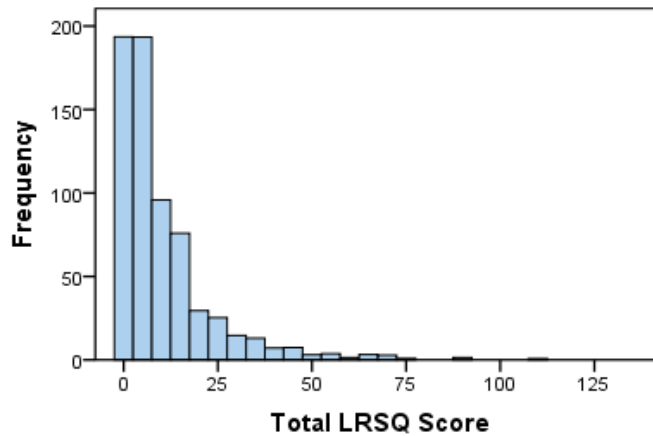
Figure 32: Histogram of Total LRSQ scores at 4 months

Total LRSQ Sores in those Exposed and Unexposed to Risk Factors and Exposures

Summary Statistics comparing demographics, exposures and risk factors are shown in table 10. Males had a significantly higher total respiratory symptom questionnaire score than females (z=-3.214 p=0.001); see figure 33. Infants born to mothers aged 25-29 years had significantly higher scores than children born to mothers in age groups older than this (p<0.05). Infants born to mothers less than 20 years of age had a higher score than those born to mothers aged over 45 years (p=0.046); see figure 34. Those with a family history of atopy had a significantly higher total score than those without (z=-2.322 p=0.02); see figure 35. Those who shared a bedroom had a lower score than those who did not share a bedroom (z=-2.361 p=0.018); see figure 36.

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Table 10: Comparison of LRSQ scores between different exposure/risk factor groups in the LBBS at 4 months

		25%	Median	75%	Mean	Mode
*Infant's Sex**	*Male*	*3*	*7*	*15*	*11.88*	*2*
	Female	*1*	*5*	*12*	*9.03*	*1*
Multiple Birth	Single Birth	2	6	14	10.45	1
	Multiple Birth	1.71	5.42	13.21	9.96	0
Ethnicity	White	2	6	14	10.7	0
	Other	2	5	10.63	7.757	5
*Maternal Age**	*<20*	*2*	*9.41*	*10*	*6.83*	*10*
	20-24	*3*	*6.76*	*13.38*	*6.76*	*0*
	25-29	*3*	*6*	*16.49*	*13.37*	*5*
	30-34	*1*	*4.64*	*10*	*7.42*	*1*
	35-39	*1*	*4*	*12*	*7.8*	*1*
	40-44	*1.82*	*4*	*13.38*	*7.39*	*1*
	>=45	*1.03*	*1.89*	*-*	*1.66*	*2*
IMD	1	2	7	15	11.7	0
	2	2	5	12.56	8.85	0
	3	2	5	14	9.71	0
	4	2	6	12	9.33	0
	5	2	5.09	12	11.13	1
	6	1.92	5.5	14.08	8.2	6
	7	1.09	5	10.31	7.57	1
	8	1	4	10.85	6.76	0
	9	2	3.14	12.07	7.62	2
	10	5.21	12.86	19.82	10.7	7
Maternal Qualification	Degree or Higher	2	5	11	8.16	2
	Higher Education	2	8	14.16	11.43	1
	A Level	2	7	28.1	16.43	0
	GCSE	2	6	16	11.23	1
	Other	2	7.62	15	12.92	0
	None	5	10.11	20	17.82	5
Premature Birth	No	2	5.68	14	10.4	1
	Yes	2	6.32	14	10.78	0
Low Birth Weight	No	2	6	14	10.58	1
	Yes	1	5.38	12.74	8.97	0
Maternal Smoking In Pregnancy	No	2	5	14	10.42	1
	Yes	3	7	13	10.6	4
Other Household Smoking In Pregnancy	No	2	5	14	10.22	1
	Yes	3	7	14	11.24	0
Any Smoke Exposure in Pregnancy	No	2	5	14	10.13	1
	Yes	3	7	14.06	11.36	3
Home Smoking	No	2	6	14	10.19	1
	Yes	2	6	14.62	11.39	0
Breastfeeding	No	2	7.95	15	12.62	0
	Yes	2	5	13	9.41	1
Breastfeeding Time	Never	2	7.95	15	12.62	0
	<1 Month	2	6.26	14.42	10.99	1
	1-4 Months	2	5	13.95	8.8	2
	>4 Months	2	5	12	8.51	1
*Family History of Atopy**	*No*	*2*	*5*	*12.02*	*8.7*	*0*
	Yes	*2*	*5*	*15*	*11.64*	*2*
Nursery Attendance	No	2	6	14	10.43	1
	Yes	2.9	5	12.15	11.25	5
Other Household Children	No	2	5	13	9.86	5
	Yes	2	6	15.91	11.49	1
*Shares a Bedroom**	*No*	*3*	*7*	*15*	*12*	*5*
	Yes	*2*	*5*	*14*	*9.79*	*1*

*indicates significant result (p<0.05)
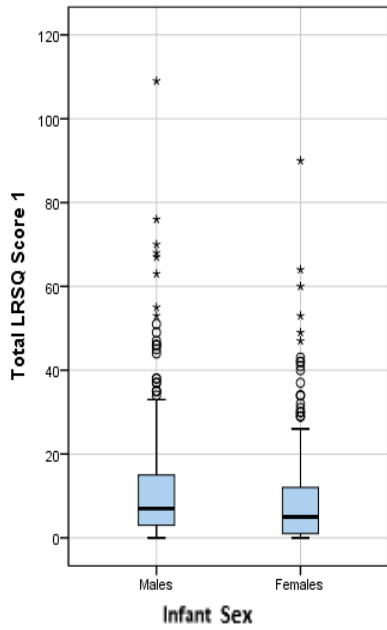
Figure 33: Total LRSQ scores by infant sex at 4 months
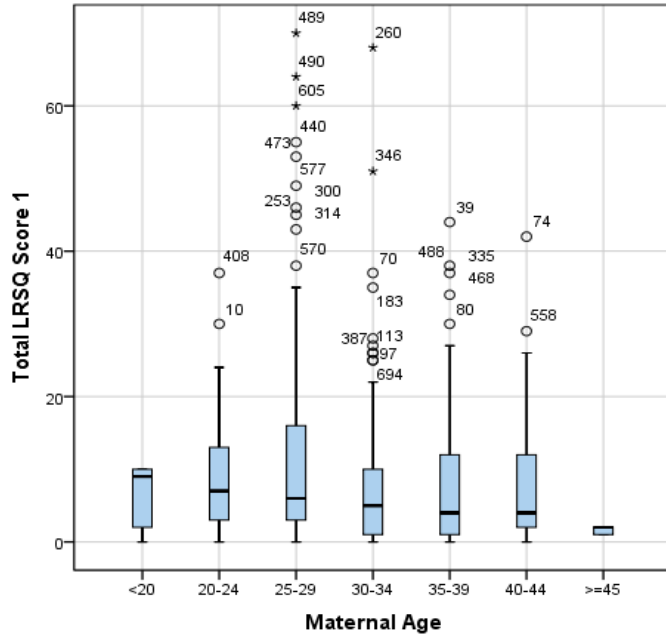
Figure 34: Total LRSQ Scores by maternal age group at 4 months
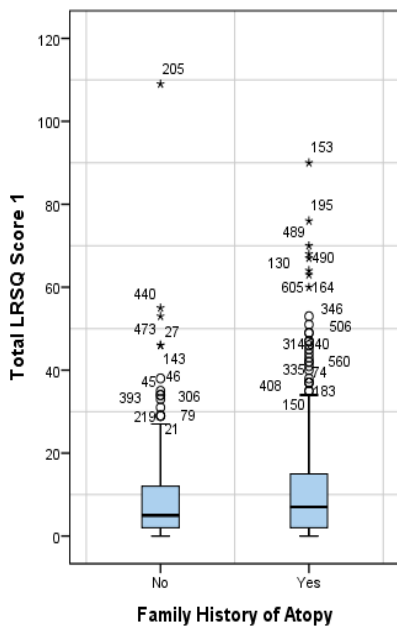
Figure 35: Total LRSQ scores by FH of atopy at 4 months
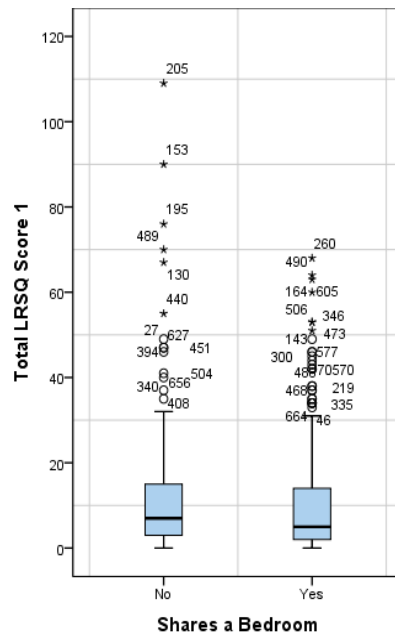
Figure 36: Total LRSQ scores by sharing a bedroom at 4 months

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LRSQ Domain Sores in the First 4 Months

The summary statics of the domain scores in the first four months of life are shown in table 14. Symptoms with colds and night-time symptoms were the highest scoring domains. 'Symptoms on increased activity' was the lowest scoring domain. Domains seven and eight are QoL domains and are discussed elsewhere.

Table 11: Summary statistics of domain scores at 4 months

	Min	Median	Max	Mean	SD
Domain 1 **Day Time Symptoms**	0	1	15	1.44	2.01
Domain 2 **Night-time Symptoms**	0	2	19	2.14	2.37
Domain 3 **Symptoms with Colds**	0	1	21	2.33	3.17
Domain 4 **Symptoms without Colds**	0	0	16	0.78	1.6
Domain 5 **Symptoms on Increased Activity**	0	0	16	0.48	1.43
Domain 6 **Other Respiratory Symptoms**	0	0	12	1.16	1.9
Domain 7 **Childs Quality of Life**	0	0	12	0.64	1.56
Domain 8 **Parents Quality of Life**	0	0	16	0.98	2.17

Sex

Males scored higher in 'daytime symptoms' (z=-2.112 p=0.035), 'night-time symptoms' (z=-2.923 p=0.003) and 'other respiratory symptoms' (z=-2.77 p=0.006) than females.

Maternal Age

Kruskal-Wallis testing revealed variance between different maternal age categories in the domains 'day time symptoms' (χ^2=13.90 p=0.033 DoF=6), 'night-time symptoms' (χ^2=14.71 p=0.022 DoF=6), and 'symptoms without colds' (χ^2=13.97 p=0.030 DoF=6). Post hoc testing revealed those infants born to mothers aged 25-29 years of age scored higher for 'daytime symptoms' than those born to mothers aged 30-34 (p=0.002) and 35-39 years old (p=0.016). Those born to mother 25-29 year of age scored higher for 'night-time symptoms' and 'symptoms without colds' than those born to mothers aged 30-34 (p=0.003 and p=0.005), 35-39 (p=0.009 and p=0.006) and those aged 40-44 (p=0.042 and p=0.030) years of age.

Gestation

Preterm babies scored higher than term babies for 'symptoms without colds' (z=-2.148 p=0.032).

Breastfeeding

Children who were breastfed scored lower for 'symptoms on increased activity' than children who were not breastfed (z=-2.198 p=0.028). 'Night-time symptoms' scores varied depending on the length of time that the child was breastfed for (χ^2 =8.735 p=0.033 DF=3). Post hoc analysis showed those who were still being breastfed at four months had lower 'night-time symptom' scores than: those who were never breastfed (p=0.016); those who were breastfed for only up to one month (p=0.03); and those who were breastfed for one to four months (p=0.025).

Family History of Atopy

Infants with a family history of atopy scored higher than those without a family history of atopy for 'symptoms without colds' (z=-2.122 p=0.034), 'symptoms on increased activity' (z=-2.193 p=0.033) and 'other respiratory symptoms' (z=-2.193 p=0.028).

Other Household Children

Infants who lived in households with other children scored higher for 'symptoms with colds' than children who lived in households with no other children (z=-2.079 p=0.038).

Sharing a Bedroom

Infants who shared a bedroom scored lower for 'symptoms with colds' (z=-2.971 p=0.003) than those children who slept in their own bedroom.

Respiratory Symptom Prevalence in First 4 months of Life

89.85% (n=602) of the cohort had respiratory symptoms in the first four months of life. Snoring was the most reported symptom affecting 62.09% (n=416) of the cohort. 61.94% (n=415) of the cohort had at least one cold in the first four months of life. The lowest reported respiratory symptom was SoB, reported by only 12.54% (n=84) of the cohort. The prevalence of the symptoms in the previous three months of life per 100 infants are shown in figure 37.
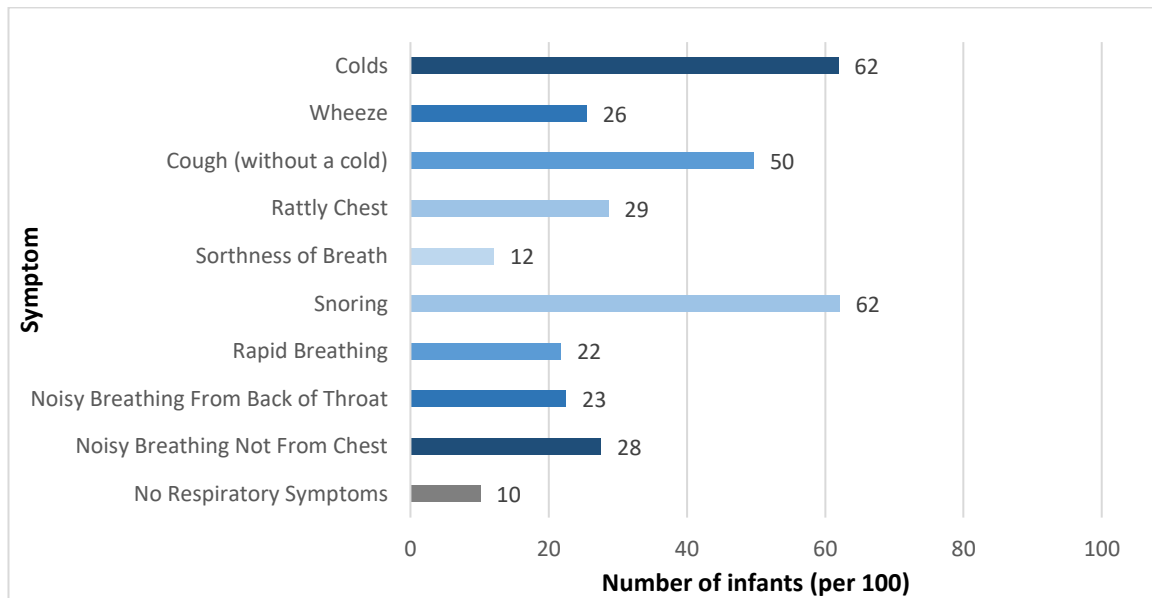
Figure 37: Respiratory symptom prevalence per 100 infants in the first 4 months of life

Prevalence of Symptoms Compared to Risk Factors and Exposures

Sex

Males had a higher prevalence of SoB (χ^2=10.91 p<0.05 DF=1), snoring (χ^2=9.98 p<0.05 DF=1), 'noisy Breathing from the throat' (χ^2=6.75 p<0.05 DF=1) and 'noisy breathing not from the chest' (χ^2=10.44 p<0.05 DF=1) than females.

Ethnicity

White infants had a higher prevalence of rattily chest (χ^2=6.22 p<0.05 DF=1), snoring (χ^2=6.63 p<0.05 DF=1) and raid breathing (χ^2=5.68 p<0.05 DF=1) than other ethnicities.

Maternal Age

χ^2 testing showed variation in the prevalence of wheeze (χ^2=15.28 p<0.05 DF=6), rattily chest (χ^2=19.18 p<0.05 DF=6), SoB (χ^2=17.16 p<0.05 DF=6) and rapid breathing (χ^2=15.11 p<0.05 DF=6) in infants born to mothers of different ages. Post hoc analysis revealed that the prevalence of wheeze was higher in infants born to mothers aged 25-29 than those born to

mothers aged 30-34 (χ^2 =9.76 p<0.05 DF=1) and 35-39 (χ^2 =10.58 p<0.05 DF=1). The prevalence of rattily chest was higher in infants born to mothers aged 25-29 than infants born to mothers aged 30-34 (χ^2 =14.70 p<0.05 DF=1), 35-39 (χ^2 =7.40 p<0.05 DF=1) and 40-45 (χ^2 =6.14 p<0.05 DF=1). The prevalence of SoB was higher in those infants born to mothers aged 25-29 than in mothers aged 30-34 (χ^2 =14.14 p<0.05 DF=1) and 35-39 (χ^2 =5.02 p<0.05 DF=1). The prevalence of rapid breathing was higher in infants born to mothers aged less than 20 compared to those born to mothers aged 20-24 (χ^2 =7.12 Fisher's Exact Test p=0.022 DF=1), 30-34 (χ^2 =8.16 Fisher's Exact Test p=0.015 DF=1), 35-39 (χ^2 =5.58 Fisher's Exact Test p=0.037 DF=1) and 40-44 (χ^2 =9.61 Fisher's Exact Test p=0.001 DF=1). Rapid breathing was also higher in infants born to mothers aged 25-29 compared to infants born to mothers aged 30-34 (χ^2 =4.52 p<0.05 DF=1) and 40-44 (χ^2 =3.9 p<0.05 DF=1).

Maternal Qualification

Kruskal-Wallis testing showed there was variation in the prevalence of rattily chest (χ^2 =13.39 p<0.05 DF=5) and SoB (χ^2 =14.77 p<0.05 DF=5) in infants born to mothers with different levels of education. Post hoc analysis revealed that the prevalence of rattily chest was lower in those infants born to mothers with a degree or post graduate degree than those born to mothers who attended higher education (χ^2 =6.54 p<0.05 DF=1), had a-levels (χ^2 =5.42 p<0.05 DF=1) or GCSE's (χ^2 =5.88 p<0.05 DF=1). Those infants born to mothers with A-levels had a higher prevalence of SoB than those who were born to mothers with a degree or postgraduate degree (χ^2 =9.38 p<0.05 DF=1), those who attended higher education (χ^2 =12.16 p<0.05 DF=1) or those with GCSE's (χ^2 =5.63 p<0.05 DF=1).

Gestation

Infants born preterm had a lower prevalence of colds than those who were born term (χ^2 =4.46 p<0.05 DF=1) but had a higher prevalence of rapid breathing (χ^2 =5.26 p<0.05 DF=1).

Birth Weight

Infants born with a low birth weight had a higher incidence of colds than those who were born with a normal birth weight (χ^2 =5.39 p<0.05 DF=1).

Breastfeeding

The prevalence of wheeze (χ^2 =12.17 p<0.05 DF=1) and SoB (χ^2 =4.51 p<0.05 DF=1) were lower in those who were breastfed than those who were not breastfed.

Family History of Atopy

Infants with a family history of atopy had a higher prevalence of 'noisy breathing from the throat' (χ^2=7.04 p<0.05 DF=1) and 'noisy breathing not from the chest' (χ^2=5.38 p<0.05 DF=1) than those with no family history of atopy.

Nursery Attendance

Those who attended nursery reported a higher prevalence of snoring (χ^2=6.63 p<0.05 DF=1) than those who did not attend nursery.

Other Household Children

Infants who lived in households with other household children reported a higher prevalence of colds than those who did not live with other children (χ^2=4.24 p<0.05 DF=1), however they reported a lower prevalence of snoring than those who did not live with other children (χ^2=5.50 p<0.05 DF=1).

Sharing a Bedroom

Infants who shared a bedroom had a lower prevalence of cough (χ^2=4.99 p<0.05 DF=1), SoB (χ^2=6.67p<0.05 DF=1) and colds (χ^2=19.66 p<0.05 DF=1) than infants who slept alone.

Health Care Service Attendance due to Respiratory symptom

15.82% (n=106) of the cohort attended the GP in the first four months of life with respiratory symptoms. 6.27% (n=42) attended the hospital with respiratory symptoms. GP attendance was higher in those infants who were exposed to tobacco smoke in pregnancy (χ^2=9.33 p<0.05 DF=1), attended nursery (χ^2 =5.54 p<0.05 DF=1), lived with other children (χ^2 =18.79 p<0.05 DF=1) and shared a bedroom (χ^2 =4.63 p<0.05 DF=1) but was reduced in those who were breastfed (χ^2 =10.60 p<0.05 DF=1). Hospital attendance was increased in males (χ^2 =6.69 p<0.05 DF=1), those born preterm (χ^2=7.76 p<0.05 DF=1) and those who live with other children (χ^2 =17.87 p<0.05 DF=1) but was reduced in those who were breastfed (χ^2=30.13 p<0.05 DF=1). Infants born to mothers with increasing maternal age reduced both GP and hospital attendance whereas infants born to mothers with a lower level of education attended more frequently. This is shown in figure 38 and 39. There was no association between IMD decile and health care service use.
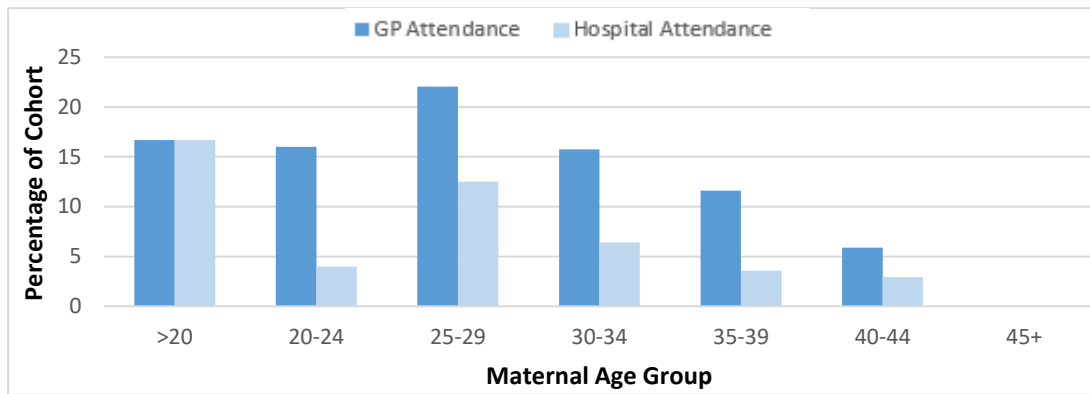
Figure 38: Percentage of the cohort that attended their GP or hospital with respiratory symptoms in the first 4 months of life by maternal age group
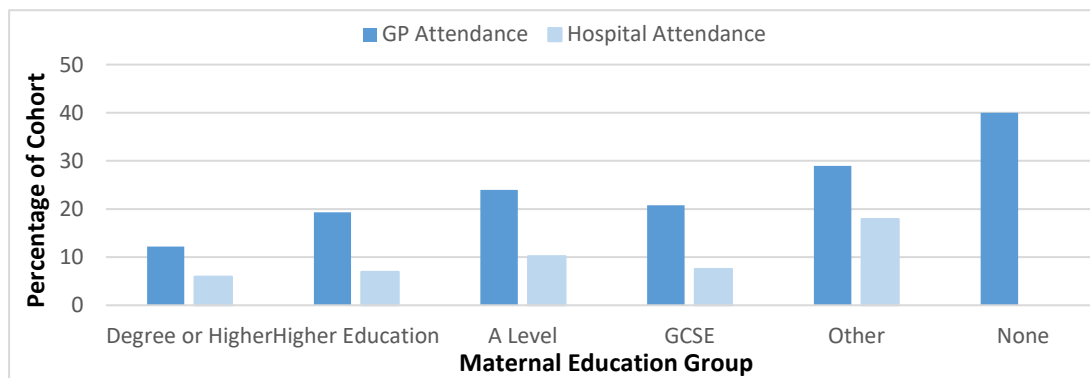
Figure 39: Percentage of the cohort that attended their GP or hospital with respiratory symptoms in the first 4 months of life by highest maternal qualification attained

The Impact of Respiratory Symptoms on QoL

The impact of respiratory symptoms on the QoL of the infant and their mother's is shown figures 40 and 41 respectively. The QoL of 22.8% (n=153) of the infants in the cohort was effected by their respiratory symptoms. The QoL of 29.7% (n=199) of the mothers were effected by their infants respiratory symptoms. Children who shared a bedroom were reported to have a better QoL than those who slept alone (z=-2.427 p=0.015) whereas children who lived in households with at least one other children had a worse QoL than those who did not live with other children (z=-2.055 p=0.04). Mothers of males reported a worse QoL due to their child's respiratory symptoms compared to mothers of females (z=-3.411 p=0.001). Mothers of infants with a family history of atopy reported a worse QoL compared to mothers of infants without a family history of atopy (z=-2.015 p=0.044) and mothers of children who lived in households with other children reported that they had a worse QoL than those who lived in a household with no other children (z=-2.156 p=0.031).
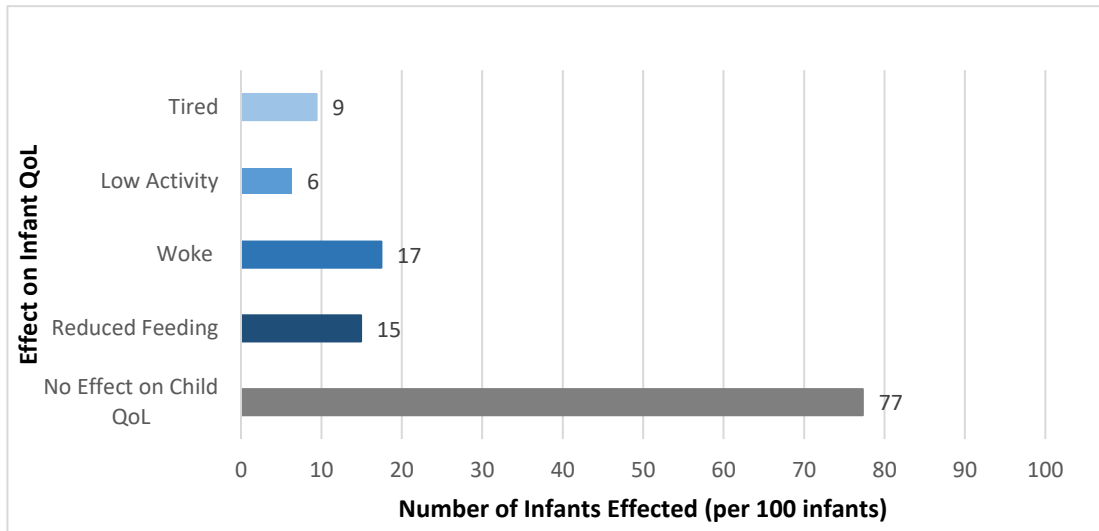
Figure 40: The impact of respiratory disease on the infant's QoL in the first 4 months in the LBBS (per 100 infants)
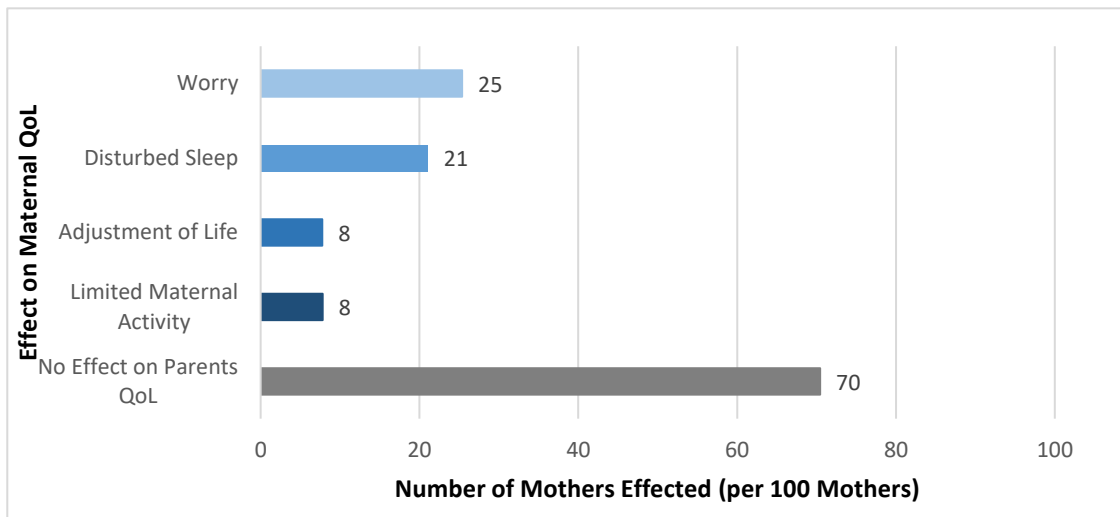
Figure 41: The impact of respiratory disease on the infant's mother's QoL in the first 4 months in the LBBS (per 100 infants)

Spearman's rank correlation analysis showed that higher Respiratory symptom scores were correlated with higher QoL domain scores indicating a worse QoL (r_s=0.674 p<0.001). This is shown in figure 42.
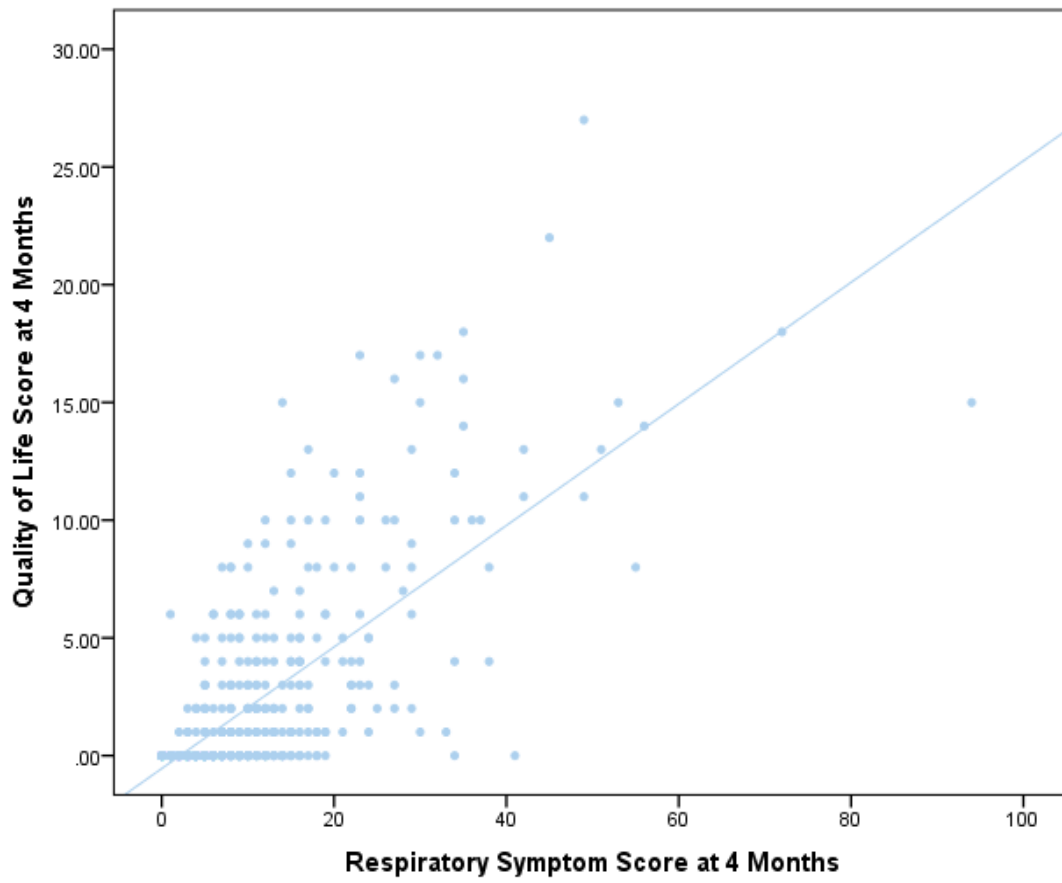
Figure 42: Scatter graph of respiratory symptom scores and quality of life scores at 4 months

3.5.2-Questionnaire 2- 10 Months

Cohort Profile, Exposures and Risk Factors at 10 Months

Nursery Attendance, Other Household Children and Sharing a Bedroom

At 10 months 26.93% (n=101) of the cohort attended nursery. 43.47% (n=163) of the cohort lived with at least one other child. The number of other children in these households is shown in figure 43. 61.33% (n=230) of the cohort shared a bedroom. Of these 80.69% (n=117) shared with their parents and 18.62% (n=28) shared with other children without their parents. One infant shared a bedroom with another family member.
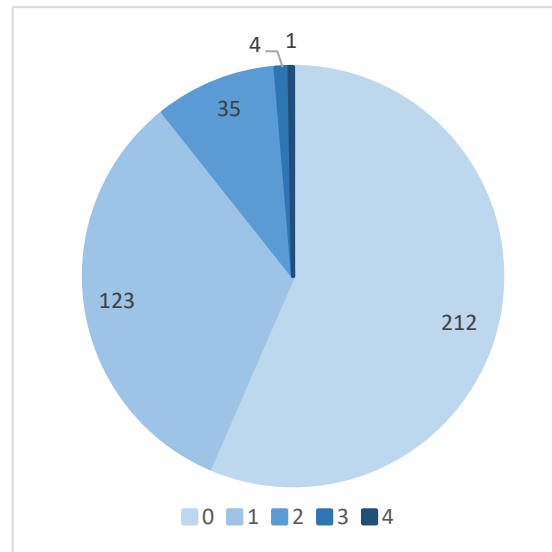
Figure 43: Number of children in households at 10 months

Household Smoking

17.6% (n=66) of the infants in the cohort were exposed to ETS in the previous three months; see figure 44. Of these smokers 4.5% (n=3) smoked inside, 95.5% (n=63) smoked outside, 3.0% (n=2) smoked in the car and 4.5% (n=3) smoked elsewhere. This reported rate of smoking was significantly lower than the smoking prevalence in Liverpool in 2012 (χ^2 =8.86 p<0.05 DF=1) and in 2015 (χ^2 =6.13 p<0.05 DF=1).
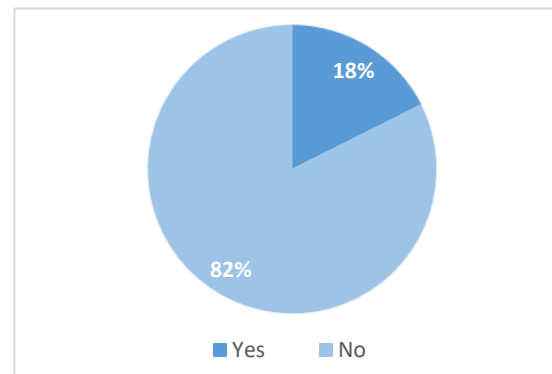
Figure 44: Household smoking at 10 months

Underlying Medical Conditions

By 10 months 9.05% (n=34) of the cohort had at least one underlying medical condition. The underlying health conditions in the LBBS cohort at 10 months are shown in table 15.

Table 12: Underlying medical conditions in the LBBS at 10 months

Type of Underlying Condition	Underlying Condition	Frequency
Cardiac (3)	Congenital Heart Disease	3
Gastrointestinal (3)	Imperforated Anus	1
	Milk Intolerance	1
	Reflux	1
Other (18)	Eczema	10
	Allergies	3
	Clotting Disorders	2
	Hip Dysplasia	2
	Umbilical Hernia	1
Respiratory (6)	Asthma	2
	Bronchomalacia	1
	Chronic Lung Disease	1
	Constant Wheeze	1
	'Scaring of the lungs requiring oxygen therapy'	1
Urinary (2)	Vesico-ureteric Reflux	1
	Dilated Kidneys	1

Total LRSQ Score

At 10 months the lowest total score was 0 and the highest score was 114. The mean score was 13.50, the median was nine and the mode was 6. The distribution of the Totals LRSQ scores at 10 months is shown in figure 45.
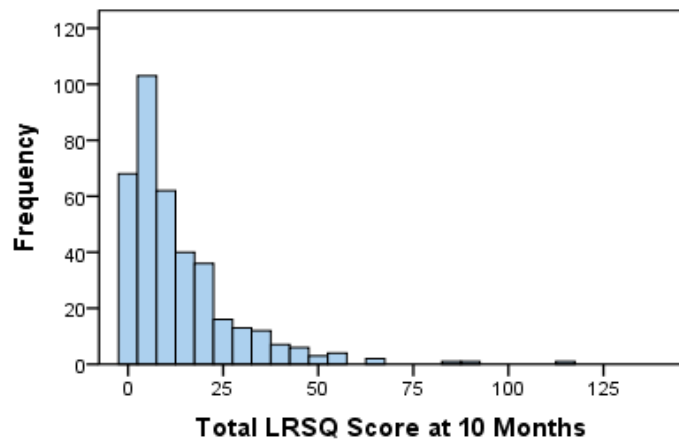
Figure 45: Histogram of Total LRSQ Scores at 10 Months

Total LRSQ Score in Those Expose and Unexposed to Risk Factors and Exposures

Summary Statistics comparing demographics, confounding factors, exposures and risk factors are shown in table 13. Males had significantly higher LRSQ scores than females (z=-3.059 p=0.002); see figure 46. White babies had higher LRSQ scores than those in other ethnic groups (z=-2.771 p=0.006); see figure 47. Babies born preterm had higher LRSQ scores than those born term (z=-1.978 p=0.048); see figure 48. Those infants that had attended nursery had higher LRSQ scores than those who did not (z=-4.952 p<0.001); see figure 49. Infants born to mothers aged 20-29 years of age had higher LRSQ scores than those born to mothers aged 34-44 (p<0.05); see figure 50.

