The Liverpool Baby Breathing Study

A Cross-Sectional and Longitudinal Assessment of Respiratory Symptoms in the First Five Years of Life, and Their Impact on Quality of Life

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master of Philosophy by Conor James Naylor

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Errata

Following *viva voce* examination on 22nd July 2021, the following amendments have been made to the thesis, in response to the recommendations received from its examiners: Dr Louise Oni and Dr Jonathan Read.

- **Section 3.10**

The process behind how duplicated data was dealt with in the LBBS has been further clarified. Previously, the removal of duplicated data was only alluded to. The section now includes information about which duplicate was removed, and which was kept.

- **Section 3.11.5.4 and 3.11.5.5**

Previously, statistically significant differences in symptom prevalence and healthcare service usage were reported using χ^2 and Fisher's Exact Testing. It was suggested that these differences would be better to report as odds ratios. The method has therefore been updated to reflect this.

- **Section 3.11.6**

A more comprehensive overview of how the longitudinal analysis was conducted, has been included in the method. Additional details about the stepwise nature of the analysis have been added and referenced. The random and fixed effects included in the multi-level mixed effects model have been made more explicit too.

- **Section 4.5**

The cross-sectional analyses of symptom prevalence and healthcare service usage are now reported as odds ratios, instead of χ^2 and Fisher's Exact Tests.

- **Section 4.5.11**

A table has been inserted, to summarise the risk factors that influenced four key outcomes, across the ten cross-sectional timepoints. The four outcomes were deemed to be the most clinically-relevant: Total LRSQ Score, Domain 7 Score, GP Attendance and Hospital Attendance

- **Section 5.2.4**

Further discussion points have been included. One reflects upon the potentially non-linear correlation between total LRSQ score and total QoL score. The other discusses how co-variates can have a confounding effect upon the univariate analyses of the cross-sectional analysis.

Abstract

The Liverpool Baby Breathing Study: A Cross-Sectional and Longitudinal Assessment of Respiratory Symptoms in the First Five Years of Life, and Their Impact on Quality of Life – by Conor James Naylor

Aims**:** *The objectives of the Liverpool Baby Breathing Study were: 1) to compare the study population, to the eligible study population; 2) to identify which characteristics were associated with an increased drop-out rate; 3) to analyse risk factors for poor respiratory health at different ages in the pre-school period; 4) to analyse risk factors for poor respiratory health throughout the entire pre-school period; and 5) to validate the Liverpool Respiratory Symptom Questionnaire for longitudinal use.*
Introduction**:** *The Liverpool Baby Breathing Study was founded to assess the natural history of respiratory health in a cohort of pre-school-aged children in Liverpool. The city hosts many pre-established risk factors for paediatric respiratory disease, which makes it ideal for assessing which risk factors are most important in the development of future disease. The study also assesses the impact of respiratory symptoms on the quality of life of children and their parents, through the use of the Liverpool Respiratory Symptom Questionnaire.*
Methods**:** *Between January 2013 and November 2014, newborns were recruited from the post-natal and neonatal wards of Liverpool Women's Hospital. Over a period of five years, the infants' parents completed biannual questionnaires about their child's respiratory wellbeing. Questionnaires were delivered electronically, and consisted of a Liverpool Respiratory Symptom Questionnaire – as well as additional questions about the child's exposure to potential risk factors. Data collection ran from May 2013 to January 2020.*
Results**:** *The Liverpool Baby Breathing Study cohort consisted of 687 infants, which represented 5.5% of the eligible study population. Compared to the eligible study population, the study cohort was less deprived, more Caucasian, less breastfed and more premature; their mothers were older, more educated and less likely to smoke. Those who were from a deprived background, or with a less educated mother, were more likely to be lost to attrition throughout the study. Based on cross-sectional and longitudinal analyses, the most apparent risk factors for poor respiratory health during the pre-school period (i.e. more frequent respiratory symptoms) were found to be: having a co-morbidity, attending nursery, being male, having a family history of atopy, not sharing a bedroom, and having a younger mother. The Liverpool Respiratory Symptom Questionnaire displayed good to excellent internal consistency when used longitudinally.*
Conclusions**:** *Not only was the Liverpool Baby Breathing Study able to further endorse well-established risk factors as important to the development of paediatric respiratory disease, but it was also able to support the importance of less-established risk factors too. The Liverpool Respiratory Symptom Questionnaire can now be used as a validated tool in future longitudinal studies of pre-school-aged children.*

Collaboration

The Liverpool Baby Breathing Study is the work of not just myself, but several clinical academics and MPhil students. Outlined below, are those who contributed to the study, before my involvement began…

- **Dr Jennifer Barclay**

  recruitment; questionnaire distribution
- **Dr Bethan Griffiths**

  protocol development; questionnaire development; recruitment
- **Dr Steven Lane**

  analysis
- **Professor Paul McNamara**

  protocol development; Liverpool Respiratory Symptom Questionnaire development & validation
- **Dr Sanjay Patel**

  questionnaire development; recruitment
- **Dr Rosanna Pickles**

  protocol development; questionnaire development; recruitment
- **Dr Colin Powell**

  Liverpool Respiratory Symptom Questionnaire development & validation
- **Professor Calum Semple**

  chief investigator; protocol development
- **Professor Ben Shaw**

  protocol development; Liverpool Respiratory Symptom Questionnaire development & validation; data extraction from Liverpool Women's Hospital
- **Dr Arturo Solis**

  Liverpool Respiratory Symptom Questionnaire development & validation
- **Professor Kevin Southern**

  protocol development
- **Dr Joshua Stead**

  preliminary analysis

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It is thanks to the support of various people, that the production of this thesis was even possible. Given the impact that the COVID-19 pandemic had on research in 2020/21, their support was especially valued. Therefore, I would like to take the opportunity to acknowledge said people.

Firstly, I would like to thank my family for their continued and unwavering support. I simply could not have gotten this far into my medical 'career' without them. They have always provided emotional, financial and social support. This has been particularly evident over the past year.

I would like to thank too, those who laid the groundwork on which my thesis could be built. Had they not established it, there would be no Liverpool Baby Breathing Study without the work of: Professor Kevin Southern, Professor Paul McNamara, Professor Ben Shaw, Bethan Griffith and Rosanna Pickles. Thanks also go to Sanjay Patel and Jennifer Barclay for continuing the study during its intermediary years. A particular thank you must go to Joshua Stead, whose personal advice and prior work has proved invaluable over the past year.

I should also like to thank Dr Steven Lane. For a novice like myself, his knowledge of statistics offered a lifeline towards the completion of this thesis. Without him, there would be nothing to show for the hard work that so many people have put into the Liverpool Baby Breathing Study over the last decade.

Finally, my gratitude goes out to Professor Calum Semple. Throughout the pandemic, his time and attention were regularly required elsewhere, yet he continued to ensure that I followed the right track. His guidance and expertise were irreplaceable.

Table of Contents

Errata i

Abstract ii

Collaboration iii

Acknowledgements iv

Table of Contents v

Table of Figures viii

Table of Tables xi

List of Abbreviations xiii

Chapter 1: Objectives 1

Chapter 2: Introduction 3

2.1 Common Respiratory Diseases in Children 3

2.2 Common Respiratory Symptoms in Children 8

2.3 Risk Factors for Paediatric Respiratory Health 11

2.4 The Liverpool Respiratory Symptom Questionnaire 18

2.5 Other Paediatric Respiratory Symptom Questionnaires 21

2.6 Respiratory Health in Liverpool 30

2.7 Previous Birth Cohort Studies 33

Chapter 3: Methodology 38

3.1 Study Protocol 39

3.2 Ethical Approval 39

3.3 Sponsorship 40

3.4 Development of the Questionnaires 40

3.5 Development of Additional Study Materials 43

3.6 Recruitment 44

3.7 Questionnaire Distribution 46

3.8 Data Storage 49

3.9 Coding 49

3.10 Data Cleansing 50

3.11 Data Analysis 51

3.12 Choice of Statistical Package 58

Chapter 4: Results 59

4.1 Recruitment and Enrolment 60

4.2 Profile of the Family Cohort 62

4.3 Profile of the Infant Cohort 68

4.4 Attrition 72

4.5 Cross-Sectional Analysis 81

4.6 Longitudinal Analysis 196

4.7 Validation of the LRSQ 199

Chapter 5: Discussion 200

5.1 Principle Findings 200

5.2 Strengths and Weaknesses 201

5.3 Future Opportunities 211

Chapter 6: Conclusions 213

References 214

Appendix 225

Appendix 1: Study Protocol 225

Appendix 2: The Original LRSQ 234

Appendix 3: Consent Form (Postal Version) 236

Appendix 4: Questionnaire One 238

Appendix 5: Recruitment Postcards 243

Appendix 6: Recruitment Posters 244

Appendix 7: Exemplar Email 245

Appendix 8: Coding 246

Appendix 9: Weighting Factors 249

Appendix 10: Adjusted Codes 250

Table of Figures

Figure 1: flowchart of recruitment throughout the LBBS 61
Figure 2: prevalence of breastfeeding in the LBBS, compared to LWH and Liverpool and England 62
Figure 3: breastfeeding in the LBBS by duration 63
Figure 4: IMD deciles in the LBBS, compared to LWH and Liverpool 64
Figure 5: maternal ages in the LBBS, compared to LWH and Liverpool and England 65
Figure 6: maternal education levels in the LBBS, compared to Liverpool and England 66
Figure 7: prevalence of antenatal smoking in the LBBS, compared to LWH and Liverpool and England .. 67
Figure 8: antenatal ETS exposure in the LBBS by location 67
Figure 9: birthweight of infants in the LBBS, compared to LWH and England & Wales 68
Figure 10: ethnicity of infants in the LBBS, compared to LWH and England & Wales 69
Figure 11: gestational age of infants in the LBBS, compared to LWH and England & Wales 70
Figure 12: multiple pregnancy rate in the LBBS, compared to LWH and Liverpool and England 71
Figure 13: change in questionnaire response rate 72
Figure 14: flowchart of attrition throughout the LBBS 73
Figure 15: proportion of mothers over time by antenatal smokig status 77
Figure 16: proportion of infants over time by birthweight classification 77
Figure 17: proportion of mothers over time by breastfeeding status 77
Figure 18: proportion of families over time by IMD decile 78
Figure 19: proportion of infants over time by ethnicity 78
Figure 20: proportion of infants over time by gestational age 79
Figure 21: proportion of mothers over time by highest educational level 79
Figure 22: proportion of mothers over time by age at the time of delivery 80
Figure 23: proportion of infants over time by twin or singleton status 80
Figure 24: proportion of infants over time by sex 80
Figure 25: infants with a family history of atopy, by relative(s) and disease(s), at 4-months-old 82
Figure 26: distribution of total and domain LRSQ scores at 4-months-old 84
Figure 27: correlation between total LRSQ score and total QoL score at 4-months-old 87
Figure 28: prevalence of respiratory symptoms at 4-months-old 87
Figure 29: GP and hospital attendance rates at 4-months-old 90
Figure 30: correlation between total LRSQ score and GP attendance rate at 4-months-old 91
Figure 31: correlation between total LRSQ score and hospital attendance rate at 4-months-old 91
Figure 32: infants with a family history of atopy, by relative(s) and disease(s), at 10-months-old 93
Figure 33: distribution of total and domain LRSQ scores at 10-months-old 95
Figure 34: correlation between total LRSQ score and total QoL score at 10-months-old 98
Figure 35: prevalence of respiratory symptoms at 10-months-old 99
Figure 36: GP and hospital attendance rates at 10-months-old 102

Figure 37: correlation between total LRSQ score and GP attendance rate at 10-months-old 103
Figure 38: correlation between total LRSQ score and hospital attendance rate at 10-months-old..... 103
Figure 39: infants with a family history of atopy, by relative(s) and disease(s), at 16-months-old..... 104
Figure 40: distribution of total and domain LRSQ scores at 16-months-old 106
Figure 41: correlation between total LRSQ score and total QoL score at 16-months-old..... 110
Figure 42: prevalence of respiratory symptoms at 16-months-old 110
Figure 43: GP and hospital attendance rates at 16-months-old..... 113
Figure 44: correlation between total LRSQ score and GP attendance rate at 16-months-old 114
Figure 45: correlation between total LRSQ score and hospital attendance rate at 16-months-old..... 114
Figure 46: toddlers with a family history of atopy, by relative(s) and disease(s), at 22-months-old 115
Figure 47: distribution of total and domain LRSQ scores at 22-months-old 117
Figure 48: correlation between total LRSQ score and total QoL score at 22-months-old..... 120
Figure 49: prevalence of respiratory symptoms at 22-months-old 121
Figure 50: GP and hospital attendance rates at 22-months-old..... 123
Figure 51: correlation between total LRSQ score and GP attendance rate at 22-months-old 124
Figure 52: correlation between total LRSQ score and hospital attendance rate at 22-months-old..... 124
Figure 53: toddlers with a family history of atopy, by relative(s) and disease(s), at 28-months-old 126
Figure 54: distribution of total and domain LRSQ scores at 28-months-old 128
Figure 55: correlation between total LRSQ score and total QoL score at 28-months-old..... 132
Figure 56: prevalence of respiratory symptoms at 28-months-old 132
Figure 57: GP and hospital attendance rates at 28-months-old..... 135
Figure 58: correlation between total LRSQ score and GP attendance rate at 28-months-old 136
Figure 59: correlation between total LRSQ score and hospital attendance rate at 28-months-old..... 136
Figure 60: toddlers with a family history of atopy, by relative(s) and disease(s), at 34-months-old 137
Figure 61: distribution of total and domain LRSQ scores at 34-months-old 139
Figure 62: correlation between total LRSQ score and total QoL score at 34-months-old..... 143
Figure 63: prevalence of respiratory symptoms at 34-months-old 144
Figure 64: GP and hospital attendance rates at 34-months-old..... 146
Figure 65: correlation between total LRSQ score and GP attendance rate at 34-months-old 147
Figure 66: correlation between total LRSQ score and hospital attendance rate at 34-months-old..... 147
Figure 67: children with a family history of atopy, by relative(s) and disease(s), at 40-months-old..... 149
Figure 68: distribution of total and domain LRSQ scores at 40-months-old 151
Figure 69: correlation between total LRSQ score and total QoL score at 40-months-old..... 155
Figure 70: prevalence of respiratory symptoms at 40-months-old 155
Figure 71: GP and hospital attendance rates at 40-months-old..... 158
Figure 72: correlation between total LRSQ score and GP attendance rate at 40-months-old 159
Figure 73: correlation between total LRSQ score and hospital attendance rate at 40-months-old..... 159
Figure 74: children with a family history of atopy, by relative(s) and disease(s), at 46-months-old..... 161

Figure 75: distribution of total and domain LRSQ scores at 46-months-old 163
Figure 76: correlation between total LRSQ score and total QoL score at 46-months-old 166
Figure 77: prevalence of respiratory symptoms at 46-months-old 167
Figure 78: GP and hospital attendance rates at 46-months-old 169
Figure 79: correlation between total LRSQ score and GP attendance rate at 46-months-old 170
Figure 80: correlation between total LRSQ score and hospital attendance rate at 46-months-old 170
Figure 81: children with a family history of atopy, by relative(s) and disease(s), at 52-months-old 172
Figure 82: distribution of total and domain LRSQ scores at 52-months-old 174
Figure 83: correlation between total LRSQ score and total QoL score at 52-months-old 178
Figure 84: prevalence of respiratory symptoms at 52-months-old 178
Figure 85: GP and hospital attendance rates at 52-months-old 181
Figure 86: correlation between total LRSQ score and GP attendance rate at 52-months-old 182
Figure 87: correlation between total LRSQ score and hospital attendance rate at 52-months-old 182
Figure 88: children with a family history of atopy, by relative(s) and disease(s), at 58-months-old 183
Figure 89: distribution of total and domain LRSQ scores at 58-months-old 185
Figure 90: correlation between total LRSQ score and total QoL score at 58-months-old 189
Figure 91: prevalence of respiratory symptoms at 58-months-old 190
Figure 92: GP and hospital attendance rates at 58-months-old 192
Figure 93: correlation between total LRSQ score and GP attendance rate at 58-months-old 193
Figure 94: correlation between total LRSQ score and hospital attendance rate at 58-months-old 193

Table of Tables

Table 1: phenotypes of childhood cough 8
Table 2: phenotypes of childhood wheeze 10
Table 3: paediatric respiratory symptom questionnaires, by number of citations 22
Table 4: timeline of personnel involvement in the LBBS 38
Table 5: questionnaire preferabilities from the PPI sessions 41
Table 6: content of questionnaires in the LBBS 43
Table 7: inclusion/exclusion criteria 44
Table 8: overview of the pilot recruitment study 45
Table 9: timeline of questionnaire distribution 48
Table 10: frequency of data collection discrepancies and missing information 51
Table 11: risk factors assessed in the LBBS 54
Table 12: domains in the LRSQ 55
Table 13: recruitment rate into the LBBS 60
Table 14: enrolment rate onto the LBBS 61
Table 15: questionnaire response rate, and change in response rate 72
Table 16: LBBS cohort by number of completed questionnaires 74
Table 17: co-morbidities of the LBBS cohort at 4-months-old 83
Table 18: descriptive statistics of the total and domain LRSQ scores at 4-months-old 83
Table 19: co-morbidities of the LBBS cohort at 10-months-old 94
Table 20: descriptive statistics of the total and domain LRSQ scores at 10-months-old 94
Table 21: co-morbidities of the LBBS cohort at 16-months-old 105
Table 22: descriptive statistics of the total and domain LRSQ scores at 16-months-old 105
Table 23: co-morbidities of the LBBS cohort at 22-months-old 116
Table 24: descriptive statistics of the total and domain LRSQ scores at 22-months-old 116
Table 25: co-morbidities of the LBBS cohort at 28-months-old 127
Table 26: descriptive statistics of the total and domain LRSQ scores at 28-months-old 127
Table 27: co-morbidities of the LBBS cohort at 34-months-old 138
Table 28: descriptive statistics of the total and domain LRSQ scores at 34-months-old 138
Table 29: co-morbidities of the LBBS cohort at 40-months-old 150
Table 30: descriptive statistics of the total and domain LRSQ scores at 40-months-old 150
Table 31: co-morbidities of the LBBS cohort at 46-months-old 162
Table 32: descriptive statistics of the total and domain LRSQ scores at 46-months-old 162
Table 33: co-morbidities of the LBBS cohort at 52-months-old 173
Table 34: descriptive statistics of the total and domain LRSQ scores at 52-months-old 173
Table 35: co-morbidities of the LBBS cohort at 58-months-old 184
Table 36: descriptive statistics of the total and domain LRSQ scores at 58-months-old 185

Table 37: summary table of risk factor impact on select outcomes 195
Table 38: the muli-level mixed effects model for total LRSQ score 196
Table 39: the muli-level mixed effects model for domain 1 of the LRSQ 196
Table 40: the muli-level mixed effects model for domain 2 of the LRSQ 197
Table 41: the muli-level mixed effects model for domain 3 of the LRSQ 197
Table 42: the muli-level mixed effects model for domain 4 of the LRSQ 197
Table 43: the muli-level mixed effects model for domain 5 of the LRSQ 198
Table 44: the muli-level mixed effects model for domain 6 of the LRSQ 198
Table 45: the muli-level mixed effects model for domain 7 of the LRSQ 198
Table 46: the muli-level mixed effects model for domain 8 of the LRSQ 199
Table 47: internal consistency of the eight LRSQ domains 199

List of Abbreviations

95% CI	95% Confidence Interval
AFC®	Adobe FormsCentral®
ALSPAC	Avon Longitudinal Study of Parents and Children
BiB	Born in Bradford
C-GULL	Children Growing Up In Liverpool
COPD	Chronic Obstructive Pulmonary Disease
DoB	Date of Birth
ETS	Environmental Tobacco Smoke
FEV_1	Forced Expiratory Volume in 1 Second
GDPR	General Data Protection Regulation
GP	General Practice / General Practitioner
HIV	Human Immunodeficiency Virus
IMD	Index of Multiple Deprivation
MAAS	Manchester Asthma and Allergy Study
LBBS	Liverpool Baby Breathing Study
LRSQ	Liverpool Respiratory Symptom Questionnaire
LWH	Liverpool Women's Hospital
NHS	National Health Service
NO_2	Nitrogen Dioxide
OR	Odds Ratio
PPI	Public and Patient Involvement
QoL	Quality of Life
QR	Quick Response
REC	Research Ethics Committee
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Infection
SOB	Shortness of Breath
SPSS	Statistical Product and Service Solutions
SSL	Secure Socket Layer
SSN®	SelectSurvey.NET®
TCRS	Tucson Children's Respiratory Study
UK	United Kingdom

Chapter 1: Objectives

The Liverpool Baby Breathing Study (LBBS, previously known as the Liverpool Respiratory Birth Cohort Study) began in 2012 – with recruitment occurring from January 2013 to November 2014, and data collection running from May 2013 to January 2020. It is a longitudinal birth cohort study, in which pre-school-aged children born in Liverpool are assessed for their prevalence of respiratory symptoms, and how such symptoms affect their and their parents' quality of life (QoL). The assessments are performed by using the parentally-completed Liverpool Respiratory Symptom Questionnaire (LRSQ), every six months, between the ages of 4 and 58-months-old. By completing these assessments, the primary objective – as outlined by the study protocol (**Appendix 1**) – can be fulfilled: "to describe parentally-reported respiratory symptoms within a population-based birth cohort, as they are followed longitudinally." Alongside the LRSQ, parents complete another questionnaire. This questionnaire asks about a child's exposure to demographic and socioeconomic risk factors for paediatric respiratory disease. By using this second questionnaire, the secondary objective outlined in the study protocol can be achieved too: "to examine any associations between different respiratory symptoms, and exposure to different risk factors." Throughout the thesis, there will be further exploration of: how the study was set up, why Liverpool is an ideal location to assess paediatric respiratory health, why the LRSQ is the best way of evaluating respiratory symptoms, and what the most influential risk factors are upon paediatric respiratory health.

Whilst the objectives of the LBBS have been outlined above, the objectives of this thesis are as follows:

- Provide an overview of the literature that has already been conducted into the natural history of paediatric respiratory health, including many of the published studies that have relied upon the LRSQ.
- Explain the methodology of the LBBS, as well as the ideology behind it when necessary.
- Evaluate the study's recruitment and attrition rates and compare these to previous birth cohort studies.

- Create demographic and socioeconomic profiles of the infants and families involved in the LBBS and contrast it with profiles of the wider local population and the national population.
- Analyse the cross-sectional results for each questionnaire in the LBBS series, by looking at: risk factor exposure, total LRSQ scores, LRSQ domain scores, symptom prevalence, health service usage, and QoL.
- Analyse the longitudinal results of the LBBS, by using mixed-effects modelling to identify the risk factors that collectively pose the greatest threat to respiratory health during the pre-school period.
- Validate the LRSQ for use in longitudinal studies, and publish said validation in a peer-reviewed journal.

Chapter 2: Introduction

Chapter 1 serves as an introduction to the themes involved in the LBBS. An overview of common paediatric respiratory conditions is given to show the burden that respiratory disease places on children and healthcare services, and hence why more understanding is needed into its natural history. The most common symptoms that children with these respiratory conditions present with are also described, in order to inform questionnaire choice. Risk factors for paediatric respiratory disease are summarised, to support their assessment in the LBBS. A thorough description of the study's chosen respiratory symptom questionnaire: the LRSQ, is provided; a justification for its use is also given. This is followed by an overview of the various other paediatric respiratory symptom questionnaires that are available, but were not suitable for the LBBS. A historical review of health and social inequality in Liverpool is also presented, as a means to support the city's aptness for this particular study. Finally, a summary of some previous birth cohort studies is presented, in order to inform the LBBS's study design – as well as anticipate its outcomes.

2.1 Common Respiratory Diseases in Children

Respiratory disease accounts for the most hospital admissions amongst children. [1] In the United Kingdom (UK), 25% of paediatric hospitalisations and 33-50% of primary care consultations are for respiratory disease. [2] Respiratory disease cost the UK economy £11.1 billion in 2014 – up from £6.6 billion in 2004. [3] Respiratory disease was responsible for 31% of deaths amongst 0 to 14-year-olds in 1968, though had fallen to 11% in 2012. [4,5] Approximately three-quarters of these deaths were attributable to: pneumonia, asthma or cystic fibrosis (CF). [4] Globally, pneumonia is the biggest killer of children under 5-years-old: 15% of said children across the world died from the disease in 2017. [6]

2.1.1 Allergic Rhinitis

Also known as hay fever, allergic rhinitis is a common childhood disease, in which the nasal epithelium becomes inflamed. [7] When the nasal mucosa is exposed to an allergen, an IgE-mediated immune response is launched; IgE stimulates mast cells to degranulate – thus releasing inflammatory mediators into the mucosa. [7,8] The nasal

mucosa becomes further inflamed, as it is infiltrated by more immune cells. [8] The disease is characterised by sneezing, rhinorrhoea, nasal congestion and itchy eyes, ears and nose. The pattern of allergic rhinitis depends on what allergens a child is sensitive to. Pollen is usually responsible for allergic rhinitis in the summer months (seasonal), but year-round allergic rhinitis is typically caused by dust mites, pet dander and/or mould. Where possible, allergic rhinitis can be managed by avoiding allergens – though intranasal corticosteroids and antihistamines are still frequently used. [7]

2.1.2 Asthma

Asthma is the most common chronic disease amongst children. [2] Approximately 3% of pre-school-aged children had a diagnosis of asthma in 2012 – representing a huge decline in lifetime prevalence since the start of the millennium. [9] The condition is characterised by obstruction of the small airways, which can be reversed with bronchodilators. [10,11] There are several 'triggers' capable of inducing an asthmatic response from the airways, such as: allergens, exercise, environmental tobacco smoke (ETS), cold weather and respiratory tract infections (RTI). [7,11] Upon exposure to a 'trigger', various immune cells secrete pro-inflammatory cytokines into the airway mucosa via a complex pathway. These cytokines subsequently cause airway mucosae to become oedematous, smooth muscle to constrict/hypertrophy, and mucus to hyper-secrete. The three phenomena ultimately cause airway lumina to narrow. [2,10] Asthma that is 'triggered' by an allergen is known as atopic asthma, and is often associated with eczema and/or hay fever too. [2] The classic symptoms of asthma are: dyspnoea, chest tightness, tachypnoea, coughing and wheezing. These symptoms can last anywhere between a few minutes and a few days, and are generally worse at night. [2,11] Many children 'grow out' of the disease as they get older. [9] All children with asthma are initially treated with a short-acting bronchodilator; if their asthma remains uncontrolled, then some children will also require inhaled corticosteroids. For pre-school-aged children, leukotriene receptor antagonists can be used if asthma still remains uncontrolled. [12] In exceptional circumstances, children are referred to an asthma specialist so that they can receive alternate therapies. [12]

2.1.3 Bronchiolitis

Bronchiolitis is a viral lower RTI, which predominantly affects children under the age of 2-years-old. The majority of infections are caused by respiratory syncytial virus (RSV), but other viruses have been implicated too. [10] As such, bronchiolitis in the UK is especially common during the Winter months. [13] The infecting virus induces inflammation of the bronchioles, so that their mucosae become oedematous and their lumina fill with mucus; infection of the type II alveolar cells leads to surfactant deficiency too, which results in a loss of airway patency. [10,14] The small airways therefore become narrow and obstructed. Following coryzal symptoms, children usually present with: wheezing, a cough, fine respiratory crackles and signs of respiratory distress. Most children will recover from bronchiolitis, so long as they receive supportive care. [15] However, a small proportion of children (usually under 9-months-old) require hospitalisation for severe bronchiolitis. In hospital, such children may receive oxygen therapy, nasogastric feeding and/or mechanical ventilation. [2,15]

2.1.4 Croup

Croup is the diagnostic term for an infection of the laryngotracheal tract. It is a viral disease – most commonly associated with parainfluenza – that is particularly prevalent in the Autumn, between 6-months and 3-years-old. [16] Due to mucosal oedema, the already-narrow laryngotracheal tract becomes further narrowed; this results in increased airway resistance, which can pose a threat to airway patency. [16] Croup typically presents with: a 'barking' cough, low-grade fever, harsh stridor, voice hoarseness, laboured breathing, and subcostal/intercostal recessions. [16] With supportive care and an oral/intramuscular steroid, most children will recover quickly from croup. However, those with impending respiratory failure require hospitalisation, in order to receive nebulised adrenaline and/or oxygen therapy and/or nebulised steroids. Mechanical ventilation is reserved for the most critical cases. [2,16]

2.1.5 Cystic Fibrosis

CF is a life-limiting multi-system disease, which is the most common genetic disease amongst Caucasians. CF is caused by the autosomal recessive inheritance of a mutated CFTR gene. Over one thousand mutations are associated with the disease, yet 80% of mutations in the UK are ΔF508. [1] Since CFTR proteins are chloride channels, defective

CFTR genes result in the dysfunctional transportation of chloride ions across epithelial surfaces. Without an ionic gradient, the epithelial surfaces of exocrine glands become dehydrated and their secretions become thick. [1,11] Children with CF often experience RTIs, because bacteria are able to colonise within the thick 'plugs' of mucus that obstruct the respiratory tract; recurrent infections eventually result in bronchiectasis. Productive coughs, nasal polyps and sinusitis are common too. [2,11] Children can experience digestive, skeletal, hepatopancreatic and reproductive problems as well. [17] Nowadays, most cases of CF are detected via newborn screening. [2] At the simplest level, CF is managed with a combination of: antibiotic prophylaxis, airway clearance techniques, mucolytic agents, nutritional interventions and regular exercise. Further support is available for those with cystic-fibrosis-related diabetes, active RTIs, low bone mineral density, liver disease and/or exocrine pancreatic insufficiency. [18]

2.1.6 Epiglottitis

Epiglottitis refers to inflammation of the tissues above the glottis. 90% of cases are the result of a *Haemophilus influenzae* B (HiB) infection, and most cases occur during the pre-school period. [19] Due to the narrow structure of children's airways, oedema in the epiglottal region can suddenly obstruct the upper respiratory tract; for this reason, epiglottitis is a medical emergency. [16] Children typically present with a rapid onset of: a high-grade fever, soft stridor, dysphagia, a sore throat, drooling and a visibly-inflamed epiglottis. They also appear 'toxic', and tend to sit in an upright (tripod/sniffing) position. [16,19] Epiglottis requires urgent endotracheal intubation, followed by intravenous antibiotics. [2] Since the introduction of a HiB vaccination, the incidence of epiglottis has declined drastically. [19]

2.1.7 Influenza

Influenza is a viral respiratory infection, which is transmitted when a mucosal surface comes into contact with respiratory secretions – typically between December and March. [11,20,21] The infection can be caused by one of three types of influenza virus: A, B or C. Influenza A is the most common circulating strain of the virus, and is responsible for larger and more frequent outbreaks of the disease; influenza B is responsible for smaller and less frequent outbreaks – though it is still accountable for a significant proportion of childhood infections. Influenza C is a relatively uncommon strain of the

virus. [22,23] Pro-inflammatory cytokines are produced by immune cells in response to the virus infecting the respiratory tract, which subsequently leads to the latter's inflammation. [24] Most children with influenza will suffer mild symptoms: a fever, a dry cough, headaches, myalgia, arthralgia, malaise, a sore throat and/or rhinorrhoea. [22] They can be treated with supportive care. [1] However, those who are clinically at-risk (i.e. they have an underlying medical condition) or who have a genetic disposition, are susceptible to developing: primary viral pneumonia, secondary bacterial pneumonia, myocarditis or encephalopathy. These children are eligible to receive antiviral treatment too. [1,25]

2.1.8 Pneumonia

Pneumonia is the infection of lung parenchyma, in which alveoli and bronchioles become inflamed. [11] In newborns, pneumonia is predominantly caused by Group B Streptococcus or *Escherichia coli*; pneumonia is more likely to be viral or caused by *Streptococcus pneumoniae*/*Haemophilus influenzae* in pre-school-aged children. [2,26] Whilst the presentation of childhood pneumonia varies from child to child, hallmark features generally include: a fever, tachypnoea, a cough (± sputum), dyspnoea, lethargy, poor feeding and respiratory crackles. Children can also present with: wheezing, pleuritic chest pain and signs of respiratory distress. [1,11,26] Antibiotics are often prescribed to treat a pneumonia, and can usually be given from home. More severely ill children may require hospitalisation for oxygen therapy, analgesia and/or intravenous fluids. [2]

2.1.9 Upper Respiratory Tract Infections

On average, children experience six to ten upper RTIs per year – making them one of the most popular reasons for primary care visitation. [1,27] An upper RTI is caused by the infection of one part or more of the upper respiratory tract (i.e. the nasal cavity, middle ear, pharynx, tonsils, sinuses and larynx). Most upper RTIs are viral in origin, but some can be bacterial too. Rhinovirus and RSV are particularly common infectious agents, Group A Streptococcus is not uncommon in tonsillitis, and *Streptococcus pneumoniae*/*Haemophilus influenzae* are known to cause otitis media. [2] The infection causes certain structures of the upper respiratory tract to inflame, which results in symptoms. Non-specific symptoms generally include: rhinorrhoea, nasal congestion,

coughing, a sore throat, otalgia, cervical lymphadenopathy, facial tenderness and fevers. [2] Most RTIs are simply managed with supportive care, but those that are bacterial in origin may require antibiotics too. [2,28]

2.2 Common Respiratory Symptoms in Children

Childhood respiratory diseases tend to display similar symptoms. The most common such symptoms are: coughing, wheezing, dyspnoea, stridor and coryza. [1] Infants will suffer with these respiratory symptoms for an average of four weeks per year. [29] Coughing, in particular, accounts for the most complaints of paediatric respiratory disease. [2] The prevalence of the various respiratory symptoms is poorly-described in the existing literature however, so symptom prevalence will be explored later in the thesis.

2.2.1 Cough

Children cough in order to clear their airway, whenever it is irritated by particulates, secretions or inflammation. Upon the mechanical or chemical stimulation of a cough receptor in the respiratory tract, afferent nerve impulses are transmitted to the brainstem. [30] From the brainstem, efferent impulses initiate a large intake of breath to maximise intra-thoracic pressure; the glottis subsequently closes of the larynx, and muscles of the chest, abdomen and pelvis all contract. Intra-thoracic pressure further increases as the muscles contract, eventually leading to the forceful expulsion of air through the airways. [30,31] Sometimes, when the airways are irritated or inflamed, the tracheobronchial tree will hyper-produce mucus – which is ejected as sputum whilst coughing. [31] Many diseases can cause a child to cough, including: asthma, inhaled foreign bodies, tracheomalacia, tuberculosis, CF and gastro-oesophageal reflux disease.

Character	Underlying Pathology
Productive of Coloured Sputum	Infection
Exercise-Induced/Night-Induced	Asthma
Barking	Croup
Violent Paroxysms, Followed by Inspiratory Whoop ± Vomiting	Pertussis

Table 1: phenotypes of childhood cough

The character of a child's cough can give an indication of the underlying pathology (**Table 1**). [2,31]

2.2.2 Dyspnoea

Dyspnoea is the discomfort that is felt when more effort is put into breathing, due to an increase in respiratory drive or a decrease in ventilation. [31–33] It is often referred to as 'shortness of breath' (SOB). [32] The symptom is one of the main reasons that people seek medical attention, and though it often has a respiratory basis, it can be caused by: neurological, cardiac, psychological and metabolic disease too. [31,32]

2.2.3 Rales

Also known as respiratory crackles, rales are discrete 'popping' sounds that are generally heard during inspiration, but can be heard during expiration too. [11,31] They originate from the presence of respiratory secretions, which obstruct the airways. As the airways expand during inspiration, the pressure gradient is able to equalise across any obstructions; this process causes the airway walls to vibrate, which results in 'crackling' sounds. [31] Rales can be described as either 'course' or 'fine'. The former are lower-pitched, longer in duration and originate in larger airways; the latter are higher-pitched, shorter in duration and originate in smaller airways. [11,31] In children, rales are usually seen in conjunction with pneumonia or asthma. [31]

2.2.4 Stridor

Stridor is a harsh, high-pitched, monophonic sound produced by turbulent airflow through a partially-obstructed upper airway. [16,34] When an airway is narrowed, the Venturi Effect causes airflow velocity to increase; such an increase creates a vacuum, which then collapses the airway. This is the Bernoulli Principle. Upon its collapse, resistance rises within the airway – resulting in turbulent airflow and increased work of breathing. [34] Most stridor is inspiratory in origin, which indicates a narrowing at the level of the vocal cords. However, it can also be expiratory or biphasic – indicating a narrowing of the bronchi or subglottal region, respectively. [16,35] Infections account for the majority of stridor, but it is also associated with: inhaled foreign bodies, trauma, anaphylaxis, laryngomalacia ('floppy larynx') and tumours. [2,35]

2.2.5 Wheeze

A wheeze is a high-pitched sound, created by the lower airways narrowing. It typically occurs during expiration, because at this time, the lower airways become compressed by high levels of intra-thoracic pressure. Upon further compression to the already narrow airways, airflow velocity increases. A wheeze is produced by the airway walls vibrating in response to the increased airflow velocity. [2,31] Wheezes are monophonic when there is a focal area of narrowing (e.g. an inhaled foreign body or a tumour), but are polyphonic when multiple branches of the tracheobronchial tree are obstructed simultaneously (e.g. asthma, bronchitis or bronchiolitis). [10,31] Approximately half of children have experienced at least one episode of wheezing, yet despite having become almost synonymous with asthma, less than 10% of childhood wheezers are diagnosed with asthma. [36–38] Therefore, an increasing amount of research is looking at the different phenotypes of childhood wheeze (**Table 2**).

Phenotype	Description
Distinguished by Duration	
Transient Early Wheeze [38,39]	Wheezing persists until 3-years-old, but not thereafter
Prolonged Early Wheeze [39]	Wheezing persists until 5-years-old, but not thereafter
Intermediate-Onset Wheeze [39]	Wheezing begins after 18-months-of-age, and persists thereafter. There is a strong association with atopy.
Late-Onset Wheeze [38,39]	Wheezing begins after 3-years-of-age, and persists thereafter. There is a strong association with atopy.
Persistent Wheeze [38,39]	Wheezing persists from infancy, throughout all of childhood
Distinguished by Frequency	
Episodic Wheeze [40]	Wheezing only occurs at distinct points in time, with no symptoms in-between. Often seen in conjunction with a viral RTI.
Multiple-Trigger Wheeze [40]	Wheezing is continuous, but there are obvious periods of exacerbation. May be associated with atopy.

Table 2: phenotypes of childhood wheeze

2.3 Risk Factors for Paediatric Respiratory Health

There is an abundance of research about the factors – both intrinsic and extrinsic to a child – that pose the greatest threat to their overall respiratory wellbeing. Research has also identified which factors are protective towards paediatric respiratory health. Outlined below are some of the most widely recognised risk factors.

2.3.1 Air Pollution

Between birth and 6-years-old, the lungs experience their greatest period of development. Therefore, if exposed to air pollution, they are more susceptible to impaired lung growth and function, immune dysfunction, and faulty repair mechanisms. [41–44] A major source of air pollution is busy roads, as they are where nitrogen dioxide (NO_2) and fine particulate matter levels are highest. NO_2 and fine particulate matter are noxious when inhaled. Children who live close to a busy road are more likely to be diagnosed with asthma or have an asthma attack. They are also more likely to experience: wheezing, coughing, pneumonia and RTIs. [45–48] These symptoms are common in all highly-polluted areas though. [49–51] Asthma-like symptoms are more common in areas of high air pollution, and often result in the hospitalisation of school-aged children. [43,52] Pre-school-aged children are more likely to be hospitalised with pneumonia or acute bronchitis when they live in a polluted area. [52] Living in a rural area, or near green space, is actually protective against asthma. [46,53]

2.3.2 Breastfeeding

Breastfeeding is widely considered to protect children's respiratory health. Children who are breastfed for the first nine months of life experience less coughing, wheezing and/or phlegm production, compared to those who are breastfed for any longer or shorter. [54] Infants who are breastfed for more than twelve weeks are less likely to suffer RTIs too – though this phenomenon is more applicable to the first half of infancy. [55–57] In fact, the overall protective effect of breastfeeding appears to be most apparent in the first 2 years of life, before diminishing with age. [58,59] Numerous studies agree that breastfeeding is protective against wheezing and/or asthma. However, infants may need to be breastfed for up to six months – or even a year – in order to reap any benefits. [54,59–62] Breastfeeding can also reduce the risk of hospitalisation with

lower respiratory tract disease, and may reduce a child's susceptibility to the effects of ETS. [63,64]

2.3.3 Co-morbidities

Various co-morbidities are associated with paediatric respiratory disease. Pulmonary and neurological co-morbidities are particularly associated with influenza hospitalisations, but any co-morbidity will increase the risk of being hospitalised for a lower RTI. [65,66] Respiratory symptoms are more prevalent in HIV sufferers – as is poor lung function. [67] Neurodisability has been connected to an increased chance of experiencing chronic respiratory symptoms. [68] RTIs may increase the risk of childhood asthma, but asthma may increase the risk of RTIs too – especially those requiring hospitalisation. Childhood obesity also increases one's asthma risk. [46,59,69,70] Congenital airway abnormalities are more frequent amongst those with: neurological defects, chromosomal abnormalities, and cleft lips/palates. [71]

2.3.4 Deprivation

Living in deprivation can increase a child's exposure to: poor nutrition, prematurity, antenatal smoking, poor air quality, damp housing, overcrowding, poor vaccination uptake and lack of green space. [72] These are all pre-established risk factors for poor paediatric respiratory health. Deprived children are more likely to be admitted to hospital with acute respiratory failure or an RTI. It is likely that deprivation increases the risk of contracting an RTI too, but there is conflicting evidence. [55,72–77] The association between deprivation and asthma also has conflicting evidence. There might not be a link between the two, yet some data suggests that asthma is less prevalent in deprived children. Asthmatic children can experience more severe symptoms however, if they come from a deprived background. [78,79]

2.3.5 Ethnicity

Recent years have shown an increasing interest into the effect of ethnicity on respiratory health. Caucasian children have greater FEV_1 and forced vital capacity measurements, as well as greater functional residual capacity (when standing), compared to children of other ethnicities – especially black children. [80,81] Black children are 1.7 times more likely to suffer from respiratory disease at 3-years-old, with tonsillopharyngitis and lower RTIs being particularly more common by school-age. [70,82]

Children with black parents may have an increased chance of being asthmatic too. [83] Non-Caucasian children have a higher risk of influenza-related hospitalisation, and with the exception of Asian/Pacific Islander infants, are more likely to die from a lower RTI during infancy. [65,84]

2.3.6 Family History of Atopy

The relationship between familial atopy and wheezing disorders has been thoroughly established. [85–89] A *maternal* history of asthma is strongly associated with wheezy and/or asthmatic children; sibling and paternal histories are still associated – albeit to a lesser extent. [29,59,88,89] In fact, a maternal history of asthma may subdue the protective effects of breastfeeding, because asthma is more common amongst breastfed 6-year-olds when their mother has the disease too. [62] A maternal history of asthma will increase the risk of infantile lower RTIs, whilst a maternal history of hay fever will decrease the prevalence of childhood respiratory symptoms. [29,55,90] The same cannot be said for children with a paternal and/or sibling history of hay fever however, as such children are more likely to wheeze. [88]

2.3.7 Household Population

There is inconsistent research into how the composition of a child's household affects their respiratory health. Household crowding, and the presence of older siblings, are correlated with an increased incidence of lower RTIs. [55,91–93] However, they are also associated with lower rates of asthma and atopic disease. [53,89,91,94] Infants are still more likely to be hospitalised with an RSV infection, when they have older siblings though. [75] These trends imply that (older) siblings expose children to infectious agents in early life (resulting in more RTIs). Such exposures then prime the immune system, so that it doesn't become sensitised to innocuous agents in later life – thus preventing atopy. [89]

2.3.8 Living Conditions

A child's living conditions are known to influence their respiratory health. Families of a lower socioeconomic status report living in worse conditions, so are exposed to more potential triggers of paediatric respiratory disease. [83] Children experience more respiratory symptoms, whenever their household air contains traces of: NO_2, calcium, chlorine or silicon. [95] Pests and water leaks are known to increase the risk of

developing asthma, but damp and mould in particular, can increase the risk by 30-50%. Mould also leads to more emergency hospital admissions amongst asthmatic children, when it grows in their bedrooms. [59,83,96] Living on a farm is said to be protective of asthma. [59] The presence of household damp, mould and/or humidity raises the incidence of respiratory infections. [70,97]

2.3.9 Low Birth Weight

Most research suggests that a 'low birthweight' is a risk factor for respiratory disease in children – especially amongst 2 to 6-year-olds, and those exposed to ETS. [98] There is some data to suggest that respiratory symptoms are actually more common amongst children of a higher birthweight. [29] A 'low birthweight' is connected to poorer lung function, which can even persist into adulthood (especially amongst males). [99,100] Asthma and wheezing is more prevalent amongst those born at less than 2.5kg. However, recurrent wheezing may be less common within this demographic during infancy. [29,59,87,101,102] Infants born at less than 2.5kg also have a greater risk of dying from a RTI – possibly because they are more likely to suffer from severe RSV infections. [84,103]

2.3.10 Maternal Age

Research is increasingly looking at the role of maternal age, in paediatric respiratory disease. Children born to a mother aged less than 25-years-old, are more likely to: be hospitalised with RSV, have airway disease, or die of a lower RTI. [84,103,104] Of course, the fact that younger mothers tend to be more deprived and tend to smoke more, could influence these statistics. [105] A maternal age of less than 20-years-old has been associated with an increased prevalence of childhood asthma. This phenomenon has been observed across the globe, but in Mexican-American women, a young maternal age is protective against childhood asthma – suggesting a degree of cultural dependency to this particular risk factor. [106–108]

2.3.11 Nursery Attendance

The majority of data implies that nursery attendance is a significant risk factor for respiratory health. Children who attend nursery experience more respiratory symptoms; wheezing is particularly common during the infantile years. [29,86–88,109] RTIs are more likely when children attend nursery, so the fact that attendees visit a doctor

twice as often as non-attendees is not surprising. [110,111] Diagnosable respiratory diseases are also more common amongst nursery attendees, and the risk of atopic disease is higher when children enter nursery before 6-months-old. [51,89] However, since nursery attendance can increase a child's exposure to infectious/sensitising agents, there may actually be a protective effect associated with it. Such an effect may only become apparent in later childhood though. [89]

2.3.12 Nutrition

2.3.12.1 Maternal Diet

A mother's diet during pregnancy can influence her child's future respiratory health. Infants appear to wheeze more, if their mother ate a lot of fast-food during pregnancy; the risk of wheezing also increases, as maternal body mass index increases. Childhood asthma is associated with maternal obesity too. [59,87,112] If their mothers had carbohydrate-rich diets during pregnancy, infants are more likely to have severe RSV infections. [113] On the other hand, a 'Mediterranean diet' during pregnancy is believed to be beneficial to children's airway functioning – and to the prevention of wheezing. Fish and apples are particular protective against asthma/atopy. [114–116] Benefits to infantile respiratory health have also been seen from maternal diets that are rich in: fibre, zinc, vitamin D and vitamin E. [59,115,117]

2.3.12.2 Child's Diet

Just as maternal diet can impact a child's respiratory health, so too can a child's diet. Again, 'Western diets' and too much fast-food can lead to an increased prevalence of wheezing, RTIs and dyspnoea amongst pre-school-aged children. [118,119] Obesity is also associated with an increased asthma risk again. [59] Fortunately, asthma and wheezing are thought to be preventable by adhering to a 'Mediterranean diet'. Fruits provide more of a protective effect than vegetables, but this becomes more apparent as children become older. [59,119,120] Symptoms of an upper RTI can be minimised by following a diet of green vegetables, beef, and dairy products. [121] Any malnutrition however, can cause the respiratory system to under-develop – especially in the first three years of life. [72]

2.3.13 Parental Education

Parental education has recently emerged as a potential risk factor for paediatric respiratory disease. Diagnosable respiratory diseases are more common amongst children whose fathers have a poor education. [51] An incomplete maternal high school education increases the risk of respiratory failure in preterm infants, whilst less than twelve years of maternal education raises an infant's lower RTI mortality risk. [84,122] The risk of developing asthma is greater in children whose mothers have a low level of education, and even amongst diagnosed asthmatics, having less educated parents is associated with poorer control over the disease. [123,124] When a child's parents are less educated, their FEV_1 is lower, and they are more likely to be hospitalised with influenza. [65,125]

2.3.14 Prematurity

Premature birth (<37 weeks) is a well-documented risk factor for poor paediatric respiratory health, where children with the smallest gestational ages bear the greatest risk. [59,126] However, children who are born late-preterm or early-term still experience more respiratory symptoms than their full-term counterparts. Late-preterm infants are hospitalised more often than full-term infants too. [127,128] The risk that prematurity poses, can partly be explained by its association with bronchopulmonary dysplasia. Bronchopulmonary dysplasia is more common in extremely premature births (<28 weeks), and is known to result in a higher prevalence of respiratory symptoms and poorer lung functioning. [126,129] Lung function is poor in many premature infants though – especially males. [99,130] Infantile respiratory infections are more frequent in those born very prematurely (<32 weeks). [126] Wheezing and asthma are more common amongst prematurely-born children, and again, the most premature children are the most likely to be wheezy/asthmatic. [109,131,132]

2.3.15 Sex

The majority of literature identifies males as being at a higher risk of respiratory disease, compared to females. This risk may be even greater for males born prematurely. [126] They experience more respiratory symptoms, and visit healthcare services for said symptoms, 50% more often. [29,110] Wheezing is particularly more common amongst boys. [85–89,109] Boys are more likely to suffer and die from lower RTIs,

as well as be hospitalised with RSV – possibly because they have smaller airways, and are thus more susceptible to the pathophysiologic sequalae of an RTI. [75,84,111,133] Conversely, girls may experience upper RTIs more frequently. [70]

2.3.16 Sharing a Bedroom

Sharing a bedroom in childhood appears to be detrimental to paediatric respiratory health, although with a relatively limited evidence base, it is difficult to conclude how significant the risk is. [91] The likelihood of an RSV-associated lower RTI (in the first three months of life) increases, as more people share a bedroom with said infant. [133] Lower RTIs are more common when the bedroom is shared with another pre-school-aged child; sharing with an adult makes upper RTIs more common. [111] When toddlers share an actual bed, then they are deemed to be at greater risk of asthma in later life. [134]

2.3.17 Smoking

Exposure to second-hand tobacco smoke is responsible for a significant amount of chronic respiratory disease. [96] Children can be exposed to tobacco smoke in two different stages of life: antenatally and/or postnatally…

2.3.17.1 Antenatal Smoking

Evidence consistently links smoking during pregnancy, with poor paediatric respiratory health. However, some research suggests that any detriment will dwindle throughout infancy, whilst other research suggests that school-age children are worst-affected by antenatal smoking. There might even be a lifelong risk of respiratory disease. [29,56,59,135] Amongst children whose mothers smoked antenatally, lung function is poorer and RSV-associated hospitalisations are higher. [75,136] Wheezing is also more prevalent, especially if a child's mother smoked in the second and/or third trimester. [87–89,137] Not only is bronchiolitis commoner in infants whose mothers smoked during pregnancy, but the mortality risk from the disease (and other lower RTIs) is greater too. [84,138] Antenatal smoking can increase the risk of prematurity and 'low birthweight': two known risk factors for poor respiratory health – which may exacerbate the effects of smoking during pregnancy. [56]

2.3.17.2 Postnatal Smoking

Approximately 65,000 children die from the underlying effects of ETS every year, across the world. [139] Pre-school-aged children are at a particular detriment to the effects of ETS. [59] RTIs are more common amongst those exposed to ETS, as are asthma and asthma attacks. [83,93,96,111,140,141] Maternal smoking presents a larger risk than paternal smoking, in the development of: upper RTIs, asthma and wheezing. [87,140,141] When a child lives with more than two smokers, they are at a heightened risk of acquiring severe pneumonia. [142]

2.4 The Liverpool Respiratory Symptom Questionnaire

2.4.1 Origins of the LRSQ

The LRSQ is an accepted respiratory symptom questionnaire, which has been validated for use amongst pre-school-aged children. Powell *et al.* developed it in Alder Hey Children's Hospital and Liverpool Women's Hospital (LWH) because at the time, there was no standardised questionnaire for assessing the prevalence nor natural history of respiratory symptoms in the pre-school age group. [143] The most widely-used respiratory symptom questionnaire was the ISAAC questionnaire, but it was only validated in school-aged children. [144]

The original questionnaire contained thirty-four items, derived from existing respiratory symptom questionnaires. The items were divided into four domains: 'daytime symptoms', 'night time symptoms', 'impact of the symptoms on the child', and 'impact on the family'. [143] Each item utilised a five-point Likert scale, as used in a previous parentally-completed questionnaire by Usherwood *et al.* [145] The original questionnaire can be found in **Appendix 2**.

The questionnaire was validated, based on responses from 114 caregivers. Each caregiver completed the LRSQ on two separate occasions. This allowed its short-term reliability to be tested; using Cohen's kappa, all questions – bar one, about 'noisy breathing from the throat' – showed at least moderate short-term reliability. Both Cronbach's alpha and factor analysis were used to assess the internal consistency of each domain – with all four domains showing moderate to excellent internal consistency. When the LRSQ scores of children who had been officially diagnosed with

asthma (based upon physician expertise) were compared with non-asthmatic children, all domains of the LRSQ were deemed sensitive to differentiating between asthmatic and 'well' children. This is testament to the questionnaire's criterion validity. The content validity of the LRSQ (i.e. whether it adequately encompasses all relevant areas of paediatric respiratory health) was deemed acceptable by two respiratory paediatricians. [143]

Despite the apparent success of the LRSQ, during factor analysis, four questions were found to have poor internal consistency with the rest of their domains, so they were removed from the questionnaire. In light of this, the questionnaire was reorganised into eight domains. Three of the new domains had excellent internal consistency: an alpha score of ≥0.91, with the remaining domain possessing acceptable internal consistency. [143]

2.4.2 Usage of the LRSQ

The LRSQ has been validated to distinguish between children who are 'well' with CF, and those who don't have the disease. [146,147] The questionnaire has also been validated for distinguishing children – up to the age of twelve – who are 'well' with CF, against those who are experiencing an exacerbation. [147]

The LRSQ is has been employed in studies that assess respiratory symptoms in children with neuro-disabilities. [148] One such study adapted the LRSQ, by removing the 'symptoms with activity' domain. It found that children with neuro-disabilities have significantly higher total scores, than those without. [68] Another study found that neuro-disabled children have higher total scores, when their gastroesophageal reflux is treated surgically – compared to no surgery at all. [148] A future study will assess respiratory symptoms in neuro-disabled children who take a year of prophylactic azithromycin. [149]

The questionnaire is commonly used in studies that explore the natural history of asthma. Researchers in the Netherlands have used the LRSQ for multiple projects that aim to identify a biomarker for the inflammatory disease. [150–152] In doing so, they have found that future asthmatics have higher LRSQ scores during the pre-school period than transient wheezers do. [150]

The LRSQ has frequently been used to investigate the association between respiratory symptoms and prematurity. [128,130,132,153–157] By using the questionnaire, Edwards *et al.* found that increasing prematurity will increase the prevalence of respiratory symptoms. They also discovered that an early-term birth was associated with more prevalent respiratory symptoms, and more frequent healthcare attendance. [128,132] Others researchers have shown that prematurity will increase the total LRSQ score, due to the fact that a child is more likely to suffer from chronic lung disease. [153,154]

The LRSQ has been used to understand the effect of other risk factors on respiratory health too. It has been used to highlight the protective effect that a high-fibre maternal diet can have on a growing foetus' respiratory health. [115] The questionnaire has been able to demonstrate the particular risk that passive smoking has on African-American children as well. [158] Mattes *et al.* adapted the LRSQ, and observed that optimised asthma control during pregnancy can reduce the incidences of bronchiolitis and croup in the first year of life. [159] Even another cohort study has used the questionnaire, to investigate the risk factors for wheezing in childhood. [85]

There are more instances of the LRSQ being used. [160–165] The questionnaire was used to assess the prevalence of long-term respiratory symptoms amongst children who had contracted an RTI during chemotherapy. [160] The LRSQ was also used to compare the respiratory symptoms of three-years-olds, based to their history of RSV-bronchiolitis or RSV-induced wheeze in infancy. [161] By using the questionnaire, another study investigated the respiratory morbidity of neonates who were born to mothers who had undergone an amniotransfusion. [162]

2.4.3 The LRSQ in the LBBS

The LRSQ is the ideal questionnaire to use in the LBBS. It is targeted at the correct age group: pre-school-aged children, and it assesses non-specific respiratory symptoms. It assesses QoL too. The LRSQ is relatively modern, and can be used on children with various co-morbidities. The version of the LRSQ used in the LBBS contains 33 questions, 32 of which are assessed on a five-point Likert scale. A question about 'ever wheezing' was omitted, as the longitudinal nature of the study should have been able to detect all incidences of wheezing from birth.

2.5 Other Paediatric Respiratory Symptom Questionnaires

Respiratory symptom questionnaires are used in healthcare to aid clinicians in understanding their patient's condition. They are easy to administer, quick to complete and simple to interpret – which makes them ideal for use in time-deprived settings (e.g. primary care, emergency departments or clinics). As well as the LRSQ, there are numerous options available. Some are generic respiratory symptom questionnaires that enquire about a wide range of symptoms, and are often used for epidemiological purposes. Other types of respiratory symptom questionnaire focus on a specific symptom – usually to understand how it affects a patient's QoL. However, the majority of respiratory symptom questionnaires focus on a particular disease. Disease-specific questionnaires tend to assess a patient's control over their condition, or how it affects their QoL.

Some respiratory symptom questionnaires are more widely established than others. **Table 3** identifies how many times certain pre-validated respiratory symptom questionnaires (including the LRSQ) have been cited in literature, according to three different sources. This is followed by brief outlines of said questionnaires.