Table 13: Comparison of LRSQ scores between different exposure/risk factor groups in the LBBS at 10 months

		25%	Median	75%	Mean	Mode
*Infant's Sex**	*Male*	*5*	*9.85*	*21*	*15.97*	*6*
	Female	*3*	*7*	*17*	*11.87*	*2*
Multiple Birth	Single Birth	4	8.86	20	14.14	0
	Multiple Birth	2	2.52	16.84	9.19	2
*Ethnicity**	*White*	*4*	*9*	*20*	*14.42*	*6*
	Other	*2*	*4*	*12.79*	*7.89*	*2*
*Maternal Age**	*<20*	*1*	*11.52*	*23.34*	*11.59*	*1*
	20-24	*7*	*15.1*	*21.99*	*14.95*	*3*
	25-29	*4*	*10.28*	*28*	*18.07*	*4*
	30-34	*4*	*9.27*	*19*	*12.94*	*0*
	35-39	*2*	*5.85*	*11.7*	*11.11*	*1*
	40-44	*2.46*	*3.63*	*11.95*	*7.06*	*3*
	>=45	*-*	*19*	*-*	*-*	*-*
IMD	1	3	8	21	14.91	0
	2	3	8	15.5	11.2	1
	3	2.04	5.17	14.15	11.58	2
	4	4.76	12	27.27	18.18	2
	5	4.08	10.17	14.37	11.6	6
	6	2.5	9.49	12.62	11.36	0
	7	4.39	10.42	17.37	12.48	1
	8	4	11	18	11.33	4
	9	6.32	16.07	32.61	22.64	0
	10	4.43	19	-	18.67	4
Maternal Qualification	Degree or Higher	4	8	17.28	12.23	6
	Higher Education	2.46	7.37	16	11.23	2
	A Level	6	20	36	22.29	1
	GCSE	2.52	12	29.09	18.95	2
	Other	5	9.53	22.57	14.21	5
	None	2.12	5.81	20	9.71	3
*Premature Birth**	*No*	*3*	*8*	*19*	*13.41*	*0*
	Yes	*5*	*12.67*	*21*	*18.46*	*5*
Low Birth Weight	No	3	8	19	14.01	0
	Yes	4	12.82	21	13.25	1
Maternal Smoking In Pregnancy	No	3	8	20	14.06	6
	Yes	3	6	20.19	12.84	5
Other Household Smoking In Pregnancy	No	3	8	20	14.05	0
	Yes	4	10	18.85	13.52	5
Any Smoke Exposure in Pregnancy	No	3	8	20	13.92	0
	Yes	4	10	19.52	14.03	5
Home Smoking	No	4	8	20	14.13	0
	Yes	3	8	16.55	13.19	2
Breastfeeding	No	4	11	22.05	15.98	5
	Yes	3	8	9	13.07	0
Breastfeeding Time	Never	4	11	22.05	15.98	5
	<1 Month	2.05	8	20	14.99	1
	1-4 Months	3.35	8.05	17.82	11.57	3
	>4 Months	3.25	8	18.76	12.46	0
Family History of Atopy	No	3	8.46	18	13	0
	Yes	4	8	20	14.67	6
*Nursery Attendance**	*No*	*3*	*7*	*16*	*11.85*	*2*
	Yes	*6*	*14*	*26*	*19.77*	*5*
Other Household Children	No	4	9	18.49	12.39	6
	Yes	3	8	22	15.8	0
Shares a Bedroom	No	4	8	19	13.78	6
	Yes	3	9	20	14.2	0

*indicates significant result (p<0.05)
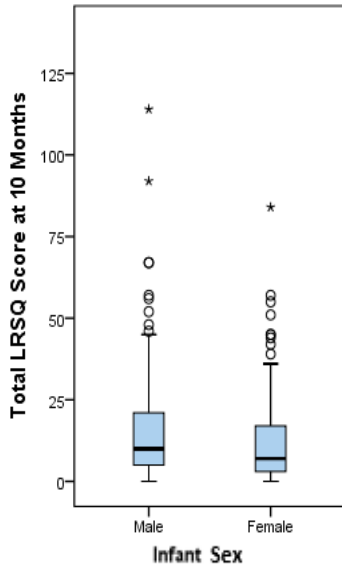
Figure 46: Total LRSQ scores at 10 months by infant sex
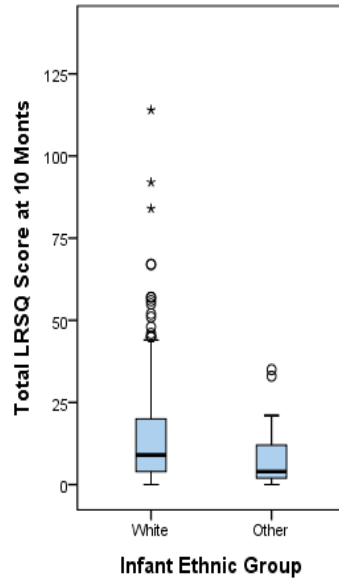
Figure 47: Total LRSQ score at 10 months by infant ethnicity
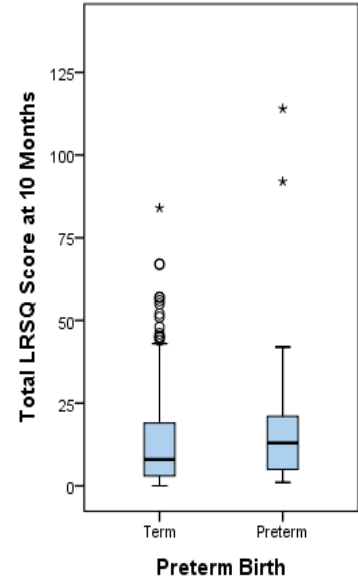
Figure 48: Total LRSQ score at 10 months by preterm birth
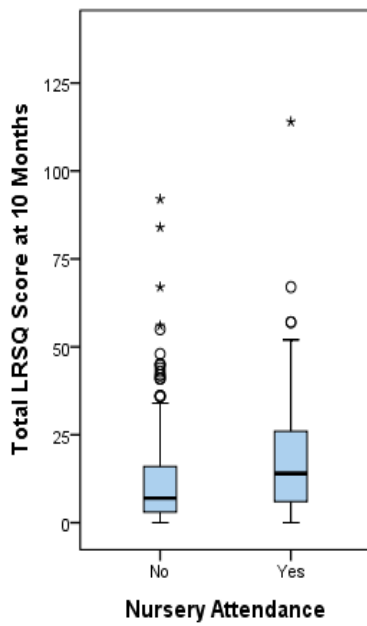
Figure 49: Total LRSQ at 10 months by nursery attendance
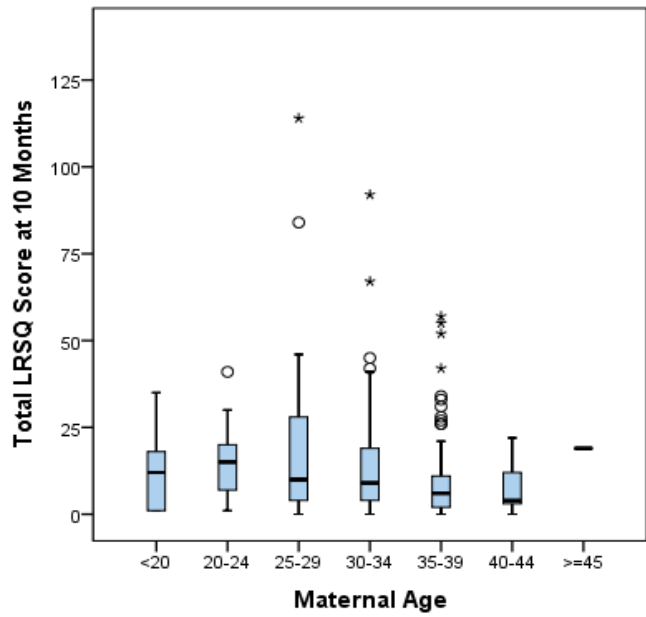
Figure 50: Total LRSQ score at 10 months by maternal age

LRSQ Domain Scores in Months 4-10

The summary statics of the domain scores for months 4-10 are shown in the table 14. 'Symptoms with colds' and 'night-time symptoms' were the highest scoring domains. Symptoms on 'increased activity' was the lowest scoring domain. Domains seven and eight are QoL domains and are discussed elsewhere.

Table 14: Summary statistics of domain scores at 10 months

	Min	Median	Max	Mean	SD
Domain 1 **Day Time Symptoms**	0	1	15	1.9	2.3
Domain 2 **Night-time Symptoms**	0	2	18	2.5	2.6
Domain 3 **Symptoms with Colds**	0	3	20	4.1	3.6
Domain 4 **Symptoms without Colds**	0	1	12	0.7	1.5
Domain 5 **Symptoms on Increased Activity**	0	0	15	0.6	1.6
Domain 6 **Other Respiratory Symptoms**	0	0	9	0.7	1.5
Domain 7 **Childs Quality of Life**	0	0	13	1.4	2.2
Domain 8 **Mothers Quality of Life**	0	0	14	1.5	2.6

Sex

Males had significantly higher scores for 'day time symptoms' (z=-2.006 p=0.045), 'night-time symptoms' (z=-3.658 p<0.001), 'symptoms with colds' (z=-3.123 p=0.034) and 'symptoms on increased activity' (z=-3.466 p=0.001) when compared to females.

Ethnicity

White infants had higher scores for 'day time symptoms' (z=-2.108 p=0.002), 'night-time symptoms' (z=-2.137 p=0.033), 'symptoms without colds' (z=-2.275 p=0.023) and 'symptoms on increased activity' (z=-2.188 p=0.029) compared to infants in other ethnic groups.

Maternal Age

Kruskal-Wallis Testing revealed differences in scores for infants born to mothers of different maternal ages for 'day time symptoms' (χ^2=19.72 p<0.05 DF=6), 'symptoms with colds' (χ^2=21.71 p<0.05 DF=6), 'symptoms without colds' (χ^2=16.22 p<0.05 DF=6), and 'symptoms on increased activity' (χ^2=13.31 p<0.05 DF=6).

Post Hoc Testing Domain 1- Day Time Symptoms

Infants born to mothers aged 20-24, 25-29 and 30-34 had higher scores than infants born to mothers aged 35-39 (p=0.031, p=0.002, p=0.009) and 40-44 (p=0.006, p=0.002, p=0.005).

Post Hoc Testing Domain 3- Symptoms with Colds

Infants born to mothers aged 20-24 had higher scores than infants born to mothers aged 35-39 (p=0.02) and 40-44 (p=0.009). Infants born to mothers aged 25-29 had higher scores than infants born to mothers aged 30-34 (p=0.008), 35-39 (p=0.001) and 40-44 (p=0.001). Infants born to mothers aged 35-29 had higher scores than infants born to mothers aged 40-44 (p=0.049).

Post Hoc Testing Domain 4- Symptoms without Colds

Infants born to mothers aged less than 20, 25-29 and over 45 years had higher scores than infants born to mothers aged 35-39 (p=0.014, p=0.003, p=0.034) and 40-44 (p=0.027, p=0.04, p=0.038). Infants born to mothers aged 30-34 had higher scores than those born to mothers aged 35-39 (p=0.042).

Post Hoc Testing Domain 5- Symptoms on Increased Activity

Infants born to mothers aged 40-44 had lower scores than infants born to mother aged 20-24 (p=0.014), 25-29 (p=0.007), 30-34 (p=0.018), 35-39 (0.013) and over 45 years (p<0.001). Infants born to mothers over 45 years had a higher score than those born to mothers under 20 years (p=0.014).

Maternal Education

Kruskal-Wallis Testing revealed differences in domain scores for infants born to mothers with different levels of education for 'day time symptoms' (χ^2 =11.96 p<0.05 DF=5), 'symptoms without colds' (χ^2 =32.35 p<0.05 DF=5), and 'symptoms on increased activity' (χ^2 =22.04 p<0.05 DF=6).

Post Hoc Testing Domain 1- Day Time Symptoms

Infants born to mothers with a degree or a post graduate degree had lower scores than infants born to mothers with A-levels (p=0.027). Infants born to mothers who had attended higher education had lower scores than infants born to mothers with A-levels (p=0.009), GCSE's (p=0.048) and no qualifications (p=0.036).

Post Hoc Testing Domain 4- Symptoms without Colds

Infants born to mothers with A-levels had higher scores than infants born to mothers with a degree or post graduate degree (p<0.001) or who had attended higher education (p<0.001).

Infants born to mothers with GCSE's had higher scores than infants born to mothers or who had attended higher education (p=0.006) and those who had A-levels (p=0.015). Infants born to mothers with A-levels had higher scores than infants born to mothers or who had no qualifications (p=0.013) and those with 'other' qualifications (p=0.035).

Post Hoc Testing Domain 5- Symptoms on Increased Activity

Infants born to mothers with a degree or post graduate degree had lower scores than infants born to mothers with A-levels (p<0.001) and infants born to mothers who attended higher education had lower scores than infants born to mothers with A-levels (p<0.001) and GCSE's(p=0.006). Infants born to mothers with A-levels had lower scores than infants born to mothers with GCSE's (p=0.015) and those with no qualifications (p=0.013). Infants born to mothers with 'other' qualifications had lower scores than infants born to mothers with A-levels (p=0.035).

Smoking Exposure in Pregnancy

Those infants who were exposed to tobacco smoke in pregnancy whether that be maternal or other household smokers had lower scores 'without colds' than those who were not exposed (z=-2.228 p=0.026).

Breastfeeding

Those who were breastfed had lower scores for 'symptoms without colds' than those who were not breastfed (z=-2.56 p=0.011). Further testing revealed those who infants who were breastfed for four months or more had the lowest scores, and this was significantly lower when compared to those who had never been breastfed (p=0.004).

Family History of Atopy

Those infants with a family history of atopy scored significantly higher for 'symptoms with colds' than those who did not have a family history of atopy (z=-2.108 p=0.035).

Nursery Attendance

Those who attended nursery had higher scores for 'daytime symptoms' (z=-5.196 p<0.001), 'night-time symptoms' (z=-4.637 p<0.001), 'symptoms with colds' (z=-5.078 p<0.001), 'symptoms without colds' (z=-3.117 p=0.002) and 'other respiratory symptoms' (z=-2.52 p=0.012).

Respiratory Symptom Prevalence at 10 Months

93.1% (n=349) of the cohort had respiratory symptoms in the previous three months at 10 months of age. Colds were the highest reported respiratory symptom with 85.6% (n=321) of the cohort having at least one cold in the previous three months. The lowest reported respiratory symptom was rapid breathing reported by only 16.80% (n=63) of the cohort. The prevalence of the respiratory symptoms per 100 infants in the three months prior to 10 months of age are shown in figure 51.
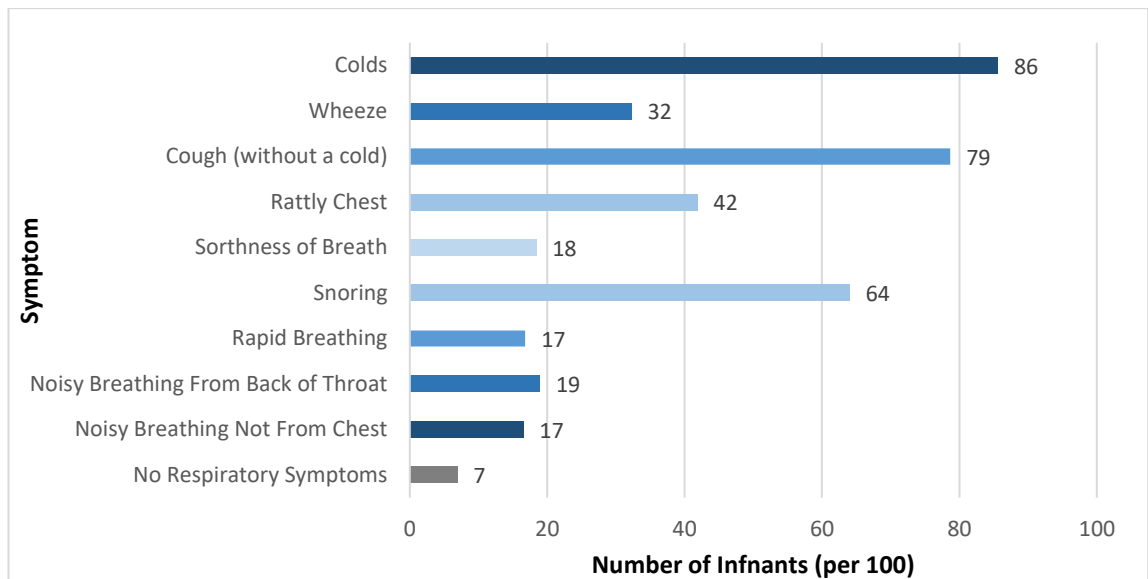
Figure 51: Respiratory symptom prevalence at 10 months per 100 infants

Respiratory Symptom Prevalence in Those Exposed and Unexposed to Risk Factors

Males had a higher prevalence of cough (χ^2 =4.60 p<0.05 DF=1) and snoring (χ^2 =6.11 p<0.05 DF=1) than females. White infants had a higher prevalence of wheeze (χ^2 =4.81 p<0.05 DF=1) and rattily chest (χ^2 =5.77 p<0.05 DF=1) than infants of other ethnic groups. Preterm babies had a higher prevalence of rapid breathing than those who were born at term (χ^2 =6.70 p<0.05 DF=1). The prevalence of colds was higher in low birth weight babies than in babies born at a normal weight (χ^2 =5.64, Fishes Exact Test p=0.0128 DF=1). The prevalence of SoB (χ^2 =5.49 p<0.05 DF=1) and 'noisy breathing from the throat' (χ^2 =6.24 p<0.05 DF=1) was lower in babies that were breastfed. The prevalence of cold symptoms was higher in those infants with a family history of atopy when compared to those without a family history (χ^2 =8.05 p<0.05 DF=1). Infants who attended nursery had a higher prevalence of wheeze (χ^2

=6.19 p<0.05 DF=1), cough (χ^2 =4.75 p<0.05 DF=1), rattily chest (χ^2 =16.90 p<0.05 DF=1), colds (χ^2 =4.70 p<0.05 DF=1), and 'noisy breathing from the throat' (χ^2 =11.88 p<0.05 DF=1) than those who did not attend nursery. The prevalence of snoring was lower in those babies who shared a bedroom compared to those who slept alone (χ^2 =16.38 p<0.05 DF=1).

Health Care Service Attendance in Months 4-10

In months 4-10 29.07% (n=109) of the cohort attended the GP with respiratory symptoms. 8.80% (n=33) attended the hospital with respiratory symptoms. GP attendance was higher in those with a family history of atopy (χ^2 =14.09 p<0.05 DF=1), those who were born with a low birth weight (χ^2 =5.85 p<0.05 DF=1) and those who attended nursery (χ^2 =12.40 p<0.05 DF=1) but was reduced in those who were breastfed (χ^2 =5.83 p<0.05 DF=1). Hospital attendance was increased in infants with a family history of atopy (χ^2 =14.09 p<0.05 DF=1) and those who were born with a low birth weight (χ^2 =4.51 p<0.05 DF=1) but was reduced in those who were breastfed (χ^2 =9.52 p<0.05 DF=1). Increasing maternal age reduced both GP and hospital attendance; see figure 52. The relationship between maternal education and health care service attendance is shown in figure 53.
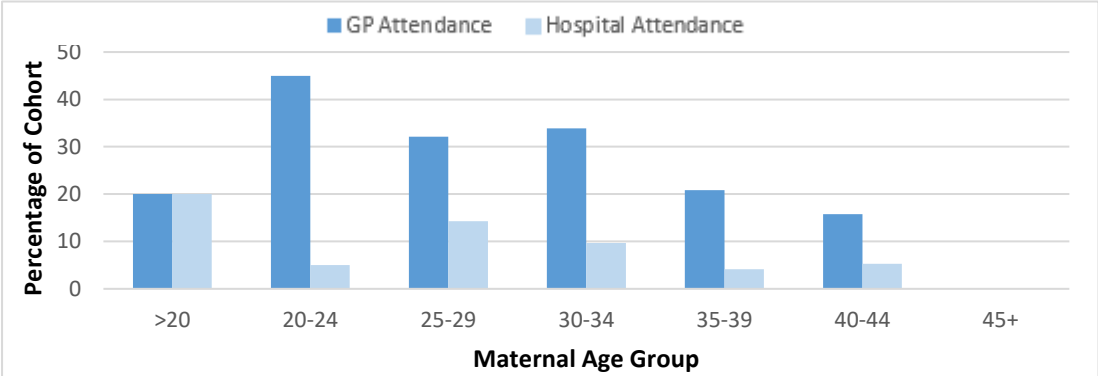
Figure 52: Percentage of the cohort that attended their GP or hospital with respiratory symptoms in months 4-10 of life by maternal age group
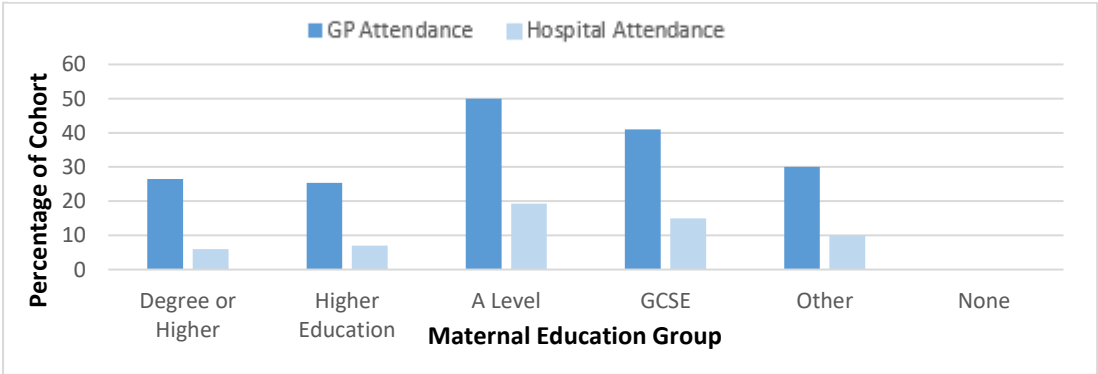
Figure 53: Percentage of the cohort that attended their GP or hospital with respiratory symptoms in months 4-10 of life by highest maternal qualification attained

The Impact of Respiratory Symptoms on QoL in Months 4-10

The impact of respiratory symptoms on the QoL of the infant and their families are summarised in figures 54 and 55 respectively. The QoL of 43.5% (n=163) of the infants in the cohort was effected by their respiratory symptoms. The QoL of 45.3% (n=163) of the cohorts mothers were effected by their infants respiratory symptoms.
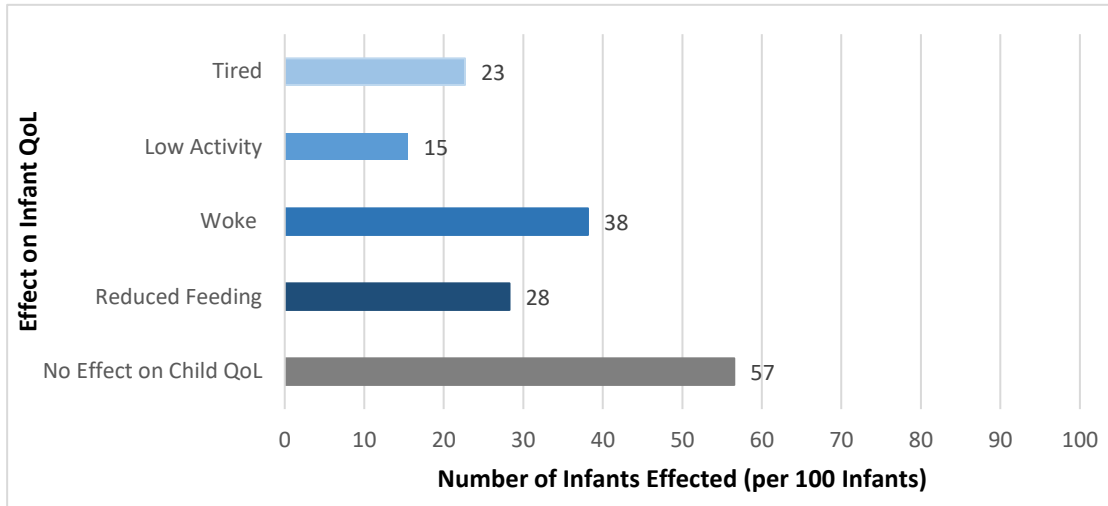
Figure 54: The impact of respiratory disease on the infant's QoL at 10 months in the LBBS (per 100 infants)
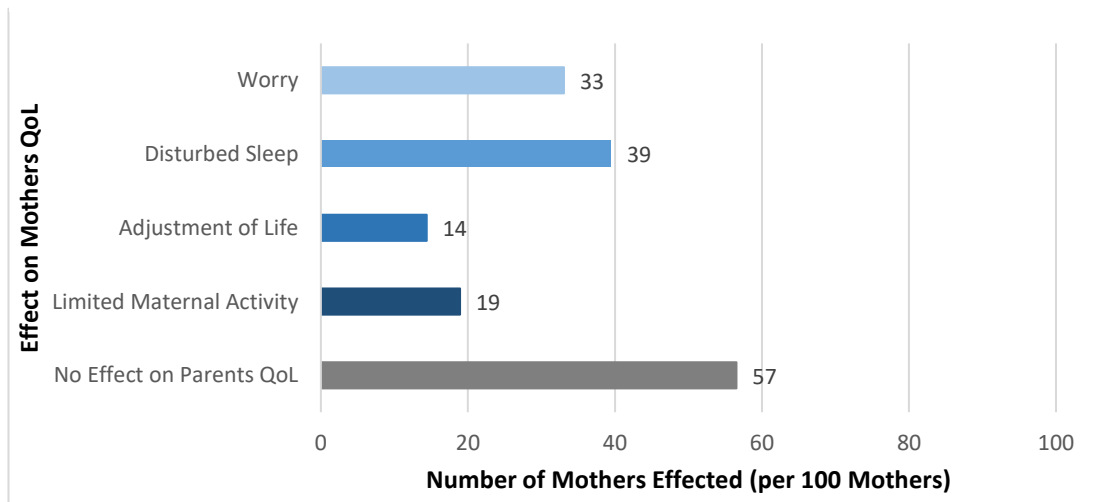
Mothers reported that males had a worse QoL due to their respiratory symptoms than females (z=-3.411 p=0.001). White infants were reported to have a worse QoL when compare to infants of other ethnicity (z=-2.752 p=0.006). Kruskal-Wallis Testing revealed differences in QoL scores in infants born to mothers with different levels of education (χ^2 =17.41 p=0.004 DF=5). Post hoc testing revealed infants born to mothers with a degree or postgraduate degree and those who attended higher education had a better QoL due to respiratory symptoms than those born to mothers with A-Levels (p=0.001 and p=0.014) and GCSE's (p<0.001 and p=0.005). Infants born to mothers with A-Levels had a better QoL than those

infants born to mothers with no qualifications (p=0.018) or other qualifications (p=0.038). Those born to mothers with GCSE's had a worse QoL than those born to mothers no qualifications (p=0.047). Infants born preterm had a worse QoL than infants who were born term (z=-2.122 p=0.034). Infants who attended nursery had a worse QoL due to respiratory symptoms than those who did not attend nursery (z=-3.838 p<0.001) and those who lived with other children had a worse QoL than those who did not live in a household with other children (z=-2475 p=0.013).

Mothers of male infants reported a worse QoL due to their child's respiratory symptoms than mothers of females (z=-2.697 p=0.007). Likewise, mothers of white infants had a worse QoL due to their child's respiratory symptoms when compared to mothers of infants to other ethnic groups (z=-3.197 p=0.001). Kruskal-Wallis Testing revealed differences in QoL scores in infants born to mothers with different levels of education (χ^2 =19.447 p=0.002 DF=5). Pot hoc testing mothers with A-levels had a worse QoL due to their child's respiratory symptoms than mothers with a degree or post graduate degree (p=0.001), mothers who attended higher education (p<0.001) and mothers with 'other' qualifications (p=0.027). Mothers with GCSE's had a worse QoL due to their child's respiratory symptoms than mothers with a degree or post graduate degree (p=0.014) or who attended higher education (p=0.005). Mothers of infants born preterm had a worse QoL than mothers of infants who were born term (z=-2.054 p=0.012). Mothers of infants who attended nursery had a worse QoL due to their child's respiratory symptoms than mothers of infants who did not attend nursery (z=-3.488 p<0.001).

Spearman's rank correlation analysis showed that higher respiratory symptom scores were correlated with higher QoL domain scores indicating a worse QoL (r_s =0.744 p<0.001). This is shown in figure 56.
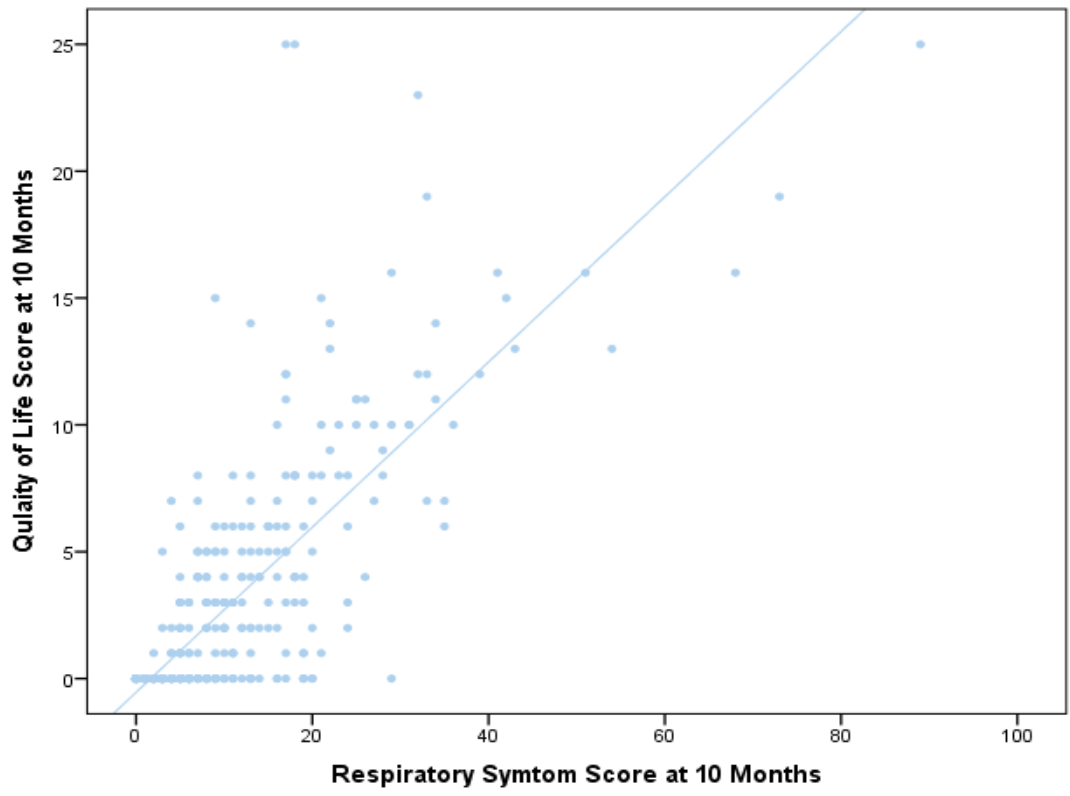
Figure 56: Scatter diagram showing respiratory symptom scores against QoL Scores at 10 months

3.5.3-Questionnaire 3- 16 Months

Cohort Profile, Exposures and Risk Factors at 16 Months

Nursery Attendance, Other Household Children and Sharing a Bedroom

At 16 months 51.6% (n=142) of the cohort attended nursery. 53.8% (n=148) of the cohort lived in a household with another child. Unfortunately a problem with the questionnaire meant that there was a large amount of missing data with regards the number of other household children. 33.1% (n=91) of the cohort shared a bedroom. 72.5% of these shared a bedroom with their parents, 28.6% (n=26) shared with another child and 2.2% (n=1) shared with another family member.

Household Smoking

13.82% (n=38) of the cohort were exposed to ETS in the three months before 16 months of age; see figure 57. 5.3% (n=2) of these smokers smoked inside, 84.2% (n=32) smoked outside, 2.6% (n=1) smoked in the car and 18.4% (n=7) smoked elsewhere. The proportion of the cohort exposed to smoke was significantly lower than the smoking rates in Liverpool in both 2012 (χ^2 =15.90 p<0.05 DF=1) and 2015 (χ^2 =12.71 p<0.05 DF=1).
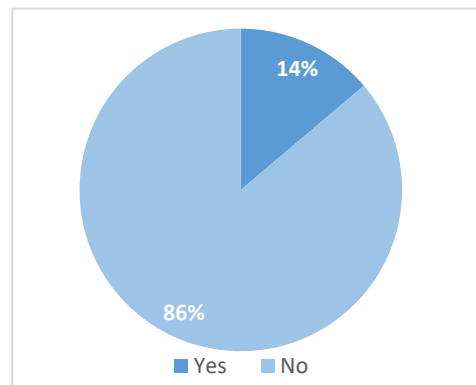
Figure 57: Household smoking in the LBBS at 16 months

Underlying Medical Conditions

By 16 months old 7.64% (n=21) of the cohort had at least one underlying medical conditions. The underlying medical conditions in the cohort are shown in table 17.

Table 15: Underlying medical conditions in the LBBS at 16 months

Type of Underlying Condition	Underlying Condition	Frequency
Cardiac (3)	Congenital Heart Disease	3
Gastrointestinal (1)	'Not Described'	1
Other (16)	Eczema	8
	'Not Described'	4
	Allergies	1
	Congenital Talipes Equinovarus	1
	Hip Dysplasia	1
Respiratory (2)	Asthma	1
	Chronic Lung Disease	1
Urinary (1)	Vesico-ureteric Reflux	1

Total LRSQ Score

At 16 months the lowest total LRSQ score was 0 and the highest score was 92. The mean score was 15.31, the median was 10 and the mode was 6. The distribution of the Totals LRSQ scores at 16 months is shown in figure 58.
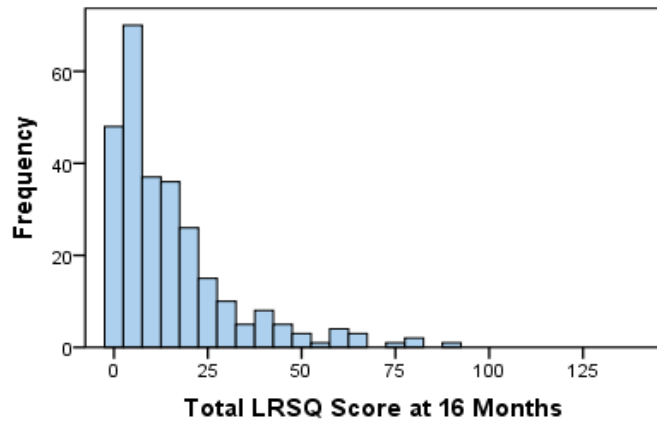
Figure 58: Histogram of the total LRSQ scores at 16 months

Total LRSQ Score in Those Expose and Unexposed to Risk Factors and Exposures

Summary Statistics comparing demographics, confounding factors, exposures and risk factors are shown in table 16. Male infants had significantly higher LRSQ scores than females (z=-3.009 p=0.003); see figure 59. Those who attended nursery had a higher LRSQ than those who did not attend nursery (z=-5.272 p<0.001); see figure 60. Paradoxically those who were exposed to ETS in pregnancy but whose mother who didn't smoke had a lower LRSQ score than those who were not exposed at all (z=-1.977 p=0.048); see figure 61. IMD decile of the cohort was established using their postcode. Decile one was the most deprived and decile 10 was the least deprived. Infants in IMD decile nine had a greater LRSQ score than those in deciles one, tow, three and four (p<0.05). Those in decile seven had a higher LRSQ score than those in deciles three and four (p<0.05). Those in decile five had a higher LRSQ sore than those in decile three (p<0.05); see figure 62.