Average Rank	Questionnaire	Dimensions	Semantic Scholar	Web of Science
7	**ACQ** [166]	157	184	144
24	**Asthma Quiz for Kidz** [167]	33	37	32
8	**ATAQ** [168]	114	141	112
31	**ATS-DLD-78-C** [169]	N/A	N/A	2
30	**Best ACT-P** [170]	5	4	2
15	**BPAS** [171]	55	62	47
18	**Breathmobile Case Identification Survey** [172]	51	41	49
3	**C-ACT** [173]	516	598	478
25	**CAN** [174]	24	38	25
13	**CA13Q** [175]	69	61	55
10	**CFQ** [176]	84	109	71
9	**CHSA** [177]	116	131	106
16	**Easy Breathing Survey** [178]	52	64	46
14	**EISL-WQ** [179]	55	77	51
5	**Functional Severity of Asthma Scale** [180]	188	219	184
21	**HAY** [181]	38	52	28

11	**Integrated Therapeutics Group Child Asthma Short Form** [182]	78	91	65
1	**ISAAC** [144]	2316	2893	2287
19	**LASS** [183]	41	47	43
4	**LCQ** [184]	489	541	406
20	**Leicester Respiratory Cohorts Questionnaire** [185]	35	47	39
17	**LRSQ** [143]	49	64	48
26	**MeDALL** [186]	22	33	19
27	**PACCI** [187]	26	25	20
28	**PAC-QoL** [188]	9	6	7
22	**PACT** [189]	38	40	34
2	**PAQLQ** [190]	804	921	726
29	**PCQ** [191]	4	15	3
23	**PC-QOL** [192]	34	40	31
6	**PRQLQ** [193]	178	208	163
12	**TRACK** [194]	75	76	68

Table 3: paediatric respiratory symptom questionnaires, by number of citations

2.5.1 ACQ: Asthma Control Questionnaire

The ACQ was designed by Juniper *et al.* to measure asthma control in adults, butwas validated for use in children in 2010. [166,195,196] The questionnaire can be used on any child older than 5-years-old, but an interviewer needs to deliver it, if the child is under 10-years-old. [166] The ACQ comprises of seven items about the preceding week, which are all scored on a seven-point Likert scale. [197,198] Three shorter versions of the ACQ have been created, are proven to be equally as valid as the original. [198] The total score is the mean score from each of the seven items; a total score of ≥1.5 is representative of uncontrolled asthma. [195,197] A change in score of greater than 0.4-0.5 is judged to be clinically significant. [166,198,199]

2.5.2 Asthma Quiz for Kidz

The Asthma Quiz is used to identify children with poor asthma control. [167] It contains six items, which are self-completed by children who are older than 9-years-old, or parentally-completed for younger children. Any child scoring ≥2 should have their asthma control reviewed. Since the questionnaire was designed in Quebec, it exists in both French and English. [167]

2.5.3 ATAQ: Asthma Therapy Assessment Questionnaire

Adapted from the adult version by Skinner *et al.*, the ATAQ identifies potential issues in a patient's asthma management, in order to optimise care. [168,200] The questionnaire can be completed by the parent of any child older than 4-years-old. [168,196,201] It is composed of twenty items, split into four domains – one of which is 'asthma control'. A score of ≥4 in this domain is associated with poor asthma control, and an increased likelihood of hospitalisation. [196,202]

2.5.4 ATS-DLD-78-C

The ATS-DLD-78-C is a parentally-completed questionnaire for children who are under 12-years-old. It was designed to be similar to the adult version: ATS-DLD-78. Despite being a relatively old questionnaire, it still enquires about a child's exposure to risk factors – which makes it useful for epidemiological studies. [169]

2.5.5 Best ACT-P: Best Asthma Control Test for Preschoolers

Sato *et al.* designed the Best ACT-P to assess whether pre-school-aged children in Japan have *optimised* asthma control, as opposed to just poor control. The questionnaire was based on the Japanese Paediatric Asthma Guidelines. Since the Best ACT-P is geared towards pre-school-aged children, it is a parentally-completed questionnaire of six items, which are each answered on a five-point Likert scale. [170]

2.5.6 BPAS: Brief Paediatric Asthma Screen

Wolf *et al.* created the BPAS, so as to detect potential asthma diagnoses amongst schoolchildren. It is a five-item parentally-completed questionnaire, whereby each item asks about events/symptoms in the preceding year. [171] A modified version: the BPAS+, has been developed to help identify children who may have allergic rhinitis. [203] The BPAS has also been validated in Spanish. [204]

2.5.7 Breathmobile Case Identification Survey

Jones *et al.* developed the Breathmobile Case Identification Survey, as a tool for detecting asthma amongst 5 to 11-year-old schoolchildren. [172,201] The questionnaire has seven parentally-completed items; six of these items are measured on a five-point Likert scale – with the remaining item being made-up of five 'yes/no' sub-questions. Seven different answer patterns have been deemed discriminatory for detecting

asthma; the survey is therefore 86.5% sensitive and 83.6% specific, when one of these answer patterns is fulfilled. [172] The survey is available in both English and Spanish. [172] A slightly modified version of the survey has been validated for identifying children with uncontrolled asthma, as well as those with moderate-to-severe disease activity. [205]

2.5.8 C-ACT: Childhood Asthma Control Test

Any asthmatic child between 4 and 11-years-old can use the C-ACT; children older than 12-years-old should use the original ACT. [206] The C-ACT is a seven-item asthma control questionnaire, with a maximum score of 27 – unlike the ACT, which is out of 25. [173,207] Four of the items are completed by the child (with the help of a visual aid), and the remaining three are completed by a parent. [196] With a score of ≤19, children are deemed to have 'uncontrolled asthma', and with a score of ≤12, children are considered to have '**very** uncontrolled asthma'. [207,208] A change in score of ≥2 is clinically significant. [206] Due to its widespread use, the C-ACT is not only available in English – but Spanish, Portuguese, Turkish and Chinese too. [209–212]

2.5.9 CAN: Asthma Control in Children

CAN is a Spanish test for asthma control in children aged 2 to 14-years-old. There are nine items, which are each assessed on a five-point Likert scale. The questionnaire can be parentally-completed for all children, yet children aged 9 to 14-years-old can self-complete the it too. A total CAN score of ≥8 is considered to exceed the threshold for poor asthma control. The questionnaire is proven to be sensitive to change over time as well. [174]

2.5.10 CAQ: Childhood Asthma Questionnaire

The CAQ measures QoL and disease severity in childhood asthma. [175] There are three versions of the questionnaire: the CAQ-A is aimed at 4 to 7-year-olds; the CAQ-B is aimed at 8 to 11-year-olds; and the CAQ-C is aimed at 12 to 16-year-olds. [213] Each version encourages the child to self-complete as much of the questionnaire as possible, but the CAQ-A/CAQ-B still require some parental input. All three CAQs use Likert scales: the CAQ-A has four-point scales and the CAQ-B/CAQ-C have five-point scales. The questionnaires get longer as children get older, because more areas of QoL start to be assessed. [175]

2.5.11 CFQ: Cystic Fibrosis Questionnaire

There are multiple versions of the CFQ. Originally, there were three: one for people over ≥14-years-old (CFQ 14+), and two for those aged 8-13 (CFQ Child). [176] For the 'CFQ Child', one option was parentally-reported and one was self-reported (though an interviewer was required to administer it to children under 11-years-old). [176,214] When the questionnaires were translated into English, the 'CFQ Child' questionnaires were found to be valid in 6 and 7-year-olds too. [214,215] All three questionnaires have been adapted into age-specific 'CFQ-R's – which are the most widely-used instruments for assessing QoL in CF patients. [216] A 10-point worsening in CFQ-R score has been shown to be indicative of a CF exacerbation in pre-school-aged children. [217] The 'CFQ-R' has been translated and validated in over thirty languages, including: German, Spanish, Turkish and Portuguese. [176,216,218–220]

2.5.12 CHSA: Children's Health Survey for Asthma

The Children's Health Survey for Asthma was developed by the 'American Academy of Pediatrics', in order to measure QoL in asthmatic children. It is aimed at children aged 5 to 12-years-old. A five-point Likert scale is employed across forty-eight items; these forty-eight items are classified into one of five domains, and are to be answered by a parent. [177] Another version exists as well, which can be completed by the child themselves. [221]

2.5.13 Easy Breathing Survey

The aim of the Easy Breathing Survey is to assist primary care physicians in diagnosing paediatric asthma. There are twenty-five items: twelve are clinical, and 13 enquire about demographic measures. Four of the items are highly sensitive to detecting (persistent) asthma when answered with a positive response. [178]

2.5.14 EISL-WQ: Estudio Internacional de Sibilancias en Lactantes Written Questionnaire

The original purpose of the EISL-WQ was to study the prevalence of recurrent wheezing amongst infants (<1-year-old) in Latin America and parts of Europe. [179] More recently, a shortened version has been validated for use in 12 to 36-month-olds, which can assess the likelihood of said children being asthmatic. The questionnaire itself is

parentally-completed, and consists of forty-five items about the: prevalence, nature and risk factors of wheezing. The EISL-WQ is available in Spanish and Portuguese. [222]

2.5.15 Functional Severity of Asthma Scale

The Functional Severity of Asthma Scale measures the severity of asthma in schoolchildren, over the preceding year. [180] Of its six items, five of them are answered on a five-point Likert scale, whilst the remaining item is a simple 'yes/no' answer. [223] The questionnaire is delivered by an interviewer. [180] The marks from each item are summated to achieve a total score out of 24. Depending on their score, children are allocated an asthma severity of: low, mild, moderate or high. [180,223]

2.5.16 HAY: How Are You?

HAY is a Dutch respiratory symptom questionnaire, that is used to assess the QoL of asthmatic children. It can be administered to children aged 8 to 12-years-old – with both self-reported and parentally-reported versions available. Four-point Likert scales and 'yes/no' questions are used to answer thirty-two generic items about QoL, and forty asthma-specific items about QoL. HAY is responsive to changes in asthma status, and is also capable of differentiating between symptomatic and non-symptomatic patients. [181]

2.5.17 Integrated Therapeutics Group Child Asthma Short Form

In 1999, McGrath *et al.* constructed a long-form QoL questionnaire for asthmatic children, by combining a previously-existing asthma questionnaire and the Child Health Questionnaire-Parent Form (CHQ-PF50). In 2000, a short-form adaptation, which would be more suitable for use in clinical practice, was created by taking eight items from a modified version of the asthma questionnaire. [145,182,224] These eight items are distributed into three domains, and are each assessed on a five-point Likert scale. The 'Integrated Therapeutics Group Child Asthma Short Form' has been proven to identify better QoL in mild asthmatics, and poorer QoL in severe asthmatics. [182]

2.5.18 ISAAC: International Study of Asthma and Allergies in Childhood Questionnaire

The ISAAC questionnaire is an epidemiological tool, which was designed to measure the worldwide prevalence of atopic diseases. [144] It is the most widely used respiratory symptom questionnaire worldwide – with over one million children, from nearly one

hundred different countries, having been surveyed with it. [143,225] The ISAAC questionnaire is therefore available numerous languages; it is also available in a video and telephone format. [143,226] ISAAC is frequently used in cohort studies. [186] Two versions of the questionnaire exist: one parentally-completed twenty-one-item questionnaire for children aged 6 to 7-years-old, and one self-completed twenty-item questionnaire for 13 to 14-year-olds. [144,227]

2.5.19 LASS: Lara Asthma Symptom Scale

The LASS measures asthma control amongst children in non-English-speaking populations. It contains eight parentally-completed items, which assess the frequency of asthma symptoms on a five-point Likert scale. [183] The score from each item is summated to produce a total score, but no cut-off has yet been established for differentiating between poor and adequate asthma control. [228] The questionnaire was originally validated in English and Spanish, but has now been translated into additional languages (e.g. Chinese). [183,229]

2.5.20 LCQ: Leicester Cough Questionnaire

The LCQ was originally designed to measure the QoL of adults with a chronic cough. [184] However, it is also able to measure the QoL of 7 to 18-year-old (Spanish) children with CF. [230] There are nineteen self-completed items – each categorised into one of three domains (social, physical or psychological). Every item is assessed on a seven-point Likert scale. [184] The total score, which is responsive to changes over time, is obtained by calculating the mean domain score. [184,230]

2.5.21 Leicester Respiratory Cohorts Questionnaire

In 1990, Luyt *et al*. created a questionnaire to measure the prevalence and natural history of respiratory symptoms in pre-school-aged children, as part of the Leicester Respiratory Cohort Study. [231,232] Silverman and Kuehni modified the original questionnaire by adding questions from the ISAAC questionnaire, whenever they expanded the cohort study in 1998. [185,232] The modified questionnaire has since been validated for assessing the prevalence of respiratory symptoms in 1 to 2-year-old children. [232] It has been validated in Portuguese too. [233]

2.5.22 MeDALL: Mechanisms of the Development of Allergy Questionnaire

The MeDALL questionnaire provides a standardised tool that can be used by multiple birth cohorts, when studying atopic diseases. This allows data from various studies can be accumulated together – thus creating larger sample sizes, increasing statistical power and allowing more direct comparison between data sets. Each questionnaire contains a set of 'core' (mandatory) items, as well as 'supplementary' (optional) items to be included at a researcher's discretion. Items concern both symptom prevalence and risk factor exposure. There is only a parentally-completed form for children aged 4 to 9-years-old, but there are self-completed **and** parentally-completed forms for 14 to 18-year-old children. Since it was originally designed for use across Europe, the questionnaire has been translated from English, into: Dutch, Danish, French, Italian, Spanish, Swedish, German and Greek. [186]

2.5.23 PACCI: Paediatric Asthma Control and Communication Instrument

The PACCI assesses both asthma control, and asthma-specific QoL in children. [187,234] It contains twelve items, which are answered by a parent. A total PACCI score of ≥3 has the greatest sensitivity to detecting uncontrolled asthma in children. [187] The questionnaire was designed to better-represent ethnic minority groups in the United States, so is validated in Spanish and English. [187,234] A modified version of the questionnaire (PACCI-ED) is used to help emergency physicians assess a child's asthma control accurately, in a time-sensitive environment. [235]

2.5.24 PAC-QoL: Parent-Proxy Children's Acute Cough-Specific Quality of Life Questionnaire

Anderson-James *et al*. developed the PAC-QoL, so as to measure the QoL of children with an acute cough. The questionnaire contains sixteen items, each answered on a seven-point Likert scale by a parent. The questionnaire is sensitive to changes over time, but its use may be limited to younger children. [188]

2.5.25 PACT: Paediatric Asthma Control Tool

The PACT is a ten-item, parentally-completed questionnaire, which is used to monitor asthma control in schoolchildren. [189,201] Five items concern the frequency/severity of asthma exacerbations in the preceding three months; the other five items concern symptoms in-between exacerbations. All ten items are scored on a six-point Likert

scale. [189] A smaller-scale version of the PACT (M-PACT) has been designed to aid emergency physicians in identifying children with persistent asthma. [236]

2.5.26 PAQLQ: Paediatric Asthma Quality of Life Questionnaire

The PAQLQ measures QoL in 7 to 17-year-old asthmatic children. [190] On a seven-point Likert scale, the twenty-three self-completed items assess: symptoms, emotional function and limitation of activity. [190] The final score is the mean score from all twenty-three items, and is responsive to changes over time. [190,237,238] The PAQLQ has been validated in: Portuguese, Dutch, Swedish, Italian, Arabic and Spanish. [238–243] A thirteen-item 'mini PAQLQ' has been validated too. [166,244]

2.5.27 PCQ: Paediatric Cough Questionnaire

Paul *et al*. created the PCQ to assess the QoL of children with a chronic cough. The original questionnaire contained five items, each answered on a seven-point Likert scale; however, the validated questionnaire actually uses six-point scales instead. [191,245] The PCQ has been proven to show clinically significant changes in score over time. [191]

2.5.28 PC-QOL: Parent Cough-Specific Quality of Life Questionnaire

The PC-QOL is a parentally-completed questionnaire, for measuring the QoL of children with chronic coughs. It was created due to the absence of such a questionnaire for the paediatric population, as well as the unsuitability of disease-specific questionnaires. [192] The PC-QOL contains twenty-seven items. [192]

2.5.29 PRQLQ: Paediatric Rhinoconjunctivitis Quality of Life Questionnaire

Juniper *et al.* developed the PRQLQ to measure QoL in 6 to 12-year-old children with hay fever. There are twenty-three items in the PRQLQ – distributed across five domains – which are all answered on a seven-point Likert scale. The items concern symptoms over the prior week. Questions are answered by the child, but delivered by an interviewer. The total PRQLQ score has been found to be responsive to change in disease status over time. [193]

2.5.30 TRACK: Test for Respiratory and Asthma Control in Kids

TRACK is an asthma control questionnaire, targeted at pre-school-aged children. It has five items, each scored on a five-point Likert scale, to give a total score out of 100. [194] A score of <80 indicates poor asthma control, and a change in score of ≥10 is deemed to

be clinically significant. [196,246] TRACK has been validated in multiple foreign languages, including: Portuguese, Korean, Chinese, Turkish and Spanish. [247–251]

2.6 Respiratory Health in Liverpool

Liverpool, Merseyside is a city in the North West of England, with a population of almost half-a-million people. [252] The city is burdened by major health inequalities, which severely impact its population. Infants born from 2016 to 2018 can expect to have an average life expectancy of 78.2-years-old. This is 2.2 years shorter than the Merseyside average, and 3.2 years shorter than the English average. [253] For example, a baby born in Kensington, Liverpool from 2009 to 2013 can expect to live 77.4 years; a baby born in Kensington, London will be expected to live 9.2 years longer. [254] Alongside cancer and cardiovascular disease, one of the main reasons behind the widening discrepancy in life expectancy has proven to be respiratory disease. [255]

Respiratory disease has long been a major cause of mortality in Liverpool. In the late nineteenth century, approximately 1% Liverpool's residents would die from respiratory disease – cementing it as the city's leading cause of death, which is remained so until at least 1940. [256] Respiratory disease is now the third-leading cause of premature death (i.e. under 75-years-old) in Liverpool, and such deaths are projected to increase in the coming years. [255] From 2016 to 2018, 66 of every 100,000 people in the city died from respiratory disease: nearly twice the national average. 63% of these deaths were considered preventable. [257] Smoking accounted for 22% of Liverpool's preventable deaths in 2016 – vastly more than the English or North Western averages. [96,258–260] Given the well-established association between smoking and chronic obstructive pulmonary disease (COPD)/lung cancer, Liverpool therefore places amongst the ten worst local authorities in England for COPD-related deaths, and amongst the five worst for lung cancer-related deaths. [258,260]

Irregardless of mortality, respiratory disease will always place a burden on patients' QoL, as well as local resources. Liverpool is one of the ten worst local authorities in England for COPD prevalence: 7% of people over 40-years-old were diagnosed with the condition in 2018. [257,261] The prevalence only seems to be increasing, and so, the number of disability-adjusted life years in the city are increasing with it. [96,255,257,259]

Liverpool's asthma prevalence is lower than expected. Despite a surge in asthma cases during the nineties, which was associated with fuel stockpiling at Bootle's docks, just 5.8% of residents had a diagnosis in 2019. [257,262] Emergency hospital admissions for asthma remain higher in Liverpool than in England however. [96,257] The number of respiratory-related emergency hospital admissions in Liverpool has been steadily increasing over the last half-a-decade; approximately one-third of admissions are for pneumonia, and one-fifth are for COPD. [96,257] The burden of respiratory disease is now so severe in Liverpool, that compared to the national average, Liverpool Clinical Commissioning Group spent £16 more on respiratory care per capita in 2015/16. [96]

One of the leading contributors to Liverpool's poor respiratory health is smoking. In 2019, 41% of the population were reported to be ever-smokers. However, the past decade has seen an increase in smoking cessation – meaning that the prevalence of current smokers is no longer significantly different to England's. [258] Hospital admissions attributable to smoking, and the proportion of women smoking during pregnancy, are still higher than the national average though. In 2019, 21.5% of women admitted to smoking at the point of their booking appointment; this statistic fell to 13% by the time of delivery. [258] Additionally, COPD and asthma patients in the city are known to be 2.8 and 1.6 times more likely to smoke respectively, compared to residents without either condition. [96]

Another factor that contributes to the poor respiratory health of Liverpool is air pollution. On average, there was 9.6µg/m^3 of fine particulate matter in the air across the city in 2010. Although this fell to 8.1µg/m^3 in 2017, which is lower than the national average, some areas of Liverpool still breach the World Health Organisation's fine particulate matter target of 10µg/m^3. [43,158,263] Some of this pollution will originate from the docks of North Liverpool. Canada Dock has been repurposed for recycling scrap metal – a process that produces a toxic amount of heavy metal fumes, which can be carcinogenic when inhaled. [264] Tonnes of coal and petroleum coke used to be stockpiled in the docks of North Liverpool too, and dust from these stores may still pollute air in the surrounding area. [262] Some parts of Liverpool also exceed the government's target for roadside NO_2 levels: 40µg/m^3. [43] Pollution from fine particulate matter and NO_2 is known to increase the risk of childhood asthma, RTIs,

asthma exacerbations, COPD exacerbations and bronchopulmonary dysplasia. In 2011, said pollution contributed to over 300 deaths within Liverpool – many of which will have had a respiratory basis. [43]

Deprivation also has an effect on respiratory health in Liverpool. Until 2010, Liverpool was the most deprived local authority in England; it now ranks third behind Blackpool and Knowsley. [265] 48% of residents inhabit an area within the lowest index of multiple deprivation (IMD) decile – with most of these areas being northern suburbs of the city. [96,265] It is therefore not surprising, that Liverpool's ongoing problem with air pollution affects northern areas of the city the most – especially since this is where the majority of dock work is now conducted. [43,264] There is also a stark contrast in smoking prevalence between the most deprived areas of the city and the least deprived. [96] Given that the five-year lung cancer risk is highest in the most deprived neighbourhoods, any underlying associations with air pollution and smoking are unlikely to be wholly coincidental. [266]

2.6.1 Paediatric Respiratory Health in Liverpool

Nearly 100,000 Liverpool residents are under 18-years-old, with roughly one-third of these being under 5-years-old. [252] Much like the general population, 57% of children in the city live within the lowest IMD decile; this is likely to explain why the child poverty rate (26%) was 10% higher than the national average in 2016. [253,265] Amongst the under-1-year-olds, emergency hospital admissions for bronchiolitis are significantly more common in Liverpool, than they are nationwide. For a lower RTI, the number of such admissions amongst pre-school-aged children has increased more than four-fold since 2015. Emergency hospital admissions for asthma are also significantly higher than the national average; seven additional children can be admitted per day, when air pollution is particularly bad. [43,253,257] Unsurprisingly, children who live within 2km of Liverpool's docks more frequently experience: school absenteeism, respiratory symptoms and asthma. [262,267]

2.6.2 Liverpool and the LBBS

There is a strong argument for using Liverpool as the setting of a respiratory birth cohort study. Children born in the city today will have a shorter life-expectancy than other English children – with many of these premature deaths being attributable to

respiratory disease. Liverpool is rife with risk factors for such respiratory disease, such as: ETS, air pollution and antenatal smoking. Over half of children in the city live within the lowest IMD decile, thus exposing them towards multiple more risk factors for respiratory disease. Children in Liverpool are also more likely to be admitted to hospital with asthma/lower RTIs.

2.7 Previous Birth Cohort Studies

The LBBS is novel, in that it is the UK's first birth cohort study to be conducted online. However, it is not the first birth cohort study to take place. In fact, the UK's oldest birth cohort study: The National Survey of Health and Development (NSHD), has been running since 1946. [268] The NSHD is a national study, unlike the LBBS, which operates at a regional level. Since national and regional (and international) birth cohort studies are often designed differently, it is important for the LBBS to have an insight into the methodologies of previous regional birth cohort studies – so that a better understanding can be gathered of the potential challenges which may face the study.

2.7.1 Avon Longitudinal Study of Parents and Children (ALSPAC)

Sometimes known as 'Children of the 90s', ALSPAC was the first regional birth cohort study in the UK. [269,270] It was initially developed as one part of the 'European Longitudinal Study of Pregnancy and Childhood': a series of birth cohort studies throughout Europe, which were endorsed by the World Health Organisation. [271] The aim of ALSPAC was to identify the factors that most influenced foetal/child health. [270]

Recruitment for ALSPAC took place between April 1991 and December 1992. [269] All pregnant women living (and giving birth) in one of the three health districts of Avon were eligible for recruitment. [271] At maternity services across the region, cards were distributed for women to express their interest in the study; if an card was returned, then unless they opted-out, an initial questionnaire would be sent to all interested (and eligible) women. [271] The study was advertised: in the press, at healthcare services, on radio/television, in nurseries and in public spaces. [272] This method of recruitment lead to 72% of eligible pregnancies being recruited. [269,271] Further attempts were made to recruit eligible families, who had initially been missed, after the age of 7-years-old. Through this process, 75% of eligible pregnancies and 76% of eligible live births were

eventually recruited. [271] Recruitment was disproportionately high amongst Caucasian and wealthy populations – despite Avon being demographically representative of Britain in many ways. [270,273]

Data collection for ALSPAC began during pregnancy, and ran throughout childhood. In the antenatal period, women provided details about their pregnancy and social background. [270] After giving birth, mothers were then required to complete a series of 25 questionnaires about their child(ren)'s health – until the age of 18. [271] They completed questionnaires about their own health simultaneously. [273] The children in the study also completed 34 questionnaires about themselves, though not before the age of 5. Children were invited for up to seven clinical assessments too. Data was also collected from teacher questionnaires and clinical records. [271,272]

After running for five years, around 80% of ALSPAC participants were still returning questionnaires. [274] The majority of attrition was seen in the first two years of life, but the attrition rate also increased during late adolescence (i.e. 16 to 18-years-old). [271] Families were kept engaged with the study through various means (newsletters, social media, birthday cards, kids' activity packs and the press). This may have contributed to the low attrition rate. [271,272] Reminder letters were sent too, whenever a questionnaire had not been answered within 7 or 10 days; after a month with no response, a phone call/home visit would be made, in order to prompt questionnaire completion. [272]

2.7.2 The Manchester Asthma and Allergy Study (MAAS)

MAAS was a respiratory-centric regional birth cohort study, designed to tackle the paucity of research behind the rising prevalence of childhood asthma. A secondary goal of the study was to investigate whether strict environmental conditions could prevent atopy, amongst those with a strong family history of the condition. [275]

The study recruited expectant parents, from October 1995 to June 1997, whilst they attended their 'booking appointment' at 8 to 10 weeks of gestation. At the appointment, parents were given skin-prick tests and a questionnaire to complete (regardless of their actual enrolment onto the study). [275] Recruitment occurred at Stepping Hill Hospital and Wythenshawe Hospital, both in South Manchester. [276] Ultimately, 63% of eligible pregnancies were enrolled onto the study. [275]

Children were allocated to a study arm, according to their parents' atopic status. Those in the 'high risk' group had two atopic parents, those in the 'medium risk' group had one atopic parent, and those in the 'low risk' group had no atopic parents. [275] The children were followed-up at the ages of: 1, 3, 5, 8 and 11 – as well as at some point between 13 and 16-years-old. [276] Most follow-ups were conducted at a clinic, where a collection of pre-validated questionnaires would be completed. The questionnaires *could* be completed online/via post/during a home visit, but the clinic setting allowed biological samples to be taken and respiratory function tests to be performed too. [276]

Excluding the children who were withdrawn from MAAS before they were even born, there was a 92% follow-up rate at 3-years-old. [275] At 5-years-old, 89% were able to be reviewed. [277]

2.7.3 Tucson Children's Respiratory Study (TCRS)

Back in the eighties, TCRS was one of the first respiratory-focused birth cohort studies to be established. It aimed to evaluate the risk factors for lower RTIs in the first three years of life, as well as the risk factors for obstructive airway disease in later life. [278]

Between May 1980 and January 1984, children were recruited from the largest health maintenance organisation (HMO) in Tucson. [278] Soon after giving birth, paediatricians would approach new mothers to briefly explain the study; any interested mothers would then be visited by a research nurse – who could explain the study further and gain consent. Research nurses operated six days a week. [278] All healthy babies, who were cared for by the HMO, were eligible to participate. Using these criteria, 78% of eligible infants were enrolled onto TCRS. [278] Despite the HMO's patients being representative of the wider Tucson area, infants in the study were more likely to have: married parents, a family history of atopy, a Caucasian ethnicity and older, more educated parents. [278]

Since the iteration of the study in 1980, questionnaires about respiratory health have been distributed at sixteen timepoints … and distribution is ongoing. At eight timepoints, the opportunity has been taken to: perform lung function tests, collect sputum samples, perform skin-prick tests, and collect blood samples (for immunological testing). [279] Siblings and parents are subject to similar tests too. [278] For

the first three years of TCRS, children were also required to visit a paediatrician at the HMO whenever they developed a respiratory illness. If the child had symptoms of a lower RTI, then the research nurses would be contacted to take: a more detailed history, a blood sample, and nasopharyngeal/throat swabs. [278,280] Additionally, a sample of families were contacted about unreported lower RTI symptoms during the Winter season. [278]

At the beginning of the study, it was estimated that 20-25% of participants would be lost to attrition in the first five years. [278] Only 13% dropped-out in the first five years, and just 22% had dropped-out after twenty-two years; most attrition was seen within the first year of study. [278,280] The average attrition rate was therefore 1.3% per year. [280] The long-term involvement of many research nurses in the study, helped to establish positive relationships with the families – potentially reducing attrition rates. [280]

2.7.4 Born in Bradford (BiB)

At its conception, BiB was a regional birth cohort study designed to examine the effects of various risk factors on paediatric health and development, in a deprived area. It also aimed to investigate health differences between Caucasian and Pakistani children. [281] Bradford was considered the optimal location for the study, due to its multiculturalism and high child morbidity/mortality rates. [274]

Recruitment for BiB occurred from March 2007, to November 2010. Any woman who planned to give birth at Bradford Royal Infirmary was eligible to participate. [274,281] Most women were recruited into BiB, whilst undergoing their oral glucose tolerance test at 26-28 weeks of gestation – though many were introduced to the study by a midwife at their 'booking appointment'. [274] 17% of mothers were recruited at an alternative stage of pregnancy. [281] Fathers were recruited opportunistically throughout the antenatal period, or immediately after delivery. The study also advertised (in various languages) via: the press, radio, television, primary care organisations, religious groups and schools. [274] 10,000 infants were wanted for the study, and even though just 54% of eligible births were recruited, this target was still achieved. [274,281] The recruited cohort was largely representative of Bradford, yet contained: older mothers, fewer premature infants, and more South Asian mothers. Additionally, because of Bradford's demographic make-up, the cohort wasn't necessarily representative of the UK. [281]

As Bradford's Pakistani community would be making up a large proportion of the BiB cohort, its study materials (e.g. information leaflets and questionnaires) needed to be adapted into Urdu and Mirpuri, as well as English. [274] All women completed a questionnaire upon recruitment, which was partly delivered by interview, and comprised of various pre-validated questionnaires; fathers completed a questionnaire as well, but were not interviewed. [274] Women provided a blood sample, a urine sample and anthropomorphic measurements too, whilst fathers/infants just provided a saliva sample/anthropomorphic measurements respectively. [274] During BiB's pilot study, there was a response rate of just 30% to follow-up postal questionnaires, so the majority of follow-up was achieved by accessing linked health records. [281] There were two sub-groups within the cohort who were more intensely followed-up; the children in one of these groups (BiB1000) were required to be followed-up with a questionnaire and anthropomorphic measurements at: 6, 12, 18, 24 and 36 months. [281,282]

It was anticipated that ≈25% of the BiB cohort would drop-out within the first five years of the study's running. [274] In order to minimise attrition, a family liaison officer was employed to keep families engaged with the study; they did this through the use of: a website, birthday cards, social media, local government, newsletters, religious groups, meetings and educational facilities. [281] Although the attrition rate from BiB has not been reported, the response rate at each of the BiB1000 timepoints was: 77%, 75%, 74%, 70% and 70% respectively. Amongst children in BiB1000, 'failure to contact' was identified as the main cause of attrition. [282]

2.7.5 Children Growing Up In Liverpool (C-GULL)

Although it has only recently been established, C-GULL is another regional birth cohort study based in Liverpool. It will aim to recruit 10,000 infants from LWH over a 3.5-year period. It will collect data about various areas of paediatric health, from the antenatal period through to the pre-school period – sometimes using clinical and educational records to do so. [283]

Chapter 3: Methodology

The purpose of Chapter 3 is to describe the methodology of the LBBS. A summary of the study design details how the LBBS: drew up the study protocol, applied for ethical approval, obtained sponsorship, developed and distributed its questionnaire, stored data, and initiated recruitment. Theses by Rosanna Pickles and Bethan Griffith describe the study design in more depth. [284,285] The remainder of Chapter 3 provides an overview of how the collected data was organised, coded and statistically processed.

The LBBS has been running as an MPhil project since 2012, so various students have been involved with it over the last nine years. Different people have overseen different phases of the study, as outlined in **Table 4**.

Phase	Time Period	Personnel
Protocol Development, Ethical Approval and Sponsorship Procurement	May 2012	Bethan Griffith Professor Paul McNamara Rosanna Pickles Professor Ben Shaw Professor Calum Semple Professor Kevin Southern
Questionnaire Development	September 2012 – January 2013	Bethan Griffith Rosanna Pickles
	June 2015	Sanjay Patel
Recruitment	January 2013 – October 2014	Jennifer Barclay Bethan Griffith Sanjay Patel Rosanna Pickles
Questionnaire Distribution	September 2013 – August 2015	Jennifer Barclay
Analysis	September 2016 – June 2017	Joshua Stead
	September 2020 – July 2021	Conor Naylor

Table 4: timeline of personnel involvement in the LBBS

3.1 Study Protocol

The study protocol (**Appendix 1**) was written in 2012 by Rosanna Pickles and Bethan Griffith, with the support of Professors Calum Semple, Paul McNamara, Kevin Southern, and Ben Shaw.

3.2 Ethical Approval

Ethical approval for the LBBS, including its associated materials and online consent, was granted by the East Midlands (Nottingham 1) Research Ethics Committee (REC) on the 8th May 2012. The REC reference number was: 12/EM/0194.

3.2.1 Batch Testing

In order to achieve ethical approval, the LBBS was required to employ a technique that would periodically identify participants who died, a particular risk during the early years of the study. This was done through batch testing for the first two years of the study. The IT Department at Alder Hey Children's Hospital received an encrypted list of study participants on a monthly basis; the department would cross-check this list with the hospital's patient database – thereby identifying any recently deceased children. Alder Hey keep their database up-to-date by receiving death notifications from a national data base, which is informed by reports from general practices, hospices and palliative care teams; they also compare it against the 'National Health Service (NHS) Personal Demographics Service' regularly. Where a death was identified, the child's family was removed from the list of active participants, so they would no longer be contacted. To enquire about their deceased child's health, was predicted to cause undue distress.

3.2.2 Consent

The Declaration of Helsinki demands that consent be given by the parents of any child involved in the LBBS. [286] For those receiving online questionnaires, the consent form was incorporated into the initial questionnaire at 4-months-old. Consent was finalised by parents selecting a tick-box to show their interest in the study, then entering their initials into a text field. A paper-based consent form was posted to parents who wished to receive their questionnaires via post. The consent form can be found in **Appendix 3**.

3.3 Sponsorship

The LBBS was co-sponsored by the University of Liverpool and Liverpool Women's Hospital. The University of Liverpool acted as the lead sponsor. They were required, to provide institutional oversight of the study's integrity and insurance. [287]

3.4 Development of the Questionnaires

When the LBBS was conceptualised, it was intended to be the UK's first predominantly online birth cohort study. Previous regional birth cohort studies have collected data with: postal questionnaires, in-person assessments, and interviews. [272,276,278,279] BiB relied almost exclusively on clinical and educational records to follow-up its participants; ALSPAC used such records too, and so will C-GULL. [272,281,283] Some data suggests that online questionnaires can achieve similar response rates to postal questionnaires, whilst being cheaper and environmentally-friendlier. Online data should also be of higher quality, as participants are forced to complete all necessary questions before submitting their responses. [288] These were considered to be valid reasons for creating a series of questionnaires, that were capable of being accessed electronically.

3.4.1 Design

Public and Patient Involvement (PPI) sessions were organised, to help tailor the questionnaires towards prospective parents. It was theorised that by creating the 'ideal' questionnaire, parents would be inclined to complete every questionnaire that the LBBS offered. 20 volunteers, who met all of the LBBS's inclusion/exclusion criteria (**Table 7**), were recruited from LWH. They were shown a range of prototype questionnaires, which each varied in one design aspect, then asked to indicate which variation was most preferable to them. The volunteers were also asked to indicate how they would prefer to complete the questionnaires, based on their accessibility to internet-compatible devices. **Table 5** summarises the results of the PPI sessions. [284,285]

Design Aspect	Variations	Preferability
Accessibility	Laptop/Computer	65% (n = 13)
	Smartphone	25% (n = 5)
	Tablet	10% (n = 2)
	Postal	0% (n = 0)

Use of Colour	Neutral	35% (n = 7)
	Neutral, with Coloured Text	30% (n = 6)
	Light Use of Background Colour	25% (n = 5)
	Heavy Use of Background Colour	5% (n = 1)
	No Preference	5% (n = 1)
Font Size	Medium – Arial, size 16	75% (n = 15)
	Small – Arial, size 12	15% (n = 3)
	Large – Arial, size 20	10% (n = 2)
Question Density	Medium – similar questions grouped together on one page	65% (n = 13)
	Low – one question per page	15% (n = 3)
	High – every question on one page	15% (n = 3)
	No Preference	5% (n = 1)
Use of Graphics	Cartoon Children (in the Footer)	65% (n = 13)
	None	20% (n = 4)
	Pencils (in the Footer)	10% (n = 2)
	Forest (as a Background)	5% (n = 1)
	No Preference	5% (n = 1)

Table 5: questionnaire preferabilities from the PPI sessions

Based on the PPI sessions, it was decided to conduct online questionnaires; they were more appealing to contemporary participants, than postal questionnaires. The questionnaires would group similar questions together on one page, and be written in size 16 font. The background would be plain, but a graphic of cartoon children in the questionnaire's footer would provide an element of colour. Volunteers expressed the need to include an adequate explanation of the study at the beginning of any questionnaire, as well as an estimate of the time requirement. They preferred brevity, as well as closed questions. [284,285]

3.4.2 Format

The PPI sessions proved that parents were interested in online questionnaires, so a suitable platform was needed to construct said questionnaires. Following an in-depth analysis of four platforms, which can be found elsewhere, Adobe FormsCentral® (AFC®) was deemed to be the best option. [284,285] The other three platforms were:

Google Docs®, SelectSurvey.NET® (SSN®) and SurveyMonkey®. AFC® was the optimal platform, because it:

- had excellent usability
- provided a variety of question types (e.g. radio button, dropdown box, text field)
- allowed an unlimited number of graphics to be inserted
- had the ability to incorporate 'skip logic' into the questionnaires
- allowed help boxes to be included with each question
- kept completed forms on a secure server
- easily exported data into both Microsoft Excel® and SPSS®
- offered technological support via both email and phone
- could replicate the 'ideal' design, as identified in PPI sessions

To ensure that AFC® was the right platform, further PPI sessions were conducted to compare it with SSN®. 16 volunteers were recruited from LWH, using the same inclusion/exclusion criteria as before. They completed prototype questionnaires in both AFC® and SSN®, then indicated their preferred platform. AFC® was preferred by 62.5% volunteers, as it "appeared more concise". [284,285] The ability to include 'skip logic' made the questionnaire "feel shorter", as unnecessary questions were automatically omitted. [284,285]

In July 2015, two years after questionnaire distribution had commenced, AFC® was 'retired' with little warning. An alternative platform was therefore needed, for participants to complete their questionnaires. JotForm® was chosen to continue the data collection, as it was a near-identical service to AFC®. It also cost significantly less, and when hosted on a European server, was compliant with the General Data Protection Regulation (GDPR). [289] The questionnaires had to be reconstructed in JotForm®, and then linked to the automated emailing system (see Section 3.7). [290]

3.4.3 Content

In every questionnaire, there were ten questions that enquired about risk factors and healthcare service usage. Every questionnaire included the 33-item LRSQ. At the end of every questionnaire, parents could provide feedback about the study/questionnaire and opt-in to the study's newsletter too. The first questionnaire (**Appendix 4**)

contained one-off questions regarding: personal details, demographic information and socioeconomic information. **Table 6** provides an overview of the topics covered in each questionnaire. Because of 'skip logic', it was possible for many parents to avoid unnecessary follow-up questions. As the study progressed, children were referred to differently in each questionnaire: "your new baby" (in questionnaire 1), "your baby" (in questionnaires 2-3), "your toddler" (in questionnaires 4-6) and "your child" (in questionnaires 7-10).

Questionnaire One Only	All Questionnaires
• Baby's Name • Baby's Sex • Baby's DoB • Baby's Ethnicity • Gestational Age at Birth • Multiple Birth • Baby's Birthweight • Antenatal Smoking Status • ETS Exposure in Pregnancy • Breastfeeding Status • Maternal Education • Parents' Names • Maternal Age • Address (inc. Postcode) • Email Address • Phone Number	• Family History of Atopy • ETS Exposure • Nursery Attendance • Other Household Children • Bedroom Sharing • Co-Morbidities • GP Attendances • Hospital Attendances • LRSQ • Study Newsletter Opt-In • Study Feedback

Table 6: content of questionnaires in the LBBS

3.5 Development of Additional Study Materials

Additional materials were produced, in order to advertise the study and facilitate recruitment onto it. Postcards (**Appendix 5**) allowed parents to provide their contact details to a recruiter (see Section 3.6). Posters (**Appendix 6**) were also created for display in the patient areas of LWH; the purpose of the posters was to advertise *and* recruit. The postcards and the posters contained a quick response (QR) code, which

allowed interested parents to join the study's mailing list outside of recruitment hours. The same theme was used for the questionnaires and the study materials, to create a recognisable brand for the study. All materials referred to the study as the 'Liverpool Baby Breathing Study', as this was clearer to prospective parents than 'The Liverpool Respiratory Birth Cohort Study'.

Feedback was opportunistically sought about the additional study materials, whilst conducting PPI sessions about the questionnaire's format (see Section 3.4.2). Twelve of the volunteers provided such feedback. Overall, there was a positive opinion of the materials. Appreciation was directed towards the consistent theme of the posters, postcards and questionnaires. Two-thirds of volunteers knew what QR codes were, and how to use them – yet none indicated that they would choose to join the study via a QR code. [284,285]

3.6 Recruitment

Infants were recruited into the LBBS between January 2013 and November 2014. Originally, midwives and paediatricians at LWH were to approach new parents about enrolment into the study. However, their busy schedules made this unfeasible. The recruitment drive was therefore conducted by MPhil students.

To be eligible to participate in the LBBS, infants had to meet certain inclusion/exclusion criteria (**Table 7**). An MPhil student attended LWH's postnatal wards four-days-a-week (Mondays, Tuesdays, Thursdays and Fridays), where they would receive a patient list each day. Using this list, those who failed to meet the study's location and language requirements could be excluded from the recruitment drive; by speaking to the ward manager, those who failed to meet the remainder of the inclusion criteria could also be excluded.

Inclusion Criteria	Exclusion Criteria
born at LWH	born outside of LWH
lived within the L1-L38 postcode area	lived outside the L1-L38 postcode area
parents spoke English well	parents could not speak English
expected to live	had a poor prognosis at birth
continued living with parents	placed into local authority care

Table 7: inclusion/exclusion criteria

Every endeavour was made to recruit eligible infants, by personally attending the postnatal wards. Following an explanation of the study, a newborn's parents would be given a postcard on which to fill out their contact details. This postcard could either be immediately returned to the MPhil student, or posted into a collection box upon discharge. The parents of most infants on the neonatal unit were approached on the postnatal ward, but a collection box was placed in the neonatal unit too, so they could opt-in to the study at a less stressful time. The scannable QR codes, on both the study posters and postcards, allowed parents to return their details via a web-based form. Contact details collected from the postcards were manually inputted into a secure database; details from the web-based form were automatically entered. Following recruitment, an infant's parents were sent an email to welcome them to the LBBS and to thank them for their interest/participation.

3.6.1 Pilot Recruitment Study

In January and February 2013, a four-week pilot study was run to determine the most effective strategy for recruiting infants into the LBBS. This pilot was conducted by the original MPhil students attached to the LBBS. [284,285] A different recruitment strategy was tested in each of the four weeks (**Table 8**). [284,285] Parents were approached on the postnatal wards of LWH, as described in Section 1.6. Any infant less than 4-months-old, who attended the CF clinic for the first time during the trial period, could be invited into the study by the clinic's consultant too.

Week	Strategy	Days	Times	Recruitment Rate
1	5 Full Days	Monday – Friday	9:30 – 16:30	58%
2	6 Mornings	Monday – Saturday	9:30 – 12:00	65%
3	4 Full (Alternate) Days	Monday, Wednesday, Friday, Sunday	9:30 – 16:30	61%
4	7 Full Days	Monday – Sunday	9:30 – 16:30	78%

Table 8: overview of the pilot recruitment study

During the trial period, there were 605 births at LWH. 334 were recruited by directly approaching parents on postnatal wards; 3 were recruited via the collection box on the neonatal unit; and another 2 were recruited from the CF clinic. Following an analysis of each week's recruitment rate of eligible infants (**Table 8**), the alternative option of recruiting on four full weekdays per week was touted. An additional pilot study for this option was run in March 2013, and yielded a recruitment rate of 69%. A 9:30 start time was also found to be most appropriate. [284,285] The 'four full weekdays per week' recruitment strategy was used henceforth.

3.7 Questionnaire Distribution

The first questionnaires were distributed in May 2013 – four months after the first infants were recruited. Parents received subsequent questionnaires every six months; by the time their child reached 58-months-old, all ten should have been administered. The last questionnaires were sent in October 2019. Most were distributed through an automated emailing system, but some were sent through the post. By the second questionnaire (at 10-months-old), distribution was solely via email because the postal questionnaires had an inadequate response rate.

MailChimp® was chosen to distribute the online questionnaires, following a thorough investigation of the potential distribution options. [284,285] MailChimp® was decided upon, due to the fact that it offers:

- the ability to send automated emails, according to date of birth (DoB) – meaning that the correct questionnaire would be sent at the right time
- the option for participants to remove themselves from the mailing list – meaning that they had the opportunity to withdraw
- the ability to include personalised text fields – meaning that emails could incorporate parents' names, children's names, children's DoB and unique ID numbers for an inter-personal touch
- a secure server on which to hold the mailing list – meaning that participant data would be safe
- the ability to personalise emails with the study's brand – meaning that continuity can be created across all of the study's resources

- the option for parents to automatically add themselves to the mailing list by scanning a QR code – meaning that recruitment could continue outside of the recruitment hours

Using the personalised text fields, each email was addressed to the parent who signed up for the study (predominantly mothers). Emails included a reminder of each child's unique ID number, as this was needed to complete the questionnaires. The questionnaires themselves were embedded within a hyperlink, which would take participants to either Adobe FormsCentral® or JotForm®. An exemplar email can be found in **Appendix 7**.

MailChimp® allowed emails to be distributed a certain number of days, after a child's birth (**Table 9**). This feature ensured that the appropriate questionnaire for a child's age was automatically sent. However, the original automation instructions meant that receiving the next questionnaire in the series was dependent on completing the previous one. This contributed to a large amount of attrition from the LBBS in its first two years. The automation instructions were therefore adjusted, so that parents were able to continue completing questionnaires – even if they hadn't completed the previous one.

Reminder emails were issued, to further reduce attrition from the study. Parents were emailed reminders to complete a questionnaire, if they failed to open the email or access the embedded link. These reminders were scheduled to be delivered after two, three and four weeks of the original questionnaire being sent. Birthday e-cards were sent to children on their birthdays, as they are known to improve retention rates. [291]

Time Since Infant's DoB	**Email Contents**
122 days	Questionnaire 1: 4-Months-Old
136 days	Questionnaire 1: Reminder #1
143 days	Questionnaire 1: Reminder #2
150 days	Questionnaire 1: Reminder #3
305 days	Questionnaire 2: 10-Months-Old
319 days	Questionnaire 2: Reminder #1
326 days	Questionnaire 2: Reminder #2
333 days	Questionnaire 2: Reminder #3

1 year	Happy 1st Birthday E-Card
488 days	Questionnaire 3: 16-Months-Old
502 days	Questionnaire 3: Reminder #1
509 days	Questionnaire 3: Reminder #2
516 days	Questionnaire 3: Reminder #3
671 days	Questionnaire 4: 22-Months-Old
685 days	Questionnaire 4: Reminder #1
692 days	Questionnaire 4: Reminder #2
699 days	Questionnaire 4: Reminder #3
2 years	Happy 2nd Birthday E-Card
854 days	Questionnaire 5: 28-Months-Old
868 days	Questionnaire 5: Reminder #1
875 days	Questionnaire 5: Reminder #2
882 days	Questionnaire 5: Reminder #3
1037 days	Questionnaire 6: 34-Months-Old
1051 days	Questionnaire 6: Reminder #1
1058 days	Questionnaire 6: Reminder #2
1065 days	Questionnaire 6: Reminder #3
3 years	Happy 3rd Birthday E-Card
1220 days	Questionnaire 7: 40-Months-Old
1234 days	Questionnaire 7: Reminder #1
1241 days	Questionnaire 7: Reminder #2
1248 days	Questionnaire 7: Reminder #3
1403 days	Questionnaire 8: 46-Months-Old
1417 days	Questionnaire 8: Reminder #1
1424 days	Questionnaire 8: Reminder #2
1431 days	Questionnaire 8: Reminder #3
4 years	Happy 4th Birthday E-Card
1586 days	Questionnaire 9: 52-Months-Old
1600 days	Questionnaire 9: Reminder #1
1607 days	Questionnaire 9: Reminder #2
1614 days	Questionnaire 9: Reminder #3
1769 days	Questionnaire 10: 58-Months-Old
1783 days	Questionnaire 10: Reminder #1
1790 days	Questionnaire 10: Reminder #2
1797 days	Questionnaire 10: Reminder #3
5 years	Happy 5th Birthday E-Card

Table 9: timeline of questionnaire distribution

3.8 Data Storage

Completed postcards, which contained participant contact details, were archived at the Institute of Child Health, Alder Hey Children's Hospital. All of the completed online questionnaires were stored on the AFC® and JotForm® servers, which were Secure Socket Layer (SSL) secure. [289] The collected data from each questionnaire was exported into an Excel® spreadsheet – where it was subsequently encrypted with a strong password. Excel® spreadsheets were stored on a secure server, hosted by the University of Liverpool.

To minimise the amount of personal information collected throughout the study, such information was only collected in the first questionnaire. Subsequent questionnaires could identify individuals with their unique ID number; this number was included in all email correspondence, and was required to be entered before questionnaires could begin.

3.9 Coding

The data exported into Excel® was raw: responses appeared as they did in the questionnaire. For statistical packages (see Section 3.12) to process the data however, it needed to be converted into a numerical form. This was done in Excel® for the most part, using the 'find-and-replace' function to allocate an integer to each individual response for every question. The specific integers allocated to each response, for each question, can be found in **Appendix 8**.

The responses to a minority of questions had to be coded using alternative methods. Birthweight could be provided in either kilograms or pounds-and-ounces, so the latter was converted to the former during the coding process. Analysing a single unit of measurement (kilograms) was considered to be easier than analysing mixed units (pounds-and-ounces). IMD deciles were coded by using an online governmental postcode converter, to calculate participants' IMD deciles from their postcodes. [292] Co-morbidities were allocated to one of seven categories using author discretion – and where there was uncertainty, the ICD-10. [293] Maternal age was calculated by subtracting a mother's year-of-birth, from her infant's year-of-birth.

3.10 Data Cleansing

Whilst coding the raw data, a few issues were noticed, which would have impacted the integrity of the data. These issues had to be corrected. **Table 10** outlines the frequency of each issue in each questionnaire.

The first issue concerned the question: "Have you, your child's father, or any of your child's brothers or sisters ever been told by a doctor that they, or you, have asthma, hay fever or eczema?". Some parents reported the atopic status of second-degree relatives (e.g. aunts and half-siblings); some parents reported the atopic status of the child, who was the focus of the questionnaire. [294] As these responses didn't meet the inclusion criteria for the question, they were omitted from the dataset. For the question: "What is your postcode?", five parents didn't provide a postcode (or address), so no IMD data could be calculated for their family. As these families accounted for a very small proportion of the total cohort, the corresponding children were kept in the study because the absence of their IMD decile would have a negligible effect on the overall data analysis. The same approach was taken with the questions: "What best describes your new baby's ethnic group or background?" and "How much did your baby weigh at birth?". Two parents did not state their child's ethnicity, and three parents did not state their child's birthweight. Some parents reported that their child had been exposed to vaping, in response to the question: "Does any member of your household smoke, anywhere?". As the question was asking about ETS, any responses about vaping were omitted from the data. Parents were able to return questionnaires two through ten, despite having not completed the baseline questionnaire; this meant that their child's exposure status to most various risk factors (**Table 11**) had not been established. A similar problem arose whenever parents returned a questionnaire without their child's unique ID number, because it could not be determined whether any information was held about their child's exposure status. In both cases, respondents were removed from the dataset – so as not to skew the results of the longitudinal and cross-sectional analyses, which relied upon knowing a child's exposure status. The final issue related to the duplication of questionnaire responses. The response that was completed *closest* to the expected completion date was kept in the dataset, meaning that duplicated responses could be removed.

Issue	Frequency of Issue									
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
"Have you, your child's father, or any of your child's brothers or sisters ever been told by a doctor that they, or you, have asthma, hay fever or eczema?"						4	1	2	2	
"What is your postcode?"	5									
"What best describes your new baby's ethnic group or background?"	2									
"How much did your baby weigh at birth?"	3									
"Does any member of your household smoke, anywhere?"									1	1
Late Additions		3	1	2	17	25	16	25	27	26
Missing ID Codes						4	1	2	1	
Duplicated Questionnaires					4	2	6	16	7	4

Table 10: frequency of data collection discrepancies and missing information

3.11 Data Analysis

The analysis of the LBBS was separated into seven areas, which are described in more detail in the forthcoming:

- Analysis of Recruitment and Enrolment
- Analysis of the Family Cohort
- Analysis of the Infant Cohort
- Analysis of Attrition
- Cross-Sectional Analysis
- Longitudinal Analysis
- Validation of the LRSQ

3.11.1 Recruitment and Enrolment

The recruitment rate was analysed by calculating the number of parents who expressed interest in the study, as a proportion of the number of births and the number of *eligible* births at LWH during the recruitment period. Those who completed the baseline questionnaire, and issued consent, were considered to be enrolled in the study. The enrolment rate was analysed by calculating the number of enrolled participants, as a proportion of the number of births and the number of *eligible* births at LWH during the recruitment period, as well as the number of recruited participants.

Data about the births at LWH during the recruitment period was obtained from Professor Ben Shaw at LWH. Reasons for non-recruitment and non-enrolment of these births were identified by Dr Joshua Stead, as part of his MPhil thesis; they have been replicated for the purposes of this thesis. [290]

3.11.2 Profile of the Family Cohort

A profile of the families involved in the LBBS was constructed, to report the frequency at which children were exposed to (mostly socioeconomic) risk factors. Statistically significant differences in risk factor exposure were sought between the study cohort, and the eligible births in LWH during the recruitment period. Differences were sought between the study cohort and the wider population of Liverpool and/or England during the recruitment period too. A statistically significant difference was confirmed when χ^2 testing returned a p-value of ≤ 0.05.

Data about the LWH's eligible births was obtained from Professor Ben Shaw. Postcodes of the eligible births were converted into IMD deciles using online governmental postcode converters. [292] Data regarding the proportion of Liverpool in each IMD decile was sourced from the Ministry of Housing, Communities & Local Government. [295] Data about antenatal smoking and breastfeeding, in Liverpool and England, was extracted from official NHS statistics. [296–298] Data about maternal age and maternal education was taken from the Office for National Statistics. [299,300]

3.11.3 Profile of the Infant Cohort

A profile of the infants enrolled in the LBBS was constructed, to describe the frequency of their exposure to (mostly demographic) risk factors. Statistically significant

differences in risk factor exposure were sought between the study cohort, and the eligible births in LWH during the recruitment period. Differences were sought between the study cohort and the wider population of Liverpool and/or England during the recruitment period too. A statistically significant difference was confirmed when χ^2 testing returned a p-value of ≤0.05.

Data regarding the eligible births at LWH was obtained from Professor Ben Shaw. The Office for National Statistics provided data about: sex, ethnicity, gestational age, multiple pregnancies and birthweight in England. [301–304] Data about the prevalence of multiple pregnancies in Liverpool was sourced from Public Health England. [253]

3.11.4 Attrition

Attrition from the LBBS was analysed by calculating the number of responses to each of the ten questionnaires, as a proportion of the number of enrolled participants. The percentage change in response rate between successive questionnaires was also determined. Reasons for attrition were identified where possible – again, using Dr Joshua Stead's MPhil thesis for reference. [290]

The demographic and socioeconomic characteristics of the study cohort were analysed at each questionnaire timepoint, to detect disproportionate drop-out rates amongst certain groups. Disproportionate drop-out was used to inform the use of statistical techniques, to mitigate for such losses in the cross-sectional/longitudinal analyses.

3.11.5 Cross-Sectional Analysis

The cross-sectional analysis of the LBBS examined the responses received to all ten questionnaires, but in isolation from each other. It was divided into four sections:

- Analysis of Risk Factor Exposure
- Analysis of Total LRSQ Scores and Domain Scores
- Analysis of Symptom Prevalence
- Analysis of Healthcare Service Usage

Due to large amounts of attrition from the LBBS, the study cohort gradually became less representative of LWH's eligible study population – especially in terms of deprivation (see Section 4.4). Therefore, to make the cohort more accurately reflect the spread of deprivation seen amongst births in LWH during the recruitment period,

the cross-sectional analysis applied factor weighting. It was used to analyse: total LRSQ scores, LRSQ domain scores, symptom prevalence and healthcare service utilisation, between different exposure groups. The weighting factors allocated to each IMD decile for each questionnaire can be found in **Appendix 9**.

Whilst conducting the cross-sectional analysis, further adjustments were made to the data coding process. Children were recategorised according to their gestational age at birth; those born before 37 weeks of gestation were coded as premature, and those born at 37 weeks or later were coded as term. Children were also recategorised, based on their birthweight; those born at <2.5kg were coded as 'low birthweight', whilst those born at 2.5kg or above were coded as 'normal' birthweight. Responses about: ethnicity, maternal age, deprivation and maternal education were recategorised too. In order to account for the under-representation of certain groups within the LBBS, and increase the statistical power, these responses were condensed into fewer – but larger – groups. The adjusted codes can be found in **Appendix 10**.

3.11.5.1 Exposure to Risk Factors

- Antenatal Smoking Status
- Bedroom Sharing
  - Bedroom Sharing with Whom
- Birthweight
- Breastfeeding Status
  - Duration of Breastfeeding
- Co-Morbidities
- Ethnicity
- ETS Exposure During Pregnancy
  - Location of ETS Exposure During Pregnancy
- Family History of Atopy
- Gestational Age
- Maternal Age
- Maternal Education
- Multiple Pregnancy
- Nursery Attendance
- Other Household Children
  - Number of Other Household Children
- Postnatal ETS Exposure
  - Location of Postnatal ETS Exposure
- Sex

Table 11: risk factors assessed in the LBBS

The LBBS assessed children's exposure to many risk factors, as outlined in **Table 11**. The exposure prevalence to six particular risk factors was analysed at each timepoint: nursery attendance, other household children, bedroom sharing, ETS exposure, family history of atopy and co-morbidities. These six risk factors were liable to change for an individual throughout the course of the study, so had to be described at every timepoint.

Using data from Pubic Health England, χ^2 testing compared the ETS exposure in each questionnaire, to the smoking prevalence in Liverpool and England. [258] A p-value of ≤0.05 was deemed to indicate a statistically significant difference. The remaining five risk factors were analysed with descriptive statistics.

3.11.5.2 LRSQ Score (Total and Domain)

Descriptive statistics were used to analyse the total LRSQ scores, from every questionnaire. They were used to analyse the LRSQ domain scores; an overview of the LRSQ's domains is provided in **Table 12**. Both the total and domain scores were calculated using Microsoft Excel, after the data had been coded into a numerical format.

Domain	Description	Maximum Score
1	Daytime Symptoms	16
2	Night-Time Symptoms	20
3	Symptoms with Colds	21
4	Symptoms without Colds	16
5	Symptoms with Increased Activity	16
6	Other Respiratory Symptoms	12
7	QoL of the Child	16
8	QoL of the Parent	16

Table 12: domains in the LRSQ

Mann-Whitney U and Kruskal-Wallis testing were used to analyse which risk factors resulted in higher LRSQ scores , based upon a child's degree of exposure. The former was used when only two exposure groups existed for the risk factor being assessed (e.g. sex); the latter was used when there were more than two groups (e.g. maternal age). If Kruskal-Wallis testing revealed a statistically significant difference between the exposure groups of a risk factor, then post-hoc testing was conducted with Dunn's test. Analysing for these differences allowed the risk factors that most affected a child's LRSQ score – and thus, their respiratory wellbeing – to be identified. Spearman's Rank Correlation was used to analyse the strength of the relationship

between total LRSQ score and total QoL score. A child's total QoL score was their combined score from Domain 7 and Domain 8. Across all of the inferential tests, a p-value of ≤0.05 was considered to reveal a statistically significant difference.

3.11.5.3 Use of Multiple Testing Correction

In the cross-sectional analysis, Kruskal-Wallis testing was used to detect statistically significant differences in total/domain LRSQ score, between children with varying levels of: deprivation, maternal age, maternal education, and breastfeeding time. Since Kruskal-Wallis testing cannot identify between which specific levels there is a statistically significant difference, Dunn's test was used for post-hoc analysis. Dunn's test uses numerous pairwise comparisons to recognise where the statistically significant differences exist. [305] The test is therefore subject to multiple testing, which means that as more analyses are conducted, the chance of encountering a significant result increases – potentially leading to a type I error. [306]

One way of minimising the likelihood of a type I error, is to perform a Bonferroni adjustment; this technique 'lowers' the threshold at which a p-value is deemed to be significant. In the LBBS, it was decided that correcting for multiple testing would not be used. As the goal of the cross-sectional analysis was to identify trends in total/domain LRSQ score, between the different levels of an individual risk factor, using a Bonferroni adjustment was considered to be too conservative – potentially causing important trends to be overlooked (a type II error). Bonferroni adjustment is also unsuitable for use when independent variables have a degree of interdependence – as they do in the LBBS. [306] The fact that multiple testing was used, should be taken into account when considering the significance of results with borderline significance.

3.11.5.4 Symptom Prevalence

For each timepoint, descriptive statistics were used to analyse the overall prevalence of respiratory symptoms in the cohort. Descriptive statistics were also used to analyse the prevalence of specific symptoms. For each specific symptom, binary logistic regression was used to calculate multiple odds ratios (ORs). Each OR shows how likely a symptom was to occur whenever a certain risk factor was present, compared to when that risk factor was absent. Statistically significant ORs were considered to be

evident when the p-value was ≤0.05, and/or the 95% confidence interval (95% CI) did not include 1.

3.11.5.5 Healthcare Service Usage

General practice (GP) and hospital attendance were analysed with descriptive statistics. For both GP and hospital attendance, binary logistic regression was used to calculate multiple odds ratios (ORs). Each OR shows how likely attendance was to occur whenever a certain risk factor was present, compared to when that risk factor was absent. Spearman's Rank Correlation was used to assess any associations between total LRSQ score and GP/hospital attendance rates. If a p-value was calculated to be ≤0.05, and/or the 95% confidence interval (95% CI) did not include 1, then a statistically significant result existed.

3.11.6 Longitudinal Analysis

The longitudinal analysis of the LBBS was performed using stepwise multi-level mixed effects modelling. [307] This technique could account for participants who did not complete every questionnaire, whilst ensuring that the model only contained the most predictive of the many inter-related risk factors for total/domain LRSQ score. [307,308] A series of univariate analyses were run, to establish which risk factors caused the total/domain LRSQ scores to significantly increase or decrease throughout the entire pre-school period. A p-value of ≤0.05 was deemed to indicate a statistically significant change. Risk factors that returned a p-value of ≤0.05 were then manually entered into a mixed effects model for the score that they affected – as a fixed effect. Such factors were added to the model incrementally, in order of ascending p-value. If a risk factor's p-value remained at ≤0.05, even upon the addition of other variables, then it was kept in the mixed effects model; if a factor's p-value became >0.05, then it was removed from the mixed effects model.

As with the cross-sectional analysis, the longitudinal analysis needed reflect the actual spread of deprivation seen amongst the births in LWH during the recruitment period. This was achieved by including a child's IMD decile as a random effect, in both the univariate analyses and mixed effects models. 'Questionnaire number' was another random effect, because it allowed those who did not complete all ten questionnaires to be represented.

3.11.7 LRSQ Validation

Using Cronbach's alpha, the internal consistency of all eight domains in the LRSQ were evaluated. All responses were used, regardless of attrition. When $\alpha \geq 0.7$, the domain was deemed to have acceptable internal consistency; when $\alpha \geq 0.8$, the domain was deemed to have good internal consistency; and when $\alpha \geq 0.9$, the domain was deemed to have excellent internal consistency. An α of <0.7 was considered unacceptable.

3.12 Choice of Statistical Package

The cross-sectional analysis, the profiles of the families and infants in the study, and attrition from the study were analysed using SPSS Statistics (Version 26). STATA (Version 14) was used to conduct the longitudinal analysis, and validate the LRSQ. R (Version 4.0.3) was used to create graphs and figures.

Chapter 4: Results

Chapter 4 presents the results of the LBBS, in the seven previously-outlined areas. Recruitment and enrolment rates are summarised. Profiles of the study's family and infant cohorts are provided, which compares their characteristics, to the characteristics of LWH, Liverpool and England. Attrition from the LBBS is described, alongside an analysis of how the cohort's characteristics changed throughout the study in response to drop-out.

The later analyses encompass the most original and important findings of this thesis, and conclude the LBBS. The cross-sectional analysis demonstrates the risk factors that exerted the largest influence upon paediatric respiratory health at different ages. The longitudinal analysis identifies the risk factors that cumulatively contributed to poor paediatric respiratory health throughout the first five years of life. An analysis of the LRSQ's internal consistency shows whether the questionnaire can be validated for use in longitudinal studies.

4.1 Recruitment and Enrolment

This section of the results is dedicated to the analysis of recruitment and enrolment into the LBBS. The recruitment rate reflects the number of parents who expressed interest in participating in the study. The enrolment rate reflects the number of parents who completed the baseline questionnaire. Reasons for non-recruitment and non-enrolment are also outlined.

Recruitment is illustrated by the flowchart in **Figure 1**. 2,344 infants were recruited into the LBBS between 23rd January 2013 and 3rd November 2014, as their parents expressed interest in being involved with the study. 15.1% of the total births at LWH during the recruitment period (n = 15,492) were therefore recruited. 7.0% (n = 1,083) of infants were born during documented breaks in recruitment, 11.1% (n = 1,722) were born outside of the study's postcode area, 0.7% (n = 102) were born to parents who did not speak English, 0.4% (n = 58) had a poor prognosis at births, and 0.5% (n = 75) were not eligible for recruitment for other reasons. Since there was no way for these infants to ever be recruited, the recruitment rate amongst the **eligible** births at LWH during the recruitment period (n = 12,452) was actually 18.8% (**Table 13**). 80.6% (n = 10,040) of eligible infants were 'missed' at LWH during recruitment. The parents of just 0.5% (n = 68) of eligible infants actively declined to be involved with the LBBS.

	Total Births at LWH	Eligible Births at LWH
Number	15,492	12,452
Percentage of Infants Recruited	15.1%	18.8%

Table 13: recruitment rate into the LBBS

689 infants were enrolled onto the LBBS, as their parents completed the baseline questionnaire and issued consent to being involved in the study. 1.5% (n = 36) of the recruited infants did not have consent provided on their behalf, 0.3% (n = 7) died before the study had begun, 10.8% (n = 253) could not be contacted – due to an incorrect email/postal address, and the remaining 58.0% (n = 1,359) were assumed to be 'lost to follow-up'. 29.4% of the recruited infants were therefore enrolled onto the LBBS (**Table 14**).

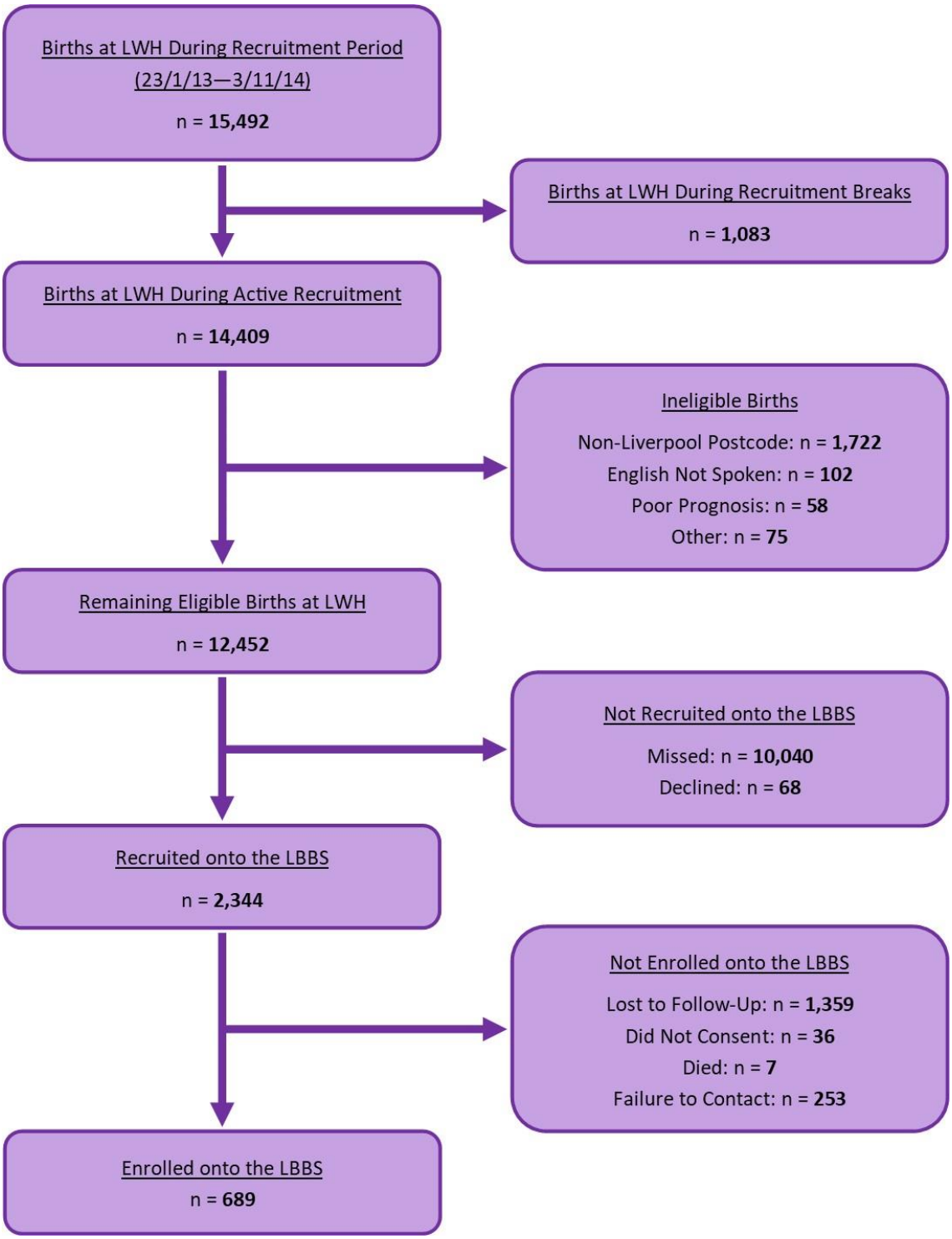


Figure 1: flowchart of recruitment throughout the LBBS

	Total Births at LWH	Eligible Births at LWH	Recruited Infants
Number	15,492	12,452	2,344
Percentage of Infants Enrolled	4.4%	5.5%	29.4%

Table 14: enrolment rate onto the LBBS

4.2 Profile of the Family Cohort

This section of the results is dedicated to the analysis of the family cohort. Amongst the LBBS' families, the following have been calculated:

- breastfeeding prevalence
- duration of breastfeeding
- distribution of IMD deciles
- distribution of maternal ages
- distribution of maternal education levels
- antenatal smoking prevalence
- exposure to ETS during pregnancy

Where possible, the LBBS cohort has also been compared to the eligible births from LWH and/or Liverpool and/or England.

4.2.1 Breastfeeding Status

70.6% (n = 480) of mothers in the LBBS breastfed for some duration of time, whereas 29.4% (n = 200) didn't breastfeed at all (**Figure 2**).

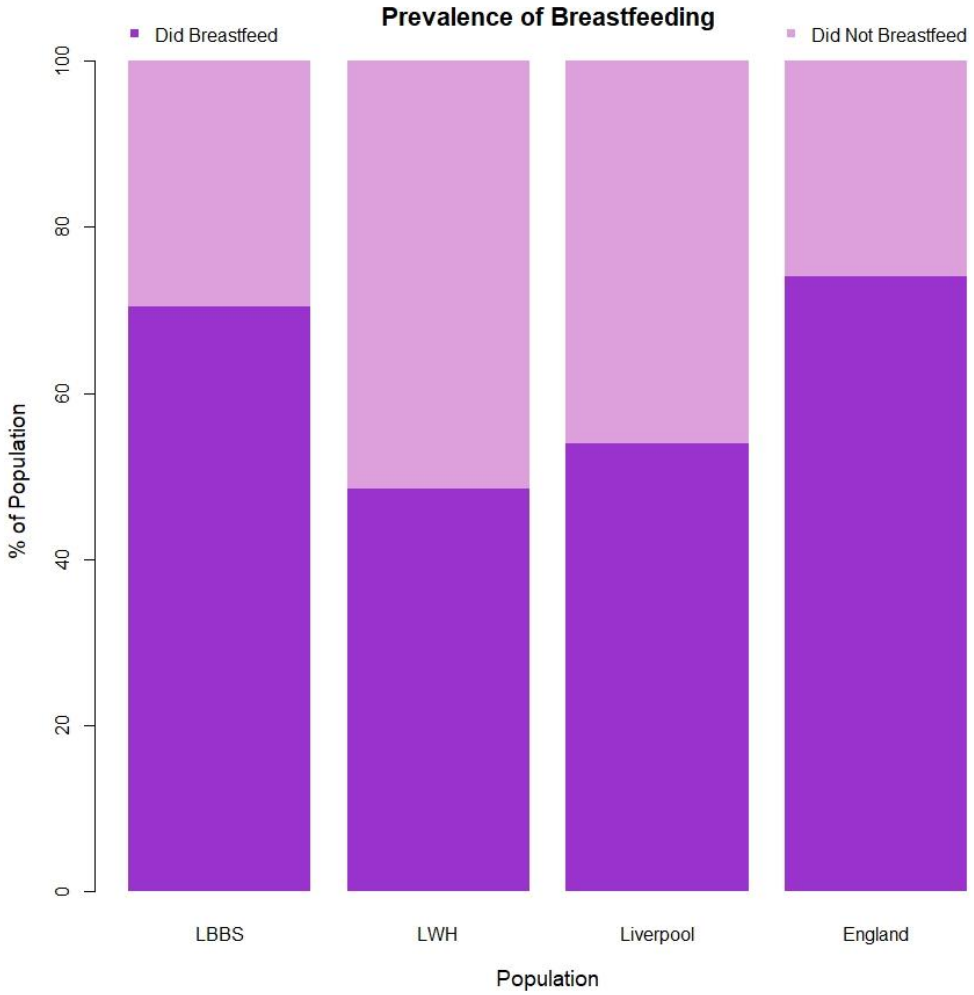


Figure 2: prevalence of breastfeeding in the LBBS, compared to LWH and Liverpool and England

Compared to the eligible births from LWH, the uptake of breastfeeding was higher in the LBBS (χ^2 = 126.71, p = <0.001, df = 1). The uptake of breastfeeding was higher too, when compared to the whole of Liverpool (χ^2 = 71.22, p = <0.001, df = 1). The prevalence of breastfeeding in the LBBS was significantly lower than in England (χ^2 = 4.45, p = 0.03, df = 1).

4.2.1.1 Duration of Breastfeeding

In the LBBS, 30.2% (n = 145) of the mothers who breastfed, did so for less than one month. 20.0% (n = 96) of the breastfeeding mothers stopped doing so after one to four months. 49.8% (n = 239) continued to breastfeed for longer than four months (**Figure 3**).

Figure 3: breastfeeding in the LBBS by duration

4.2.2 Deprivation

36.0% (n = 245) of families in the LBBS lived within the first (most deprived) IMD decile. 17.1% (n = 116) lived in the second decile, 7.9% (n = 54) in the third decile, 6.5% (n = 44) in the fourth decile, and 9.4% (n = 64) in the fifth decile. 6.5% (n = 44) lived in the sixth decile, 7.8% (n = 53) in the seventh decile, 4.3% (n = 29) in the eighth decile, and 2.2% (n = 15) in the ninth decile. Just 1.6% (n = 11) of the families lived within the tenth (least deprived) decile (**Figure 4**). 0.7% (n = 5) of families did not declare their postcode, so no deprivation data could be retrieved.