Table 16: Comparison of LRSQ scores between different exposure/risk factor groups in the LBBS at 16 months

		25%	Median	75%	Mean	Mode
Infant's Sex*	*Male*	*6*	*12*	*24*	*19.4*	*6*
	Female	*3*	*9*	*19.14*	*12.07*	*3*
Multiple Birth	Single Birth	4	11	21	15.75	6
	Multiple Birth	3.46	14.86	36.73	17.62	5
Ethnicity	White	4	10.16	21	15.84	6
	Other	6.15	12.5	25.04	15.02	16
Maternal Age	<20	1	1	-	1	1
	20-24	6	7.26	13	9.48	6
	25-29	3	13.26	26.88	21.31	1
	30-34	3	10.87	17	13.12	2
	35-39	3.88	10	21	13.54	5
	40-44	6	10.28	16	11.02	6
	>=45	-	15	-	-	-
IMD*	*1*	*3*	*12*	*21.27*	*17.04*	*1*
	2	*4*	*9*	*16.72*	*11.33*	*6*
	3	*2*	*5.69*	*19.53*	*11.88*	*0*
	4	*3*	*5.95*	*17.15*	*9.71*	*3*
	5	*5.84*	*12*	*31.27*	*19.53*	*6*
	6	*6*	*13*	*24.64*	*19*	*1*
	7	*7.25*	*14*	*22.79*	*17*	*4*
	8	*4.39*	*7.55*	*15.17*	*9.58*	*6*
	9	*11.18*	*25.69*	*33.75*	*28.63*	*6*
	10	*1.88*	*18.36*	*-*	*11.25*	*0*
Maternal Qualification	Degree or Higher	5	9.84	20	13.93	6
	Higher Education	3	10.1	18.41	16.05	1
	A Level	5	18.25	24.62	17.65	5
	GCSE	5.78	13	20.39	20.03	0
	Other	2.11	17.48	52.63	23.41	2
	None	6.28	7	-	6.76	7
Premature Birth	No	4	10	20.36	15.05	6
	Yes	6	15	30.27	22.27	13
Low Birth Weight	No	4	11	21	16	6
	Yes	5	10	18.4	12.48	5
Maternal Smoking In Pregnancy	No	4	12	21	16.02	6
	Yes	3.67	9.18	13	13.11	3
Other Household Smoking In Pregnancy*	*No*	*4*	*12*	*21.36*	*16.89*	*6*
	Yes	*3.03*	*7.09*	*14.55*	*9.7*	*8*
Any Smoke Exposure in Pregnancy	No	4	12	22	16.92	6
	Yes	3.58	8	15	11.52	3
Home Smoking *	*No*	*5*	*12*	*21*	*16.61*	*6*
	Yes	*3*	*7.19*	*16*	*11.48*	*3*
Breastfeeding	No	2.28	8	21	15.53	6
	Yes	5	11	21	15.86	6
Breastfeeding Time	Never	2.28	8	21	15.53	6
	<1 Month	5	12	24	19.55	13
	1-4 Months	3.81	12	22.14	16.5	0
	>4 Months	5	10	20	13.16	6
Family History of Atopy	No	3	10	19.63	14.99	6
	Yes	5	11	22	16.39	6
Nursery Attendance*	*No*	*2.42*	*6*	*16*	*11.6*	*6*
	Yes	*7*	*15*	*25*	*20.26*	*6*
Other Household Children	No	4	10	20	13.19	6
	Yes	4	12	24	18.47	1
Shares a Bedroom	No	4	10	21.2	15.5	6
	Yes	4.87	12	20	16.33	1

*indicates significant result (p<0.05)
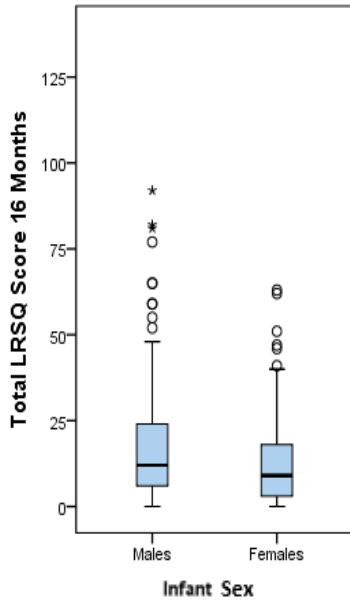
Figure 59: Total LRSQ scores at 16 months by infant sex
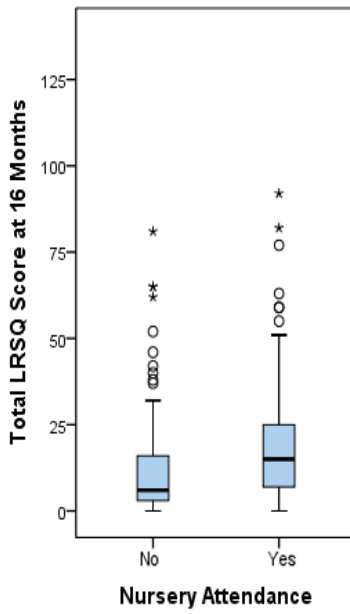
Figure 60: Total LRSQ score at 16 months by nursery attendance
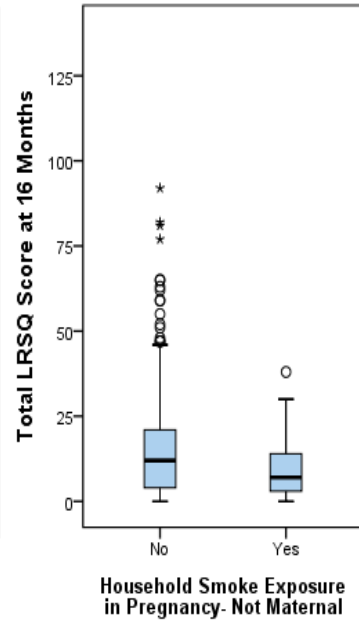
Figure 61: Total LRSQ scores at 16 months by ETS exposure in pregnancy
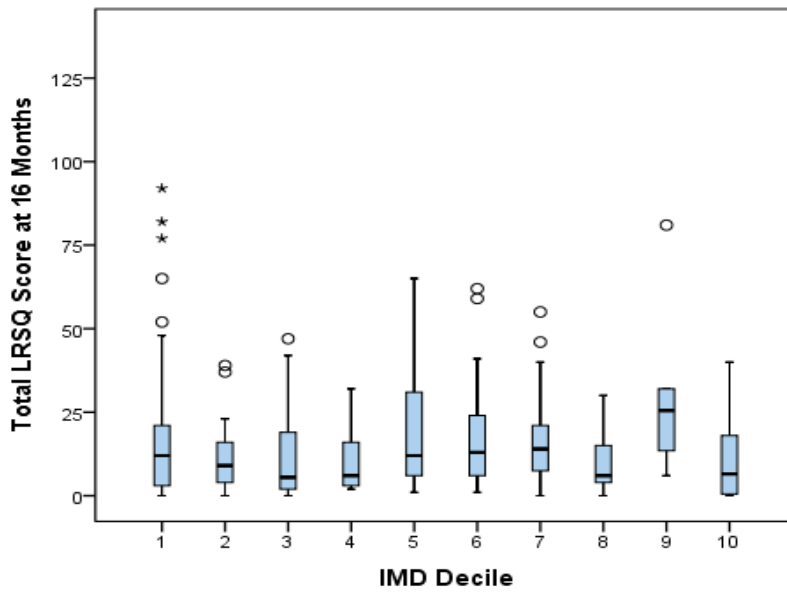
Figure 62: Total LRSQ score at 16 months by IMD decile

LRSQ Domain Scores in Months 10-16

The summary statics of the domain scores for months 10-16 are shown in table 18. 'Symptoms with colds' and 'night-time symptoms' were the highest scoring domains. 'Symptoms on increased activity' and 'other respiratory symptoms' were the lowest scoring domains. Domains seven and eight are QoL domains and are discussed elsewhere.

Table 17: Summary statistics of domain scores at 16 months

	Min	Median	Max	Mean	SD
Domain 1 **Day Time Symptoms**	0	1	12	2.1	2.4
Domain 2 **Night-time Symptoms**	0	2	16	2.8	2.8
Domain 3 **Symptoms with Colds**	0	4	19	4.7	3.8
Domain 4 **Symptoms without Colds**	0	0	12	0.9	2.0
Domain 5 **Symptoms on Increased Activity**	0	0	12	0.7	1.9
Domain 6 **Other Respiratory Symptoms**	0	0	10	0.7	1.6
Domain 7 **Childs Quality of Life**	0	0	12	1.5	2.3
Domain 8 **Mothers Quality of Life**	0	0	13	1.8	2.8

Sex

Males had significantly higher scores for 'daytime symptoms' (z=-2.774 p=0.006), 'night-time symptoms' (z=-2.1148 p=0.032), 'symptoms with colds' (z=-3.225 p=0.001) and 'symptoms on increased activity' (z=-3.439 p=0.001) when compared to females.

Maternal Age

Kruskal-Wallis Testing revealed differences in domain scores for infants born to mothers of different maternal ages for 'symptoms without colds' (χ^2 =16.22 p<0.05 DF=6). Post hoc testing revealed Infants born to mothers aged 25-29 years had higher scores than infants born to mothers aged 35-39 years (p=0.011) but lower scores than those infants born to mothers aged 40-44 (p=0.006). Infants born to mothers aged 45 or older scored lower than those aged 40-44 years (p=0.04).

IMD

Kruskal-Wallis Testing revealed differences in domain scores for infants living in different IMD deciles for 'day time symptoms' (χ^2 =18.196 p=0.033 DF=6) and 'symptoms without colds' (χ^2 =23.557 p=0.005 DF=6). Post hoc analysis showed 'day time symptoms' were higher in those

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who lived in IMD deciles one (p=0.043), five (p= 0.034), six (p=0.017), seven (p=0.025) and eight (p=0.011) compared to those who lived in IMD decile three. Likewise those who lived in IMD decile nine had higher 'day time symptoms' scores than those who live in IMD decile one (p=0.025), two (p=0.007) and three (p=0.11) and four (p=0.002). For 'symptoms without colds' those who lived in IMD decile four had lower scores than those who lived in IMD decile one (p=0.046) and five (p=0.034). Those who lived in decile nine had higher scores than those who lived in deciles one to four (p=0.035, p=0.005, p=0.013, p=0.004 respectively).

Maternal Education

Kruskal-Wallis Testing revealed differences in domain scores for infants born to mothers with different levels of education for 'other respiratory symptoms' (χ^2 =16.162 p=0.006 DF=5). Post hoc testing showed infants born to mothers with 'other' qualifications had higher scores than: infants born to mothers with a degree or postgraduate degree (p=0.007), infants born to mothers who attended higher education (p=0.001) and infants born to mothers who had GCSE's (p=0.002). Infants born to mothers who had attended higher education and those born to mothers with only GCSE's had lower scores than infants born to mothers with A-levels (p=0.028 and p=0.031).

Preterm Birth

Infants who were born preterm had higher domain scores than term babies for 'night-time symptoms' (z=-2.466 p=0.014), 'symptoms with colds' (z=-2.049 p=0.04), and for 'other respiratory symptoms' (z=-3.006 p=0.003).

Smoking Exposure

Those infants who were exposed to ETS in pregnancy from other household smokers had lower scores than those who were not exposed for the domains 'symptoms without colds' (z=-2.2882 p=0.004) and 'symptoms on increased activity' (z=-3114 p=0.002). Those who were exposed to any tobacco smoke during pregnancy whether that be maternal smoking or other household smokers showed the same result (z=-2.838 p=0.005 and z=-3.122 p=0.002). Those who were exposed to tobacco smoke exposure in the last six months showed lower domain scores for 'daytime symptoms' (z=-2.371 p=0.018), 'symptoms with colds' (z=-2.531 p=0.011) and 'symptoms on increased activity' (z=-2.118 p=0.034) than those who were not exposed.

Breastfeeding

Those who were breastfed showed lower scores on 'increased activity' than those who were not breastfed (z=-2.202 p=0.028).

Family History of Atopy

Those with a family history of atopy scored higher for 'symptoms without colds' (z=-2.18 p=0.029) and 'symptoms on increased activity' (z=-2.255 p=0.029) compared to infants without and family history of atopy.

Nursery Attendance

Those who attended nursery had higher scores for 'daytime symptoms' (z=-4.169 p<0.001), 'night-time symptoms' (z=-4.609 p<0.001), 'symptoms with colds' (z=-5.706 p<0.001), 'symptoms without colds' (z=-3.117 p=0.002) and 'other respiratory symptoms' (z=-3.649 p=0.012) compared to those who did not attend nursery.

Respiratory Symptom Prevalence in Months 10-16

At 16 months of life 96.0% (n=264) of the cohort had respiratory symptoms in the previous three months. Colds were the highest reported respiratory symptom with 91.3% (n=251) of the cohort having at least one cold in the previous three months. The lowest reported respiratory symptom was 'noisy breathing from the back of the throat' with only 16.4% (n=45) of the cohort reporting 'noisy breathing from the back of the throat'. The prevalence of the respiratory symptoms in the previous three months per 100 infants are shown in figure 63.
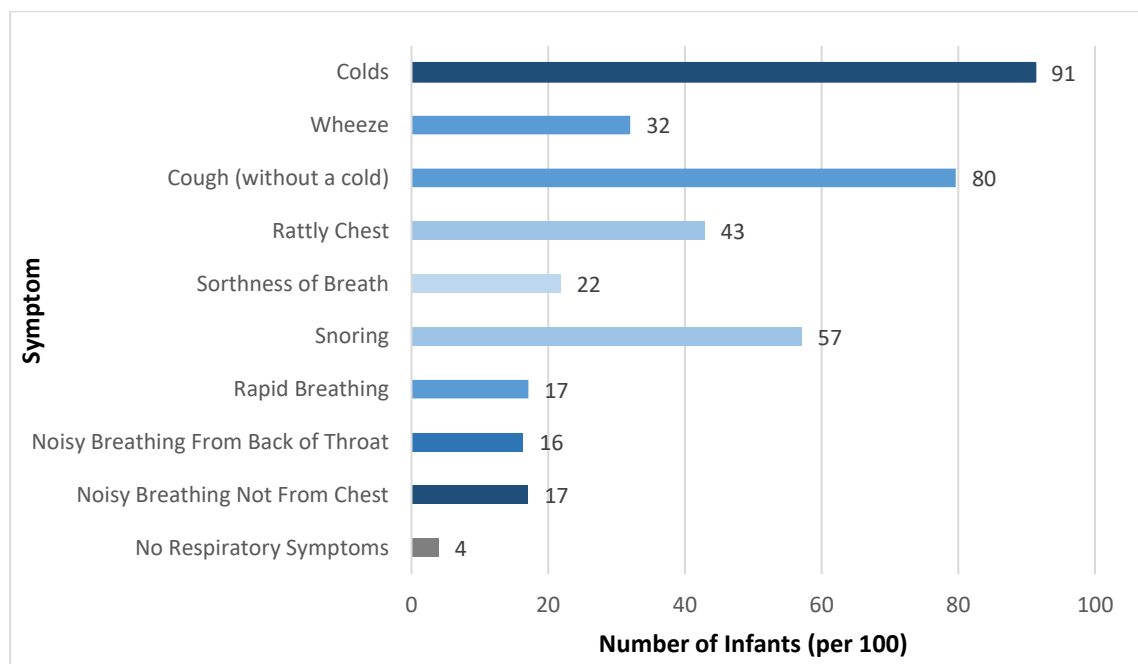
Figure 63: Respiratory symptom prevalence in the LBBS at 16 months

Respiratory symptom prevalence in Those Exposed and Unexposed to Risk Factors

Maternal Age

Kruskal-Wallis testing showed there was variation in the prevalence of cough (χ^2 =16.963 p<0.05 DF=6), rattily chest (χ^2 =13.05 p<0.05 DF=6), and 'noisy breathing not from the chest' (χ^2 =13.01 p<0.05 DF=6) in infants born to mothers of different ages. Post hoc analysis showed that infants born to mothers aged less than 20 had a lower prevalence of cough than those born to mothers ages 20-24 (χ^2 =17 Fisher's exact test p=0.007 DF=1), 35-39 (χ^2 =5.07 Fisher's exact test p=0.039 DF=1) and 40-44 (χ^2 =8.11 Fisher's exact test p=0.016 DF=1). Those born to mothers aged 20-24 had a higher prevalence of cough than those born to mothers 30-34 (χ^2 =5.32 Fisher's exact test p=0.020 DF=1). Infants born to mothers aged 25-29 had a higher prevalence of rattily chest than infants born to mothers ages 35-39 (χ^2 =5.64 p<0.05 DF=1) and 40-44 (χ^2 =7.81 p<0.05 DF=1) and infants born to mothers aged 30-34 had a higher prevalence of rattily chest than those born to mothers aged 40-44 (χ^2 =4.79 p<0.05 DF=1). Infants born to mothers aged 25-29 had a higher prevalence of 'noisy breathing not from the chest' than infants born to mothers aged 30-34 (χ^2 =6.00 p<0.05 DF=1).

Maternal Qualification

Kruskal-Wallis testing showed there was variation in the prevalence of 'noisy breathing not from the chest' (χ^2 =17.64 p<0.05 DF=5) and rapid breathing (χ^2 =14.51 p<0.05 DF=5) in infants born to mothers with different levels of education. Post hoc analysis revealed infants born to mothers who attended higher education had a lower prevalence of 'noisy breathing not from the chest' than those with A-levels (χ^2 =6.52 Fisher's Exact Test p=0.030 DF=1) and those with no education (χ^2 =8.69 Fisher's Exact Test p=0.003 DF=1). Likewise, those with A-levels had a lower prevalence than those with GCSE's (χ^2 =8.52 Fisher's Exact Test p=0.006 DF=1) and those born to mothers with GCSE's had a lower prevalence than those with no education (χ^2 =6.23 Fisher's Exact Test p=0.039 DF=1) or other qualifications (χ^2 =12.24 Fisher's Exact Test p=0.020 DF=1). Those born to mothers with other qualifications had a higher prevalence of rapid breathing than those born to mothers with a degree or post graduate degree (χ^2 =11.53 Fisher's Exact Test p=0.003 DF=1), those who attended higher education (χ^2 =12.29 Fisher's Exact Test p=0.023 DF=1), those with A-levels (χ^2 =5.98 Fisher's Exact Test p=0.031 DF=1) and those with GCSE's (χ^2 =5.54 Fisher's Exact Test p=0.044 DF=1).

Smoking Exposure

Those infants who's mothers smoked in pregnancy had a higher prevalence of snoring compared to those whose mother did not smoke (χ^2 =11.56 p<0.05 DF=1). Infants that were exposed to any smoking in pregnancy whether that be maternal or other household tobacco

smokers had a lower prevalence of SoB (χ^2 =4.17 p<0.05 DF=1) but a higher prevalence of snoring (χ^2 =4.84 p<0.05 DF=1). Those infants exposed to tobacco smoke in the last six months had a higher prevalence of snoring than those who were not exposed to tobacco smoke (χ^2 =7.35 p<0.05 DF=1).

Gestation

Infants that were born preterm had a higher prevalence of snoring (χ^2 =7.64 p<0.05 DF=1), 'noisy breathing from the throat' (χ^2 =6.26, Fisher's exact test p<0.024 DF=1) and 'noisy breathing not from the chest' (χ^2 =8.14 Fisher's exact test p=0.010 DF=1).

Breastfeeding

Infants who were breastfed for any duration of time had a lower prevalence of cough than infants who were not breastfed (χ^2 =11.92 p<0.05 DF=1).

Nursery Attendance

Infants who attended nursery had a higher prevalence of cough (χ^2 =13.13 p<0.05 DF=1), rattily chest (χ^2 =12.93 p<0.05 DF=1), snoring (χ^2 =5.55 p<0.05 DF=1), 'noisy breathing from the throat' (χ^2 =7.47 p<0.05 DF=1), 'noisy breathing not from the chest' (χ^2 =8.43 p<0.05 DF=1) and rapid breathing (χ^2 =6.74 p<0.05 DF=1) than those infants who did not attend nursery.

Health Care Service Attendance in Months 10-16

In the three month prior to being 16 months old 33.09% (n=91) of the cohort attended health care services with respiratory symptoms. 6.55% (n=18) attended the hospital with respiratory symptoms. GP attendance was higher in males (χ^2 =10.61 p<0.05 DF=1), infants with a family history of atopy (χ^2 =4.61 p<0.05 DF=1 and infants who attended nursery (χ^2 =15.06 p<0.05 DF=1). There was no clear trends between health care attendance and maternal age or maternal education at 16 months therefore these graphs have not been shown.

The Impact of Respiratory Symptoms on QoL in Months 10-16

The impact of respiratory symptoms on the QoL of the infant and their mothers are summarised in the figures 64 and 65. The QoL of 45.8% (n=126) of the infants in the cohort was effected by their respiratory symptoms and 49.1% (n=135) of the cohort's mothers were effected by their infants' respiratory symptoms.
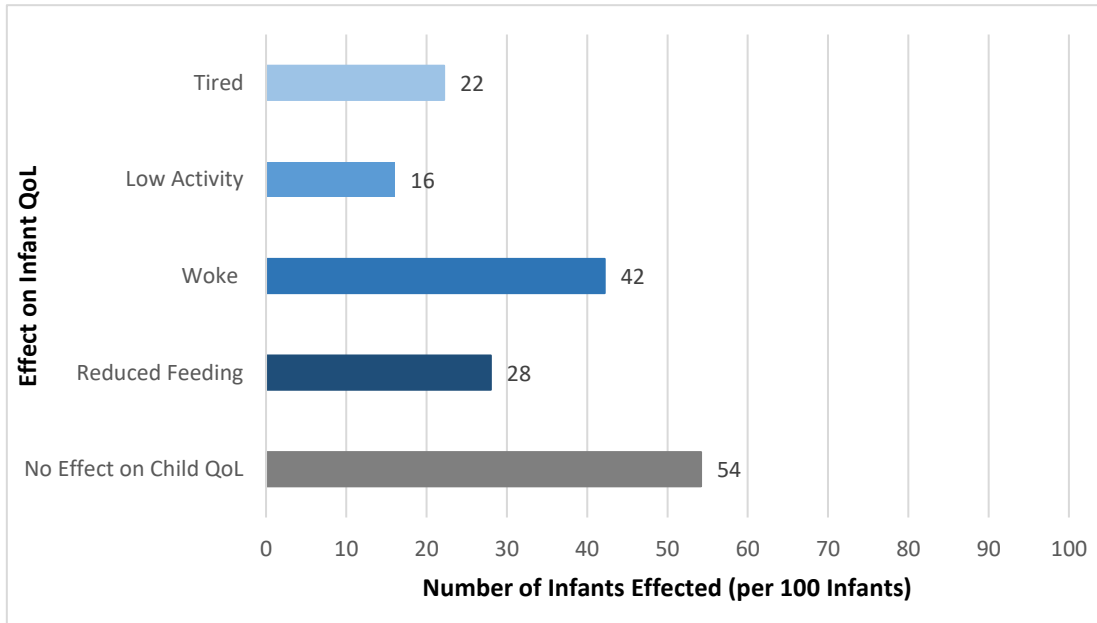
Figure 64: The impact of respiratory disease on the infant's QoL 16 months in the LBBS (per 100 infants)
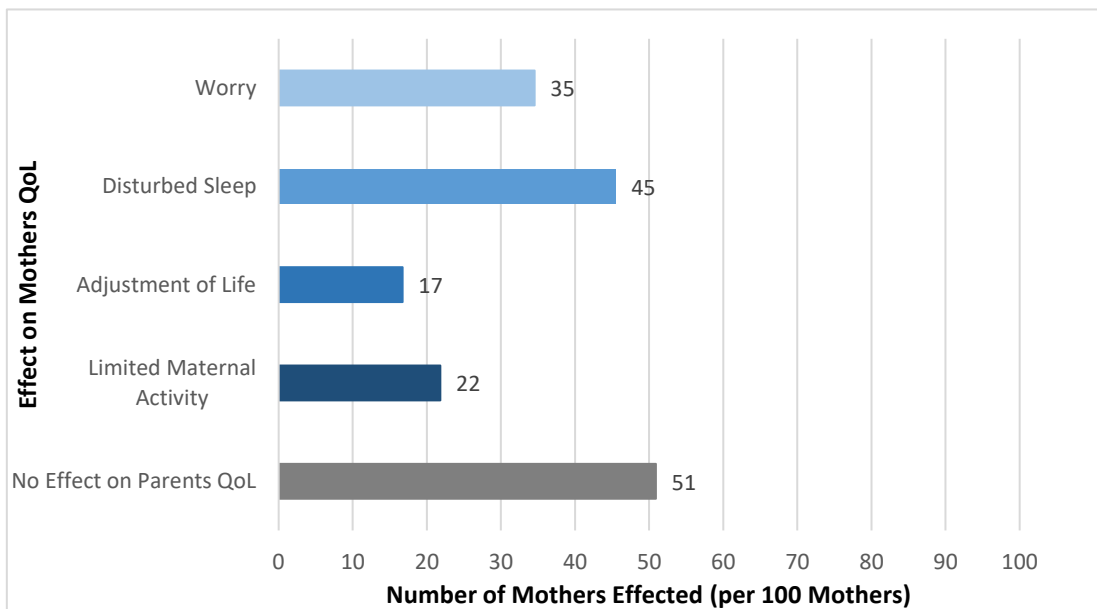
Figure 65: The impact of respiratory disease on the infant's mother's QoL at 16 months in the LBBS (per 100 infants)

Mothers reported that males had a worse QoL due to their respiratory symptoms than females (z=-2.99 p=0.003). Infants who attended nursery had a worse QoL due to respiratory symptoms than those who did not attend nursery (z=-3.699 p<0.001). Inexplicably at this time point, infants who were exposed to tobacco smoke in pregnancy whether that be maternal or from other household smokers had a better QoL reported than those who were not exposed to tobacco smoke in pregnancy (z=-2.047 p=0.041).

Mothers of male infants reported a worse QoL due to their child's respiratory symptoms than mothers of females (z=-2.711p=0.007). Mothers of infants who attended nursery had a worse QoL due to their child's respiratory symptoms than mothers of infants who did not attend nursery (z=-3.435 p=0.001). Mothers who live in households with more than one child reported a worse QoL due to their child's respiratory symptoms than mothers who lived with only one child (z=-2.929 p=0.003).

Spearman's rank correlation analysis showed that higher respiratory symptom scores were correlated with higher QoL domain scores indicating a worse QoL (r_s=0.78 p<0.001). This is shown in figure 66.
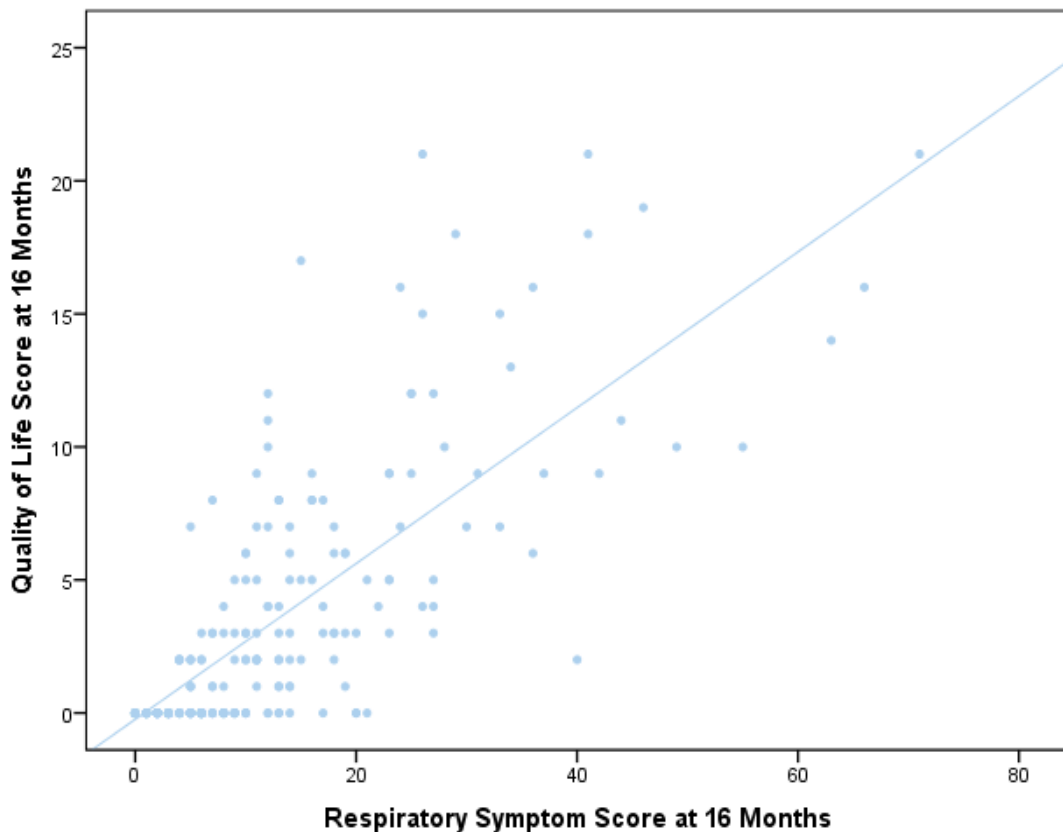
Figure 66: Scatter diagram of respiratory symptom score and quality of life score at 16 months

3.5.4-Questionnaire 4- 22 Months

Cohort Profile, Exposures and Risk Factors at 22 Months

Nursery Attendance, Other Household Children and Sharing a Bedroom

At 22 months of age 56.81% (n=146) of the cohort attended nursery. 49.42% (n=127) of the cohort lived in households with other children. Unfortunately a technical problem with the questionnaire meant that there was a large amount of missing data with regards the question number of other household children and this detail cannot be reported with confidence.27.63% (n=71) of the cohort shared a bedroom at 22 months of age. 64.8% (n=46) of these infants shared their bedroom with their parents, 39.4% (n=28) of these shared with at least one other child and 7.04% (n=5) shared with another family member.

Household Smoking

15.18% (n=39) of the cohort were exposed to household tobacco smoke in months 16-22; see figure 67. 5.1% (n=2) of these smokers smoked inside the home, 92% (n=36) smoked outside, 5.1% (n=2) smoked in the car and 10.3% (n=4) smoked elsewhere. These smoking rates were significantly lower than the smoking prevalence in Liverpool in both 2012 (χ^2=11.55 p<0.05 DF=1) and 2015 (χ^2=8.89 p<0.05 DF=1).
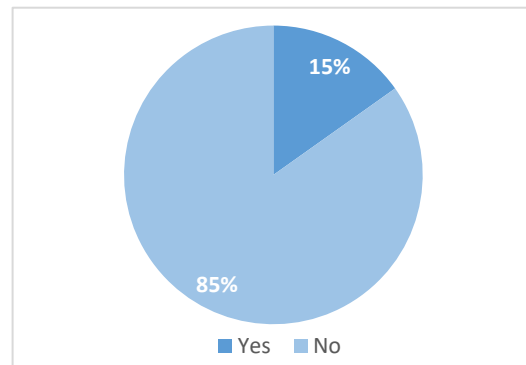
Figure 67: Household smoking in the LBBS cohort at 22 months

Underlying Medical Conditions

By 22 months, 15.18% (n=39) of the children in the cohort had underlying medical conditions. The underlying health conditions in the LBBS at 16 months are shown table 18.

Table 18: Underlying medical conditions in the LBBS at 16 months

Type of Underlying Condition	Underlying Condition	Frequency
Cardiac (3)	Congenital Heart Disease	3
Gastrointestinal (1)	Not otherwise specified	1
Neurological (2)	Hypotonia	1
	Not otherwise specified	1
Other (28)	Eczema	18
	Not otherwise specified	4
	Allergies	2
	Congenital Talipes Equinovarus	1
	Developmental Delay	1
	Hip Dysplasia	1
	Trisomy 21	1
Respiratory (6)	Asthma	5
	Bronchomalacia	1
Urinary (2)	Vesico-ureteric Reflux	1
	Tubular Sclerosis	1

Total LRSQ Score

At 22 months the lowest total score was 0 and the highest score was 68. The mean score was 14.1, the median was eight and the mode was 5. The distribution of the Totals LRSQ scores at 22 months is shown in the figure 68.
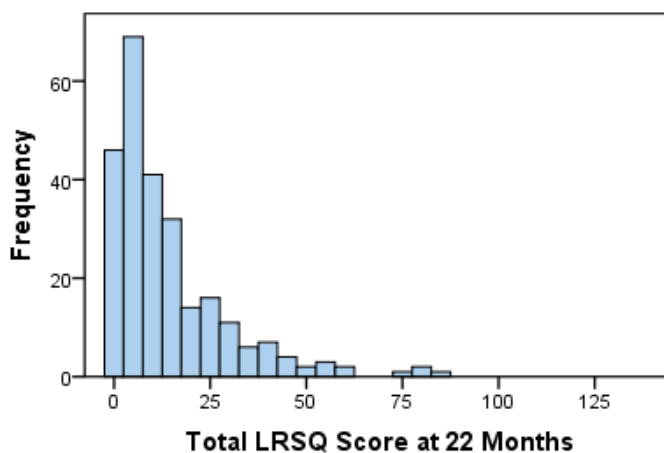
Figure 68: Histogram of total LRSQ scores at 22 months

Total LRSQ Score in Those Expose and Unexposed to Risk Factors and Exposures

Summary statistics comparing demographics, confounding factors, exposures and risk factors are shown in table 19. Those infants born to mothers with a degree or post graduate degree had higher LRSQ scores than those born to mothers who only attended higher education (p=0.003) and had GCSE's (p<0.001). Those born to mothers who attended higher education had lower score than those born to mothers who had no qualifications

Table 19: Comparison of LRSQ scores between different exposure/risk factor groups in the LBBS at 22 months

		25%	Median	75%	Mean	Mode
Infant's Sex	Male	3	6.4	15.94	11.47	4
	Female	4	8	20.08	14.54	5
Multiple Birth	Single Birth	4	8	17	13.18	5
	Multiple Birth	3	13.24	19.11	11.99	3
Ethnicity	White	3	13.24	19.11	11.99	3
	Other	5.54	12	20	13	1
Maternal Age	<20	-	-	-	-	-
	20-24	6.3	10	17	12.43	10
	25-29	3	5	13	10.86	4
	30-34	4	7	17.79	14.61	0
	35-39	4.85	8	16.73	13.43	8
	40-44	3.42	14	20.58	13.78	14
	>=45	-	-	-	-	-
IMD	1	4	88	17	13.18	0
	2	2.04	7.92	18.14	11.59	2
	3	37	7	14.85	10.8	0
	4	3.01	6	9	7.08	6
	5	3.38	7.76	18.71	14.03	1
	6	3.45	12.62	28.4	15.05	1
	7	5.12	11.87	28.27	20.26	1
	8	5.12	11.87	28.27	20.26	1
	9	4.09	5.33	21.37	10.71	5
	10	13	50.43	-	24.25	0
*Maternal Qualification**	*Degree or Higher*	*5*	*11*	*25*	*16.32*	*5*
	Higher Education	*1*	*7*	*10.68*	*8.71*	*1*
	A Level	*3*	*10.75*	*16.73*	*10.82*	*3*
	GCSE	*2*	*4*	*10*	*6.95*	*0*
	Other	*2.54*	*10*	*13.64*	*10.53*	*10*
	None	*7.45*	*15.3*	*35.27*	*20.41*	*6*
Premature Birth	No	4	8	17	13.35	0
	Yes	3.27	6.2	18.21	10.82	2
Low Birth Weight	No	4	8	17.47	13.41	5
	Yes	2	6.13	13.17	8.33	2
Maternal Smoking In Pregnancy	No	4	8	17	13.16	0
	Yes	1	8.67	26	12.95	1
*Other Household Smoking In Pregnancy**	*No*	*3*	*7.82*	*16*	*12.19*	*5*
	Yes	*5*	*13*	*25.5*	*17.33*	*0*
Any Smoke Exposure in Pregnancy	No	4	8	17.07	12.52	5
	Yes	3	10.33	17.63	15.33	1
Home Smoking	No	4	8	18	13.61	0
	Yes	3	5.52	16.6	10.21	1
Breastfeeding	No	3	8	14	11.26	0
	Yes	4	8	18	13.78	0
Breastfeeding Time	Never	3	8	14	11.26	0
	<1 Month	2	7	11.76	13.62	1
	1-4 Months	4	14	24.27	16.43	4
	>4 Months	4	8	16.36	12.66	5
Family History of Atopy	No	5	10	19.1	13.93	8
	Yes	3	6.96	16	12.54	4
*Nursery Attendance**	*No*	*2*	*7.96*	*15.9*	*11.11*	*0*
	Yes	*5*	*9*	*19.79*	*14.98*	*5*
Other Household Children	No	4	8	17	13.67	5
	Yes	3	8	17.76	12.63	1
Shares a Bedroom	No	4	8	17.63	13.81	4
	Yes	3.11	8	16	11.55	8

*indicates significant result (p<0.05)

(p=0.01). Those born to mothers with A-Levels had higher scores that those born to mothers with GCSE's (p=0.045) however those born to mothers with GCSE's had lower scores than infants born to those with no qualifications (p=0.005). This is shown in figure 69. Those who were exposed to smoking in pregnancy but whose mother who didn't smoke had a higher LRSQ score than those who were not exposed (z=-2.102 p=0.036); see figure 70. Those who attended nursery had higher LRSQ scores than those who did not attend nursery (z=-1.975, p=0.048); see figure 71.
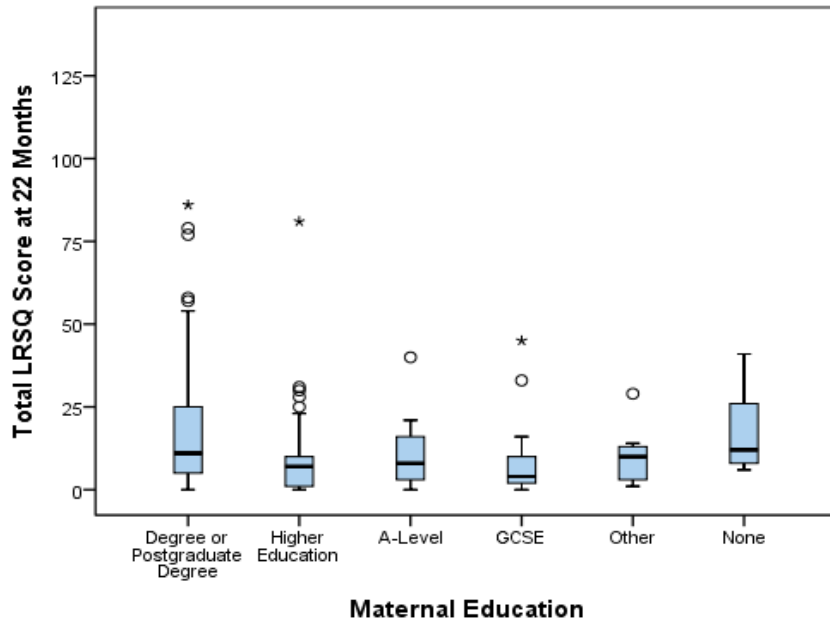
Figure 69: Total LRSQ scores at 22 months by maternal education
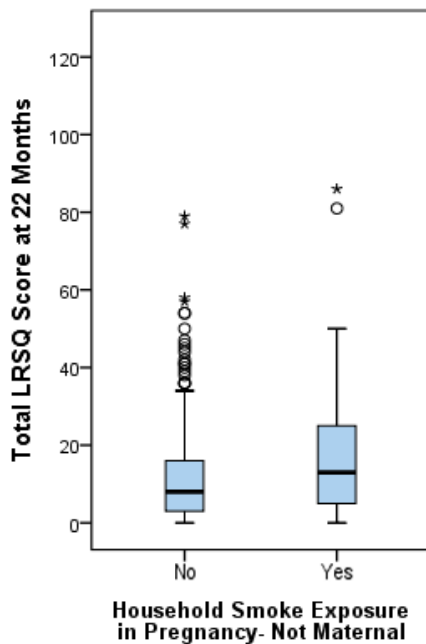
Figure 70: Total LRSQ score at 22 months by other household smoking in pregnancy
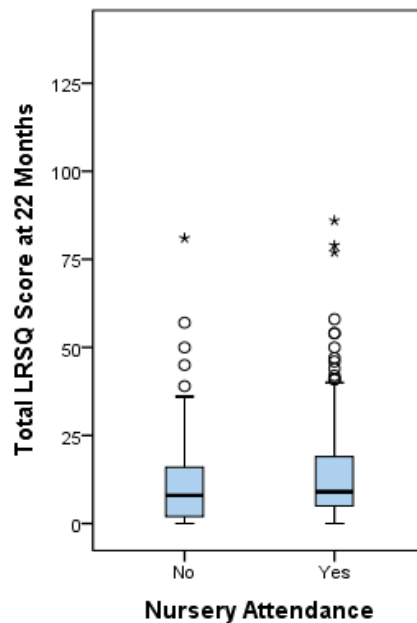
Figure 71: Total LRSQ scores at 22 months by nursery attendance

LRSQ Domain Scores in Months 16-22

The summary statics of the domain scores for months 16-22 are shown in the table 20. 'Symptoms with colds' and 'night-time symptoms' were the highest scoring domains. 'Symptoms on increased activity' and 'other respiratory symptoms' were the lowest scoring domain. Domains seven and eight are QoL domains and are discussed elsewhere.