When compared to the eligible births from LWH, the LBBS saw higher IMD decile scores (χ^2 = 81.21, p = <0.001, df = 9). Higher IMD decile scores were also seen, when the LBBS was compared to the entire Liverpool population (χ^2 = 70.55, p = <0.001, df = 9).

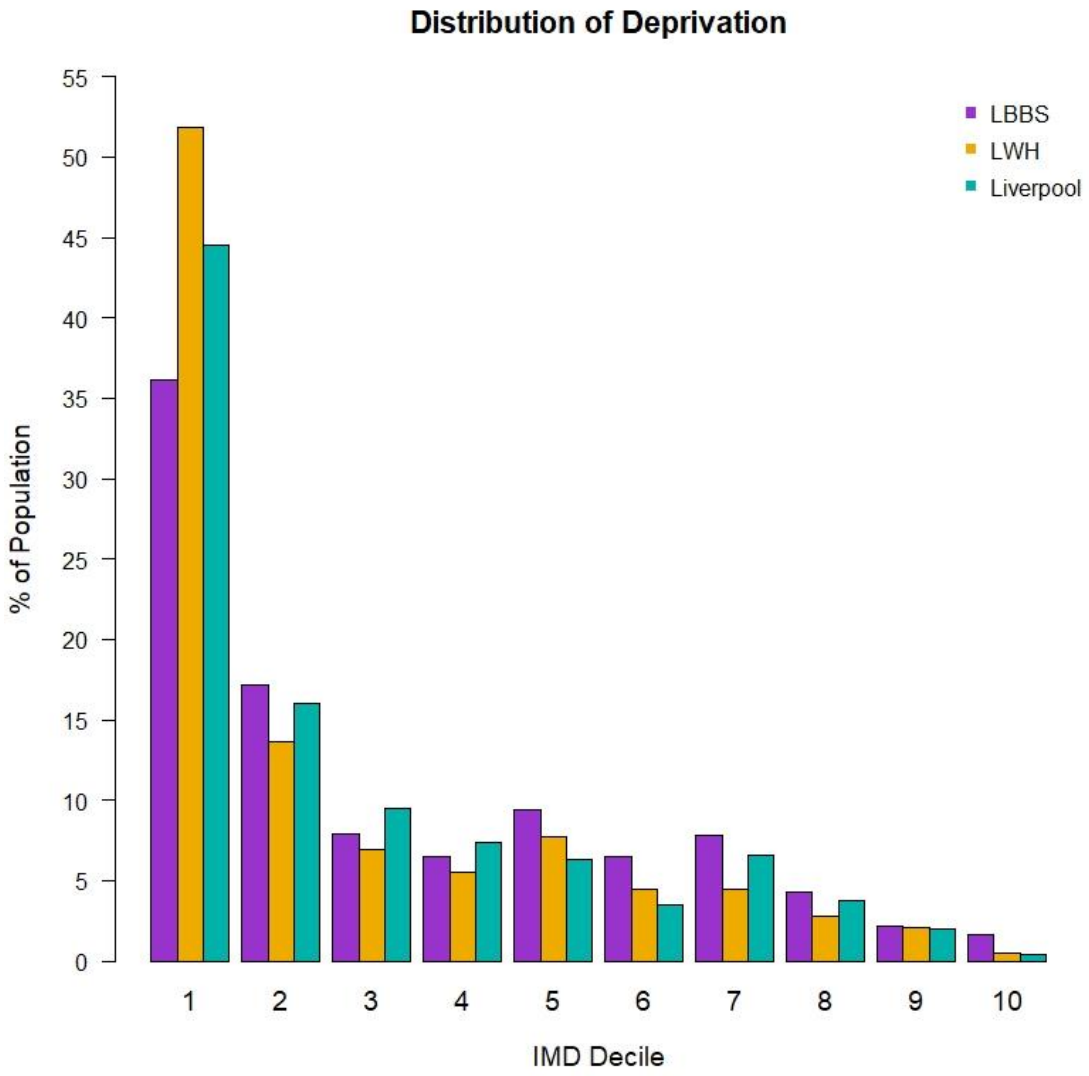


Figure 4: IMD deciles in the LBBS, compared to LWH and Liverpool

4.2.3 Maternal Age

The question regarding maternal age was not added to the questionnaire until after the pilot recruitment study had been conducted; therefore, 19.3% (n = 126) of mothers did not provide their maternal age. Of the mothers who did provide their age: 1.1% (n = 6) were younger than 20-years-old, 8.3% (n = 46) were 20 to 24-years-old, 23.4% (n = 130) were 25 to 29-years-old, 37.6% (n = 209) were 30 to 34-years-old, 22.3% (n = 124) were 35 to 39-years-old, 6.8% (n = 38) were 40 to 44-years-old, and 0.5% (n = 3) were 45-years-old or older (**Figure 5**).

Maternal age was older in the LBBS – as compared to the LWH's eligible births (χ^2 = 35.18, p = <0.001, df = 6), the whole of Liverpool (χ^2 = 122.05, p = <0.001, df = 6) and the whole of England (χ^2 = 71.23, p = <0.001, df = 6).

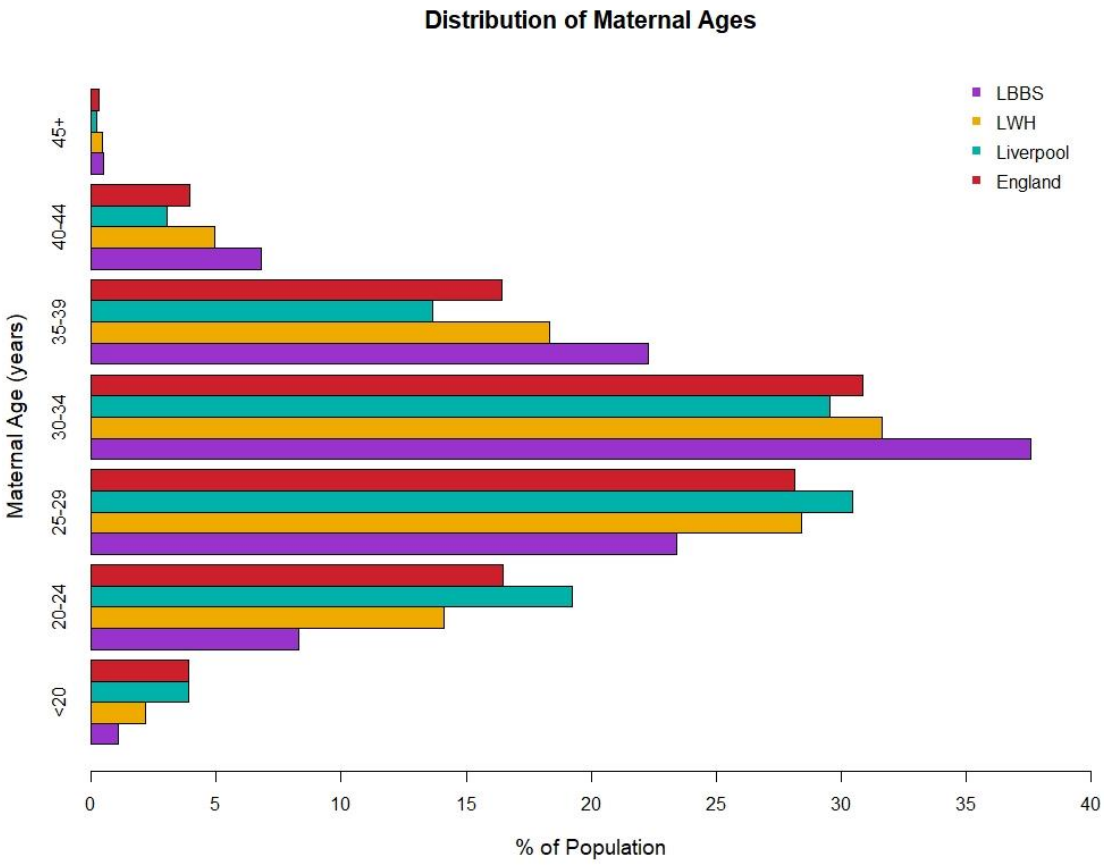


Figure 5: maternal ages in the LBBS, compared to LWH and Liverpool and England

4.2.4 Maternal Education

1.6% (n = 11) of mothers in the LBBS possessed no qualifications. 1.9% (n = 13) were educated to Level 1 (i.e. they finished secondary school, but with less than five passing GCSEs/O-Levels). 15.3% (n = 104) were educated to Level 2 (i.e. they had five or more GCSEs/O-Levels), and 7.5% (n = 51) were educated to Level 3 (i.e. they had at least two A-Levels). 50.3% (n = 342) were educated to Level 4 or above (i.e. they had at a degree). 16.8% (n = 114) had completed a vocational qualification (e.g. NVQs), and 6.6% (n = 45) had completed an apprenticeship or other qualification (**Figure 6**). [1]

[1] Mothers with a vocational qualification were excluded from the χ^2 testing, as their level of training could not be differentiated.

Compared to the educational level of parents in Liverpool, mothers in the LBBS were more educated (χ^2 = 315.40, p = <0.001, df = 5). The same difference existed between mothers in the LBBS, and parents in England (χ^2 = 219.43, p = <0.001, df = 5).

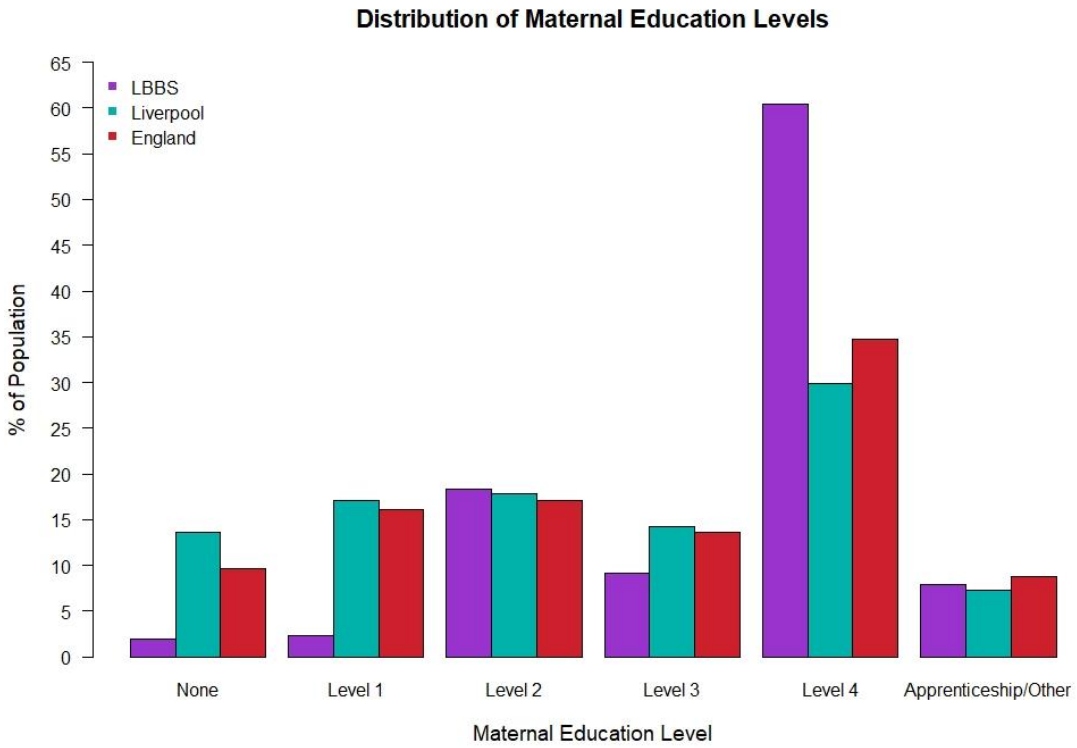


Figure 6: maternal education levels in the LBBS, compared to Liverpool and England

4.2.5 Smoking

4.2.5.1 Antenatal Smoking Status

90.6% (n = 616) of mothers in the LBBS did not smoke during pregnancy. However, this means that 9.4% (n = 64) continued the habit whilst pregnant (**Figure 7**).

Compared to the eligible births from LWH, the prevalence of antenatal smoking was lower in the LBBS (χ^2 = 31.70, p = <0.001, df = 1). The prevalence of antenatal smoking was also lower in the LBBS, when compared to Liverpool (χ^2 = 25.74, p = <0.001, df = 1) and England (χ^2 = 4.00, p = 0.05, df = 1).

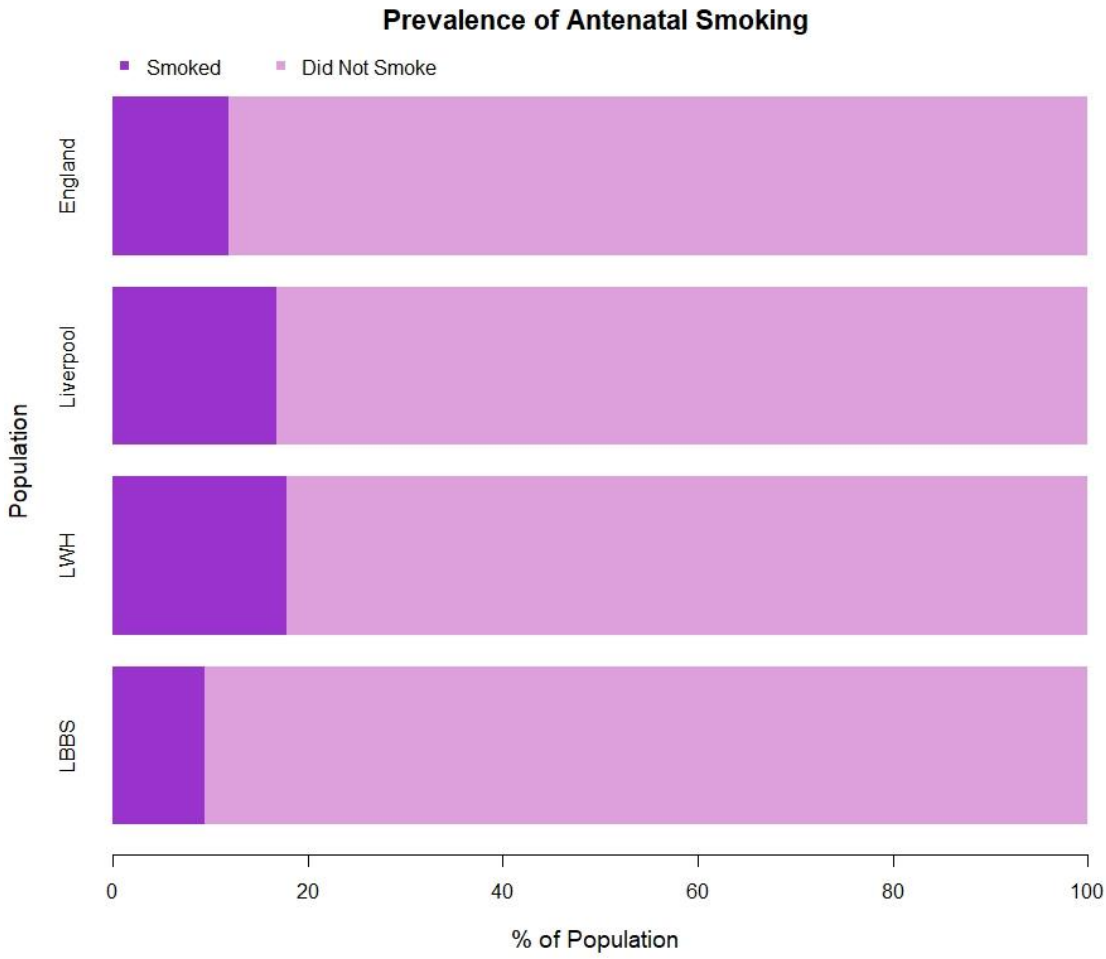


Figure 7: prevalence of antenatal smoking in the LBBS, compared to LWH and Liverpool and England

4.2.5.2 ETS Exposure During Pregnancy

Figure 8: antenatal ETS exposure in the LBBS by location

19.6% (n = 133) of mothers in the LBBS were exposed to ETS which originated from another person. During their pregnancies: 21.1% (n = 28) of these mothers were exposed to ETS inside the home, 87.2% (n = 116) were exposed to ETS outside of the home, 8.3% (n = 11) were exposed to ETS inside the car, 9.0% (n = 12) were exposed to ETS inside another location (e.g. work), and 3.8% (n = 5) were exposed to ETS elsewhere (**Figure 8**).

4.3 Profile of the Infant Cohort

This section of the results is dedicated to the analysis of the infant cohort. Amongst the LBBS' infants, the following have been calculated:

- prevalence of low birthweight
- distribution of infant ethnicity
- rate of prematurity
- rate of post-term birth
- prevalence of multiple pregnancies
- distribution of infant sex

Where possible, the LBBS cohort has also been compared to the eligible births from LWH and/or Liverpool and/or England.

4.3.1 Birthweight

9.0% (n = 62) of infants in the LBBS were classed as being of 'low birthweight', since they were born at <2.5kg. 90.6% (n = 624) of infants were not deemed to be of a low birthweight, and no birthweight was provided for 0.4% (n = 3) of infants. The distribution of birthweights in the LBBS can be seen in **Figure 9**.

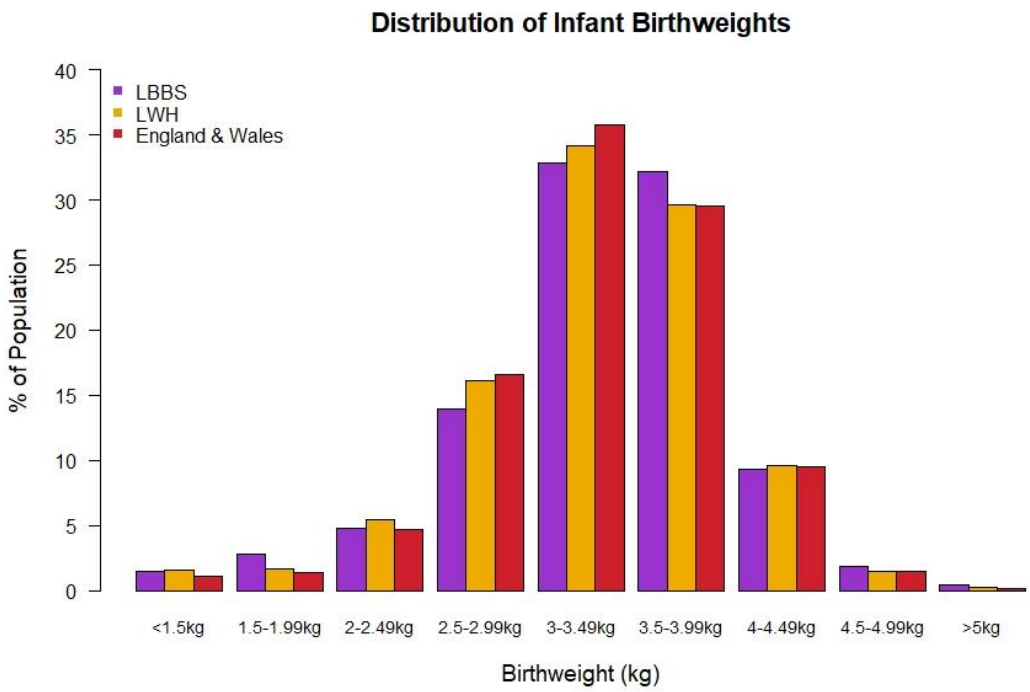


Figure 9: birthweight of infants in the LBBS, compared to LWH and England & Wales

There was not a significant difference between the proportion of 'low birthweight' infants seen in the LBBS, when compared to the eligible births at LWH ($\chi^2 = 0.12$, $p = 0.73$, df = 1). However, there were fewer 'low birthweight' infants born in England around the same time ($\chi^2 = 3.95$, $p = 0.05$, df = 1).

4.3.2 Ethnicity

The majority of infants in the LBBS were white: 90.9% (n = 626). Just 0.9% (n = 6) of infants were black, and only 0.4% (n = 3) of infants were Asian – Indian, Pakistani or Bangladeshi. 7.6% (n = 52) identified as another ethnicity – including mixed race (**Figure 10**). 0.3% (n = 2) did not declare their ethnicity.

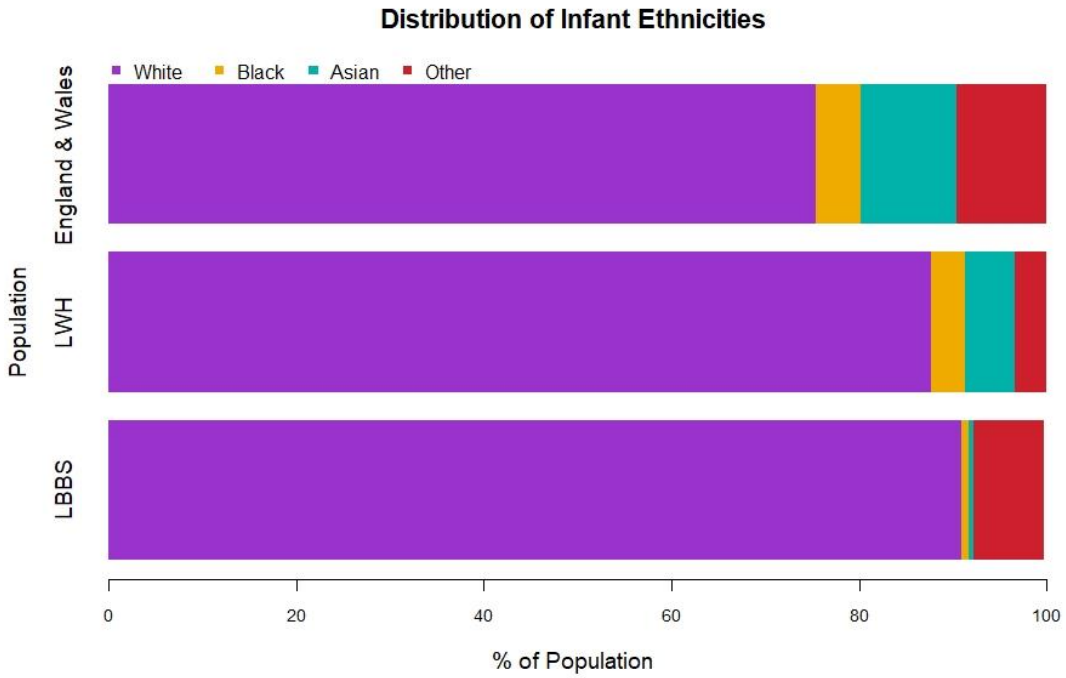


Figure 10: ethnicity of infants in the LBBS, compared to LWH and England & Wales

The prevalence of white infants in the LBBS was higher than all other ethnicities, when compared to the eligible births in LWH (χ^2 = 7.21, p = 0.007, df = 1), and in England & Wales (χ^2 = 91.47, p = <0.001, df = 1).

4.3.3 Gestational Age

Prematurity was seen in 12.5% (n = 86) of the LBBS' infants, and 24.2% (n = 167) of the infants were born post-term. The distribution of gestational ages in the LBBS can be seen in **Figure 11**.

The rate of prematurity in the LBBS was higher than the rate of prematurity amongst the eligible births at LWH (χ^2 = 5.16, p = 0.02, df = 1). The rate of prematurity was also higher than England's (χ^2 = 25.33, p = <0.001, df = 1).

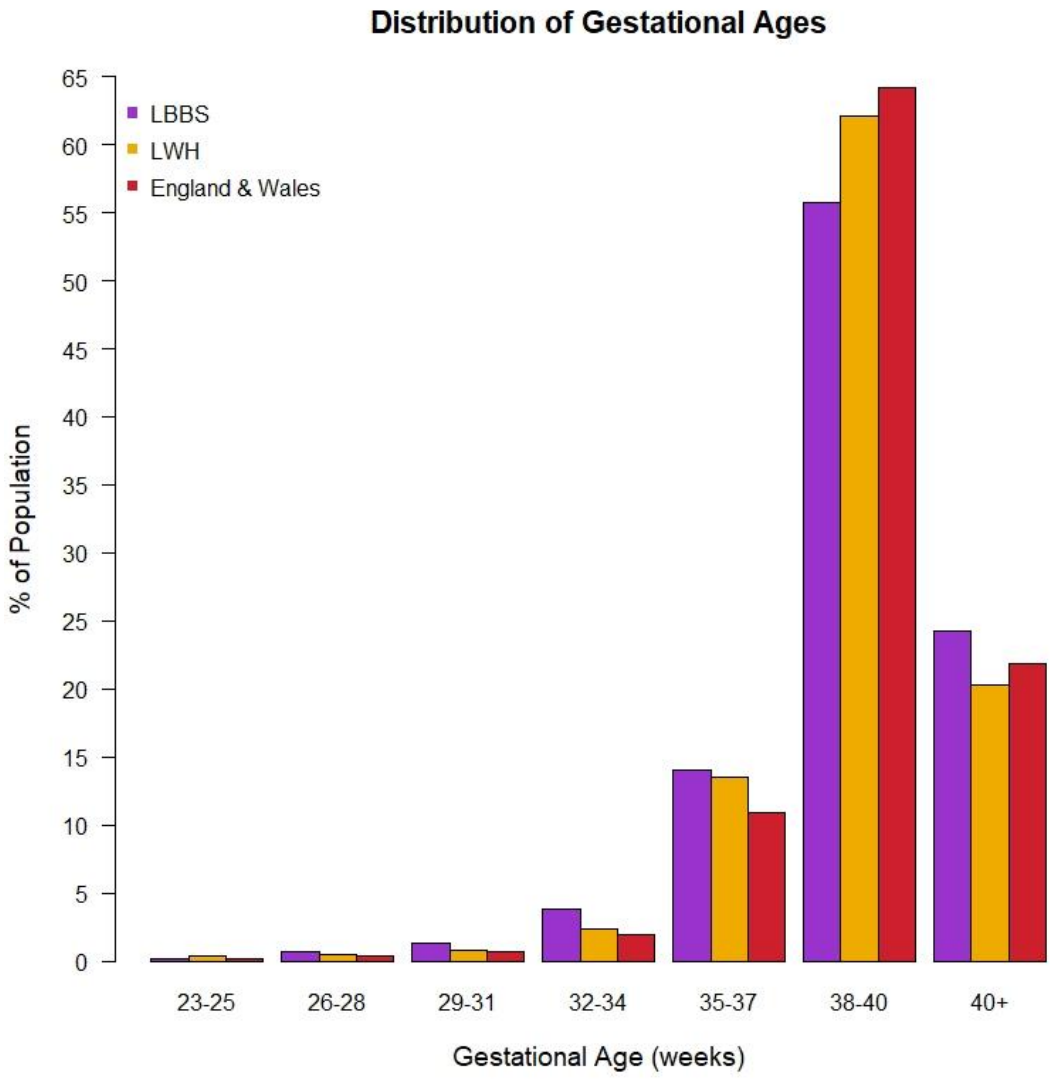


Figure 11: gestational age of infants in the LBBS, compared to LWH and England & Wales

4.3.4 Multiple Pregnancies

There were 9 pairs of twins enrolled onto the LBBS – accounting for 1.3% of the pregnancies represented in the study. Therefore, the LBBS had a multiple pregnancy rate of 10.3 per 1000 pregnancies (**Figure 12**).

The rate of multiple pregnancies in the LBBS was not significantly different to the multiple pregnancy rate seen amongst the eligible births at LWH ($\chi^2 = 0.31$, $p = 0.58$, $df = 1$). The study's multiple pregnancy rate was neither significantly different to the whole of Liverpool's ($\chi^2 = 0.03$, $p = 0.87$, $df = 1$), nor England & Wales' ($\chi^2 = 0.37$, $p = 0.54$, $df = 1$).

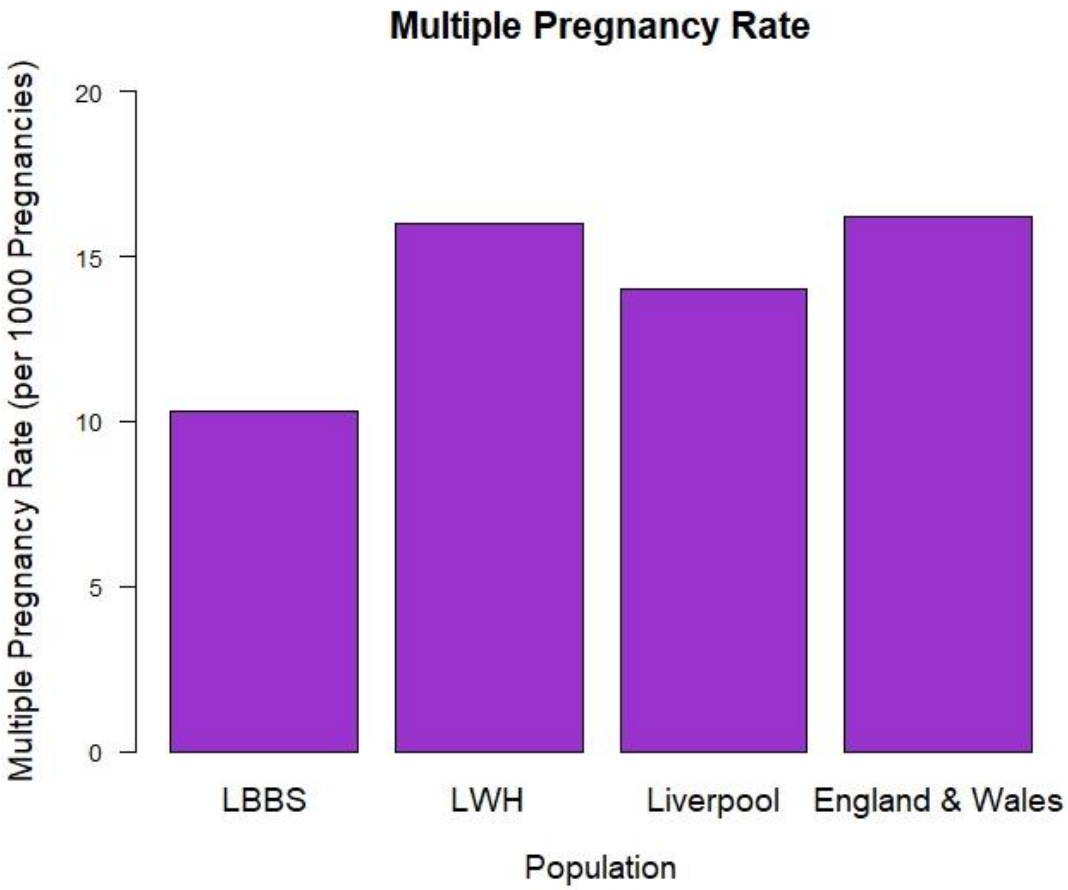


Figure 12: multiple pregnancy rate in the LBBS, compared to LWH and Liverpool and England

4.3.5 Sex

49.49% (n = 341) of the infants in the LBBS male, whilst 50.51% (n = 348) were female.

As compared to the eligible births in England & Wales, the split between male and female infants was not considered to be significantly different ($\chi^2 = 0.91$, $p = 0.34$, $df = 1$). No data was available from LWH, for which to draw any comparisons.

4.4 Attrition

This section of the results is dedicated to the analysis of attrition from the LBBS. The rates of attrition between successive questionnaires, and from the first questionnaire, have been calculated. An overview of reasons for attrition from the study is also given. Changes to the demographics of the cohort (as a result of attrition) are described too.

4.4.1 Rate of Attrition

Of the 689 infants enrolled onto the LBBS: 97.1% (n = 667) were accounted for in questionnaire one, 54.1% (n = 372) were accounted for in questionnaire two, 39.6% (n = 272) were accounted for in questionnaire three, 36.8% (n = 253) were accounted for in questionnaire four, and 32.8% (n = 225) were accounted for in questionnaire five. 33.5% (n = 230) were accounted for in questionnaire six, 31.3% (n = 215) were accounted for in questionnaire seven, 36.4% (n = 250) were accounted for in questionnaire eight, 31.0% (n = 213) were accounted for in questionnaire nine, and 31.9% (n = 219) were accounted for in questionnaire ten. **Table 15** describes the change in response rate between successive questionnaires, and **Figure 13** shows the change graphically.

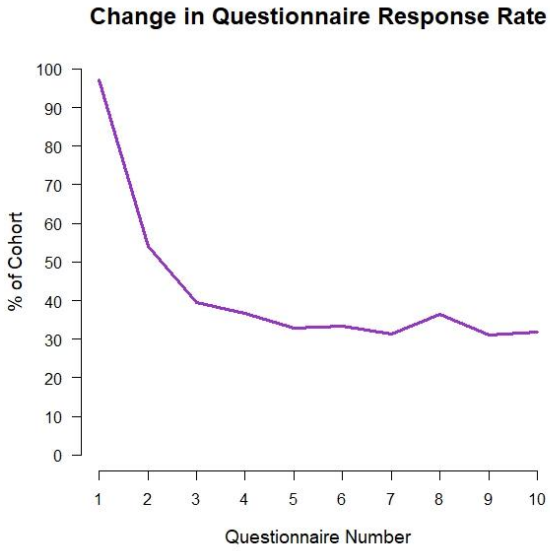


Figure 13: change in questionnaire response rate

		Respondents	Response Rate from Total LBBS Cohort	Δ% in Response Rate from Previous Questionnaire
Questionnaire Number	**1**	667	97.1%	
	2	372	54.1%	-44.2%
	3	272	39.6%	-26.9%
	4	253	36.8%	-7.0%
	5	225	32.8%	-11.1%
	6	230	33.5%	+2.2%
	7	215	31.3%	-6.5%
	8	250	36.4%	+16.3%
	9	213	31.0%	-14.8%
	10	219	31.9%	+2.8%

Table 15: questionnaire response rate, and change in response rate

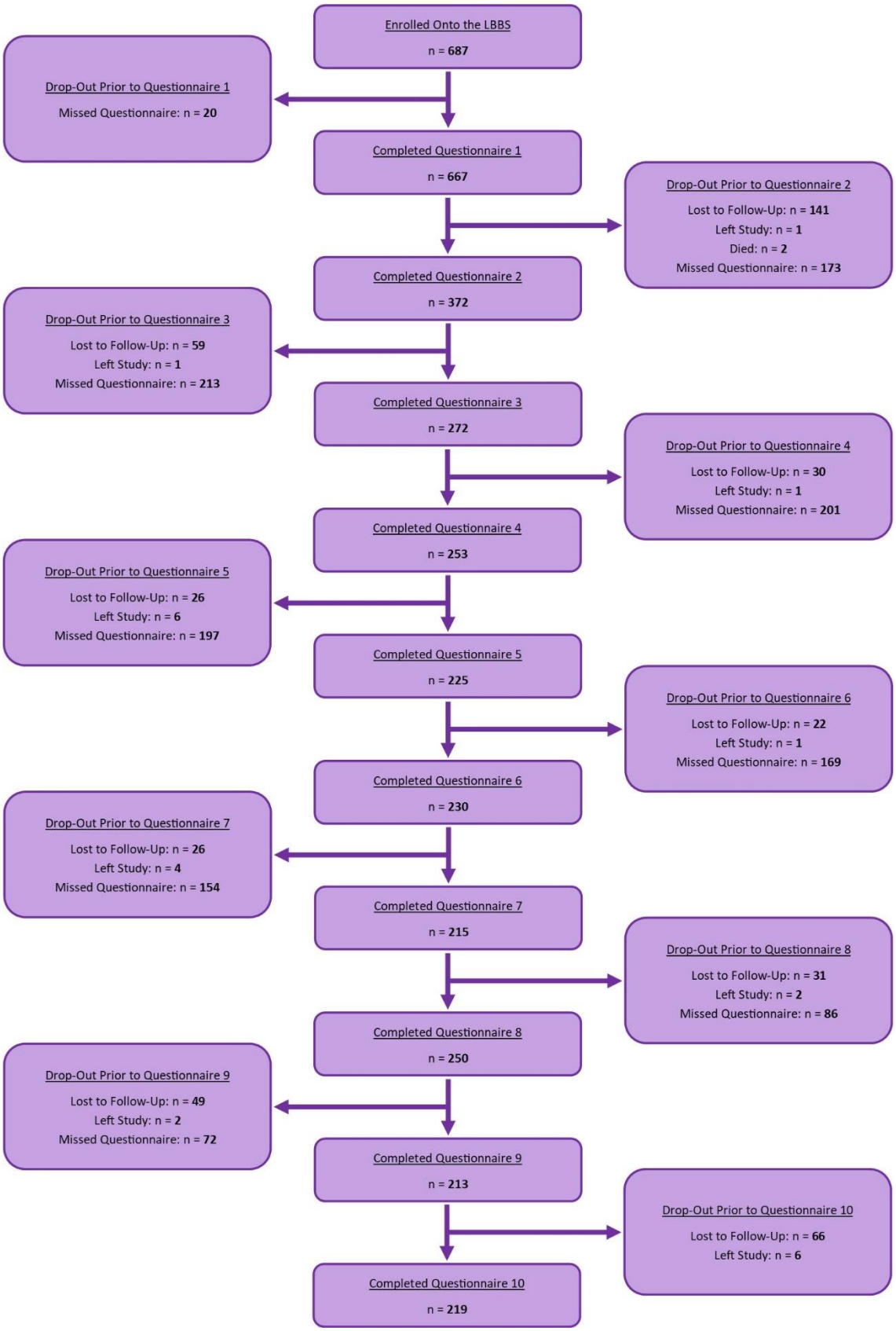


Figure 14: flowchart of attrition throughout the LBBS

Participants were deemed to have permanently dropped-out if they: left the study (i.e. deliberately removed themselves from mailing list), or died, or were lost to follow-up (i.e. didn't complete any further questionnaires). Those who missed a questionnaire (i.e. went on to complete at least one future questionnaire) were deemed to have temporarily dropped out. **Figure 14** shows the reasons for attrition between every questionnaire.

		Respondents	% of Total LBBS Cohort
Number of Completed Questionnaires	1	143	20.8
	2	118	17.2
	3	91	13.2
	4	50	7.3
	5	65	9.5
	6	38	5.5
	7	53	7.7
	8	45	6.6
	9	43	6.3
	10	41	6.0

Table 16: LBBS cohort by number of completed questionnaires

Further analysis showed that for the majority of infants: 20.9% (n = 143), just one questionnaire was returned. 41.5% (n = 285) of the cohort completed at least half of the questionnaires. A complete dataset was achieved for 6.0% (n = 41) of infants – meaning that all ten questionnaires were returned (**Table 16**).

4.4.2 Demographic Change of the Study Cohort

Throughout the LBBS, fluctuations in the demographic profile of the cohort were apparent. Attrition can be held accountable for some of these changes, as within each of the different demographics, certain groups were more likely to drop-out of the study. The following sub-headings describe how the cohort changed across the ten questionnaires, in ten distinct areas, as previously described in Section 4.2 and Section 4.3.

4.4.2.1 Antenatal Smoking Status

The proportion of mothers who smoked during pregnancy decreased by an average of 0.22% between each questionnaire (**Figure 15**). Since the proportion of mothers who didn't smoke increased by 0.22%, there was a disproportionate drop-out rate amongst those who smoked antenatally.

4.4.2.2 Birthweight

The average rate of attrition between each questionnaire was 0.36% for 'low birthweight' infants (**Figure 16**). Since the proportion of 'normal birthweight' infants grew by 0.33% between each questionnaire, there was a disproportionate amount of attrition amongst 'low birthweight' infants.

4.4.2.3 Breastfeeding Status

On average, the breastfed population increased by 0.57% between each questionnaire, whilst the non-breastfed population fell by 0.57% (**Figure 17**). Non-breastfed infants therefore dropped-out of the study to a greater extent than breastfed infants did.

4.4.2.4 Deprivation

The proportion of respondents in the first and second IMD deciles declined by an average of 0.75% and 0.29% respectively between each of the ten questionnaires (**Figure 18**). On average, the other eight deciles saw an increase (or a negligible change) in the proportion of respondents within them. A disproportionate rate of attrition was seen from the most deprived participants.

4.4.2.5 Ethnicity

The proportion of white infants rose by 0.29% between each questionnaire in the LBBS, whilst the proportion of non-white infants declined by 0.24% (**Figure 19**). There were no Asian participants remaining in the study from the third questionnaire, onwards. Non-white infants therefore dropped-out of the LBBS at a disproportionately higher rate than white infants.

4.4.2.6 Gestational Age

The average rate of attrition between each questionnaire was 0.36% for premature infants; the proportion of term infants grew by 0.36% between questionnaires (**Figure 20**). Infants who were born prematurely dropped-out of the LBBS at a slightly greater rate than those who were born at term.

4.4.2.7 Maternal Age

The proportion of women with a maternal age of less than 25-years-old fell by an average of 0.33% between each questionnaire; the proportion of women with a maternal age of 25 to 34-years-old fell by 0.57% (**Figure 21**). The proportion of

mothers aged ≥35-years-old rose by 0.92% between each questionnaire - even though all mothers older than 45-years-old had departed the study by the fourth questionnaire. The overall trend in attrition shows that younger mothers were lost from the LBBS disproportionately more so than older mothers were.

4.4.2.8 Maternal Education

The proportion of mothers who were degree-educated increased throughout the study: by an average of 1.6% between each questionnaire (**Figure 22**). Decreases were seen in the proportion of mothers from all other educational levels - showing that attrition was more common amongst less-educated mothers.

4.4.2.9 Multiple Pregnancy

There was a negligible change in the proportion of responses that came from twins, and the proportion that came from singletons, throughout the LBBS (**Figure 23**).

4.4.2.10 Sex

There was a negligible change in the proportion of male and female infants throughout the study (**Figure 24**).

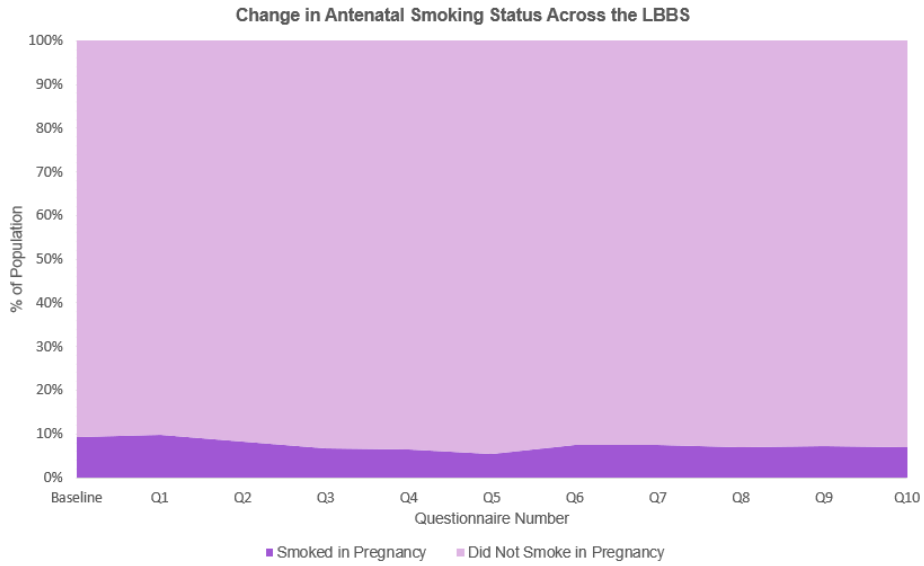


Figure 15: proportion of mothers over time by antenatal smokig status

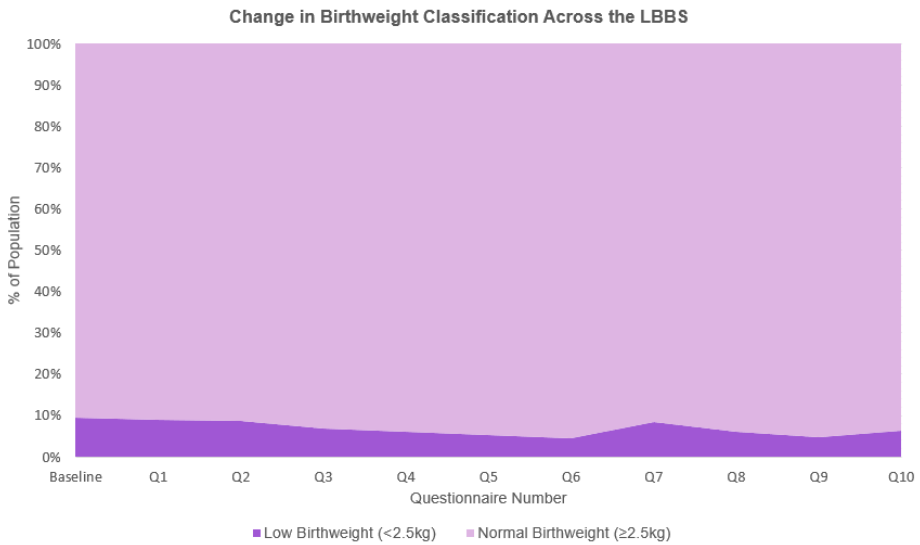


Figure 16: proportion of infants over time by birthweight classification

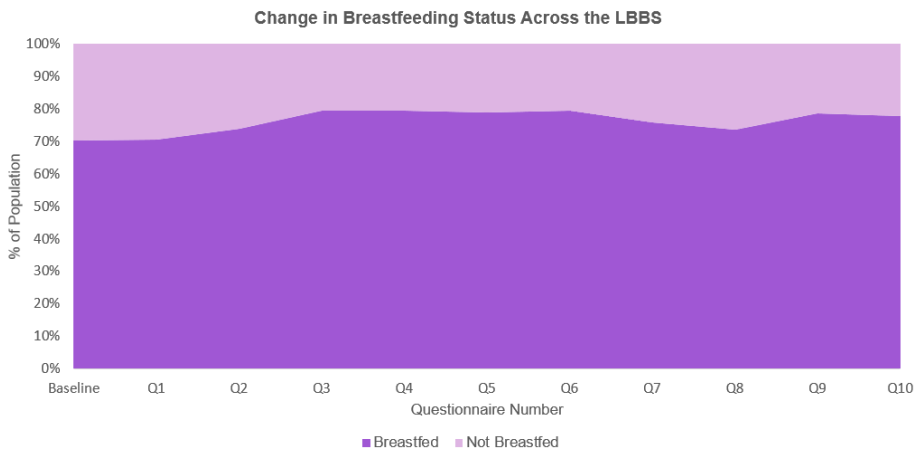


Figure 17: proportion of mothers over time by breastfeeding status

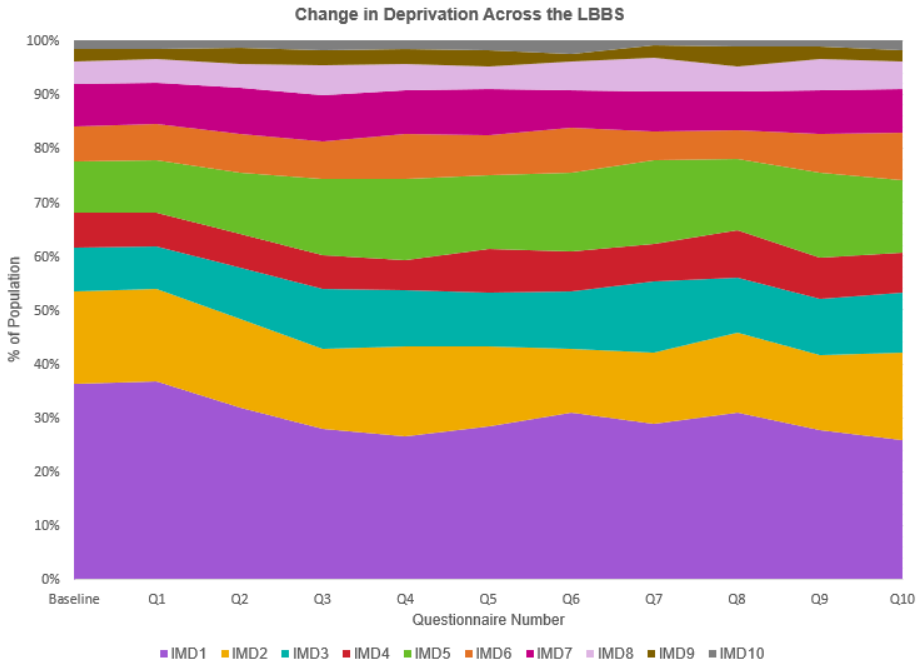


Figure 18: proportion of families over time by IMD decile

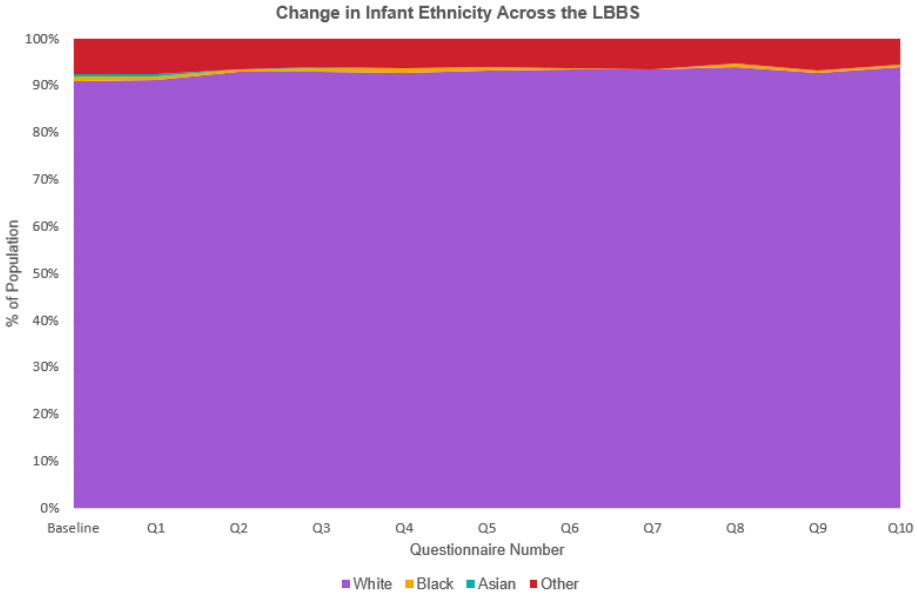


Figure 19: proportion of infants over time by ethnicity

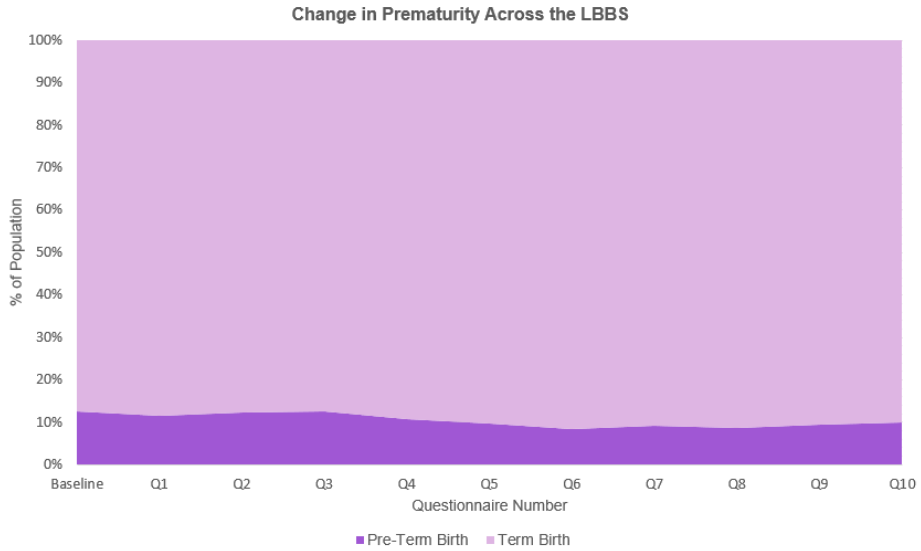


Figure 20: proportion of infants over time by gestational age

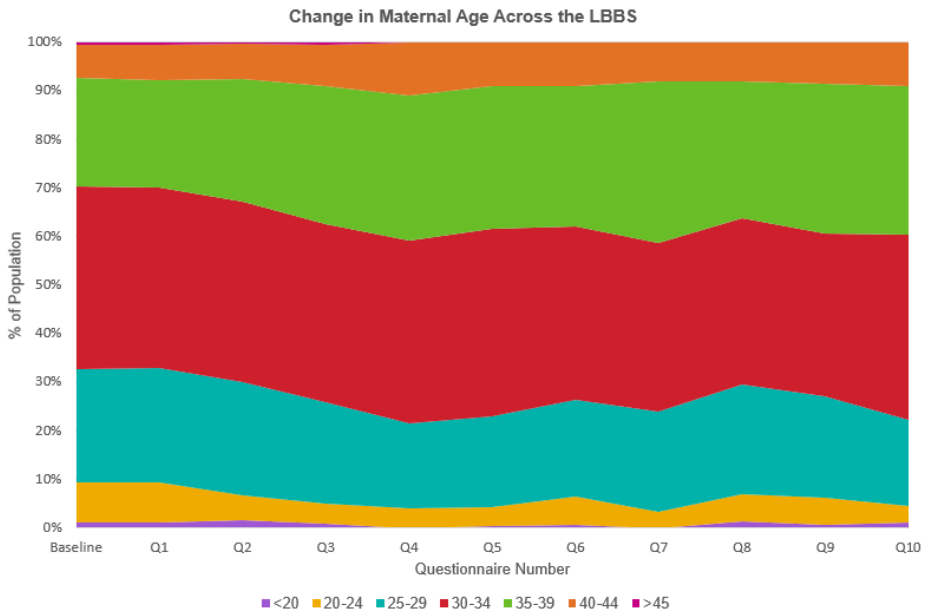


Figure 21: proportion of mothers over time by highest educational level

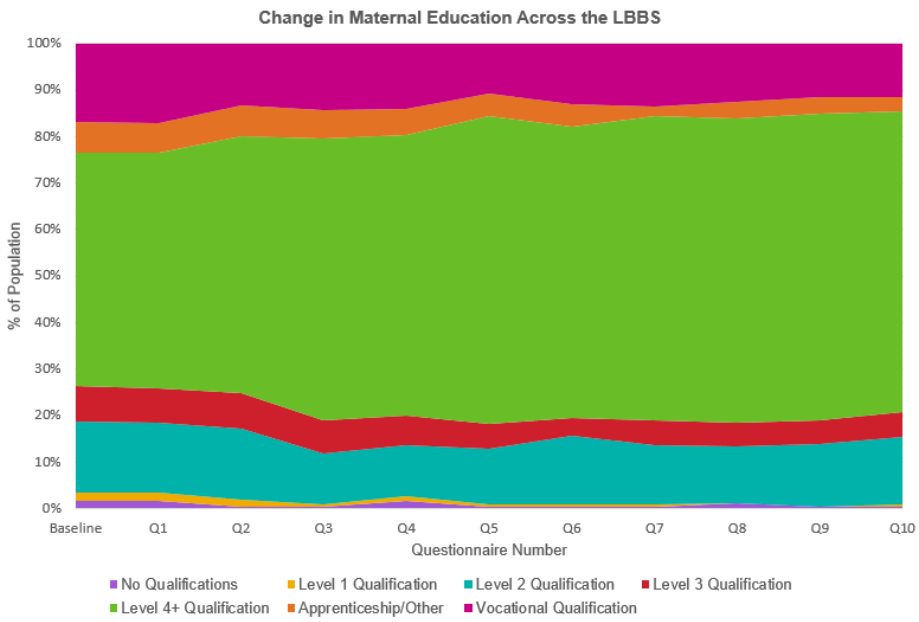


Figure 22: proportion of mothers over time by age at the time of delivery

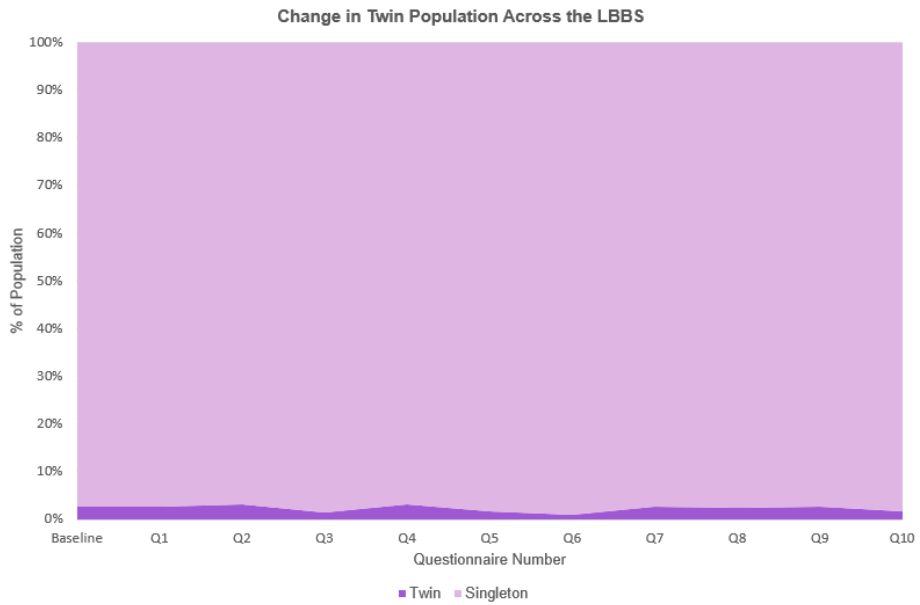


Figure 23: proportion of infants over time by twin or singleton status

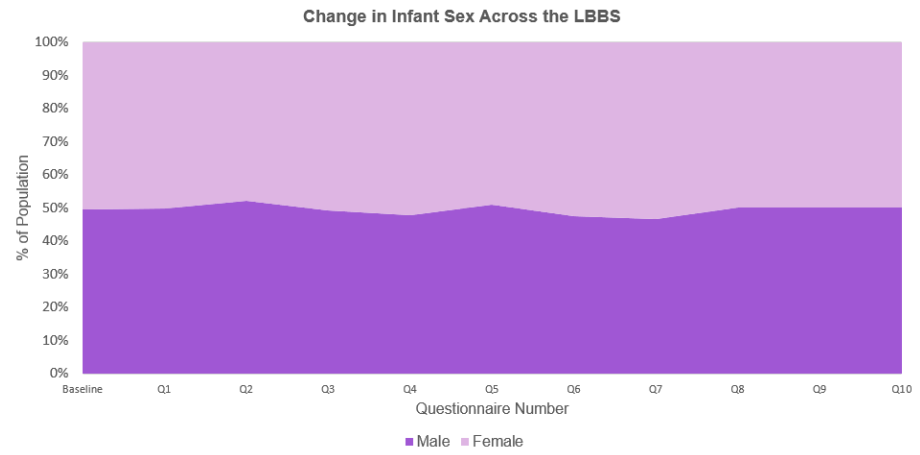


Figure 24: proportion of infants over time by sex

4.5 Cross-Sectional Analysis

This section of the results is dedicated to the cross-sectional analysis of the LBBS. The prevalence of the following risk factors has been described for each of the ten questionnaire timepoints: nursery attendance, other household children, bedroom sharing, ETS exposure, family history of atopy and co-morbidities. At every timepoint, the distribution of total/domain LRSQ scores, the prevalence of different respiratory symptoms, and the frequency of healthcare service attendance have been calculated. Inferential statistical tests have been used to analyse how a child's exposure to certain risk factors, can affect their LRSQ score and symptom prevalence and healthcare service attendance at ten different ages.

4.5.1 Questionnaire 1: 4-Months-Old

4.5.1.1 Exposure to Risk Factors

4.5.1.1.1 Nursery Attendance

At 4-months-old, 4.2% (n = 28) of infants attended nursery.

4.5.1.1.2 Other Household Children

36.1% (n = 241) of infants lived with at least one other child at 4-months-old. 71.8% (n = 171) lived with only one other, 22.7% (n = 54) lived with two others, 3.4% (n = 8) lived with three others, 1.7% (n = 4) lived with four others, and 0.4% (n = 1) lived with seven others.

4.5.1.1.3 Bedroom Sharing

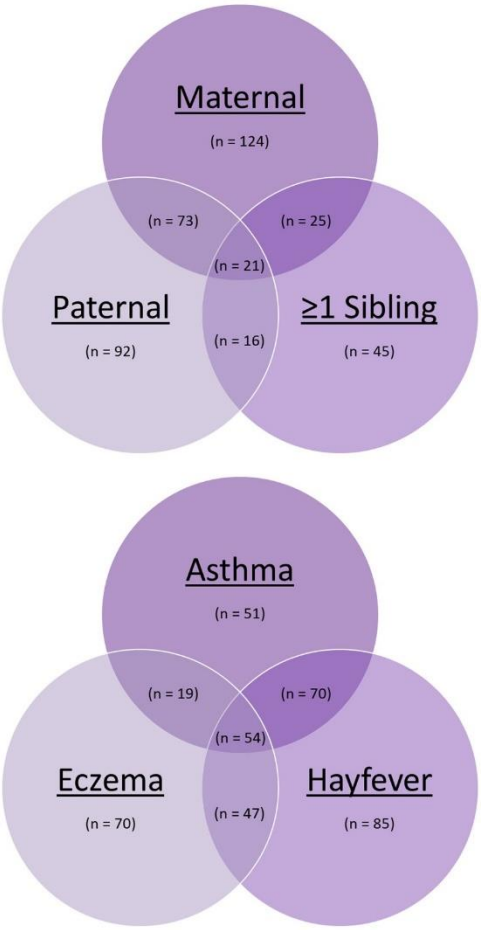
At 4-months-old, 69.3% (n = 462) of infants shared a bedroom. 93.4% (n = 450) shared with their parent(s), 5.8% (n = 28) shared with one other child, and 0.8% (n = 4) shared with someone else.

4.5.1.1.4 ETS Exposure

18.6% (n = 124) of infants were exposed to ETS at 4-months-old. 8.9% (n = 13) were exposed to ETS from inside the home, 82.2% (n = 120) were exposed to ETS from outside of the home, 2.7% (n = 4) were exposed to ETS from inside the car, 5.5% (n = 8) were exposed to ETS from within another location (e.g. work), and 0.7% (n = 1) were exposed to ETS from elsewhere.

At 4-months-old, the prevalence of ETS exposure amongst infants in the LBBS was not significantly different to the prevalence of smoking in England in 2013-15 ($\chi^2 = 0.50$, p = *0.48*, df = 1). However, it was lower than the prevalence of smoking in Liverpool in 2013-15 ($\chi^2 = 7.22$, p = 0.007, df = 1).

4.5.1.1.5 Family History of Atopy



At 4-months-old, 59.4% (n = 396) of infants had a family history of atopy.

From those with a family history of atopy: 61.4% (n = 243) had an atopic mother, 51.0% (n = 202) had an atopic father, and 27.0% (n = 107) had at least one atopic sibling. There was a family history of: asthma in 49.0% (n = 194) of these infants, hay fever in 64.6% (n = 256), and eczema in 48.0% (n = 190). **Figure 25** shows how familial atopy was inter-related at 4-months-old.

Figure 25: infants with a family history of atopy, by relative(s) and disease(s), at 4-months-old

4.5.1.1.6 Co-Morbidities

7.8% (n = 52) of infants had a co-morbid disease at 4-months-old. The gastrointestinal system was the most common co-morbid system at this age, whilst eczema was the most common co-morbidity overall. **Table 17** shows the co-morbidities seen at 4-months-old – as reported by parents, and grouped according to organ system.

Type of Co-Morbidity	Underlying Condition	Frequency
Respiratory (n = 6)	Cystic Fibrosis	2
	Laryngomalacia	2
	Atelectasis	1
	Chronic Lung Disease of Prematurity	1
	Scarring of the Lungs	1
Cardiac (n = 7)	Congenital Heart Disease	4
	Heart Murmur	3
Renal (n = 2)	Duplex Kidney	1
	Vesicoureteral Reflux	1
Neurological (n = 2)	Hydrocephalus	1
	Intracranial Haemorrhage	1
Gastrointestinal (n = 11)	Gastro-Oesophageal Reflux	8
	Hernia	2
	"Blood in Stools"	1
Other (n = 30)	Eczema	17
	Food Allergy	4
	Developmental Dysplasia of Hips	3
	Blood Blister	1
	Cleft Palate	1
	Down's Syndrome (Trisomy 21)	1
	Hypospadias	1
	Neonatal Alloimmune Thrombocytopenia	1
	Sagittal Craniosyntosis	1

Table 17: co-morbidities of the LBBS cohort at 4-months-old

4.5.1.2 LRSQ Scores

Measures of central tendency and dispersion for the total LRSQ score, and LRSQ domain scores, at 4-months-old are shown in **Table 18**. The distribution of scores are shown graphically in **Figure 26**.

	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Standard Deviation
Total Score	0	2	5	13	109	9.98	12.80
Domain 1	0	0	1	2	15	1.45	2.01
Domain 2	0	0	2	3	19	2.15	2.37
Domain 3	0	0	1	3	21	2.34	3.17
Domain 4	0	0	0	1	16	0.78	1.60
Domain 5	0	0	0	0	16	0.49	1.43
Domain 6	0	0	0	2	12	1.16	1.90
Domain 7	0	0	0	0	8	0.45	1.14
Domain 8	0	0	0	1	16	0.98	2.18

Table 18: descriptive statistics of the total and domain LRSQ scores at 4-months-old

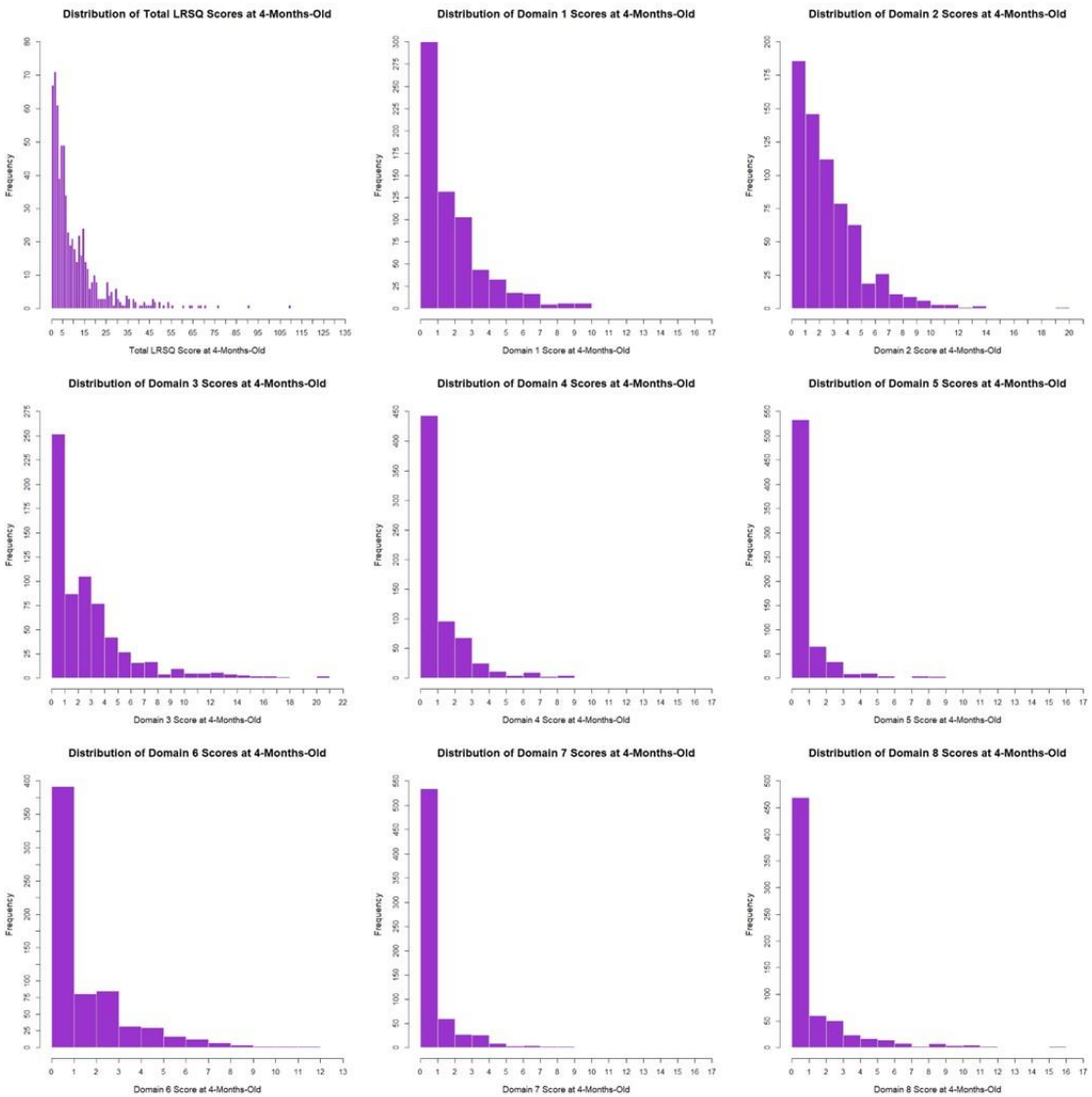


Figure 26: distribution of total and domain LRSQ scores at 4-months-old

4.5.1.2.1 Impact of Risk Factor Exposure on Total LRSQ Score

Total LRSQ scores were higher amongst infants who: did not share a bedroom (U = 40784, p = 0.023), had a family history of atopy (U = 45622, p = 0.010) or had a co-morbidity (U = 10123, p = <0.001). They were also higher amongst males (U = 45955, p = 0.001).