Table 20: Summary statistics of domain scores at 22 months

	Min	Median	Max	Mean	SD
Domain 1 **Day Time Symptoms**	0	1	11	2.1	2.3
Domain 2 **Night-time Symptoms**	0	2	13	2.9	2.7
Domain 3 **Symptoms with Colds**	0	3	21	4.4	4.1
Domain 4 **Symptoms without Colds**	0	0	11	0.7	1.6
Domain 5 **Symptoms on Increased Activity**	0	0	10	0.7	1.7
Domain 6 **Other Respiratory Symptoms**	0	0	9	0.6	1.4
Domain 7 **Childs Quality of Life**	0	0	16	1.4	2.4
Domain 8 **Mothers Quality of Life**	0	0	16	1.5	2.5

Sex

Females had significantly higher 'symptoms with colds' (z=-2.22 p=0.027) and 'symptoms without colds' than males (z=-1.99 p=0.047).

Ethnicity

Infants of other ethnicity had higher scores for 'symptoms without colds' (z=-2.27 p=0.023) and 'symptoms on increased activity' (z=-3.55 p<0.001) than white infants.

Maternal Education

Kruskal-Wallis Testing revealed differences in domain scores for infants born to mothers with different levels of education for 'daytime symptoms' (χ^2 =22.76 p<0.001 DF=5), 'night-time symptoms' (χ^2 =25.74 p<0.001 DF=5), 'symptoms with colds' (χ^2 =16.67 p=0.005 DF=5), 'symptoms without colds' (χ^2 =13.31 p=0.021 DF=5) and 'symptoms on increase activity' (χ^2 =11.49 p=0.042 DF=5).

Post Hoc Testing Domain 1- Day Time Symptoms

Infants born to mothers with a degree or a post graduate degree scored higher than infants born to mothers who attended higher education (p=0.011) or had GCSE's (p<0.001). Infants born to mothers with no qualifications had higher scores than those born to mothers who attended higher education (p=0.005), had A-levels (p=0.033) or GCSE's (p<0.001).

Post Hoc Testing Domain 2- Night-time Symptoms

Infants born to mothers with a degree or a post graduate degree scored higher than infants born to mothers who attended higher education (p=0.023). Infants born to mothers with GCSE's had lower scores than infants born to mothers with a degree or post graduate degree (p<0.001), attended higher education (p=0.013), had A-levels (p=0.007), had other qualifications (p=0.031) or no qualifications (p=0.002).

Post Hoc Testing Domain 3- Symptoms with Colds

Infants born to mothers with a degree or a post graduate degree scored higher than infants born to mothers who attended higher education (p=0.003) or had GCSE's (p=0.003). Those with no qualifications had higher scores than those who attended higher education (p=0.034) and those with GCSE's (p=0.019).

Post Hoc Testing Domain 4- Symptoms without Colds

Infants born to mothers with a degree or a post graduate degree scored higher than infants born to mothers who attended higher education (p=0.006) or had GCSE's (p=0.017). Those with no qualifications had higher scores than those who attended higher education (p=0.046) and those with GCSE's (p=0.004).

Post Hoc Testing Domain 5- Symptoms on Increased Activity

Infants born to mothers with a degree or a post graduate degree scored higher than infants born to mothers who attended higher education (p=0.022) or had GCSE's (p=0.042).

Smoking in Pregnancy

Those who were exposed to other household tobacco smoke in pregnancy but not maternal tobacco smoke had higher scores for 'daytime symptoms' (z=-2.528 p=0.011) and 'symptoms with colds' (z=-1.97 p=0.049).

Household Smoking

Those who were not exposed to household smoking in the last six months had higher scores for 'other respiratory symptoms' then those who were exposed (z=-2.009 p=0.045).

Breastfeeding

Those who were breastfed had higher scores for 'night-time symptoms' than those who were not breastfed (z=-1.967 p=0.049). Further analysis showed that this difference was between those who were breastfed for between one and four months and those who were never breastfed (p=0.003). Those breastfed for greater than four months did not have significantly higher scores (p=0.192).

Nursery Attendance

Those who attended nursery had higher scores for 'night-time symptoms' (z=-2.956 p=0.003) and 'symptoms with colds' (z=-1.964 p=0.049) than those who did not attend nursery.

Other Household Children

Those who lived with other household children had lower scores on 'increased activity' than those who did not have other household children (z=-2.218 p=0.027).

Respiratory Symptom Prevalence in Months 16-22

93.8% (n=241) of the cohort had respiratory symptoms in the previous three months at 22 months of age. Colds were the highest reported respiratory symptom with 85.6% (n=220) of the cohort having at least one cold in the previous three months. The lowest reported respiratory symptom was 'noisy breathing not from the chest' with only 9.34% (n=24) of the cohort reporting 'noisy breathing not from the chest'. The prevalence of the respiratory symptoms in the previous three months per 100 infants are shown in figure 72.
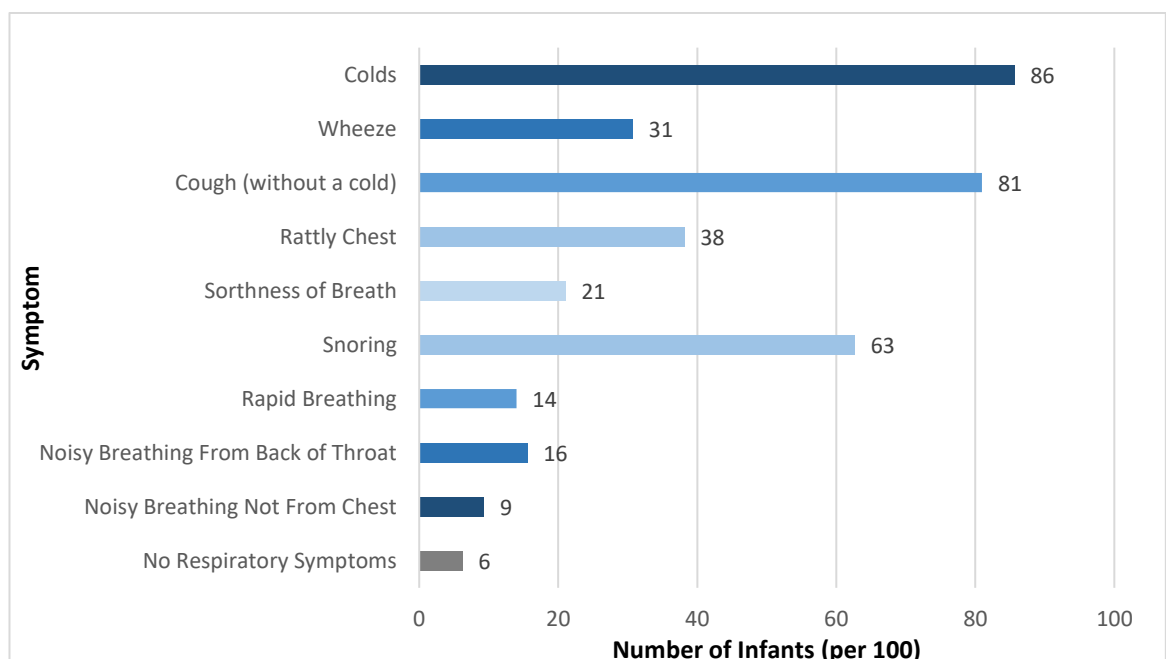
Figure 72: Respiratory symptom prevalence at in the three months prior to 22 months old in the LBBS

Respiratory symptom prevalence in Those Exposed and Unexposed to Risk Factors

Sex

Females had higher prevalence of wheeze (χ^2 =4.85 p<0.05 DF=1) and colds (χ^2 =5.38p<0.05 DF=1) than males at 22 months of age.

Maternal Age

Kruskal-Wallis testing showed there was variation in the prevalence of colds (χ^2 =13.15 p<0.05 DF=5) in infants born to mothers of different ages. Post hoc analysis showed that infants born to mothers aged 20-24 had a higher prevalence of colds than those born to mothers aged 25-29 (χ^2 =4.62 Fisher's Exact Test p=0.0495 DF=1). Those born to mothers aged 35-39 had a higher prevalence of colds than those born to mothers aged 40-44 (χ^2 =5.46 Fisher's Exact Test p=0.033 DF=1). Those born to mothers aged 25-29 and 30-34 had a lower prevalence of colds than those infants born to mothers aged 35-39 (χ^2 =10.09 p<0.05 DF=1 and χ^2 =5.83 p<0.05 DF=1 respectively).

Maternal Qualification

Kruskal-Wallis testing showed there was variation in the prevalence of wheeze (χ^2 =12.06 p<0.05 DF=5), cough (χ^2 =13.62 p<0.05 DF=5), rattily chest (χ^2 =18.79 p<0.05 DF=5) and snoring (χ^2 =17.15 p<0.05 DF=5) in infants born to mothers with different levels of education. Post hoc analysis revealed infants born to mothers with a post graduate degree had a higher prevalence of wheeze, cough, rattily chest and snoring than those who attended higher education (χ^2 =5.28 p<0.05 DF=1, χ^2 =8.54 p<0.05 DF=1, χ^2=7.07 p<0.05 DF=1 and χ^2=4.13 p<0.05 DF=1 respectively) and those with GCSE's (χ^2 =5.47 p<0.05 DF=1, χ^2 =6.32 p<0.05 DF=1, χ^2 =10.91 p<0.05 DF=1 and χ^2=7.89 p<0.05 DF=1 respectively). Those with no qualifications had a higher prevalence of wheeze, rattily chest and snoring than those with GCSE's (χ^2 =5.37 Fisher's Exact Test p=0.040 DF=1, χ^2 =5.63 Fisher's Exact Test p=0.037 DF=1 and χ^2 =10.0 Fisher's Exact Test p=0.003 DF=1 respectively). Those with infants born to mothers who attended higher education and those with GCSE's had a lower prevalence of rattily chest than those who had 'other' qualifications (χ^2 =5.97 Fisher's Exact Test p=0.030 DF=1 and χ^2 =9.78 Fisher's Exact Test p=0.004 DF=1 respectively). Infants born to mothers with no education had a higher prevalence of snoring than those who attended higher education (χ^2 =7.53 Fisher's Exact Test p=0.006 DF=1) as did those born to mothers with A-levels compared to those born to mothers with GCSE's (χ^2 =4.86 p<0.05 DF=1).

Smoking Exposure

Unexpectedly in this cohort those exposed to tobacco smoke in the last six months had a lower prevalence of SoB than those who were not exposed (χ^2 =4.52 p<0.05 DF=1).

Nursery Attendance

Those who attended nursery had a higher prevalence of cough (χ^2 =9.20 p<0.05 DF=1), SoB (χ^2 =5.08 p<0.05 DF=1), snoring (χ^2 =8.95 p<0.05 DF=1) and colds (χ^2 =9.28 p<0.05 DF=1) than those who did not attend nursery in the last six months.

Health Care Service Attendance at 22 Months

23.74% (n=61) of the cohort attended the GP in the previous three months at 22 of life with respiratory symptoms. 5.45% (n=14) attended hospital with respiratory symptoms. GP attendance was increased in those who were exposed to tobacco smoking in pregnancy but not maternal smoking (χ^2 =4.32. p<0.05 DF=1). Health care use in different maternal age categories and maternal education categories are shown in figures 73 and 74.
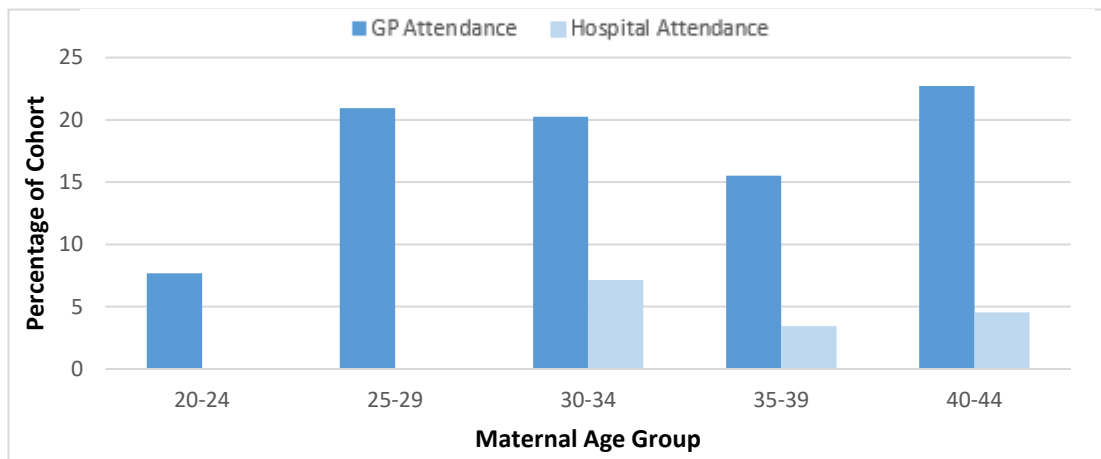
Figure 73: Percentage of the cohort that attended their GP or hospital with respiratory symptoms at 22 months of life by maternal age group
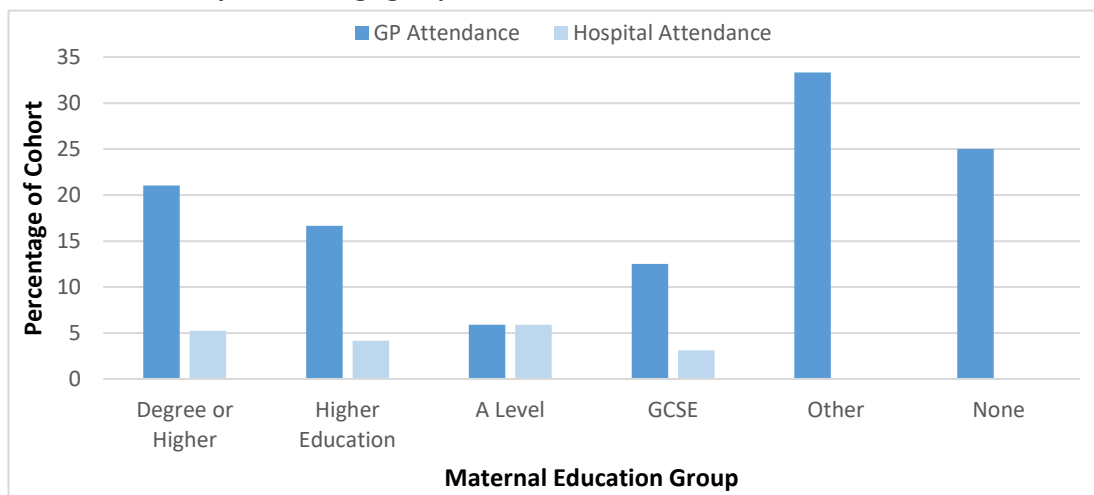
Figure 74: Percentage of the cohort that attended their GP or hospital with respiratory symptoms at 22 months of life by highest maternal qualification attained

The Impact of Respiratory Symptoms on QoL in Months 16-22

The impact of respiratory symptoms on the QoL of the infant and their families in months 16-22 are summarised in figures 75 and 76. The QoL of 41.2% (n=106) of the infants in the cohort was affected by their respiratory symptoms and 40.9% (n=105) of the cohort's mothers were affected by their infant's respiratory symptoms.
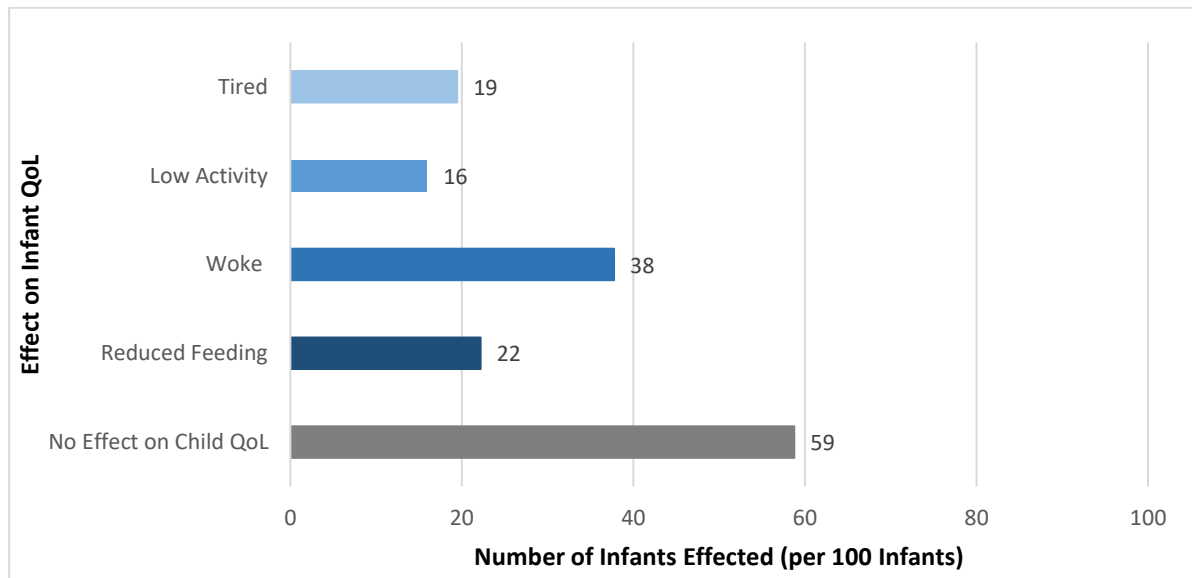
Figure 75: The impact of respiratory disease on the infant's QoL at 22 months in the LBBS (per 100 infants)
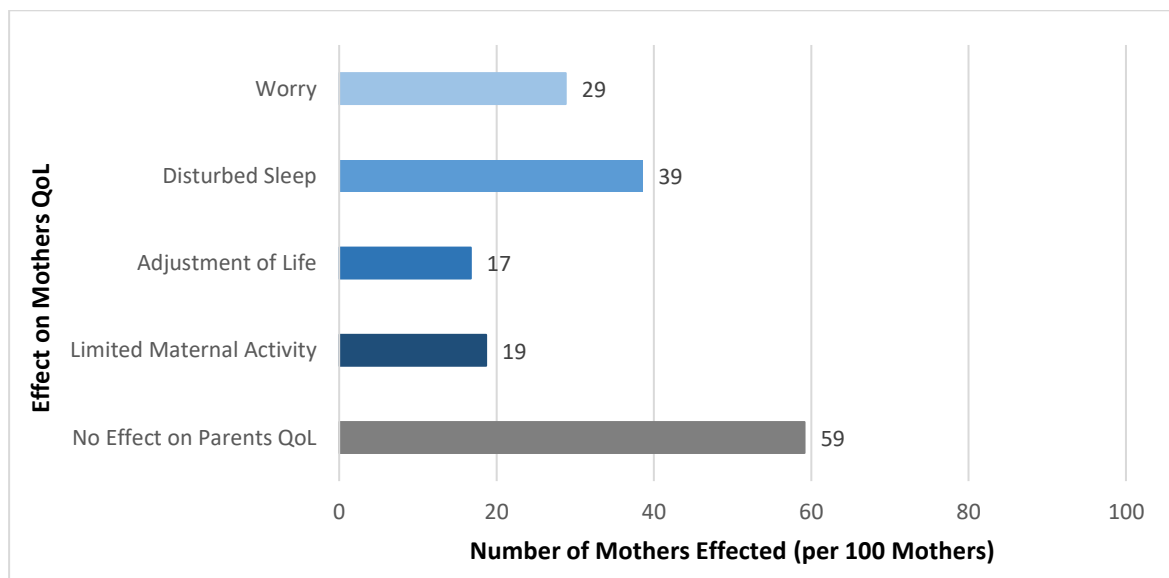
Figure 76: The impact of respiratory disease on the infant's mother's QoL at 22 months in the LBBS (per 100 infants)

Kruskal-Wallis testing revealed differences in QoL scores of infants born to mothers with different levels of education (χ^2=19.69 p=0.001 DF=5). Post hoc testing revealed those with a degree or postgraduate degree had a worse QoL due to respiratory symptoms than those born to mothers who attended higher education (p=0.003) had GCSE's (p=0.009) and other

qualifications (p=0.049). Those infants born to mother with no qualifications had a worse QoL than those infants born to mothers with other qualifications (p=0.015), GCSE's (p=0.006), and those who attended higher education (p=0.006).

Kruskal-Wallis testing revealed differences in QoL scores of the families of infants born to mothers with different levels of education (χ^2 =19.69 p=0.001 DF=5). Post hoc testing revealed those families with infants born to mothers with a degree or postgraduate degree had a worse QoL due to respiratory symptoms than those born to mothers who attended higher education (p=0.003) or had GCSE's (p=0.009). Those families with infants born to mothers with no qualifications had a worse QoL than those infants born to mothers with other qualifications (p=0.015), GCSE's (p=0.006), A-levels (p=0.046) and those who attended higher education (p=0.006). Those families with infants born to mothers with A-levels had a worse QoL than those who had GCSE's (p=0.024) and those who had attended higher education (p=0.044).

Spearman's rank correlation analysis showed that higher Respiratory symptom scores were correlated with higher QoL domain scores indicating a worse QoL (r_s=0.756 p<0.001). This is shown in figure 77.
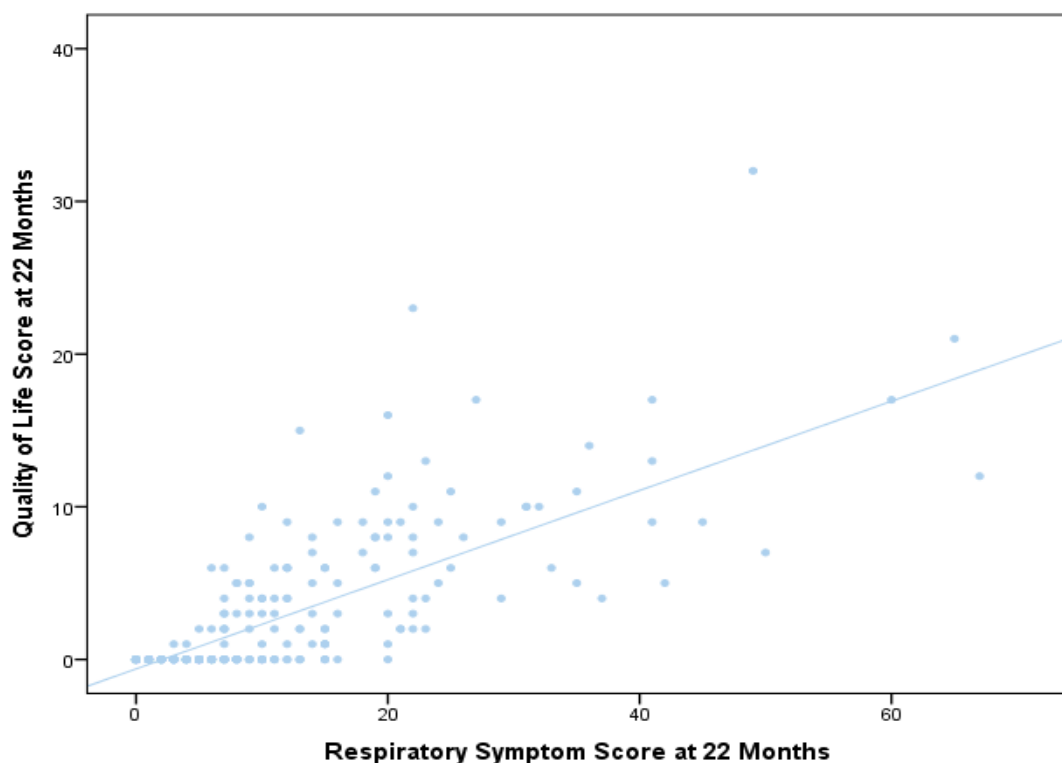
Figure 77: Scatter diagram of respiratory symptom score and quality of life score at 22 months

3.6-Longitudinal Analysis

The longitudinal analysis of the LBBS data is shown below. Longitudinal analysis was performed by multilevel mixed effects model analysis. The final multi-level model had three levels; 1.IMD decile, 2.Maternal Education, 3.Questionnaire. The development of this final model is described in section 2.2.8. The final multi-level models and their coefficients and significance levels are shown in the tables below. The longitudinal analysis has allowed the following aim of this thesis to be achieved;

- To determine the change in the LRSQ scores over time and the variability in this change between different population groups in the LBBS.

3.6.1-Total LRSQ Score

Nursery attendance, being male and living in a household with other children increased total LRSQ score over time. Sharing a bedroom and breastfeeding for on increasing amount of time, up to four months of age, decreased total LRSQ scores over time. See table 21.

Table 21: Multi-level mixed effects model for Total LRSQ scores

Exposure	Increase/Decrease Score	Coefficient	95% CI	p
Nursery	Increase	5.44	3.75-7.13	<0.001
Infant's Sex	Boys > Girls	-2.02	-3.43- -0.62	0.005
Sharing a Bedroom	Decrease	-1.75	-3.21- -0.28	0.020
Increasing Breastfeeding Time	Decrease	-0.75	-1.34- -0.16	0.013
Other Household Children	Increased	2.11	0.67-3.56	0.004

3.6.2-Day Time Symptoms

Attending nursery and being male increased day time symptom score over time. Breastfeeding for an increasing amount of time, up to four months of age, decreased day time symptom score over time. See table 22.

Table 22: Multi-level mixed effects model for domain 1 (day time symptoms)

Exposure	Increase/Decrease Score	Coefficient	95% CI	p
Nursery	Increase	0.91	0.66-1.17	<0.001
Infant's Sex	Boys > Girls	-0.31	-0.53- -0.10	0.004
Increasing Breastfeeding Time	Decrease	-0.11	-0.20- -0.018	0.018

3.6.3-Night-time Symptoms

Attending nursery, being male, increasing number of household children and increasing birth weight increase night-time symptom score over time. Breastfeeding for an increasing amount of time, up to four months of age, decreased night-time symptom score over time. See table 23.

Table 23:Multi-level mixed effects model for domain 2 (night-time symptoms)

Exposure	Increase/Decrease Score	Coefficient	95% CI	p
Nursery	Increase	1.03	0.73-1.32	0.001
Infant's Sex	Boys > Girls	-0.43	-0.67- -0.18	<0.001
# Household Children	Increase	0.27	0.10-0.43	0.002
Birth Weight	Increase	0.00020	0.0001-0.0004	0.038
Increasing Breastfeeding Time	Decrease	-0.10	-0.20-0.008	0.071

3.6.4-Symptoms with Colds

Nursery attendance, being male, living with other household children and increasing birth weight increased symptoms with colds over time. Sharing a bedroom reduces symptom with colds over time. See table 24.

Table 24:Multi-level mixed effects model for domain 3 (symptoms with colds)

Exposure	Increase/Decrease Score	Coefficient	95%CI	p
Nursery	Increase	1.68	1.25-2.11	<0.001
Infant's Sex	Boys > Girls	-0.32	-0.67- -0.03	0.077
Shares a Bedroom	Decrease	-0.72	-1.09- -0.35	<0.001
Other Children	Increase	0.47	0.11-0.83	0.011
Birth Weight	Increase	0.0001	-0.00003-0.0005	0.079

3.6.5-Symptoms without Colds

Nursery attendance and being born preterm increased symptoms without colds over time. Breastfeeding for an increasing amount of time, up to four months of age, decreases symptoms without colds over the first 22 months of life See table 25.

Table 25:Multi-level mixed effects model for domain 4 (symptoms without colds)

Exposure	Increase/Decrease Score	Coefficient	95% CI	p
Increasing Breastfeeding Time	Decrease	-0.14	-0.21- -0.07	<0.001
Nursery	Increase	0.25	0.06 – 0.43	0.011
Preterm Birth	Increase	0.18	-0.03- 0.39	0.099

3.6.6-Symptoms on Increased Activity

Nursery attendance, being male, and a family history of atopy increased symptoms on increased activity scores over time. Breastfeeding for an increasing amount of time, up to four months of age, and increasing gestational age decreased symptoms on increased activity scores over time. See table 26.

Table 26: Multi-level mixed effects model for domain 5 (symptoms on increased activity)

Exposure	Increase/Decrease Score	Coefficient	95% CI	p
Nursery	Increase	0.33	0.15-0.52	<0.001
Increasing Breastfeeding Time	Decrease	-0.10	-0.17- -0.03	0.003
Infant's Sex	Boys > Girls	-0.21	-0.37- -0.06	0.08
Gestation	Decrease	-0.03	-0.062- 0.004	0.082
FH Atopy	Increase	0.14	-0.02-0.30	0.079

3.6.7-Other Respiratory Symptoms

Being male increased other respiratory symptoms scores over time. Breastfeeding, for any amount of time, and increasing gestational age decreased other respiratory symptoms scores over time. See table 27.

Table 27: Multi-level mixed effects model for domain 6 (other respiratory symptoms)

Exposure	Increase/Decrease Score	Coefficient	95% CI	p
Infant's Sex	Boys > Girls	-0.21	-0.38- -0.038	0.016
Breastfeeding	Decrease	-0.07	-0.14- 0.003	0.059
Gestation	Decrease	-0.03	-0.07-0.0009	0.057

3.6.8-Childs QoL

Nursery attendance and increasing number of household children decreased the infant's QoL due to respiratory symptoms over time. Sharing a bedroom, breastfeeding for an increasing

amount of time, up to four months of age, and unexpectedly, household tobacco smoke exposure improved the reported infant's QoL over time. See table 28.

Table 28:Multi-level mixed effects model for domain 7 (infant's quality of life- higher score indicates worse quality of life)

Exposure	Increase/Decrease Score	Coefficient	95% CI	p
Nursery	Increase	0.63	0.40-0.87	<0.001
# Household Children	Increase	0.38	0.24-0.50	<0.001
Sharing a Bedroom	Decrease	-0.31	-0.51- -0.10	0.004
Increasing Breastfeeding Time	Decrease	-0.09	-0.18- -0.01	0.023
Home Smoking	Decrease	-0.34	-0.60- -0.08	0.011

3.6.9-Family QoL

Nursery attendance, other household children, being male, and a FH of atopy decreased the parents' QoL over time. Parents to infants who were breastfed for an increasing amount of time, up to four months of age, and shared a bedroom had an improved QoL over time. See table 29.

Table 29:Multi-level mixed effects model for domain 8 (mother's quality of life- higher score indicates worse quality of life)

Exposure	Increase/Decrease Score	Coefficient	95% CI	p
Nursery	Increase	0.62	0.33-0.90	<0.001
Other Household Child	Increase	0.42	0.17-0.67	0.001
Infant's Sex	Boys > Girls	-0.29	-0.53- -0.05	0.019
Increasing Breastfeeding Time	Decrease	-0.11	-0.21- -0.007	0.035
FH Atopy	Increase	0.25	0.004-0.49	0.046
Shares Bedroom	Decrease	-0.25	-0.50- 0.005	0.055

3.7-Questionnaire Validation

This section describes the validation of the LRSQ in the LBBS. This allowed the following aim of this thesis to be achieved;

- To validate the LRSQ in a longitudinal study.

The internal consistency of the LRSQ was assessed using Cronbach's alpha coefficients. The questionnaire demonstrated acceptable to good internal consistency. Night-time symptoms and 'other respiratory symptoms' showed acceptable internal consistency ($\alpha > 0.07$) and the remaining domains showed good internal consistency ($\alpha > 0.8$). None of the domains showed excellent internal consistency ($\alpha > 0.9$). The internal consistency of each of the domain is shown in table 30.

Table 30: Cronbach's alpha coefficients for the LRSQ domains in the LBBS cohort

Domain	Cronbach Alpha	Internal Consistency
1- Day Time Symptoms	0.81	Good
2- Night-time Symptoms	0.77	Acceptable
3- Symptoms with Colds	0.86	Good
4- Symptoms without Colds	0.81	Good
5- Symptoms on Increased Activity	0.85	Good
6- Other respiratory symptoms	0.78	Acceptable
7- Child's QoL	0.85	Good
8- Family's QoL	0.86	Good

Chapter 4- Discussion

The aims of the current thesis were to;

- To create a profile of the infants and mothers enrolled in the LBBS and make a comparison with the population of Liverpool and those born in the LWH.
- To describe respiratory symptoms of preschool children using the LRSQ from birth until 22 months of age.
- To determine the differences in LRSQ scores in the different populations at each questionnaire time point.
- To determine the change in the LRSQ scores over time and the variability in this change between different population groups in the LBBS.
- To validate the LRSQ in a longitudinal study.

These aims have been achieved by analysing the LBBS data using the methods describes in section 2.2. The results found in chapter three are discussed below. The results are summarised and then discussed in line with previous findings. Unexpected results and the potential reasons for them are discussed in detail.

4.1-Recruitment and Response Rates

Recruitment was performed by MPhil students in the LWH and by respiratory physicians during CF diagnosis consultations. The use of face-to-face recruitment in the LBBS, rather than using posters and advertising alone, is likely to have increased participation. Recruitment was reduced over Christmas and there were recruitment breaks for one week during April 2013 and throughout August 2013. These breaks were due to a lack of available recruiters during holidays and at other times due to the lack of MPhil students being available to take ownership of the study.

Recruitment from a tertiary centre that provides care to the whole population of Liverpool has given the study access to the majority of births in the study area. The use of the LWH also meant routine data was available on all the eligible births in the LWH. This data allowed the comparison between the LBBS cohort and those born in the LWH. It was shown that although there were some discrepancies between the LBBS cohort and LWH births, the cohort was fairly representative of the white population of the infants born in the LWH. The majority of discrepancies could be reduced with weighting during analysis, which makes the results of the LBBS more valid.