4.5.1.2.2 Impact of Risk Factor Exposure on LRSQ Domain Scores

4.5.1.2.2.1 Domain 1

Domain 1 scores were higher amongst males (U = 48776, p = 0.034), and those with a co-morbidity (U = 11190, p = 0.001).

There were differences in domain 1 score between the different levels of maternal education (H = 6.75, p = 0.034, df = 2). Post-hoc analysis revealed that infants with

school-educated mothers scored higher than those with degree-educated mothers ($p = 0.012$).

4.5.1.2.2.2 Domain 2

Domain 2 scores were higher amongst males ($U = 46825$, $p = 0.004$), and those with a co-morbidity ($U = 10751$, $p = <0.001$).

There were differences in domain 2 score between the different levels of maternal education ($H = 7.63$, $p = 0.022$, $df = 2$). Post-hoc analysis revealed that infants with school-educated mothers scored higher than those with degree-educated mothers ($p = 0.011$). There were differences in domain 2 score amongst breastfed infants, depending on how long they were breastfed for ($H = 7.10$, $p = 0.029$, $df = 2$). It also revealed that infants who were breastfed for more than 4 months scored lower, compared to those who were breastfed for less than 1 month ($p = 0.028$) or for 1-4 months ($p = 0.031$).

4.5.1.2.2.3 Domain 3

Domain 3 scores were higher amongst infants who: lived with other children ($U = 44619$, $p = 0.032$), did not share a bedroom ($U = 39374$, $p = 0.003$), or had a co-morbidity ($U = 12485$, $p = 0.020$).

4.5.1.2.2.4 Domain 4

Domain 4 scores were higher amongst infants who had: a family history of atopy ($U = 47208$, $p = 0.023$), or a co-morbidity ($U = 13150$, $p = 0.038$). They were also higher amongst premature infants ($U = 18990$, $p = 0.020$).

There were differences in domain 4 score between the different levels of maternal education ($H = 16.80$, $p = <0.001$, $df = 2$) and deprivation ($H = 10.20$, $p = 0.037$, $df = 4$). Post-hoc analysis revealed that infants with degree-educated mothers scored lower, compared to those with school ($p = <0.001$) and vocationally-educated mothers ($p = 0.014$). Post-hoc analysis revealed that infants living in the most-deprived IMD quintile scored higher than those living in the second-most deprived IMD quintile ($p = 0.015$).

4.5.1.2.2.5 Domain 5

Domain 5 scores were higher amongst infants who: had a family history of atopy ($U = 47996$, $p = 0.025$), had a co-morbidity ($U = 11742$, $p = <0.001$), or were not breastfed ($U = 41419$, $p = 0.018$).

4.5.1.2.2.6 Domain 6

Domain 6 scores were higher amongst males ($U = 47768$, $p = 0.006$), and those who had: a co-morbidity ($U = 11151$, $p = <0.001$), or a family history of atopy ($U = 46814$, $p = 0.020$).

4.5.1.2.2.7 Domain 7

Domain 7 scores were higher amongst infants who: did not share a bedroom ($U = 42435$, $p = 0.027$), had a family history of atopy ($U = 48423$, $p = 0.045$) or had a co-morbidity ($U = 13115$, $p = 0.011$).

4.5.1.2.2.8 Domain 8

Domain 8 scores were higher amongst infants who: lived with other children ($U = 45334$, $p = 0.028$), had a family history of atopy ($U = 47604$, $p = 0.031$), were not breastfed ($U = 41493$, $p = 0.043$), or had a co-morbidity ($U = 10577$, $p = <0.001$). They were also higher amongst males ($U = 46965$, $p = 0.001$).

4.5.1.2.3 Total LRSQ Score vs Total QoL Score

There was a positive correlation between an infant's total LRSQ score, and their total QoL score ($r_s = 0.739$, $p = <0.001$). **Figure 27** shows the correlation graphically. A higher total LRSQ score is more strongly correlated with a poor QoL for parents, than with a poor QoL for infants ($r_s = 0.718$, $p = <0.001$ vs $r_s = 0.598$, $p = <0.001$). Infants who regularly suffer with respiratory symptoms, and their parents, therefore experience a worse QoL.

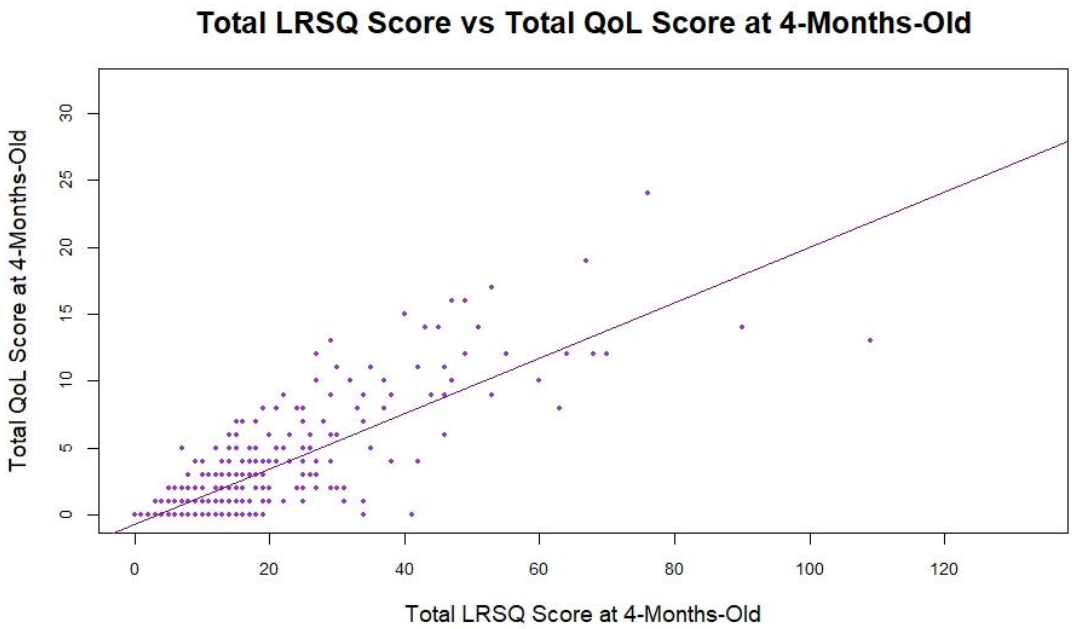


Figure 27: correlation between total LRSQ score and total QoL score at 4-months-old

4.5.1.3 Symptom Prevalence

90.0% (n = 600) of infants experienced at least one type of respiratory symptom at 4-months-old. Snoring was the most common symptom, as it was experienced by 62.2% (n = 415) of infants; SOB was the least common symptom, as it was experienced by 12.4% (n = 83) of infants. **Figure 28** demonstrates the prevalence of individual symptoms.

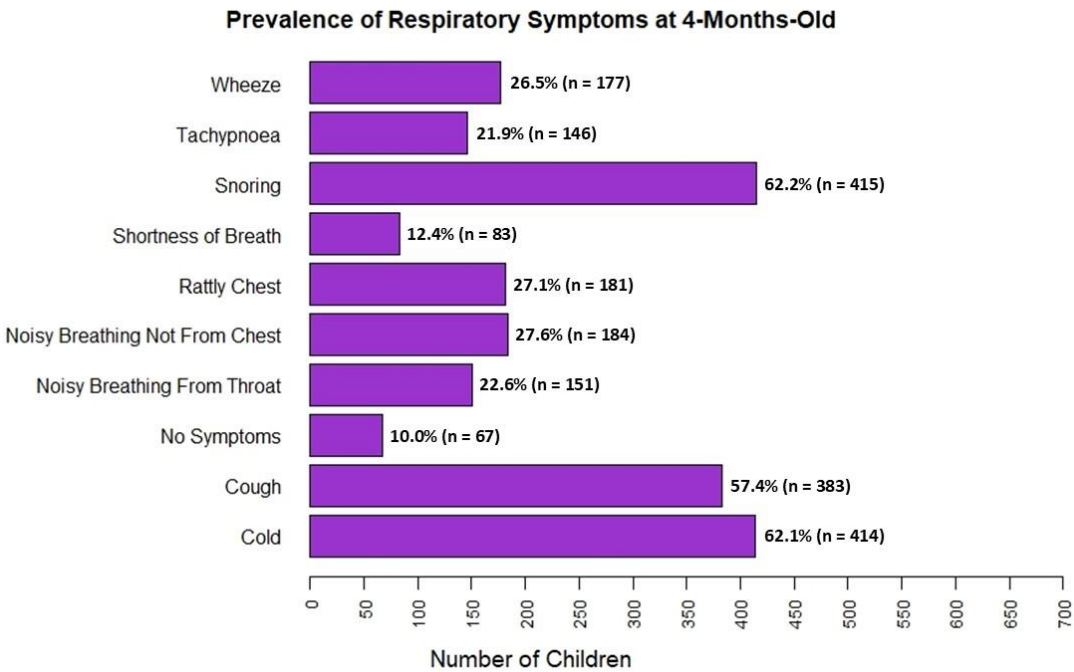


Figure 28: prevalence of respiratory symptoms at 4-months-old

4.5.1.3.1 Impact of Risk Factor Exposure on Symptom Prevalence

4.5.1.3.1.1 Colds

Colds were more likely amongst: infants who were born at term (OR = 1.66, 95% CI = 1.01 – 2.72), 'normal' birthweight infants (OR = 1.88, 95% CI = 1.09 – 3.24), infants who lived with other children (OR = 1.51, 95% CI = 1.08 – 2.11), and infants who did not share a bedroom (OR = 1.73, 95% CI = 1.21 – 2.49).

4.5.1.3.1.2 Coughing

There were no risk factors that affected the prevalence of coughing, at 4-months-old.

4.5.1.3.1.3 No Symptoms

Being asymptomatic was more likely amongst twins (OR = 3.31, 95% CI = 1.09 – 10.05), and 'low birthweight' infants (OR = 2.61, 95% CI = 1.28 – 5.32).

4.5.1.3.1.4 Noisy Breathing – From Throat

Noisy breathing from the throat was more likely amongst infants: with a family history of atopy (OR = 1.70, 95% CI = 1.16 – 2.50), males (OR = 1.63, 95% CI = 1.13 - 2.35), and infants with a co-morbidity (OR = 3.39, 95% CI = 1.90 - 6.05). Noisy breathing from the throat was also more likely amongst children with vocationally-educated mothers, compared to those with degree-educated mothers (OR = 1.58, 95% CI = 1.02 - 2.45).

4.5.1.3.1.5 Noisy Breathing – Not From Chest

Noisy breathing that did not come from the chest was more likely amongst: infants whose mothers smoked during pregnancy (OR = 1.88, 95% CI = 1.09 - 3.24), infants who lived with other children (OR = 1.51, 95% CI = 1.08 – 2.11), infants who did not share a bedroom (OR = 1.73, 95% CI = 1.21 – 2.49), and males (OR = 1.71, 95% CI = 1.21 - 2.41).

4.5.1.3.1.6 Rattly Chest

Rattly chests were more likely amongst infants with a co-morbidity (OR = 2.42, 95% CI = 1.37 – 4.28), and Caucasian infants (OR = 2.29, 95% CI = 1.17 – 4.49). Rattly chests were also more likely amongst infants with school or vocationally-educated mothers, compared to those with degree-educated mothers (respectively: OR = 1.95, 95% CI = 1.32 – 2.89 and OR = 1.64, 95% CI = 1.08 - 2.47).

4.5.1.3.1.7 Shortness of Breath

SOB was more likely amongst infants who: had a co-morbidity (OR = 4.24, 95% CI = 2.28 – 7.87), were not breastfed (OR = 1.72, 95% CI = 1.09 – 2.70), or did not share a bedroom (OR = 1.77, 95% CI = 1.12 – 2.80). It was also more prevalent amongst males (OR = 1.60, 95% CI = 1.02 – 2.51). SOB was also more likely amongst infants with school-educated mothers, compared to those with vocationally (OR = 1.99, 95% CI = 1.08 - 3.67) or degree-educated mothers (OR = 1.86, 95% CI = 1.12 - 3.07). Infants with SOB, were more likely to be deprived too – since infants became 1.14 times less likely to have SOB for every increase in IMD decile (OR = 1.14, 95% CI = 1.02 - 1.28).

4.5.1.3.1.8 Snoring

Snoring was more likely amongst males (OR = 1.64, 95% CI = 1.20 – 2.25), and Caucasians (OR = 2.00, 95% CI = 1.19 – 3.35). Snoring was also more likely amongst infants who were breastfed for 1-4 months, compared to those who were breastfed for more than 4 months (OR = 2.31, 95% CI = 1.34 - 3.98).

4.5.1.3.1.9 Tachypnoea

Tachypnoea was more likely amongst infants with a co-morbidity (OR = 2.35, 95% CI = 1.30 – 4.25), Caucasian infants (OR = 2.54, 95% CI = 1.14 – 5.68), and premature infants (OR = 1.86, 95% CI = 1.09 - 3.15). Tachypnoea was also more likely amongst infants who were breastfed for 1-4 months, compared to those who were breastfed for more than 4 months (OR = 2.06, 95% CI = 1.17 - 3.63).

4.5.1.3.1.10 Wheezing

Wheezing was more likely amongst infants who were not breastfed (OR = 1.91, 95% CI = 1.34 – 2.71), and Caucasian infants (OR = 1.95, 95% CI = 1.00 – 3.80). Wheezing was also more likely amongst infants who were born to mothers aged less than 25 to 34-years-old, compared to those born to mothers aged more than 35-years-old (OR = 1.65, 95% CI = 1.02 - 2.66). Infants who wheezed, were more likely to be deprived too – since infants became 1.12 times less likely to wheeze for every increase in IMD decile (OR = 1.12, 95% CI = 1.04 - 1.22).

4.5.1.4 Healthcare Service Usage

At 4-months-old, 15.7% (n = 105) of infants were taken to their GP for a respiratory problem. Of these infants: 54.3% (n = 57) visited once, 27.6% (n = 29) visited twice, 11.4% (n = 12) visited thrice, 3.8% (n = 4) visited four times, 1.0% (n = 1) visited five times and 1.9% (n = 2) visited more than five times. 6.1% (n = 41) of infants were taken to hospital for a respiratory problem. 65.9% (n = 27) of these infants visited once, 19.5% (n = 8) visited twice, 7.3% (n = 3) visited thrice, 2.4% (n = 1) visited four times and 4.9% (n = 2) visited five times. **Figure 29** presents GP and hospital attendance rates graphically.

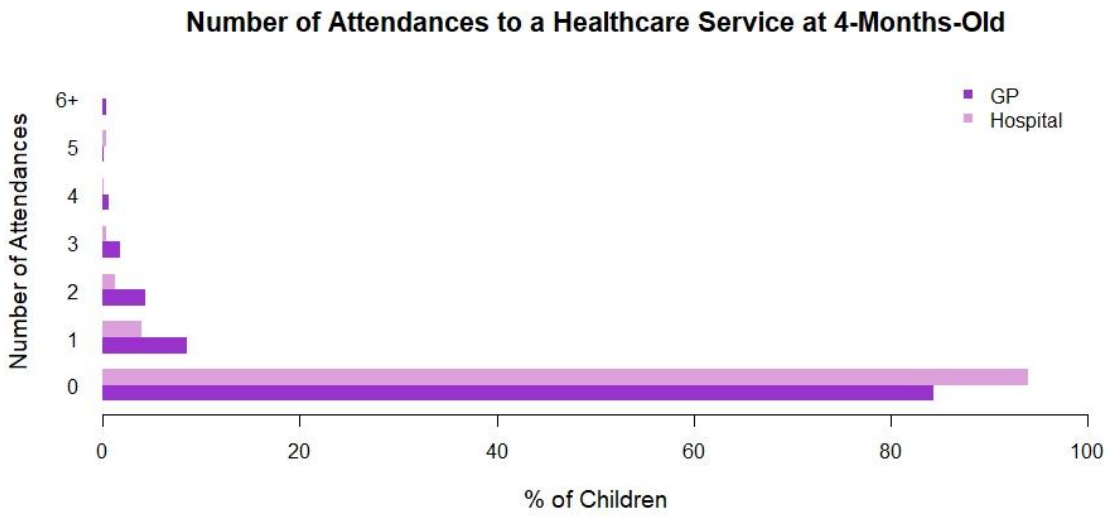


Figure 29: GP and hospital attendance rates at 4-months-old

4.5.1.4.1 Impact of Risk Factor Exposure on Healthcare Service Usage

4.5.1.4.1.1 GP Attendance

Visits to a GP for a respiratory problem were more likely amongst: infants who lived with other children (OR = 2.53, 95% CI = 1.68 - 3.82), infants who attended nursery (OR = 2.67, 95% CI = 1.17 - 6.13), and infants who shared a bedroom (OR = 1.76, 95% CI = 1.08 - 2.84). They were also more likely amongst: infants who were not breastfed (OR = 1.98, 95% CI = 1.31 - 2.99), infants with a co-morbidity (OR = 2.25, 95% CI = 1.2 - 4.23), and infants whose mother was exposed to ETS during pregnancy (OR = 1.98, 95% CI = 1.26 - 3.09).

GP visits were more likely amongst infants with school or vocationally-educated mothers, compared to those with degree-educated mothers (respectively: OR = 2.37,

95% CI = 1.46 - 3.84 and OR = 1.92, 95% CI = 1.15 - 3.21). Infants born to mothers aged 25 to 34-years-old were also more likely to visit a GP, compared to those born to mothers aged more than 35-years-old (OR = 2.01, 95% CI = 1.08 - 3.71). Infants who visited a GP, were more likely to be deprived too – since infants became 1.12 times less likely to visit a GP for every increase in IMD decile (OR = 1.12, 95% CI = 1.02 - 1.24).

4.5.1.4.1.2 Hospital Attendance

Hospital visitations for a respiratory problem were more likely amongst: males (OR = 2.09, 95% CI = 1.12 - 3.91), twins (OR = 3.57, 95% CI = 1.08 - 11.82), and premature infants (OR = 2.97, 95% CI = 1.45 - 6.10). Visits to a hospital were also more likely amongst: infants who were not breastfed (OR = 3.32, 95% CI = 1.81 - 6.10), infants who lived with other children (OR = 3.81, 95% CI = 2.02 - 7.17), and infants with a co-morbidity (OR = 3.05, 95% CI = 1.37 - 6.77). Infants born to mothers aged 25 to 34-years-old were more likely to visit a hospital too, compared to those born to mothers aged more than 35-years-old (OR = 2.81, 95% CI = 1.03 - 7.69).

4.5.1.4.2 Total LRSQ Score vs Healthcare Service Usage

At 4-months-old, there was a moderate correlation between total LRSQ score and GP attendance rate (r_s = 0.463, p = <0.001). There was a weak correlation between total LRSQ score and hospital attendance rate (r_s = 0.300, p = <0.001). These results suggest the infants with the most severe respiratory disease, are not necessarily the ones who are more likely to seek medical assistance. **Figures 30** and **31** show the correlations graphically.

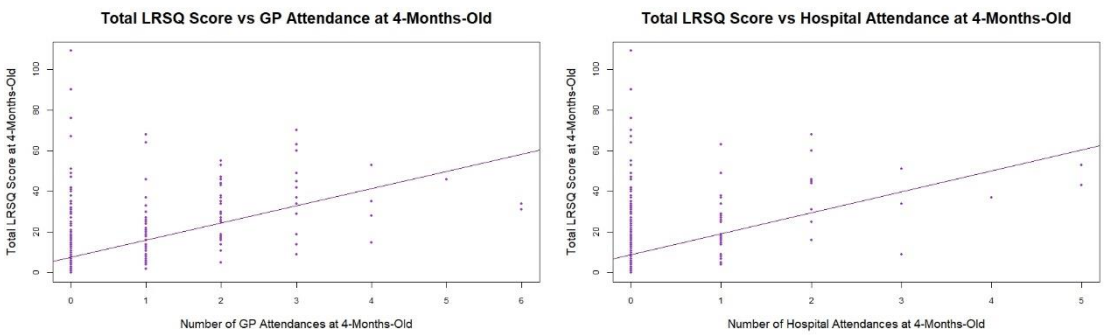


Figure 30: correlation between total LRSQ score and GP attendance rate at 4-months-old
Figure 31: correlation between total LRSQ score and hospital attendance rate at 4-months-old

4.5.2 Questionnaire 2: 10-Months-Old

4.5.2.1 Exposure to Risk Factors

4.5.2.1.1 Nursery Attendance

At 10-months-old, 27.2% (n = 101) of infants attended nursery.

4.5.2.1.2 Other Household Children

43.0% (n = 160) of infants lived with at least one other child at 10-months-old. 75.6% (n = 121) lived with only one other, 21.3% (n = 34) lived with two others, 2.5% (n = 4) lived with three others, and 0.6% (n = 1) lived with four others.

4.5.2.1.3 Bedroom Sharing

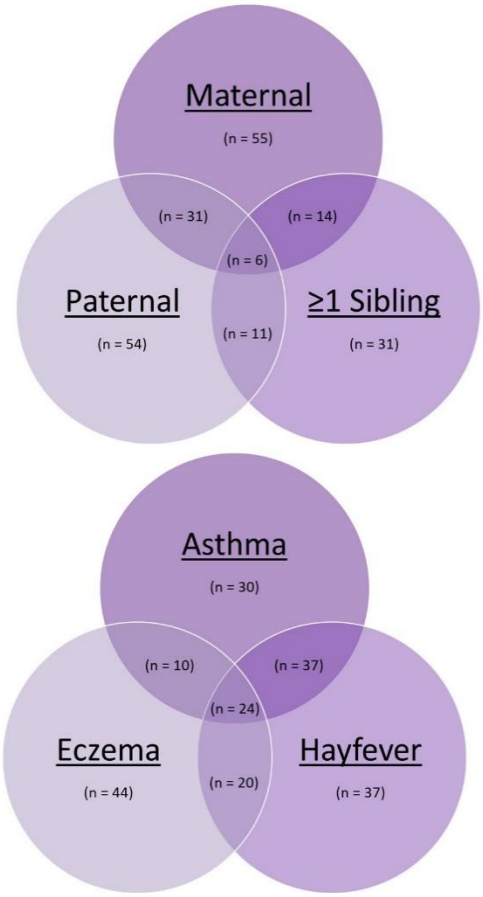
At 10-months-old, 38.7% (n = 144) of infants shared a bedroom. 79.2% (n = 114) shared with their parent(s), 16.7% (n = 24) shared with one other child, 1.4% (n = 2) shared with more than one other child, and 2.8% (n = 4) shared with someone else.

4.5.2.1.4 ETS Exposure

17.5% (n = 65) of infants were exposed to ETS at 10-months-old. 4.6% (n = 3) were exposed to ETS from inside the home, 95.4% (n = 62) were exposed to ETS from outside of the home, 3.1% (n = 2) were exposed to ETS from inside the car, 1.5% (n = 1) were exposed to ETS from within another location (e.g. work), and 3.1% (n = 2) were exposed to ETS from elsewhere.

At 10-months-old, the prevalence of ETS exposure amongst infants in the LBBS was not significantly different to the prevalence of smoking in England in 2014/15 ($\chi^2 = 0.004$, $p = 0.95$, $df = 1$). However, it was lower than prevalence of smoking in Liverpool in 2014/15 ($\chi^2 = 6.31$, $p = 0.01$, $df = 1$).

4.5.2.1.5 Family History of Atopy



At 10-months-old, 54.3% (n = 202) of infants had a family history of atopy.

From those with a family history of atopy: 52.5% (n = 106) had an atopic mother, 50.5% (n = 102) had an atopic father, and 30.7% (n = 62) had at least one atopic sibling. There was a family history of: asthma in 50.0% (n = 101) of these infants, hay fever in 58.4% (n = 118), and eczema in 48.5% (n = 98). **Figure 32** shows how familial atopy was inter-related at 10-months-old.

Figure 32: infants with a family history of atopy, by relative(s) and disease(s), at 10-months-old

4.5.2.1.6 Co-Morbidities

8.3% (n = 31) of infants had a co-morbid disease at 10-months-old. The gastrointestinal system was the most common co-morbid system at this age, whilst eczema was the most common co-morbidity overall. **Table 19** shows the co-morbidities seen at 10-months-old – as reported by parents, and grouped according to organ system.

Type of Co-Morbidity	Underlying Condition	Frequency
Respiratory (n = 7)	Asthma	3
	Bronchomalacia	1
	"Chronic Lung Disease"	1
	"Constant Wheeze"	1
	Laryngomalacia	1
	"Scarring of Lung Tissue"	1
Cardiac (n = 2)	Congenital Heart Disease	2

Renal (n = 2)	Hydronephrosis	1
	Vesicoureteral Reflux	1
Neurological (n = 1)	Hypotonia	1
Gastrointestinal (n = 4)	Gastro-Oesophageal Reflux	2
	Imperforate Anus	1
	Umbilical Hernia	1
Other (n = 16)	Eczema	10
	Food Allergy	3
	Blood Clotting Disorder	2
	Developmental Dysplasia of Hips	1

Table 19: co-morbidities of the LBBS cohort at 10-months-old

4.5.2.2 LRSQ Scores

Measures of central tendency and dispersion for the total LRSQ score, and LRSQ domain scores, at 10-months-old are shown in **Table 20**. The distribution of scores are shown graphically in **Figure 33**.

	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Standard Deviation
Total Score	0	4	9	19	114	13.58	14.88
Domain 1	0	0	1	3	15	1.90	2.34
Domain 2	0	1	2	4	18	2.55	2.56
Domain 3	0	2	3	6	20	4.17	3.63
Domain 4	0	0	0	1	12	0.69	1.55
Domain 5	0	0	0	0	15	0.58	1.61
Domain 6	0	0	0	1	9	0.75	1.50
Domain 7	0	0	0	2	13	1.39	2.19
Domain 8	0	0	0	2	14	1.56	2.61

Table 20: descriptive statistics of the total and domain LRSQ scores at 10-months-old

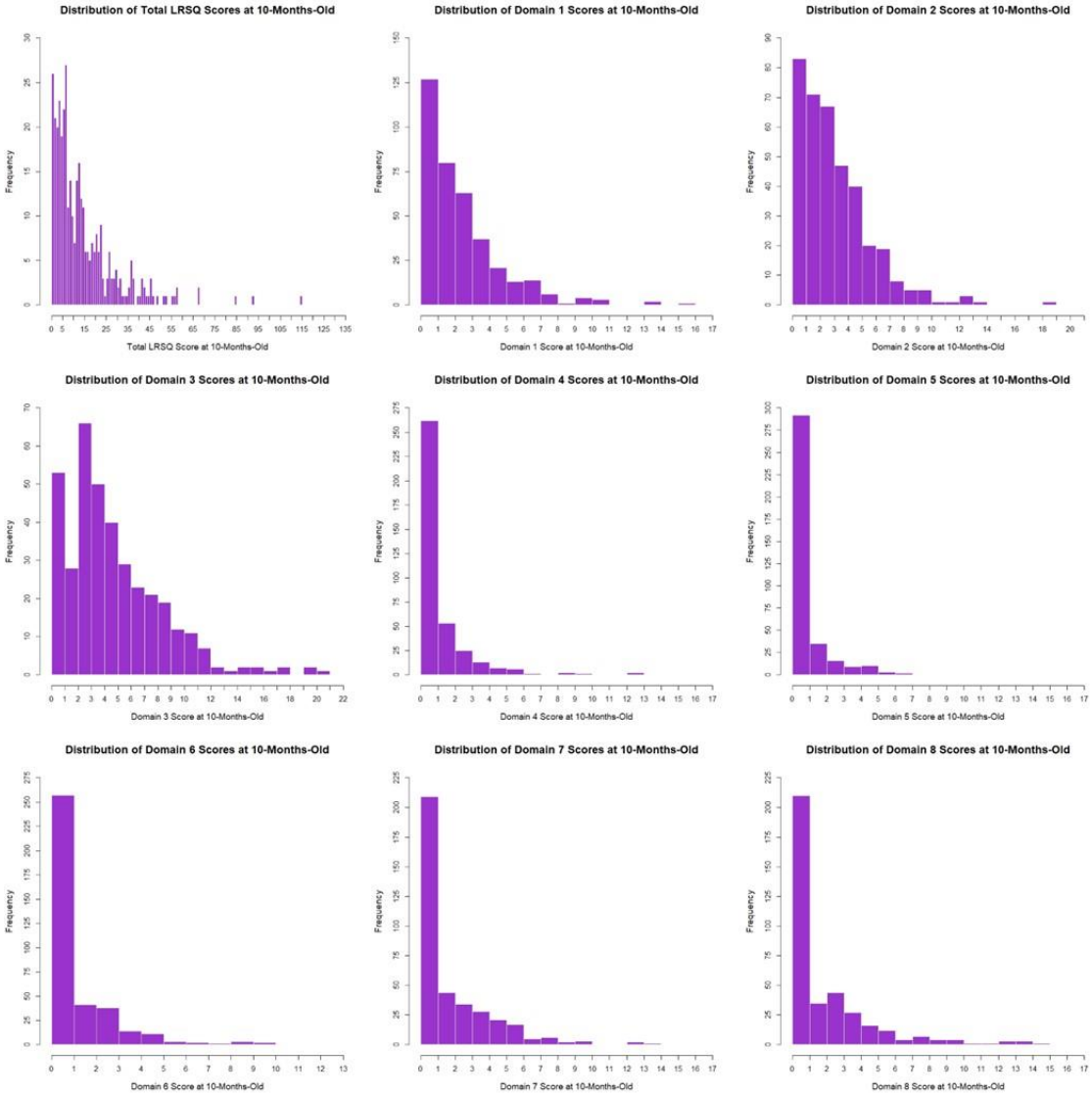


Figure 33: distribution of total and domain LRSQ scores at 10-months-old

4.5.2.2.1 Impact of Risk Factor Exposure on Total LRSQ Score

Total LRSQ scores were higher amongst infants who attended nursery (U = 16447, p = <0.001) or had a co-morbidity (U = 6569, p = 0.004). They were also higher amongst males (U = 24289, p = 0.002) and Caucasians (U = 5532, p = 0.010).

There were differences in total LRSQ score between the different levels of maternal education (H = 7.57, p = 0.023, df = 2) and maternal age (H = 14.01, p = <0.001, df = 2). Post-hoc analysis revealed that infants with school-educated mothers scored higher, compared to those with degree (p = 0.045) or vocationally-educated mothers (p = 0.008). It also revealed that infants born to mothers aged ≥35-years-old scored lower, than those born to mothers under 25-years-old (p = 0.002) or aged 25 to 34-years-old (p = 0.002).

4.5.2.2.2 Impact of Risk Factor Exposure on LRSQ Domain Scores

4.5.2.2.2.1 Domain 1

Domain 1 scores were higher amongst Caucasian infants (U = 5946, p = 0.035), and those with a co-morbidity (U = 7097, p = 0.020). They were also higher amongst infants who attended nursery (U = 16329, p = <0.001).

There were differences in domain 1 score between the different levels of maternal education (H = 11.02, p = 0.004, df = 2) and maternal age (H = 15.40, p = <0.001, df = 2). Post-hoc analysis revealed that infants with school-educated mothers scored higher, compared to those with degree (p = 0.036) or vocationally-educated mothers (p = 0.001). It also revealed that infants born to mothers aged ≥35-years-old scored lower than those born to mothers under 25-years-old (p = 0.008), or aged 25 to 34-years-old (p = <0.001).

4.5.2.2.2.2 Domain 2

Domain 2 scores were higher amongst infants who: attended nursery (U = 17069, p = <0.001), lived with other children (U = 25380, p = 0.037), or had a co-morbidity (U = 6662, p = 0.005). They were also higher amongst males (U = 23471, p = <0.001).

4.5.2.2.2.3 Domain 3

Domain 3 scores were higher amongst infants with a family history of atopy (U = 25425, p = 0.034) or a co-morbidity (U = 7209, p = 0.032). They were also higher amongst males (U = 25494, p = 0.024) and nursery attenders (U = 16208, p = <0.001).

There were differences in domain 3 score between the different levels of maternal education (H = 6.25, p = 0.044, df = 2) and maternal age (H = 14.55, p = 0.001, df = 2). Post-hoc analysis revealed that infants with school-educated mothers scored higher than those with vocationally-educated mothers (p = 0.014). It also revealed that infants born to mothers aged ≥35-years-old scored lower, compared to those born to mothers under 25-years-old (p = 0.001) or aged 25 to 34-years-old (p = 0.004).

4.5.2.2.2.4 Domain 4

Domain 4 scores were higher amongst infants who: had a co-morbidity (U = 5963, p = <0.001), were not breastfed (U = 20249, p = 0.005), were exposed to ETS

(U = 15280, p = 0.025), or attended nursery (U = 19640, p = 0.005). They were also higher amongst Caucasians (U = 6124, p = 0.026).

There were differences in domain 4 score between the different levels of maternal education (H = 15.97, p = <0.001, df = 2) and maternal age (H = 8.67, p = 0.013, df = 2). Post-hoc analysis revealed that infants with school-educated mothers scored higher, compared to those with degree (p = 0.002) or vocationally-educated mothers (p = <0.001). It also revealed that infants born to mothers aged ≥35-years-old scored lower than those born to mothers aged 25 to 34-years-old (p = 0.005).

4.5.2.2.2.5 Domain 5

Domain 5 scores were higher amongst infants who were male (U = 24737, p = <0.001) or Caucasian (U = 6346, p = 0.035). They were also higher amongst those with a co-morbidity (U = 6857, p = <0.001).

There were differences in domain 5 score between the different levels of maternal education (H = 17.04, p = <0.001, df = 2). Post-hoc analysis revealed that infants with degree-educated mothers scored lower, compared to those with school (p = <0.001) or vocationally-educated mothers (p = <0.001).

4.5.2.2.2.6 Domain 6

Domain 6 scores were higher amongst infants who attended nursery (U = 19879, p = 0.012) or had a co-morbidity (U = 5190, p = <0.001).

4.5.2.2.2.7 Domain 7

Domain 7 scores were higher amongst infants who: attended nursery (U = 18379, p = <0.001), had a co-morbidity (U = 6666, p = 0.002), or lived with other children (U = 24718, p = 0.006). They were also higher amongst Caucasians (U = 5652, p = 0.007) and males (U = 26071, p = 0.040).

There were differences in domain 7 score between the different levels of maternal education (H = 11.71, p = 0.003, df = 2) and maternal age (H = 7.29, p = 0.026, df = 2). Post-hoc analysis revealed that infants with school-educated mothers scored higher than those with vocationally (p = <0.001) or degree-educated mothers (p = 0.002). It also revealed that infants born to mothers aged ≥35-years-old scored lower, compared

to infants born to mothers under 25-years-old (p = 0.039) or aged 25 to 34-years-old (p = 0.018).

4.5.2.2.2.8 Domain 8

Domain 8 scores were higher amongst infants who were: Caucasian (U = 5313, p = 0.002), male (U = 25526, p = 0.014), born at a 'low birthweight' (U = 6543, p = 0.043), or born prematurely (U = 9264, p = 0.027). They were also higher amongst infants who attended nursery (U = 18703, p = 0.001) or had a co-morbidity (U = 7218, p = 0.019).

There were differences in domain 8 score between the different levels of maternal education (H = 16.19, p = <0.001, df = 2). Post-hoc analysis revealed that infants with degree-educated mothers scored lower, compared to those with school (p = 0.002) or vocationally-educated mothers (p = <0.001).

4.5.2.2.3 Total LRSQ Score vs Total QoL Score

There was a strong positive correlation between an infant's total LRSQ score, and their total QoL score (r_s = 0.835, p = <0.001). **Figure 34** shows the correlation graphically. A higher total LRSQ score is more strongly correlated with a poor QoL for parents, than with a poor QoL for infants (r_s = 0.817, p = <0.001 vs r_s = 0.796, p = <0.001). Infants who regularly suffer with respiratory symptoms, and their parents, therefore experience a worse QoL.

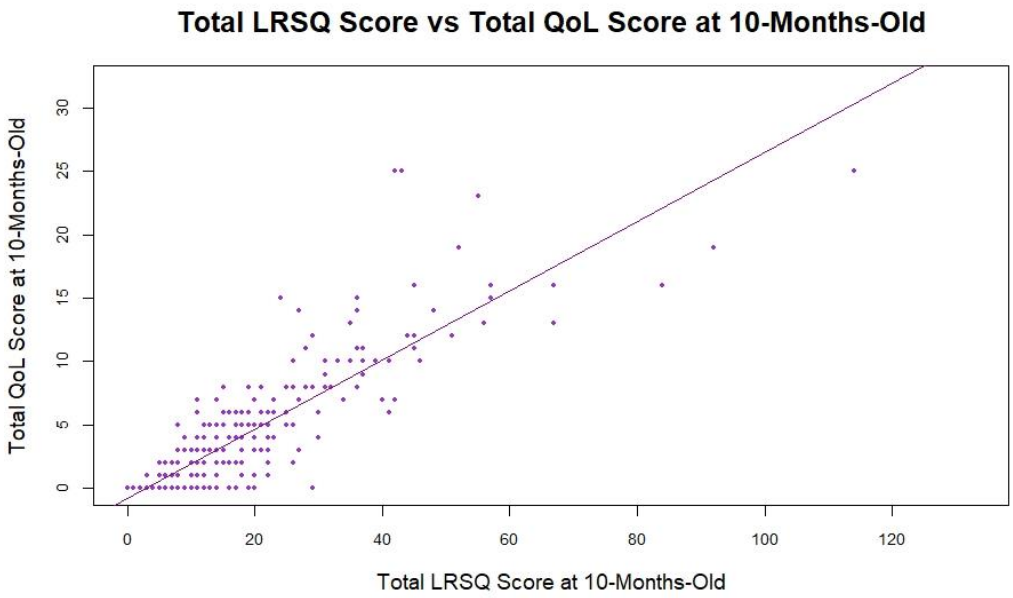


Figure 34: correlation between total LRSQ score and total QoL score at 10-months-old

4.5.2.3 Symptom Prevalence

93.0% (n = 346) of infants experienced at least one type of respiratory symptom at 10-months-old. A cold was the most common symptom, as it was experienced by 85.8% (n = 319) of infants; noisy breathing that didn't come from the chest was the least common symptom, as it was experienced by 16.4% (n = 61) of infants. **Figure 35** demonstrates the prevalence of individual symptoms.

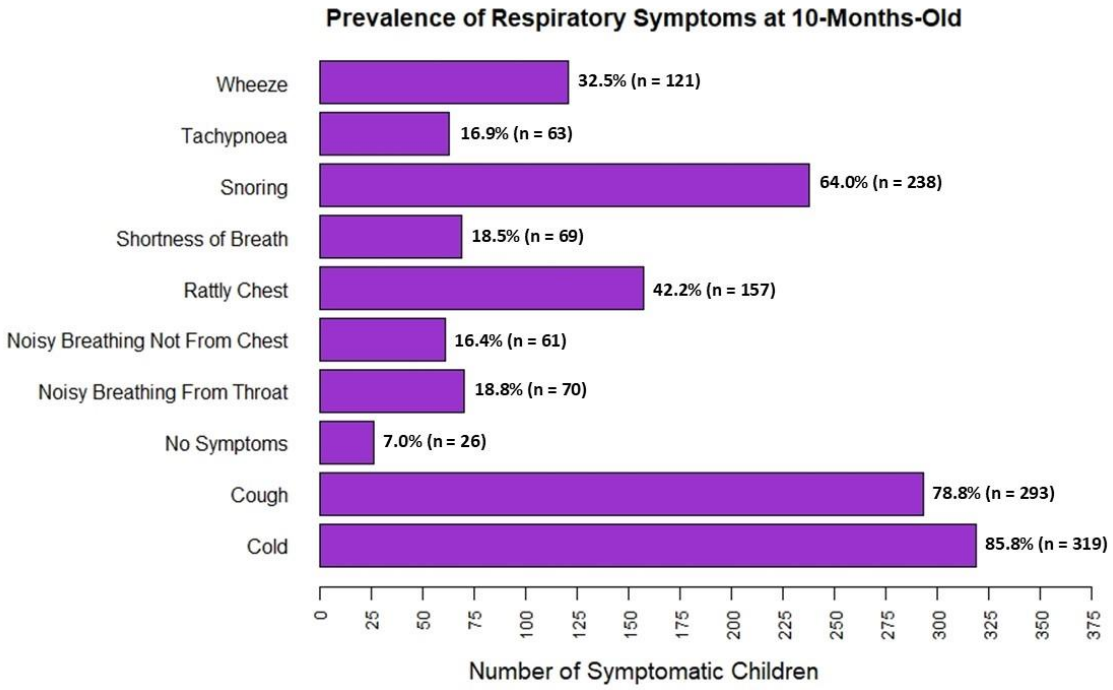


Figure 35: prevalence of respiratory symptoms at 10-months-old

4.5.2.3.1 Impact of Risk Factor Exposure on Symptom Prevalence

4.5.2.3.1.1 Colds

Colds were more likely amongst infants who attended nursery (OR = 2.36, 95% CI = 1.09 – 5.12), or had a family history of atopy (OR = 2.08, 95% CI = 1.17 - 3.71). Colds were also more likely amongst infants who were born to mothers aged 25 to 34-years-old, compared to those born to mothers aged more than 35-years-old (OR = 2.03, 95% CI = 1.08 - 3.81).

4.5.2.3.1.2 Coughing

Coughing was more likely amongst males (OR = 1.76, 95% CI = 1.07 – 2.90), and infants who attended nursery (OR = 1.93, 95% CI = 1.04 – 3.58).

4.5.2.3.1.3 No Symptoms

There were no risk factors that affected the prevalence of asymptomatic infants, at 10-months-old.

4.5.2.3.1.4 Noisy Breathing – From Throat

Noisy breathing from the throat was more likely amongst: males (OR = 1.73, 95% CI = 1.02 – 2.93), infants with a co-morbidity (OR = 4.37, 95% CI = 2.07 – 9.25), and infants who attended nursery (OR = 2.57, 95% CI = 1.50 – 4.40). Noisy breathing from the throat was also more likely amongst infants who were breastfed for less than 1 month, compared to those who were breastfed for 1-4 months (OR = 3.50, 95% CI = 1.08 - 11.27).

4.5.2.3.1.5 Noisy Breathing – Not From Chest

Noisy breathing that did not come from the chest was more likely amongst infants with a co-morbidity (OR = 2.57, 95% CI = 1.16 - 5.64).

4.5.2.3.1.6 Rattly Chest

Rattly chests were more likely amongst infants who attended nursery (OR = 2.39, 95% CI = 1.04 – 3.83), and Caucasian infants (OR = 3.03, 95% CI = 1.14 – 8.08). Rattly chests were more likely amongst infants with school-educated mothers, compared to those with degree (OR = 1.82, 95% CI = 1.12 - 2.96) or vocationally-educated mothers (OR = 3.08, 95% CI = 1.66 - 5.72). Infants born to mothers aged less than 25-years-old were also more likely to snore, compared to those born to mothers aged more than 35-years-old (OR = 2.64, 95% CI = 1.07 - 6.52).

4.5.2.3.1.7 Shortness of Breath

SOB was more likely amongst infants who were not breastfed (OR = 1.81, 95% CI = 1.06 – 3.09), and infants with a co-morbidity (OR = 2.62, 95% CI = 1.21 – 5.65). SOB was more likely amongst infants with school-educated mothers, compared to those with degree-educated mothers (OR = 2.13, 95% CI = 1.18 - 3.78). Infants born to mothers aged 25 to 34-years-old were also more likely to snore, compared to those born to mothers aged more than 35-years-old (OR = 2.23, 95% CI = 1.11 - 4.47). SOB was more likely amongst infants who were breastfed for 1-4 months, compared to those who were breastfed for less than 1 month (OR = 2.51, 95% CI = 1.01 - 6.22).

4.5.2.3.1.8 Snoring

Snoring was more likely amongst males (OR = 1.75, 95% CI = 1.15 – 2.68), and infants with a co-morbidity (OR = 3.22, 95% CI = 1.24 – 8.37).

4.5.2.3.1.9 Tachypnoea

Tachypnoea was more likely amongst infants with a co-morbidity (OR = 4.08, 95% CI = 1.91 – 8.71).

4.5.2.3.1.10 Wheezing

Wheezing was more likely amongst infants with a co-morbidity (OR = 2.67, 95% CI = 1.28 – 5.55), and Caucasian infants (OR = 3.53, 95% CI = 1.12 - 11.15). Wheezing was more likely amongst infants with school-educated mothers, compared to those with vocationally (OR = 2.16, 95% CI = 1.17 - 4.00) or degree-educated mothers (OR = 2.06, 95% CI = 1.25 - 3.40). Infants born to mothers aged less than 25-years-old or 25 to 34-years-old were also more likely to wheeze, compared to those born to mothers aged more than 35-years-old (respectively: OR = 4.36, 95% CI = 1.72 - 11.06 and OR = 2.15, 95% CI = 1.23 - 3.76).

4.5.2.4 Healthcare Service Usage

At 10-months-old, 29.3% (n = 109) of infants were taken to their GP for a respiratory problem. Of these infants: 56.0% (n = 61) visited once, 22.0% (n = 24) visited twice, 10.1% (n = 11) visited thrice, 3.7% (n = 4) visited four times, 0.9% (n = 1) visited five times and 7.3% (n = 8) visited more than five times. 8.9% (n = 33) were taken to hospital for a respiratory problem. 60.6% (n = 20) of these infants visited once, 27.3% (n = 9) visited twice, 6.1% (n = 2) visited thrice, and 6.1% (n = 2) visited more than five times. **Figure 36** presents GP and hospital attendance rates graphically.

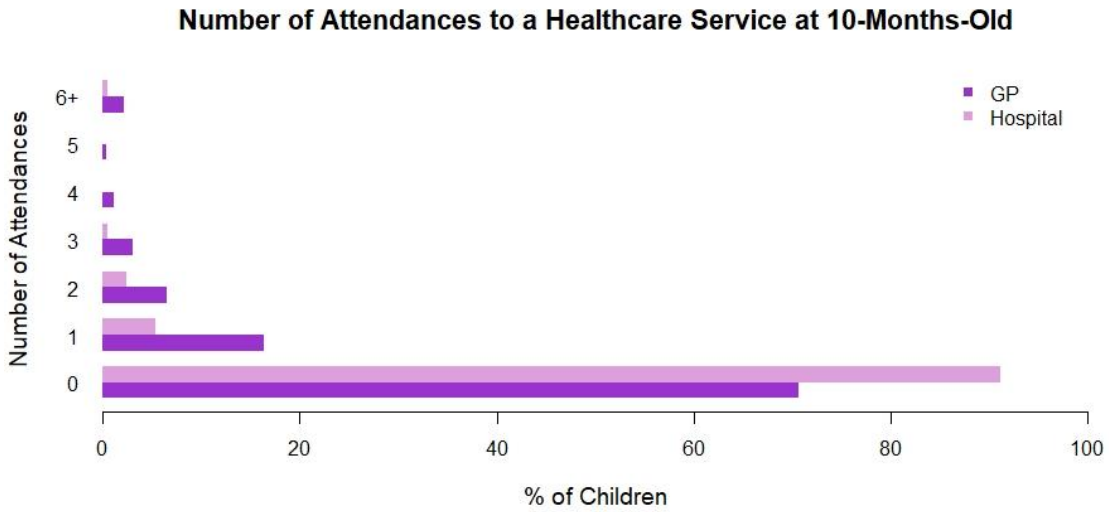


Figure 36: GP and hospital attendance rates at 10-months-old

4.5.2.4.1 Impact of Risk Factor Exposure on Healthcare Service Usage

4.5.2.4.1.1 GP Attendance

Visits to a GP for a respiratory problem were more likely amongst: premature infants (OR = 2.84, 95% CI = 1.16 - 6.94), infants with a family history of atopy (OR = 1.74, 95% CI = 1.10 - 2.76), 'low birthweight' infants (OR = 2.26, 95% CI = 1.04 - 4.91), infants who attended nursery (OR = 2.15, 95% CI = 1.33 - 3.49), and infants who were not breastfed (OR = 1.73, 95% CI = 1.07 - 2.79). GP visitation was more likely amongst infants with school-educated mothers, compared to those with degree (OR = 1.85, 95% CI = 1.11 - 3.09) or vocationally-educated mothers (OR = 2.13, 95% CI = 1.12 - 4.06). Infants born to mothers aged less than 25-years-old (OR = 2.63, 95% CI = 1.02 - 6.78) or 25 to 34-years-old (OR = 1.87, 95% CI = 1.06 - 3.32) were also more likely to visit a GP, compared to those born to mothers aged more than 35-years-old.

4.5.2.4.1.2 Hospital Attendance

Hospital visitations for a respiratory problem were more likely amongst: infants with a co-morbidity (OR = 2.72, 95% CI = 1.04 - 7.12), premature infants (OR = 2.84, 95% CI = 1.16 - 6.94), and 'low birthweight' infants (OR = 3.10, 95% CI = 1.12 - 8.10). Visits to a hospital were also more likely amongst infants with school-educated mothers, compared to those with vocationally (OR = 2.89, 95% CI = 1.03 - 8.10) or degree-educated mothers (OR = 2.98, 95% CI = 1.35 - 6.59).

4.5.2.4.2 Total LRSQ Score vs Healthcare Service Usage

At 10-months-old, there was a strong correlation between total LRSQ score and GP attendance rate (r_s = 0.615, p = <0.001). There was a moderate correlation between total LRSQ score and hospital attendance rate (r_s = 0.401, p = <0.001). These results suggest the infants with the most severe respiratory disease, are slightly more likely to seek medical assistance from a GP, but not necessarily from the hospital. **Figures 37** and **38** show the correlations graphically.

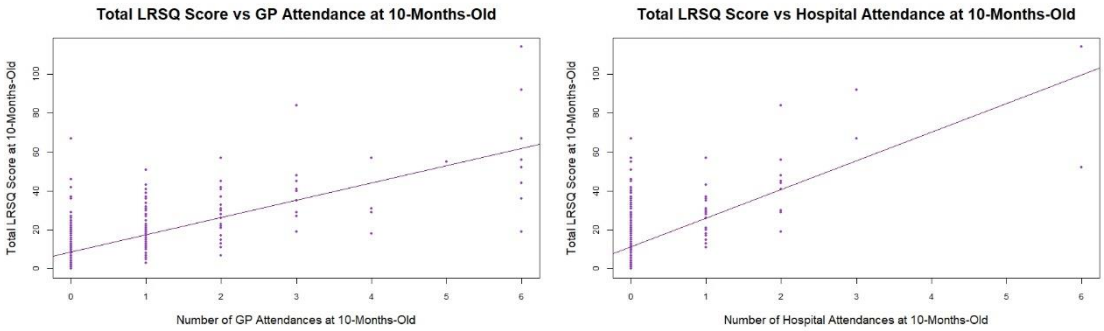


Figure 37: correlation between total LRSQ score and GP attendance rate at 10-months-old
Figure 38: correlation between total LRSQ score and hospital attendance rate at 10-months-old

4.5.3 Questionnaire 3: 16-Months-Old

4.5.3.1 Exposure to Risk Factors

4.5.3.1.1 Nursery Attendance

At 16-months-old, 51.8% (n = 141) of infants attended nursery.

4.5.3.1.2 Other Household Children

45.6% (n = 124) of infants lived with at least one other child at 16-months-old. A technical error with the online questionnaires meant that the number of other household children couldn't be reported.

4.5.3.1.3 Bedroom Sharing

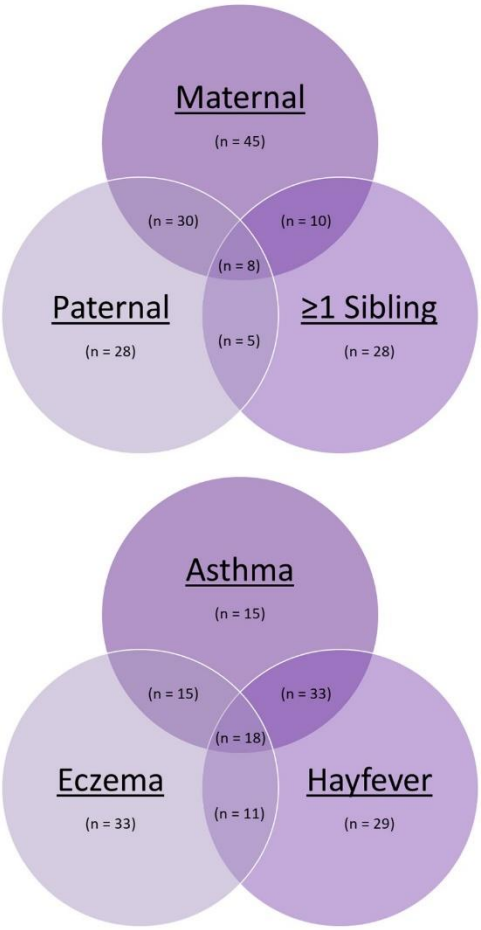
At 16-months-old, 33.1% (n = 90) of infants shared a bedroom. 71.1% (n = 64) shared with their parent(s), 23.3% (n = 21) shared with one other child, 2.2% (n = 2) shared with more than one other child, and 4.4% (n = 4) shared with someone else.

4.5.3.1.4 ETS Exposure

13.6% (n = 37) of infants were exposed to ETS at 16-months-old. 5.4% (n = 2) were exposed to ETS from inside the home, 83.8% (n = 31) were exposed to ETS from outside of the home, 2.7% (n = 1) were exposed to ETS from inside the car, 5.4% (n = 2) were exposed to ETS from within another location (e.g. work), and 10.8% (n = 4) were exposed to ETS from elsewhere.

At 16-months-old, the prevalence of ETS exposure amongst infants in the LBBS was not significantly different to the prevalence of smoking in England in 2014/15 ($\chi^2 = 2.66$, $p = 0.10$, df = 1). However, it was lower than the prevalence of smoking in Liverpool in 2014/15 ($\chi^2 = 13.43$, $p = <0.001$, df = 1).

4.5.3.1.5 Family History of Atopy



At 16-months-old, 56.6% (n = 154) of infants had a family history of atopy.

From those with a family history of atopy: 60.4% (n = 93) had an atopic mother, 46.1% (n = 71) had an atopic father, and 33.1% (n = 51) had at least one atopic sibling. There was a family history of: asthma in 52.6% (n = 81) of these infants, hay fever in 59.1% (n = 91), and eczema in 50.0% (n = 77). **Figure 39** shows how familial atopy was inter-related at 16-months-old.

Figure 39: infants with a family history of atopy, by relative(s) and disease(s), at 16-months-old

4.5.3.1.6 Co-Morbidities

7.4% (n = 20) of infants had a co-morbid disease at 16-months-old. The respiratory system was the most common co-morbid system at this age, whilst eczema was the

most common co-morbidity overall. **Table 21** shows the co-morbidities seen at 16-months-old – as reported by parents, and grouped according to organ system.

Type of Co-Morbidity	Underlying Condition	Frequency
Respiratory (n = 2)	Asthma	1
	"Chronic Lung Disease"	1
	"Constant Wheeze"	1
Cardiac (n = 4)	Congenital Heart Disease	4
Renal (n = 1)	Vesicoureteral Reflux	1
Other (n = 12)	Eczema	9
	Food Allergy	2
	Club Foot (Talipes Equinovarus)	1
	Developmental Dysplasia of Hips	1

Table 21: co-morbidities of the LBBS cohort at 16-months-old

4.5.3.2 LRSQ Scores

Measures of central tendency and dispersion for the total LRSQ score, and LRSQ domain scores, at 16-months-old are shown in **Table 22**. The distribution of scores are shown graphically in **Figure 40**.

	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Standard Deviation
Total Score	0	4	10	21	92	15.40	16.43
Domain 1	0	0	1	3	12	2.16	2.44
Domain 2	0	1	2	4	16	2.81	2.80
Domain 3	0	2	4	7	19	4.73	3.85
Domain 4	0	0	0	1	12	0.93	1.97
Domain 5	0	0	0	0	12	0.75	1.90
Domain 6	0	0	0	1	10	0.75	1.60
Domain 7	0	0	0	2	12	1.49	2.28
Domain 8	0	0	0	3	13	1.80	2.76

Table 22: descriptive statistics of the total and domain LRSQ scores at 16-months-old

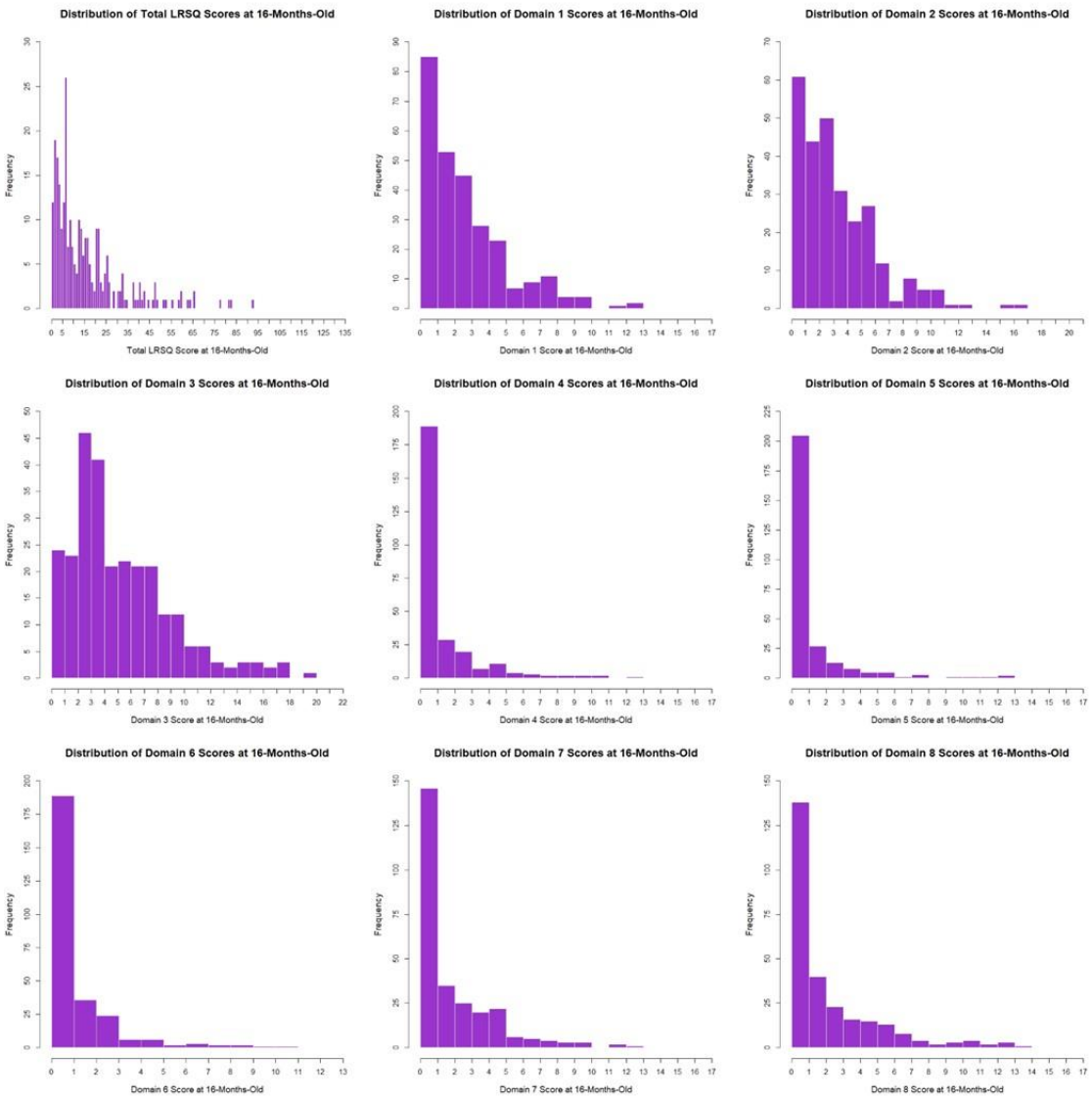


Figure 40: distribution of total and domain LRSQ scores at 16-months-old

4.5.3.2.1 Impact of Risk Factor Exposure on Total LRSQ Score

Total LRSQ scores were higher amongst infants who were male (U = 11873, p = 0.003) or born prematurely (U = 4535, p = 0.033). They were also higher amongst those who attended nursery (U = 9447, p = <0.001).

There were differences in total LRSQ score between the different levels of deprivation (H = 15.20, p = 0.004, df = 4). Post-hoc analysis revealed that infants living in the second-most deprived IMD quintile scored lower, compared to those living in the most-deprived (p = 0.036), third-most deprived (p = 0.005), least-deprived (p = 0.005), and second-least deprived (p = 0.005) quintiles. Infants living in the most-deprived IMD quintile scored lower than those living in the least-deprived quintile (p = 0.038).

4.5.3.2.2 Impact of Risk Factor Exposure on LRSQ Domain Scores

4.5.3.2.2.1 Domain 1

Domain 1 scores were higher amongst infants who attended nursery (U = 10558, p = <0.001) and who were not exposed to ETS (U = 5818, p = 0.050). They were also higher amongst males (U = 12159, p = 0.008).

There were differences in domain 1 score between the different levels of deprivation (H = 19.00, p = 0.001, df = 4). Post-hoc analysis revealed that infants living in the second-most deprived IMD quintile scored lower, compared to those living in the most-deprived (p = 0.006), third-most deprived (p = 0.001), least-deprived (p = 0.002), and second-least deprived (p = 0.001) quintiles. Infants living in the most-deprived IMD quintile scored lower than those living in the least-deprived quintile (p = 0.031).

4.5.3.2.2.2 Domain 2

Domain 2 scores were higher amongst infants who were: born prematurely (U = 4289, p = 0.009) or male (U = 12674, p = 0.039). They were also higher amongst nursery attenders (U = 9993, p = <0.001).

4.5.3.2.2.3 Domain 3

Domain 3 scores were higher amongst infants who were male (U = 11874, p = 0.003) or born prematurely (U = 4488, p = 0.026). They were also higher amongst those who attended nursery (U = 9212, p = <0.001), and who were not exposed to ETS (U = 5725, p = 0.038).

There were differences in domain 3 score between the different levels of deprivation (H = 20.60, p = <0.001, df = 4). Post-hoc analysis revealed that infants living in the second-most deprived IMD quintile scored lower, compared to those living in the third-most deprived (p = 0.001), least-deprived (p = 0.021), and second-least deprived (p = 0.001) quintiles. Infants living in the most-deprived IMD quintile scored lower than those living in the third-most deprived (p = 0.007) and second-least deprived quintiles (p = 0.007).

4.5.3.2.2.4 Domain 4

Domain 4 scores were higher amongst infants who: had a family history of atopy (U = 12582, p = 0.025), attended nursery (U = 12101, p = 0.001) or were born

prematurely (U = 4805, p = 0.042). They were also higher amongst those whose mothers were not exposed to ETS during pregnancy (U = 5476, p = 0.010).

There were differences in domain 4 score between the different levels of deprivation (H = 10.76, p = 0.029, df = 4) and maternal age (H = 7.08, p = 0.029, df = 2). Post-hoc analysis revealed that infants living in the least-deprived IMD quintile scored higher, compared to those living in the most-deprived (p = 0.005), second-most deprived (p = 0.002), third-most deprived (p = 0.016) and second-least deprived (p = 0.007) quintiles. It also revealed that infants born to mothers aged ≥35-years-old scored lower than infants born to mothers aged 25 to 34-years-old (p = 0.020).

4.5.3.2.2.5 Domain 5

Domain 5 scores were higher amongst infants who: had a family history of atopy (U = 12744, p = 0.028), had a co-morbidity (U = 3220, p = 0.041), were not breastfed (U = 8569, p = 0.020), or lived with other children (U = 12760, p = 0.014). They were also higher amongst males (U = 12303, p = 0.001), and those whose mothers were not exposed to ETS during pregnancy (U = 5492, p = 0.006).

There were differences in domain 5 score amongst breastfed infants, depending on how long they were breastfed for (H = 6.77, p = 0.034, df = 2). Post-hoc analysis revealed that infants who were breastfed for less than 1 month scored higher than those who were breastfed for more than 4 months (p = 0.009).

4.5.3.2.2.6 Domain 6

Domain 6 scores were higher amongst infants who wore born prematurely (U = 4301, p = 0.002) or attended nursery (U = 11962, p = 0.001).

There were differences in domain 6 score between the different levels of deprivation (H = 10.13, p = 0.038, df = 4). Post-hoc analysis revealed that infants living in the least-deprived IMD quintile scored higher, compared to those living in the most-deprived (p = 0.039), second-most deprived (p = 0.027), and second-least deprived (p = 0.019) quintiles. Infants living in the third-most deprived IMD quintile scored lower than those living in the second-least deprived quintile (p = 0.032). There were differences in domain 6 score amongst breastfed infants, depending on how long they were breastfed for (H = 6.90, p = 0.032, df = 2). Post-hoc analysis revealed that

infants who were breastfed for less than 1 month scored higher, compared to those who were breastfed for more than 4 months (p = 0.013) or for 1-4 months (p = 0.045).

4.5.3.2.2.7 Domain 7

Domain 7 scores were higher amongst infants whose mothers were not exposed to ETS during pregnancy (U = 5440, p = 0.019), as well as males (U = 12084, p = 0.004). They were also higher amongst infants who attended nursery (U = 11380, p = <0.001) or lived with other children (U = 11945, p = 0.003).

4.5.3.2.2.8 Domain 8

Domain 8 scores were higher amongst infants who: lived with other children (U = 11616, p = 0.001), attended nursery (U = 11482, p = <0.001), or were born prematurely (U = 4669, p = 0.041). They were also higher amongst males (U = 12128, p = 0.005), and those whose mothers were not exposed to ETS during pregnancy (U = 5152, p = 0.005).

4.5.3.2.3 Total LRSQ Score vs Total QoL Score

There was a strong positive correlation between an infant's total LRSQ score, and their total QoL score (r_s = 0.858, p = <0.001). **Figure 41** shows the correlation graphically. A higher total LRSQ score is more strongly correlated with a poor QoL for parents, than with a poor QoL for infants (r_s = 0.832, p = <0.001 vs r_s = 0.818, p = <0.001). Infants who regularly suffer with respiratory symptoms, and their parents, therefore experience a worse QoL.

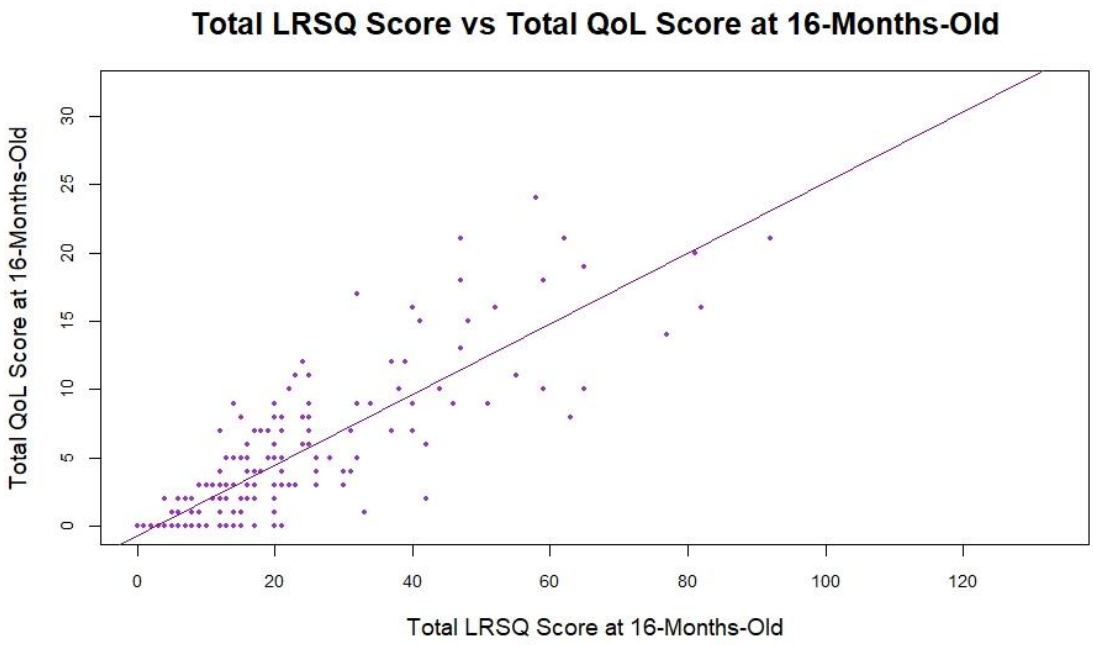


Figure 41: correlation between total LRSQ score and total QoL score at 16-months-old

4.5.3.3 Symptom Prevalence

95.6% (n = 256) of infants experienced at least one type of respiratory symptom at 16-months-old. A cold was the most common symptom, as it was experienced by 91.2% (n = 248) of infants; noisy breathing from the throat was the least common symptom, as it was experienced by 16.5% (n = 45) of infants. **Figure 42** demonstrates the prevalence of individual symptoms.

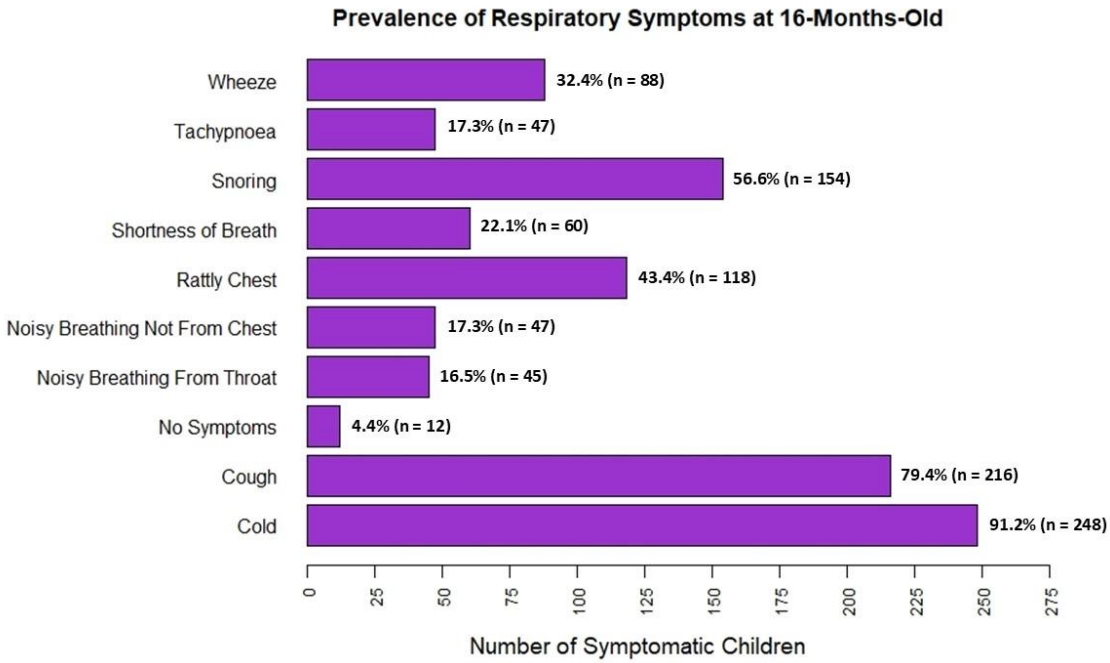


Figure 42: prevalence of respiratory symptoms at 16-months-old

4.5.3.3.1 Impact of Risk Factor Exposure on Symptom Prevalence

4.5.3.3.1.1 Colds

Colds were more likely amongst infants without a co-morbidity (OR = 3.21, 95% CI = 1.11 - 9.27). Colds were more likely amongst infants who were born to mothers aged more than 35-years-old, compared to those born to mothers aged 25 to 34-years-old (OR = 3.59, 95% CI = 1.15 - 11.23). Infants with colds, were less likely to be deprived too – since infants became 1.36 times less likely to cough for every increase in IMD decile (OR = 1.36, 95% CI = 1.05 - 1.76).

4.5.3.3.1.2 Coughing

Coughing was more likely amongst infants who attended nursery (OR = 3.83, 95% CI = 2.01 – 7.33). Infants who coughed, were less likely to be deprived – since infants became 1.19 times less likely to cough for every increase in IMD decile (OR = 1.19, 95% CI = 1.02 - 1.36).

4.5.3.3.1.3 No Symptoms

Being asymptomatic was more likely amongst those who had a co-morbidity (OR = 5.16, 95% CI = 1.28 - 20.92).

4.5.3.3.1.4 Noisy Breathing – From Throat

Noisy breathing from the throat was more likely amongst infants who attended nursery (OR = 2.51, 95% CI = 1.25 – 5.05), and premature infants (OR = 3.27, 95% CI = 1.37 – 7.81). Noisy breathing from the throat was also more likely amongst infants who were breastfed for less than 1 month, compared to those who were breastfed for 1-4 months (OR = 4.10, 95% CI = 1.16 - 14.52) or for more than 4 months (OR = 2.69, 95% CI = 1.18 - 6.15).

4.5.3.3.1.5 Noisy Breathing – Not From Chest

Noisy breathing that did not come from the chest was more likely amongst infants who attended nursery (OR = 2.75, 95% CI = 1.38 – 5.51), and premature infants (OR = 2.57, 95% CI = 1.06 - 6.21).

4.5.3.3.1.6 Rattly Chest

Rattly chests were more likely amongst males (OR = 1.78, 95% CI = 1.10 - 2.90), and those who attended nursery (OR = 2.43, 95% CI = 1.49 - 3.97). Rattly chests were also

more likely amongst infants who were born to mothers aged 25 to 34-years-old, compared to those born to mothers aged more than 35-years-old (OR = 2.10, 95% CI = 1.16 - 3.79).

4.5.3.3.1.7 Shortness of Breath

There were no risk factors that affected the prevalence of SOB, at 16-months-old.

4.5.3.3.1.8 Snoring

Snoring was more likely amongst infants who were exposed to ETS (OR = 2.88, 95% CI = 1.33 – 6.20), premature infants (OR = 3.27, 95% CI = 1.28 – 8.39), infants whose mother smoked during pregnancy (OR = 4.49, 95% CI = 1.41 – 14.34), and infants who attended nursery (OR = 1.81, 95% CI = 1.11 – 2.95).

4.5.3.3.1.9 Tachypnoea

Tachypnoea was more likely amongst infants who attended nursery (OR = 2.02, 95% CI = 1.08 – 3.78).

4.5.3.3.1.10 Wheezing

Wheezing was more likely amongst infants with school-educated mothers, compared to those with degree (OR = 1.95, 95% CI = 1.07 - 3.56) or vocationally-educated mothers (OR = 3.34, 95% CI = 1.48 - 7.51). Infants who were breastfed for less than 1 month were also more likely to wheeze, compared to those who were breastfed for more than 4 months (OR = 2.27, 95% CI = 1.18 - 4.36).

4.5.3.4 Healthcare Service Usage

At 16-months-old, 33.5% (n = 91) of infants were taken to their GP for a respiratory problem. Of these infants: 53.8% (n = 49) visited once, 24.2% (n = 22) visited twice, 15.4% (n = 14) visited thrice, 3.3% (n = 3) visited four times, 1.1% (n = 1) visited five times and 2.2% (n = 32) visited more than five times. 6.6% (n = 18) of infants were taken to hospital for a respiratory problem. 77.8% (n = 14) of these infants visited once, 11.1% (n = 2) visited twice, 5.6% (n = 1) visited thrice, and 5.6% (n = 1) visited four times. **Figure 43** presents GP and hospital attendance rates graphically.

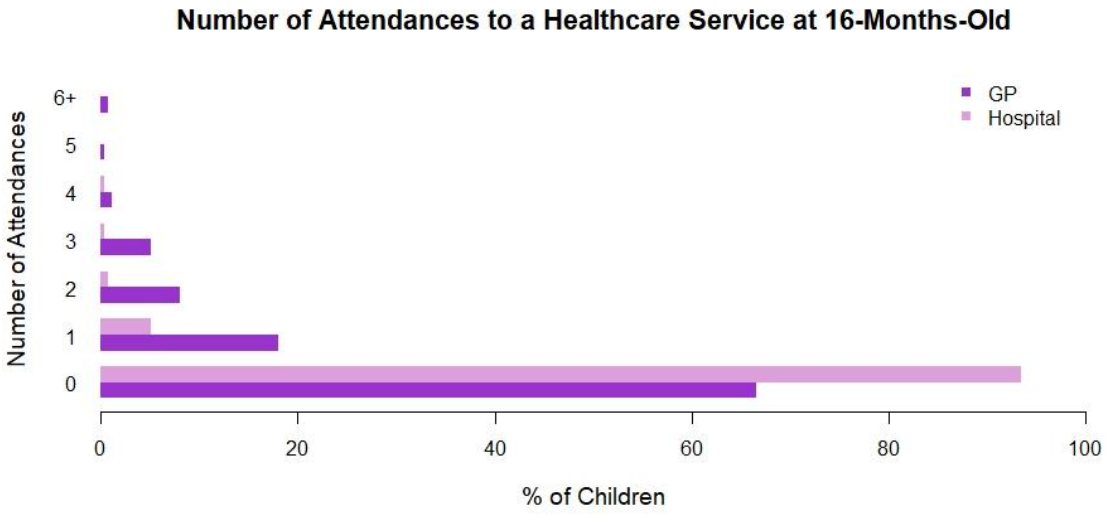


Figure 43: GP and hospital attendance rates at 16-months-old

4.5.3.4.1 Impact of Risk Factor Exposure on Healthcare Service Usage

4.5.3.4.1.1 GP Attendance

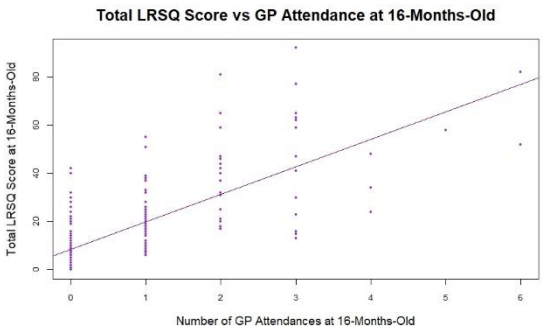
Visits to a GP for a respiratory problem were more likely amongst: infants with a family history of atopy (OR = 1.80, 95% CI = 1.07 - 3.04), infants who attended nursery (OR = 2.71, 95% CI = 1.61 - 4.56), and males (OR = 2.29, 95% CI = 1.37 - 3.84). GP visitation was also more likely amongst infants with school-educated mothers, compared to those with degree (OR = 2.47, 95% CI = 1.35 - 4.53) or vocationally-educated mothers (OR = 2.81, 95% CI = 1.30 - 6.07).

4.5.3.4.1.2 Hospital Attendance

Hospital visitations for a respiratory problem were more likely amongst infants with school-educated mothers, compared to those with degree-educated mothers (OR = 3.37, 95% CI = 1.22 - 9.31).

4.5.3.4.2 Total LRSQ Score vs Healthcare Service Usage

At 16-months-old, there was a strong correlation between total LRSQ score and GP attendance rate (r_s = 0.700, p = <0.001). There was a weak correlation between total LRSQ score and hospital attendance rate (r_s = 0.326, p = <0.001). These results suggest the infants with the most severe respiratory disease, are slightly more likely to seek medical assistance from a GP, but not necessarily from the hospital. **Figures 44** and **45** show the correlations graphically.



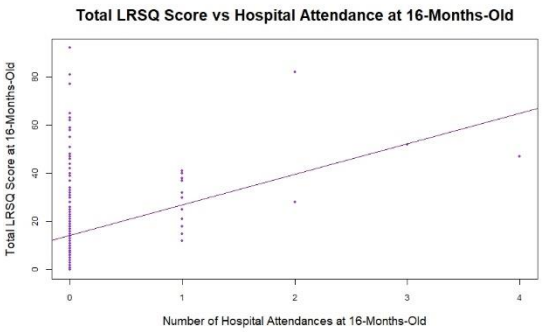


Figure 44: correlation between total LRSQ score and GP attendance rate at 16-months-old
Figure 45: correlation between total LRSQ score and hospital attendance rate at 16-months-old

4.5.4 Questionnaire 4: 22-Months-Old

4.5.4.1 Exposure to Risk Factors

4.5.4.1.1 Nursery Attendance

At 22-months-old, 56.9% (n = 144) of toddlers attended nursery.

4.5.4.1.2 Other Household Children

48.6% (n = 123) of toddlers lived with at least one other child at 22-months-old. A technical error with the online questionnaires meant that the number of other household children couldn't be reported.

4.5.4.1.3 Bedroom Sharing

At 22-months-old, 27.7% (n = 70) of toddlers shared a bedroom. 64.3% (n = 45) shared with their parent(s), 37.1% (n = 26) shared with one other child, 1.4% (n = 1) shared with more than one other child, and 2.9% (n = 2) shared with someone else.

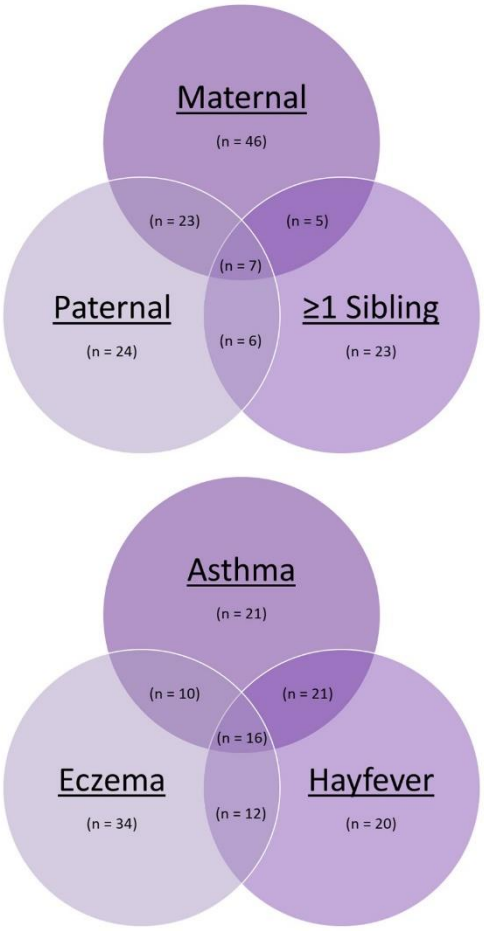
4.5.4.1.4 ETS Exposure

15.4% (n = 39) of toddlers were exposed to ETS at 22-months-old. 5.1% (n = 2) were exposed to ETS from inside the home, 92.3% (n = 36) were exposed to ETS from outside of the home, 5.1% (n = 2) were exposed to ETS from inside the car, 5.1% (n = 2)

were exposed to ETS from within another location (e.g. work), and 5.1% (n = 2) were exposed to ETS from elsewhere.

At 22-months-old, the prevalence of ETS exposure amongst toddlers in the LBBS was not significantly different to the prevalence of smoking in England in 2015/16 ($\chi^2 = 0.11$, $p = 0.74$, $df = 1$). However, it was lower than the prevalence of smoking in Liverpool in 2015/16 ($\chi^2 = 4.73$, $p = 0.03$, $df = 1$).

4.5.4.1.5 Family History of Atopy



At 22-months-old, 53.0% (n = 134) of toddlers had a family history of atopy.

From those with a family history of atopy: 60.4% (n = 81) had an atopic mother, 44.8% (n = 60) had an atopic father, and 30.6% (n = 41) had at least one atopic sibling. There was a family history of: asthma in 50.7% (n = 68) of these toddlers, hay fever in 51.5% (n = 69), and eczema in 53.7% (n = 72). **Figure 46** shows how familial atopy was inter-related at 22-months-old.

Figure 46: toddlers with a family history of atopy, by relative(s) and disease(s), at 22-months-old

4.5.4.1.6 Co-Morbidities

13.8% (n = 35) of the toddlers had a co-morbid disease at 22-months-old. The respiratory system was the most common co-morbid system at this age, whilst eczema was the most common co-morbidity overall. **Table 23** shows the co-morbidities seen at 22-months-old – as reported by parents, and grouped according to organ system.

Type of Co-Morbidity	Underlying Condition	Frequency
Respiratory (n = 10)	Asthma	6
	Viral-Induced Wheeze	2
	Bronchomalacia	1
	Laryngomalacia	1
Cardiac (n = 3)	Congenital Heart Disease	3
Renal (n = 1)	Vesicoureteral Reflux	1
Neurological (n = 1)	Hypotonia	1
Other (n = 25)	Eczema	17
	Allergies	3
	Club Foot (Talipes Equinovarus)	1
	Developmental Delay	1
	Developmental Dysplasia of Hips	1
	Tuberous Sclerosis	1

Table 23: co-morbidities of the LBBS cohort at 22-months-old

4.5.4.2 LRSQ Scores

Measures of central tendency and dispersion for the total LRSQ score, and LRSQ domain scores, at 22-months-old are shown in **Table 24**. The distribution of scores are shown graphically in **Figure 47**.

	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Standard Deviation
Total Score	0	4	8	20	86	14.23	15.53
Domain 1	0	0	1	3	11	2.03	2.28
Domain 2	0	1	2	4	13	2.91	2.70
Domain 3	0	2	3	6	21	4.46	4.13
Domain 4	0	0	0	1	11	0.70	1.59
Domain 5	0	0	0	0.5	10	0.70	1.67
Domain 6	0	0	0	0	9	0.56	1.36
Domain 7	0	0	0	2	16	1.39	2.37
Domain 8	0	0	0	3	16	1.49	2.54

Table 24: descriptive statistics of the total and domain LRSQ scores at 22-months-old

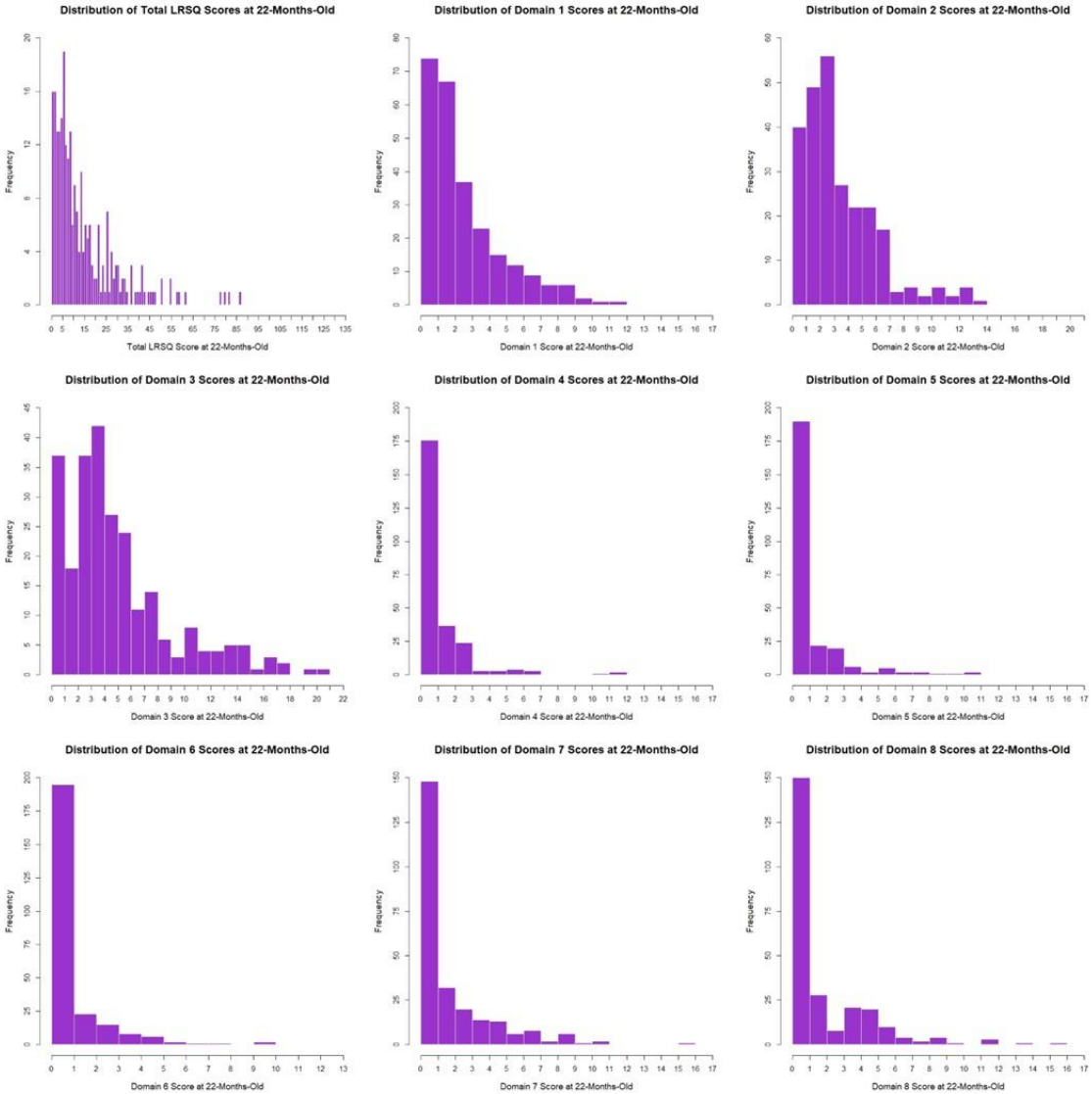


Figure 47: distribution of total and domain LRSQ scores at 22-months-old

4.5.4.2.1 Impact of Risk Factor Exposure on Total LRSQ Score

Total LRSQ scores were higher amongst toddlers who had: no family history of atopy ($U = 10366$, $p = 0.020$), or no co-morbidities ($U = 5149$, $p = 0.021$). They were also higher amongst toddlers who attended nursery ($U = 10500$, $p = 0.028$).

There were differences in total LRSQ score between the different levels of maternal education ($H = 12.73$, $p = 0.002$, $df = 2$). Post-hoc analysis revealed that toddlers with degree-educated mothers scored higher, compared to those with vocationally ($p = 0.006$) or school-educated mothers ($p = 0.004$).

4.5.4.2.2 Impact of Risk Factor Exposure on LRSQ Domain Scores

4.5.4.2.2.1 Domain 1

Domain 1 scores were higher amongst those toddlers who attended nursery ($U = 10694$, $p = 0.045$), or whose mothers were exposed to ETS during pregnancy ($U = 5352$, $p = 0.012$). They were higher amongst those without a family history of atopy ($U = 10428$, $p = 0.021$).

There were differences in domain 1 score between the different levels of maternal education ($H = 11.11$, $p = 0.004$, $df = 2$). Post-hoc analysis revealed that toddlers with degree-educated mothers scored higher, compared to those with vocationally ($p = 0.030$) or school-educated mothers ($p = 0.003$).

4.5.4.2.2.2 Domain 2

Domain 2 scores were higher amongst toddlers who attended nursery ($U = 9897$, $p = 0.003$), or were not breastfed ($U = 7164$, $p = 0.037$).

There were differences in domain 2 score between the different levels of maternal education ($H = 12.97$, $p = 0.002$, $df = 2$). Post-hoc analysis revealed that toddlers with degree-educated mothers scored higher, compared to those with vocationally ($p = 0.040$) or school-educated mothers ($p = 0.001$).

4.5.4.2.2.3 Domain 3

Domain 3 scores were higher amongst the toddlers who had no family history of atopy ($U = 10478$, $p = 0.028$), or no co-morbidities ($U = 5018$, $p = 0.011$). They were also higher amongst toddlers who attended nursery ($U = 10467$, $p = 0.024$).

There were differences in domain 3 score between the different levels of maternal education ($H = 10.85$, $p = 0.004$, $df = 2$). Post-hoc analysis revealed that toddlers with degree-educated mothers scored higher, compared to those with vocationally ($p = 0.012$) or school-educated mothers ($p = 0.006$).

4.5.4.2.2.4 Domain 4

Domain 4 scores were higher amongst non-Caucasian toddlers ($U = 2262$, $p = 0.013$) and those whose mothers were exposed to ETS during pregnancy ($U = 5758$, $p = 0.031$).

There were differences in domain 4 score between the different levels of maternal education (H = 6.51, p = 0.039, df = 2). Post-hoc analysis revealed that toddlers with degree-educated mothers scored higher than those with vocationally-educated mothers (p = 0.012).

4.5.4.2.2.5 Domain 5

Domain 5 scores were higher amongst toddlers who did not live with other children (U = 11028, p = 0.036), or attended nursery (U = 10832, p = 0.017). They were also higher amongst non-Caucasian toddlers (U = 1841, p = <0.001).

There were differences in domain 5 score between the different levels of maternal education (H = 12.89, p = 0.002, df = 2). Post-hoc analysis revealed that toddlers with degree-educated mothers scored higher, compared to those with vocationally (p = 0.012) or school-educated mothers (p = 0.002).

4.5.4.2.2.6 Domain 6

At 22-months-old, there were no risk factors that impacted a toddler's domain 6 score.

4.5.4.2.2.7 Domain 7

There were differences in domain 7 score between the different levels of maternal education (H = 13.75, p = 0.001, df = 2). Post-hoc analysis revealed that toddlers with degree-educated mothers scored higher, compared to those with vocationally (p = 0.001) or school-educated mothers (p = 0.018).

4.5.4.2.2.8 Domain 8

There were differences in domain 8 score between the different levels of maternal education (H = 10.34, p = 0.006, df = 2). Post-hoc analysis revealed that toddlers with degree-educated mothers scored higher than those with vocationally-educated mothers (p = 0.002).

4.5.4.2.3 Total LRSQ Score vs Total QoL Score

There was a strong positive correlation between a toddler's total LRSQ score, and their total QoL score (r_s = 0.847, p = <0.001). **Figure 48** shows the correlation graphically. A higher total LRSQ score is more strongly correlated with a poor QoL for toddlers, than with a poor QoL for parents (r_s = 0.812, p = <0.001 vs r_s = 0.833, p = <0.001). Toddlers

who regularly suffer with respiratory symptoms, and their parents, therefore experience a worse QoL.

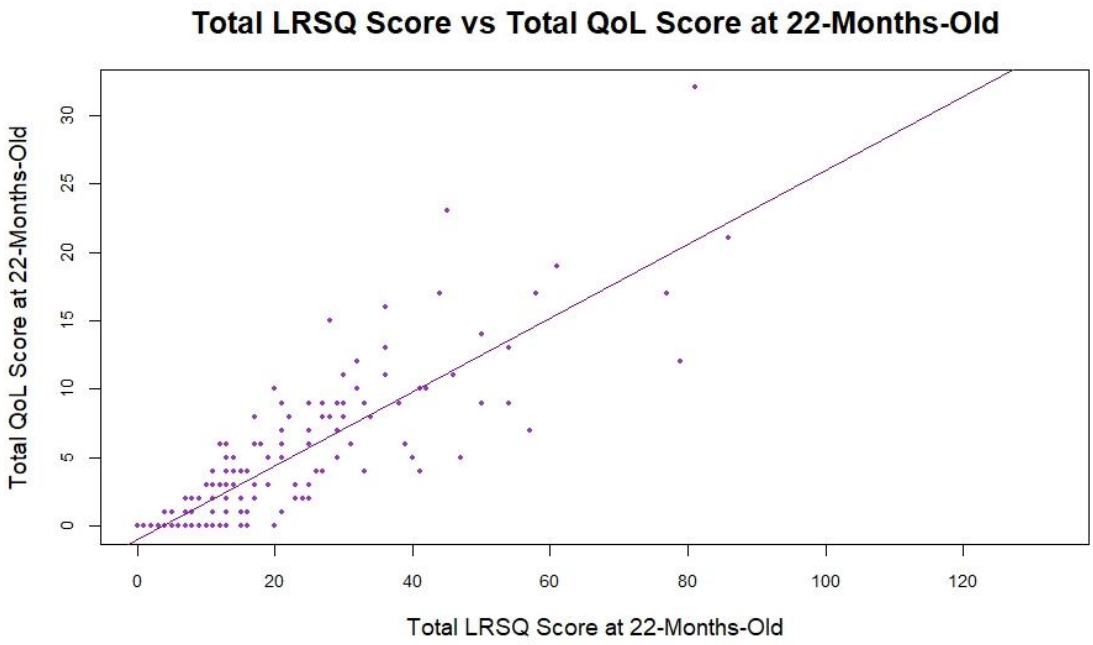


Figure 48: correlation between total LRSQ score and total QoL score at 22-months-old

4.5.4.3 Symptom Prevalence

93.7% (n = 237) of toddlers experienced at least one type of respiratory symptom at 22-months-old. A cold was the most common symptom, as it was experienced by 85.4% (n = 216) of toddlers; noisy breathing that didn't come from the chest was the least common symptom, as it was experienced by 9.0% (n = 23) of toddlers. **Figure 49** demonstrates the prevalence of individual symptoms.

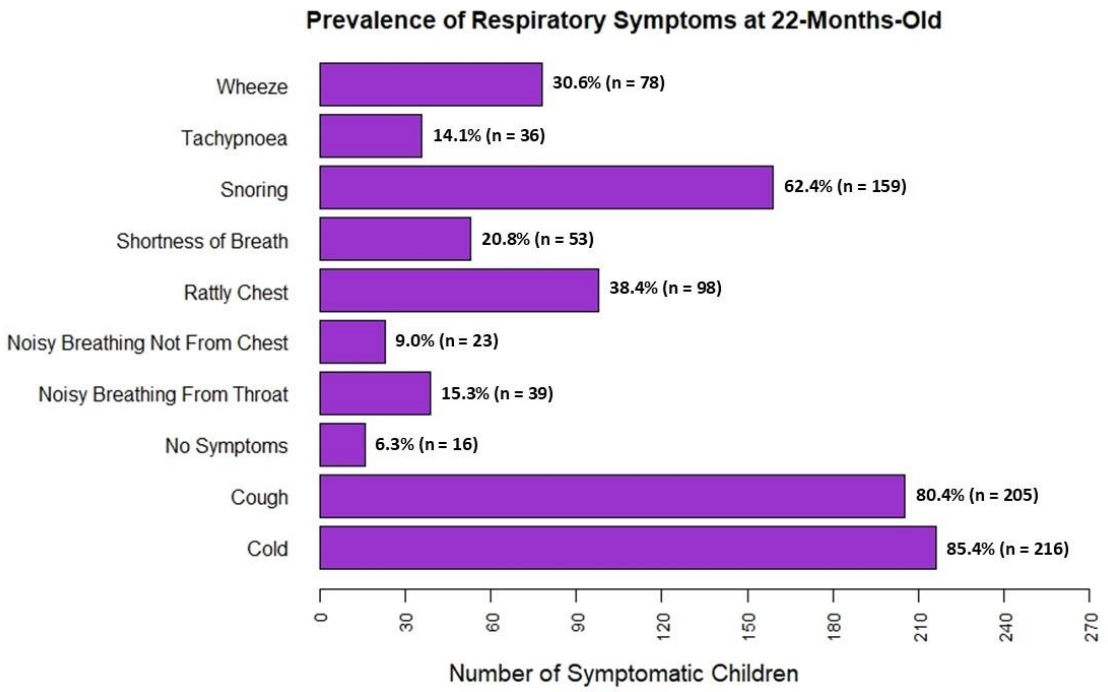


Figure 49: prevalence of respiratory symptoms at 22-months-old

4.5.4.3.1 Impact of Risk Factor Exposure on Symptom Prevalence

4.5.4.3.1.1 Colds

Colds were more likely amongst: females (OR = 2.10, 95% CI = 1.06 – 4.15), singletons (OR = 6.54, 95% CI = 1.23 – 34.96), toddlers who attended nursery (OR = 2.63, 95% CI = 1.29 – 5.35), and toddlers without a co-morbidity (OR = 2.36, 95% CI = 1.09 – 5.11). Colds were also more likely amongst toddlers who were born to mothers aged more than 35-years-old, compared to those born to mothers aged 25 to 34-years-old (OR = 2.60, 95% CI = 1.13 - 6.03).

4.5.4.3.1.2 Coughing

Coughing was more likely amongst toddlers who attended nursery (OR = 2.69, 95% CI = 1.42 - 5.11), and toddlers without a family history of atopy (OR = 1.96, 95% CI = 1.03 - 3.74). Coughing was more likely amongst toddlers with degree-educated mothers too, compared to those with school-educated mothers (OR = 2.97, 95% CI = 1.48 - 5.96).

There were differences in the prevalence of coughing amongst the different levels of maternal education ($\chi^2 = 7.58$, $p = 0.023$, $df = 2$). Toddlers with degree-educated mothers were more likely to cough than those with vocationally or school-educated

mothers. Toddlers with vocationally-educated mothers were more likely to cough than those with school-educated mothers too.

4.5.4.3.1.3 No Symptoms

Being asymptomatic was more likely amongst toddlers who did not attend nursery (OR = 3.80, 95% CI = 1.28 - 11.33).

4.5.4.3.1.4 Noisy Breathing – From Throat

There were no risk factors that affected the prevalence of noisy breathing from the throat, at 22-months-old.

4.5.4.3.1.5 Noisy Breathing – Not From Chest

There were no risk factors that affected the prevalence of noisy breathing that did not come from the chest, at 22-months-old.

4.5.4.3.1.6 Rattly Chest

Rattly chests were more likely amongst toddlers with degree-educated mothers, compared to those with vocationally (OR = 2.31, 95% CI = 1.07 - 5.01) or school-educated mothers (OR = 2.41, 95% CI = 1.17 - 4.96). Toddlers who were breastfed for 1-4 months were also more likely to have rattly chests, compared to those who were breastfed for less than 1 month (OR = 2.46, 95% CI = 1.07 - 5.66).

4.5.4.3.1.7 Shortness of Breath

SOB was more likely amongst toddlers who attended nursery (OR = 2.32, 95% CI = 1.28 - 4.44). SOB was also more likely amongst toddlers with degree-educated mothers, compared to those with school-educated mothers (OR = 2.44, 95% CI = 1.17 - 5.07).

4.5.4.3.1.8 Snoring

Snoring was more likely amongst toddlers who attended nursery (OR = 1.81, 95% CI = 1.08 – 3.01).

4.5.4.3.1.9 Tachypnoea

Tachypnoea was more likely amongst toddlers who were breastfed (OR = 3.17, 95% CI = 1.00 – 10.01).

4.5.4.3.1.10 Wheezing

Wheezing was more likely amongst males (OR = 1.83, 95% CI = 1.04 – 3.22). Wheezing was also more likely amongst toddlers with degree-educated mothers, compared to those with school-educated mothers (OR = 3.29, 95% CI = 1.32 - 8.22).

4.5.4.4 Healthcare Service Usage

At 22-months-old, 24.1% (n = 61) of toddlers were taken to their GP for a respiratory problem. Of these toddlers: 52.5% (n = 32) visited once, 24.6% (n = 15) visited twice, 13.1% (n = 8) visited thrice, 4.9% (n = 3) visited four times, and 4.9% (n = 3) visited more than five times. 5.5% (n = 14) of toddlers were taken to hospital for a respiratory problem. 64.3% (n = 9) of these toddlers visited once, 7.1% (n = 1) visited twice, 14.3% (n = 2) visited thrice, 7.1% (n = 1) visited four times, and 7.1% (n = 1) visited more than five times. **Figure 50** presents GP and hospital attendance rates graphically.

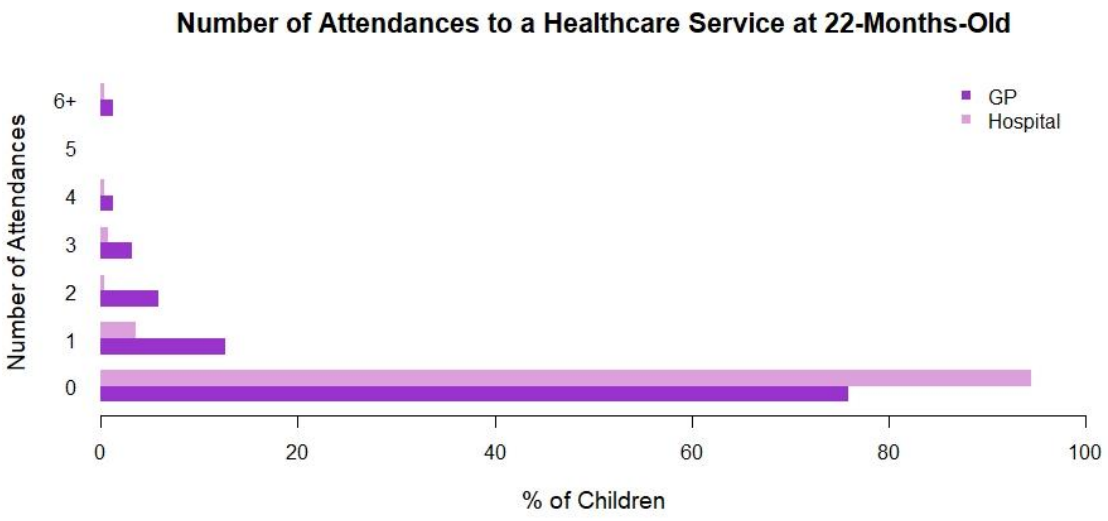


Figure 50: GP and hospital attendance rates at 22-months-old

4.5.4.4.1 Impact of Risk Factor Exposure on Healthcare Service Usage

4.5.4.4.1.1 GP Attendance

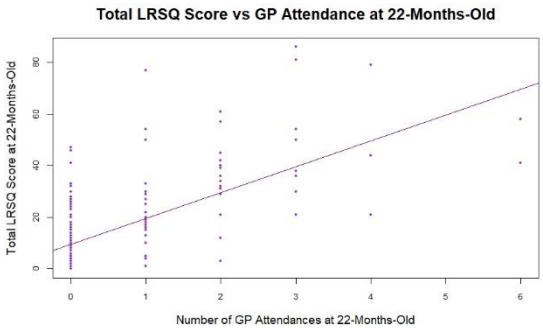
Visits to a GP for a respiratory problem were more likely amongst toddlers with degree-educated mothers, compared to those with school-educated mothers (OR = 2.46, 95% CI = 1.03 - 5.86).

4.5.4.4.1.2 Hospital Attendance

The rate of hospital attendance for a respiratory problem was not impacted by any of the risk factors being assessed, at 22-months-old.

4.5.4.4.2 Total LRSQ Score vs Healthcare Service Usage

At 22-months-old, there was a moderate correlation between total LRSQ score and GP attendance rate (r_s = 0.546, p = <0.001). There was a weak correlation between total LRSQ score and hospital attendance rate (r_s = 0.291, p = <0.001). These results suggest the toddlers with the most severe respiratory disease, are not necessarily the ones who are more likely to seek medical assistance. **Figures 51** and **52** show the correlations graphically.



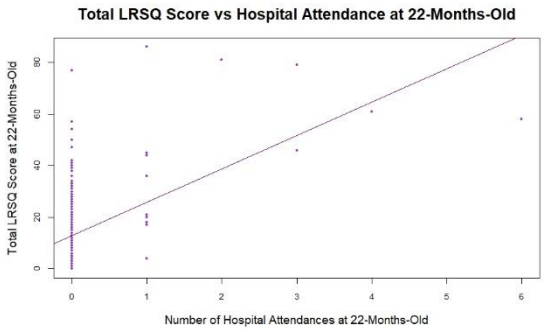


Figure 51: correlation between total LRSQ score and GP attendance rate at 22-months-old
Figure 52: correlation between total LRSQ score and hospital attendance rate at 22-months-old

4.5.5 Questionnaire 5: 28-Months-Old

4.5.5.1 Exposure to Risk Factors

4.5.5.1.1 Nursery Attendance

At 28-months-old, 67.1% (n = 151) of toddlers attended nursery.

4.5.5.1.2 Other Household Children

55.1% (n = 124) of toddlers lived with at least one other child at 28-months-old. 81.5% (n = 101) lived with only one other, 13.7% (n = 17) lived with two others, and 4.8% (n = 6) lived with three others.

4.5.5.1.3 Bedroom Sharing

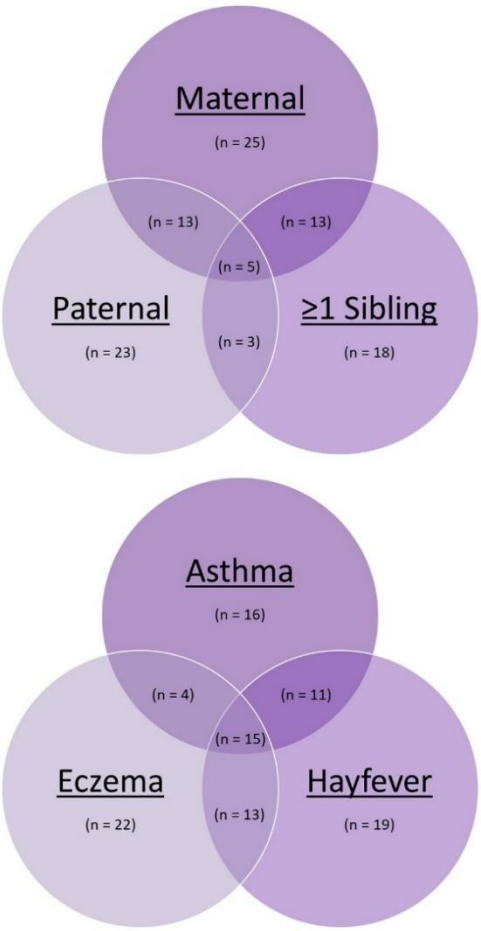
At 28-months-old, 25.8% (n = 58) of toddlers shared a bedroom. 55.2% (n = 32) shared with their parent(s), 46.6% (n = 27) shared with one other child, 1.6% (n = 1) shared with more than one other child, and 1.6% (n = 1) shared with someone else.

4.5.5.1.4 ETS Exposure

13.8% (n = 31) of toddlers were exposed to ETS at 28-months-old. 6.5% (n = 2) were exposed to ETS from inside the home, 87.1% (n = 27) were exposed to ETS from outside of the home, 6.5% (n = 2) were exposed to ETS from inside the car, and 16.1% (n = 5) were exposed to ETS from within another location (e.g. work).

At 28-months-old, the prevalence of ETS exposure amongst toddlers in the LBBS was not significantly different to the prevalence of smoking in England in 2015/16 ($\chi^2 = 0.97$, $p = 0.32$, $df = 1$). However, it was lower than the prevalence of smoking in Liverpool in 2015/16 ($\chi^2 = 7.05$, $p = 0.008$, $df = 1$).

4.5.5.1.5 Family History of Atopy



At 28-months-old, 44.4% (n = 100) of toddlers had a family history of atopy.

From those with a family history of atopy: 56.0% (n = 56) had an atopic mother, 44.0% (n = 44) had an atopic father, and 39.0% (n = 39) had at least one atopic sibling. There was a family history of: asthma in 46.0% (n = 46) of these toddlers, hay fever in 58.0% (n = 58), and eczema in 54.0% (n = 54). **Figure 53** shows how familial atopy was inter-related at 28-months-old.

Figure 53: toddlers with a family history of atopy, by relative(s) and disease(s), at 28-months-old

4.5.5.1.6 Co-Morbidities

15.1% (n = 34) of the toddlers had a co-morbid disease at 28-months-old. The respiratory system was the most common co-morbid system at this age, whilst eczema was the most common co-morbidity overall. **Table 25** shows the co-morbidities seen at 28-months-old – as reported by parents, and grouped according to organ system.

Type of Co-Morbidity	Underlying Condition	Frequency
Respiratory (n = 12)	Asthma	8
	Viral-Induced Wheeze	2
	Laryngomalacia	1
	Hay Fever	1
Cardiac (n = 2)	Congenital Heart Disease	2
Renal (n = 2)	Hydronephrosis	1
	Vesicoureteral Reflux	1
Neurological (n = 4)	Cerebral Palsy	1
	Epilepsy	1
	Hypotonia	1
	Pilocytic Astrocytoma	1
Other (n = 22)	Eczema	11
	Allergies	5
	Haemophilia	2
	Autism Spectrum Disorder	1
	Developmental Delay	1
	Developmental Dysplasia of Hips	1
	Tuberous Sclerosis	1

Table 25: co-morbidities of the LBBS cohort at 28-months-old

4.5.5.2 LRSQ Scores

Measures of central tendency and dispersion for the total LRSQ score, and LRSQ domain scores, at 28-months-old are shown in **Table 26**. The distribution of scores are shown graphically in **Figure 54**.

	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Standard Deviation
Total Score	0	2	9	17	111	12.98	15.58
Domain 1	0	0	1	2.5	14	1.69	2.19
Domain 2	0	0	2	3	18	2.38	2.72
Domain 3	0	1	3	6	21	4.01	3.91
Domain 4	0	0	0	1	13	0.74	1.63
Domain 5	0	0	0	1	13	0.68	1.70
Domain 6	0	0	0	1	10	0.70	1.70
Domain 7	0	0	0	2	13	1.35	2.24
Domain 8	0	1	2	4	14	2.96	2.57

Table 26: descriptive statistics of the total and domain LRSQ scores at 28-months-old

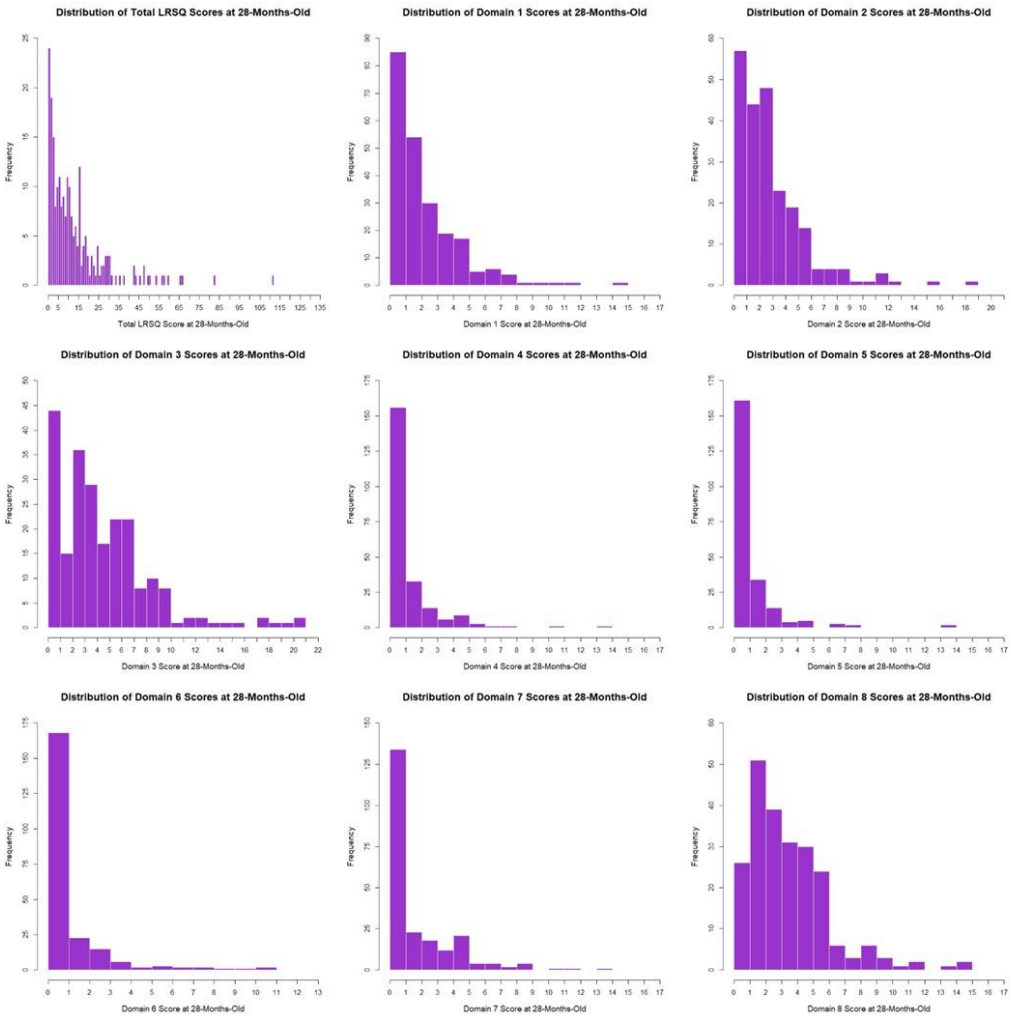


Figure 54: distribution of total and domain LRSQ scores at 28-months-old

4.5.5.2.1 Impact of Risk Factor Exposure on Total LRSQ Score

Total LRSQ scores were higher amongst toddlers with: a family history of atopy (U = 7896, p = 0.003), a co-morbidity (U = 3121, p = <0.001), or a 'normal' birthweight (U = 1121, p = 0.027). They were also higher amongst males (U = 8185, p = 0.008), and those who attended nursery (U = 5997, p = <0.001).

There were differences in total LRSQ score between the different levels of deprivation (H = 13.31, p = 0.010, df = 4). Post-hoc analysis revealed that toddlers living in the second-most deprived IMD quintile scored lower, compared to those living in the most-deprived (p = 0.006), third-most deprived (p = 0.004) and second-least deprived (p = 0.016) quintiles. Toddlers living in the least-deprived IMD quintile scored lower than those living in the third-most deprived quintile (p = 0.037).

4.5.5.2.2 Impact of Risk Factor Exposure on LRSQ Domain Scores

4.5.5.2.2.1 Domain 1

Domain 1 scores were higher amongst males (U = 8398, p = 0.016). They were also higher amongst toddlers who: attended nursery (U = 6226, p = <0.001), had a family history of atopy (U = 8072, p = 0.004), or had a co-morbidity (U = 2886, p = <0.001).

4.5.5.2.2.2 Domain 2

Domain 2 scores were higher amongst toddlers who: attended nursery (U = 7205, p = 0.008), had a family history of atopy (U = 8475, p = 0.027), or had a co-morbidity (U = 3406, p = <0.001). They were also higher amongst males (U = 7773, p = 0.001).

4.5.5.2.2.3 Domain 3

Domain 3 scores were higher amongst toddlers who were: male (U = 7698, p = 0.001) or born at a 'normal' birthweight (U = 1172, p = 0.041). They were also higher amongst toddlers who: had a co-morbidity (U = 3587, p = 0.001), attended nursery (U = 5841, p = <0.001), or had a family history of atopy (U = 7477, p = <0.001).

There were differences in domain 3 score between the different levels of deprivation (H = 15.82, p = 0.003, df = 4) and maternal age (H = 7.78, p = 0.020, df = 2). Post-hoc analysis revealed that toddlers living in the second-most deprived IMD quintile scored lower, compared to those living in the most-deprived (p = 0.015), third-most deprived (p = 0.004) and second-least deprived (p = 0.004) quintiles. Those living in the least-deprived quintile scored lower than those in the third-most deprived (p = 0.013) and second-least deprived (p = 0.034) quintiles. It also revealed that toddlers born to mothers aged less than 25-years-old scored higher, compared to toddlers born to mothers aged ≥35-years-old (p = 0.006) and mothers aged 25 to 34-years-old (p = 0.019).

4.5.5.2.2.4 Domain 4

Domain 4 scores were higher amongst toddlers who: shared a bedroom (U = 7059, p = 0.037), attended nursery (U = 7626, p = 0.018), had a family history of atopy (U = 8806, p = 0.040), had a co-morbidity (U = 2980, p = <0.001), or were born at a 'normal' birthweight (U = 1177, p = 0.015). They were also higher amongst males

(U = 8739, p = 0.026), and those whose mothers were not exposed to ETS during pregnancy (U = 3487, p = 0.005)

4.5.5.2.2.5 Domain 5

Domain 5 scores were higher amongst toddlers who were not exposed to ETS (U = 3986, p = 0.007), and toddlers whose mothers were not exposed to ETS during pregnancy (U = 3446, p = 0.003). They were also higher amongst toddlers with a family history of atopy (U = 8851, p = 0.045), or a co-morbidity (U = 2954, p = <0.001) was also associated with domain 5 scores.

There were differences in domain 5 score between the different levels of maternal age (H = 7.26, p = 0.026, df = 2). Post-hoc analysis revealed that toddlers born to mothers aged 25 to 34-years-old scored higher than those born to mothers aged less than 25-years-old (p = 0.014). There were also differences in domain 5 score amongst breastfed toddlers, depending on how long they were breastfed for (H = 7.57, p = 0.023, df = 2). Post-hoc analysis revealed that toddlers who were breastfed for 1-4 months scored lower, compared to those who were breastfed for less than 1 month (p = 0.007) or for more than 4 months (p = 0.041).

4.5.5.2.2.6 Domain 6

Domain 6 scores were higher amongst 'normal' birthweight toddlers (U = 1268, p = 0.029), and those whose mother smoked during pregnancy (U = 1755, p = 0.016). They were also higher amongst toddlers who shared a bedroom (U = 6893, p = 0.011), or had a co-morbidity (U = 3893, p = 0.001).

4.5.5.2.2.7 Domain 7

Domain 7 scores were higher amongst those toddlers who: attended nursery (U = 7060, p = 0.002), had a co-morbidity (U = 3080, p = <0.001), or were born at a 'normal' birthweight (U = 1231, p = 0.041).

There were differences in domain 7 score between the different levels of deprivation (H = 9.54, p = 0.049, df = 4). Post-hoc analysis revealed that toddlers living in the third-most deprived IMD quintile scored higher, compared to those living in the least-deprived (p = 0.032) and the second-most deprived (p = 0.009) quintiles.

4.5.5.2.2.8 Domain 8

Domain 8 scores were higher amongst males (U = 7418, p = <0.001). They were also higher amongst those who: attended nursery (U = 6786, p = 0.001), had a family history of atopy (U = 7872, p = 0.002), or had a co-morbidity (U = 3611, p = 0.001).

There were differences in domain 8 score between the different levels of deprivation (H = 13.31, p = 0.010, df = 4) and maternal age (H = 6.28, p = 0.043, df = 2). Post-hoc analysis revealed that toddlers living in the second-most deprived IMD quintile scored lower, compared to those living in the most-deprived (p = 0.012), third-most deprived (p = 0.016) and second-least deprived (p = 0.033) quintiles. Those living in the least-deprived quintile scored lower than those in the third-most deprived (p = 0.012) and second-least deprived (p = 0.015) quintiles. It also revealed that toddlers born to mothers aged less than 25-years-old scored higher, compared to toddlers born to mothers aged ≥35-years-old (p = 0.014) and mothers aged 25 to 34-years-old (p = 0.044).

4.5.5.2.3 Total LRSQ Score vs Total QoL Score

There was a strong positive correlation between a toddler's total LRSQ score, and their total QoL score (r_s = 0.934, p = <0.001). **Figure 55** shows the correlation graphically. A higher total LRSQ score is more strongly correlated with a poor QoL for parents, than with a poor QoL for toddlers (r_s = 0.846, p = <0.001 vs r_s = 0.801, p = <0.001). Toddlers who regularly suffer with respiratory symptoms, and their parents, therefore experience a worse QoL.

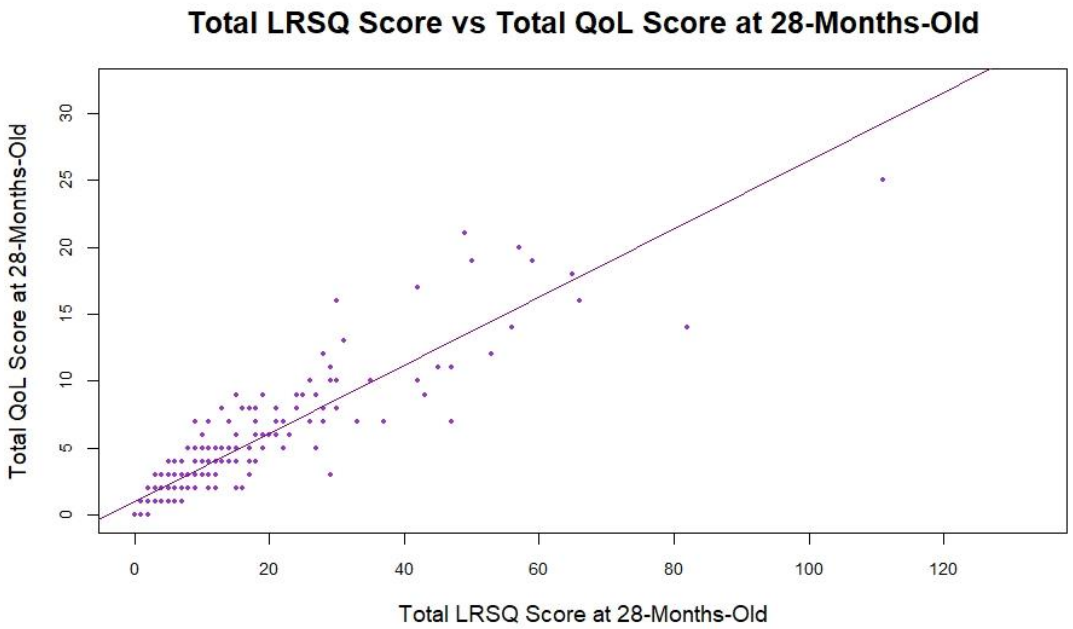


Figure 55: correlation between total LRSQ score and total QoL score at 28-months-old

4.5.5.3 Symptom Prevalence

89.3% (n = 201) of toddlers experienced at least one type of respiratory symptom at 28-months-old. A cold was the most common symptom, as it was experienced by 80.4% (n = 181) of toddlers; tachypnoea was the least common symptom, as it was experienced by 12.9% (n = 29) of toddlers. **Figure 56** demonstrates the prevalence of individual symptoms.

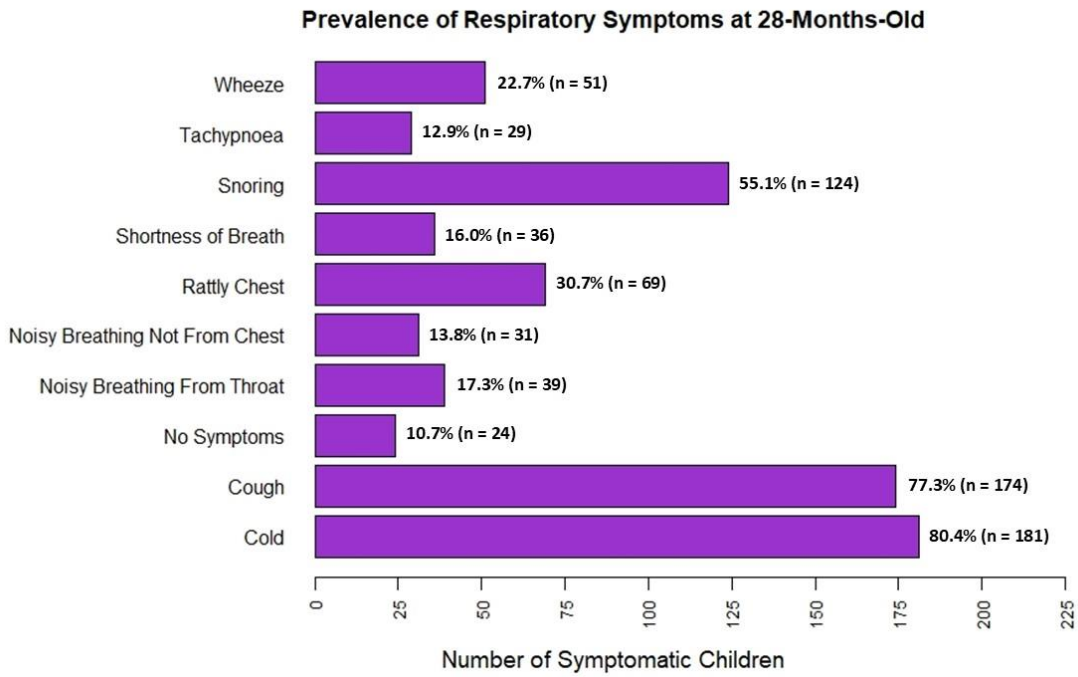


Figure 56: prevalence of respiratory symptoms at 28-months-old

4.5.5.3.1 Impact of Risk Factor Exposure on Symptom Prevalence

4.5.5.3.1.1 Colds

Colds were more likely amongst toddlers who attended nursery (OR = 32.23, 95% CI = 1.62 – 6.45). Colds were also more likely amongst toddlers more likely amongst toddlers who were born to mothers aged 25 to 34-years-old, compared to those born to mothers aged more than 35-years-old (OR = 2.27, 95% CI = 1.10 - 4.70).

4.5.5.3.1.2 Coughing

Coughing was more likely amongst: males (OR = 2.77, 95% CI = 1.44 – 5.35), toddlers who attended nursery (OR = 2.32, 95% CI = 1.23 – 4.40), toddlers with a family history of atopy (OR = 3.09, 95% CI = 1.55 – 6.15), and toddlers whose mother was exposed to ETS during pregnancy (OR = 8.55, 95% CI = 1.28 – 57.18).

4.5.5.3.1.3 No Symptoms

Being asymptomatic was more likely amongst: toddlers who did not attend nursery (OR = 3.89, 95% CI = 1.54 – 9.86), females (OR = 3.52, 95% CI = 1.28 – 9.68), and twins (OR = 13.12, 95% CI = 1.02 - 168.34). Being asymptomatic was also more likely amongst toddlers who were born to mothers aged more than 35-years-old, compared to those born to mothers aged 25 to 34-years-old (OR = 3.11, 95% CI = 1.17 - 8.28).

4.5.5.3.1.4 Noisy Breathing – From Throat

Noisy breathing from the throat was more likely amongst toddlers who shared a bedroom (OR = 2.43, 95% CI = 1.20 – 4.94), and toddlers with a co-morbidity (OR = 4.45, 95% CI = 2.01 – 9.85).

4.5.5.3.1.5 Noisy Breathing – Not From Chest

Noisy breathing that did not come from the chest was more likely amongst: toddlers who shared a bedroom (OR = 2.32, 95% CI = 1.08 - 5.02), toddlers whose mothers smoked during pregnancy (OR = 3.40, 95% CI = 1.09 - 10.67), and toddlers with a co-morbidity (OR = 4.34, 95% CI = 1.87 - 10.06).

4.5.5.3.1.6 Rattly Chest

Rattly chests were more likely amongst toddlers who attended nursery (OR = 2.66, 95% CI = 1.36 – 5.19), and toddlers with a family history of atopy (OR = 2.62, 95% CI = 1.46 – 4.70). Rattly chests were also more likely amongst toddlers who were born

to mothers aged less than 25-years-old, compared to those born to mothers aged 25 to 34-years-old (OR = 9.87, 95% CI = 2.25 - 43.30) or more than 35-years-old (OR = 11.07, 95% CI = 2.40 - 51.03).

4.5.5.3.1.7 Shortness of Breath

SOB was more likely amongst toddlers with a family history of atopy (OR = 2.57, 95% CI = 1.22 – 5.45), and toddlers with a co-morbidity (OR = 3.57, 95% CI = 1.57 – 8.10).

4.5.5.3.1.8 Snoring

Snoring was more likely amongst males (OR = 1.87, 95% CI = 1.10 – 3.18). Snoring was more likely amongst toddlers who were born to mothers aged less than 25-years-old, compared to those born to mothers aged more than 35-years-old (OR = 7.55, 95% CI = 1.10 - 51.65). Toddlers who were breastfed for less than 1 month or for more than 4 months were also more likely to snore, compared to those who were breastfed for 1-4 months (respectively: OR = 4.17, 95% CI = 1.63 - 10.66 and OR = 2.67, 95% CI = 1.18 – 6.03

4.5.5.3.1.9 Tachypnoea

Tachypnoea was more likely amongst toddlers with a co-morbidity (OR = 2.87, 95% CI = 1.22 – 6.73). Tachypnoea was also more likely amongst toddlers who were breastfed for less than 1 month or more than 4 months, compared to those who were breastfed for 1-4 months (respectively: OR = 18.44, 95% CI = 1.21 - 281.40 and OR = 18.53, 95% CI = 1.29 - 265.99).

4.5.5.3.1.10 Wheezing

Wheezing was more likely amongst toddlers with a family history of atopy (OR = 2.10, 95% CI = 1.12 – 3.91) or a co-morbidity (OR = 3.93, 95% CI = 1.85 - 8.326).

4.5.5.4 Healthcare Service Usage

At 28-months-old, 16.9% (n = 38) of toddlers were taken to their GP for a respiratory problem. Of these toddlers: 63.2% (n = 24) visited once, 26.3% (n = 10) visited twice, 5.3% (n = 2) visited thrice, 2.6% (n = 1) visited four times, and 2.6% (n = 1) visited five times. 4.0% (n = 9) of toddlers were taken to hospital for a respiratory problem. 55.6% (n = 5) of these toddlers visited once, 33.3% (n = 3) visited twice, and 11.1% (n = 1) visited five times. **Figure 57** presents GP and hospital attendance rates graphically.