18.84% of all the eligible births in the LWH declared their interest in participating in the LBBS. This is low compared to the 69% expression of interest that was produced during the pilot

study of the recruitment strategy, however the research team may not have fully anticipated the workload required for both recruitment and administration of the study. This workload increased as the study grew and this may be reflected in these recruitment rates. Other birth cohort study recruitment strategies have led to recruitment of between 50% and 98% of the eligible population (135, 144); regional cohort studies report between 84.3% and 50% recruitment (141, 144). Recruitment rates in the current study are therefore disappointing when compared to other similar studies.

A significant factor in the poor recruitment rate is that the students did not have access to all the eligible births, as they were only present in the LWH four days a week. Infants who had an uneventful delivery and a short postnatal stay are likely to have been missed. Figures of all the eligible births in the LWH hospital, obtained from Professor Ben Shaw, included those infants who died very shortly after birth; the recruitment team are likely to have missed these. As the study progressed, the recruitment team reduced from two persons to one; the workload for one person to run a cohort study and recruit participants simultaneously means that it is likely to have been impossible to recruit all of the eligible births. Previous studies have used midwives and GP's to recruit mothers into the studies and have often involved antenatal or postnatal questionnaires at time of delivery. This means mothers who attend for any form of antenatal care are asked to participate in the study and eligible births are less likely to be missed. Using midwifes to help with recruitment during mothers prenatal care in the current study would have meant eligible participants were less likely to have been missed by the recruitment team. The LBBS did not have a translated version so mothers who did not speak an appropriate level of English could not be consent or reliably complete the questionnaire and would not be included. The use of a translated version of the LRSQ would increase access to the study, and may reduce the under representation of the minor ethnic groups.

Recruitment at birth in the LBBS reduced the long term recall bias of the risk factors during pregnancy; the mothers only had to wait four months to describe these risk factors which is a relatively short period of time when compared to some other birth cohort studies. Recruitment was throughout all seasons of the year removed any seasonal variations in birth and disease patterns. This is a strength of the study that many birth cohorts (which only recruit for one week of the year) do not possess (134-136).

Overall, recruitment in the LBBS was disappointing, however the response rates shown the LBBS can be accounted for and is understandable given the limitation of personnel and the workload required during recruitment for a study of this scale.

Response rates in the LBBS overall are somewhat disappointing. 29.6% of the mothers who declared their interest in the study, equating to 5.57% of all the eligible births, gave consent and completed questionnaire one when their child was four months old (defined as study enrolment). Of those enrolled, 54.0% responded at 10 months, 39.6% responded at 16 months and 37.0% responded at 22 months. Drop out from the study was initially high, but has reduced as the study has progressed.

Drop out was reduced in two ways. Three reminders were sent to participants at weekly intervals if they had not completed a questionnaire and a birthday e-card was sent to the participant on their infant's birthday. The use of reminders and birthday e-cards has been used elsewhere and shown to be beneficial (49) so it is likely to have enhanced the participation in this study. The initial response rate of 29.6% is disappointing in comparison to other birth cohort studies. This may be due to a combination of contributing factors. Along with the low recruitment rate in the LBBS, mothers had to wait four months after declaring their interest in the LBBS before giving consent and completing the first questionnaire. In other study's, the initial assessment of risk factors for disease has been assessed before birth or immediately postnatally by midwives (136, 141, 143). Waiting four months before beginning the study may have contributed to the initial drop out of interested mothers. The Breathmobile study used a $25 school supply gift voucher as an incentive to participate which successfully increase response rates to their questionnaire (95). Mothers mentioned this during feasibility testing for the study as a way of increasing response rates. This was unfortunately not feasible in the current study. When previously used the LRSQ produced response rates of 64% and 56% when sent by post (1, 16). Although this is somewhat higher than the response rate in the LBBS the comparison must be must with caution due to the difference in study designs.

Drop out from questionnaire one to questionnaire four is fairly high compared to other similar studies. The ALSPAC study was able to trace 97.4% of its cohort at two years giving a 2.6% drop out over the first two years compared to 63% drop out in the current study. The highest drop out in a similar study was 15.7% in the first year and 26.1% over the first five years. Similar to the results for recruitment, this may be due to limited personnel being involved with the study. Other cohort studies are linked to national databases or involved schools to track changes of address and have personnel dedicated to reducing attrition. The current study relies heavily on email addresses and participants giving correct information. It has not had the resource to fully investigate participant who did not respond to questionnaires to maximise participation. Other cohort studies, particularly national birth

cohorts, have produced low attrition rates, but have had the benefit of tracing the participants using their schools, something that is just not possible in a preschool cohort; these studies showed a much higher dropout rate once participants leave school and become harder to trace (134-136). Likewise, in the other cohort studies there were massive efforts to improve recruitment and reduce attrition rates by contacting and tracking missing participants (142). This has not been possible in this study for a variety of reasons, mostly due to the limited personnel in the study team.

Another contributing factor to the high dropout may be that the study changed to a fully online study; this reduces the access for the whole population of the cohort as not all of the cohort may have computer access. This adds a potential source of bias. On the other hand as shown in the Aberdeen Cohort Study, the use of an online system can be more accurate and prone to fewer mistakes than traditional paper based questionnaires which may have benefited the study overall (138).

In previous studies a good relationship between the study and participants has been built to reduce attrition. This has been done using birthday e-cards, newsletters and a website (49). This is an area where the LBBS may have neglected. The fully online system sent out birthday e-cards and the study had a website and asked if the participants would like to receive a newsletter, the website was very rarely updated and newsletters were not sent regularly to the cohort. This is likely again to have been down the workload for a very small research team. Taking this further the study could have used social media to build a better relationship with the cohort, and better advertise the study. The use of advertisement before the study in the IoM cohort study lead to very high participation rates and low attrition rates (140).

Although unintentional, once participants missed a questionnaire they were not sent any further questionnaires. This will have led to a drop out in participants who had not intended to leave the study, but had not completed a questionnaire for a variety of reasons. Had this not been the case the dropout rates earlier on in the study may have been significantly less. Between questionnaires three and four drop out reduced dramatically. This is due to participants who had not completed the previous questionnaire being invited back into the study; inviting participants back to the study after missing a questionnaire has been done before in the ALSPAC study to reduce attrition (139).

Conclusion

Overall, recruitment and retention in the LBBS has been disappointing. This is most likely to be due to the limitation of personnel involved in the study, and due to the large time waited

from expression of interest shortly after birth to enrolment at four months of age. This large amount of dropout has caused bias within the study that required adjustment during analysis. Results and conclusions taken from the study must be approached with this in mind.

4.2-Profiles of Mothers in the Liverpool Baby Breathing Study

Mothers in the LBBS were older, less deprived, less likely to smoke in pregnancy and more likely to breastfeed than the mothers to eligible births in the LWH and the population of Liverpool. They were more highly educated than the population of Liverpool.

National cohort studies have previously produced cohorts with similar characteristics to the population of England, however smaller regional studies have found it more difficult to be representative of the study population. For example in the ALSPAC study, mothers were more likely to be white, own a home and car, be married and have a higher socioeconomic status and live in an overcrowded home that the eligible population (139, 162). The BiB cohort contained older, more educated mothers (49, 163, 164). The PIAMA study's cohort of mothers was more highly educated and more likely to breastfeed than the population of the Netherlands (144). The differences between the LBBS cohort and the eligible population may be characteristic of small cohort studies. It could be argued that the more highly educated population are less likely to smoke in pregnancy and more likely to breast-feed and this is has produced bias in the LBBS. This is, however, a fairly sweeping statement and would need further investigation before making formal conclusions. Another reason for these discrepancies in smoking and breastfeeding could be due to social desirability bias. It is well documented that socially desirable characteristics are over reported in questionnaires and undesirable characteristics are underreported in questionnaire (165). The over reporting of breastfeeding and underreporting of smoking have both been shown in previous studies (166, 167).

In a study of infants with severe bronchiolitis, successful follow-up was more likely in: those with private health care, those who had a higher income, females and from households with fewer than three children (168). In the LBBS the mothers that responded were less likely to be deprived which mimics the bronchiolitis study. The importance of socioeconomic status in a respiratory study in Liverpool is imperative due the deprived nature of the population of Liverpool (13) and the well documented risk of socioeconomic status on respiratory health (56, 65, 66). The LBBS cohort was less deprived than that of the population of Liverpool and the eligible births in the LWH. This was accounted for during analysis of this study so conclusions were valid and could be applied to the population of Liverpool. This was done by factor weighting during cross-sectional analysis and by using IMD decile as a level during the

longitudinal multi-level mixed effects model analysis. The use of IMD deciles in the LBBS has unfortunately led to relatively few participants in the least deprived deciles. This may have skewed the data during analysis. Analysis of the LBBS may have been better and produced results more concordant with previous findings if quintiles had been used.

It was shown that over the course of the study that less deprived, older, more educated mothers who breastfed and did not smoke in pregnancy were more likely to remain in the study. These differences were reduced to some extent by adjusting the data using factor weighting at each time point during cross-sectional analysis so as to represent the eligible births in the LWH. Using IMD decile and maternal qualification as model levels accounted for this in the longitudinal analysis of the study. Unfortunately, with the exception of socioeconomic status, the inconsistency in drop out was not completely removed from the study. Therefore any conclusions made in the study, especially as the study has grown older, must take this into consideration.

4.3-Profile of Infants in the Liverpool Baby Breathing Study

The LBBS cohort had a similar male to female ratio and a similar proportion of multiple births to the population of Liverpool. The ethnicity of the cohort was predominantly white, with a higher proportion of mixed ethnicity baby's compared to the population Liverpool. This is likely to be due to the questionnaire only being available English. Therefore the conclusions drawn from this study must be used with caution when applying them to infants of the underrepresented, minor ethnicities. Poor representation of the minor ethnicities has been seen in previous cohort studies in England (135, 169).

The LBBS cohort had more preterm babies compared to all the births at the LWH during the recruitment period. This however could be due to preterm babies having increased length of stay in hospital after birth due to complications and monitoring. This would mean they were more likely to be recruited compared to term babies whose stay in hospital after birth is shorter. The LBBS cohort had a similar proportion of low weight births in the cohort compared to all the eligible births in the LWH during the recruitment period. However it had a higher proportion of low weight births compared to the population of England. In 2014, Liverpool as a whole had a similar proportion of low birth weight births compared to all the births in England (170). The higher proportion of low birth weight births in the LBBS may be due to the recruitment centre (the LWH) being a tertiary centre for the whole of Liverpool. Mothers to low birth weight babies may be more likely to attend the LWH than their general district hospital and therefore are more likely to be recruited into the study. Babies born with

a low birth weight are more likely to have an increased duration of postnatal stay in hospital so are more likely to be recruited into the LBBS.

Overall although the profile of the infants enrolled in the LBBS did not represent all the eligible births in the LWH or that of Liverpool. However the LBBS cohort is a good representation of the white population of the Liverpool given the methods of recruitment and workload for the small research team.

4.4- The Clinical Relevance of the LRSQ Score

The LRSQ is a measure of parental reported symptoms and impact of quality of life. It is a measure of what is parentally important and is not a clinical measure of disease severity. Therefore a clinically significant difference in scores between those exposed and not exposed to risk factors is difficult to determine. What difference in questionnaire score represents a parentally important difference is yet to be formally established. Further studies and discussions with mothers to determine a parentally important difference and possibly a clinically significant difference in LRSQ score would be beneficial. It would make future use of the questionnaire more clinically relevant and meaningful.

This being said, the LBBS study has shown which risk factors may increase or decrease the LRSQ score in preschool infants. An increased LRSQ score may mean clinically that the infant may have a larger variety of symptoms, more frequent symptoms or a combination of the two. A larger the difference in LRSQ score between those exposed and unexposed to risk factors is more likely to be a clinically significant as this indicates more frequent or a larger variety of symptoms in an infant. A larger difference in score may be the difference between having symptoms 'every day' rather than 'a few days', and this difference may be in multiple symptoms. A statistically significant result may however, be due to a small increase in LRSQ score. This may not be clinically significant. A small increase in score may be due to having one symptom 'some days' rather than 'a few days'; this difference is clearly open to interpretation and may not be clinically significant when measuring symptoms over the previous 3 months.

Interpretation of the LBBS results must be approached with this in mind. The LBBS has successfully shown which risk factors and exposures may affect the LRSQ score in infants. This statistically significant change in score may not be clinically significant or parentally important. However, an accumulation of many risk factors which have an effect on LRSQ score is more likely to cause a parentally important and clinically significant change in symptoms.

4.5-Cross-sectional Analysis

The cross-sectional analysis of the data in the LBBS has allowed the description of respiratory symptoms in preschool children from birth until 22 months of age in Liverpool. Analysis compared LRSQ scores, symptom prevalence and health care service use between those exposed and those not exposed to risk factors for respiratory disease at each of the four time points studied.

4.5.1-Sex

Male infants consistently had more respiratory symptoms than females from birth to 16 months of age. Females however, had more respiratory symptoms than males at 22 months of age. Males had higher LRSQ scores at 4, 10 and 16 months. At four months, males had a higher prevalence of SoB and noisy breathing and attended their GP more frequently with respiratory symptoms than females. At 10 months, males had a higher prevalence of cough and SoB and were more likely to attend hospital with respiratory symptoms than female infants. At 16 months, males were still more likely to attend the hospital with respiratory symptoms than female infants. By 22 months however, females scored higher for 'symptoms with colds' showing a swing in the prevalence of respiratory symptoms from males to females. The increased respiratory symptoms in males is had a detrimental effect on their QoL at 10 and 16 months and their families QoL throughout the first three questionnaires.

In previous work it has been shown that males wheeze more frequently and are more likely to have a physician diagnosis of asthma and be hospitalised due to their asthma than females throughout the first five years of life (25, 46). It has been shown previously that males from Liverpool are at an increased risk of asthma (151). Although most of the previous findings concentrate solely on wheeze and asthma diagnosis, the LBBS has given similar results in showing that males have more respiratory symptoms earlier on in life than females. The prevalence of noisy breathing was higher in males at four months than females. This may well have been wheeze that was wrongly identified as 'noisy breathing from the throat' or "noisy breathing not from the chest' due to lack of parental expertise in identifying wheeze.

4.5.2-Multiple Birth

There is very little published work on the effect of multiple births on respiratory symptoms. No differences were observed in the LBBS between infants born as part of a multiple birth and those born as single births. Due to the very small population of infants from multiple births in this cohort, this study would not be suitable from which to draw conclusions. A further study with a larger population of multiple births would be more appropriate.

4.5.3-Ethnicity

Due to the underrepresentation of minor ethnic groups, the over representation of white and mixed race infants in the cohort and the unequal drop out between different ethnic groups, the cohort was split into 'white' and 'other ethnic groups'. Therefore conclusions relating to the ethnicity must be treated with caution. This uneven drop out, very extreme grouping, along with the small sample size of 'other ethnic groups' may have caused the results to be unreliable and inconsistent with previous findings.

Although there was no difference in total LRSQ score or domain scores between white and other ethnicities at four months, white infants had a higher prevalence of rattily chest, snoring, and rapid breathing compared to other ethnicities. At 10 months, white babies had a higher LRSQ scores compared to other ethnicities. The prevalence of wheeze and rattily chest was higher in white babes than other ethnicities. These results were mimicked in the QoL scores for white infants and their families. At 22 months, other ethnicities had higher scores for 'symptoms without colds' and 'symptoms on increased activity'.

The millennium cohort study found that in the first three years of life Black Caribbean's reported higher rates of 'ever asthma' and wheeze compared to the white population of Britain, whereas Bangladeshi population reported a lower prevalence of 'ever asthma' (171). In the analysis of the LBBS cohort we combined these two populations so any discrepancies in respiratory symptoms between these ethnicities may have been missed. The Leicester respiratory cohort observed that South Asian infants had a lower prevalence of wheeze than the white infant population of England but they attended hospital more frequently (172). Again in the current study if this relationship was present it may well have also been missed due to the grouping of the populations.

4.5.4-Maternal Age

At four months, infants born to younger mothers had higher LRSQ scores than children born to older mothers. The prevalence of wheeze, rattily chest, SoB and rapid breathing was higher in infants born to younger mothers than those born to older mothers. The percentage of infants attending GP and hospital decreased as maternal age increased, possibly reflecting confidence of older mothers to manage minor illness in the youngest of infants. Similarly at 10 months, infants born to younger mothers had higher LRSQ scores than those born to older mothers. There were a few exceptions to this rule. Infants born to mothers aged over 45 years had higher scores 'with colds' than infants born to mothers aged 35-44 and higher scores 'on activity' than those born to mothers under 20 years. At 16 months the trends between younger mothers and infant respiratory disease became less consistent and

convincing; there was no clear trend in the results when comparing age groups. At 22 months drop out caused the loss of the categories of mothers under 20 and over 45 years. At 22 months there was no obvious trend between respiratory symptoms and maternal age.

The general trend throughout the study has been that infants to younger mothers had more respiratory symptoms than infants born to babies of older mothers, particularly in the first 10 months of life. In previous work there is mixed consensus of the effects of maternal age on respiratory health in infancy. It has been shown that infants to younger mothers are more at risk of LRTI in the first four months of life (173), and that infants born to mothers at the extremes of reproductive age were associated with early remitting wheeze. This being said, the same study showed low maternal age was protective of persistent and relapsing wheeze (77). Our study agrees with these findings somewhat. At early survey points in the LBBS (4m & 10m) the relationship between maternal age and respiratory disease is more convincing than in the second half of the study (16m & 22m). The inconsistent relationship between maternal age and respiratory symptoms in the second half LBBS may be due to the small sample size of the age groups at the extremes of maternal age. Drop out caused the loss of infants born to mothers aged less than 20 year and over 45 years. Because of this, findings related to the extremes of maternal age must be treated with caution. This relationship shown between maternal age and infant respiratory disease in the first 22 months of life may be due to confounding factors which are more apparent in younger mothers than in older mothers. This however, requires further investigation. In the early stages of the study younger mothers attended GPs and hospitals with their infants due to respiratory symptoms more frequently than older mothers. Although this matches the trend of respiratory symptoms in the LBBS, it must be questioned if this trend is due to parenting experience or if there is a physiological explanation for this.

4.5.5-Maternal Education

At four months the prevalence of rattily chest and SoB was lower in those infants born to mothers with a higher level of education compared to those born to mothers with a lower level of education. Likewise health care attendance was higher in those infants whose mothers had less education. The only exception to this was that no infants born to mothers with no qualifications attended hospital in the first four months of life. This may be due to lack of access to healthcare, the small sample size of infants born to mothers with no qualifications or the due to poor symptom recognition by the least educated mothers. At 10 months the general trend in the results was that those born to mothers with a higher education had lower scores for 'daytime symptoms', 'symptoms without colds' and

'symptoms on increased activity'. The only exception to this trend was that infants born to mothers with A-levels had higher scores than those who had no qualifications and other qualifications for 'symptoms with colds' and 'symptoms on increased activity'. These trends were mimicked in GP and hospital attendance and QoL domains for both the infant and their family. However those who had no qualifications had no attendance to health care; this could be due to similar reasons discussed at four months. At 16 months infants born to mothers who had a higher level of education had a lower prevalence of 'noisy breathing not from the chest' and rapid breathing than those born to mothers who were less well educated.

In general total LRSQ score decreased with increasing education at 22 months. Contrastingly domain analysis shows increased scoring in both the most educated and the least educated. This trend was mimicked in symptom prevalence and QoL scoring. For example infants born to mothers with a post graduate degree had a higher prevalence of wheeze, cough, rattily chest and snoring than those who attended higher education and those with GCSE's where as those with no qualifications had a higher prevalence of wheeze and rattily chest and snoring than those with GCSE's. Likewise infants born to mothers with a degree or postgraduate degree and no qualifications had a worse QoL due to respiratory symptoms than those born to mothers who attended higher education, had GCSE's or other qualifications.

These findings at 22 months are interesting. It could be explained by the increased drop out in less educated mothers through the study, however this would not fully account for the increased scoring at 22 months in the more educated families. Maternal education will have a significant impact on many risk factors what have been previously described in the literature and a combination of these factors could contribute to the respiratory health of the cohort. Although there has been very little published regarding the influence of maternal education on their infant's respiratory health, other factors, which could be linked to maternal education, have been investigated. It has been shown that poor housing increases respiratory disease in the first two years of life (57) and children from poorer families had an increased risk of LRTI. Likewise the prevalence of childhood asthma was increased in children from families with low socioeconomic status (56, 65, 66). Poverty in early childhood was associated with increased risk of asthma attacks by four years (174). A western diet with high levels of trans fatty acids may increase the risk of asthma, whereas a diet high in fish, fruit and vegetables may be protective (75, 76). The current study may agree with these previous findings if maternal education was to be used as a marker of the above risk factors for respiratory disease. The increase in respiratory symptoms in the more educated at 22 months

may be due to other factors described in the literature for which maternal education could be a marker for. Perhaps this may be a marker for exposure to excessively clean environments during pregnancy and excessive household cleaning chemicals during infancy. These exposures are associated with increased wheezing, persistent wheezing and lung function abnormalities (175) in line with the hygiene hypothesis of asthma (67). Although the above may provide some explanation for the influence of maternal education on respiratory disease in the LBBS, these are very sweeping statements and these concept needs exploring further before any formal conclusions can be made.

4.5.6-Gestation

Preterm infants were shown to have more respiratory disease from birth to 16 months of age than term infants. Preterm infants had a higher total LRSQ score and a higher prevalence of rapid breathing at four and 10 months of age. Preterm infants scored higher for a variety of domains, and had a higher prevalence of snoring and noisy breathing at 16 months. These results were mimicked in the QoL of both the infant and their family at 10 months of age. Interestingly and contrary to what might be expected, preterm infants had a lower prevalence of colds at four months; this result is difficult to explain and may need further investigation. It may result from reduced community exposure due to protective parenting. Disregarding the decreased prevalence of colds at four months, similar results have been replicated in previous studies. It has been shown that preterm birth is associated with wheezing, the use of inhalation therapy and hospitalisation due to respiratory disease in the first year of life (50) and this increase in wheeze had been shown to be persist for the first seven years of life(49). Although we were not able to show that that wheeze specifically was increased in the first year of life we were able to show that noisy breathing was increased in the first year of life. Contrary to this, there has been some mixed evidence on the frequency of respiratory symptoms in premature babies (51) and this discrepancy may account for the lower prevalence of colds at four months in preterm babies in this study. This finding could also be due to the fairly small sample size in the preterm birth category.

4.5.7-Birth weight

Infants born with a low birth weight had a higher incidence of colds and were more likely to use health care services due to respiratory symptoms than those who were born with a normal birth weight at four months and at 10 months. This is somewhat replicated in previous findings. It has been shown that babies with smaller birth weight have reduced lung function at six weeks of age (176) and are at an increased risk of wheezing disorders in the first five years of life (46, 55). Although the current study did not manage to replicate the

exact symptoms shown in previous work, it did show that infants born with low birth weight had more respiratory symptoms than those born at normal birth weight. In the LBBS the sample size of low birth weight infants was still fairly small and drop out caused a further reduction in this sample as the study progressed. This could account for the findings in the current study not being as prevalent and convincing as in previous work.

4.5.8-Breastfeeding

At four months children who were breastfed scored lower for 'symptoms on increased activity' than children who were not breastfed and those who were still being breastfed at four months had lower night-time symptom scores than those who were either not breastfed or breastfed for fewer than four months. The prevalence of SoB and healthcare attendance was lower in those that were breastfed than those who were not breastfed. At 10 months those who were breastfed had lower scores for symptoms without colds than those who were not breastfed. Those who were breastfed for over four months had the lowest scores, indicting a beneficial dose effect for duration of breastfeeding. The prevalence of SoB, noisy breathing from the throat and health service attendance was lower in babies that were breastfed. At 16 months those who were breastfed showed lower scores in symptoms on increased activity than those who were not breastfed. Infants who were breastfed had a lower prevalence of cough than infants who were not breastfed. However at 22 month those who were breastfed had higher scores at night-time than those who were not breastfed. Overall, those who were breastfed had lower respiratory symptoms than those who were not breastfed and increasing breastfeeding time increased this protective effect.

Similar results were shown in the Southampton's women's cohort were breastfeeding was shown to be protective of adverse respiratory symptoms; this was proportional to length of time of breastfeeding (7). Likewise breastfeeding, particularly exclusive and prolonged breastfeeding, was shown to be protective against hospitalization for LRTI in the first three years of life. It was estimated that 25% of LRTI requiring hospitalization could have been avoided by breastfeeding (173, 177). Although we cannot show the cause of hospital admissions with current data, the study has been able to show that breastfeeding has reduced hospital attendance due to respiratory symptoms by 11.1% at four months and 9.1% at 10 months. In previous work it had been shown that infants who were breastfed were more likely to have asthma (72) which could not be shown in the LBBS as there was no structured assessment of the participants by health care professionals as part of the study protocol. It is reported that breastfeeding has no long-term effect on adult lung function (178); in the LBBS cohort the beneficial effect of breastfeeding is reduced by 22 months. This

could be due to the reduction in beneficial effect of breastfeeding or alternatively could be due to the uneven drop out between the breastfeeding and non-breastfeeding groups. Although weighting of the data reduced this uneven drop out somewhat, it didn't completely eliminate this. The implications of these findings on clinical practice are that breastfeeding where possible should be encouraged due to the beneficial effect on respiratory health in infants in the first 16 months of life.

4.5.9-Smoking Exposure

Smoking exposure in Pregnancy

In the first four months of infancy, GP attendance was more likely in those infants who were exposed to any source of tobacco smoke in pregnancy. Paradoxically at 10 months those infants who were exposed to any tobacco smoke in pregnancy had lower 'scores without colds' than those who were not exposed to tobacco smoke in pregnancy. At 16 months those who were exposed to smoking in pregnancy from other household smokers had a lower LRSQ score than those who were not exposed. Those infants who were exposed to smoking in pregnancy had a lower prevalence of SoB but a higher prevalence of snoring. At 22 months those who were exposed to smoking in pregnancy but whose mother who didn't smoke had a higher LRSQ score than those who were not.

Although some results in the current study agree with the well documented adverse relationships between smoke exposure in pregnancy and infant respiratory health, the results from the current study are not convincing. The results produced between 10 months and 22 months are contradicting what has been previously published. Maternal smoking in pregnancy has been repeatedly shown to increase the incidence of wheeze and asthma diagnosis up to six years of life (5, 42, 43, 179). The lack of concordance in the current study are likely to be due to the underrepresentation of the population who were exposed to smoke in pregnancy in the study cohort when compared to the population of Liverpool. Although weighting of the data reduced this under representation somewhat, the population exposed to smoking in pregnancy was still smaller than in the population of Liverpool. Drop out was higher in the exposed group than in the non-exposed group; again weighting reduced this unequal drop out but it could not completely eliminate the differences. The exposed group was also fairly small in comparison to the non-exposed group and by 22 months the exposed group sample size was incredibly small which also could account for the unexpected results. All this said, the results at 22 months were as expected, with the exposed group showing higher LRSQ scores than the non-exposed group and it will be intriguing to see if this trend continues in the future questionnaires in the study.

Environmental Tobacco Smoke Exposure after Birth

The proportion of the cohort that was exposed to household tobacco smoke after birth decreased through the study. This could have been due to the reducing prevalence of smoking in Liverpool over the study period (180) or due to the increased drop out in smokers as the study aged. It is likely to be a combination of the two. There was no difference in respiratory symptoms between those who were exposed to ETS and those who were not in the first 10 months of life. Paradoxically, at 16 months however those who were exposed to ETS exposure in the last six months showed lower domain scores for 'daytime symptoms', 'symptoms with colds' and 'symptoms on increased activity' than those who were not exposed. Those exposed had a higher prevalence of snoring than those who were not exposed to tobacco smoke. At 22 months those infants exposed to tobacco smoke had a lower prevalence of SoB than those who were not exposed.

Like smoke exposure during pregnancy, these results were not as expected considering how well documented the negative impact of ETS exposure is on infant respiratory health. Infants exposed to ETS have been shown to be more likely to have a LRTI in the first three years of life, younger at the time of their first infection and require more antibiotic treatment and admissions to hospital for LRTI than those who are not exposed to ETS (6, 45, 46). Household smoking is associated with an increase incidence of wheeze in the first (47) and second year of life (5) and an increase in asthma and allergic symptoms in the first two years of life and a decrease in remission from these symptoms (48). Like smoke exposure during pregnancy the smoking population in the LBBS cohort was largely under represented, and although weighting of the data reduced this to some extent there was still a difference between the population of the cohort exposed to ETS and the rates of smoking in Liverpool. Drop out in the study was also higher in the population exposed to ETS than in the population that was not exposed to ETS. A study in Canada showed that smoking mothers under reported their child's cough (181). Liverpool mothers who smoked may have systematically underreported symptoms in the LBBS. All these factors combined could be responsible for the unexpected results found in the current study, however it is hard to justify this. The results shown in the current study with regards tobacco smoke exposure were not expected.

4.5.10-Family History of Atopy

Over the first 16 months, those with a FH of atopy scored higher in a variety of domains than those without a family history of atopy. Infants with a family history of atopy had significantly higher total LRSQ scores at four months. They had a higher prevalence of noisy breathing from the throat and noisy breathing not from the chest than those with no family history of

atopy. Their mothers reported a worse QoL. At 10 months these infants had a higher prevalence of colds. GP and hospital attendance was more likely in those with a family history of atopy. At 16 months those with a family history of atopy were more likely to attend the GP with respiratory symptoms.

In previous studies, atopy had been linked with an increase in wheeze and asthma particularly around the age of two years(70). The current study population is not yet two years of age so it will be interesting to see how the prevalence of wheeze is effected in future sweeps of the study. In the first four months of life there was an increase in noisy breathing in infants with a family history of atopy. This could have been wheeze misinterpreted by the mothers however this cannot be used to make formal conclusions.

Further analysis should be undertaken to look at differences in which family member had atopy to see differences in respiratory symptom patterns. Others' work has shown that maternal asthma is a risk factor for wheeze in males at two years and above and females in five years and above whereas paternal asthma was risk factors for males only between two and five years of age (71).

4.5.11-Nursery Attendance

Nursery attendance increased over time as recorded at each of the four questionnaires. The biggest increase in attendance was between 10 and 16 months and is likely to be due to mothers retuning to work after maternity leave. In the first four months of life very few infants attended nursery. Those who attended nursery in the first four months reported a higher prevalence of snoring, and were more likely to attend the GP with respiratory symptoms than those who did not. From 10 months onwards those who attended nursery had higher total LRSQ scores and scored higher in a variety of domains than those who did not attend nursery. They also had a higher prevalence of a variety of symptoms from 10 months onwards and were more likely to attend the GP at 10 and 16 months. At 10 and 16 months both the infant and their families had a worse quality of life due to respiratory symptoms than those who did not attend nursery.

The association between nursery attendance and respiratory symptoms in preschool infants was the most consistent finding in the LBBS; similar domain scores and the prevalence of similar symptoms were consistently increased throughout the study. The smaller impact of nursery on respiratory symptoms in the first four months of life is likely to be due to the low numbers of attendees at this time.

Similar findings have been published in previous work; infants who attended nursery were more likely to have LRTI in in the first year of life (45) and throughout infancy (173) than those who did not attend. Early nursery attendance was associated with increased airway symptoms in the first four years of life (74). Others have reported that nursery had no effect on respiratory symptoms after four years and have described reduced prevalence of wheeze at five years (182) but it remains to be seen if this will be replicated in the current study. Our study finds that nursery attendance is associated with an increase in respiratory symptoms over the first 22 months of life, however its remains to be seen how nursery attenders will be affected in the LBBS after 22 months of life. Previous studies have shown that there is no long-term detrimental effect of nursery attendance on respiratory health, and that it may be protective after four years of age (74). Our findings should be approached with caution when using them to decide whether an infant should attend nursery, and must be balanced with potential benefits for child development and allowing opportunities for mothers to return to employment.

4.5.12-Sharing a Bedroom

Over time the proportion of the cohort sharing a bedroom decreased, as did the proportion of the infants who shared a bedroom who shared with their parents.

At four months sharing a bedroom had a protective effect on infants' respiratory symptoms. Those who shared a bedroom had a lower total LRSQ score and lower scores with colds than those children who slept alone. Infants who shared a bedroom had a lower prevalence of cough, SoB and colds than children who slept alone. This was mimicked in the QoL scores. In contrast, GP attendance was more likely in infants who shared a bedroom. By 10 months this protective effect had reduced, by which time infants who shared a bedroom only had a lower prevalence of snoring. By 16 months there was no difference between those who shared a bedroom and those who did not.

In previous literature there is very little evidence on the effect of bedroom sharing on respiratory health in infancy. From our study, there may be an association between sharing a bedroom with parents and respiratory symptoms. The decrease in respiratory symptoms in the bed sharing population throughout the study and the reduction in the proportion of the cohort sharing a bedroom with their parents may show this. A formal relationship cannot be concluded from this study however and further investigation of this trend is required.

In some cases sharing a bedroom may be associated with household overcrowding which is associated with increased respiratory disease (58). Household overcrowding can be due to low socioeconomic status (183). In this study the opposite association is seen between

respiratory disease and bedroom sharing which could be due to the cohort sharing a bedroom by choice of the parents rather than due to household overcrowding or low socioeconomic status. The reduction of infants sharing a bedroom throughout the study, particularly in those who share a bedroom with their parents could be proof of this. The lack of information on the household overcrowding in the cohort makes it impossible to make formal conclusions regarding this although may highlight an area for further research.

4.5.13-Household Children

At four months infants who lived in households with other children had higher scores with colds and had a higher prevalence of colds than children who lived with no other children. GP and hospital attendance due to respiratory symptoms was higher in those who lived with other children. Both the infants who lived with other children and their mothers reported a worse QoL. In contrast, children who lived with other children reported a lower prevalence of snoring than those who did not live with other children. By 10 months the association between living with other household children and increasing respiratory symptoms was no longer present.

Although there was no difference in respiratory symptoms, infants who lived with other household children were still deemed to have a worse QoL at 10 months and their mothers reported a worse QoL at 16 months. At 22 months infants that lived with other household children reported lower scores on increased activity than infants who did not live with other children.

Previous work has shown that having other siblings at home was associated with decreased risk of asthma diagnosis between 4.5 and 14 years of life years of life (59-61). Although this is outside the age range of the current study, the LBBS has shown that there is no increased risk of wheezing or noisy breathing in households with other household children. In contrast household overcrowding has been shown to increase the risk of lower respiratory tract infection in children (58). In the current study, in the first four months of life in infants who shared a household with other infants were at an increased risk of colds. Unfortunately in the current study we do not have information household overcrowding. However, households with other infants are more likely to be over crowed than households with only one infant. This means the findings in the LBBS could be in line with previous research. Further research would be required before formal conclusions could be made. The decrease in scores on increased activity at 22 months may be in line with the hygiene hypothesis of asthma (68, 69). It will be intriguing to see if this relationship develops further as the study continues.

4.6-Longitudinal Analysis

The longitudinal analysis of the LBBS data has allowed the study team to determine the change in the LRSQ scores over time and the differences of this change in those exposed to risk factors by creating multi-level mixed effect models.

The longitudinal analysis of questionnaire scores using multilevel mixed effects models has been scarce in previous study reports. The majority of cohort studies have analysed the prevalence of specific symptoms in exposed and non-exposed groups over time by univariate and multivariate regression analysis. The use of multilevel mixed effects models in the pre-school age group seems to be quite novel.

We have shown that over time nursery attendance, being a male and the presence of other household children increases total LRSQ scores over time most dramatically. The biggest protective factors over time are sharing a bedroom and breastfeeding. Although analysis in this way is scarce in the preschool age group, these findings would agree in general with previous research as discussed earlier.

The LBBS agrees with studies by others that infants who attended nursery had an increased prevalence of an array of respiratory symptoms at various age groups up to four years of life (74, 173, 184). The LBBS is novel in showing that these symptoms increase over time. The change in scores over time may however be due to the low numbers of infants attending nursery at four months. The effect of nursery attendance on respiratory symptoms over time may therefore not be as large as this study portrays.

Likewise males have been shown to have an increase in various respiratory symptoms at various time points through the first five years of life when compared to females in previous work. The Tucson study found that the peak of wheeze in males was between six to eight years of age (45) which unfortunately is outside the scope of this study. It will be interesting to see of the effect of being male on respiratory symptoms over time is as large as the study progresses further towards its end at five years of age.

The presence of other household children has been shown to increase respiratory symptoms over 22 months. As before, there has been little work on the presence of other household children and its effect on respiratory disease in preschool children. What research that has been done is conflicting: having other siblings at home was associated with decreased risk of asthma diagnosis but household overcrowding has been shown to increase LRTI in pre-school children (59-61). Taking all this into account it may be appropriate to conclude that ours is a

novel finding and may require further investigation in the future to allow formal conclusions to be made.

There is very little prior evidence on sharing a bedroom and its impact on preschool children's respiratory health over time. This study has shown a reduction of LRSQ score over time in those that shared a bedroom compared to those who did not. This phenomenon is difficult to explain. One explanation for this may be the significant change in the sample sharing a bedroom over time in the cohort; there is a large reduction in those who share a bedroom, particularly in the cohort sharing with their parents. It may be this changing sample, and infants moving between exposed and unexposed groups throughout the study that has caused this finding. A further study to look into this relationship in the future would be helpful in explaining this relationship.

Breastfeeding has been shown to reduce LRSQ score over time. This is as expected as there is a large amount of literature showing the benefits effect of breastfeeding on infant's respiratory health (40, 41, 185). However other studies found this benefit to be fairly short lived and has no long-term effects on adult lung function (39, 178). It will be interesting to see if the protective effects on breastfeeding over time persist beyond 22 months of age or are reduced as previous literature has indicated.

4.7-Questionnaire Validity

The internal validity of the LRSQ was deemed as acceptable to good in this study. This is similar to that seen in previous studies that have used the LRSQ. The comparison to previous studies is shown in table 31.

Table 31: Comparison of the internal validity of the LRSQ in the LBBS compared to previous studies

Domain	LBBS	Powell et al. (1)	Trinick et al. (16)
1- Day Time Symptoms	0.81 (Good)	0.95 (excellent)	0.76 (Acceptable)
2- Night-time Symptoms	0.77 (Acceptable)	0.80(Good)	0.64 (Poor)
3- Symptoms with Colds	0.86 (Good)	0.95(excellent)	0.66 (Poor)
4- Symptoms without Colds	0.81 (Good)	0.95(excellent)	0.81 (Good)
5- Symptoms on Activity	0.85 (Good)	0.95(excellent)	0.79 (Acceptable)
6- Other Respiratory Symptoms	0.78 (Acceptable)	0.95(excellent)	0.80 (Good)
7- Childs QoL	0.85 (Good)	0.91(excellent)	0.89 (Good)
8- Family's QoL	0.86 (Good)	0.87 (Good)	0.79 (Acceptable)

Comparison to previous studies shows that although the internal constancy is not as good as described by Powel et al. in some domains, it is better in most parts than Trinick et al. Trinick et al. used the LRSQ on older children with Cystic Fibrosis (CF). The fact the current study has shown better internal consistency than Trinick et al. shows the LRSQ may be more consistent in assessing individuals of a whole preschool population rather than specifically CF patients, or is more consistent when used in longitudinal studies rather than in a one-off assessment. It may appear that Powell et al. shows the LRSQ to be more consistent in their study than the current study however Powell et al. combined domains one, three, five and sixe to assess day time symptoms which may have improved the internal consistency of these domains. LRSQ has shown acceptable to good internal consistency in the LBBS. This adds strength to the study and proves that the LRSQ is an acceptable measure of respiratory symptoms in longitudinal analysis of a predominantly white, preschool population in Liverpool.

4.8 The Use of Contemporary Technology in the LBBS

In June 2015, AFC® was suspended and the study changed to using JotForm® for questionnaire completion and response storage. At this point, the LBBS became an online study that was fully automated. MailChimp® was used for the distribution of emails containing the questionnaire link to the cohort.

The change to the fully automated online system had a number of advantages, although it may have reduced the access to the study for those without email access. The use of a fully automated online system is a novel concept in a study of this kind. It has reduced drop out due to migration and moving house as participants can be tracked by email. However this does not account for people who change email address. Another advantage for the online system is that the entire questionnaire must be fully completed for the questionnaire to be returned to the research team. This means all data is fully completed and is of good quality. There is only a small amount of missing data in the study. A small proportion of maternal ages are missing, as this question was added to the study at a later date. Where this was missing efforts were made by the research team to input this data at a later date. Some data on the number of household children from questionnaire three and four is missing. This was due to a problem with the questionnaire formatting and has now been resolved. The use of a fully automated online system also reduced the heavy workload for the small research team, which has allowed their efforts to be focused elsewhere. This has improved the quality of other aspects of the study including analysis.

The change to a fully online automated system, although it added benefit to the study by reducing the workload of the research team and improving accuracy of questionnaire

completion, reduced the access to the study for people without Internet access. Given widespread ownership of smart phones, this is likely to be a very low number of participants in the study, however it is still a source of bias within the study that must be taken into consideration.

4.9-Strengths of the LBBS

There are many strengths that the LBBS possesses that have meant that overall the study has successfully investigated the natural history of maternal reported respiratory disease in preschool children from birth to 22 months in Liverpool. The use of questionnaires has allowed the assessment of many risk factors in the study at one time and the majority (although not all) of the results in the study have been shown to be replicated to some extent in previous work. The consistency with previous findings adds strength and validity to the findings of this study. The use of the LRSQ is a strength of the study as it has been previously validated in this age group and in the Liverpool population. It was shown to have acceptable to good validity in the current study.

Although recruitment rates were fairly low compared to other cohort studies, there is still a respectable sample size in this study with an adequate number of infants being exposed and not exposed to the majority of risk factors and the cohort was fairly representative of the white population of the infants born in the LWH. The use of a pilot study to optimise recruitment, questionnaire design and overall running of the study has allowed the study to run at an optimal level given the lack of personnel and funding for the study. The study was accessible and acceptable to the participants (2, 3). The use of both emails and postal questionnaires in the early stages of the study has increased the accesses to the study and allowed people without accesses to email to participate. This has reduced sampling bias in the study.

The use of a tertiary centre for recruitment gave the study access to the majority of births in Liverpool. All year round recruitment reduced seasonal variations of birth. The use of routine birth data allowed the comparison between the LBBS cohort and those born in the LWH.

Recruitment at birth reduced recall bias of the risk factors during pregnancy that were studied in the LBBS. Recall bias was reduced throughout the LBBS by using a short time period between questionnaires and by asking mothers to only recall from the previous three months.

4.10-Weaknesses of the LBBS

The LBBS has similar weaknesses that are shown by the majority of birth cohort studies. The use of questionnaires introduces recall bias into the study although this was minimised by asking mothers only to recall from the previous three months and having regular questionnaires. Longitudinal studies are also prone to attrition; this was very prominent in the LBBS. Although there were efforts made to reduce attrition, the lack of and changing personnel in the LBBS research team is likely to have contributed to the large attrition rates compared to similar studies. The lack of ownership of the study was due to university holidays and the changeover of the study from student to student, year on year. Drop out in the LBBS was unequal in exposed and unexposed groups, particularly in the more deprived, those who were exposed to smoking and those who were not breastfed. The large and uneven attrition in the LBBS has added confounding factors to the study.

In the LBBS there is no formal assessments of the infants by health care professionals, neither is there serological confirmation of RTIs. The study relies fully on the infants' parental assessment of respiratory symptoms that may not reflect a medical assessment; however this study deliberately focuses on the parental experience.

Participation rates in the study were low and there are many sources of sampling bias in the study. The infants in the study are more likely to have been hospital for longer periods which means the proportion of 'non-healthy' babies are likely to be higher than the population of Liverpool. Similarly, there was no translation of the questionnaire, which meant that participants needed to speak sufficient English to participate. This led to an under representation of the minor ethnic groups in the LBBS. Babies with social issues or involved with the authorities were also not recruited into the study. Although the use of the LWH as a base for recruitment gave access to the majority of births in Liverpool this did not allow for the recruitment of any infants born at home or those born in the other general district hospitals in the area.

Like seen in pervious birth cohort studies the profile of the mothers and infants in the LBBS was not representative of the population of the eligible births in the LWH and that of Liverpool. Mothers were older and lived in postcode with a more affluent IMD decile than the general population of Liverpool. Infants were more likely to be of white ethnicity, be preterm, be breastfed and less likely to have been exposed to smoke during pregnancy.

Drop out in the LBBS was not uniform; younger, more deprived mothers who did not breastfeed and who smoked in pregnancy were more likely to drop out of the LBBS. This was

accounted for somewhat by weighting of the study during analysis and the use of multi-level models to analyse the study, however these differences were not completely removed from the study. This weakness of the study reduces the validity of the results when applying them to the population of Liverpool.

The cohort has very strict inclusion criteria, including only a very small well defined population specific to that of Liverpool; this means the findings from the LBBS study must be used very cautiously when applying them to the whole population of England.

Although the majority of findings in this study agree with previous literature there are some discrepancies in the findings especially with regarding smoke exposure. These discrepancies are a weakness of the study given how well documented the effect of smoke on infants respiratory disease is. The lack of findings concordant with previous work regarding smoking is a concerning and may mean the findings of the LBBS unfortunately must be approached with caution.

4.11-Future Recommendations

Future recommendations for the remainder of the study are to continue the analysis of the study in a similar way as in this thesis. This may however, become more difficult as drop out increases and exposed and non-exposed groups become smaller and fewer student are willing to undertake intercalated MPhil research degrees. It will be interesting to see if the protective effect of breastfeeding disappears completely in the future of the study and if smoking exposure becomes a significant negative risk factor for respiratory health preschool infants. It will be interesting to see if evidence supporting the hygiene hypothesis of allergy and asthma becomes more apparent as the study continues.

In the future another study of this kind would be recommended with an improved study design and recruitment strategies. The use of the LRSQ in a longitudinal study using an online automated system was a novel, exciting and successful concept. It is disappointing the study could not produce higher initial recruitment rates and lower attrition rates, otherwise this would have created a larger and more representative cohort study whose results would have been more likely to be concordant with previous findings. To improve the study design a bigger research team would be required with less changes of personal and changes in ownership of the study. Members should be dedicated to different rolls within the study whether that be recruitment, administration or analysis. The use of the fully automated online system from the beginning for the study, with no postal questionnaires may reduce

the workload of the research team and therefore make the running of a study of a future study of this kind more efficient.

In the future a translated version of the LRSQ should be produced and validated; this would allow studies like the LBBS to recruit from minor ethnicities and remove language barriers in studies using the LRSQ This would reduce the under representation of minor ethnicities in future studies.

Further studies investigating the roll of household overcrowding, multiple births, maternal education, maternal age and bedroom sharing on the respiratory health of preschool infants are recommended to further investigate the findings of the current study. There current study was not sufficient to assess these variables with confidence.

The LRSQ should be further analysed to identify questions that have reduced the internal validity of the questionnaire. The improved questionnaire may be more appropriate for use in longitudinal studies of this kind. It would also be beneficial to work with parents to develop what a clinically significant difference or a parentally meaningful difference in symptom questionnaire scores would be. This would make the questionnaire and findings of this study more clinically relevant.

Chapter 5-Conclusions from the LBBS

A profile of the mothers, families and infants in the LBBS was created and compared to the population of Liverpool and eligible births in the LWH. Mothers in the LBBS were older, less deprived, higher educated, less likely to smoke and more likely to breastfeed than the population of Liverpool. Throughout the study, younger, more deprived, less educated mothers who smoked and did not breastfeed were more likely to drop out of the study. This profile of mothers, who were more likely to participate and be retained in a birth cohort study, has been seen in previous work and was expected. To adjust for this effect, the study analysis was weighted so the deprivation in the study was identical to that of all the eligible births in the LWH. Infants in the LBBS were more likely to be of white or of mixed ethnicity and be preterm than the population of Liverpool and the births in the LWH.

The LBBS has described risk factors and protective factors for respiratory disease in the preschool population of Liverpool in the first 22 months of life. Risk factors (shown in either cross-sectional or longitudinal analysis) for respiratory disease are: being male, being born to a younger mother, having a family history of atopy, nursery attendance, preterm birth, low birth weight and living with other household children. Protective factors for respiratory disease were sharing a bedroom and breastfeeding. There was a beneficial positive effect of prolonged breast-feeding. There appears to be a complex relationship between maternal education and respiratory disease in preschool infants in Liverpool that warrants further investigation. The findings in the LBBS for the relationship between tobacco smoke exposure and infant respiratory disease conflict in part with previous findings.

Respiratory symptoms had an impact on the QoL of both the infants and their mothers in the LBBS. Respiratory symptom scores were consistently correlated with QoL scores throughout the study. Respiratory symptoms most commonly affected the infant's sleep through the first 22 months of life. In the first four months of life the biggest effect on the infant's mother was causing worry. There after the biggest effect on the infant's mothers QoL was disturbing their sleep.

Being male, living with other household children, being preterm and attending nursery all reduced QoL in infants due to their respiratory symptoms at various time points through the study. Maternal education had an impact on the infants QoL due to their respiratory symptoms but there was no clear trend. Sharing a bedroom increase the infants QoL at four months as did smoking exposure in pregnant at 16 months; this finding is again disappointing

due to the well documented negative impact of smoking in pregnancy on infants respiratory health.

Mothers of males, of infants with a family history of atopy, who had more than one child, of infants who were born preterm, and of infants who attended nursery had a worse QoL due to their infant's respiratory symptoms. Like infants QoL, maternal education had an impact on mothers QoL but the trend of relationship was not clear and needs further investigation.

The LRSQ was shown to be a valid questionnaire to assess maternal reported respiratory symptoms in infants up to 22 months of age in a longitudinal study of infants from Liverpool. The LRSQ had acceptable to good internal consistency for all domains in the LBBS.

Appendix

Appendix 1- Search terms used for the literature review of birth cohort studies

A literature review was conducted between September 2016 and January 2017. Database 'Scopus' was used with unrestricted epoch. Reference lists of papers were checked to find National, International and Regional Birth Cohort Studies. Cohort study findings with regards respiratory disease in preschool children was identified using the cohort profile papers.

	Search Terms	Results
1	Birth Cohort Study	39,460
2	British Birth Cohort Study	1,141
3	Respiratory Birth Cohort Study	2,995
4	Respiratory British Birth Cohort Study	64
5	Preschool Birth Cohort Study	7,380
6	Preschool Respiratory Birth Cohort Study	897

Appendix 2- Summary of Cohort Studies found during literature review; analysis of study design and key findings.

The 1946 British Cohort Study

The 1946 British Cohort study was initiated by the Royal College of Obstetricians and the Population Investigation Committee to investigate the falling national fertility rate and the impact of the cost of parenthood. It also aimed to determine the distribution of obstetric and midwifery services nationally and determine their impact on the health of mothers and infants and the reduction of premature deaths. The study was funded by the Nuffield Foundation and The National Birthday Trust fund (134, 186). Data collection and analysis is now in its 70th year and continues (187). Those born between the 3rd and 9th of March 1946 in England, Scotland and Wales were eligible for recruitment (n=16,695). 13,687 (81.98%) mothers completed a questionnaire at delivery. Subsequently 5,362 children (39% of the enrolled cohort) have been followed up. The sample of children was geographically distributed in line with national population; analysis has shown shows that the population of the cohort is similar to the national population (134).

In the first four years 12.6% of the cohort was lost. This increased to 19.9% by 15 years, 36.2% by the end of 35 years, and 43.2% by 53 years. These losses were due to death, refusals, living abroad, emigrations and being unable to trace participants. At 53 years 73% of the participants had given information at 17 or more of the 20 data collection points. Only 7% had taken part in ten or less. The study holds high response rates considering the length of its follow up. The study maintains annual contact with the cohort using birthday cards. This has allowed changes in address or contact information to be updated throughout the study (134).

The study found benefit from health visiting and infant care services. The study described the geographical and socioeconomic variation in cost of childbirth, health and survival (134). Subsequently, data has been collected from 5,362 of these children matched to the characteristics of the national population. Other smaller samples of the cohort have been followed including a sample of first born offspring and women between 47 and 54 years of age (186).

Poor housing, parental respiratory disease and air pollution were associated with increased respiratory disease in the first two years of life. Risk factors associated with respiratory disease in the cohorts first offspring were been born to manual working class parents,

parental respiratory disease and parental smoking (57). Deoxyribonucleic acid (DNA) was obtained from the cohort at 53 years which found that that carriers of the gene SERPINA1 Z and S (who have low alpha-1 antitrypsin levels) had increased risk of LRTI in infancy but this had no effect on adult respiratory health (188).

The 1958 British Cohort Study

The 1958 British Cohort Study aimed to identify factors linked to the non-improving national stillbirth rate. It was funded by the National Children's Bureau. All mothers that gave birth in England, Wales and Scotland during one week in 1958 were eligible. 98.76% (n=17,416) of eligible mothers gave access to their maternal health records and completed a questionnaire (135).

Attrition in the 1956 birth cohort was relatively low. Of the 17,416 participants in the cohort 99.3%, 71.1% and 51.8% were successfully contacted at 7, 23 and 55 years respectively (135, 189). Children were located during follow up throughout childhood using their schools. Follow up at 23 years used the subject's most recent address for contact (169). Data collection at 23 years was significantly smaller due to participants leaving school, making contact more difficult. Attrition was more common in those from disadvantaged backgrounds, poor readers, those with short stature, non-whites and children in social care, so the retained cohort is no longer representative of the population (135, 169). At 42 years, refusal had resulted in 13.2% of the cohort's drop out (135).

The study found that smoking was associated with stillbirth, neonatal mortality and reduced birth weight (190). 35% of childhood wheeze resolved by early adulthood, however 5% of the cohort had persistent symptoms and the remainder had intermittent symptoms. Recurrence of wheeze was more common in active smokers. Pneumonia, asthma and wheezing before seven years of age was associated with a cough at 23 years (169). Wheezing between the age of seven and 16 years was associated with childhood pneumonia, eczema and hay fever, whereas wheezing between the ages 17 and 33 years was associated with personal smoking, hay fever and maternal smoking (191). A history of childhood pneumonia was associated with a lower forced expiratory volume in one second (FEV1) and forced vital capacity level (FVC) that is not reversed by salbutamol (192).

The 1970 British Cohort Study

The 1970 British Cohort Study was established in 1970 and underwent its tenth sweep in July 2016 (193). It was funded by the National Birthday Trust and Royal College of Obstetricians and Gynaecologists. The 1970 British Cohort Study set out to examine the association

between maternal characteristics and neonatal morbidity (136, 193). Later, sweeps aimed to assess the factors determining child health, development, transitions into adult life and subsequent health, abilities, attainment and employment in adulthood (136).

All born during one week in April 1970 were eligible to join the study. Eligible births were assessed by midwives using a parental interview and a physical examination. Recruitment led to the enrolment of 16,571 births in the study, 95.9% of the eligible births. Those born in Northern Ireland were dropped from the study after the initial questionnaire (193).

Cohort members were traced for follow up, using school records, at 5, 10 and 16 years 78.9%, 89.8% and 70.1% of the original sample responding at each time point. The increase in responses between five and 10 years was due to immigrants born in the recruitment period being added to the study (135, 136, 169, 193). Although this has allowed the investigation of the effects of immigration on health, the addition of immigrants to the cohort has changed the cohort's demographics. Caution should therefore be taken when assessing trends in this study over time. After 16 years there was a large drop out (54.3% of the original cohort remained in the study at 26 years) due to participants leaving school, and therefore becoming harder to trace (136).

Infants who were male, had mothers who smoked and had a low birthweight were more likely to wheeze in the first five years of life (46). Maternal smoking was associated with a higher incidence of bronchitis and hospital admissions for LRTI during the first five years of life and increased the incidence of wheeze by 1.8% in the first 10 years of life (194). The incidence of wheezy bronchitis had a dose response relationship with maternal smoking; the incidence was 14% in children whose mothers smoked four cigarettes a day compared to 49% in those who smoked 14 cigarettes a day (195). 80% of children who had wheeze in the first five years of life were wheeze-free in their 9th year of life and 85% had no wheezing in their 16th year of life (46). A higher incidence of wheeze before five years increased the risk of continuing to wheeze at 10 years but there was no association between the age of first attack and prognosis (196). A damp home environment was associated with increased cough and phlegm production at 10 years of age (56). Those born under 2kg were nearly twice as likely to be diagnosed with asthma at 26 years when compared to those born between 3kg and 3.5kg (197). Wheezing was reported more often in those who were not breastfed; this relationship did not persist when adjusted for parental asthma (198).

The Millennium Cohort study began in 2000 and aimed to collect a range of data assessing health, childcare, education and employment and their inequalities. It is funded by the Economic and Social Research Council and the UK Government (137, 199). Children born in England and Wales between 1st September 2000 and 31st August 2001 and in Scotland and Northern Ireland between 24th November 2000 and 11 January 2002, alive at nine months and eligible to receive child benefit (as identified by the government child benefit records) were eligible to join the study (137, 199). This criteria and recruitment strategy has given almost universal coverage of the UK population (missing only asylum seekers). The use of a yearlong recruitment period compensates for seasonal variation in the outcomes of birth. The study sample was representative of the UK population (137). Recruitment led to a cohort of 18,827 children at baseline. Hard to research populations were intentionally over sampled to ensure an adequate sample size for analysis. Analysis of these small sub populations is a strength of the study, however this disproportionate sampling needed adjusting for during analysis of the whole population (137).

Follow up occurred in participants who remained in the UK at three, five, seven and 11 years. Response was 82.8%, 82.2%, 73.5% and 70.6% at each sweep of data collection respectively (137). Attrition rates are relatively low considering the time period of the study. Dropout was due to non-response, refusal, non-contact, emigration and death. Dropout was higher in ethnic minorities and disadvantaged areas (137). This disproportionate attrition was adjusted for during analysis.

Data was collected using Computer Aided Self Completion Interviews and assessment by healthcare professionals which has covered a large range of data using standardized measures (199). This combination of data collection has increased the quality of the data and is a strength of the study.

The millennium cohort has led to some key respiratory related publications. Exclusive and prolonged breastfeeding protected against hospitalization for LRTI in the first eight months of life. Breastfeeding for any amount of time showed some benefit (177). It was estimated that 27% of LRTI requiring hospitalization could have been avoided by exclusive breastfeeding and 25% prevented with partial breastfeeding. This protective effect diminished soon after withdrawal of breastfeeding (177). Male sex, maternal age, body mass index (BMI), atopy, smoking during pregnancy, preterm birth, breastfeeding, exposure to other children and household furry pets were independently associated with both early

remitting and persistent wheezing over the first seven years of life (79). Compared to the white population, in the first three years of life, 'Black Caribbean' and 'Bangladeshi' infants reported a higher and lower rate of 'ever asthma' and wheeze respectively. These findings may be due to socioeconomic and cultural differences (171). After adjusting for confounding factors there was a relationship between household income and respiratory health in children (66). Poverty in early childhood was found to be associated with increased risk of asthma attacks and chronic respiratory illness by four years of age (174). Children born to parents with subfertility and who had a longer time to conception were at an increased risk of asthma and used more asthma medications at both five and seven years of age (200). Obese children used more medications for respiratory conditions than children wither lower BMI between five and 11 years of age (201).

The millennium cohort profile has allowed mapping of the trajectories of asthma symptoms in the first seven years of life. This has shown that those with high levels of wheeze and atopic symptoms have an increasing risk of wheeze over the first five years of life that then reduces until seven years. This reduction is less than those without atopic symptoms. In those with low levels of wheeze, asthma symptoms reduce from birth to seven years, more so in the first five years of life (202). Between the 1970 cohort and Millennium cohort, there has been an increase in allergic conditions, including asthma (203).

Regional British Cohort Studies

Aberdeen Children of the 1950's Cohort Study

The Aberdeen Children of the 1950's study was established and funded by the American Association for the Aid of the Crippled Child to research the cause of cognitive problems in childhood. Aberdeen was chosen due to its high standard of maternal record keeping in the Aberdeen Maternal and Neonatal Databank (204). This contains research standard records on around 85% of births in Aberdeen (138, 205). Aberdeen also routinely collects data from home visits, school records, childhood growth data, immunizations data and social background data. Through the study birth and obstetric data was combined with an assessment of height, weight, cognition, family socioeconomic circumstances, attitudes, and behaviours and a teacher's assessment of behaviour. Mortality data, hospital admissions, cancer registrations were also included. Further follow up of the cohort has been designed to look at various specific hypothesis (138, 205).

All children born in Aberdeen between 1950 and 1956 who were in primary school in 1962 (aged between six and 12 years of age) and their siblings were eligible for the study. 99% of

the eligible population of Aberdeen was traced during initial data collection (n=12,013), along with 7,080 second generation births. Response rates of 64% to the postal questionnaire in 2002-2003 were achieved. Response was highest amongst females with married, non-manual working class parents and fewer siblings. There were 611 deaths in the cohort by the end of September 2005 (138).

This cohort is almost a complete population of a well-defined area with high rates of follow up in the early stages. This was achieved by using the Aberdeen Maternal and Neonatal Databank. This is a unique feature of the study that increased the quality of the data. This, along with the use of Christmas cards, was used to track changes of address to increase participation throughout the study period (138). The cohort has given a large insight into cognition, the natural history of coronary heart disease and mental health (138, 205), but there were no publications on respiratory disease in preschool children.

Avon Children of the 90's Study

The Avon Longitudinal Study of Parents and Children (ALSPAC), also known as "Children of the 90's", is part of the European Longitudinal Study of Pregnancy and Childhood (ELSPAC). ELSPAC was established by the WHO. It was designed to investigate how phenotypes combine with environmental factors to influence health and development of children and their mothers. The Medical Research Council, the Wellcome Trust and the University of Bristol fund the study. Data collection is now in its 25th year (162, 206) .

14,541 pregnancies were opportunistically recruited by midwives between 1st April 1991 and 31st December 1992 from a defined area in South West England. Pregnant women who moved to the area were eligible until the point of delivery. Those who moved away and had not completed a questionnaire in the third trimester were excluded (139, 162, 207). Children born during the recruitment period that were missed were added to the study at seven and eight years of age. This has led to 15,390 children being enrolled in the study by eight years.

Enrolled mothers were more likely to be white, own a home and car, be married and live in overcrowded house when compared to census data, despite having a higher average socioeconomic status than the population of Britain (139). The children in the cohort at 16 years were more likely to be female, of white ethnicity, higher educated and less likely to be eligible to free school meals than the national population (162).

Attrition was highest during the children's infancy and increased again as the participants entered adulthood, however because children were free to re-join the study up to 18 years of age the cohort population has remained fairly large. Of the 14,062 eligible live births 97.4%

and 84.4% were followed up at two years and 18 years respectively. 100 children had died, 2018 were untraceable and 782 withdrew from the study. During adolescence only 48.2% responded to all 12 data collection sweeps. 75% of the cohort had responded at least once (162).

Over 1200 papers have been published using data from this cohort. Babies that sleep prone and on their side had an increased incidence of respiratory symptoms at six months (208). This relationship was no longer apparent by 18 months (175). An important finding that led to change in National guidance was that Sudden Infant Death Syndrome was reduced in babies who slept on their back (209). Children of mothers who had greatest use of household chemicals in pregnancy were at an increased risk of persistent wheeze and lung function abnormalities (210). Maternal smoking in pregnancy increase infant wheezing during early childhood, regardless of postnatal ETS exposure (43). The prevalence of wheeze was also higher in children born to mothers that consumed paracetamol in the third trimester (211). The prevalence of asthma was higher in children whose mother had anxiety in pregnancy (212). Wheezing and eczema was more prevalent between 30 and 42 months of life in those who were exposed to excessively clean environments after adjustment for all confounding factors (67). The incidence of asthma was higher in seven and eight year olds with a lower socioeconomic status (65). The Filaggrin gene was associated with asthma, eczema and sensitization to allergens (213).

Born In Bradford

The BiB Cohort Study began in 2007 in response to the high rates of child morbidity and mortality in Bradford. It aimed to identify modifiable risk factors that cause or contribute to ill health and produce health promotion interventions in this deprived multi-ethnic population. The study collaborates with the European Child Cohort network, which allows links with other national and international birth cohort studies (49, 163, 214). The largely bi-ethnic cohort has allowed comparisons of health outcomes to be made between two ethnic groups (49).

All births between March 2007 and November 2010 at the Bradford Royal Infirmary were invited into the study. The recruitment rate was 64% (13,776 pregnant woman and 3,448 of their partners). The recruited population had a lower proportion of younger mothers and a higher proportion of South Asian and nulliparous mothers. There were differences in gestational age, however this was due to the recruitment strategy of the study because those

born before 28 weeks gestation were not recruited. Despite this the cohort was shown to be representative of the population in Bradford making the cohort valid (164). .

The BiB study has a good relationship with the participants and the hospital. This relationship was maintained using birthday cards, newsletters, and a study website (49). The BiB cohort was split into many sub cohorts during investigation. The BiB1000 sub-study showed response rates of 77%, 75%, 74%, 70% and 70% at 6, 12, 18, 24 and 26 months respectively with 47% of the cohort completing all follow up. The majority of attrition in this cohort was due to not being able to contact the participants even with the use of telephone calls, reference to electronic health records and opportunistic visits to family homes (215).

There have been around 140 publications produced from this cohort. Maternal smoking (16.4%) and drinking (30.6%) rates in pregnancy were relatively low compared to white British mothers (33.7% and 67.4% for respectively). While babies born to mothers of Pakistani ancestry were lighter and they were less likely to be exposed to risk factors of sudden infant death syndrome (49).

The study has shown that between birth and three years of age the incidence of wheeze is higher in boys than in girls and low birth weight increases the risk of wheezing disorders (25).Rapid growth between three and 12 months of age increased the risk of wheeze (55).

The Isle of Man (IoM) Cohort Study

The IoM Birth Cohort study began as part of the ELSPAC study. The aims specific to the IoM study were to measure the prevalence of diseases in children and their parents, detect health advantages and disadvantages, to study the effects of migration on the population and to determine any island specific features of that may influence health (140). After a period of publicity on the Isle of Man, every mother expecting a baby between 1st January 1991 and 30th June 1992 was invited to join the study (n=1,384). This led to 1,314 live births being enrolled in the study. Mothers leaving the island (n=161) were not followed up, however children who had moved to the island born in the recruitment period were opportunistically added to the study at seven years. This led to 1,411 participants available for follow up at seven years. Between 15 and 16 years, 1,125 participants were available for follow up (140, 216).

The main source of attrition in this cohort was emigration off the island. This large proportion of drop out is a particular weakness of the study however the publicity for the study and its robust data collection methods have produced near 100% response rates (140). The inclusion criteria allows for the analysis of the whole island population and comparison between the

Manx Population and those who have immigrated to the island; this adds a unique element to this study. The high participation rate in this cohort shows the benefit to publicity and structured recruitment when compared to opportunistic recruitment, such as used in the AVON Cohort.

Funding by various charitable organisations on the island has not been sufficient. Although data is complete it is not ready for analysis (140, 216). Because of this, no publications assessing the IoM alone have been published. There are however, publications comparing the IoM Cohort with the ALSPAC cohort (217).

The Newcastle Thousand Baby Study

The Newcastle Thousand Families 1947 Birth Cohort was established in response to the high infant mortality rate in Newcastle. The original aim of the study was to identify risk factors of infection in infancy and has continued as a longitudinal study to assess health, education and family life throughout childhood (141, 218). It was funded by the Newcastle City Health Department, the City Health Committee and the Nuffield Foundation (141, 218).

The cohort consisted of 1,146 (84%) children born in May and June of 1947 in Newcastle upon Tyne who were followed through their first year of life. The original cohort was representative of the social spectrum of the city (141). Data collection began in pregnancy using midwife's reports and continued every six weeks throughout infancy and quarterly up until five years of age. Follow up included assessments by paediatricians and health visitors. The cohort was tracked by NHS central registry enabling mortality figures to be updated. This added accuracy to figures reported in publications. The cohort was also linked to GP and hospital records (141, 218).

In the first year of the study 44 participants died and 125 participants left the study area. 73.9% and 65.4% of the cohort were followed until the end of the 5th and 15th year of life respectively. At 50 years 89% of the surviving cohort were traced; 50.1% returned a questionnaire and 40.0% (n=412) attended for a clinical examination (141). Although these are high attrition rates compared to other cohort studies the most recent follow up showed that the cohort was representative of the original sample for the majority early life factors. The sex of the cohort is no longer representative of the original sample (141). The high attrition rates, along with a fairly small sample size reduce the strength of this study as a whole.

There is very little published work addressing paediatric respiratory health from this cohort, however work has been published on long term respiratory function and of overall infant's

health. Key findings included: Children from poorer families with household over-crowding were at the highest risk of respiratory infection (58). Children who had a severe lung infection before five years of age were seven times more likely to develop chronic lung disease in adulthood (58). Breastfeeding had no long-term beneficial effects on adult lung function (219).

The Southampton Women's and Children's survey was established in 1998 by the University of Southampton and the Medical Research Council to investigate the effects of dietary and lifestyle factors on the health of mothers and their children. The study now follows the children born into the study to determine pre-natal risk factors for chronic disease (142, 176).

Between 1998 and 2002 GP's in Southampton recruited female patients between 20 and 34 years of age by sending them a leaflet which was followed up with a telephone call. A trained nurse performed the initial assessment of interested women at their home. To maximise response rates, a repeat letter was sent to those who did not respond to the telephone call. If there was still no response the home was visited. The study was publicised locally at events and in supermarkets to increase participation. These efforts led to at 75% participation rate (142, 176). 12,583 women gave pre-pregnant profiles and were followed throughout pregnancy. Participants and their GP's were asked to contact the study team if they or their patient become pregnant. This recruitment strategy led to 3,158 babies available for follow up (176). Response rates were 95%, 93%, 86% and 81% at six months and one, two and three years respectively (142).

The study has a small respiratory specific sub-study of 150 babies who underwent lung function testing, by means of rapid thoracoabdominal compression, at six weeks of age and completed symptom diaries in the first year of life. Urine samples were obtained from the cohort of infants and skin prick testing was conducted on their parents. Dust samples were collected from participant's homes. (142, 176).

This sub-study found that greater maternal adiposity was associated with increased transient wheeze in childhood, however it had no association with asthma or allergy (220). Babies who had smaller birthweights and those who had high weight gain postnatally had poorer lung function at six weeks of age (176). Greater relative weight and adiposity gains were associated with increased wheeze at three years (54). Poorer lung function at six months was associated with a higher incidence of wheezing in the first five years of life (221).

Breastfeeding was shown to be protect against respiratory disease. This protective effect was proportional to the duration of breastfeeding (7).

This cohort has a good participation produced a large sample for a regional cohort study. However there was a small age range invited to the study so a large proportion of the pregnant population was missed. Likewise the design of the study meant that those who were not registered with a GP or don't attend GP's regularly were less likely to be invited to the study. These are significant sources of selection bias. Although the use of GP's will have reduced the drop out, there was likely to be a significant number of women who forgot to or intentionally did not contact the study team when they become pregnant (142, 176).

International Collaborative Birth cohort studies

The European Longitudinal Study of Pregnancy and Childhood (ELSPAC)

The European Longitudinal Study of Pregnancy and Childhood (ELSPAC) was established by the WHO in Europe in 1985 to identify the factors influencing health in childhood in European Countries (222). It is coordinated in Bristol by the ALSPAC team (206). The aims of the study were to determine the biological, psychological, social, economic and environmental factors that influence pregnancy, birth, health and development (223). The study was established in the Isle of Man, Czech Republic, United Kingdom, Slovakia and Ukraine and partly in Greece, Spain, Croatia and Estonia. It was agreed to follow the cohort until 21 years of age and potentially beyond, however poor funding in various countries has meant that continuing data collection was not possible (224). Recruitment occurred in Great Britain, the Isle of Man and Czech Republic between 1991 and 1992 and varied from 1992 to 1995 in the remaining countries (223, 225). The cohort contains over 40,000 children and their families and at 17 years the study participation rate remained relatively high considering the time consuming nature of the questionnaire at around 50% (225).

To date there has only been a few publications produced as a result of the ELSPAC study. The majority of publications have only included data from a single country. This is disappointing considering the scale and the potential impact of collaboration in this study. Findings from the ALSPAC study and Isle of Man Cohorts have been discussed earlier.

Respiratory Specific Birth Cohort Studies

Manchester Asthma and Allergy Study (MAAS)

The Manchester Asthma and Allergy Study (MAAS) was established in 1995 to understand the development of asthma and allergies in young children. 3,618 mothers and 2,172 fathers were originally recruited at routine antenatal booking appointments. Parents underwent skin

prick testing to common allergens to divide the cohort of infants into risk groups, each of which had different study aims (24, 143, 226). There was no comment on of the cohort's representation of the eligible population of Manchester.

1,499 parents consented to the study, which led to 1,085 children being enrolled into the study (2). 6.9% were lost to follow up in the first year and 8.3% were lost by three years. 969 children (89.3%) remained in the cohort at five years (226) . Although the sample size is not particularly large compared to some other cohort studies, attrition rates were low over the first five years of the study. Follow up was by means of symptom questionnaires at one, three and five years assessing asthma, eczema, rhinitis and medication use and by objective measures of lung function at three and five years. GP notes were reviewed for formal diagnoses (24, 143, 226). The use of risk-stratified groups by means of skin prick testing is a unique aspect to this study.

Children in the 'high risk' group who wheezed had a significantly worse lung function at 1 month of age (227). Persistent wheeze after three years was predicted by poor lung function (228). Those children whose environment was controlled to reduce allergen exposure, used significantly fewer asthma medications than those whose environment was not controlled (229). Sensitisation to allergens was associated with a higher prevalence of asthma (228). Dust mite exposure was associated with increased bronchial airway reactivity regardless of prior sensitisation to dust mites, though asthma was more severe in those who were sensitised (78). Similarly, sensitization to dogs and cats was associated with asthma (230). ETS was associated with an increased prevalence of asthma (230) and increases the risk of wheezing in the first year of life (47). Nursery attendance was associated with reduced wheeze at five years. This association was strongest in those who attended nursery between six and 12 months of age (73). Significantly more wheezers between three and five years of age had been prescribed antibiotics in the first year of life for LRTI when compared to non wheezers. This may indicate a roll for early antibiotic exposure in the aetiology of wheeze (231). Exposure to particulate matter and nitrogen dioxide was associated with small but significant reductions in lung volume growth in children (232).