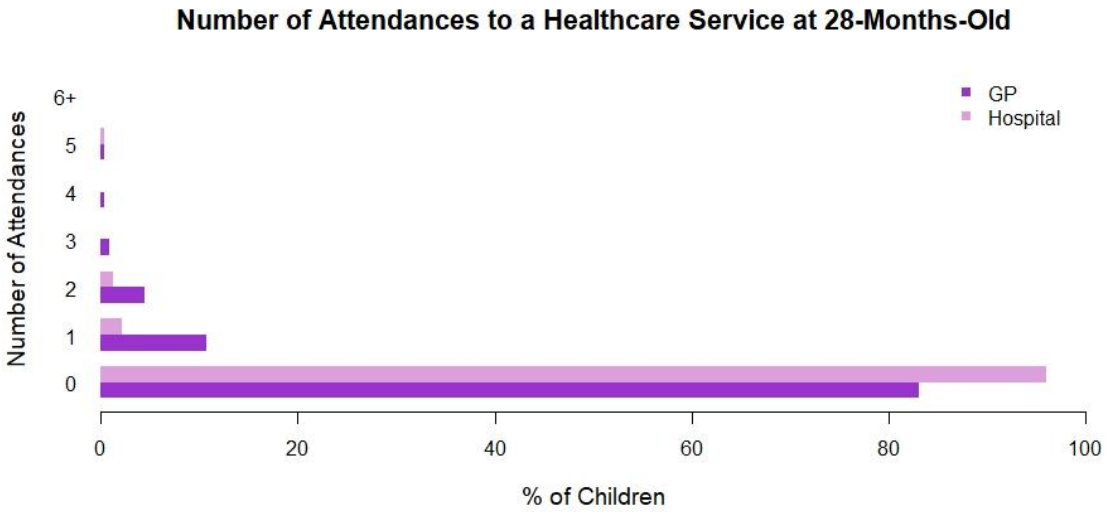


Figure 57: GP and hospital attendance rates at 28-months-old

4.5.5.4.1 Impact of Risk Factor Exposure on Healthcare Service Usage

4.5.5.4.1.1 GP Attendance

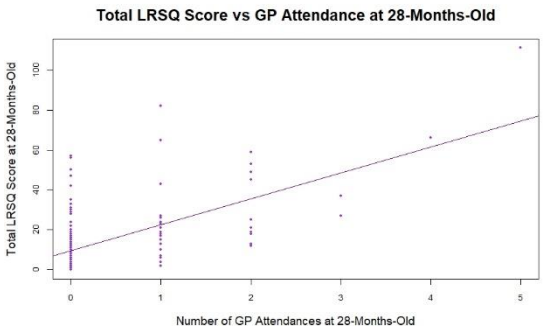
Visits to a GP for a respiratory problem were more likely amongst toddlers with a co-morbidity (OR = 3.80, 95% CI = 1.74 - 8.33), toddlers with a family history of atopy (OR = 2.15, 95% CI = 1.08 - 4.27), and toddlers who did not live with other children (OR = 4.00, 95% CI = 1.93 - 8.28).

4.5.5.4.1.2 Hospital Attendance

Hospital visitations for a respiratory problem were more likely amongst toddlers with a co-morbidity (OR = 8.49, 95% CI = 2.21 - 32.69), and toddlers who shared a bedroom (OR = 8.05, 95% CI = 1.78 - 36.42).

4.5.5.4.2 Total LRSQ Score vs Healthcare Service Usage

At 28-months-old, there was a moderate correlation between total LRSQ score and GP attendance rate (r_s = 0.470, p = <0.001). There was a weak correlation between total LRSQ score and hospital attendance rate (r_s = 0.285, p = <0.001). These results suggest the toddlers with the most severe respiratory disease, are not necessarily the ones who are more likely to seek medical assistance. **Figures 58** and **59** show the correlations graphically.



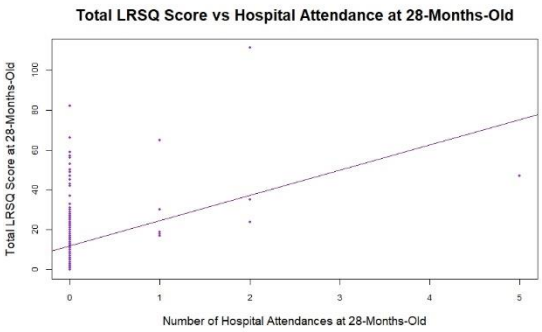


Figure 58: correlation between total LRSQ score and GP attendance rate at 28-months-old
Figure 59: correlation between total LRSQ score and hospital attendance rate at 28-months-old

4.5.6 Questionnaire 6: 34-Months-Old

4.5.6.1 Exposure to Risk Factors

4.5.6.1.1 Nursery Attendance

At 34-months-old, 74.3% (n = 171) of toddlers attended nursery.

4.5.6.1.2 Other Household Children

53.0% (n = 122) of toddlers lived with at least one other child at 34-months-old. 78.7% (n = 96) lived with only one other, 16.4% (n = 20) lived with two others, 4.1% (n = 5) lived with three others, and 0.8% (n = 1) lived with four others.

4.5.6.1.3 Bedroom Sharing

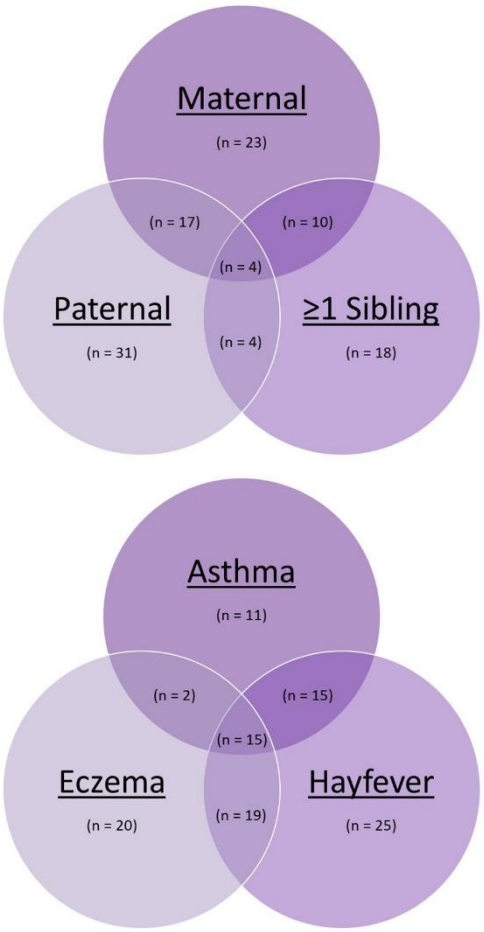
At 34-months-old, 27.8% (n = 64) of toddlers shared a bedroom. 51.6% (n = 33) shared with their parent(s), 46.9% (n = 30) shared with one other child, and 3.1% (n = 2) shared with more than one other child.

4.5.6.1.4 ETS Exposure

16.1% (n = 37) of toddlers were exposed to ETS at 34-months-old. 9.5% (n = 4) were exposed to ETS from inside the home, 91.9% (n = 34) were exposed to ETS from outside of the home, 2.7% (n = 1) were exposed to ETS from inside the car, and 7.1% (n = 3) were exposed to ETS from within another location (e.g. work).

At 34-months-old, the prevalence of ETS exposure amongst toddlers in the LBBS was not significantly different to the prevalence of smoking in either England ($\chi^2 = 0.14$, $p = 0.71$, $df = 1$) or Liverpool ($\chi^2 = 0.20$, $p = 0.66$, $df = 1$) in 2016/17.

4.5.6.1.5 Family History of Atopy



At 34-months-old, 46.5% (n = 107) of toddlers had a family history of atopy.

From those with a family history of atopy: 50.5% (n = 54) had an atopic mother, 52.3% (n = 56) had an atopic father, and 33.6% (n = 36) had at least one atopic sibling. There was a family history of: asthma in 40.2% (n = 43) of these toddlers, hay fever in 69.2% (n = 74), and eczema in 52.3% (n = 56). **Figure 60** shows how familial atopy was inter-related at 34-months-old.

Figure 60: toddlers with a family history of atopy, by relative(s) and disease(s), at 34-months-old

4.5.6.1.6 Co-Morbidities

12.6% (n = 29) of the toddlers had a co-morbid disease at 34-months-old. The respiratory system was the most common co-morbid system at this age, whilst eczema

was the most common co-morbidity overall. **Table 27** shows the co-morbidities seen at 34-months-old – as reported by parents, and grouped according to organ system.

Type of Co-Morbidity	Underlying Condition	Frequency
Respiratory (n = 10)	Asthma	6
	Viral-Induced Wheeze	2
	Hay Fever	1
Cardiac (n = 2)	Congenital Heart Disease	2
Renal (n = 2)	Hydronephrosis	1
	Vesicoureteral Reflux	1
Neurological (n = 1)	Cerebral Palsy	1
Other (n = 23)	Eczema	10
	Allergies	6
	Club Foot (Talipes Equinovarus)	1
	Down's Syndrome (Trisomy 21)	1
	Metatarsus Varus	1
	Pes Planus	1
	Tuberous Sclerosis	1

Table 27: co-morbidities of the LBBS cohort at 34-months-old

4.5.6.2 LRSQ Scores

Measures of central tendency and dispersion for the total LRSQ score, and LRSQ domain scores, at 34-months-old are shown in **Table 28**. The distribution of scores are shown graphically in **Figure 61**.

	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Standard Deviation
Total Score	0	3	8	19	72	13.20	14.09
Domain 1	0	0	1	3	9	1.80	2.01
Domain 2	0	1	2	4	11	2.67	2.57
Domain 3	0	2	3	6	21	4.30	3.91
Domain 4	0	0	0	1	6	0.74	1.38
Domain 5	0	0	0	1	7	0.68	1.43
Domain 6	0	0	0	0	11	0.60	1.57
Domain 7	0	0	0	1	11	1.11	2.04
Domain 8	0	1	3	5	11	3.23	2.56

Table 28: descriptive statistics of the total and domain LRSQ scores at 34-months-old

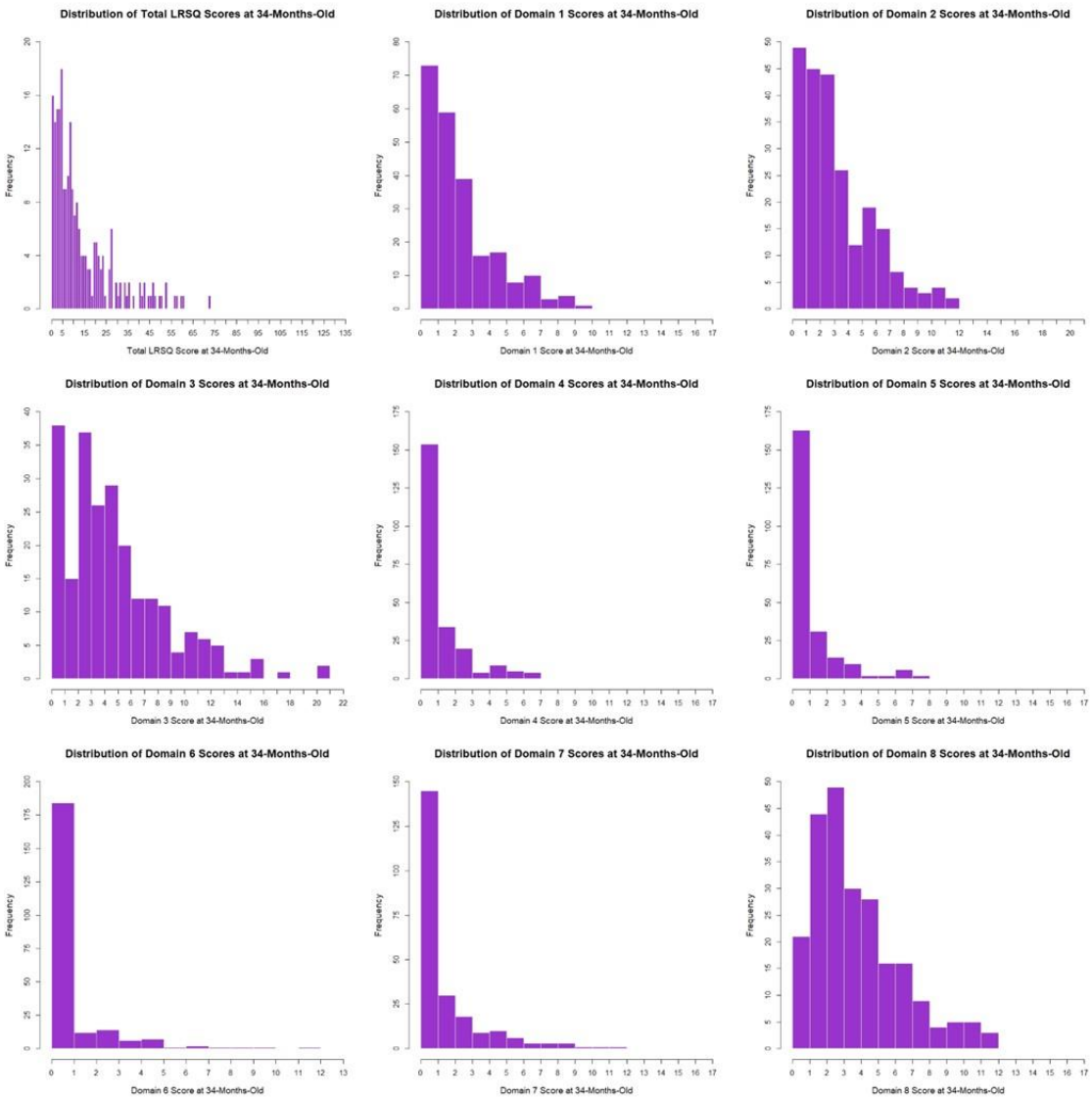


Figure 61: distribution of total and domain LRSQ scores at 34-months-old

4.5.6.2.1 Impact of Risk Factor Exposure on Total LRSQ Score

Total LRSQ scores were higher amongst toddlers who were: non-Caucasian (U = 1909, p = 0.041), breastfed (U = 6284, p = 0.019), or a singleton birth (U = 52, p = 0.044). They were also higher amongst those who: had a co-morbidity (U = 3174, p = 0.005), attended nursery (U = 5771, p = <0.001), did not live with other children (U = 8748, p = 0.002), or had a family history of atopy (U = 9544, p = 0.042).

There were differences in total LRSQ score between the different levels of deprivation (H = 13.31, p = 0.010, df = 4) and maternal age (H = 8.38, p = 0.015, df = 2). Post-hoc analysis revealed that toddlers living in the most-deprived IMD quintile scored higher, compared to those living in the least-deprived (p = 0.013) and second-most deprived (p = 0.005) quintiles. Those living in the third-most deprived IMD quintile scored higher

than those in the most-deprived (p = 0.027) quintile. It also revealed that toddlers born to mothers aged less than 25-years-old scored higher, compared to toddlers born to mothers aged ≥35-years-old (p = 0.004) and mothers aged 25 to 34-years-old (p = 0.010).

4.5.6.2.2 Impact of Risk Factor Exposure on LRSQ Domain Scores

4.5.6.2.2.1 Domain 1

Domain 1 scores were higher amongst toddlers whose mothers did not smoke during pregnancy (U = 2502, p = 0.023), as well as non-Caucasians (U = 1830, p = 0.020). They were also higher amongst toddlers who: attended nursery (U = 5997, p = <0.001), had a co-morbidity (U = 3289, p = 0.009), or did not live with other children (U = 8829, p = 0.002).

There were differences in domain 1 score between the different levels of deprivation (H = 10.90, p = 0.028, df = 4). Post-hoc analysis revealed that toddlers living in the least-deprived IMD quintile scored lower, compared to those living in the least-deprived (p = 0.014) and the third-most deprived (p = 0.040) quintiles. Toddlers living in the second-most deprived IMD quintile scored lower than those living in the most-deprived quintile (p = 0.017).

4.5.6.2.2.2 Domain 2

Domain 2 scores were higher amongst non-Caucasian toddlers (U = 1761, p = 0.013). They were also higher amongst toddlers who: attended nursery (U = 6138, p = <0.001), shared a bedroom (U = 7633, p = 0.026), or did not live with other children (U = 8878, p = 0.002).

There were differences in domain 2 score between the different levels of maternal age (H = 12.16, p = 0.002, df = 2). Post-hoc analysis revealed that toddlers born to mothers aged less than 25-years-old scored higher, compared to toddlers born to mothers aged ≥35-years-old (p = <0.001) and mothers aged 25 to 34-years-old (p = 0.003).

4.5.6.2.2.3 Domain 3

Domain 3 scores were higher amongst toddlers who were: male (U = 8761, p = 0.002), born at a ‘normal’ birthweight (U = 905, p = 0.047), or a singleton birth (U = 46, p = 0.038). They were also higher amongst those who: attended nursery (U = 5951,

p = <0.001), or had a co-morbidity (U = 3383, p = <0.019). Toddlers whose mothers did not smoke during pregnancy had higher domain 3 scores too (U = 2078, p = 0.001).

There were differences in domain 3 score between the different levels of deprivation (H = 9.83, p = 0.043, df = 4) and maternal age (H = 9.07, p = 0.011, df = 2). Post-hoc analysis revealed that toddlers living in the second-most deprived IMD quintile scored lower, compared to those living in the most-deprived (p = 0.026) and third-most deprived (p = 0.022) quintiles. Those living in the least-deprived IMD quintile scored lower than those living in the most-deprived (p = 0.044) and third-most deprived (p = 0.032) quintiles. It also revealed that toddlers born to mothers aged less than 25-years-old scored higher, compared to toddlers born to mothers aged ≥35-years-old (p = 0.003) and mothers aged 25 to 34-years-old (p = 0.007).

4.5.6.2.2.4 Domain 4

Domain 4 scores were higher amongst toddlers who: attended nursery (U = 6407, p = <0.001), had a co-morbidity (U = 3510, p = 0.016), did not live with other children (U = 9140, p = 0.002), or were not exposed to ETS (U = 5103, p = 0.021).

There were differences in domain 4 score between the different levels of deprivation (H = 11.34, p = 0.023, df = 4). Post-hoc analysis revealed that toddlers living in the most-deprived IMD quintile scored higher, compared to those living in the least-deprived (p = 0.035) and the second-most deprived (p = 0.014) quintiles. There were also differences in domain 4 score amongst breastfed toddlers, depending on how long they were breastfed for (H = 8.68, p = 0.013, df = 2). Post-hoc analysis revealed that toddlers who were breastfed for 1-4 months scored higher, compared to those who were breastfed for less than 1 month (p = 0.005) or for more than 4 months (p = 0.016).

4.5.6.2.2.5 Domain 5

Domain 5 scores were higher amongst breastfed toddlers (U = 6275, p = 0.004), and toddlers who: had a co-morbidity (U = 3430, p = 0.006), attended nursery (U = 7087, p = 0.003), or did not live with other children (U = 9357, p = 0.004).

There were differences in domain 5 score amongst breastfed toddlers, depending on how long they were breastfed for (H = 22.35, p = <0.001, df = 2). Post-hoc analysis

revealed that toddlers who were breastfed for 1-4 months scored higher, compared to those who were breastfed for less than 1 month (p = <0.001) or for more than 4 months (p = 0.002). Toddlers who were breastfed for more than 4 months scored higher than those who were breastfed for less than 1 month (p = 0.012) too.

4.5.6.2.2.6 Domain 6

Domain 6 scores were higher amongst toddlers who: had a co-morbidity (U = 3576, p = 0.007), were not exposed to ETS (U = 5278, p = 0.019), or did not live with other children (U = 9965, p = 0.031).

There were differences in domain 6 score amongst breastfed toddlers, depending on how long they were breastfed for (H = 6.12, p = 0.047, df = 2). Post-hoc analysis revealed that toddlers who were breastfed for more than 4 months scored higher, compared to those who were breastfed for less than 1 month (p = 0.016).

4.5.6.2.2.7 Domain 7

Domain 7 scores were higher amongst toddlers who: had a co-morbidity (U = 3653, p = 0.045), were breastfed (U = 6203, p = 0.005), attended nursery (U = 6979, p = 0.003), or did not live with other children (U = 8789, p = <0.001).

4.5.6.2.2.8 Domain 8

Domain 8 scores were higher amongst toddlers who: were breastfed (U = 6415, p = 0.031), had a family history of atopy (U = 9426, p = 0.027), shared a bedroom (U = 7061, p = 0.002), or attended nursery (U = 6430, p = <0.001). They were also higher amongst males (U = 9028, p = 0.006), non-Caucasians (U = 1794, p = 0.017) and those who did not live with other children (U = 9330, p = 0.016).

There were differences in domain 8 score between the different levels of maternal age (H = 21.88, p = <0.001, df = 2). Post-hoc analysis revealed that toddlers born to mothers aged less than 25-years-old scored higher, compared to toddlers born to mothers aged ≥35-years-old (p = <0.001) and mothers aged 25 to 34-years-old (p = <0.001).

4.5.6.2.3 Total LRSQ Score vs Total QoL Score

There was a strong positive correlation between a toddler's total LRSQ score, and their total QoL score (r_s = 0.912, p = <0.001). **Figure 62** shows the correlation graphically. A

higher total LRSQ score is more strongly correlated with a poor QoL for parents, than with a poor QoL for toddlers (r_s = 0.833, p = <0.001 vs r_s = 0.764, p = <0.001). Toddlers who regularly suffer with respiratory symptoms, and their parents, therefore experience a worse QoL.

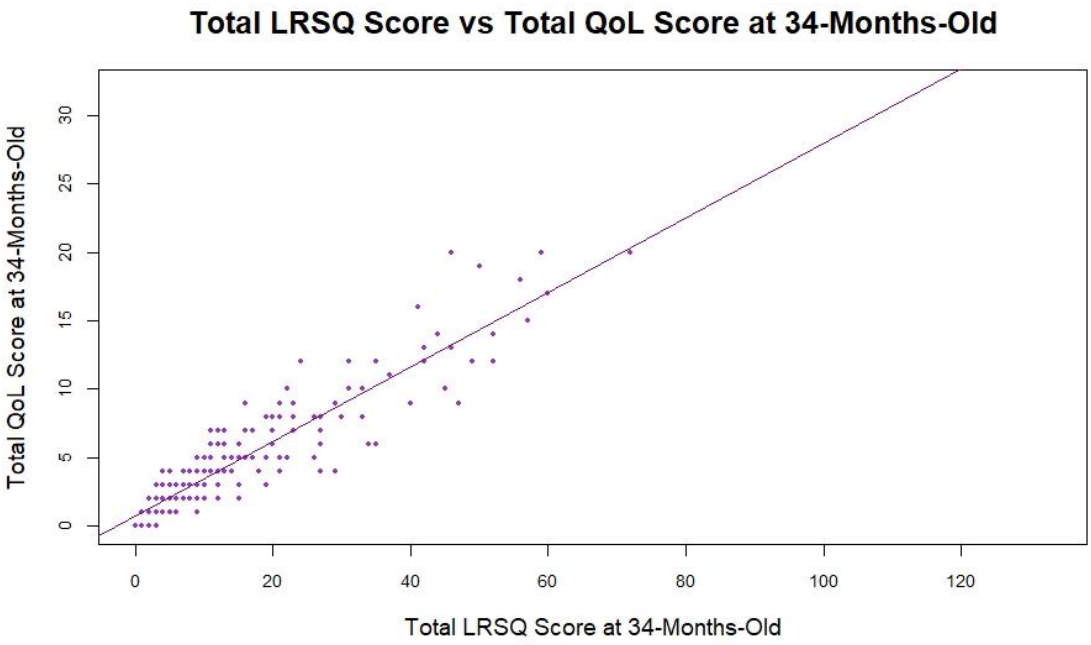


Figure 62: correlation between total LRSQ score and total QoL score at 34-months-old

4.5.6.3 Symptom Prevalence

93.0% (n = 214) of toddlers experienced at least one type of respiratory symptom at 34-months-old. A cold was the most common symptom, as it was experienced by 83.5% (n = 192) of toddlers; noisy breathing that didn't come from the chest was the least common symptom, as it was experienced by 10.4% (n = 24) of toddlers. **Figure 63** demonstrates the prevalence of individual symptoms.

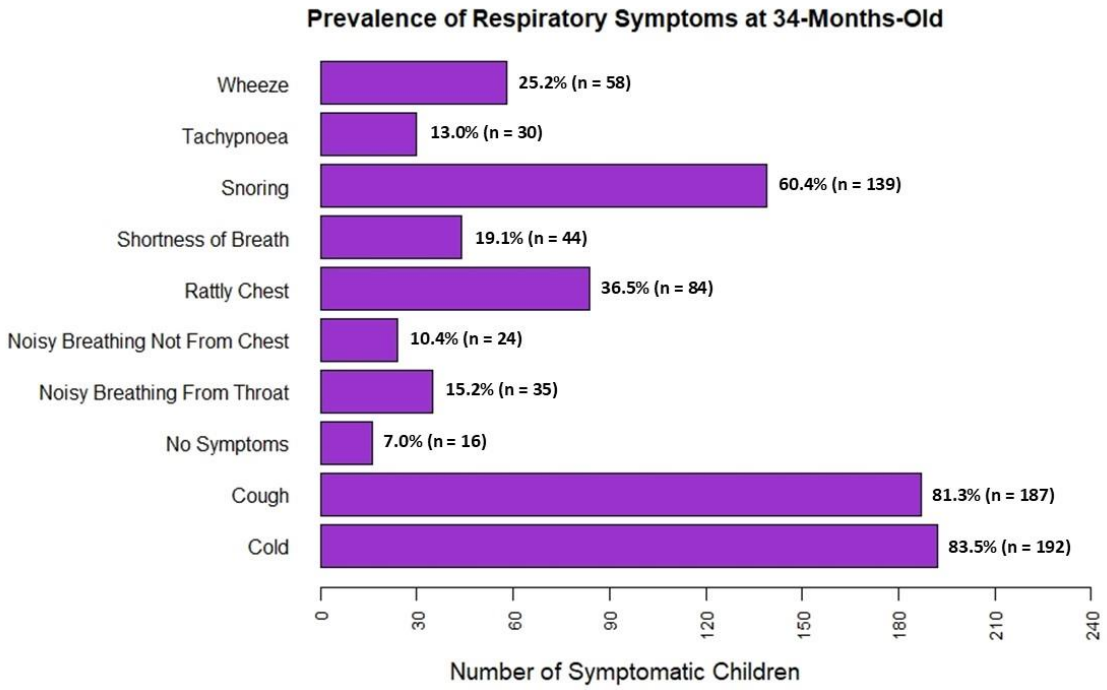


Figure 63: prevalence of respiratory symptoms at 34-months-old

4.5.6.3.1 Impact of Risk Factor Exposure on Symptom Prevalence

4.5.6.3.1.1 Colds

Colds were more likely amongst 'normal birthweight' toddlers (OR = 5.13, 95% CI = 1.18 – 22.34), and toddlers whose mother did not smoke during pregnancy (OR = 5.31, 95% CI = 2.04 – 13.78).

4.5.6.3.1.2 Coughing

Coughing was more likely amongst toddlers who attended nursery (OR = 2.67, 95% CI = 1.33 – 5.35), or did not live with other children (OR = 2.18, 95% CI = 1.09 – 4.39).

4.5.6.3.1.3 No Symptoms

Being asymptomatic was more likely amongst breastfed toddlers (p = 0.044, Fisher's Exact Test).

Asymptomatic toddlers, were less likely to be deprived – since toddlers became 1.23 times more likely to be asymptomatic for every increase in IMD decile (OR = 1.23, 95% CI = 1.02 - 1.50).

4.5.6.3.1.4 Noisy Breathing – From Throat

Noisy breathing from the throat was more likely amongst toddlers who had not been exposed to ETS (OR = 5.28, 95% CI = 1.08 – 25.95). Noisy breathing from the throat was also more likely amongst toddlers who were breastfed for 1-4 months, compared to those who were breastfed for less than 1 month (OR = 6.02, 95% CI = 1.28 - 28.29).

4.5.6.3.1.5 Noisy Breathing – Not From Chest

Noisy breathing that did not come from the chest was more likely amongst toddlers with a co-morbidity (OR = 2.46, 95% CI = 1.02 - 5.93), and toddlers who did not live with other children (OR = 2.95, 95% CI = 1.08 - 8.06).

4.5.6.3.1.6 Rattly Chest

Rattly chests were more likely amongst toddlers who attended nursery (OR = 3.81, 95% CI = 1.88 - 7.75).

4.5.6.3.1.7 Shortness of Breath

SOB was more likely amongst toddlers who did not live with other children (OR = 3.77, 95% CI = 1.86 - 7.66), and toddlers who attended nursery (OR = 2.75, 95% CI = 1.15 - 6.52). SOB was also more likely amongst toddlers who were born to mothers aged less than 25-years-old, compared to those born to mothers aged 25 to 34-years-old (OR = 3.28, 95% CI = 1.12 - 9.64) or more than 35-years-old (OR = 4.73, 95% CI = 1.38 - 16.22).

4.5.6.3.1.8 Snoring

Snoring was more likely amongst toddlers who attended nursery (OR = 2.01, 95% CI = 1.12 – 3.60), or toddlers who did not live with other children (OR = 1.82, 95% CI = 1.06 - 3.11). Snoring was also more likely amongst toddlers who were born to mothers aged less than 25-years-old, compared to those born to mothers aged more than 35-years-old (OR = 4.01, 95% CI = 1.07 - 15.03)

4.5.6.3.1.9 Tachypnoea

Tachypnoea was more likely amongst toddlers with a co-morbidity (OR = 3.82, 95% CI = 1.55 - 9.43), and toddlers who did not live with other children (OR = 2.78, 95% CI = 1.26 - 6.15).

4.5.6.3.1.10 Wheezing

Wheezing was more likely amongst: males (OR = 1.89, 95% CI = 1.05 - 3.41), toddlers who shared a bedroom (OR = 1.99, 95% CI = 1.07 - 3.68), toddlers who attended nursery (OR = 3.47, 95% CI = 1.54 - 7.82), toddlers with a co-morbidity (OR = 2.34, 95% CI = 1.02 – 5.36), and toddlers who did not live with other children (OR = 2.23, 95% CI = 1.22 - 4.08). Wheezing was also more likely amongst toddlers who were born to mothers aged less than 25-years-old, compared to those born to mothers aged more than 35-years-old (OR = 4.448, 95% CI = 1.427 - 13.865).

4.5.6.4 Healthcare Service Usage

At 34-months-old, 22.2% (n = 51) of toddlers were taken to their GP for a respiratory problem. Of these toddlers: 51.0% (n = 26) visited once, 31.4% (n = 16) visited twice, 7.8% (n = 4) visited thrice, 2.0% (n = 1) visited four times, and 7.8% (n = 4) visited five times. 5.2% (n = 12) of toddlers were taken to hospital for a respiratory problem. 75.0% (n = 9) of these toddlers visited once, 16.7% (n = 2) visited twice, and 8.3% (n = 1) visited four times. **Figure 64** presents GP and hospital attendance rates graphically.

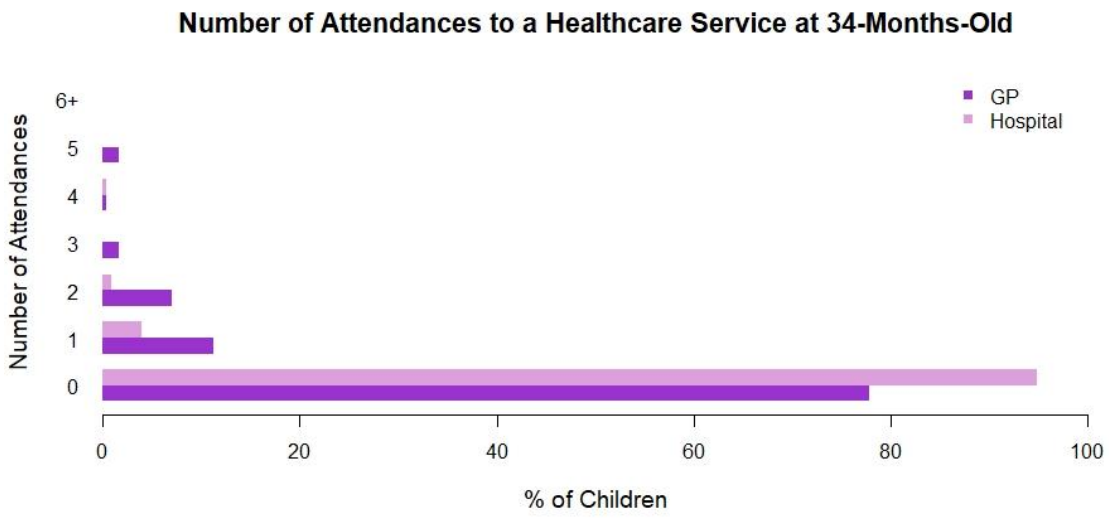


Figure 64: GP and hospital attendance rates at 34-months-old

4.5.6.4.1 Impact of Risk Factor Exposure on Healthcare Service Usage

4.5.6.4.1.1 GP Attendance

Visits to a GP for a respiratory problem were more likely amongst: toddlers who had a family history of atopy (OR = 2.04, 95% CI = 1.09 - 3.80), toddlers who did not live with other children (OR = 2.93, 95% CI = 1.52 - 5.64), and toddlers who were not breastfed (OR = 2.32, 95% CI = 1.18 - 4.55). GP visitation was more likely amongst toddlers with vocationally-educated mothers, compared to those with degree-educated mothers (OR = 2.55, 95% CI = 1.23 - 5.29). Toddlers born to mothers aged less than 25-years-old were also more likely to visit a GP, compared to those born to mothers aged 25 to 34-years-old (OR = 2.97, 95% CI = 1.07 - 8.22) or more than 35-years-old (OR = 4.89, 95% CI = 1.55 - 15.43).

4.5.6.4.1.2 Hospital Attendance

Hospital visitations for a respiratory problem were more likely amongst toddlers who shared a bedroom (OR = 2.96, 95% CI = 1.02 - 8.65), and toddlers who did not live with other children (OR = 3.77, 95% CI = 1.06 - 13.34).

4.5.6.4.2 Total LRSQ Score vs Healthcare Service Usage

At 34-months-old, there was a strong correlation between total LRSQ score and GP attendance rate (r_s = 0.601, p = <0.001). There was a weak correlation between total LRSQ score and hospital attendance rate (r_s = 0.357, p = <0.001). These results suggest the toddlers with the most severe respiratory disease, are slightly more likely to seek medical assistance from a GP, but not necessarily from the hospital. **Figures 65** and **66** show the correlations graphically.

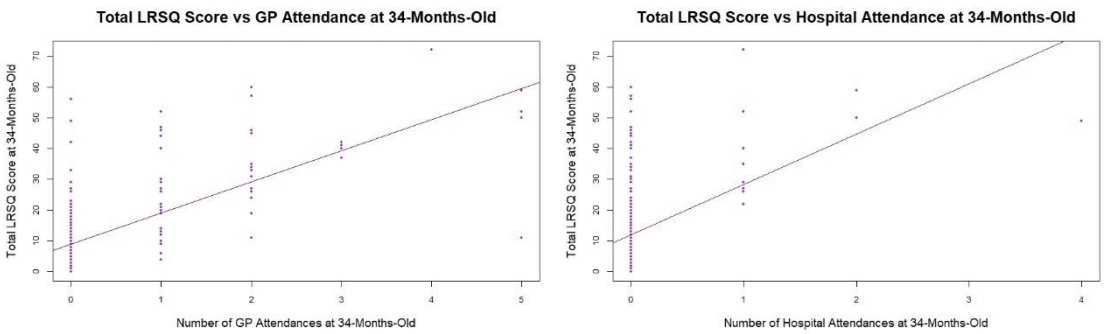


Figure 65: correlation between total LRSQ score and GP attendance rate at 34-months-old
Figure 66: correlation between total LRSQ score and hospital attendance rate at 34-months-old

4.5.7 Questionnaire 7: 40-Months-Old

4.5.7.1 Exposure to Risk Factors

4.5.7.1.1 Nursery Attendance

At 40-months-old, 89.8% (n = 193) of children attended nursery.

4.5.7.1.2 Other Household Children

64.2% (n = 138) of children lived with at least one other child at 40-months-old. 78.8% (n = 108) lived with only one other, 16.8% (n = 23) lived with two others, 2.9% (n = 4) lived with three others, 0.7% (n = 1) lived with four others, and 0.7% (n = 1) lived with five others.

4.5.7.1.3 Bedroom Sharing

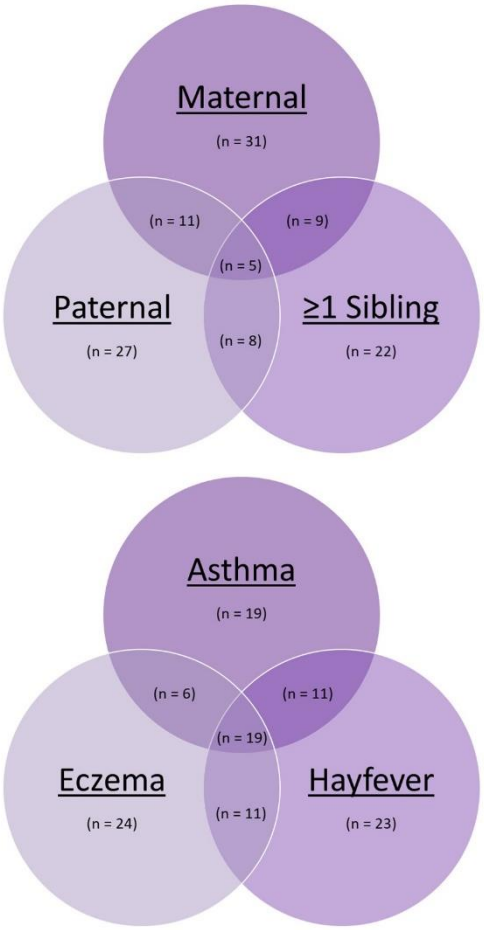
At 40-months-old, 26.5% (n = 57) of children shared a bedroom. 26.3% (n = 15) shared with their parent(s), 80.7% (n = 46) shared with one other child, and 1.8% (n = 1) shared with more than one other child.

4.5.7.1.4 ETS Exposure

13.0% (n = 28) of children were exposed to ETS at 40-months-old. 7.1% (n = 2) were exposed to ETS from inside the home, 96.4% (n = 27) were exposed to ETS from outside of the home, 7.1% (n = 2) were exposed to ETS from inside the car, and 7.1% (n = 2) were exposed to ETS from within another location (e.g. work).

At 40-months-old, the prevalence of ETS exposure amongst children in the LBBS was not significantly different to the prevalence of smoking in either England ($\chi^2 = 0.79$, $p = 0.37$, $df = 1$) or Liverpool ($\chi^2 = 2.63$, $p = 0.11$, $df = 1$) in 2016/17.

4.5.7.1.5 Family History of Atopy



At 40-months-old, 52.6% (n = 113) of children had a family history of atopy.

From those with a family history of atopy: 49.6% (n = 56) had an atopic mother, 45.1% (n = 51) had an atopic father, and 38.9% (n = 44) had at least one atopic sibling. There was a family history of: asthma in 48.7% (n = 55) of these children, hay fever in 56.6% (n = 64), and eczema in 53.1% (n = 60). **Figure 67** shows how familial atopy was inter-related at 40-months-old.

Figure 67: children with a family history of atopy, by relative(s) and disease(s), at 40-months-old

4.5.7.1.6 Co-Morbidities

16.7% (n = 36) of the children had a co-morbid disease at 40-months-old. The respiratory system was the most common co-morbid system at this age, whilst eczema was the most common co-morbidity overall. **Table 29** shows the co-morbidities seen at 40-months-old – as reported by parents, and grouped according to organ system.

Type of Co-Morbidity	Underlying Condition	Frequency
Respiratory (n = 12)	Asthma	7
	Hay Fever	1
	Laryngomalacia	1
	Sleep Apnoea	1
	Viral-Induced Wheeze	1
Cardiac (n = 3)	Congenital Heart Disease	3
Neurological (n = 4)	Cerebral Palsy	1
	Epilepsy	1
	Hypotonia	1
	Spinal Muscular Atrophy	1
Gastrointestinal (n = 1)	Toddler's Diarrhoea	1
Other (n = 23)	Eczema	12
	Allergies	4
	Haemophilia	2
	Autism Spectrum Disorder	1
	Developmental Dysplasia of Hips	1
	Down's Syndrome (Trisomy 21)	1
	Tuberous Sclerosis	1
	Von Willebrand's Disease	1

Table 29: co-morbidities of the LBBS cohort at 40-months-old

4.5.7.2 LRSQ Scores

Measures of central tendency and dispersion for the total LRSQ score, and LRSQ domain scores, at 40-months-old are shown in **Table 30**. The distribution of scores are shown graphically in **Figure 68**.

	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Standard Deviation
Total Score	0	3	7	14	67	11.13	12.35
Domain 1	0	0	1	2	12	1.46	2.01
Domain 2	0	1	2	3	13	2.45	2.52
Domain 3	0	1	3	5	18	3.67	3.34
Domain 4	0	0	0	1	12	0.67	1.43
Domain 5	0	0	0	1	12	0.69	1.59
Domain 6	0	0	0	0	10	0.39	1.23
Domain 7	0	0	0	1	12	0.87	1.76
Domain 8	0	1	2	4	11	2.93	2.48

Table 30: descriptive statistics of the total and domain LRSQ scores at 40-months-old

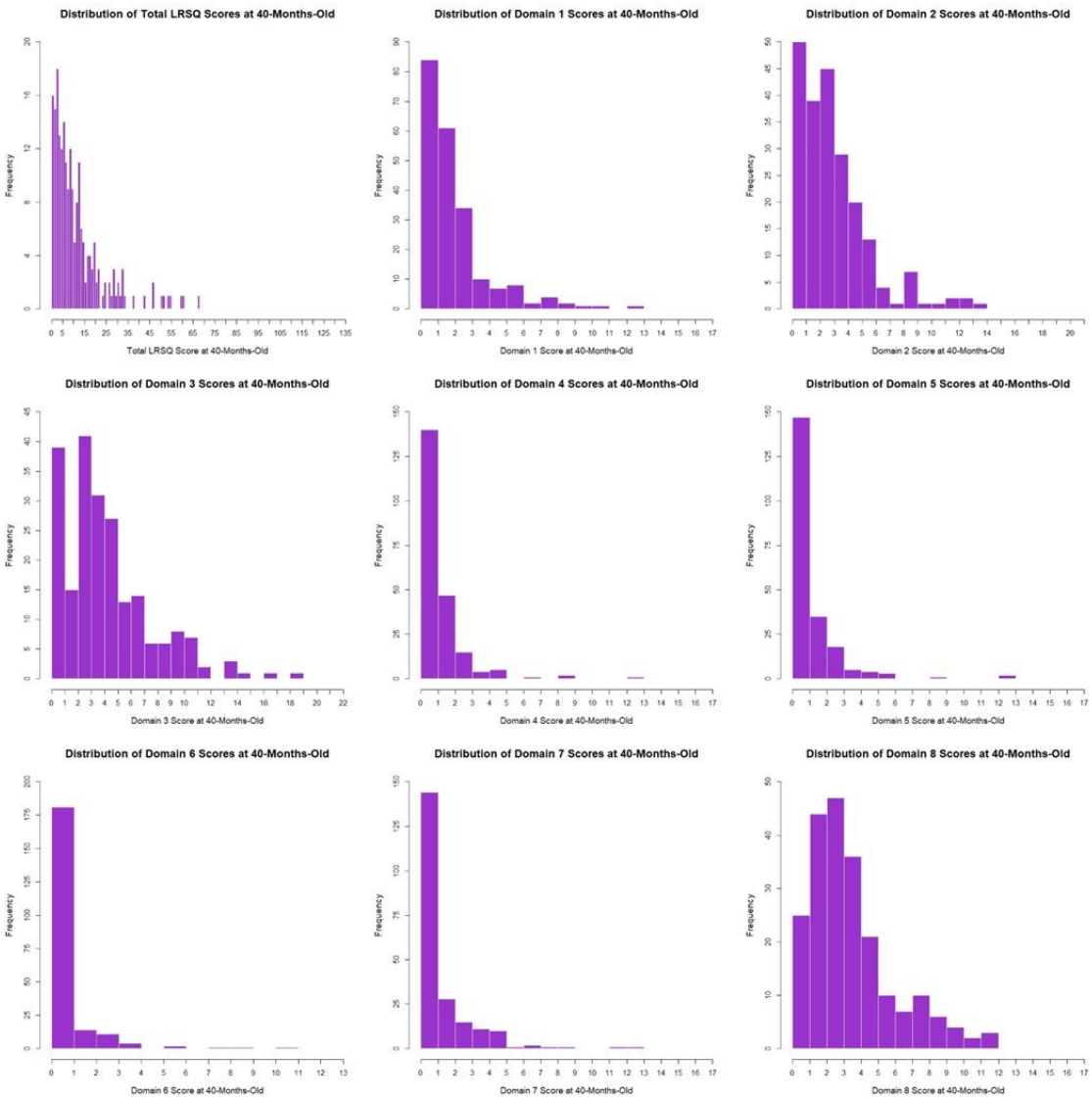


Figure 68: distribution of total and domain LRSQ scores at 40-months-old

4.5.7.2.1 Impact of Risk Factor Exposure on Total LRSQ Score

Total LRSQ scores were higher amongst children who: were born at term (U = 1543, p = 0.050), attended nursery (U = 1332, p = 0.001), had a family history of atopy (U = 4689, p = <0.001), or had a co-morbidity (U = 2202, p = <0.001). They were also higher amongst males (U = 5292, p = 0.010).

There were differences in total LRSQ score between the different levels of deprivation (H = 12.86, p = 0.012, df = 4) and maternal age (H = 12.81, p = 0.002, df = 2). Post-hoc analysis revealed that children living in the second-most deprived IMD quintile scored lower, compared to those living in the most-deprived (p = 0.005) and second-least deprived (p = 0.017) quintiles. Children living in the third-most deprived quintile scored lower than those in the second-least deprived (p = 0.050) quintile. It also revealed that

children born to mothers aged ≥35-years-old scored lower, compared to children born to mothers aged less than 25-years-old (p = 0.013) or aged 25 to 34-years-old (p = 0.001).

4.5.7.2.2 Impact of Risk Factor Exposure on LRSQ Domain Scores

4.5.7.2.2.1 Domain 1

Domain 1 scores were higher amongst males (U = 5486, p = 0.024), and those whose mothers did not smoke during pregnancy (U = 1921, p = 0.034). They were also higher amongst children who: attended nursery (U = 1286, p = <0.001), had a co-morbidity (U = 2962, p = <0.001), or had a family history of atopy (U = 5037, p = 0.001).

There were differences in domain 1 score amongst breastfed children, depending on how long they were breastfed for (H = 9.18, p = 0.010, df = 2). Post-hoc analysis revealed that children who were breastfed for less than 1 month scored lower, compared to those who were breastfed for 1-4 months (p = 0.011) or for more than 4 months (p = 0.007).

4.5.7.2.2.2 Domain 2

Domain 2 scores were higher amongst children who: were exposed to ETS (U = 2740, p = 0.008), had a family history of atopy (U = 4872, p = <0.001), attended nursery (U = 1316, p = 0.001), or had a co-morbidity (U = 2624, p = <0.001).

There were differences in domain 2 score between the different levels of maternal age (H = 7.04, p = 0.030, df = 2). Post-hoc analysis revealed that children born to mothers aged ≥35-years-old scored lower, compared to children born to mothers aged less than 25-years-old (p = 0.043) or aged 25 to 34-years-old (p = 0.026).

4.5.7.2.2.3 Domain 3

Domain 3 scores were higher amongst males (U = 4785, p = <0.001). They were also higher amongst children who: had a family history of atopy (U = 4902, p = 0.001), had a co-morbidity (U = 2443, p = <0.001), or attended nursery (U = 1514, p = 0.009).

There were differences in domain 3 score between the different levels of deprivation (H = 12.29, p = 0.015, df = 4) and maternal age (H = 16.74, p = <0.001, df = 2). Post-hoc analysis revealed that chilldren living in the most-deprived IMD quintile scored higher

than those living in the second-most deprived quintile (p = 0.004). It also revealed that children born to mothers aged ≥35-years-old scored lower, compared to children born to mothers aged less than 25-years-old (p = 0.019) or aged 25 to 34-years-old (p = <0.001).

4.5.7.2.2.4 Domain 4

Domain 4 scores were higher amongst the children with: a family history of atopy (U = 5225, p = 0.001), or a co-morbidity (U = 2990, p = <0.001).

There were differences in domain 4 score between the different levels of maternal age (H = 7.21, p = 0.027, df = 2). Post-hoc analysis revealed that children born to mothers aged ≥35-years-old scored lower, compared to children born to mothers aged less than 25-years-old (p = 0.008) or aged 25 to 34-years-old (p = 0.035).

4.5.7.2.2.5 Domain 5

Domain 5 scores were higher amongst children who: had a family history of atopy (U = 5130, p = 0.001), had a co-morbidity (U = 2648, p = <0.001), or were not breastfed (U = 4505, p = 0.047).

There were differences in domain 5 score between the different levels of maternal age (H = 8.73, p = 0.013, df = 2). Post-hoc analysis revealed that children born to mothers aged ≥35-years-old scored lower than children born to mothers aged less than 25-years-old (p = 0.007).

4.5.7.2.2.6 Domain 6

Domain 6 scores were higher amongst children who: shared a bedroom (U = 4648, p = 0.010), had a co-morbidity (U = 3427, p = 0.001), or were not breastfed (U = 4392, p = 0.005). They were also higher amongst those whose mother smoked during pregnancy (U = 2135, p = 0.049).

4.5.7.2.2.7 Domain 7

Domain 7 scores were higher amongst children who: attended nursery (U = 1660, p = 0.015), or had a co-morbidity (U = 2974, p = <0.001).

There were differences in domain 7 score between the different levels of maternal age (H = 10.46, p = 0.005, df = 2). Post-hoc analysis revealed that children born to mothers

aged ≥35-years-old scored lower, compared to children born to mothers aged less than 25-years-old (p = 0.031) or aged 25 to 34-years-old (p = <0.001).

4.5.7.2.2.8 Domain 8

Domain 8 scores were higher amongst children who were: male (U = 5370, p = 0.015), born at term (U = 1437, p = 0.018), exposed to ETS (U = 2635, p = 0.004), or not breastfed (U = 4370, p = 0.045). They were also higher amongst children whose mothers smoked during pregnancy (U = 1673, p = 0.004), or were exposed to ETS during pregnancy (U = 3098, p = 0.018). Nursery attendance (U = 1593, p = 0.018), having a co-morbidity (U = 2288, p = <0.001), or having a family history of atopy (U = 5112, p = 0.003) resulted in higher domain 8 scores too.

There were differences in domain 8 score between the different levels of deprivation (H = 11.01, p = 0.026, df = 4) and maternal age (H = 14.73, p = 0.001, df = 2). Post-hoc analysis revealed that children living in the most-deprived IMD quintile scored higher than those living in the second-most deprived quintile (p = 0.002). It also revealed that children born to mothers aged ≥35-years-old scored lower, compared to children born to mothers aged less than 25-years-old (p = 0.031) or aged 25 to 34-years-old (p = <0.001).

4.5.7.2.3 Total LRSQ Score vs Total QoL Score

There was a strong positive correlation between a child's total LRSQ score, and their total QoL score (r_s = 0.907, p = <0.001). **Figure 69** shows the correlation graphically. A higher total LRSQ score is more strongly correlated with a poor QoL for parents, than with a poor QoL for children (r_s = 0.805, p = <0.001 vs r_s = 0.745, p = <0.001). Children who regularly suffer with respiratory symptoms, and their parents, therefore experience a worse QoL.

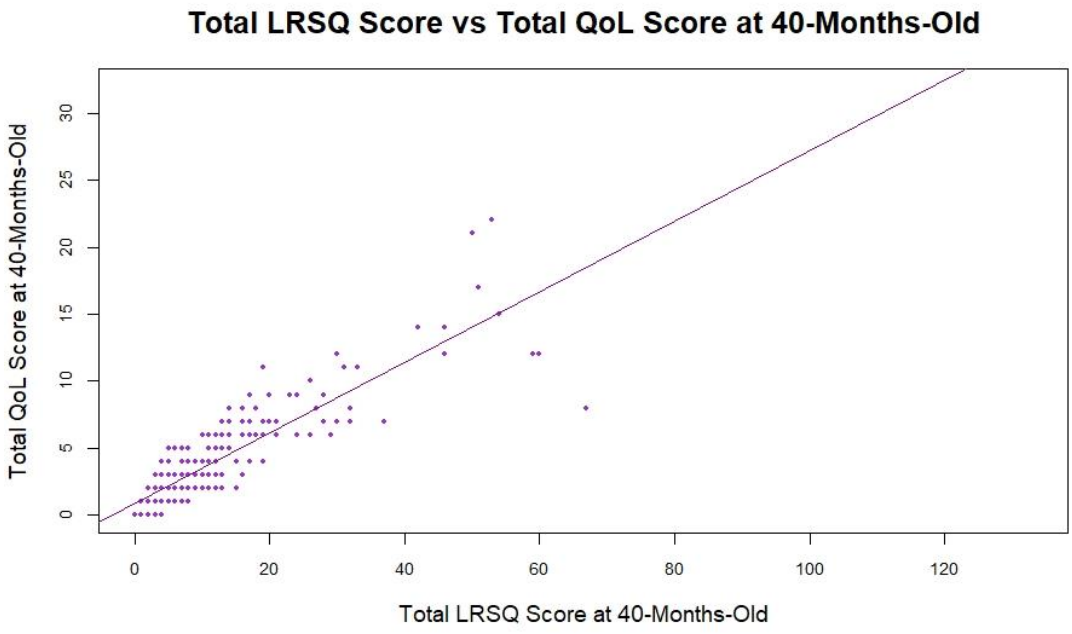


Figure 69: correlation between total LRSQ score and total QoL score at 40-months-old

4.5.7.3 Symptom Prevalence

92.6% (n = 199) of children experienced at least one type of respiratory symptom at 40-months-old. A cold was the most common symptom, as it was experienced by 81.9% (n = 176) of children; tachypnoea and noisy breathing that didn't come from the chest were the least common symptoms, as they were both experienced by 7.4% (n = 16) of children. **Figure 70** demonstrates the prevalence of individual symptoms.

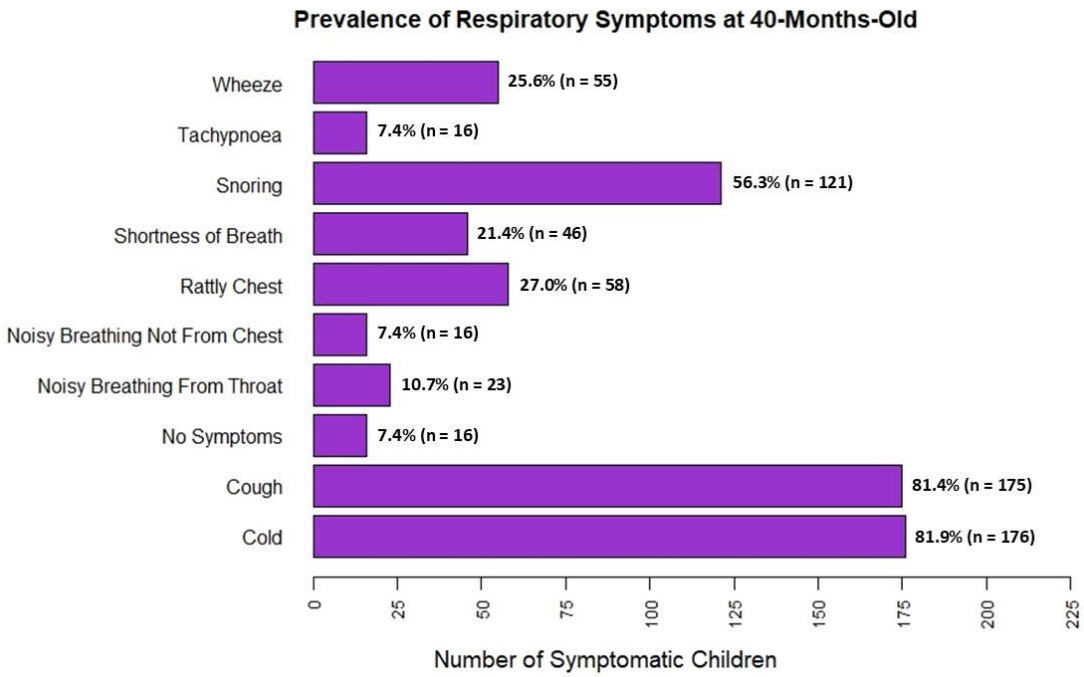


Figure 70: prevalence of respiratory symptoms at 40-months-old

4.5.7.3.1 Impact of Risk Factor Exposure on Symptom Prevalence

4.5.7.3.1.1 Colds

Colds were more likely amongst: children whose mother was exposed to ETS during pregnancy (OR = 8.24, 95% CI = 1.12 – 60.55), males (OR = 2.35, 95% CI = 1.04 – 5.27), singletons (OR = 15.74, 95% CI = 1.87 – 132.26), and children born at term (OR = 4.33, 95% CI = 1.49 – 12.59). Colds were more likely amongst children who were born to mothers aged 25 to 35-years-old, compared to those born to mothers aged more than 35-years-old (OR = 4.68, 95% CI = 1.89 - 11.63). Children who were breastfed for more than 4 months were also more likely to have colds, compared to those who were breastfed for less than 1 month (OR = 3.15, 95% CI = 1.22 - 8.14).

4.5.7.3.1.2 Coughing

Coughing was more likely amongst: males (OR = 3.69, 95% CI = 1.62 – 8.41), children born at term (OR = 2.98, 95% CI = 1.02 – 8.70), and children who attended nursery (OR = 3.38, 95% CI = 1.26 – 9.05). Coughing was also more likely amongst children who were born to mothers aged 25 to 34-years-old, compared to those born to mothers aged more than 35-years-old (OR = 2.30, 95% CI = 1.07 – 4.92).

4.5.7.3.1.3 No Symptoms

Being asymptomatic was more likely amongst: ‘low birthweight’ children (OR = 5.26, 95% CI = 1.31 – 21.07), and twins (OR = 16.84, 95% CI = 2.33 – 121.77). Being asymptomatic was more likely amongst children who were born to mothers aged 25 to 34-years-old, compared to those born to mothers aged more than 35-years-old (OR = 4.68, 95% CI = 1.89 – 11.63). Children who were breastfed for less than 1 month were also more likely to be asymptomatic, compared to those who were breastfed for more than 4 months (OR = 5.21, 95% CI = 1.21 - 22.37).

4.5.7.3.1.4 Noisy Breathing – From Throat

Noisy breathing from the throat was more likely amongst children who shared a bedroom (OR = 2.89, 95% CI = 1.22 – 6.82), and children who were not breastfed (OR = 2.63, 95% CI = 1.11 – 6.27).

4.5.7.3.1.5 Noisy Breathing – Not From Chest

Noisy breathing that did not come from the chest was more likely amongst children who had a co-morbidity (OR = 6.39, 95% CI = 2.45 - 16.69), and children who were not breastfed (OR = 2.95, 95% CI = 1.16 - 7.54).

4.5.7.3.1.6 Rattly Chest

Rattly chests were more likely amongst: males (OR = 2.26, 95% CI = 1.25 - 4.07), children with a family history of atopy (OR = 2.43, 95% CI = 1.33 - 4.45), children who attended nursery (OR = 5.99, 95% CI = 1.14 - 31.57), and children with a co-morbidity (OR = 3.66, 95% CI = 1.84 - 7.28).

4.5.7.3.1.7 Shortness of Breath

SOB was more likely amongst children who were not breastfed (OR = 2.28, 95% CI = 1.17 – 4.44), and children with a co-morbidity (OR = 4.41, 95% CI = 2.17 – 8.94). SOB was more likely amongst children who were born to mothers aged 25 to 34-years-old, compared to those born to mothers aged more than 35-years-old (OR = 3.05, 95% CI = 1.26 - 7.41). Children who were breastfed for 1-4 months were also more likely to have SOB, compared to those who were breastfed for less than 1 month (OR = 4.45, 95% CI = 1.26 - 15.75).

4.5.7.3.1.8 Snoring

Snoring was more likely amongst children whose mothers were exposed to ETS during pregnancy (OR = 3.20, 95% CI = 1.42 – 7.23), and children who were exposed to ETS (OR = 4.64, 95% CI = 1.80 – 11.96).

4.5.7.3.1.9 Tachypnoea

Tachypnoea was more likely amongst children who were not breastfed (OR = 3.76, 95% CI = 1.40 – 10.07), and children with a co-morbidity (OR = 4.33, 95% CI = 1.60 – 11.73). Tachypnoea was also more likely amongst children with school-educated mothers, compared to those with degree-educated mothers (OR = 5.48, 95% CI = 1.79 - 16.79).

4.5.7.3.1.10 Wheezing

Wheezing was more likely amongst children with a family history of atopy (OR = 2.29, 95% CI = 1.26 – 4.17), and children with a co-morbidity (OR = 5.47, 95% CI = 2.70 – 11.10). Wheezing was more likely amongst children who were born to

mothers aged 25 to 34-years-old, compared to those born to mothers aged more than 35-years-old (OR = 2.94, 95% CI = 1.36 - 6.33). Children who were breastfed for 1-4 months were also more likely to wheeze, compared to those who were breastfed for less than 1 month (OR = 2.82, 95% CI = 1.02 - 7.85) or for more than 4 months (OR = 2.55, 95% CI = 1.05 - 6.22). Children who wheezed, were more likely to be deprived too – since children became 1.15 times less likely to wheeze for every increase in IMD decile (OR = 1.15, 95% CI = 1.0 - 1.33).

4.5.7.4 Healthcare Service Usage

At 40-months-old, 11.6% (n = 25) of children were taken to their GP for a respiratory problem. Of these children: 64.0% (n = 16) visited once, 24.0% (n = 6) visited twice, 8.0% (n = 2) visited thrice, and 4.0% (n = 1) visited five times. 5.1% (n = 11) of children were taken to hospital for a respiratory problem. 81.8% (n = 9) of these children visited once, 9.1% (n = 1) visited twice, and 9.1% (n = 1) visited thrice. **Figure 71** presents GP and hospital attendance rates graphically.

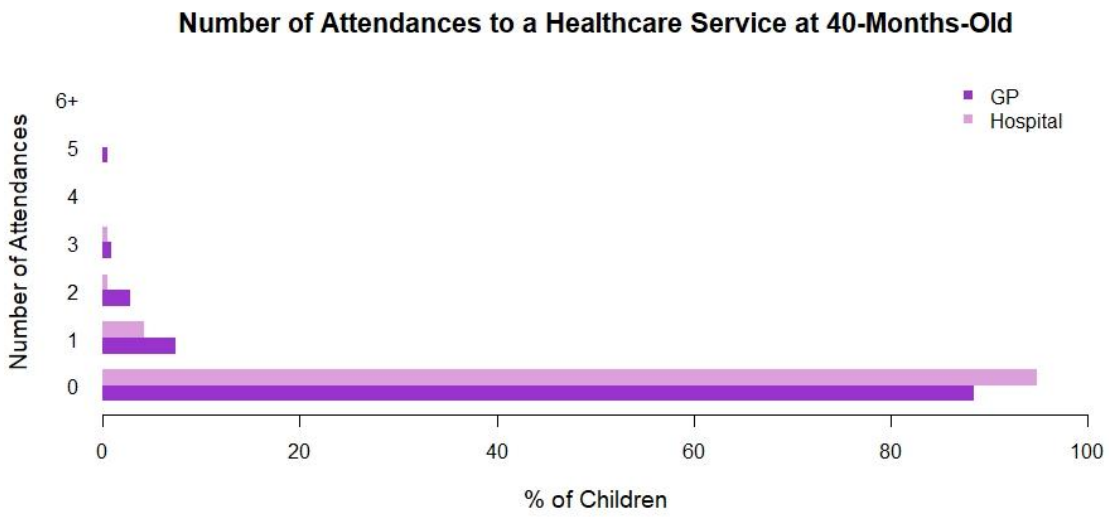


Figure 71: GP and hospital attendance rates at 40-months-old

4.5.7.4.1 Impact of Risk Factor Exposure on Healthcare Service Usage

4.5.7.4.1.1 GP Attendance

Visits to a GP for a respiratory problem were more likely amongst children with a co-morbidity (OR = 3.61, 95% CI = 1.57 - 8.29). GP visitation was more likely amongst

children who were born to mothers aged less than 25-years-old, compared to those born to mothers aged 25 to 34-years-old (OR = 4.49, 95% CI = 1.07 - 18.79). Children who were breastfed for 1-4 months were also more likely to visit a GP, compared to those who were breastfed for less than 1 month (OR = 16.45, 95% CI = 2.54 - 106.40) or more than 4 months (OR = 3.63, 95% CI = 1.32 - 9.94).

4.5.7.4.1.2 Hospital Attendance

Hospital visitations for a respiratory problem were more likely amongst females (OR = 4.19, 95% CI = 1.06 - 16.61), and children with a co-morbidity (OR = 6.37, 95% CI = 2.09 - 19.39).

4.5.7.4.2 Total LRSQ Score vs Healthcare Service Usage

At 40-months-old, there was a moderate correlation between total LRSQ score and GP attendance rate (r_s = 0.526, p = <0.001). There was a weak correlation between total LRSQ score and hospital attendance rate (r_s = 0.342, p = <0.001). These results suggest the children with the most severe respiratory disease, are not necessarily the ones who are more likely to seek medical assistance. **Figures 72** and **73** show the correlations graphically.

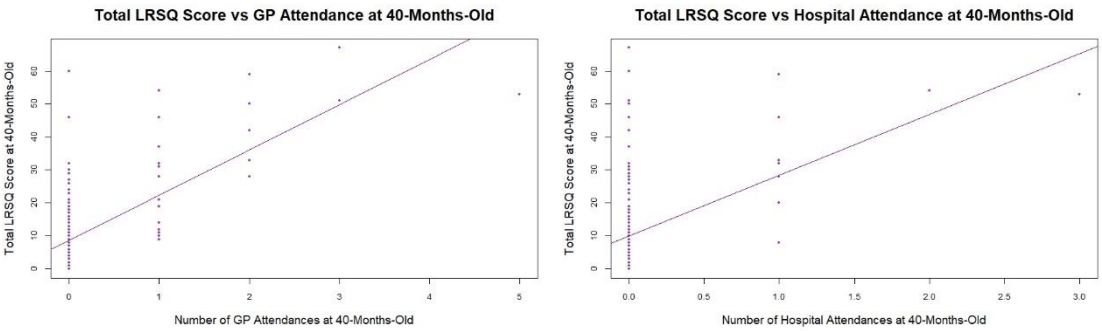


Figure 72: correlation between total LRSQ score and GP attendance rate at 40-months-old
Figure 73: correlation between total LRSQ score and hospital attendance rate at 40-months-old

4.5.8 Questionnaire 8: 46-Months-Old

4.5.8.1 Exposure to Risk Factors

4.5.8.1.1 Nursery Attendance

At 46-months-old, 98.4% (n = 246) of children attended nursery.

4.5.8.1.2 Other Household Children

68.8% (n = 155) of children lived with at least one other child at 46-months-old. 73.8% (n = 127) lived with only one other, 21.5% (n = 37) lived with two others, 4.1% (n = 7) lived with three others, and 0.6% (n = 1) lived with four others.

4.5.8.1.3 Bedroom Sharing

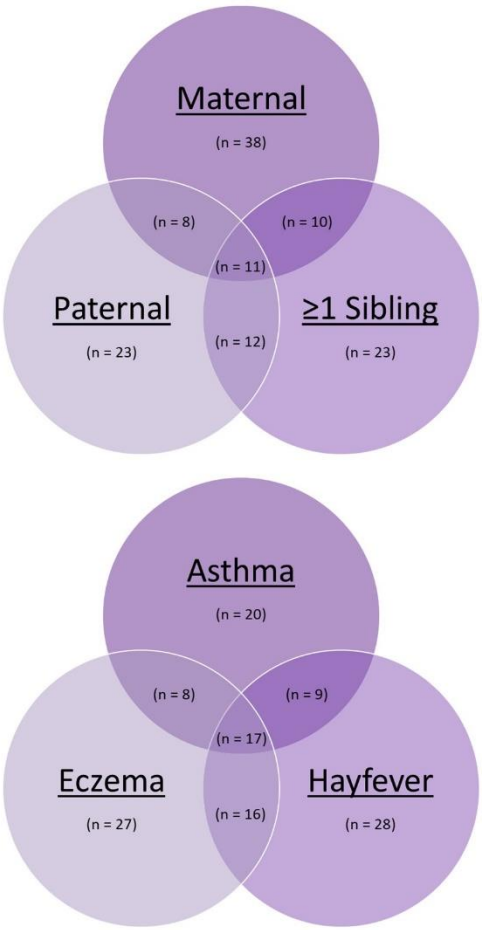
At 46-months-old, 32.4% (n = 81) of children shared a bedroom. 33.3% (n = 27) shared with their parent(s), 71.6% (n = 58) shared with one other child, and 2.5% (n = 2) shared with more than one other child.

4.5.8.1.4 ETS Exposure

16.4% (n = 41) of children were exposed to ETS at 46-months-old. 2.4% (n = 1) were exposed to ETS from inside the home, 97.6% (n = 40) were exposed to ETS from outside of the home, 4.9% (n = 2) were exposed to ETS from inside the car, and 7.3% (n = 3) were exposed to ETS from within another location (e.g. work).

At 46-months-old, the prevalence of ETS exposure amongst children in the LBBS was not significantly different to the prevalence of smoking in either England ($\chi^2 = 0.61$, $p = 0.43$, $df = 1$) or Liverpool ($\chi^2 = 0.33$, $p = 0.57$, $df = 1$) in 2017/18.

4.5.8.1.5 Family History of Atopy



At 46-months-old, 50.0% (n = 125) of children had a family history of atopy.

From those with a family history of atopy: 53.6% (n = 67) had an atopic mother, 43.2% (n = 54) had an atopic father, and 44.8% (n = 56) had at least one atopic sibling. There was a family history of: asthma in 43.2% (n = 54) of these children, hay fever in 56.0% (n = 70), and eczema in 54.4% (n = 68). **Figure 74** shows how familial atopy was inter-related at 46-months-old.

Figure 74: children with a family history of atopy, by relative(s) and disease(s), at 46-months-old

4.5.8.1.6 Co-Morbidities

15.6% (n = 39) of the children had a co-morbid disease at 46-months-old. The respiratory system was the most common co-morbid system at this age, whilst asthma and eczema were the most common co-morbidities overall. **Table 31** shows the co-morbidities seen at 46-months-old – as reported by parents, and grouped according to organ system.

Type of Co-Morbidity	Underlying Condition	Frequency
Respiratory (n = 14)	Asthma	9
	Viral-Induced Wheeze	3
Cardiac (n = 1)	Congenital Heart Disease	1
Renal (n = 1)	Vesicoureteral Reflux	1
Neurological (n = 5)	3rd Nerve Palsy	1
	Brain Tumour	1
	Hydrocephalus	1
	"Seizures"	1
	Spinal Muscular Atrophy	1
Other (n = 24)	Eczema	9
	Allergies	6
	Autism Spectrum Disorder	2
	Developmental Dysplasia of Hips	1
	Down's Syndrome (Trisomy 21)	1
	Glue Ear	1
	Haemophilia	1
	"Complications from Mastoiditis"	1
	Tuberous Sclerosis	1

Table 31: co-morbidities of the LBBS cohort at 46-months-old

4.5.8.2 LRSQ Scores

Measures of central tendency and dispersion for the total LRSQ score, and LRSQ domain scores, at 46-months-old are shown in **Table 32**. The distribution of scores are shown graphically in **Figure 75**.

	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Standard Deviation
Total Score	0	4	8	16	97	12.62	13.78
Domain 1	0	0	1	2	13	1.75	2.12
Domain 2	0	1	2	4	16	2.69	2.67
Domain 3	0	2	3	6	19	3.94	3.44
Domain 4	0	0	0	1	11	0.70	1.53
Domain 5	0	0	0	1	16	0.86	1.99
Domain 6	0	0	0	0	10	0.58	1.56
Domain 7	0	0	0	1	12	0.96	1.75
Domain 8	0	1	3	4	13	3.18	2.51

Table 32: descriptive statistics of the total and domain LRSQ scores at 46-months-old

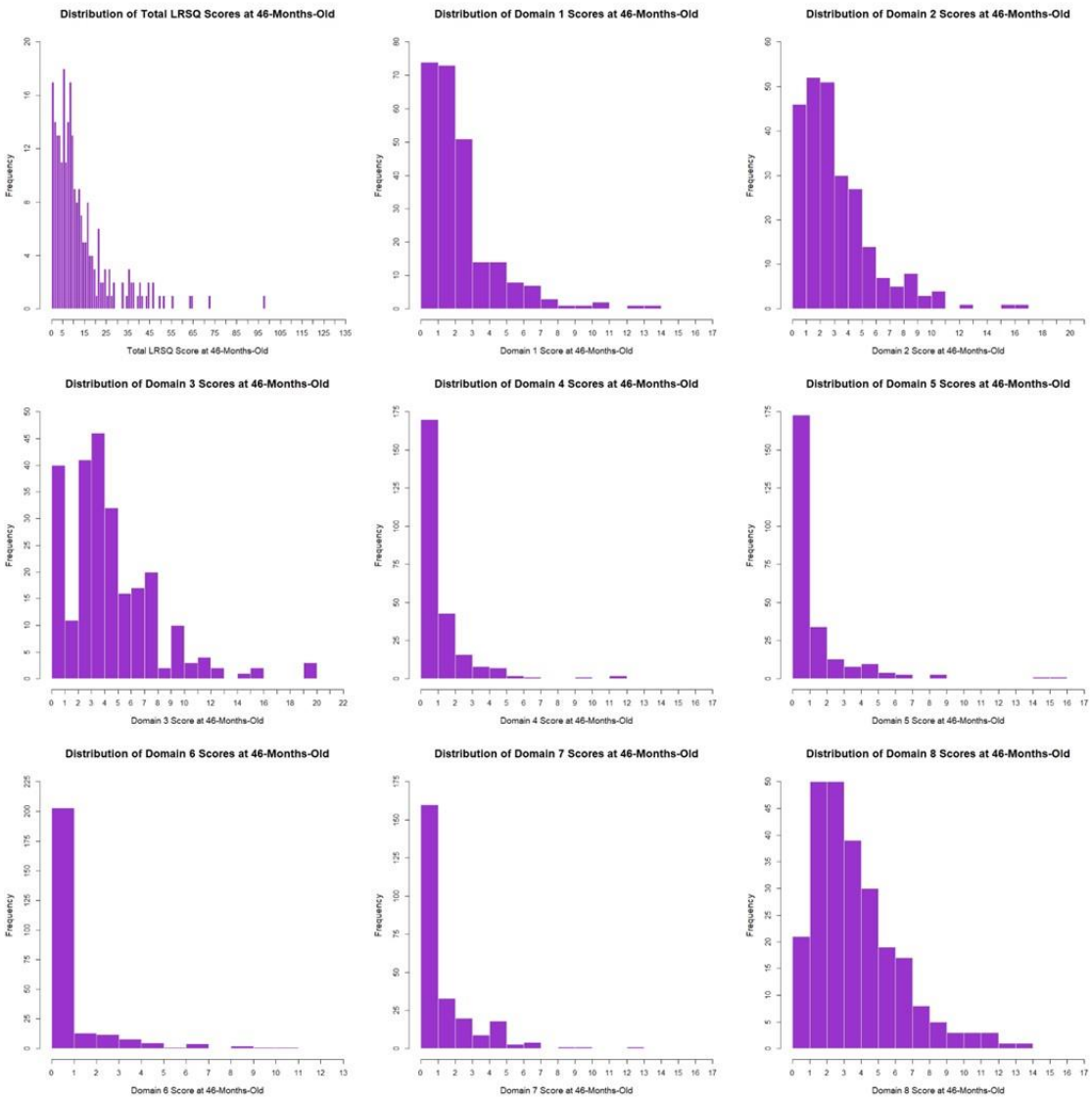


Figure 75: distribution of total and domain LRSQ scores at 46-months-old

4.5.8.2.1 Impact of Risk Factor Exposure on Total LRSQ Score

Total LRSQ scores were higher amongst children who were born prematurely (U = 2375, p = 0.006), or had a co-morbidity (U = 2958, p = <0.001).

4.5.8.2.2 Impact of Risk Factor Exposure on LRSQ Domain Scores

4.5.8.2.2.1 Domain 1

Domain 1 scores were higher amongst children who: had a co-morbidity (U = 3426, p = <0.001), or were born prematurely (U = 2388, p = 0.005).

There were differences in domain 1 score between the different levels of maternal education (H = 6.01, p = 0.050, df = 2) and deprivation (H = 11.55, p = 0.021, df = 4). Post-hoc analysis revealed that children with a degree-educated mother scored lower, compared to those with a school (p = 0.036) or vocationally-educated mother

(p = 0.014). It also revealed that children living in the third-most deprived IMD quintile scored lower, compared to those living in the most-deprived (p = 0.046), least-deprived (p = 0.038) and the second-least deprived (p = 0.003) quintiles. Children living in the second-least deprived IMD quintile scored higher than those living in the second-most deprived quintile (p = 0.030).

4.5.8.2.2.2 Domain 2

Domain 2 scores were higher amongst children who: had a family history of atopy (U = 10773, p = 0.008), were born prematurely (U = 2248, p = 0.002), or had a co-morbidity (U = 4065, p = <0.001).

There were differences in domain 2 score between the different levels of maternal age (H = 13.25, p = 0.001, df = 2). Post-hoc analysis revealed that children born to mothers aged less than 25-years-old scored higher, compared to children born to mothers aged ≥35-years-old (p = <0.001) and mothers aged 25 to 34-years-old (p = 0.001).

4.5.8.2.2.3 Domain 3

Domain 3 scores were higher amongst children who were born prematurely (U = 2468, p = 0.011), or male (U = 11127, p = 0.029). They were also higher amongst those who: attended nursery (U = 385, p = 0.046), or had a co-morbidity (U = 3865, p = <0.001).

4.5.8.2.2.4 Domain 4

Domain 4 scores were higher amongst children with a family history of atopy (U = 11574, p = 0.047), or a co-morbidity (U = 3743, p = <0.001). They were also higher amongst males (U = 11402, p = 0.026), those who were not breastfed (U = 9270, p = 0.027), and children whose mothers did not smoke during pregnancy (U = 9270, p = 0.009).

4.5.8.2.2.5 Domain 5

Domain 5 scores were higher amongst children who were: male (U = 10324, p = <0.001), a twin (U = 780, p = 0.029), or suffering from a co-morbidity (U = 3122, p = <0.001). They were also higher amongst children with a family history of atopy (U = 11304, p = 0.018), or whose mothers did not smoke during pregnancy (U = 2978, p = 0.048).

There were differences in domain 5 score between the different levels of maternal age (H = 11.35, p = 0.003, df = 2). Post-hoc analysis revealed that children born to mothers aged less than 25-years-old scored higher, compared to children born to mothers aged ≥35-years-old (p = 0.001) and mothers aged 25 to 34-years-old (p = 0.022).

4.5.8.2.2.6 Domain 6

Domain 6 scores were higher amongst children with a co-morbidity (U = 4560, p = <0.001).

4.5.8.2.2.7 Domain 7

Domain 7 scores were higher amongst children who were born: prematurely (U = 2410, p = 0.002), as a twin (U = 798, p = 0.042), or at a 'low birthweight' (U = 1662, p = 0.035). They were also higher amongst those who: did not share a bedroom (U = 10119, p = 0.020), or had a co-morbidity (U = 4528, p = <0.001).

There were differences in domain 7 score between the different levels of deprivation (H = 12.77, p = 0.012, df = 4). Post-hoc analysis revealed that children living in the third-most deprived IMD quintile scored lower, compared to those living in the most-deprived (p = 0.002), second-most deprived (p = 0.028), least-deprived (p = 0.012) and the second-least deprived (p = 0.010) quintiles.

4.5.8.2.2.8 Domain 8

Domain 8 scores were higher amongst children who: had a family history of atopy (U = 11145, p = 0.029), had a co-morbidity (U = 4167, p = <0.001), or were born prematurely (U = 2243, p = 0.002). They were also higher amongst males (U = 11186, p = 0.034).

There were differences in domain 8 score between the different levels of maternal age (H = 8.56, p = 0.014, df = 2). Post-hoc analysis revealed that children born to mothers aged less than 25-years-old scored higher, compared to children born to mothers aged ≥35-years-old (p = 0.003) and mothers aged 25 to 34-years-old (p = 0.013).

4.5.8.2.3 Total LRSQ Score vs Total QoL Score

There was a strong positive correlation between a child's total LRSQ score, and their total QoL score (r_s = 0.889, p = <0.001). **Figure 76** shows the correlation graphically. A higher total LRSQ score is more strongly correlated with a poor QoL for parents, than

with a poor QoL for children (r_s = 0.802, p = <0.001 vs r_s = 0.745, p = <0.001). Children who regularly suffer with respiratory symptoms, and their parents, therefore experience a worse QoL.

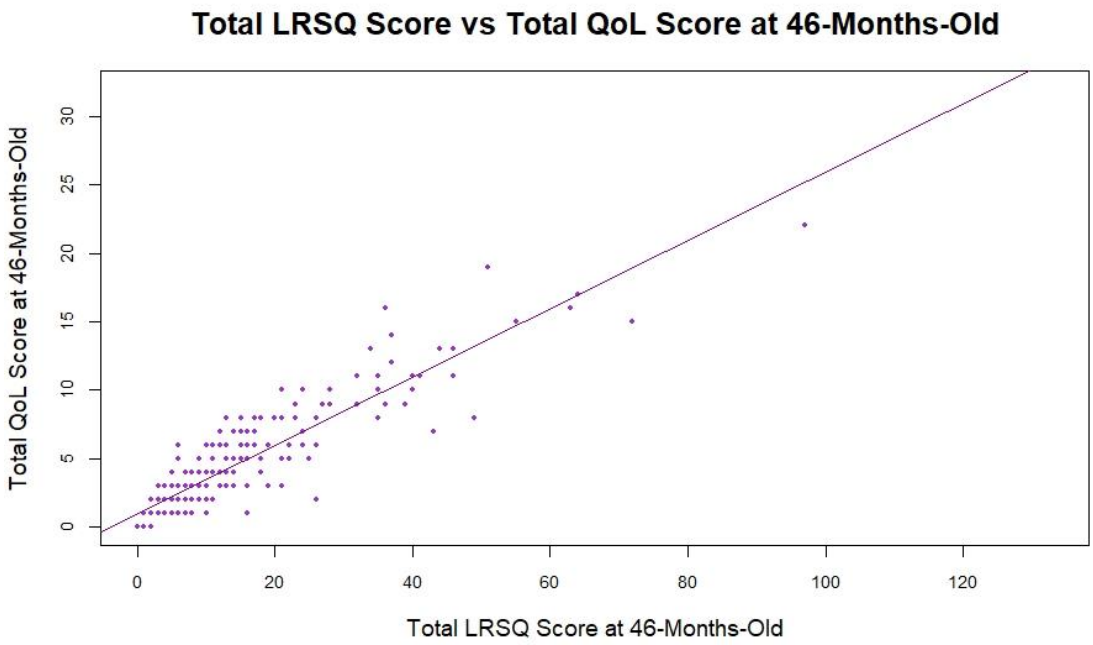


Figure 76: correlation between total LRSQ score and total QoL score at 46-months-old

4.5.8.3 Symptom Prevalence

93.2% (n = 233) of children experienced at least one type of respiratory symptom at 46-months-old. A cold was the most common symptom, as it was experienced by 84.0% (n = 210) of children; tachypnoea was the least common symptom, as it was experienced by 9.6% (n = 24) of children. **Figure 77** demonstrates the prevalence of individual symptoms.

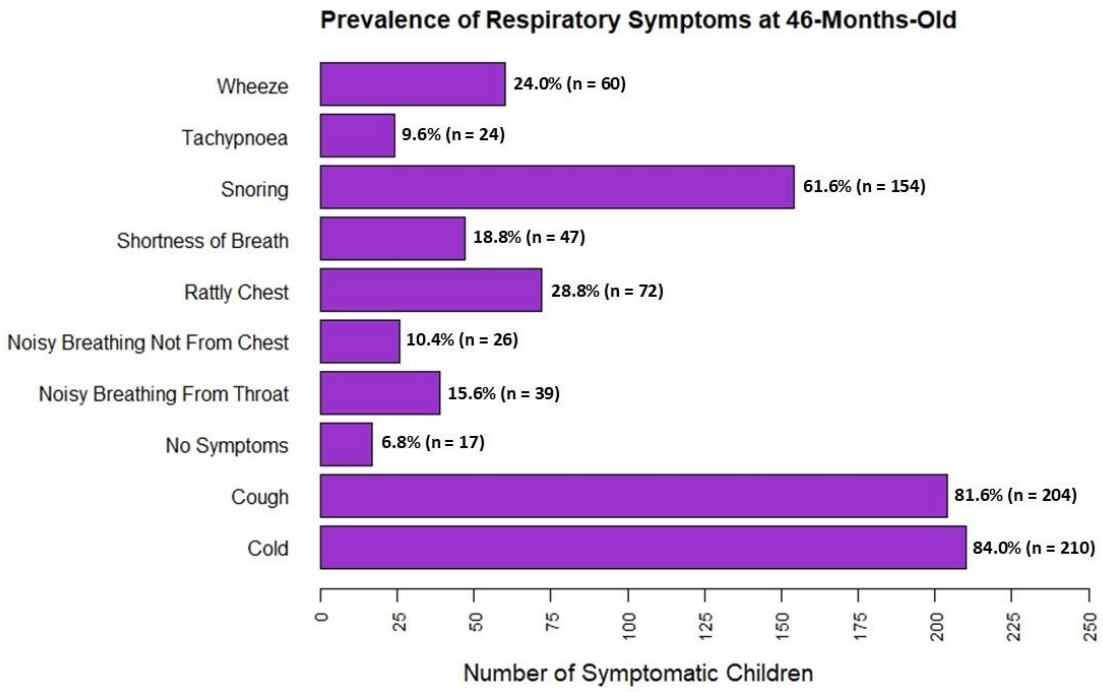


Figure 77: prevalence of respiratory symptoms at 46-months-old

4.5.8.3.1 Impact of Risk Factor Exposure on Symptom Prevalence

4.5.8.3.1.1 Colds

Colds were more likely amongst males (OR = 2.08, 95% CI = 1.07 – 4.04). Colds were more likely amongst children with school-educated mothers, compared to those with degree-educated mothers (OR = 4.00, 95% CI = 1.24 - 12.90). Children who were born to a mother aged more than 35-years-old were also more likely to have colds, compared to those born to mothers aged less than 25-years-old (OR = 3.57, 95% CI = 1.17 – 10.94)

4.5.8.3.1.2 Coughing

Coughing was more likely amongst males (OR = 2.26, 95% CI = 1.19 – 4.28), and children with a co-morbidity (OR = 12.42, 95% CI = 1.55 – 99.55).

4.5.8.3.1.3 No Symptoms

Being asymptomatic was more likely amongst males (OR = 3.09, 95% CI = 1.04 – 9.21).

4.5.8.3.1.4 Noisy Breathing – From Throat

Noisy breathing from the throat was more likely amongst children with a co-morbidity (OR = 5.22, 95% CI = 2.44 - 11.19). Noisy breathing from the throat was also more likely

amongst children who were born to mothers aged less than 25-years-old, compared to those born to mothers aged more than 35-years-old (OR = 4.67, 95% CI = 1.21 - 18.01).

4.5.8.3.1.5 Noisy Breathing – Not From Chest

Noisy breathing that did not come from the chest was more likely amongst children with a co-morbidity (OR = 6.02, 95% CI = 2.50 – 14.49). Noisy breathing that did not come from the chest was also more likely amongst children who were born to mothers aged less than 25-years-old, compared to those born to mothers aged more than 35-years-old (OR = 5.99, 95% CI = 1.26 - 28.40).

4.5.8.3.1.6 Rattly Chest

Rattly chests were more likely amongst: non-Caucasian children (OR = 3.56, 95% CI = 1.04 - 12.20), premature children (OR = 3.17, 95% CI = 1.21 - 8.33), children with a co-morbidity (OR = 3.08, 95% CI = 1.53 - 6.20), and children who were not breastfed (OR = 1.96, 95% CI = 1.04 - 3.69).

4.5.8.3.1.7 Shortness of Breath

SOB was more likely amongst: males (OR = 3.19, 95% CI = 1.63 – 6.23), premature children (OR = 3.93, 95% CI = 1.49 – 10.39), children with a co-morbidity (OR = 13.40, 95% CI = 6.15 – 29.22), and children with a family history of atopy (OR = 2.33, 95% CI = 1.26 – 4.42). SOB was also more likely amongst children who were born to mothers aged less than 25-years-old or 25 to 34-years-old, compared to those born to mothers aged or more than 35-years-old (OR = 8.70, 95% CI = 2.49 - 30.47 and OR = 3.22, 95% CI = 1.22 - 8.49)

4.5.8.3.1.8 Snoring

Snoring was more likely amongst premature children (OR = 6.32, 95% CI = 1.30 – 30.68).

4.5.8.3.1.9 Tachypnoea

Tachypnoea was more likely amongst children with a co-morbidity (OR = 7.22, 95% CI = 3.06 – 17.00), premature children (OR = 3.97, 95% CI = 1.33 – 11.89), and children with a family history of atopy (OR = 2.98, 95% CI = 1.21 – 7.34).

4.5.8.3.1.10 Wheezing

Wheezing was more likely amongst children who did not share a bedroom (OR = 1.96, 95% CI = 1.02 – 3.74), and children with a co-morbidity (OR = 6.21, 95%

CI = 3.18 - 13.73). Children born to mothers aged less than 25-years-old were also more likely to wheeze, compared to those born to mothers aged 25 to 34-years-old (OR = 3.11, 95% CI = 1.15 - 8.38) or more than 35-years-old (OR = 4.63, 95% CI = 1.53 - 13.99).

4.5.8.4 Healthcare Service Usage

At 46-months-old, 18.8% (n = 47) of children were taken to their GP for a respiratory problem. Of these children: 74.5% (n = 35) visited once, 12.8% (n = 6) visited twice, 4.3% (n = 2) visited thrice, 4.3% (n = 2) visited four times, and 4.3% (n = 2) visited five times. 5.6% (n = 14) of children were taken to hospital for a respiratory problem. 92.9% (n = 13) of these children visited once, and 7.1% (n = 1) visited four times. **Figure 78** presents GP and hospital attendance rates graphically.

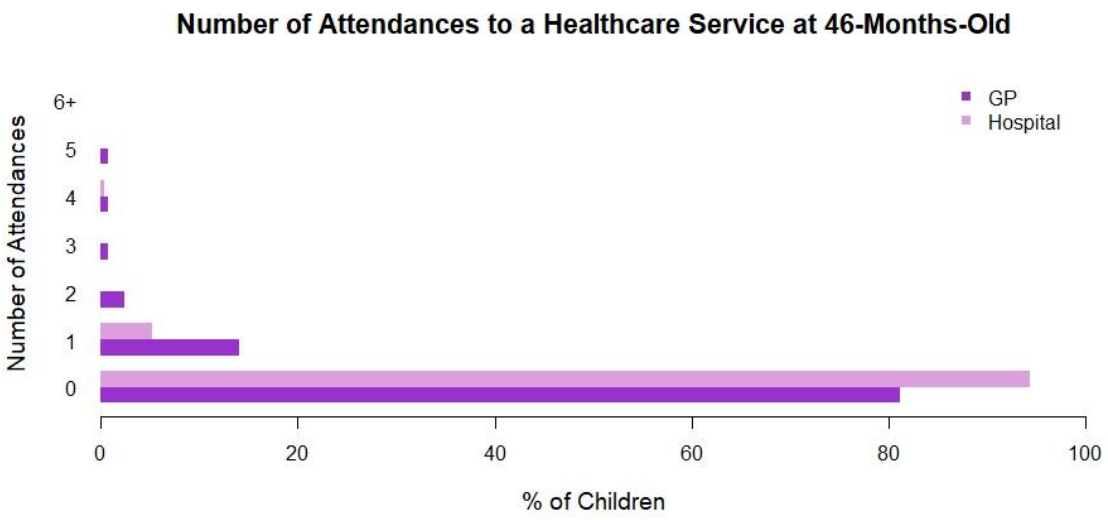


Figure 78: GP and hospital attendance rates at 46-months-old

4.5.8.4.1 Impact of Risk Factor Exposure on Healthcare Service Usage

4.5.8.4.1.1 GP Attendance

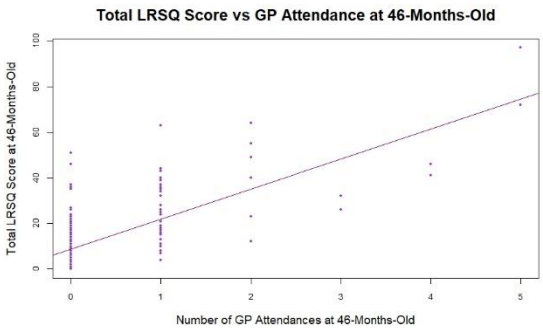
Visits to a GP for a respiratory problem were more likely amongst children with a co-morbidity (OR = 4.01, 95% CI = 1.91 - 8.43). GP visitation was more likely amongst children with vocationally-educated mothers, compared to those with degree-educated mothers (OR = 2.33, 95% CI = 1.07 - 5.08). Children born to mothers aged less than 25-years-old were also more likely to visit a GP, compared to those born to mothers aged more than 35-years-old (OR = 8.25, 95% CI = 1.23 - 55.56).

4.5.8.4.1.2 Hospital Attendance

Hospital visitations for a respiratory problem were more likely amongst children with a co-morbidity (OR = 6.55, 95% CI = 2.30 - 18.67).

4.5.8.4.2 Total LRSQ Score vs Healthcare Service Usage

At 46-months-old, there was a moderate correlation between total LRSQ score and GP attendance rate (r_s = 0.558, p = <0.001). There was a weak correlation between total LRSQ score and hospital attendance rate (r_s = 0.382, p = <0.001). These results suggest the children with the most severe respiratory disease, are not necessarily the ones who are more likely to seek medical assistance. **Figures 79** and **80** show the correlations graphically.



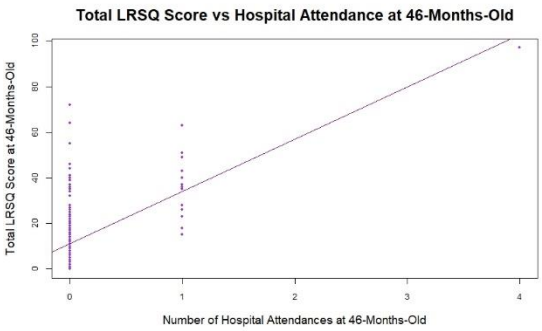


Figure 79: correlation between total LRSQ score and GP attendance rate at 46-months-old
Figure 80: correlation between total LRSQ score and hospital attendance rate at 46-months-old

4.5.9 Questionnaire 9: 52-Months-Old

4.5.9.1 Exposure to Risk Factors

4.5.9.1.1 Nursery Attendance

At 52-months-old, 84.5% (n = 180) of children attended nursery. It is worth noting, that several children were in school at this timepoint.

4.5.9.1.2 Other Household Children

72.8% (n = 155) of children lived with at least one other child at 52-months-old. 74.0% (n = 114) lived with only one other, 22.7% (n = 35) lived with two others, 2.6% (n = 4) lived with three others, and 0.6% (n = 1) lived with four others.

4.5.9.1.3 Bedroom Sharing

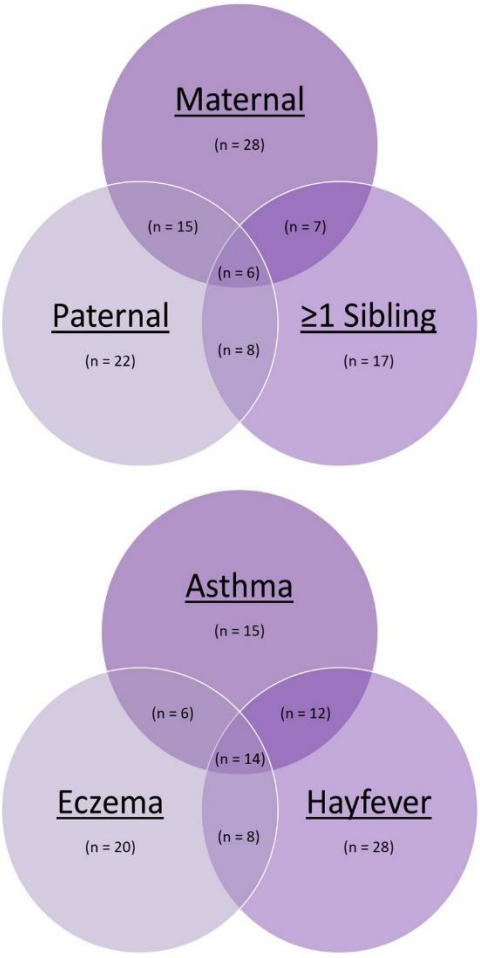
At 52-months-old, 31.5% (n = 67) of children shared a bedroom. 19.4% (n = 13) shared with their parent(s), 83.6% (n = 56) shared with one other child, and 1.5% (n = 1) shared with someone else.

4.5.9.1.4 ETS Exposure

13.1% (n = 28) of children were exposed to ETS at 52-months-old. 100.0% (n = 28) were exposed to ETS from outside of the home, 7.1% (n = 2) were exposed to ETS from inside the car, and 7.1% (n = 2) were exposed to ETS from within another location (e.g. work).

At 52-months-old, the prevalence of ETS exposure amongst children in the LBBS was not significantly different to the prevalence of smoking in either England ($\chi^2 = 0.38$, $p = 0.54$, $df = 1$) or Liverpool ($\chi^2 = 0.63$, $p = 0.43$, $df = 1$) in 2017/18.

4.5.9.1.5 Family History of Atopy



At 52-months-old, 48.4% (n = 103) of children had a family history of atopy.

From those with a family history of atopy: 54.4% (n = 56) had an atopic mother, 49.5% (n = 51) had an atopic father, and 36.9% (n = 38) had at least one atopic sibling. There was a family history of: asthma in 45.6% (n = 47) of these children, hay fever in 60.2% (n = 62), and eczema in 46.6% (n = 48). **Figure 81** shows how familial atopy was inter-related at 52-months-old.

Figure 81: children with a family history of atopy, by relative(s) and disease(s), at 52-months-old

4.5.9.1.6 Co-Morbidities

16.0% (n = 34) of the children had a co-morbid disease at 52-months-old. The respiratory system was the most common co-morbid system at this age, whilst asthma was the most common co-morbidity overall. **Table 33** shows the co-morbidities seen at 52-months-old – as reported by parents, and grouped according to organ system.

Type of Co-Morbidity	Underlying Condition	Frequency
Respiratory (n = 15)	Asthma	14
	Hay Fever	1
Cardiac (n = 1)	Congenital Heart Disease	1
Renal (n = 1)	Vesicoureteral Reflux	1
Neurological (n = 3)	Brown's Syndrome	1
	Cerebral Palsy	1
	Spinal Muscular Atrophy	1
Diabetes (n = 1)	Diabetes	1
Other (n = 21)	Allergies	6
	Eczema	5
	Autism Spectrum Disorder	2
	Haemophilia	2
	Developmental Dysplasia of Hips	1
	Down's Syndrome (Trisomy 21)	1
	Glue Ear	1
	"Inability to Store Iron"	1
	Pectus Carinatum	1
	Sensory Processing Disorder	1

Table 33: co-morbidities of the LBBS cohort at 52-months-old

4.5.9.2 LRSQ Scores

Measures of central tendency and dispersion for the total LRSQ score, and LRSQ domain scores, at 52-months-old are shown in **Table 34**. The distribution of scores are shown graphically in **Figure 82**.

	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Standard Deviation
Total Score	0	2	7	14.5	101	12.15	15.27
Domain 1	0	0	1	2	12	1.68	2.16
Domain 2	0	1	2	4	16	2.57	2.76
Domain 3	0	1	3	5	19	3.44	3.49
Domain 4	0	0	0	1	12	0.94	1.76
Domain 5	0	0	0	1	11	0.87	1.74
Domain 6	0	0	0	0	9	0.51	1.38
Domain 7	0	0	0	1	11	1.04	1.94
Domain 8	0	1	2	4	11	2.81	2.45

Table 34: descriptive statistics of the total and domain LRSQ scores at 52-months-old

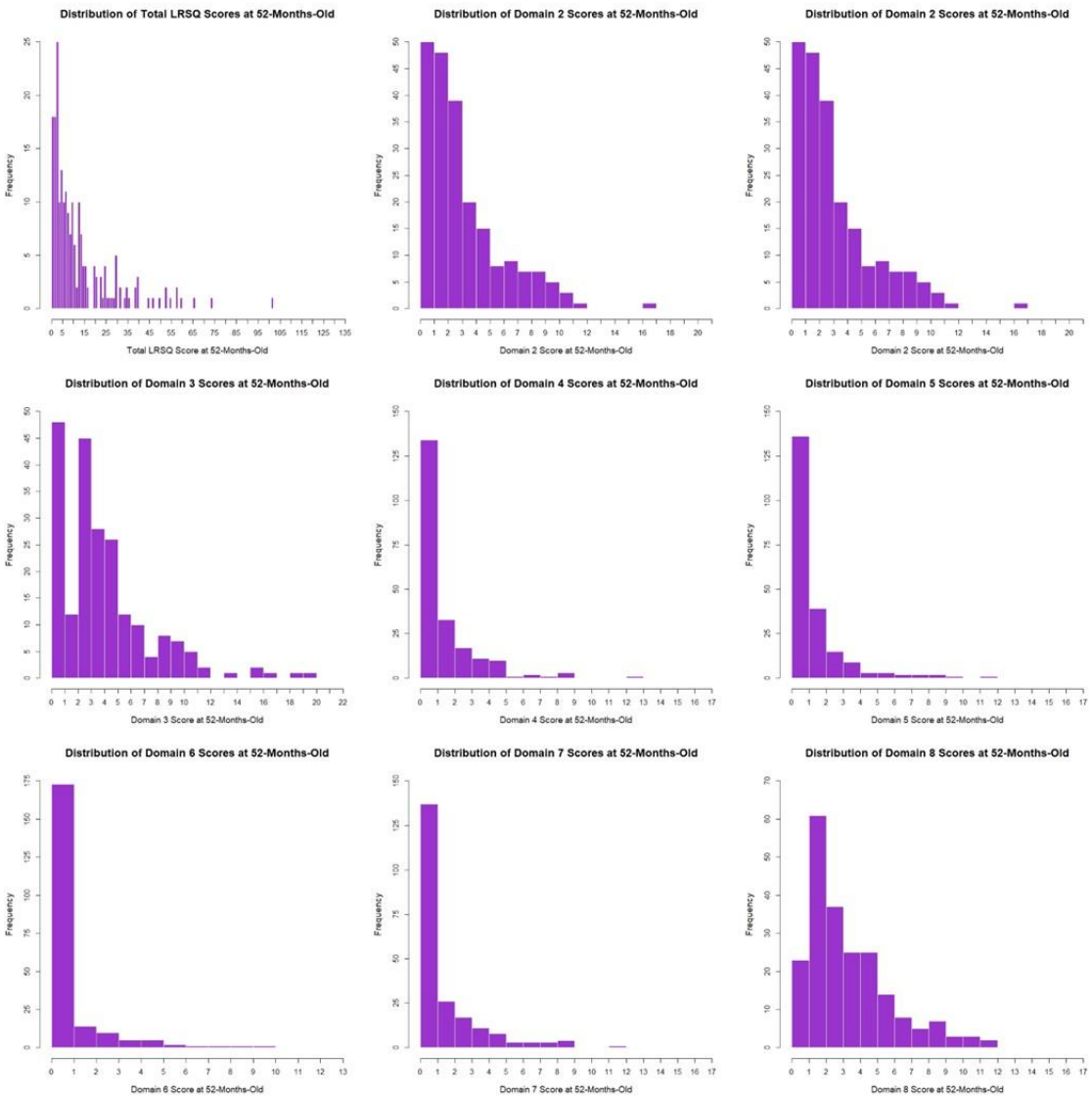


Figure 82: distribution of total and domain LRSQ scores at 52-months-old

4.5.9.2.1 Impact of Risk Factor Exposure on Total LRSQ Score

Total LRSQ scores were higher amongst children who had been exposed to ETS (U = 2497, p = 0.001), or whose mothers had been exposed to ETS during pregnancy (U = 2915, p = 0.048). They were also higher amongst children who were: male (U = 4762, p = 0.001), or born at a 'normal' birthweight (U = 708, p = 0.024). Children with a co-morbidity (U = 1476, p = <0.001), or a family history of atopy (U = 4873, p = 0.002) had higher total LRSQ scores too.

There were differences in total LRSQ score between the different levels of maternal education (H = 9.93, p = 0.007, df = 2) and maternal age (H = 7.72, p = 0.021, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower than those with a school-educated mother (p = 0.002). It also revealed that children

born to mothers aged less than 25-years-old scored higher than those born to mothers aged ≥35-years-old (p = 0.007).

4.5.9.2.2 Impact of Risk Factor Exposure on LRSQ Domain Scores

4.5.9.2.2.1 Domain 1

Domain 1 scores were higher amongst children who were: exposed to ETS (U = 2930, p = 0.029), born at a 'normal' birthweight (U = 770, p = 0.043), a singleton birth (U = 519, p = 0.044), or male (U = 5033, p = 0.005). They were also higher amongst children with a family history of atopy (U = 4814, p = 0.001), or with a co-morbidity (U = 1527, p = <0.001).

There were differences in domain 1 score between the different levels of maternal age (H = 6.67, p = 0.036, df = 2). Post-hoc analysis revealed that children born to mothers aged less than 25-years-old scored higher than children born to mothers aged ≥35-years-old (p = 0.015).

4.5.9.2.2.2 Domain 2

Domain 2 scores were higher amongst males (U = 5202, p = 0.015), as well as those with a co-morbidity (U = 1599, p = <0.001) or a family history of atopy (U = 5395, p = 0.046). They were also higher amongst children who had been exposed to ETS (U = 2730, p = 0.007), or whose mothers had been exposed to ETS during pregnancy (U = 2753, p = 0.015).

There were differences in domain 2 score between the different levels of maternal education (H = 7.69, p = 0.021, df = 2) and maternal age (H = 7.16, p = 0.028, df = 2). Post-hoc analysis revealed that children with degree-educated mother scored lower than those with a school-educated mother (p = 0.006). It also revealed that children born to mothers aged less than 25-years-old scored higher than children born to mothers aged ≥35-years-old (p = 0.008).

4.5.9.2.2.3 Domain 3

Domain 3 scores were higher amongst children who had been exposed to ETS (U = 2924, p = 0.032), or whose mothers smoked during pregnancy (U = 1809, p = 0.021). They were also higher amongst children who: had a family history of atopy

(U = 4634, p = <0.001), had a co-morbidity (U = 1734, p = <0.001), were male (U = 4784, p = 0.001), or were born at a 'normal' birthweight (U = 632, p = 0.008).

There were differences in domain 3 score between the different levels of maternal age (H = 6.63, p = 0.036, df = 2). Post-hoc analysis revealed that children born to mothers aged less than 25-years-old scored higher than children born to mothers aged ≥35-years-old (p = 0.012).

4.5.9.2.2.4 Domain 4

Domain 4 scores were higher amongst children with a co-morbidity (U = 2129, p = <0.001) or a family history of atopy (U = 4902, p = 0.001).

There were differences in domain 4 score between the different levels of maternal age (H = 6.72, p = 0.035, df = 2). Post-hoc analysis revealed that children born to mothers aged less than 25-years-old scored higher than children born to mothers aged ≥35-years-old (p = 0.010).

4.5.9.2.2.5 Domain 5

Domain 5 scores were higher amongst children who were: male (U = 5266, p = 0.009), Caucasian (U = 832, p = 0.005), or exposed to ETS (U = 2971, p = 0.021). They were also higher amongst children with a family history of atopy (U = 4978, p = 0.001), or a co-morbidity (U = 2079, p = <0.001).

There were differences in domain 5 score between the different levels of maternal education (H = 9.54, p = 0.008, df = 2) and maternal age (H = 7.34, p = 0.025, df = 2). Post-hoc analysis revealed that children with a school-educated mother scored higher, compared to those with a vocationally (p = 0.027) or degree-educated mother (p = 0.012). It also revealed that children born to mothers aged ≥35-years-old scored lower, compared to children born to mothers aged less than 25-years-old (p = 0.011) or aged 25 to 34-years-old (p = 0.011).

4.5.9.2.2.6 Domain 6

Domain 6 scores were higher amongst children who **did not** attend nursery (U = 2154, p = 0.017) or live with other children (U = 4248, p = 0.010). They were also higher amongst children with a co-morbidity (U = 1793, p = <0.001).

4.5.9.2.2.7 Domain 7

Domain 7 scores were higher amongst children who: were born at a normal 'birthweight' (U = 794, p = 0.035), had a co-morbidity (U = 1807, p = <0.001), or had a family history of atopy (U = 5082, p = 0.003). They were also higher amongst males (U = 5462, p = 0.031).

4.5.9.2.2.8 Domain 8

Domain 8 scores were higher amongst children who were: born at a 'normal' birthweight (U = 708, p = 0.022), male (U = 5034, p = 0.005), exposed to ETS (U = 2909, p = 0.028), or not breastfed (U = 3979, p = 0.046). They were also higher amongst children who had: a family history of atopy (U = 4884, p = 0.002), a co-morbidity (U = 1842, p = <0.001), or a mother who smoked during pregnancy (U = 1768, p = 0.014).

There were differences in domain 8 score between the different levels of maternal education (H = 17.83, p = <0.001, df = 2) and maternal age (H = 6.68, p = 0.036, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower than those with a school-educated mother (p = <0.001). It also revealed that children born to mothers aged less than 25-years-old scored higher than children born to mothers aged ≥35-years-old (p = 0.018).

4.5.9.2.3 Total LRSQ Score vs Total QoL Score

There was a strong positive correlation between a child's total LRSQ score, and their total QoL score (r_s = 0.926, p = <0.001). **Figure 83** shows the correlation graphically. A higher total LRSQ score is more strongly correlated with a poor QoL for parents, than with a poor QoL for children (r_s = 0.861, p = <0.001 vs r_s = 0.802, p = <0.001). Children who regularly suffer with respiratory symptoms, and their parents, therefore experience a worse QoL.

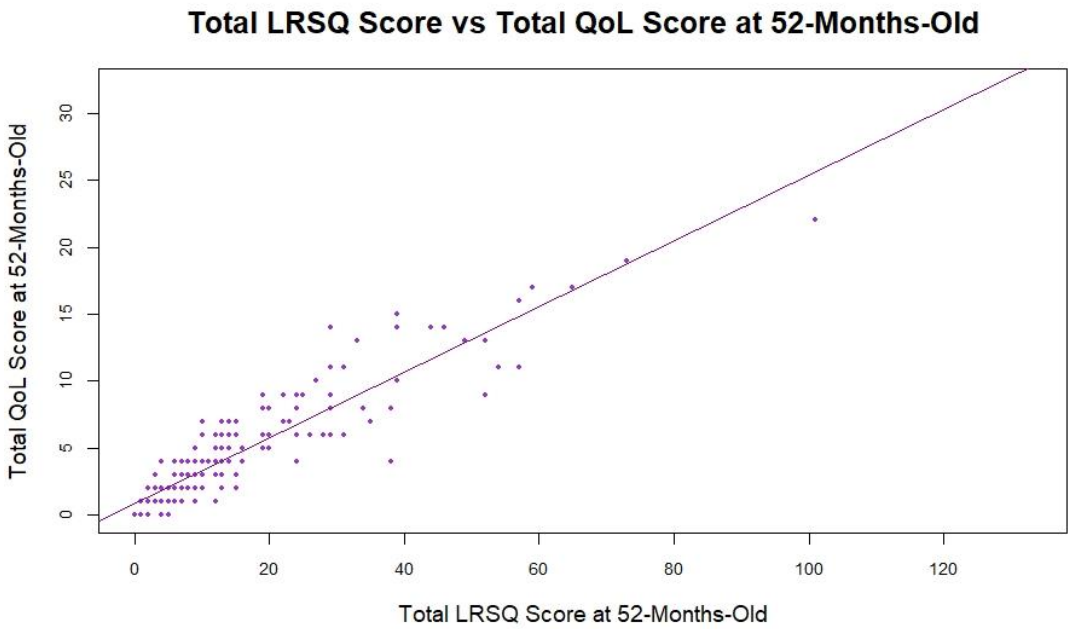


Figure 83: correlation between total LRSQ score and total QoL score at 52-months-old

4.5.9.3 Symptom Prevalence

91.5% (n = 195) of children experienced at least one type of respiratory symptom at 52-months-old. A cough was the most common symptom, as it was experienced by 78.9% (n = 168) of children; noisy breathing that didn't come from the chest was the least common symptom, as it was experienced by 10.3% (n = 22) of children. **Figure 84** demonstrates the prevalence of individual symptoms.

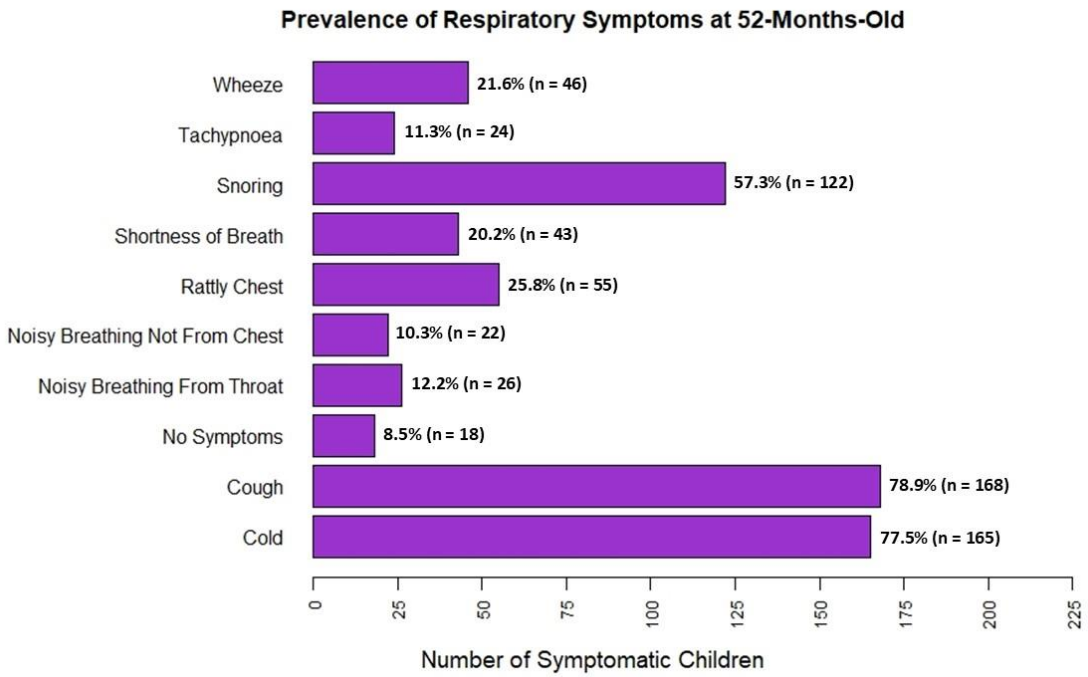


Figure 84: prevalence of respiratory symptoms at 52-months-old

4.5.9.3.1 Impact of Risk Factor Exposure on Symptom Prevalence

4.5.9.3.1.1 Colds

Colds were more likely amongst: males (OR = 2.71, 95% CI = 1.36 – 5.40), children who shared a bedroom (OR = 2.42, 95% CI = 1.09 – 5.35), and premature children (OR = 2.86, 95% CI = 1.38 – 5.95).

4.5.9.3.1.2 Coughing

Coughing was more likely amongst: children who were exposed to ETS (OR = 8.71, 95% CI = 1.39 – 54.74), males (OR = 2.86, 95% CI = 1.38 – 5.95), children with a family history of atopy (OR = 3.03, 95% CI = 1.47 – 6.26), and children with a co-morbidity (OR = 6.95, 95% CI = 1.29 – 37.56).

4.5.9.3.1.3 No Symptoms

Being asymptomatic was more likely amongst males (OR = 3.71, 95% CI = 1.06 – 12.37).

4.5.9.3.1.4 Noisy Breathing – From Throat

Noisy breathing from the throat was more likely amongst children with a co-morbidity (OR = 10.72, 95% CI = 4.49 - 25.61).

4.5.9.3.1.5 Noisy Breathing – Not From Chest

Noisy breathing that did not come from the chest was more likely amongst without a co-morbidity (OR = 6.29, 95% CI = 2.46 – 16.05), and children who lived with other children (OR = 2.05, 95% CI = 1.07 - 3.95).

4.5.9.3.1.6 Rattly Chest

Rattly chests were more likely amongst children with a co-morbidity (OR = 9.65, 95% CI = 4.31 – 21.63).

4.5.9.3.1.7 Shortness of Breath

SOB was more likely amongst: males (OR = 2.12, 95% CI = 1.09 – 4.15), children with a co-morbidity (OR = 10.14, 95% CI = 4.58 - 22.46), and children who did not attend nursery (OR = 2.40, 95% CI = 1.02 – 5.68).

4.5.9.3.1.8 Snoring

Snoring was more likely amongst: children whose mothers were exposed to ETS during pregnancy (OR = 2.59, 95% CI = 1.12 – 5.99), children with a co-morbidity (OR = 3.50,

95% CI = 1.43 – 8.60), and children who did not live with other children (OR = 2.05, 95% CI = 1.07 – 3.95). Children who snored, were more likely to be deprived too – since children became 1.13 times less likely to snore for every increase in IMD decile (OR = 1.13, 95% CI = 1.00 - 1.27).

4.5.9.3.1.9 Tachypnoea

Tachypnoea was more likely amongst children without a co-morbidity (OR = 15.94, 95% CI = 6.24 – 40.73), and children who did not live with any other children (OR = 3.12, 95% CI = 1.34 – 7.25).

4.5.9.3.1.10 Wheezing

Wheezing was more likely amongst children with a family history of atopy (OR = 2.63, 95% CI = 1.35 – 5.10), and children with a co-morbidity (OR = 10.19, 95% CI = 4.59 – 22.60). Children born to mothers aged less than 25-years-old were also more likely to wheeze, compared to those born to mothers aged 25 to 34-years-old (OR = 6.33, 95% CI = 1.18 - 33.98) or more than 35-years-old (OR = 10.67, 95% CI = 1.72 - 65.99).

4.5.9.4 Healthcare Service Usage

At 52-months-old, 15.0% (n = 36) of children were taken to their GP for a respiratory problem. Of these children: 62.5% (n = 20) visited once, 21.9% (n = 7) visited twice, 6.3% (n = 2) visited thrice, and 9.4% (n = 3) visited five times. 5.6% (n = 12) of children were taken to hospital for a respiratory problem. 83.3% (n = 10) of these children visited once, 8.3% (n = 1) visited twice, and 8.3% (n = 1) visited five times. **Figure 85** presents GP and hospital attendance rates graphically.

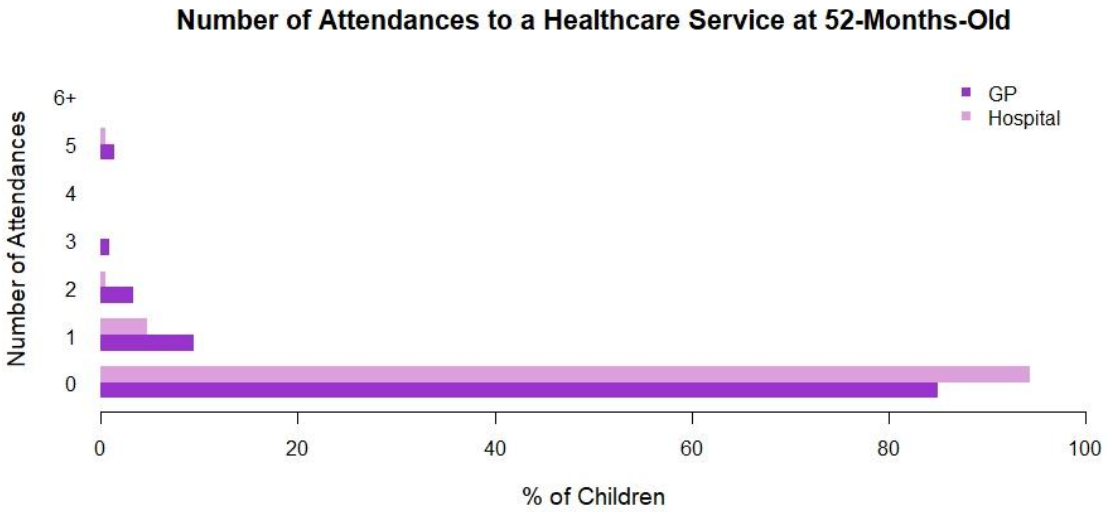


Figure 85: GP and hospital attendance rates at 52-months-old

4.5.9.4.1 Impact of Risk Factor Exposure on Healthcare Service Usage

4.5.9.4.1.1 GP Attendance

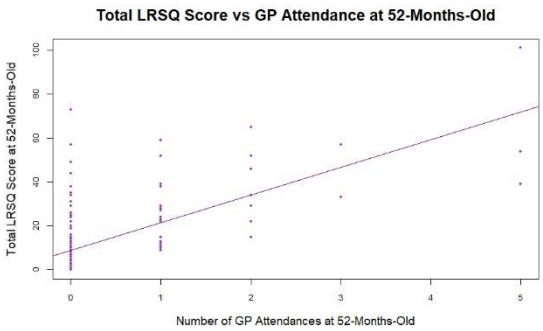
Visits to a GP for a respiratory problem were more likely amongst children who had a co-morbidity (OR = 4.42, 95% CI = 1.88 - 10.37), and children who were exposed to ETS (OR = 2.79, 95% CI = 1.16 - 6.67). GP visitation was more likely amongst children who were born to mothers aged less than 25-years-old, compared to those born to mothers aged more than 35-years-old (OR = 8.25, 95% CI = 1.23 - 55.56). Children who were breastfed for 1-4 months were also more likely to visit a GP, compared to those who were breastfed for more than 4 months (OR = 3.24, 95% CI = 1.03 - 10.18).

4.5.9.4.1.2 Hospital Attendance

Hospital visitations for a respiratory problem were more likely amongst children with a co-morbidity (OR = 4.52, 95% CI = 1.39 - 14.72), and children who were not breastfed (OR = 3.48, 95% CI = 1.09 - 11.10).

4.5.9.4.2 Total LRSQ Score vs Healthcare Service Usage

At 52-months-old, there was a moderate correlation between total LRSQ score and GP attendance rate (r_s = 0.478, p = <0.001). There was a weak correlation between total LRSQ score and hospital attendance rate (r_s = 0.320, p = <0.001). These results suggest the children with the most severe respiratory disease, are not necessarily the ones who are more likely to seek medical assistance. **Figures 86** and **87** show the correlations graphically.



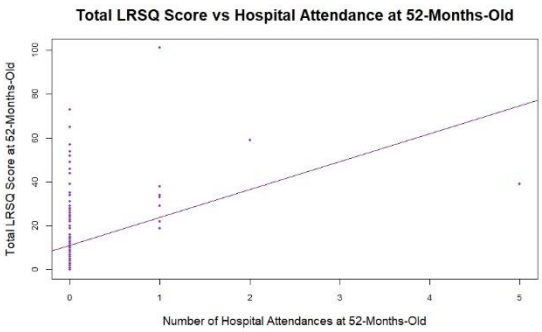


Figure 86: correlation between total LRSQ score and GP attendance rate at 52-months-old
Figure 87: correlation between total LRSQ score and hospital attendance rate at 52-months-old

4.5.10 Questionnaire 10: 58-Months-Old

4.5.10.1 Exposure to Risk Factors

4.5.10.1.1 Nursery Attendance

At 58-months-old, 58.9% (n = 129) of children attended nursery. It is worth noting, that several children were in school at this timepoint.

4.5.10.1.2 Other Household Children

74.9% (n = 164) of children lived with at least one other child at 58-months-old. 71.2% (n = 116) lived with only one other, 23.9% (n = 39) lived with two others, 4.3% (n = 7) lived with three others, and 0.6% (n = 1) lived with four others.

4.5.10.1.3 Bedroom Sharing

At 58-months-old, 31.5% (n = 69) of children shared a bedroom. 18.8% (n = 13) shared with their parent(s), and 85.5% (n = 59) shared with one other child.

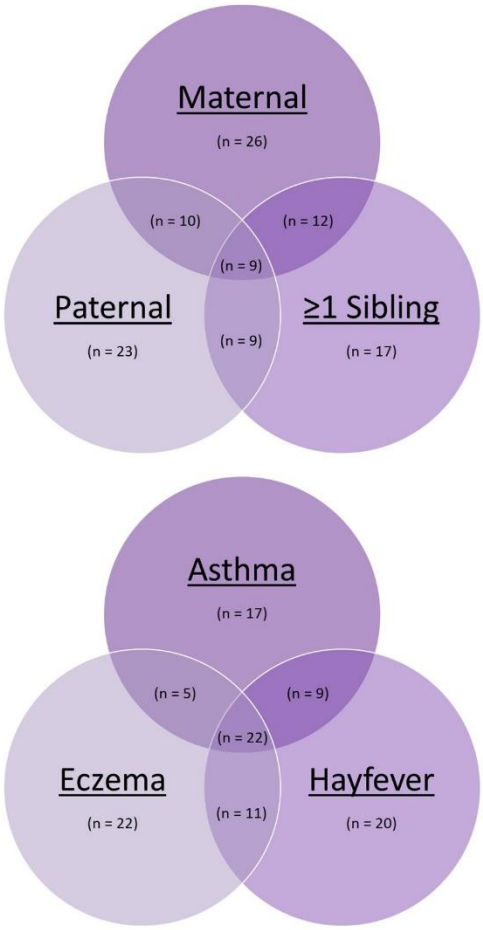
4.5.10.1.4 ETS Exposure

12.3% (n = 27) of children were exposed to ETS at 58-months-old. 3.7% (n = 1) were exposed to ETS from inside the home, 96.3% (n = 26) were exposed to ETS from

outside of the home, 7.4% (n = 2) were exposed to ETS from inside the car, and 11.1% (n = 3) were exposed to ETS from within another location (e.g. work).

At 58-months-old, the prevalence of ETS exposure amongst children in the LBBS was not significantly different to the prevalence of smoking in either England ($\chi^2 = 0.60$, $p = 0.44$, df = 1) or Liverpool ($\chi^2 = 0.76$, $p = 0.38$, df = 1) in 2018/19.

4.5.10.1.5 Family History of Atopy



At 58-months-old, 48.4% (n = 106) of children had a family history of atopy.

From those with a family history of atopy: 53.8% (n = 57) had an atopic mother, 48.1% (n = 51) had an atopic father, and 44.3% (n = 47) had at least one atopic sibling. was a family history of: asthma in 50.0% (n = 53) of these children, hay fever in 58.5% (n = 62), and eczema in 56.6% (n = 60). **Figure 88** shows how familial atopy was inter-related at 58-months-old.

Figure 88: children with a family history of atopy, by relative(s) and disease(s), at 58-months-old

4.5.10.1.6 Co-Morbidities

18.3% (n = 40) of the children had a co-morbid disease at 58-months-old. The respiratory system was the most common co-morbid system at this age, whilst asthma was the most common co-morbidity overall. **Table 35** shows the co-morbidities seen at 58-months-old – as reported by parents, and grouped according to organ system.

Type of Co-Morbidity	Underlying Condition	Frequency
Respiratory (n = 16)	Asthma	13
	Viral-Induced Wheeze	1
Cardiac (n = 2)	Congenital Heart Disease	2
Renal (n = 1)	Haematuria	1
Neurological (n = 4)	Brown's Syndrome	1
	Cerebral Palsy	1
	Hypotonia	1
	Spinal Muscular Atrophy	1
Gastrointestinal (n = 2)	Imperforate Anus	1
	"Not Specified"	1
Other (n = 26)	Eczema	7
	Allergies	6
	Autism Spectrum Disorder	3
	Haemophilia	2
	Astigmatism	1
	"Complications from Mastoiditis"	1
	Down's Syndrome (Trisomy 21)	1
	Glue Ear	1
	"Inability to Store Iron"	1
	Psoriasis	1
	Tuberous Sclerosis	1

Table 35: co-morbidities of the LBBS cohort at 58-months-old

4.5.10.2 LRSQ Scores

Measures of central tendency and dispersion for the total LRSQ score, and LRSQ domain scores, at 58-months-old are shown in **Table 36**. The distribution of scores are shown graphically in **Figure 89**.

	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Standard Deviation
Total Score	0	2	6	17	81	11.39	13.71
Domain 1	0	0	1	2	10	1.53	2.01
Domain 2	0	0	2	4	11	2.39	2.56
Domain 3	0	1	3	5	21	3.43	3.47
Domain 4	0	0	0	1	8	0.74	1.46
Domain 5	0	0	0	1	10	0.79	1.87
Domain 6	0	0	0	0	8	0.46	1.19
Domain 7	0	0	0	1	9	1.05	2.01
Domain 8	0	1	2	4	12	2.77	2.53

Table 36: descriptive statistics of the total and domain LRSQ scores at 58-months-old

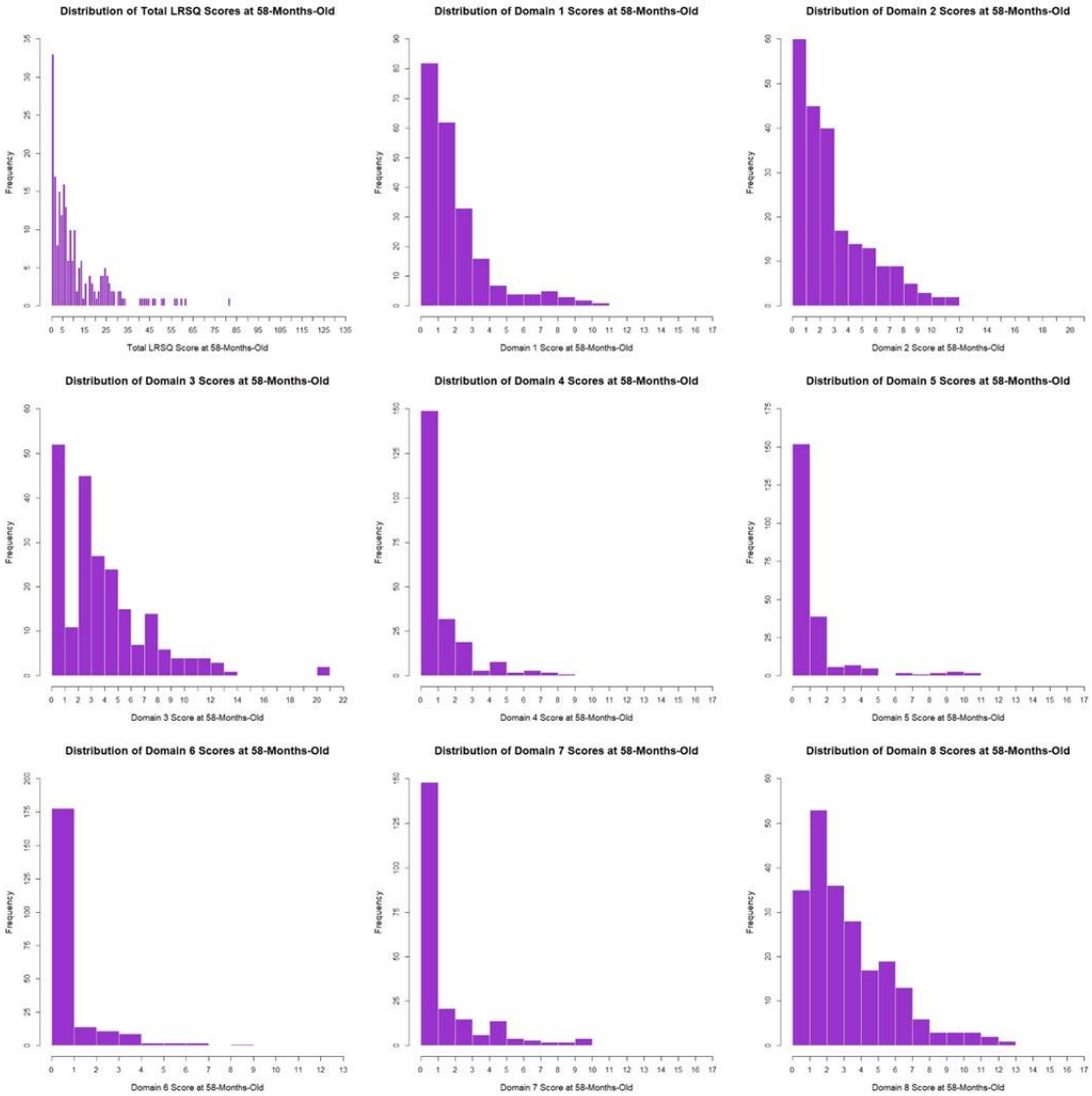


Figure 89: distribution of total and domain LRSQ scores at 58-months-old

4.5.10.2.1 Impact of Risk Factor Exposure on Total LRSQ Score

Total LRSQ scores were higher amongst children who were a twin (U = 108, p = 0.006), or born prematurely (U = 1879, p = 0.015). They were also higher amongst those with a co-morbidity (U = 3145, p = <0.001).

There were differences in total LRSQ score between the different levels of maternal education (H = 19.91, p = <0.001, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower, compared to those with a school (p = 0.010) or vocationally-educated mother (p = <0.001).

4.5.10.2.2 Impact of Risk Factor Exposure on LRSQ Domain Scores

4.5.10.2.2.1 Domain 1

Domain 1 scores were higher amongst children who were born prematurely (U = 1841, p = 0.009), or a twin (U = 70, p = 0.002). They were also higher amongst children with a co-morbidity (U = 3426, p = <0.001).

There were differences in domain 1 score between the different levels of maternal education (H = 8.63, p = 0.013, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower, compared to those with a school (p = 0.039) or vocationally-educated mother (p = 0.012).

4.5.10.2.2.2 Domain 2

Domain 2 scores were higher amongst children with a co-morbidity (U = 3022, p = <0.001), or who were a twin (U = 98, p = 0.004), or who were born prematurely (U = 1708, p = 0.003).

There were differences in domain 2 score between the different levels of maternal education (H = 14.66, p = 0.001, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower, compared to those with a school (p = 0.022) or vocationally-educated mother (p = <0.001). There were also differences in domain 2 score amongst breastfed children, depending on how long they were breastfed for (H = 6.49, p = 0.039, df = 2). Post-hoc analysis revealed that children who were breastfed for 1-4 months scored higher than those who were breastfed for more than 4 months (p = 0.011).

4.5.10.2.2.3 Domain 3

Domain 3 scores were higher amongst twins (U = 94, p = 0.004). They were also higher amongst children who: had a co-morbidity (U = 4083, p = 0.001), or were not exposed to ETS (U = 3345, p = 0.044).

There were differences in domain 3 score between the different levels of maternal education (H = 11.29, p = 0.004, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower than those with a vocationally-educated mother (p = 0.001).

4.5.10.2.2.4 Domain 4

Domain 4 scores were higher amongst children with a co-morbidity (U = 3609, p = <0.001).