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort Study

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Cohort was established in response the increasing prevalence of asthma in the Netherlands in the 1980's and 1990's. (144). Recruitment ran between 1996 and 1997 in prenatal clinics in North, Middle, and Southwest regions of the Netherlands. Mother's atopic status was assessed using a screening

questionnaire which allowed their child to be grouped by risk of atopy. This led to 3,963 children (~50% of those invited) being enrolled into the study. Children were split across two sub studies; one investigating the effects of dust mites and the other investigating the natural history of respiratory disease (233). Mothers of the PIAMA study were more highly educated and less likely to be from a non-western population than the population the Netherlands. They were however, just as likely to breastfeed and had a similar maternal age (144). The children were followed up with 10 questionnaires and medical examinations in the first eight years. At eight years 92% of the participants were still involved in the study. In 2012 and 2013 participants underwent anthropometric measurements, lung function tests, and blood tests; 800 (around 20%) of the original cohort participated (144, 234).

House dust mite impermeable covers provided a reduction in asthma symptoms for the first two years of life (235). Asthma was increased at eight years in children whose mother ate peanuts daily during pregnancy (236). Birth by caesarean section conferred a higher risk of asthma at eight years, more so in those with allergic parents (237). Lower birth weight increased the risk of respiratory symptoms in the first five years of life and this relationship was strongest in those exposed to ETS (238). Breastfeeding reduced asthma at eight years of age regardless of a family history of atopy (178). Exposure to microbial contaminants in early life may have reduced asthma and wheezing in the first four years of life (239). Frequent consumption of products containing milk fat reduced the risk of asthma symptoms in the first three years of life (240). Nursery attendance increased the risk of LRTI in the first year of life (184) and was associated with an increase in respiratory symptoms until four years of age but fewer respiratory symptoms thereafter (74). Air pollution was associated with an increased diagnosis of asthma in the first year of life (241) and at eight years of age (242). In contrast to previous thoughts, the PIAMA study described that those with nocturnal dry cough in early childhood were nearly twice as likely to be diagnosed with asthma at school age (243).

The Tucson Children's Respiratory Study

The Tucson Children's Respiratory Study was established in 1980. It examined the relationships of risk factors in the first three years of life, including LRTI, with chronic lung disease in childhood and early adulthood. The study recruited 78% (1,246 children) of all those born in Arizona between May 1980 and January 1984 (244). Participating mothers tended to be married, older, have spent longer in education, have more household members with a FH of atopy and have other older children. All other demographics were comparable to the population of Arizona (244). Drop out was 13% in the first five years. 78% of the cohort

remained traceable during 2002 and 60% of these were still living in Tucson. These are relatively low attrition rates considering the length of tim(49, 139, 140)e the study has been running (45).

A large amount of data assessing risk factors was collected prenatally and biological samples were taken at birth. In the first three year there were four data collection points which included questionnaires, skin prick tests and pulmonary function tests with airway challenge studies. Lung function was measured using rapid thoracic compression, helium dilution, forced oscillation measurements and tidal breathing analysis. During any acute LRTI the participants were asked to contact the research team for further assessment and serology tests. Between three years and 16 years of age, there were a further four data collection sweeps (45, 244). The integration of questionnaires, skin prick testing, objective measures of lung function and formal assessment of RTI's, has created a novel dataset of high quality. The assessment during infections is a novel and unique feature of this study.

LRTI occurred in 32% of infants in the first year of life. 17% and 12% of infants had a LRTI in the subsequent two years. RSV was the most common cause of LRTI followed by Parainfluenza virus (245). Infants who had LRTI in the first three years of life demonstrated reduced lung function at six years and had a higher incidence of asthma at 11 years (45). Breastfeeding for at least one month reduced LRTIs in the first four months of life (173). Infants born to younger mothers and nursery attenders were more at risk of LRTI (173). Infants with mothers who smoked were three times more likely to have a LRTI in the first three years, and the age of their first infection was lower (246).

The proportion of the cohort with an asthma diagnosis increased with every sweep of data collection until 16 years of age. The highest incidence of wheeze in males was between six and eight years of age after which it decreased. Contrastingly the incidence of wheeze in females increased after 10 years. 59% of children that wheezed before three years had stopped wheezing by six years of age (45). The diagnosis of asthma after 11 years of age was not associated with wheeze in the first three years of life, however it was associated with wheezing between six and 11 years. Children who lived with other siblings had reduced incidence of asthma symptoms between six and 13 years (60). Infants who were exclusively breastfed and have mothers with asthma are more likely to have asthma and atopic disease (72).

Infants who wheezed in the first three years of life had lung function measurements indicating smaller than normal airways before their first LRTI. Those who wheezed in the first

year of life and had one LRTI by three years of age on average had reduced lung function compared to those who did not wheeze. These observations form the hypothesis that future wheeze and LRTI may be predicted by premorbid reduced lung function in early childhood (247).

The Tucson study lead to the description of three phenotypes of wheeze. "Transient wheezers" wheezed during the first two to three years of life and had no or few episodes thereafter. They were unlikely to have atopic risk factors and had reduced lung function at three years which improved (but had not completely resolved) by six years (45).

"Non-atopic wheezers" continued to wheeze beyond the third year of life after a LRTI in early life. They had a lower lung function at six years; it was unclear if this abnormality is present before the initial LRTI. It was hypothesised that this wheeze is due to an increased response to a viral infections due to abnormal control of airway tone. This abnormality may reduce with increasing age (45).

"Atopic wheezers" were likely to have their first wheezing episode in the first six years of life. Atopic wheezes had the greatest reduction in lung function between three and six years and had the lowest level of lung function at six years of age (possibly due to ongoing damage to the lungs). They had a high level of serum IgE and were more likely to have an atopic mother (45).

Appendix 3- Summary of Large Non-Birth Cohort Respiratory Studies

The European Community Respiratory Health Survey (ECRHS)

ERCHS was established in 1990 in response to the increasing prevalence of asthma in Europe in the 1980's. Currently there have been three phases of the study (248).

ECRHS 1 included 600 participants aged between 20 and 44 years, randomly selected from 56 centres across Europe. Those who responded to an initial questionnaire were invited for detailed respiratory assessment (including a questionnaire and spirometry with bronchial response tests) (249). The questionnaire included 71 items assessing respiratory symptoms, exposure to risk factors of repository disease, the use of health services and medication use. The questionnaire was based on two validated respiratory questionnaires; the International Union against TB and Lung Disease questionnaire and the American Thoracic Society questionnaire (249).

ECRH2 was a nine year follow up study which aimed to determine the incidence and prognosis of allergy, asthma, hay fever and eczema, describe the distribution of exposures and risk factors, and identify sub groups that are more susceptible to the diseases in question. ECRH2 also established a blood bank for DNA extraction (250). The questionnaire was modified to include questions from the ISSAC questionnaire and to represent the Global Initiative for Asthma guidelines more closely (250).

ECRH3 was a 19-year follow up study. It aimed to describe the change in respiratory symptoms over time. It assessed patterns of IgE sensitisation as the participants aged and if atopic status and asthma are associated with reduced lung function and Chronic Obstructive Pulmonary Disease (COPD) development. It also described associations between obesity, physical exercise, asthma and lung function (248).

The ECRHS has shown that there is a large variety in the prevalence of asthma throughout Europe. It is highest in English speaking countries and lowest in the Mediterranean and eastern European regions (251); this correlates with warm winters and cold summers (252). There has been an increase in the diagnosis of asthma attacks and medication use but not in the prevalence of symptoms over this time. This could be due to better diagnosis leading to more people being labelled as asthmatic, or the increased use of effective treatments (253). The ECRHS has strongly supported the hygiene hypothesis of asthma and allergy; children with pets had less atopy and hay fever, and it was beneficial to grow up on farm (251). Children who had early exposure to other children, larger families, shared a bedroom and owned a dog in childhood were less likely to become atopic in adulthood (254). Other factors

that were associated with increased asthma in adulthood included indoor mould growth (255), passive smoking (256) and parental smoking, low maternal age, severe respiratory infection in early life, and long term dog keeping (257). It has been shown that respiratory symptoms have a detrimental effect on the QoL (258).

The International Study of Asthma and Allergy in Childhood (ISAAC)

The ISAAC aimed to describe the worldwide variation in prevalence and severity of asthma, rhinitis and eczema, obtain baseline measures of these diseases and provide a framework for future aetiological studies of environmental, lifestyle and genetic studies of these diseases (105).

The study had three phases:

1. Determining the (variation of) worldwide prevalence of diseases in six to seven year olds and 13 to 14 year olds (105).
2. Investigate possible aetiological and risk factors for the diseases (259).
3. Repetition of phase 1 to assess trends in severity and prevalence (260).

The study has shown that there is worldwide variation in the prevalence of the diseases in question, which worldwide variations of smoking and air pollution cannot be made responsible for (261). Population level variation in susceptibility to allergic sensitisation may party be responsible for the variations in prevalence. Countries with an incidence of Tuberculosis showed a lower prevalence of asthma (75). The prevalence of asthma was lower in rural areas than urban ones, being lowest amongst farmers (75) and in households with higher levels of dust endotoxins (64). In contrast, there was an association between pertussis and measles and asthma and rhinitis (262). Respiratory symptoms were shown to be higher in damp households (263). Asthma was associated with an increase in indoor humidity and was lower in areas with higher altitude and a larger variation in temperature (63). Eczema correlated positively with increasing latitude and negatively with increasing temperature (63).

Diet may also play a role in the aetiology of asthma. Areas with higher trans fatty acid consumption showed higher levels of asthma, rhinitis and eczema (75). In contrast, areas with higher fish, fruit and vegetable consumption, a 'Mediterranean diet', showed lower levels of wheeze (76). Obese and overweight children were shown to have higher levels of wheeze and increase airway obstruction (264). Breastfeeding was shown to be protective of wheeze in non-atopic children and this was most apparent in non-affluent areas. There was no association shown between breastfeeding and allergy (265). Phase three has shown a

worldwide increase in the prevalence for all of the diseases in question in children aged between six and seven years. However asthma was reduced in children aged 13 to 14 years of age, more so in areas with a high original prevalence (260, 266).

The Leicester Respiratory Cohort

The Leicester Respiratory Cohort was set up in 1990 due to the lack of respiratory studies in preschool children. It aimed to determine the prevalence, natural history, risk factors, phenotypes and trends of asthma and other respiratory disorders in preschool children. Leicester's large South Asian population allowed detailed study of respiratory disorders in this ethnic minority (108).

Two cohorts were selected at random from the Leicestershire health authority child health database. The 1990 cohort contained 1,650 children born between 1985 and 1990 and the 1998 cohort consisted of 8,700 children born between 1993 and 1997 (108). The selection was random and the sample was stratified so the cohort contained selected numbers of children of each age group up to four years old. The cohorts were shown to be representative of the population of Leicestershire (108) although the participants that responded tended to be of higher social economic class and have a higher maternal age (108). Participants were sent questionnaires base on validated questionnaires at baseline and every few years thereafter and were invited for physical examination in the early school years. Baseline data was 100% due to the use of routine data. Response rates for the 1990 cohort were 86.2% in 1990, 79.1% in 1998 and 57.3% in 2003. For the 1998 cohort there were 78.3% in 1998, 59.6% in 2001 and 48.6% in 2003. The high attrition rate was due to change of address with nearly half of the participants moving house at least once during the study (108, 109, 267, 268). Around 60% of those invited for laboratory studies attended (108).

In 1990 11% of the cohort had a doctor diagnosis of asthma, 16% wheezed with 13% of these having repeated attacks; in 1998 the percentage of the cohort with doctor diagnosed asthma and wheeze was 19% and 29% respectively (268). 10% of children snored regularly and nearly half of these continued to do so at four years (269). It was shown that fewer than half of preschool wheezers continue to wheeze at school age and those with a chronic cough tend not to wheeze two to four years later (270). In contrast to what was previously though, vaccinations were not associated with an increased risk of wheeze and appeared to be protective against late onset wheeze. It has been hypothesised that allergen induced wheeze and infection induced wheeze may be completely different entireties (271). Breastfeeding was associated with better lung volume in those born to asthmatic mothers. Those that were

breastfed for four months had better peak flows irrelevant of a FH of asthma (272). This study has helped to develop a simple tool for identifying the risk of continuing to wheeze at school age in preschool wheezers (273). The South Asian population had less wheezing than the white population but had a higher rate of admission to hospital (172).

The Wythenshawe Community Asthma Project (WYCAP)

WYCAP is a long-term prospective observational study of respiratory illness and asthma which observes two cohorts from two GP practices in Manchester. It was designed to develop a method for identifying those with asthma and COPD in the community both known and unknown to medical services and to evaluate the cost of treating these individuals (274, 275).

Three postal respiratory questionnaires were sent to 11,206 patients between 1993 and 1999. The questionnaire was based on the European Community Respiratory Health Questionnaire with additional questions to assess FH of asthma and current smoking. Participants were likely to have asthma if they scored four or more. Non responders were sent two reminders four and eight weeks after the initial questionnaire (274).

13.8% of patients aged 16 years or over had asthma like symptoms and around half of these were unknown to health services and may benefit from further investigation or management (274). The questionnaire showed a good positive predictive value in identifying those who clinicians thought would benefit from a trial of medication (275). The workload of assessing these unknown patients would be unfeasible and a method of prioritising patients was successfully established using the 1995 and 1999 data (276). It was estimated that 10% of the children might have had asthma that was unknown to medical services. The questionnaire was deemed to be valid in identifying children who may have asthma and may benefit from clinical review in the five to 15 year old population when compared to expert opinion (277). The number of children that would require clinical review was between 3.5% and 8%; this would significantly increase the workload of GP practices (277).

It has been shown that from 1993 to 1999 the prevalence of wheeze, being woken by cough and the recipient of asthma medication has increased in adults but decreased in children; this was more likely to be due to an increase in COPD in adults rather than the reduced asthma in children (278).

Appendix 4- Birth cohort studies not discussed in the current thesis

Study	Country	Year	Cover	Participants	Outcome Aims
All Babies in South East Sweden (279)	Sweden	1997	Regional	17055	To determine the in importance of environmental factors in diabetes development, how genetic and environmental factors interact, whether interventions change lifestyle and reduce obesity and diabetes, and build a biobank for studies on diabetes, obesity and immune mediated diseases.
ELSPAC in The Czech Republic (224)	Czech Republic	1991	Regional	7589	To determine Effect of the socioeconomic change in the country in 1989 on health.
Generation R (280)	Netherlands	2002	Regional	9778	To identify early environmental and genetic causes leading to abnormal growth, development, and health during foetal life through to adulthood.
German Multicentre Allergy Study (281)	Germany	1990	Multicentre Regional	1314	To assess the role of different exposures (mite allergen, cat allergen, ETS, infectious disease, vaccinations) in the development of asthma.
Growing Up In New Zealand (121)	New Zealand	2009	Regional	6822	To identify the determinants of developmental trajectories and what optimises these trajectories. To assess development and its association with ethnicity.
Growing Up In Scotland (282)	Scotland	2004	National	14000	To generate Scottish specific data about outcomes through childhood and into adulthood across various domains.
The Amsterdam Born Children and their Development (283)	Netherlands	2003	Regional	8226	To assess associations between maternal lifestyle, medical, psychosocial and environmental conditions during pregnancy and child's health at birth and later life.
The Bern Infant Lung Development Cohort (284)	Switzerland	1999	Regional	364 (2009)	To study the effects of environmental and genetic risk factors on the physiological properties of the developing lungs in healthy individuals.
The Danish National Birth Cohort (285)	Denmark	1996-2002	National	96986	To determine cause of reproduction failures, pre/perinatal determinants of childhood health and improve infrastructure for future studies.
The Dunedin Multidisciplinary Cohort Study (286)	New Zealand	1972	Regional	1037	To study the nature and prevalence of some developmental and health problems in three year olds and some risk factors for these problems.
The Helsinki Birth Cohort (287)	Finland	1934	Regional	13345	To assess the influences of early growth and living conditions on long term health, including cardiovascular disease, psychological disease, aging and cancers.
The Hong Kong Chinese Birth Cohort (288)	China	1997	Regional	8327	To examine the effect of ETS exposure and breastfeeding on infant health and health care utilisation in the first 18 months.
The INMA Study (289)	Spain	1997-2008	Multicentre Regional	3887	To describe prenatal exposure to polluting agents in Spain and to evaluate impact of pre and post-natal exposure to polluting agents and the effects of genetics and nutritional factors.
The Krakow Birth Cohort Study (290)	Poland	2002	Regional	493	To determine the effects of PAH components on foetal growth and early childhood health.
The Mater-University Study of Pregnancy and Childhood (291)	Australia	1981	Regional	7223	To investigate the factors associated with adverse pregnancy outcomes.
The Mother and Children's Environmental Health Study (292)	Korea	2006	Multicentre Regional	892	To determine the roles of bio-aerosols, heavy metals and endocrine disrupting chemicals in adverse birth and health

					outcomes. To assess the interaction between environmental factors and genes in disease development.
The National Children's Study (293)	USA	1999	Multicentre National	5608	To study the process of human development from conception to old age.
The North Finland Birth Cohorts (294)	Finland	1996 1985	Regional	1966- 12231 1985- 9479	To examine risk factors for preterm birth and intrauterine growth retardation and subsequent morbidity.
The Norwegian Mother and Child Cohort Study (295)	Norway	1999	National	110000	To build a knowledge base on the causes of serious disease.
The Pelotas Birth Cohort Study (296)	Brazil	1982	Regional	5914	To assess the effects of breastfeeding, and other chronic disease risk factors.
The SELMA Study (297)	Sweden	2010	Regional	2582	To investigate early life exposures during pregnancy and infancy to environmental factors with focus on endocrine disrupting chemicals.
The STEPS Study (298)	Finland	2008	Regional	1827	To determine the precursors and causes of reduced child's health and wellbeing.
The Stockholm Birth Cohort Study (299)	Sweden	2004	Regional	1953- 15117 1980-13838	To study intergenerational life course associations with health disease and mortality.
The Swiss National Cohort (300)	Switzerland	2006	National	7452075	To build and maintain the first nationwide cohort with data linkage and develop measures of socioeconomic status and procedures to identify deaths.
The Toyama Birth Cohort Study (301)	Japan	1990	Regional	8274	To study of lifestyle and health among all children.

Appendix 5- Adult respiratory symptoms questionnaires

King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire	K-BILD health status questionnaire was developed to assess the health status of patients with interstitial lung disease. It is a 15 item questionnaire which assesses three domains; breathlessness and activity, psychological and chest symptoms. It has been shown to be a valid self-completed questionnaire for the assessment of health status in patients with interstitial lung disease (302). A minimal informant difference has been determined for the response to therapy (303).
St Georges Respiratory Questionnaire	The St Georges Respiratory Questionnaire is a self-completed questionnaire with 76 items assessing symptoms, their frequency and severity, activity limitation and the impacts on psychological and social functioning. It has been validated, showing good repeatability and sensitivity and is comparable with standardised measures in adults with chronic airflow obstruction (304), asthma (305) and bronchiectasis (306). There has been a COPD (307) and Idiopathic Pulmonary Fibrosis (308) specific versions developed and validated.
The Asthma Control Test	The asthma control test is a five item questionnaire assessing symptoms, use of rescue medication, and the impact of asthma on everyday functioning (309). It has been shown to be valid and reliable in screening those with poorly controlled asthma in a multinational study (310) and is responsive to changes to asthma control (311).
The Chronic Respiratory Questionnaire	The Chronic Respiratory Questionnaire was developed to produce a measure changes of quality of life in COPD patients after treatment. It is a clinician completed questionnaire which assesses dyspnoea, fatigue, emotional function and patient's feeling of control over their disease. It has been shown to be precise, valid and responsive measure of quality of life with good internal consistency (312).
The Clinical COPD Questionnaire (CCQ)	The CCQ was developed to aid clinicians to identify the clinical status, activity limitations, emotional dysfunction and clinical improvement in COPD patients. It has 10 items assessing three domains (symptoms, functional wellbeing and emotional wellbeing) by a 7-point Linkert scale. It is a valid, reliable and responsive measure in COPD patients and is useful in identifying 'at risk' patients and assessing improvement in patients after smoking cessation (313).
The COPD Assessment Test (CAT)	The CAT was developed to help assess health status in COPD patients and enhance communication between clinician and patient. It contains eight items assessing cough, phlegm, chest tightness, breathlessness going uphill or upstairs, activity limitation at home, confidence on leaving the home, sleep and energy (314). It is a sensitive, valid and reliable standardised measure of COPD (315). It has been shown to be useful in measuring pulmonary rehabilitation response (316) and changes in health following acute exacerbations (317).
The International Union against Tuberculosis Bronchial Symptoms Questionnaire	The International Union against Tuberculosis developed the Bronchial symptoms questionnaire to measure the prevalence and distribution of asthma (318) and has shown good repeatability across Europe particularly in questions that assess asthma and wheeze(319).
The Leicester Cough Questionnaire	The Leicester Cough Questionnaire was developed to assess the quality of life in adults with Chronic Cough. It is a valid,

	repeatable, 19 item questionnaire assessing QoL over three domains; physical, psychological and social wellbeing (320). It is useful in assessing acute cough (321), non-CF Bronchiectasis (322) and COPD (323).
The Medical Research Council (MRC) Breathlessness Scale	The MRC Breathlessness Scale comprises of five statements describing the disability associated with breathlessness, from no respiratory capacity to almost complete capacity (324). It can be self-completed or completed by an interviewer (324). It has been used for stratification of treatment, survival prediction and disability measurement in COPD Patients (325).
The Quality of Life for Respiratory Illness Questionnaire (QOLRIQ)	The QOLRIQ consists of 55 items assessing seven domains; breathing problems, physical problems, emotions, general activities, situations that triggered or enhance breathing problems, daily domestic activities and social activities/relationships/sexuality (326). It has been shown to be sensitive to change longitudinally and is valid and reliable in measuring QOL in moderate to severe COPD and asthma (327)
The Wisconsin Upper Respiratory Symptom Survey	The Wisconsin Upper Respiratory Symptom Survey is a continuation of work by Jackson et al. in 1960 (328) which created a standardised measure of the symptomatic and functional impact of the common cold (329). The questionnaire contains 44 items assessed on a seven point scale (329) and is valid, responsive, reliable (330) and correlates with biomarkers of respiratory disease (331). A smaller version containing 22 items has been validated (330).

Study Protocol

The Liverpool Respiratory Birth Cohort Study

A Prospective, Longitudinal Birth Cohort study using the Liverpool Respiratory Symptom Questionnaire to conduct a biannual assessment of the respiratory symptoms of preschool children born in Liverpool from birth until the age of five years.

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Abstract

Objective: To describe respiratory symptoms of preschool children using the Liverpool Respiratory Symptom Questionnaire (LRSQ) from birth until the age of five years, in Liverpool by bi-annual assessment.

Method: Newborn infants will be recruited during their mother's stay at the Liverpool Women's Hospital (LWH). Prior to discharge, research students will provide information to mothers about the study in the form of a postcard. Mothers will be asked to fill in their contact details including email and phone number indicating their interest in taking part. Completion of the postcard implies consent to be contacted. Postcards may be deposited in collection boxes at the LWH. Once the research team have received the postcards, parents will later be sent an email or letter thanking for their interest in the study. When the baby is four months old an email will be sent to the mother, which will include an option to consent to take part and a link to the initial online questionnaire. Mothers may alternatively opt to receive the questionnaires by post. The questionnaire will then be emailed or posted to mothers six monthly until their child is five years old. Demographic details will be requested on initial enrolment and confirmed or updated during the course of the study. Data will be hosted on-line by Adobe Forms Central software in an encrypted and anonymized format and stored on secure servers at the University of Liverpool.

Analysis: Demographic, exposure and LRSQ data collected by Adobe Forms Central software, which is compatible with the statistical analysis software SPSS™. Univariate and multivariate analyses using linear regression analysis will be used to compare domain scores of the LRSQ scores with exposures/variables such as prematurity, birth weight, deprivation and exposure to cigarette smoke in pregnancy and in the household. Structural equation analysis and multinomial regression analysis will also be used to assess any relationship between exposure/demographic variables and respiratory symptoms. Cronbach's alpha coefficients will be calculated to assess internal validity.

Introductions

A literature search of birth cohort studies that explore respiratory symptoms revealed 129 studies conducted between 1961 and 2011 written in the English language. Of these 129 studies 17 separate respiratory birth cohort studies were identified. Among the UK studies identified are the AVON study using the Bristol cohort, the 'Children of the 1950's and the National Child development study. International studies specifically focusing on respiratory symptoms include the Tucson Cohort and the ISAAC study. All use a respiratory questionnaire to assess respiratory symptoms, but none assessed the impact of respiratory symptoms on both preschool children and their parents. The Liverpool Symptom Questionnaire (LRSQ) is specifically designed to assess the impact of respiratory symptoms on preschool children and their parents. This study is the first proposed birth cohort study to use the LRSQ.

Over the last few decades numerous questionnaires have been designed to explore the respiratory symptoms of adults and children. Many studies have since been conducted to examine the validity of these questionnaires. Questionnaires may be delivered by an interviewer, be completed by either the patient themselves or by the parent's of the patient. Self-completion questionnaires have proven to be more economical and also help reduce observer bias when compared to interview questions [18].

A literature search was conducted using Medline. Keywords searched include 'respiratory' 'symptom' and 'questionnaire'. The results were limited to the dates 1991 to 2011. In total 775 articles were identified and reduced to 69 after reviewing titles and abstracts to determine relevance. The 69 articles related to 36 different respiratory symptom questionnaires for both children and adults and enabled identification of the most commonly used questionnaires.

Questionnaires for respiratory symptoms commonly used in adults include the St George Respiratory Questionnaire (SQRQ), the American Thoracic Society

Standardized Respiratory Questionnaire (ATSq), the Global Allergy and Asthma European Network Questionnaire (GA2LENq) and the MRC respiratory symptom questionnaire. The most commonly used questionnaires in the studies identified are the SQRQ and modified versions of the ATSq. The primary symptoms explored using the questionnaires are cough, wheeze, and breathlessness. Many studies have edited existing questionnaires to include questions on smoking, occupational hazard and various other exposure or occupational respiratory hazards. The most commonly used questionnaire's available specifically for children include the ISAAC questionnaire for ages 6 years to 13 years, and the Test for Respiratory and Asthma Control in Kids (TRACK). Both questionnaires have been validated by numerous studies. Many of the adult questionnaires explore the impact of respiratory symptoms upon the patient. The St Georges Questionnaire for adults addresses the affect of respiratory symptoms upon patient but not upon the family. The Wisconsin Upper Respiratory Symptom Survey (WURSS 44) includes questions on whether the persons cold has affected their daily activities, work inside and outside their home, interact with others and personal life [19]. The Living with Asthma Questionnaire explores the impact of asthma on the person completing the questionnaire, however this is a questionnaire designed for adults and is specific to Asthma and doesn't necessarily incorporate any other respiratory condition [20].

As discussed many adult questionnaires explore the impact of respiratory symptoms upon the patient and their lives. However, currently no preschool questionnaire for parental completion explores the impact of these respiratory symptoms on the children and their parents. There are also very few respiratory questionnaires validated specifically for the preschool age groups and the LRSQ addresses both these issues.

The Liverpool Respiratory Score Questionnaire (LRSQ) is a validated tool that explores the prevalence of respiratory symptoms in infants and preschool children. This parental completion questionnaire was first designed using established criteria, as a follow up tool for use in neonatal studies where the outcome of children two to three years of age was of interest. A unique

feature of the LRSQ is that it also explores the impact of wheeze attacks and other respiratory symptoms upon the child and their family. The LRSQ consists of nine domains. Each domain contains between three and five questions seeking responses scored on a five point Likert scale from "not at all" (score 0) to "every day" (score 4) The first six domains assess respiratory symptoms such as wheeze and cough. The next two assess the effect on the child and their family. The final section asks for details regarding medication, GP/clinic visits, hospital admissions and labels given. All domains ask parents to consider symptoms/effect over the last three months.

Birth Cohort studies are an invaluable tool for studying the epidemiology of specific populations. This study aims to map the natural history of respiratory symptoms of preschool children born in the Liverpool. It is likely to be an invaluable tool to assess the complex relationships between childhood respiratory symptoms and deprivation, premature birth, birth weight, smoking in pregnancy and smoking by household members. Liverpool is recognised as being of the most deprived cities in the England with high rates of cigarette smoking [21]. This permits for reliable studies into these effects and makes Liverpool an ideal location for a birth cohort study. The majority of births occur at one centre facilitating recruitment.

Work underpinning this study

Three studies have been conducted using the LRSQ. The first, by C V Powell et al (2002) developed and validated the standardised questionnaire [22]. After reviewing other questionnaires we find that most do not explore the impact of specific respiratory symptoms, including wheeze, on the child and their family. However, the LRSQ does this well with two of 9 domains exploring the impact of respiratory symptoms on both the child and their family. A relatively small cohort was used for initial exploration of the questionnaire, however the authors justify this as a reasonable number, as other questionnaire used similar figures. After assessing particular areas such as response rates and reliability, the authors demonstrated that it is an acceptable questionnaire, easily completed, with good response rates [22]. However they did not attempt to examine the readability in detail or looked at factors, which may affect responses [22].

The second was a cross sectional study that explores respiratory symptoms in Cystic Fibrosis [23] .This study also further validated the questionnaire's external and internal validity. The study showed that the LRSQ has good internal validity across 6/8 domains. It covered an extensive number of symptoms while also maintaining acceptability. It also demonstrated the LRSQ as a potential tool for assessing and monitoring respiratory symptoms in preschool children with cystic fibrosis.

A small, unpublished cross-sectional study has also been conducted using the Liverpool cohort, which used the LRSQ to explore respiratory symptoms in infants following exposure to RSV bronchiolitis. This study again demonstrated good internal validity using the Cronbach's coefficient but also enabled identification on small issues with the design of the questionnaire with the possibility of many improvements that may help with data collection and improve the clarity of the questionnaire.

Justification of this study
A literature search was conducted identifying birth cohort studies that feature a respiratory component. Among the UK birth cohort studies identified were the AVON study a large longitudinal birth cohort, which recruited over 14,000 pregnant mothers from the Bristol Cohort [24]. The 'Children of the 1950's' is a large study conducted on the Aberdeen cohort followed children born in the 1950's up until adult life. The British National Child Development Study (BNCDS) started in 1958 and recruited all births within one week in the UK. International studies specifically focusing on respiratory symptoms include the Tuscon Cohort and the International Study of Asthma and Allergy in Children (ISAAC) study. Both of these use a respiratory questionnaire to assess respiratory symptoms, but did not apply it in preschool children.

The LRSQ has demonstrated potential as a tool for assessing respiratory symptoms in preschool children. The validity and utility of the LRSQ have been assessed in two previous studies, demonstrating it to be a useful tool for assessing respiratory symptoms in preschool children however further

validation is required, using a larger cohort of patients. Many large birth cohort studies have been conducted in the UK and Internationally.

This is the first proposed prospective birth cohort study to use the Liverpool Respiratory Symptom Questionnaire. This study will enable a large range of information regarding respiratory symptoms of preschool children and other risk factors predisposing children to respiratory and related disease. It enables numerous future studies to be conducted using the data collected. It allows exploration of respiratory symptoms in relation to demographic details and details of exposure to risk factors which is particularly of interest in Liverpool, as it is considered to be one of the most socially deprived cities in the United Kingdom[21].

Research Method

Study design

This is a longitudinal birth cohort study using the parent completed Liverpool Respiratory Symptom Questionnaire (LRSQ) to assess preschool children's respiratory symptoms from birth up until the age of five years old. This study will also provide the opportunity for additional cross-sectional studies to be conducted on the patient group recruited and the results gathered. It is important to note that there will be no specific interventions made by the study.

Setting: Children normally resident in Liverpool postcodes L1-38.

Recruitment

We propose a maximum recruitment strategy and aim to recruit as many infants born at the Liverpool Women's Hospital as possible from January 2013. Recruitment will be limited only to parents domiciled within the Liverpool postcodes L1-38.

Newborn infants will be recruited during their mothers stay prior to discharge from the Liverpool Women's Hospital. Research students will personally provide information to mothers about the study verbally and in the form of a postcard while the mothers are at the Liverpool Women's Hospital. Mothers will be asked to fill in their contact details including email and phone number indicating their interest in taking part. Completion of the postcard implies consent to be contacted. Mother's hospital stickers will also be attached to the postcard. In addition, the postcard will also include a QR(2D) bar code which mothers may scan using their smart phones. This QR code will direct participants immediately to an online version sign up version of the postcard.

Once completed, research students will collect the postcards. Alternatively mothers, midwives or volunteers at the Liverpool Women's Hospital may deposit the postcards in a collection box. Once the research team have received the postcards contact details will be uploaded to the database sorted on the University of Liverpool's secure server. Within a week, parents will be sent an email thanking for their interest in the study. The next point of contact will be when the baby is four months old. An email will be sent to the mother, which will include a link to the initial online questionnaire. This email will include; information about the study, consent, questions regarding demographic and exposure details and the LRSQ in a series of separate but easily understandable pages. Mothers may alternatively opt to receive the postal questionnaires, which will be first sent within a week of the baby being four months old.

Recruitment material will make no therapeutic promises, as this is only a descriptive study. The inclusion and exclusion criterion ensures that no one is unfairly excluded from the study. All data collected will be automatically deposited on a password database on a secure server in the University of Liverpool. Where parents have indicated that they would prefer hard copy (paper) correspondence, this will be sent with a stamped address envelope for return. The research student will enter this data by hand. Data will be imported into an SPSS database on a case-by-case basis.

Follow Up

Consent will be obtained when the initial questionnaire is sent, four months after birth. Following that, a second email will be sent six months later and every six months thereafter until the child is five years old. This repeat mailing questionnaire will provide an option for participants to update any contact details and will include demographic and exposure questions and the LRSQ questions.

In addition, on the date of their child's birthday, mothers will receive a personalised email thanking them for taking part in the study and wishing their child a happy birthday. In the case of no reply, two reminder emails will be sent and if no response this will be followed by one contact by telephone and one postal contact as email addresses and telephone numbers may have changed over time. Each contact attempt will be two weeks after previous attempts. For mothers without email addresses or access to computers, reminders will be made by telephone and mailed by post.

With each email sent, mothers will be given an option to sign up to updates regarding recruitment and reports on any preliminarily findings. Families who move out of the area will be asked to continue their involvement. Contact will continue by email and telephone. The questionnaire will include an option to update place of residence among other details.

Data Collection

Data will be linked from the on-line Adobe Forms Central Survey software into a SPSS database on a case-by-case basis throughout the duration of the study. The data collected from postal questionnaires will be inputted into the online survey manually by and subsequently inputted into the database by the research student.

Inclusion criteria

All infants born at the Liverpool Women's hospital, including premature births, where parents are normally resident in Liverpool postcodes (L1-38) regardless of future residence.

Exclusion criteria

Neonates born to parents normally resident outside the Liverpool postcodes L1-38.

Babies born to non-English speaking parents.

Variables and Outcomes Measures

Aim

To establish a population based longitudinal birth cohort study conducting a bi-annual assessment of respiratory symptoms of preschool children using the LRSQ from birth to the age of five in Liverpool.

Primary objective: To describe parent reported respiratory symptoms in a population based birth cohort followed longitudinally form birth to five years old using the LRSQ.

Secondary objectives: To examine any association between differences in respiratory symptoms in groups of preschool children with different social and environmental risk and protective factors.

Bias

To minimise withdrawals from the study patients will be given three reminders, two via email and one by telephone contact after initial email of the questionnaire.

Recall bias is not considered to be a problem, as the questionnaire requires parents to report respiratory symptoms in the last three months and this recall period has been validated for this questionnaire

In the three previous studies parents have not fully completed the questionnaire, which may introduce reporting bias. Using the online questionnaire may help, as software prompts parents to complete all questions and can give options for null responses rather than leaving 'blanks' on paper.

Demographics and Exposure Variables

2.1.2 Box 1. Demographics	2.1.1 Box 2. Exposure variables
• Sex of child • Age of child • Date of Birth • Postcode • Ethnicity of child • Gestation at birth • Birth Weight (kg or lb/oz) • Mother's highest qualification • Breastfeeding duration (weeks/months)	• Nursery Attendance • Persons sharing the child's bedroom • Number of siblings living in a household • Maternal smoking during pregnancy (any) • Smoking by any household member in the last 3 months regardless of location • Chronic co-morbidities • Family history of atopy

Proposed Study Size

We plan a maximum recruitment strategy from the Liverpool Women's Hospital where there are approximately 8,000 births each year. We estimate that approximately one in four mothers will complete the postcard provided. The questionnaire currently has a 13% return rate therefore we expect approximately 260 patients to participate in the study each year. Comparison of demographic data for those participating with census data will allow a check for recruitment bias.

Statistical Methods

The results from questionnaires on Adobe Forms Central will be uploaded to SPSS and analysed using the SPSS Statistical software. Rolling cumulative data analysis will be performed for the duration of five years.

Univariate and multivariate analyses using linear regression analysis will be used to compare domain scores of the LRSQ scores with exposures such as maternal smoking etc. Fishers exact test will be used to determine whether there is any relation between two categorical variables. Structural equation analysis and multinomial regression analysis will also be used to assess any relationship between exposure/demographic variables and respiratory symptoms. Cronbach's alpha coefficients will be calculated to re-assess internal validity. In this study missing data is most likely to result from failure to respond.

Data Sources: Patient Demographic Service
Data will also be collected from linked hospital episode data.

Data management
Data will be collected from questionnaire answers via the Adobe Forms Central Software and linked directly to the programme SPSS for analysis.

Consent
Mothers providing their contact details on the study information postcard implies consent to be contacted. The consent of mothers of patients will be sought when the first questionnaire is emailed or posted to participants. Mothers who are willing to participate will click on the embedded link to the questionnaire will be directed to a screen detailing more information about the study. After reading this they will be given the option to either not to participate and unsubscribe to emails, to contact the research team with any queries or to consent by clicking a button online and inserting their initials. After consenting to take part, mothers will be directed to the questionnaire. Mothers who opted for the postal questionnaire will be asked to complete a consent form alongside the initial questionnaire.

Patients and parents of patients at participating practices have the opportunity to opt out of the scheme at registration and any point thereafter by either contacting the research team or clicking a button on the email sent containing the LRSQ. [In studies involving postal questionnaires where the burdens are

insignificant and sensitive topics are not involved, the REC will normal regard the return of the questionnaire as adequate evidence of consent (IRAS guidance 2012)].

Ethical Issues
This study received REC ethical approval by proportionate review on 08/05/2012.
REC Reference: 12/EM/0194

This study also received REC approval of minor amendments on the 08/11/2012.
This allowed use of the QR barcode on the postcard for recruitment ant the use of a poster with the QR code for recruitment and advertisement of the study at the Liverpool Women's Hospital.

No physical intervention will take place. The LRSQ database will include a study ID but not direct identifiers. The study ID and contact details will be kept in an encrypted data file in a secure server hosted by the University of Liverpool. The survey has only been validated in an English Language format. There is no capacity in this student project to develop and validate the LRSQ in other languages.

Risks to Patient
There are few anticipated risks for research participants in this study. Possible risks include a breach in confidentiality with regards to contact details of patients and any personal data. Precautions will be taken to minimize the risk of this data will be stored very carefully. No identifiable data will be included in publications. Security data measures that will be taken include encrypting data with passwords, coding medical conditions and limiting access to study data.

An additional foreseeable risk identified is the risk of sending emails and questionnaires to parents of deceased children. Measures that could be taken

include linking to the National mortality database via the Patient Demographic Service. The Alder Hey Children's NHS Foundation Trust's IT department will perform weekly batch searches linking to SPINE via the Patient Demographic Service. This, however, is not a foolproof method as there will be delays between the PDS being notified by the community and by Alder Hey Children's Hospital.

Benefits to patients

There are no direct benefits to research participants taking part in this study. However there we hope that this study will benefit future preschool children by enabling us to identify risk factors associated with particular respiratory symptoms.

Risks / benefits to study

If too few participants are recruited this would compromise the results of the study. There is also the risk of loosing patients to long-term follow-up. If patients are lost the data will still be included in the results.

Research governance

The University of Liverpool will be lead sponsor and the Liverpool Women's NHS Foundation Trust will co-sponsor for the study.

The proposed study will be undertaken in accordance with the University of Liverpool's research governance procedures.

Dr MG Semple (Liverpool University), Professor Ben Shaw (Liverpool Women's) will be a joint guarantor for analysis and reports.

The Research Team

Miss Rosanna Pickles

Miss Bethan Griffiths

Dr MG Semple (Chief Investigator)

Professor Ben Shaw

Dr Kevin Southern

Dr Paul McNamara

Liverpool Baby Breathing Study
Liverpool Respiratory Birth Cohort Study

↓

Newborn babies living at postcodes L1-38 born at the Liverpool Women's Hospital (LWH) from **January 2013**

↓

Study information postcards (which include a sign off QR code) are given to mothers before being discharge from the LWH

↓

Postcards collected by research student or deposited in collection box at the LWH

Mothers sign up electronically via QR bar code on study poster or postcard

↓

Contact details added manually to database

Contact details added automatically to database

↓

Babies born **outside postcodes L1-38** excluded

↓

When baby is four months old
Mothers are emailed/posted the initial online/postal questionnaire
- *this includes consenting to taking part in the study*
-*should take no longer than 10 minutes to complete*

↓

Six months later
Mothers emailed/posted the repeat online/postal questionnaire
-*should take no longer than 5 minutes to complete*

↓

Every six months – until five years of age
Mothers emailed the brief online/postal questionnaire
- *participants are able to withdraw at any time.*

↓

Data exported on a case-by-case basis into an SPSS database

Timetable and Milestones

Phase One – completion of protocol and application to IRAS for ethical approval by May 2012

Phase Two – Development of the online questionnaire and consent form. Prior to the start of the study mothers will be interviewed regarding questionnaire aesthetics. Once the questionnaire design has been finalised the questionnaire will then be trialed at the Liverpool Women's hospital. Mothers will be interviewed while they are completing the questionnaire about the design, layout, format and content of questions; ease of used and asked to score the questionnaire out of ten. Mothers will also be asked a about anything that would motivation them to participate in the study, and encourage continued participation.

Phase Three – Recruitment of mothers and implementation of the study will begin on the 7th January 2013 and continue for a maximum of five years depending on the success of the study. The study will continue for a further five years after recruitment is complete.

Expertise

- Dr MG (Calum) Semple is a Senior Lecturer in Child Health at the University of Liverpool and Consultant in Paediatric Respiratory Medicine at Alder Hey Children's Hospital.
- Professor B Shaw, Consultant in Neonatal and Respiratory paediatrics at Liverpool Women's Hospital and the Royal Liverpool Children's Hospital.
- Dr Paul McNamara, Senior Lecturer in Child Health at the University of Liverpool and Consultant in Paediatric Respiratory Medicine at Alder Hey Children's Hospital
- Dr K Southern Reader in Paediatric Respiratory Medicine at the University of Liverpool and Consultant in Paediatric Respiratory Medicine at Alder Hey Children's Hospita

Service Use Input

Mothers of the participants will be involved in the development of the study, particularly with the development of the postcard information card and also the design, content and format of the online questionnaire. Research students will interview mothers at the Liverpool Women's Hospital about the aesthetics and format of the questionnaire and postcard. Finalised versions of the questionnaire will be piloted at the Liverpool Women's Hospital. Mothers will be interviewed while completing the online questionnaire. Interview questions will be standardised and prepared prior to seeing the parent. They will be asked to feedback on matters such as appearance and format, ease of completion, and clarity and content of the information and questions.

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Appendix 7- Results of PPI Sessions for Questionnaire and Study Development Performed by Previous MPhil Students

Rossana Pickles and Bethan Griffith developed the questionnaires through the use of PPI sessions based at the LWH. Eligibility criteria for the PPI sessions were;

- Inpatients at the LWH
- Home address in postcodes L1-L38,
- Spoke sufficient English to participate.

The properties of the questionnaire that were discussed are discussed below. The prototype questionnaires used in the PPI sessions are shown in the appendix.

Mode of Completion

65% (n=13) mothers said they would complete the online questionnaire on a laptop or personal computer. The remaining mothers said they would complete the questionnaire using another online device. No mothers in the PPI sessions were interested in receiving the questionnaire by post. Mothers made comments on the questionnaire being available in more than one format.

Question Density

Of the three questionnaire density options (see appendix) the majority of participants (n=13) opted for the 'medium density' questionnaire. There was an even split between the high density and low density questionnaires (n=3) (2, 3).

Background

35% (n=7) participants had a preference for a plain background and non-coloured text, 30% (n=6) opted for a plain background with subtly coloured text, 25% preferred a subtly coloured background. 5% (n=1) preferred lots of colour and 5% (n=1) had no preference (2, 3).

Themes, Images and Logos

Of the three theme options (see appendix) 65% (n=13) opted for the theme which was a strip of children holding hands. 20% (n=4) of the participants would prefer images to be kept to a minimum. Mothers said that the images should only be used if relevant to the study and overall the questionnaire should look professional (2, 3).

'Arial' was chosen due to its wide availably in software packages. 75% (n=15) of the participants opted for the medium sized font (size 16) (2, 3).

Other Comments

Participants said that it was vital to ensure there was enough information about the study available. The questionnaire should be kept 'short and sweet' and 'response options kept minimal'. Small incentives would make participants more likely to complete the questionnaire (3).

Questionnaire Content

The cohort demographics and infant exposures that would be assessed in the LBBS were decided after discussions with respiratory experts Dr Calum Semple (Alder Hey Children's Hospital) and Professor Ben Shaw (LWH). These are shown in figure 1. Each questionnaire included sections for demographics, risk factors, the LRSQ and health care service attendance (2).

The PPI sessions have let the research team design a questionnaire that is tailored to both the research team and the participants needs.

Infant gender,

Postcode/Index of Multiple Deprivations

Ethnicity,

Gestational age,

Birth weight,

Mother's highest qualification,

Breastfeeding (duration),

Nursery attendance,

Sharing a bedroom,

Number of household siblings,

Maternal smoking during pregnancy,

ETS exposure (before and after birth),

Co-Morbidities

FH of atopy

Figure 11: Demographics and Exposures assessed in the LBBS

An example of the final questionnaire is shown in the appendix. It was available for completion online and in a paper version sent via post. There is a medium question density on each page of the questionnaire. The theme used was a strip of children holding hands, with a plain background with subtly coloured text. Images used are only relevant to the study and are proprietary artwork of the study team. A medium font size was used.

With the exception of questionnaire 1, no patient identifiers were stored on the questionnaire platform severs. Questionnaires were linked to participants using a unique identification code which was embedded in emails sent to the participants. This minimised the patient information stored outside the University of Liverpool computer system. This

unique identification code was required to complete the questionnaires and minimised the personal information that was stored on the online questionnaire platform. All exports from the questionnaire platforms were stored on encrypted, password protected files on the University of Liverpool server.

Recruitment Material

The study name was changed from 'The Liverpool Respiratory Birth Cohort' to the "Liverpool Baby Breathing Study" (LBBS) as the research team decided it would be more attractive and understandable to parents. Posters advertising the study, containing a digital quick response code (figure 2), were put in the LWH. Participants who said they would like to join the study during recruitment were given a postcard to complete with their contact details, which was to be posted into a post-box by the entrance to

Figure 12: Quick Response code used for sign up to the LBBS

the wards. The posters and postcards had the same theme as the questionnaire and emails to give the study a professional and recognisable look. The poster and postcard design are shown in the appendix.

A fourweek pilot study for the recruitment of infants into the LBBS was performed by Rosanna Pickles and Bethan Griffith to determine the most optimal yet feasible recruitment strategy. Four different recruitment strategies were each trialled for a one week period. Recruitment strategies and their recruitment rates are shown in table 6.

Table 32: Recruitment rates during recruitment pilot study

Strategy	Days	Recruitment Rate
5 Full Days	Monday- Friday	58%
5 Mornings	Monday- Friday	65%
4 Alternate Days	Monday, Wednesday, Friday, Sunday	61%
7 Full Days	Monday- Sunday	78%

Recruitment took place on the post-natal wards and the neonatal unit at LWH. Researchers aimed to recruit all the eligible births when on the wards. Children diagnosed with CF were also invited to join the study during their initial consultation with a respiratory consultant.

The pilot study recruited 334 interested mothers from 605 births in the LWH; 332 from post-natal wards and two from CF clinics. 67 mothers were not from eligible postcodes, 119 births were missed due to the research team not being present on the wards, 36 were not approached, 24 were non-English speaking, four were not suitable for recruitment as identified by the clinical team and 21 mothers declined (2, 3).

Appendix 9- Development of the Online Questionnaire Distribution Method

Questionnaire Platform

Online survey software's were appraised for the features and services they offer. A shortlist of four software packages was produced by the research team; 1.SelectSurvey.NET (SSN) (ClassApps LLC, Kansas City, Missouri, USA) 2.Google Docs (Google Inc. California, USA), 3.Adobe FormsCentral® (AFC®) (Adobe Systems Inc. California, USA) .and 4.SurveyMonkey® (SurveyMonkey Inc. California, USA) (2, 3). The comparison of the software's is shown in the appendix.

The research team decided to opt for AFC® for the questionnaire platform; it provided a better software for the both research team and the participants, allowing the creating of a questionnaire that was outlined acceptable by the PPI sessions. AFC® was appraised against SSN in a feasibility study. AFC® scored better for first impressions and after questionnaire completion. 10 out for 16 mothers preferred the AFC® questionnaire overall (2, 3). In June 2015 AFC® was suspended to allow development as a future premium product with charges. This forced the study team to change to use JotForm® (JotForm Inc. San Francisco, USA) for questionnaire completion and response storage. It allowed the research team to reproduce the questionnaires from AFC®, whilst giving the same benefits and security as AFC® with enhanced form analysis which would help the research team resolve any issues with submissions. The properties of both AFC® and JotForm® are shown in the table7. The new questionnaires and the fully online recruitment linked to the automated questionnaire delivery system was developed by Sanjay Patel.

Table 33: Properties of AFC ® and JotForm®

Property	AFC®	JotForm®
Cost	£105.39/year	$90/year (~£70/year)
Usability	Excellent	Excellent
Skip Logic	Question and Page	Question and Page
Help Text	Yes	Yes
Logos and Themes	Unlimited	Unlimited
Field Validation	Yes	Yes
Security	SSL Encryption Security	SSL Encryption Security on Secure German Server

Data Export	SPSS & Excel Data Export	SPSS & Excel Data Export
Analysis tools	Data Summaries	Form Analysis
Support	Telephone and Email Support	Email support and User Forums

Email Platform

Factors that were considered when choosing a mailing platform for the distribution of online questionnaires were cost, deliverability, functionality, usability, security and the ability to personalise emails. The research team decided that MailChimp® (The Rocket Science Group, Atlanta, USA) would be the best platform for the distribution of emails to the cohort. MailChimp® provided a secure online server with two-tiered security and a fully automated system which precisely scheduled emails based on the participant's date of birth with minimal user input. MailChimp® tracked if emails are opened and if links within emails have been clicked; this is a benefit of the study as it will allow any issues or excessive drop out to be dealt with in sufficient time. It allows users to remove themselves from mailing lists which was important for autonomy. Participants could self-enrol into the study using a quick response code on the study advertising posters without the need of the research team. Emails could be branded with the same theme of the questionnaires, allowing all study materials to be identical.

Mode of Completion

What would be the most convenient way for you to complete a questionnaire?

Laptop or PC

Tablet

Smart Phone

Aids Visualisation

To which (if any) of these devices do you have access?

Evaluates Accessibility

Density

1

2

3

High- Represented by many questions per page

Medium-4-6 similar questions grouped together

LOW-encourages careful consideration

Background Colour

1

2a

2b

3

No colour

Mainly Colour

Some Colour

Coloured Font

Images and Themes

1

2

3

3

Subtle Image

Themed Images and Fonts

Theme in Font alone

Dominant imagery

Font Size

1

2

3

Medium

Small

Large

The Liverpool Baby Breathing Study

Dear Parent/Guardian,

Many congratulations on the birth of your new baby!

During your stay at Liverpool Women's Hospital, you spoke to a member of our research team and agreed to be contacted for our study. We understand that this has been a very busy time for you, so we really appreciate that you took the time to speak to us.

As you may recall, The Liverpool Baby Breathing study is a study that explores breathing symtpoms, such as coughs, colds and wheezing in babies and young children. The aim of our study is to understand how these symptoms change over time, and how they affect you an your family. You can read a little more about the study on the first page of the enclosed questionnaire, under the "Further Information" heading.

If you are still happy to take part in the Liverpool Baby Breathing Study, please let us know by completing the attached consent form, and the first questionnaire (it only takes 5-10 minutes of your time!). We have enclosed a stamped envelope so you can return the questionnaire to us at your earliest convenience.

If you provided an email address when you registered your interest in the study, you may have received a link to an online version of the questionnaire. Don't worry, you don't have to fill it in twice – simply complete the online *or* paper version!

If you have any questions or concerns about the study, or are having problems completing the questionnaire, or would no longer like to participate in the study, please contact the research team directly and we will be happy to help!

We look forward to hearing your responses!

Best Wishes

The Research Team
Miss Rosanna Pickles
Miss Bethan Griffith
Dr Kevin Southern
Professor Ben Shaw
Dr Calum Semple

Email: babystudy@liverpool.ac.uk
Telephone: 01512824532
Post MG Semple, Institute of Child Health, University of Liverpool, Alder Hey Children's Hospital NHS, Eaton Road, Liverpool, L12 2AP

Consent Form

Title of Project: Liverpool Baby Breathing Study (The Liverpool Respiratory Birth Cohort Study)

Name of Researchers:

Miss Rosanna Pickles, Miss Bethan Griffith, Dr Calum Semple, Dr Kevin Southern and Professor Ben Shaw

Please tick box

1. I confirm that I have read and understand the further information section dated 01/05/2013 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that our family and child's participation in the study is entirely voluntary and that we have the right to withdraw at any time without stating a reason and without affecting my care and my family's care in any way.

3. I understand that the data collected by this study will be looked at by members of the research team named above and may be scrutinised by regulatory authorities or by the host NHS Trusts.

4. I have read and understand the above consent form, I certify that I am the parent/guardian of the child recruited.

5. I give permission for our family and my child to be involved in the above study.

Child's Forename (first/given name): _____ Surname: _____

Your Child's Date of birth: Day: _____ Month: _____ Year : _____

Mother's Forename (first/given name): _____ Surname: _____

Mothers Signature for Consent: _____

Today's Date: Day: _____ Month: _____ Year : _____

Liverpool Baby Breathing Study

Questionnaire 1

The following questionnaire asks questions about your baby and what has been happening to him or her over the last three months. It should take **no longer than 10 minutes to complete.** All future questionnaires should take no more than 5 minutes to complete.

This study aims to find out more about the respiratory symptoms, such as wheezing, coughs and colds, that your child experiences, and how they affect you and your family.

Our study will help us understand what makes these symptoms more or less likely to occur and how they change over time.

It is important that every question is answered, even if your child has been perfectly well, with no problems at all.

Thank you.

Further Information
01.05.2013

Why have I been chosen?
We are asking all parents of children born at the Liverpool Women's Hospital who were living within the L1-38 post codes when their child was born to take part. We are particularly interested in the children of Liverpool as there are high levels of respiratory diseases such as asthma and bronchiolitis.

Do I have to take part?
No - it is up to you whether you decide to take part or not. You are free to withdraw at any time, without giving a reason. You and your child's future clinical care will not be affected if you do not wish to take part.

What will it involve (before/during/after?)
-We ask you to complete a questionnaire about your child. We will email you a link to the questionnaire just twice a year for five years.
-This questionnaire should take no longer than 10 minutes to complete.
-We will be asking you a few questions about your family circumstances, and your child's respiratory symptoms.
-You can choose to receive updates on how the study is running by email. At the end of the study, we will send you a summary of the results for the whole study.

Are there disadvantages of taking part?
We are not aware of any disadvantages to you or your child. All information will be treated with the strictest confidence.

Are there any advantages for taking part?
Being involved in the study will not benefit your child directly. We hope to help other children in the future by identifying what helps or worsens respiratory symptoms.

If you you have any further questions, please contact the research team directly:

Email: BabyStudy@liverpool.ac.uk
Telephone: (0151) 282 4532

Please let us know if you would not like to receive any further contact from us, or if you want to go green and start receiving your questionnaires by email!

About Your Pregnancy, Birth and New Baby
You will only need to give us these details once

1. What is your <u>new baby</u>'s first name?

[   ]

2. What is your <u>new baby</u>'s last name?

[   ]

3. Is your new baby:

○ Male   ○ Female

4. What is your new baby's date of birth?

[   ]

5. What best describes your new baby's ethnic group or background?

○ I would prefer not to say
○ White - British
○ White - Any other white background
○ Mixed or multiple ethnic groups
○ African, Caribbean or any other black ethnic group
○ Asian - Indian, Pakistani or Bangladeshi or any other ethnic group
○ Eastern Asian- Chinese or any other ethnic group
○ Other - Please Specify [   ]

6. How many <u>weeks</u> pregnant were you when you gave birth? e.g. if you gave birth at 36 weeks 5 days , please write "36"

[   ]

7. How much did your baby weigh at birth?

[   ]

8. Did **you** smoke at *any time* during your pregnancy?

○ Yes   ○ No

9. Did **any member** of your household smoke, *anywhere* or at *any time* <u>during your pregnancy</u>?
A household member means someone who sleeps or regularly takes meals at your house.

○ Yes   ○ No

Where did these people smoke?
Tick all that apply

☐ Inside the home
☐ Outside the home
☐ Inside the car
☐ Inside at another location eg. work/social
☐ Other [   ]

10. Did you breast feed your new baby at any time? *This includes expressed breast milk or bottle feeding at the same time*

○ Yes   ○ No

If yes, how long did you breast feed for?

○ Less than 1 month   ○ 1-3 months   ○ I am still breast feeding

About You and Your Household
Your information will be stored securely and will not be shared

11. Which of these qualifications do you have?

○ No qualifications
○ Completed secondary school
○ GCSE/O-Level
○ Vocational Training/ Apprenticeship
○ Diploma eg. BTEC, GNVQ
○ A Levels/Scottish Highers
○ Undergraduate Degree
○ Postgraduate Degree
○ Other (please specify) [   ]

12. Have you, your baby's father, or any of your baby's brothers or sisters ever been told by a doctor that they, or you, have of asthma, hay fever or eczema?

○ Yes   ○ No

If you answered yes to the question above, who has Asthma, Hay Fever or Eczema?

	Asthma	Hay Fever	Eczema
Me (My baby's mother)	○	○	○
My baby's father	○	○	○
My eldest child	○	○	○
My second eldest child	○	○	○
My third eldest child	○	○	○
My fourth eldest child	○	○	○

13. Does **any member** in your household smoke, anywhere?
A household member means someone who sleeps or regularly takes meals at your house. Please tick yes, even if they smoke outside

○ Yes   ○ No

If yes, where do these people smoke?
Tick all that apply

☐ Inside the home
☐ Outside the home
☐ Inside the car
☐ Inside at another location eg. work/social
☐ Other [   ]

14. Does your baby attend nursery/crèche?

○ Yes   ○ No

About Your New Baby

15. Do you have any other children who live with you?

○ Yes   ○ No

If yes, how many other children live with you?

☐ 1   ☐ 2   ☐ 3   ☐ 4   ☐ 5   ☐ 6   ☐ 7 or more

16. Does your baby share a bedroom with yourself or anybody else?

○ Yes   ○ No

If yes, who does your baby share a bedroom with?
Please tick all that apply

☐ Parent or parents   ☐ One other child   ☐ Two or more children
☐ Other [   ]

17. Has your new baby ever seen your GP because of his/her chest?

○ Yes   ○ No

If yes, how many times has your baby seen your GP because of his/her chest?

☐ Once   ☐ Twice   ☐ Three times   ☐ Four times   ☐ Five times
☐ More than 5 times

18. Has your new baby ever been to hospital because of his/her chest?

○ Yes   ○ No

If yes, how many times has your baby been to hospital because of his/her chest?

○ Once   ○ Twice   ○ Three times   ○ Four times   ○ Five times
○ More than 5 times

19. Does your new baby have any long term health conditions?

○ Yes   ○ No

What kind of long term health condition does your new baby have?

☐ Long term chest (respiratory) disease?
☐ Long term heart disease?
☐ Long term kidney disease?
☐ Long term neurological disease?
☐ Diabetes?
☐ Other [   ]

Please tell us more about the long term health condition(s) your new baby has:

[   ]

Your New Baby's Health

During the DAY(when awake) in the last three months::

20. My new baby has been wheezing (*whistling noise coming from the chest*)

○ Not at all　　○ A few days　　○ Some days　　○ Most days　　○ Every day

21. My new baby has had a cough

○ Not at all　　○ A few days　　○ Some days　　○ Most days　　○ Every day

22. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration, when placing your hands over your baby's chest*)

○ Not at all　　○ A few days　　○ Some days　　○ Most days　　○ Every day

23. My new baby has been short of breath

○ Not at all　　○ A few days　　○ Some days　　○ Most days　　○ Every day

During the NIGHT (when asleep) in the last three months:

24. My new baby has been wheezing (*whistling noise coming from the chest*)

○ Not at all　　○ A few nights　　○ Some nights　　○ Most nights　　○ Every night

25. My new baby has had a cough

○ Not at all　　○ A few nights　　○ Some nights　　○ Most nights　　○ Every night

26. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration when placing your hands over your child's chest*)

○ Not at all　　○ A few nights　　○ Some nights　　○ Most nights　　○ Every night

27. My new baby has been short of breath

○ Not at all　　○ A few nights　　○ Most nights　　○ Some nights　　○ Every night

28. My new baby has snored:

○ Not at all　　○ A few nights　　○ Most nights　　○ Some nights　　○ Every night

Your New Baby's Health

29. How many colds *(runny nose, and high temperature)* has your new baby had in the last three months?

○ 0   ○ 1   ○ 2   ○ 3   ○ 4   ○ More than 4

When my new baby has HAD A COLD in the last three months:

30. My new baby has been wheezing *(whistling noise coming from the chest)*

○ Not at all with colds   ○ A few days   ○ Some days   ○ Most days
○ Every day

31. My new baby has had a cough

○ Not at all with colds   ○ A few days   ○ Some days   ○ Most days
○ Every day

32. My new baby has had a rattly chest *(noise that you can hear and feel as a vibration when placing your hands over your child's chest)*

○ Not at all with colds   ○ A few days   ○ Some days   ○ Most days
○ Every day

33. My new baby has been short of breath

○ Not at all with colds   ○ A few days   ○ Some days   ○ Most days
○ Every day

When my new baby has NOT HAD A COLD in the last three months:

34. My new baby has been wheezing *(whistling noise coming from the chest)*

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

35. My new baby has had a cough

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

36. My new baby has had a rattly chest *(noise that you can hear and feel as a vibration when placing your hands over your child's chest)*

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

37. My new baby has been short of breath

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

Your New Baby's Health

When my new baby has been more active (e.g. crawling, walking or when excited) in the last three months:

38. My new baby has been wheezing (*whistling noise coming from the chest*)

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

39. My new baby has had a cough

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

40. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration when placing your hands over your child's chest*)

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

41. My new baby has been short of breath

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

---

Other problems my new baby may have had in the last three months:

42. My new baby has had noisy breathing that does not seem to come from the chest:

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

43. My new baby has had fast breathing:

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

44. My new baby has had noisy breathing that appears to come from the throat or back of the throat:

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

Your New Baby's Health

How my new baby's chest symptoms actually affected him or her over the last three months:

45. My new baby's chest symptoms have affected his or her feeding or eating

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

46. My new baby's chest symptoms have woken up my new baby:

○ Not at all   ○ A few nights   ○ Some nights   ○ Most nights   ○ Every night

47. My new baby's chest symptoms have reduced my new baby's activity:

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

48. My new baby's chest symptoms have made my new baby unusually tired:

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

---

How my new baby's chest symptoms have affected *me and my family* in the last three months:

49. My new baby's chest symptoms have limited MY activities:

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

50. My new baby's symptoms have resulted in adjustments being made to our family life:

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

51. My new baby's chest symptoms have disturbed our sleep:

○ Not at all   ○ A few nights   ○ Some nights   ○ Most nights   ○ Every night

52. I have been worried about my new baby's chest symptoms:

○ Not at all   ○ A few days   ○ Some days   ○ Most days   ○ Every day

Your Details

Your data will be stored securely and will not be shared

You will only need to give us these details once!

53. What is **your** first name?

54. What is **your** last name?

55. What is your new baby's **father's** first name? *(optional)*

56. What is your new baby's **father's** last name? *(optional)*

57. What is your full address

58. What is your **postcode**?

59. What is your **main** telephone number?

60. What is your **main** e-mail address?

☐ I would like to receive my future questionnaires online

☐ I want to sign up to the Liverpool Baby Study newsletter to receive updates from the study

The Liverpool Respiratory Birth Cohort Study
Thank You For Your Participation!

All the information you give us is invaluable to the research team and future children in Liverpool, even if your baby hasn't had any symptoms at all! We will be in touch with you again in around 6 months time.

If you have any questions or would like to discuss the study with the research team, please don't hesitate to contact the research team at babystudy@liverpool.ac.uk or call us on 0151 282 4532

MG Semple
Institute of Child Health,
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Eaton Road,
Liverpool,
Merseyside
L12 2AP

Appendix 12- Poster used in the LBBS

UNIVERSITY OF LIVERPOOL

Liverpool Women's
NHS Foundation Trust
Dedicated to you

You are invited to participate in...

The Liverpool Baby Breathing Study
The Liverpool Respiratory Birth Cohort Study

Have you recently had a baby here at Liverpool Women's?
Do you live in a Liverpool post code (L1-L38)?

The Liverpool Baby Breathing Study...
will study the respiratory symptoms (colds, coughs, wheezing and breathing problems) of children born in Liverpool from birth to the age of five years.

Interested?
Ask for one of the sign-up **postcards** that are available on Jeffcoate ward, Matbase or the Neonatal unit.

OR

Scan this QR code using the instructions below and sign up using our online form!

Step 1 - Go to your app store on your smartphone and search for a "QR" or "Scanner".

Step 2 - Download the highest rated free QR scanner

Step 3 - Once downloaded, OPEN the app and follow the instructions. You will need to aim your camera at the QR code and scan/photograph the QR code

Step 4 - You'll be taken to the sign up form for the study- enter your details here to take part!!

Sign-up QR code

What will it involve?
A short online or postal questionnaire, twice a year, for five years

Why are we doing this?
We want to find out more about the respiratory symptoms that your child experiences and their affect on your family, how these symptoms change over time and what makes them more or less likely to occur.

Questions?
If you would like further information, please email the research team at
BabyStudy@liverpool.ac.uk or call (0151) 282 4532

Appendix 13- Postcard Used in the LBBS

UNIVERSITY OF LIVERPOOL

Thank you for your interest in the....
Liverpool Baby Breathing Study
The Liverpool Respiratory Birth Cohort Study

Liverpool Women's NHS Foundation Trust
Dedicated to you

The Liverpool Baby Breathing Study will study the respiratory symptoms (colds, coughs, wheezing and breathing problems) of children born in Liverpool from when they are born until they are five years old.

Why are we doing this?
We want to find out more about the respiratory symptoms, such as wheezing and coughing that your child experiences and their effect on your family. The aim of our study is to try to understand how these symptoms change over time and what makes them more or less likely to occur.

Why have I been chosen?
We are asking all parents of children born at the Liverpool Women's Hospital who are living within the **L1-L38 postcodes only,** if they would like to take part. We are particularly interested in the children of Liverpool as there are high levels of respiratory diseases such as asthma and bronchiolitis.

If you agree to take part:
• We will send you a questionnaire online or by post twice a year, for five years
• The first questionnaire should take less than 10 minutes to complete
• Each follow-up questionnaire should take less than 5 minutes to complete
• Your decision to participate will not affect you or your child's future care in any way
• All responses and personal details will be handled in the strictest confidence
• You may choose to leave the study at any time

UNIVERSITY OF LIVERPOOL

Thank you for your interest in the....
Liverpool Baby Breathing Study
The Liverpool Respiratory Birth Cohort Study

Liverpool Women's NHS Foundation Trust
Dedicated to you

To register your interest in the **Liverpool Baby Breathing Study** simply fill in your details below, and give this card to a member of staff, or pop it in the collection box. Alternatively, you can enter your details online by scanning the QR code.

Baby's First Name: _____ Last Name: _____

Baby's Date of Birth: _____ Singleton: ☐ Twin: ☐ Triplet: ☐

Mother's First Name: _____ Last Name: _____

Email: _____ Postcode: L_____

Main telephone number: _____ Please contact me by: email ☐ post ☐

By providing these details I agree to be contacted by the Research team.
Don't worry, you are not committing yourself to join the study at this stage!
We will contact you in four months time to confirm that you are still interested!
If you would like any further information, you can contact the research team directly by emailing BabyStudy@liv.ac.uk or calling (0151) 2824532.

Affix Hospital Label Here

Please scan this code using your QR reader

Appendix 14- Comparison of Questionnaire Online Platforms

	SelectSurvey.NET	Google Docs	Adobe® Forms Central	SurveyMonkey®
Price (annually)	University funded	Free	£105.39	£299
Usability	Fair	Good	Excellent	Good
Appearance formatting	Colour	Templates	Unlimited	Templates
Skip Logic - question	No	No	Yes	Yes
Skip Logic – page	Yes	No	Yes	Yes
Question Piping	Yes	No	No	Yes
Answer Pre-Population	No	No	No	Some
Help text	No	Yes	Yes	No
Logos and images	1 (top of page)	No	Unlimited	1 (top of page)
Field Validation	Yes	No	Yes	Yes
Integrated email	Limited	No	No	Limited
Security	Encrypted	Data cloud	SSL encryption	SSL Encryption
Statistical analysis	SPSS export	Excel export	SPSS export	SPSS export
Data Export	Yes	Yes	Yes	Yes
Data Summary	Yes	Yes	Yes	Yes
Progress Bar	Yes	No	Yes	Yes
Telephone/Email Support	Via University	No	Both	Email

Questionnaire number	Questionnaire	1= Questionnaire 1 (4 Months)
		2= Questionnaire 2 (10 Months)
		3= Questionnaire 3 (16 Months)
		4= Questionnaire 4 (22 Months)
Babies Gender	BGENDER	0=Male
		1= Female
Single or Multiple Pregnancy	MULTIP	1=Singleton
		2=Multiple Birth
Babies Ethnicity	BETHNIC	0= I Would prefer not to say
		1= White-British
		2= White- Other
		3= Mixed/Multiple ethnic groups
		4=African/Caribbean/ Other Black
		5=Asian-Indian/Pakistani/Bangladeshi
		6=East Asian- Chinese
		7= Other
Birth Weight to be completed in pounds or Kg?	BWT	1=Pounds and Ounces
		2=Kg
Maternal Smoking in Pregnancy	MSMOKE	0= No
		1= Yes
Other Household smoker in pregnancy	OSMOKE	0= No
		1= Yes
Location of other household smoke in pregnancy	LSMOKE	1=Inside the home
		2= Outside the home
		3= Inside the car
		4=Inside another location (work/social)
		5= Other
Breast Feed	BF	0= No
		1= Yes
Breast feeding duration	BFT	1= <1 Month
		2=1-4 Months
		3= >4 Months
Highest Maternal Qualification	MQUAL	0= No Qualifications
		1= Completed secondary school
		2=GCSE
		3=Vocational Training/Apprentice/Diploma/BTECH/NVQ
		4=A-Levels
		5=Undergraduate Degree
		6=Postgraduate Degree
		7=Other
Index of Multiple Deprivation Decile	IMD	Least Deprived 1-10 Most Deprived
Nursery Attendance	NURSERY	0= No

		1= Yes
Other children living in the Household?	OCHILD	0= No
		1= Yes
Number of other children living in the household	NUMCHILD	1-7(or more)
Does the child share a bedroom?	SBED	0= No
		1= Yes
Who does the child share a bedroom with?	WSBED	0=Parent/Parents
		1= 1 other Child
		2= 2 or more children
		3= Other
Does the baby have any other health condition	BHCON	0= No
		1= Yes
Type of health condition	THCON	1=Respiratory Condition
		2=Heart Condition
		3=Kidney Condition
		4=Neurological Condition
		5=Gastrointestinal Condition
		6= Diabetes
		7= Other Health Condition
Is there a family history of atopy?	FHATOPY	0= No
		1= Yes
Who has atopy in the family?	WATOPY	1= Babies Mother
		2= Babies Father
		3=My eldest Child
		4=My Second Eldest Child
		5= My Third eldest child
		6= My 4th eldest Child
		7= Other
What atopic conditions does mother have	MATOPY	1=Asthma
What atopic conditions does father have	FATOPY	
What atopic conditions does eldest child have?	ECATOPY	2=Hay Fever
Wat atopic conditions does second eldest child have?	SECATOPY	
What atopic Conditions does third eldest child have	TECATOPY	

What atopic conditions does forth eldest child have?	FECATOPY	3=Eczema
What atopic conditions does the their family member have?	OATOPY	
Has there been smokers in the household during the last 3 months?	HSMOKE	0= No
		1= Yes
Where do the household smokers smoke?	HLSMOKE	1=Inside the home
		2= Outside the home
		3= Inside the car
		4=Inside another location (work/social)
		5= Other
Have you been the GP with a respiratory condition the last 3 months?	BGP	0= No
		1= Yes
Have you attended the hospital with respiratory conditions in the last 3 months?	BHOS	0= No
		1= Yes

	Symptoms assessed on a Linkert Scale
Not at all	0
A few Days	1
Some Days	2
Most Days	3
Every Day	4

Appendix 16- Cross-Sectional Analysis Weighting Factors

IMD	4 Months	10 Months	16 Months	22 Months
1	1.40	1.43	1.43	1.40
2	0.77	0.69	0.82	0.88
3	0.90	1.23	0.80	0.93
4	0.91	0.81	0.92	0.91
5	0.82	0.80	0.79	0.90
6	0.66	0.77	0.92	0.79
7	0.64	0.56	0.58	0.49
8	0.63	0.48	0.53	0.58
9	1.08	0.86	0.72	0.48
10	0.37	0.23	0.51	0.71

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