There were differences in domain 4 score between the different levels of maternal education (H = 8.98, p = 0.011, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower, compared to those with a school (p = 0.035) or a vocationally-educated mother (p = 0.010). There were also differences in domain 4 score amongst breastfed children, depending on how long they were breastfed for (H = 7.88, p = 0.019, df = 2). Post-hoc analysis revealed that children who were breastfed for 1-4 months scored higher than those who were breastfed for more than 4 months (p = 0.006).

4.5.10.2.2.5 Domain 5

Domain 5 scores were higher amongst children with a family history of atopy (U = 7924, p = 0.026), or a co-morbidity (U = 3502, p = <0.001).

There were differences in domain 5 score between the different levels of maternal education (H = 12.86, p = 0.02, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower, compared to those with a school (p = 0.011) or a vocationally-educated mother (p = 0.002).

4.5.10.2.2.6 Domain 6

Domain 6 scores were higher amongst the children who born prematurely (U = 2196, p = 0.028), and children with co-morbidities (U = 3741, p = <0.001).

There were differences in domain 6 score between the different levels of maternal education (H = 10.68, p = 0.005, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower than those with a vocationally-educated mother (p = 0.002).

4.5.10.2.2.7 Domain 7

Domain visits higher amongst those children who were a twin (U = 234, p = 0.024), or born prematurely (U = 2032, p = 0.019). They were also higher amongst children with a co-morbidity (U = 3664, p = <0.001).

There were differences in domain 7 score between the different levels of maternal education (H = 20.34, p = <0.001, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower, compared to those with a school (p = 0.001) or vocationally-educated mother (p = <0.001). There were also differences in domain 7 score amongst breastfed children, depending on how long they were breastfed for (H = 6.75, p = 0.034, df = 2). Post-hoc analysis revealed that children who were breastfed for 1-4 months scored higher, compared to those who were breastfed for less than 1 month (p = 0.024) or for more than 4 months (p = 0.015).

4.5.10.2.2.8 Domain 8

Domain 8 scores were higher amongst children who had a co-morbidity (U = 3465, p = <0.001). They were also higher in twins (U = 101, p = 0.005), and children who were not breastfed (U = 5469, p = 0.015).

There were differences in domain 8 score between the different levels of maternal education (H = 15.33, p = <0.001, df = 2). Post-hoc analysis revealed that children with a degree-educated mother scored lower, compared to those with a school (p = 0.029) or vocationally-educated mother (p = <0.001).

4.5.10.2.3 Total LRSQ Score vs Total QoL Score

There was a strong positive correlation between a child's total LRSQ score, and their total QoL score (r_s = 0.950, p = <0.001). **Figure 90** shows the correlation graphically. A higher total LRSQ score is more strongly correlated with a poor QoL for parents, than with a poor QoL for children (r_s = 0.890, p = <0.001 vs r_s = 0.791, p = <0.001). Children who regularly suffer with respiratory symptoms, and their parents, therefore

experience a worse QoL.

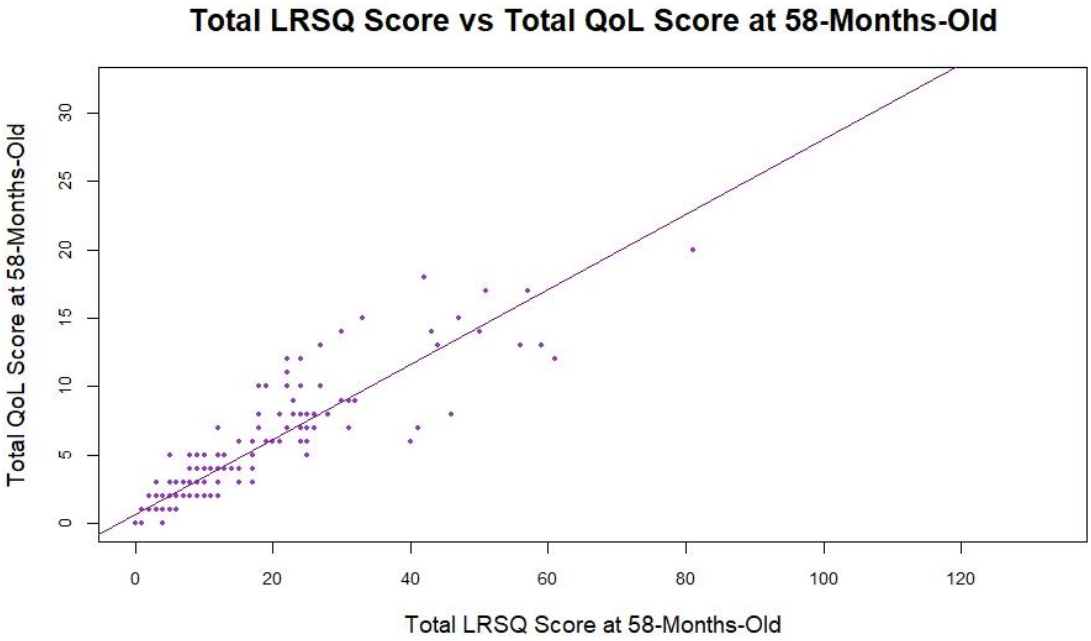


Figure 90: correlation between total LRSQ score and total QoL score at 58-months-old

4.5.10.3 Symptom Prevalence

84.9% (n = 286) of children experienced at least one type of respiratory symptom at 58-months-old. A cold was the most common symptom, as it was experienced by 76.3% (n = 167) of children; noisy breathing that didn't come from the chest was the least common symptom, as it was experienced by 9.1% (n = 20) of children. **Figure 91** demonstrates the prevalence of individual symptoms.

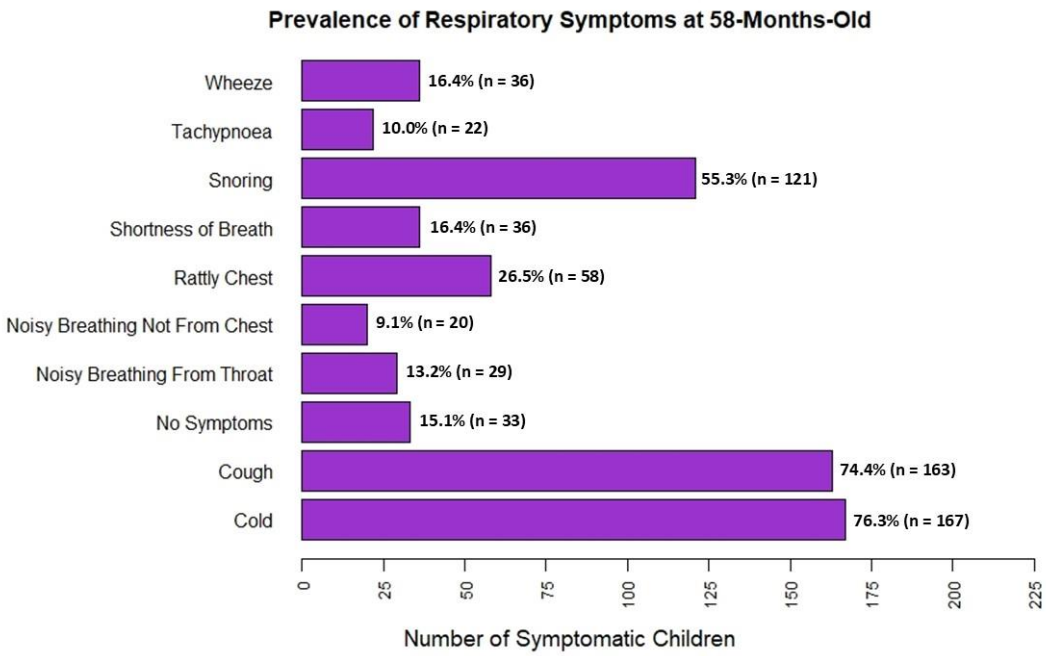


Figure 91: prevalence of respiratory symptoms at 58-months-old

4.5.10.3.1 Impact of Risk Factor Exposure on Symptom Prevalence

4.5.10.3.1.1 Colds

Colds were more likely amongst children with a family history of atopy (OR = 2.29, 95% CI = 1.20 - 4.36). Colds were also more likely amongst children with vocationally-educated mothers, compared to those with school (OR = 4.10, 95% CI = 1.11 - 15.06) or degree-educated mothers (OR = 3.96, 95% CI = 1.17 - 13.46).

4.5.10.3.1.2 Coughing

Coughing was more likely amongst children with a family history of atopy (OR = 2.00, 95% CI = 1.06 – 3.77), and children with a co-morbidity (OR = 2.82, 95% CI = 1.10 – 7.23). Coughing was also more likely amongst children with vocationally-educated mothers, compared to those with school (OR = 9.03, 95% CI = 1.32 - 61.88) or degree-educated mothers (OR = 13.17, 95% CI = 2.06 - 84.49).

4.5.10.3.1.3 No Symptoms

Being asymptomatic was more likely amongst: children who did not live with other children (OR = 2.23, 95% CI = 1.01 – 4.94), children who were breastfed (OR = 3.34, 95% CI = 1.02 – 10.94), and children who were exposed to ETS (OR = 2.94, 95% CI = 1.18 – 7.32).

There were differences in the prevalence of asymptomatic children amongst the different levels of deprivation (p = 0.040, Fisher's Exact Test). Children living in the least-deprived IMD quintile were more likely to be asymptomatic than those living in the four greater deprived quintiles.

4.5.10.3.1.4 Noisy Breathing – From Throat

Noisy breathing from the throat was more likely amongst children with a co-morbidity (OR = 5.97, 95% CI = 2.69 - 13.23), and premature children (OR = 4.03, 95% CI = 1.35 - 12.07). Noisy breathing from the throat was also more likely amongst children with school and vocationally-educated mothers, compared to those with degree-educated mothers (respectively: OR = 2.78, 95% CI = 1.12 - 6.88 and OR = 4.23, 95% CI = 1.63 - 10.99).

4.5.10.3.1.5 Noisy Breathing – Not From Chest

Noisy breathing that did not come from the chest was more likely amongst children with a co-morbidity (OR = 7.99, 95% CI = 3.16 - 20.24). Noisy breathing that did not come from the chest was also more likely amongst children with school and vocationally-educated mothers, compared to those with degree-educated mothers (respectively: OR = 5.37, 95% CI = 1.77 - 16.26 and OR = 5.61, 95% CI = 1.69 - 18.62).

4.5.10.3.1.6 Rattly Chest

Rattly chests were more likely amongst: children who attended nursery (OR = 2.13, 95% CI = 1.13 - 4.03), children with a co-morbidity (OR = 3.31, 95% CI = 1.69 – 6.48), and premature children (OR = 4.50, 95% CI = 1.55 - 13.04). Rattly chests were also more likely amongst children with vocationally-educated mothers, compared to those with degree-educated mothers (OR = 3.08, 95% CI = 1.43 - 6.62).

4.5.10.3.1.7 Shortness of Breath

SOB was more likely amongst children with a family history of atopy (OR = 3.68, 95% CI = 1.66 – 8.17), and children with a co-morbidity (OR = 8.63, 95% CI = 3.98 – 18.68). SOB was also more likely amongst children who were born to mothers aged less than 25-years-old, compared to those born to mothers aged 25 to 34-years-old (OR = 4.67, 95% CI = 1.29 - 16.94) or more than 35-years-old (OR = 9.16, 95% CI = 2.13 - 39.38)

4.5.10.3.1.8 Snoring

Snoring was more likely amongst children with a co-morbidity (OR = 4.43, 95% CI = 1.06 – 18.48), and premature children (OR = 3.21, 95% CI = 1.49 – 6.90). Snoring was more likely amongst children with school or vocationally-educated mothers, compared to those with degree-educated mothers (respectively: OR = 2.14, 95% CI = 1.09 - 4.20 and OR = 2.40, 95% CI = 1.08 - 5.33).

4.5.10.3.1.9 Tachypnoea

Tachypnoea was more likely amongst children with a co-morbidity (OR = 7.57, 95% CI = 3.11 – 18.41).

4.5.10.3.1.10 Wheezing

Wheezing was more likely amongst: children with a co-morbidity (OR = 6.47, 95% CI = 3.02 – 13.85), premature children (OR = 4.99, 95% CI = 1.73 – 14.42), and children

whose mother was exposed to ETS during pregnancy (OR = 2.32, 95% CI = 1.03 – 5.20). Wheezing was more likely amongst children with school or vocationally-educated mothers, compared to those with degree-educated mothers (respectively: OR = 2.82, 95% CI = 1.24 - 6.39 and OR = 2.67, 95% CI = 1.06 - 6.78). Children who were breastfed for 1-4 months or more than 4 months were also more likely to wheeze, compared to those who were breastfed for less than 1 month (respectively: OR = 9.44, 95% CI = 1.89 - 47.08 and OR = 4.89, 95% CI = 1.07 - 22.41).

4.5.10.4 Healthcare Service Usage

At 58-months-old, 16.4% (n = 36) of children were taken to their GP for a respiratory problem. Of these children: 58.3% (n = 21) visited once, 27.8% (n = 10) visited twice, 8.3% (n = 3) visited thrice, 2.8% (n = 1) visited four times, and 2.8% (n = 1) visited five times. 4.6% (n = 10) of children were taken to hospital for a respiratory problem. 80.0% (n = 8) of these children visited once, and 20.0% (n = 2) visited twice. **Figure 92** presents GP and hospital attendance rates graphically.

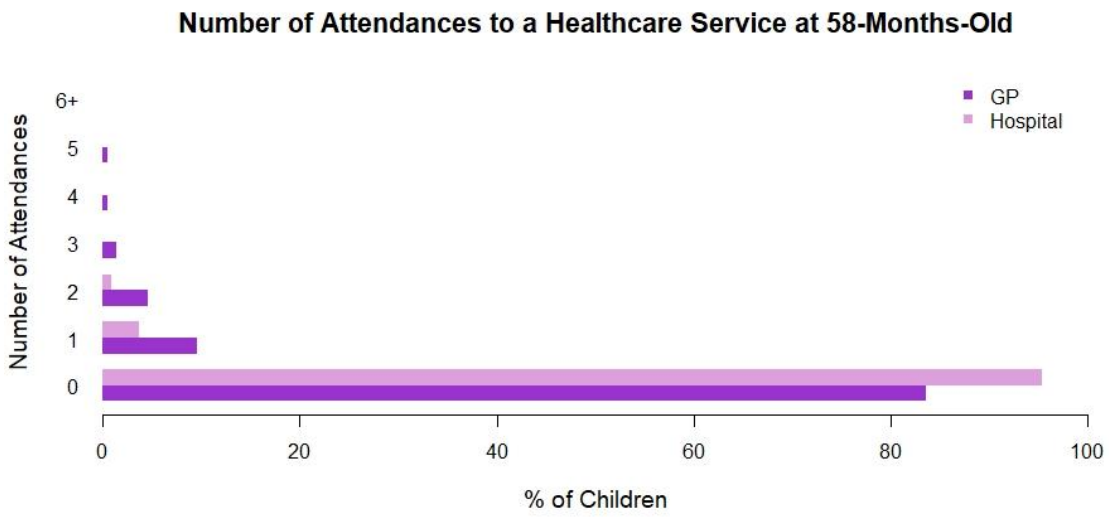


Figure 92: GP and hospital attendance rates at 58-months-old

4.5.10.4.1 Impact of Risk Factor Exposure on Healthcare Service Usage

4.5.10.4.1.1 GP Attendance

Visits to a GP for a respiratory problem were more likely amongst children who had a co-morbidity (OR = 3.12, 95% CI = 1.46 - 6.69), and children were born prematurely

(OR = 5.30, 95% CI = 1.83 - 15.34). GP visitation was also more likely amongst children with school-educated mothers, compared to those with degree-educated mothers (OR = 3.05, 95% CI = 1.37 - 6.80).

4.5.10.4.1.2 Hospital Attendance

Hospital visitations for a respiratory problem were more likely amongst children with a co-morbidity (OR = 12.17, 95% CI = 2.92 - 50.67).

4.5.10.4.2 Total LRSQ Score vs Healthcare Service Usage

At 58-months-old, there was a moderate correlation between total LRSQ score and GP attendance rate (r_s = 0.541, p = <0.001). There was a weak correlation between total LRSQ score and hospital attendance rate (r_s = 0.303, p = <0.001). These results suggest the children with the most severe respiratory disease, are not necessarily the ones who are more likely to seek medical assistance. **Figures 93** and **94** show the correlations graphically.

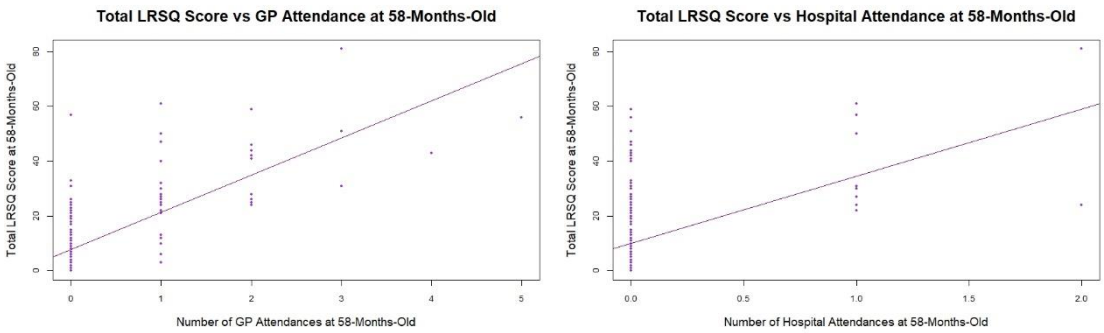


Figure 93: correlation between total LRSQ score and GP attendance rate at 58-months-old
Figure 94: correlation between total LRSQ score and hospital attendance rate at 58-months-old

4.5.11 Summary Table

Table # outlines how the four most clinically-relevant outcomes of the LBBS were affected by the various risk factors being assessed, at every age in the study. The risk factors that influenced total LRSQ and domain 7 scores are summarised – because it is important to understand what causes overall respiratory wellbeing and QoL to worsen, respectively. The risk factors that impacted GP and hospital attendance are also summarised – since it is important to understand what makes healthcare visitation more likely.

Age (months)	Total LRSQ Score	Domain 7 Score	GP Attendance	Hospital Attendance
4	Co-Morbidity Family History of Atopy Male No Bedroom Sharing	Co-Morbidity Family History of Atopy No Bedroom Sharing	Antenatal ETS Exposure Attended Nursery Bedroom Sharing Co-Morbidity Household Children More Deprived Not Breastfed Younger Mother	Co-Morbidity Male Household Children Not Breastfed Premature Twin Younger Mother
10	Attended Nursery Caucasian Co-Morbidity Less Educated Mother Male Younger Mother	Attended Nursery Caucasian Co-Morbidity Household Children Less Educated Mother Male Younger Mother	Attended Nursery Family History of Atopy Less Educated Mother Low Birthweight Not Breastfed Premature Younger Mother	Co-Morbidity Less Educated Mother Low Birthweight Premature
16	Attended Nursery Male More Deprived Premature	Attended Nursery Household Children Male No Antenatal ETS Exposure	Attended Nursery Family History of Atopy Less Educated Mother Male Premature	Less Educated Mother
22	Attended Nursery More Educated Mother No Co-Morbidity No Family History of Atopy	More Educated Mother	More Educated Mother	
28	Attended Nursery Co-Morbidity Family History of Atopy Male Normal Birthweight	Attended Nursery Co-Morbidity Normal Birthweight	Co-Morbidity Family History of Atopy No Household Children	Bedroom Sharing Co-Morbidity

34	Attended Nursery Breastfed Co-Morbidity Family History of Atopy More Deprived No Household Children Non-Caucasian Singleton Younger Mother	Attended Nursery Breastfed Co-Morbidity No Household Children	Family History of Atopy No Household Children Less Educated Mother Not Breastfed Younger Mother	Bedroom Sharing No Household Children
40	Attended Nursery Born at Term Co-Morbidity Family History of Atopy Male Younger Mother	Attended Nursery Co-Morbidity Younger Mother	Breastfed for 1-4 Months Co-Morbidity Younger Mother	Co-Morbidity Female
46	Co-Morbidity Premature	Co-Morbidity Low Birthweight No Bedroom Sharing Premature Twin	Co-Morbidity Less Educated Mother Younger Mother	Co-Morbidity
52	Antenatal ETS Exposure Co-Morbidity Family History of Atopy Exposed to ETS Less Educated Mother Male Normal Birthweight Younger Mother	Co-Morbidity Family History of Atopy Male Normal Birthweight	Breastfed for 1-4 Months Co-Morbidity Exposed to ETS Younger Mother	Co-Morbidity Not Breastfed
58	Co-Morbidity Less Educated Mother Premature Twin	Breastfed for 1-4 Months Co-Morbidity Less Educated Mother Premature Twin	Co-Morbidity Less Educated Mother Premature	Co-Morbidity

Table 37: summary table of risk factor impact on select outcomes

4.6 Longitudinal Analysis

This section of the results is dedicated to the longitudinal analysis of the LBBS. Using multi-level mixed effects modelling, the risk factors that collectively affected a child's total/domain LRSQ score the most – throughout the entire pre-school period – have been identified.

4.6.1 Total LRSQ Score

Throughout the pre-school period, total LRSQ score increased when a child: had a co-morbidity, attended nursery, had a family history of atopy and was breastfed for 1 to 4 months. The score decreased when a child's mother was degree-educated.

Risk Factor	Direction of Effect	Coefficient	95% CI	p-value
Co-Morbidity	Increase	9.93	8.37 – 11.49	<0.001
Nursery Attendance	Increase	3.22	2.20 – 4.23	<0.001
Family History of Atopy	Increase	2.05	1.03 – 3.06	0.001
1-4 Months of Breastfeeding	Increase	1.88	0.15 – 3.60	0.033
Degree-Educated Mother	Decrease	-1.72	-3.31 – -0.14	0.033

Table 38: the muli-level mixed effects model for total LRSQ score

4.6.2 Domain 1: Daytime Symptoms

Throughout the pre-school period, domain 1 score increased when a child: had a co-morbidity, attended nursery and had a family history of atopy. The score decreased when a child's mother was degree-educated.

Risk Factor	Direction of Effect	Coefficient	95% CI	p-value
Co-Morbidity	Increase	1.33	1.10 – 1.57	<0.001
Nursery Attendance	Increase	0.43	0.28 – 0.58	<0.001
Family History of Atopy	Increase	0.24	0.09 – 0.40	0.002
Degree-Educated Mother	Decrease	-0.25	-2.73 – -0.13	0.012

Table 39: the muli-level mixed effects model for domain 1 of the LRSQ

4.6.3 Domain 2: Night-Time Symptoms

Throughout the pre-school period, domain 2 score increased when a child: had a co-morbidity, attended nursery, had a family history of atopy and was breastfed for 1 to 4 months. The score decreased when a child was not born as a twin.

Risk Factor	Direction of Effect	Coefficient	95% CI	p-value
Co-Morbidity	Increase	1.50	1.18 – 1.83	<0.001
Nursery Attendance	Increase	0.60	0.39 – 0.82	<0.001
Singleton Birth	Decrease	-0.82	-1.53 – -0.10	0.025
Family History of Atopy	Increase	0.23	0.02 – 0.44	0.030
1-4 Months of Breastfeeding	Increase	0.32	0.01 – 0.64	0.042

Table 40: the muli-level mixed effects model for domain 2 of the LRSQ

4.6.4 Domain 3: Symptoms with Colds

Throughout the pre-school period, domain 3 score increased when a child: had a co-morbidity, attended nursery and had a family history of atopy. The score decreased when a child: was born at a 'low birthweight' and shared a bedroom.

Risk Factor	Direction of Effect	Coefficient	95% CI	p-value
Co-Morbidity	Increase	1.86	1.46 – 2.26	<0.001
Nursery Attendance	Increase	1.23	0.97 – 1.50	<0.001
Family History of Atopy	Increase	0.55	0.30 – 0.81	<0.001
Low Birthweight	Decrease	-0.67	-1.14 – -0.19	0.006
Sharing a Bedroom	Decrease	-0.36	-0.61 – -0.06	0.015

Table 41: the muli-level mixed effects model for domain 3 of the LRSQ

4.6.5 Domain 4: Symptoms without Colds

Throughout the pre-school period, domain 4 score increased when a child: had a co-morbidity and attended nursery, and their mother was exposed to ETS during pregnancy. The score decreased when a child's mother was ≥35-years-old at the time of their birth.

Risk Factor	Direction of Effect	Coefficient	95% CI	p-value
Co-Morbidity	Increase	1.03	0.85 – 1.21	<0.001
Maternal Age of ≥35-Years-Old	Decrease	-0.39	-0.65 – -0.13	0.003
Antenatal ETS Exposure	Increase	0.24	0.08 – 0.39	0.003
Nursery Attendance	Increase	0.12	0.01 – 0.24	0.039

Table 42: the muli-level mixed effects model for domain 4 of the LRSQ

4.6.6 Domain 5: Symptoms with Increased Activity

Throughout the pre-school period, domain 5 score increased when a child: had a co-morbidity, attended nursery, was breastfed for 1 to 4 months and had a family

history of atopy. The score decreased when a child's mother was ≥35-years-old at the time of their birth.

Risk Factor	Direction of Effect	Coefficient	95% CI	p-value
Co-Morbidity	Increase	1.31	1.09 – 1.52	<0.001
Nursery Attendance	Increase	0.27	0.12 – 0.41	<0.001
1-4 Months of Breastfeeding	Increase	0.29	0.08 – 0.50	0.008
Maternal Age of ≥35-Years-Old	Decrease	-0.40	-0.72 – -0.08	0.015
Family History of Atopy	Increase	0.17	0.02 – 0.31	0.021

Table 43: the muli-level mixed effects model for domain 5 of the LRSQ

4.6.7 Domain 6: Other Respiratory Symptoms

Throughout the pre-school period, domain 6 score increased when a child: had a co-morbidity and shared a bedroom. The score decreased when a child attended nursery.

Risk Factor	Direction of Effect	Coefficient	95% CI	p-value
Co-Morbidity	Increase	0.81	0.64 – 0.99	<0.001
Nursery Attendance	Decrease	-0.14	-0.25 – -0.02	0.025
Sharing a Bedroom	Increase	0.12	0.0004 – 0.24	0.049

Table 44: the muli-level mixed effects model for domain 6 of the LRSQ

4.6.8 Domain 7: QoL of the Child

Throughout the pre-school period, domain 7 score increased when a child: had a co-morbidity, attended nursery and had a family history of atopy. The score decreased when a child shared a bedroom.

Risk Factor	Direction of Effect	Coefficient	95% CI	p-value
Co-Morbidity	Increase	0.92	0.71 – 1.14	<0.001
Nursery Attendance	Increase	0.37	0.23 – 0.52	<0.001
Sharing a Bedroom	Decrease	-0.23	-0.38 – -0.08	0.002
Family History of Atopy	Increase	0.16	0.02 – 0.30	0.028

Table 45: the muli-level mixed effects model for domain 7 of the LRSQ

4.6.9 Domain 8: QoL of the Parent

Throughout the pre-school period, domain 8 score increased, when a child: had a co-morbidity, attended nursery, lived with other children and had a family history of atopy. The score decreased when a child was not born as a twin.

Risk Factor	Direction of Effect	Coefficient	95% CI	p-value
Co-Morbidity	Increase	1.67	1.40 – 1.95	<0.001
Nursery Attendance	Increase	1.24	1.06 – 1.42	<0.001
Living With Other Children	Increase	0.36	0.18 – 0.54	<0.001
Family History of Atopy	Increase	0.26	0.07 – 0.44	0.005
Singleton Birth	Decrease	-0.70	-1.29 – -0.10	0.021

Table 46: the muli-level mixed effects model for domain 8 of the LRSQ

4.7 Validation of the LRSQ

This section of the results describes the validation of the LRSQ. Cronbach's alpha has been calculated for each domain of the questionnaire, then used to evaluate the internal consistency of the corresponding domain.

Based upon data from all ten questionnaires, the LRSQ demonstrates good to excellent internal consistency in a longitudinal study. Excellent internal consistency – meaning an $\alpha \geq 0.9$ – was observed in four of the domains: domain 3 (symptoms with colds), domain 5 (symptoms with increased activity), domain 7 (QoL of the child) and domain 8 (QoL of the parent). Good internal consistency – meaning an $\alpha \geq 0.8$ – was observed in the other four domains: domain 1 (daytime symptoms), domain 2 (night-time symptoms), domain 4 (symptoms without colds) and domain 6 (other respiratory symptoms). **Table 47** describes the internal consistency of each domain.

Domain	Cronbach's Alpha Coefficient	Internal Consistency
1	0.8871	Good
2	0.8987	Good
3	0.9217	Excellent
4	0.8816	Good
5	0.9088	Excellent
6	0.8879	Good
7	0.9080	Excellent
8	0.9119	Excellent

Table 47: internal consistency of the eight LRSQ domains

Chapter 5: Discussion

Chapter 5 provides an opportunity to discuss the execution of the LBBS. The principle findings of the study have been outlined. Areas of strength and weakness have then been acknowledged, and compared to previous research, in each of the seven areas of analysis. Consideration has also been given as to how the LBBS can provide opportunities for future research.

5.1 Principle Findings

The primary objective of the LBBS, was "to describe parentally-reported respiratory symptoms within a population-based birth cohort, as they are followed longitudinally". Not only has the study successfully achieved this objective, but it is the first UK birth cohort study to do so via a predominantly online platform. The secondary objective of the LBBS was "to examine any associations between different respiratory symptoms, and exposure to different risk factors". Again, the study successfully achieved this aim through cross-sectional and longitudinal analyses of its cohort. The cross-sectional analysis of the LBBS produced many results, but how exposure to different risk factors affects a child's total LRSQ score, is the most important – as this is how the respiratory wellbeing of pre-school-aged children can be assessed in clinical practice. Mean and median total LRSQ scores increased until 16-months-old, then had a general decline thereafter – suggesting that respiratory wellbeing improves with age. Total LRSQ scores were most significantly increased by: having a family history of atopy, being male, having a younger mother, attending nursery, and having a co-morbidity. Higher total LRSQ scores were consistently correlated with a worse QoL for children in the LBBS, and with an even worse QoL for their parents. The longitudinal analysis revealed that throughout the entire pre-school period, nearly-all total/domain LRSQ scores were significantly increased by having a co-morbidity, attending nursery, and having a family history of atopy. Being born to a degree-educated mother, or a mother aged ≥35-years-old, resulted in lower LRSQ scores for certain domains – as did being a singleton birth.

All of the objectives of this particular thesis, have been fulfilled too. One particular objective of this thesis was to validate the LRSQ for use in longitudinal studies. This has been accomplished, because the questionnaire's eight domains show good to excellent internal consistency when used throughout the first five years of childhood.

5.2 Strengths and Weaknesses

5.2.1 Recruitment and Enrolment

The LBBS was weakened by poor recruitment and enrolment. 18.8% of eligible births at LWH were recruited into the LBBS. 29.4% of these births were actually enrolled onto the study – accounting for 5.5% of the eligible births at LWH. With greater resources, recruitment and enrolment could have been higher – especially if additional locations had been used to 'source' participants. Families from more peripheral postcode districts in the study's inclusion zone, could have been recruited from Whiston Hospital and Ormskirk Hospital. The LBBS could potentially have recruited home births with greater resources too, since 2.3% of women in England & Wales delivered at home in 2013. [309]

The LBBS's recruitment rate was lower than previous regional birth cohort studies'. ALSPAC, MAAS and BiB all began their recruitment processes antenatally, and were able to recruit 72%, 63% and 54% of their eligible populations respectively. [271,275,281] Like the LBBS, TCRS recruited immediately after birth, and achieved a recruitment rate of 78%. [278] If the LBBS had also recruited and/or begun data collection antenatally, then its recruitment and enrolment rates may have been more similar to the aforementioned studies. [271,274,275] These studies utilised midwives, paediatricians, research nurses and/or dedicated recruitment teams to manage their recruitment drives. [272,274,278,281] The LBBS relied on two MPhil students, to share the responsibility of recruiting approximately 15,000 eligible infants. Had the LBBS used additional staff to assist with recruiting eligible participants, then its recruitment rate might have been closer to the 69% projection that was borne from the pilot study. [284,285] BiB translated its study materials into Urdu and Mirpuri, which increased participation amongst non-English-speaking parents. If the LBBS had also been accessible in languages other than English, then more parents could have been recruited. In Liverpool, it would have been useful to have study materials available in Chinese, Polish, Arabic and Somali – as

these are the most widely-spoken foreign languages. The LRSQ would have to be validated in these languages first though. [310] Both ALSPAC and BiB advertised their studies in public places, especially those popular with pregnant women. [272,274] A wider use of advertising may therefore have been beneficial to the LBBS's recruitment strategy.

A strength of the recruitment process was that it was conducted near-continuously for almost two years, thereby mitigating seasonal variations in respiratory symptoms. With year-round recruitment and biannual assessments, even if a child was first followed-up in Winter (when respiratory symptoms are typically more frequent), they would next be followed-up in Summer (when respiratory symptoms are typically less common) and vice versa – thus controlling for seasonal effects across the cohort. Previous birth cohort studies in the UK have recruited for just a week, thus making them susceptible to seasonal variation. [268,311,312]

5.2.2 Cohort Profile

The representativeness of the study cohort was a weakness of the LBBS, although, this is not uncommon in regional birth cohort studies. The ALSPAC cohort was less deprived, and parents in BiB and TCRS were older, than their respective eligible study populations. TCRS had more educated parents than expected too. [273,278,281] These findings mirror what was seen in the LBBS. Like the LBBS, ALSPAC and TCRS also contained more Caucasian children than was to be expected. [273,278] BiB did not have this problem, because it translated its study materials into Urdu/Mirpuri. [274] Had the LBBS translated its study materials into different languages too, then the representativeness of ethnic minorities in its cohort could have been higher. Compared to the eligible population for the study, the LBBS cohort also contained more preterm, Caucasian and breastfed children – as well as less mothers who smoked during pregnancy. The significantly higher prevalence of premature and 'low birthweight' infants amongst the LBBS cohort, as compared to LWH and England respectively, may be explained by the recruitment location. LWH is a tertiary-level maternity centre, so can be expected to witness a higher-than-average number of premature and 'low birthweight' infants. Such infants are likely to 'visit' in the neonatal unit – where the LBBS was advertised. The increased exposure to advertising material,

from parents who were regularly visiting the neonatal unit, may therefore have prompted greater enrolment into the LBBS; parental experiences of neonatal research may also have increased their willingness to participate. Premature and 'low birthweight' infants are more likely to be kept in hospital for longer after birth too, so in the LBBS, their parents simply had a greater chance of being approached by a member of the research team.

Social desirability bias may have been another factor, which contributed to the unrepresentativeness of the LBBS cohort. Questionnaire respondents are known to be less forthcoming about 'undesirable' traits, in order to reflect themselves in a positive light. [313] The prevalence of antenatal tobacco smoking and antenatal ETS exposure (undesirable traits) within the LBBS cohort may therefore be under-reported, and the prevalence of breastfeeding (a desirable trait) may be over-reported. However, there is also a chance that antenatal tobacco smoking and ETS exposure were over-reported in the LBBS cohort. In the first questionnaire, items about smoking did not specifically refer to *tobacco smoking*, so parents may have answered these questions with regards to vaping or cannabis smoking – especially since the use of vapes was rapidly increasing throughout the recruitment period. [314]

Another weakness of the LBBS, was that it missed opportunities to find out about additional risk factor exposures from the cohort. The study had the capacity to enquire about more antenatal and postnatal risk factors, which have previously been associated with poor paediatric respiratory health. Questionnaires could have easily asked parents about their child's living conditions and diet; the first questionnaire could also have asked parents about their own diet, as well as drug use, during pregnancy. All these risk factors are known to influence respiratory wellbeing during childhood. [59,96,97,114,118] A child's exposure to air pollution could also have been estimated, based on their postcode – similar to how IMD deciles were calculated. On the other hand, by actually enquiring about multiple births, the LBBS may have been further weakened. Each child in the study should have had a unique degree of exposure to the various risk factors being assessed; however, there is likely to have been an identical degree of exposure to many risk factors (e.g. ETS or other children) between twins – due to them sharing the same environment. This makes their data

less independent, which subsequently makes the cross-sectional and longitudinal analyses harder to interpret. It may therefore have been beneficial to disregard one twin from the dataset, or to employ more advanced regression techniques. [315]

5.2.3 Attrition

Attrition from the LBBS was one of the study's weaknesses. Attrition was greatest until the third questionnaire at 16-months-old, then plateaued thereafter. After five years, 31.9% of the LBBS cohort was still responding to questionnaires. To contrast, after five years: ALSPAC was receiving responses from 80% of its cohort, MAAS was receiving responses from 89% of its cohort, and TCRS was receiving responses from 87% of its cohort. [274,277,278] The rate of attrition was therefore much higher in the LBBS, than in previous regional birth cohort studies. To keep their participants engaged, the previous studies utilised: websites, newsletters, social media updates, birthday cards, press briefings and local meetings. [271,272,281] Of these, the LBBS had birthday e-cards, a website and a newsletter. Due to the ever-changing research team, the latter two became neglected – which may have resulted in disengagement, and then attrition, from some parents. A consistent research team has previously been proven to aid participant retention, as has: sending phone call reminders, offering alternative methods of data collection, and issuing 'locator documents'. [291] Although the LBBS did not issue telephone reminders, it did use email reminders to prevent attrition. The effectiveness of reminders is contradictory however: one systematic review found them to be the most useful tool for reducing attrition, yet another found them detrimental to response rates. [291,316] The LBBS did not offer a monetary incentive either, which is known to increase questionnaire response rate. [317]

The so-called 'digital divide' may have been a limitation of the LBBS, which contributed towards attrition. 22% of parents indicated a desire to receive postal questionnaires during the pilot recruitment study, even though 97% of households with children in the UK had internet access in 2013. [318] This may have been an indication that the study was not accessible to the entire eligible study population, so when the LBBS stopped using postal questionnaires, those without internet access would have been *forced* to drop-out. That attrition was particularly high amongst deprived and less educated individuals in the LBBS, may therefore be explainable by poorer internet access rates

amongst these groups. [319,320] Given that deprivation and a lower level of maternal education are known risk factors for poor paediatric respiratory health (see Section 2.3), the 'digital divide' may also have weakened the LBBS by introducing a severity bias. If the children who were most exposed to harmful risk factors, were also being *forced* to drop-out, then only the healthiest children would remain in the LBBS – so average LRSQ scores would become lower.

Despite the LBBS's attrition rate being greater than other studies', the characteristics of those who do drop-out are similar. Mothers who were younger, who were less educated, and who lived in deprived areas, were more likely to be lost to attrition in ALSPAC. [273] Mothers with the same characteristics were lost from the LBBS at a greater rate too – especially those living in the most deprived IMD decile(s). One of the LBBS's strengths therefore, was that in order to mitigate for imbalances in IMD decile representation throughout the study, the cohort was weighted during analysis. Results would have lacked ecological validity, and been unapplicable to the population of Liverpool, had the cohort not been weighted. Additionally, Koshy *et al.* found that attrition was markedly increased amongst children whose parents smoked during pregnancy. [321] Mothers who smoked during pregnancy were lost from the LBBS at a greater rate too. In the LBBS, there was also noticeable attrition from children who were: not breastfed, born prematurely, non-Caucasian, or born at a 'low birthweight'.

Another of the LBBS's strengths, was that it had very little risk of being unable to contact participants – which should have prevented some attrition. Previous birth cohort studies have relied on contacting participants via post and landline telephone, because of poor accessibility to modern technology at the time; a change of address would therefore leave said participants uncontactable. As the LBBS was (the UK's first) online birth cohort study, only a change of email address could have resulted in a failure to contact. Some attrition in the LBBS might also have been prevented, because the study was well-accepted by many parents. In the early PPI sessions, some parents were disappointed that they could not be further involved with the study. [285] This suggests that the study's objectives were important to parents in Liverpool, and so said parents may have been endeavoured to remain involved with the study.

5.2.4 Cross-Sectional Analysis

The cross-sectional analysis of LBBS was strengthened, by the concurrence of its results with the existing literature. As outlined in Section 2.3 of this thesis, respiratory health is known to be worse amongst children who: are male, attend nursery, have a co-morbidity, have a family history of atopy, are exposed to ETS, have a younger mother, or have a mother who smoked antenatally. That previous research supports the findings of the cross-sectional analysis, implies that the study was valid. The results of the cross-sectional analysis were also made more valid, because an effort was made to increase the statistical power of some of the analyses. Similar deprivation/maternal age/maternal education groups were combined for the cross-sectional analysis, to create fewer – but larger – groups. Not only did this provide less opportunity for issues relating to multiple testing to occur, but it also provided more statistical power when analysing the effects of deprivation/maternal age/maternal education upon respiratory health. The cross-sectional analysis still had limited statistical power however, because attrition from the LBBS resulted in large amounts of missing data. If the LBBS had more resources, some missing data (e.g. healthcare service attendance rates) could have been sourced from clinical records to increase the statistical power of its analyses – just as BiB did, and C-GULL will in the future. [272,281,283]

The presence of type I errors in the results of the cross-sectional analysis, was one of the LBBS's weaknesses. Breastfeeding was associated with higher total LRSQ scores at 34-months-old. Most literature describes breastfeeding as being protective towards paediatric respiratory health, such an effect was seen in various domains at the other timepoints. [59–62] The type I error at 34-months-old is therefore likely to be a chance finding. The negative impact of smoking on respiratory health is well-established, yet at 16 and 34-months-old, higher domain scores were seen amongst children who were **not** exposed to ETS, or whose mother did **not** smoke antenatally. [56,111,135,140] These are also likely to be chance findings, but an alternative explanation is that the cross-sectional analysis was inadvertently assessing the impact of ETS *and* vaping. As mentioned in Section 5.2.2 of this thesis, some parents may have reported their vaping status rather than their tobacco smoking status. Although 'passive vaping' is believed to cause children to wheeze, cough and experience more frequent respiratory illness,

it may not be as harmful as ETS upon paediatric respiratory health – thus potentially explaining why LRSQ scores were not necessarily worse amongst children who were exposed to ETS. [322] At 28 and 52-months-old, a 'normal' birthweight was associated with higher total LRSQ scores and various domain scores. However, most research indicates that a 'low birthweight' is detrimental to paediatric respiratory health, not vice versa. [98] Given how marginal the p-values for this particular risk factor were, its significance may have been over-exaggerated in the cross-sectional analysis. Prior research suggests that sharing a bedroom is adverse towards paediatric respiratory health; despite the LBBS finding the opposite to be true at 4-months-old, a type I error should not automatically be assumed, because research in the field is often contradictory. [111,133] That type I errors clearly exist in the cross-sectional results of the LBBS, does question how valid the rest of the results are – so they should be interpreted with caution.

Inaccurate reporting of respiratory symptoms could have been another weakness of the LBBS. Most parents are not medically-qualified, so their perception of what a symptom looks/sounds like may differ greatly from a medical professional's. Cane & McKenzie found that 59% of parents could identify a wheeze from a video clip, and 47% could identify other respiratory noises (e.g. stridor). [323] If a lot of parents have misinterpreted their children's symptoms, then the prevalence of different respiratory symptoms throughout the cross-sectional analysis will have been reported in error. The impact that different risk factors have upon symptom prevalence, as well as LRSQ scores, should therefore be approached with caution too.

The cross-sectional analysis of the LBBS was also likely to have been weakened by the use of univariate statistics. In the real world, it is highly probable that a child's respiratory health will be influenced by more than one risk factor. Thus, the fact that the presence of co-variates was not considered whilst conducting the cross-sectional analysis, may potentially have confounded the results. For example, the prevalence of RTIs is known to be higher amongst children who attend nursery, or live with other children; coughing is a common symptom of RTIs. [2,55,92,93,111] Therefore, if the LBBS were to find that children who attended nursery ***and*** lived with other children had an increased prevalence of coughing, then it would not be possible to conclude whether

both risk factors were genuinely responsible for the increase – or whether they confounded each other. This is just a theoretical example. For the avoidance of doubt, multivariate statistics (e.g. multiple regression models) could have been used instead; multivariate statistics are able to establish a relationship between various risk factors, and an outcome. This removes the potentially confounding effects of co-variates, and makes results more reliable.

Another strength of the cross-sectional analysis, was the minimal risk of it being confounded by recall bias. Recall bias is a phenomenon whereby respondents to a self-report questionnaire provide incorrect responses, because of their inability to accurately recall past events. [324] As a *prospective* birth cohort study, the LBBS only required parents to recall their child's symptoms/healthcare service attendance in the three months prior to completing a questionnaire. Three months is a relatively short recall period, so the influence of recall bias should have been low. [325]

The assumed linearity of correlations between total LRSQ score and total QoL score, may be an additional weakness of the cross-sectional analysis. There is a possibility that the relationship is actually non-linear. **Figure 69** shows that at 40-months-old, total QoL score increases alongside total LRSQ score – until the latter reaches around 60; total QoL scores then appear to decrease, whilst total LRSQ scores continue to increase. Such a trend is likely apparent, because of outliers in the dataset. It should be noted however, that total QoL scores rarely reached values of more than 20 throughout the LBBS. This suggests that extreme total QoL scores are unlikely to be achieved, and so total QoL scores might plateau once the severity of a child's respiratory health (as reflected by their total LRSQ score) reaches a certain point. Such a phenomenon would lend further credence to the hypothesis, that the correlation between QoL and total LRSQ score is not entirely linear – though additional data (especially from children with high total LRSQ scores) is required to test this hypothesis.

5.2.5 Longitudinal Analysis

Missing data is inevitable in cohort studies, because participants drop-out. [316] The longitudinal analysis of the LBBS was therefore strengthened by the use of multi-level mixed effects modelling, because unlike other analytical techniques (e.g. repeated

measures or multivariate ANOVA), mixed effects modelling can be performed without a complete dataset. [308] It could have been possible to complete the dataset with imputation, which involves substituting missing data with a 'best guess' value (often based off of previous responses). [326,327] However, the fact that respiratory symptoms are prone to fluctuate over time, would have made the prediction of participants' responses inappropriate. On the other hand, if only participants with a complete dataset had been used for the longitudinal analysis, then approximately 6% of the LBBS cohort would have been analysed. This would have reduced the statistical power of any analyses performed, and also made the cohort unrepresentative of the Liverpool population. [308,326]

That questionnaires in the LBBS were completed by parents, was another strength of the longitudinal analysis. le Coq *et al.* suggest that longitudinal studies benefit from parentally-completed questionnaires, because such questionnaires are better at detecting change, compared to those completed by children. [328] If parents were able to notice changes in their child's respiratory symptoms throughout the LBBS, then the reporting of said symptoms would have been more accurate. The results of the longitudinal analysis can therefore be considered more reliable.

Most results in the longitudinal analysis agree with others' findings. As discussed in Section 2.3 of this thesis, nursery attendance, having a co-morbidity, being born at a 'low birthweight', and having a family history of atopy are all known risk factors for paediatric respiratory disease – along with having a mother who was exposed to ETS during pregnancy. Having an older and/or more educated mother is known to be beneficial to paediatric respiratory health too. [84,104,123] The existing literature contains conflicting evidence as to how sharing a bedroom, and living with other children, impacts the prevalence of paediatric respiratory disease. [89,111,133] The LBBS's longitudinal analysis also produced conflicting evidence as to how sharing a bedroom affects the prevalence of respiratory disease in the pre-school period, however living with other children was only found to be increase the prevalence of respiratory disease.

Not every result from the longitudinal analysis was supportive of existing research though. Breastfeeding is widely considered to be protective towards paediatric

respiratory health, yet the LBBS found breastfeeding for 1 to 4 months to cause an increase in total LRSQ scores, as well as domain 2 and domain 5 scores during the pre-school period. [59,61] The former two findings were marginally significant, so may be due to chance. However, it should be noted that more than four months of breastfeeding is typically associated with the protective effect – which may explain why children who were breastfed for less time had worse scores. [54,60] Also, previous research by Wright *et al.* found that breastfeeding increased the risk of wheezing amongst atopic children with atopic mothers. [62] Since having a co-morbidity and having a family history of atopy were also in the relevant mixed effects models, the apparent detrimental effect of breastfeeding for 1 to 4 months should not immediately be assumed to be a type I error.

5.2.6 Validation of the LRSQ

The internal consistency of the LRSQ was stronger when analysed longitudinally, than when analysed cross-sectionally – suggesting that the LRSQ is more suitable for longitudinal use, than for one-off use. The LRSQ showed questionable ($\alpha \geq 0.6$) to good ($\alpha \geq 0.8$) internal consistency when used cross-sectionally, which is similar to the findings of when Trinick *et al.* used the questionnaire on pre-school-aged children with CF. [147] Trinick *et al.* also found the internal consistency of domain 2 to be weakened, by including the question about snoring. [147] The LBBS does not support this finding, because the alpha of domain 2 was increased by including the question. The LBBS did however find that the internal consistency of domain 3 was marginally weakened by asking about the number of colds that a child had experienced.

The number of children used to validate the LRSQ for longitudinal use, was another strength of the validation. 114 children were used to validate the original LRSQ, which has drawn criticism from Strippoli *et al.* for being too small a sample. [143,185] All 687 children in the LBBS cohort were included in the validation, because test-retest stability was not being assessed. Test-retest stability is a measure of reliability, which represents a tool's aptitude for reproducing the same results from a user, when delivered at different timepoints. In the LBBS, it was expected that a child's responses to the LRSQ would change between timepoints – so assessing test-retest stability was not applicable. If test-retest stability had been assessed, then children would have to

of been excluded if they had missing data – as they were in the original validation – so the LBBS' sample would have been far smaller. However, test-retest stability could have been assessed *ad hoc*, using duplicated responses from the uncleansed dataset.

The accessibility of the LRSQ was a limitation of the its validation. The questionnaire is appropriately readable, because a Flesch reading ease test was conducted as part of its original validation. [143] However, because the LRSQ has not been validated in a language other than English, it cannot be used on non-English-speaking parents. This prevents it from being used in future longitudinal studies, in many locations across the world. Another weakness of the LRSQ's validation was the confounding effect of the fourth questionnaire upon all of the LRSQ's domains. There is no apparent logic behind this finding, so it likely to be due to chance. If the fourth questionnaire were to be excluded from Cronbach's alpha calculations, the internal consistency of every domain would improve – and six domains (instead of four) would display excellent internal consistency.

5.3 Future Opportunities

Previous validations of the LRSQ, including its longitudinal validation, have all been conducted by the same group of researchers. [143,146,147] For the questionnaire to have more ecological validity, it should be further validated by an independent research department outside of Liverpool. It would also be advantageous to validate the LRSQ in additional languages, to facilitate its use outside of anglophone countries. Additionally, if a clinically meaningful change in LRSQ score – according to both clinicians and parents – was calculated, then the questionnaire could be validated as not just a tool for measuring symptom prevalence, but also for monitoring disease severity/control. Many other paediatric respiratory symptom questionnaires have established clinically meaningful changes in their score, as a way of establishing whether a child's symptoms and/or QoL are worsening. [174,187,191,197,202,208,217,246]

The LBBS has clearly identified how the respiratory health of pre-school-aged children is detrimentally impacted by: being male, having a co-morbidity, attending nursery, having a family history of atopy, and having a younger mother. Therefore, future research should now focus on how less-clearly established risk factors, as identified by

the LBBS, impact paediatric respiratory health. Such research could investigate: maternal education, living with other children, sharing a bedroom, birthweight, and multiple birth.

Data collection for the LBBS ended eighteen months before the height of the COVID-19 pandemic, but the study still has access to its cohort of children and parents. If some of the cohort was willing to get reinvolved with the LBBS, then near-future research could investigate how the pandemic affected the respiratory health and QoL of primary school children, as well as their parents.

Finally, the LBBS will aim to make its (anonymised) dataset publicly available, for external researchers to use. There is potential for this dataset to be used in systematic reviews, meta-analyses or epidemiological studies. The dataset could even be incorporated into a larger birth cohort study – not unlike MeDALL. [329]

Chapter 6: Conclusions

The LBBS studied a population that somewhat differed from the actual population of Liverpool. The LBBS cohort represented 5.5% of infants who were eligible to participate. Compared to what was expected, the study cohort was comprised of: lower birthweight infants, more breastfed infants, fewer families in deprivation, more Caucasian infants, more premature infants, older mothers, more educated mothers, and fewer mothers who smoked antenatally. Over 65% of the cohort was lost to attrition – mostly in the first sixteen months of study. More deprived families and less educated mothers were particularly likely to drop-out of the LBBS, thus accentuating any disparities between the LBBS cohort and the population of Liverpool.

From the cross-sectional and longitudinal analyses, several risk factors have been found to significantly increase the prevalence of respiratory symptoms during the first five years of life. These include: having a co-morbidity, nursery attendance, having a family history of atopy, being male, not sharing a bedroom, and having a younger mother. Other risk factors affect the prevalence of respiratory symptoms too, but with less consistency. Children who experience an increased prevalence of respiratory symptoms, experience a poorer QoL as well – but not as poor as their parents'. However, said children do not necessarily frequent healthcare services more regularly. In order to reduce the prevalence of respiratory symptoms in future generations of pre-school-aged children, and subsequently improve their QoL, it will be important to address the aforementioned underlying risk factors.

The LBBS has also proven that the LRSQ is a valid tool to use in longitudinal studies of pre-school-aged children. Across the first five years of life, the questionnaire shows good to excellent internal consistency in its eight domains. It has already been established to have good face validity, but will need further validation from an independent cohort of pre-school-aged children.

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Appendix

Appendix 1: Study Protocol

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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Professor Ben Shaw

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.

2

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 (WVRSS 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

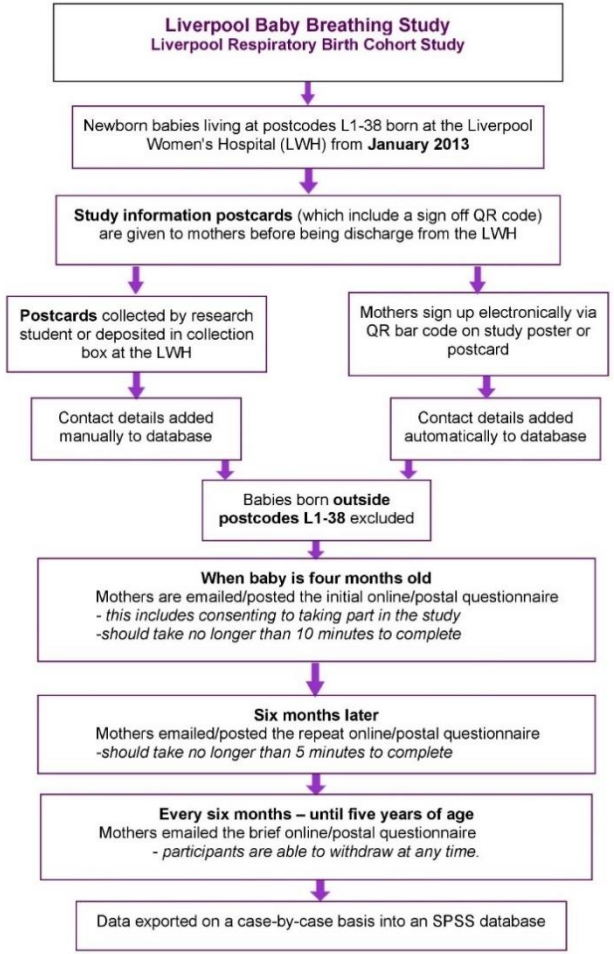
The University of Liverpool will be lead sponsor and the Liverpool Women's NHS Foundation Trust will co-sponsor for the study.

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



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 2: The Original LRSQ

Copyright Liverpool Womens Hospital

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 any time in the past?	*Yes*	*No*

2. The next questions are specifically aimed at the last three months:

A) During the day (when awake) 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*

B) During the night (when asleep) in the last three months :

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*

Name of Child **Study Number**

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

None *one* *two* *three* *more than three* *always 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*

Name of Child **Study Number**

E) When my child has been MORE ACTIVE (e.g. crawling, walking or when excited) 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 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 last three months:

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*

Name of Child **Study Number**

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

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 last three months:

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*

Appendix 3: Consent Form (Postal Version)

UNIVERSITY OF LIVERPOOL

Liverpool Women's NHS Foundation Trust
Dedicated to you

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

UNIVERSITY OF LIVERPOOL

Consent Form

Liverpool Women's NHS Foundation Trust
Dedicated to you

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 : _____

Appendix 4: Questionnaire One

UNIVERSITY OF LIVERPOOL

Liverpool Women's

Welcome, and thank you for your interest in...

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!

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Liverpool Women's

About Your Pregnancy, Birth and New Baby

You will only need to give us these details once

1. What is your new baby's first name?

2. What is your new baby's last name?

3. Is your new baby:

O Male O Female

4. What is your new baby's date of birth?

5. What best describes your new baby's ethnic group or background?

O I would prefer not to say
O White - British
O White - Any other white background
O Mixed or multiple ethnic groups
O African, Caribbean or any other black ethnic group
O Asian - Indian, Pakistani or Bangladeshi or any other ethnic group
O Eastern Asian- Chinese or any other ethnic group
O Other - Please Specify

6. How many weeks 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?

O Yes O No

9. Did **any member** of your household smoke, *anywhere* or at *any time* during your pregnancy?
A household member means someone who sleeps or regularly takes meals at your house.

O Yes O 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*

O Yes O No

If yes, how long did you breast feed for?

O Less than 1 month O 1-3 months O I am still breast feeding

UNIVERSITY OF LIVERPOOL

Liverpool Women's

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

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Liverpool Women's

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:

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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)*

O Not at all O A few days O Some days O Most days O Every day

21. My new baby has had a cough

O Not at all O A few days O Some days O Most days O 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)*

O Not at all O A few days O Some days O Most days O Every day

23. My new baby has been short of breath

O Not at all O A few days O Some days O Most days O 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)*

O Not at all O A few nights O Some nights O Most nights O Every night

25. My new baby has had a cough

O Not at all O A few nights O Some nights O Most nights O 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)*

O Not at all O A few nights O Some nights O Most nights O Every night

27. My new baby has been short of breath

O Not at all O A few nights O Most nights O Some nights O Every night

28. My new baby has snored:

O Not at all O A few nights O Most nights O Some nights O Every night

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Your New Baby's Health

29. How many colds *(runny nose, and high temperature)* has your new baby had in the last three months?

O 0 O 1 O 2 O 3 O 4 O 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)*

O Not at all with colds O A few days O Some days O Most days
O Every day

31. My new baby has had a cough

O Not at all with colds O A few days O Some days O Most days
O 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)*

O Not at all with colds O A few days O Some days O Most days
O Every day

33. My new baby has been short of breath

O Not at all with colds O A few days O Some days O Most days
O 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)*

O Not at all O A few days O Some days O Most days O Every day

35. My new baby has had a cough

O Not at all O A few days O Some days O Most days O 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)*

O Not at all O A few days O Some days O Most days O Every day

37. My new baby has been short of breath

O Not at all O A few days O Some days O Most days O Every day

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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)*

O Not at all O A few days O Some days O Most days O Every day

39. My new baby has had a cough

O Not at all O A few days O Some days O Most days O 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)*

O Not at all O A few days O Some days O Most days O Every day

41. My new baby has been short of breath

O Not at all O A few days O Some days O Most days O 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:

O Not at all O A few days O Some days O Most days O Every day

43. My new baby has had fast breathing:

O Not at all O A few days O Some days O Most days O Every day

44. My new baby has had noisy breathing that appears to come from the throat or back of the throat:

O Not at all O A few days O Some days O Most days O Every day

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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

O Not at all O A few days O Some days O Most days O Every day

46. My new baby's chest symptoms have woken up my new baby:

O Not at all O A few nights O Some nights O Most nights O Every night

47. My new baby's chest symptoms have reduced my new baby's activity:

O Not at all O A few days O Some days O Most days O Every day

48. My new baby's chest symptoms have made my new baby unusually tired:

O Not at all O A few days O Some days O Most days O 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:

O Not at all O A few days O Some days O Most days O Every day

50. My new baby's symptoms have resulted in adjustments being made to our family life:

O Not at all O A few days O Some days O Most days O Every day

51. My new baby's chest symptoms have disturbed our sleep:

O Not at all O A few nights O Some nights O Most nights O Every night

52. I have been worried about my new baby's chest symptoms:

O Not at all O A few days O Some days O Most days O Every day

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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

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Liverpool Women's

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,
University of Liverpool,
Alder Hey Children's Hospital NHS FT,
Eaton Road,
Liverpool,
Merseyside
L12 2AP

Appendix 5: Recruitment Postcards

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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.

Please scan this code using your QR reader

Affix Hospital Label Here

Appendix 6: Recruitment Posters

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 7: Exemplar Email

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Liverpool Women's NHS Foundation Trust

Liverpool Baby Breathing Study

The Liverpool Respiratory Birth Cohort Study

Dear *|FNAME|*,

After the birth of your toddler *|MMERGE3|* on *|MMERGE5|* at the Liverpool Women's Hospital, you signed up to our baby study. You have since filled in a few questionnaires about your toddler's respiratory symptoms.

We'd like to thank you for your ongoing participation in the study - we really appreciate your support!

The information you give us is invaluable, *regardless of whether your toddler suffers from respiratory any symptoms*. We hope that you are happy to fill in our next questionnaire. It should take **no longer than 5 minutes.**

Your toddler's unique ID for the questionnaire is *|MMERGE7|*

Please copy or write this down now as you will be asked for this at the start of the questionnaire

PLEASE CLICK HERE

To go straight to the questionnaire about *|MMERGE3|*

Have any of your contact details changed in the last six months?

If so, please enter you new details here, or if you prefer, let us know by replying to this email.

Further information

You can find out more about the Liverpool Baby Breathing Study by visiting our website http://pcwww.liv.ac.uk/~LRBCS/babystudy.htm

What if I no longer wish to participate?

That's not a problem! We kindly ask that you let us know by replying to this email, or remove yourself from the study by entering you email address here. Please note that your decision not to participate will not affect you or your child's future care.

We look forward to hearing from you!

Best wishes,

The Liverpool Baby Breathing Study Research Team

If you have any feedback, questions or concerns about the study, you can contact the research team by replying directly to this email, sending a message to BabyStudy@liverpool.ac.uk or by calling (0151) 282 4532.

Add us to your address book - here's how!

Appendix 8: Coding

Question	Question Code	Responses	Integer
Baby's Gender	BGENDER	Male	0
		Female	1
Multiple Birth	MULTIP	Singleton	1
		Multiple	2
Baby's Ethnicity	BETHNIC	Prefer Not to Say	0
		White – British	1
		White – Other	2
		Mixed	3
		Black	4
		Asian	5
		East Asian	6
		Other	7
Birthweight Units	BWT	Pounds-and-Ounces	1
		Kilograms	2
Antenatal Smoking Status	MSMOKE	No	0
		Yes	1
ETS Exposure During Pregnancy	OSMOKE	No	0
		Yes	1
Location of ETS Exposure During Pregnancy	LSMOKE	Inside the Home	1
		Outside the Home	2
		Inside the Car	3
		Inside Another Location	4
		Other	5
Breastfeeding Status	BF	No	0
		Yes	1
Breastfeeding Duration	BFT	<1 Month	1
		1-4 Months	2
		>4 Months	3
Maternal Education	MQUAL	No Qualifications	0
		Secondary School	1
		GCSEs	2
		Vocational Qualification	3
		A-Levels	4
		Undergraduate Degree	5
		Postgraduate Degree	6
		Other	7
Deprivation	IMD2015	1 - 10	
Nursery Attendance	NURSERY	No	0
		Yes	1
Other Household Children	OCHILD	No	0
		Yes	1
Bedroom Sharing	SBED	No	0

		Yes	1
Who Is The Bedroom Shared With	WSBED	Parent(s)	0
		1 Other Child	1
		2+ Other Children	2
		Other	3
Co-Morbidities	BHCON	No	0
		Yes	1
Type of Co-Morbidity	THCON	Respiratory Condition	1
		Cardiac Condition	2
		Renal Condition	3
		Neurological Condition	4
		Gastrointestinal Condition	5
		Diabetes	6
		Other	7
Family History of Atopy	FHATOPY	No	0
		Yes	1
Who Has Atopy in the Family	WATOPY	Mother	1
		Father	2
		Eldest Sibling	3
		Second-Eldest Sibling	4
		Third-Eldest Sibling	5
		Fourth-Eldest Sibling	6
		Other	7
What Atopic Conditions Does the Mother Have	MATOPY	Asthma	1
		Hay Fever	2
		Eczema	3
What Atopic Conditions Does the Father Have	FATOPY	Asthma	1
		Hay Fever	2
		Eczema	3
What Atopic Conditions Does the Eldest Sibling Have	ECATOPY	Asthma	1
		Hay Fever	2
		Eczema	3
What Atopic Conditions Does the Second-Eldest Sibling Have	SECATOPY	Asthma	1
		Hay Fever	2
		Eczema	3
What Atopic Conditions Does the Third-Eldest Sibling Have	TECATOPY	Asthma	1
		Hay Fever	2
		Eczema	3
What Atopic Conditions Does the Fourth-Eldest Sibling Have	FECATOPY	Asthma	1
		Hay Fever	2
		Eczema	3
What Atopic Conditions Do Additional Siblings Have	OATOPY	Asthma	1
		Hay Fever	2
		Eczema	3
ETS Exposure	HSMOKE	No	0
		Yes	1

Location of ETS Exposure	HLSMOKE	Inside the Home	1
		Outside the Home	2
		Inside the Car	3
		Inside Another Location	4
		Other	5
GP Attendance	BGP	No	0
		Yes	1
Hospital Attendance	BHOS	No	0
		Yes	1
LRSQ Items (x32)		Not at All	0
		A Few Days	1
		Some Days	2
		Most Days	3
		Every Day	4

Appendix 9: Weighting Factors

IMD	Questionnaire									
	1	2	3	4	5	6	7	8	9	10
1	1.41	1.63	1.86	1.95	1.83	1.67	1.80	1.68	1.87	2.00
2	1.79	0.83	0.92	0.82	0.92	1.15	1.03	0.93	0.98	0.84
3	0.89	0.75	0.62	0.67	0.70	0.66	0.53	0.69	0.66	0.62
4	0.86	0.88	0.88	0.99	0.68	0.75	0.78	0.62	0.73	0.75
5	0.80	0.69	0.55	0.52	0.57	0.52	0.49	0.59	0.49	0.58
6	0.67	0.63	0.64	0.53	0.59	0.54	0.86	0.84	0.63	0.51
7	0.60	0.54	0.54	0.57	0.54	0.66	0.61	0.63	0.57	0.55
8	0.63	0.63	0.50	0.58	0.70	0.54	0.46	0.62	0.49	0.55
9	1.07	0.71	0.82	0.76	0.69	1.65	0.89	0.59	0.89	1.13
10	0.35	0.38	0.28	0.33	0.29	0.20	0.59	0.44	0.53	0.28

Appendix 10: Adjusted Codes

Question	Question Code	Responses	Integer
Gestational Age	PREM	Premature Birth	0
		Term Birth	1
Birthweight	LBW	Low Birthweight	0
		Normal Birthweight	1
Deprivation	IMDQUIN	1st IMD Quintile	1
		2nd IMD Quintile	2
		3rd IMD Quintile	3
		4th IMD Quintile	4
		5th IMD Quintile	5
Maternal Education	MATED	School Educated	1
		Degree Educated	2
		Vocationally Educated	3
Maternal Age	MATAGE2	<25-Years-Old	1
		25 to 34-Years-Old	2
		≥35-Years-Old	3
Ethnicity	WHITE	White	1
		Other	2