An investigation of the association between mode of birth and childhood infectious disease and asthma

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Abstract

Background: In the past few decades, birth has changed profoundly with a steep rise in the rates of caesarean birth in most high-income countries and elsewhere. Observational studies have linked caesarean birth to some long-term adverse health outcomes during childhood. These include asthma and its common symptom – wheezing, however little is known about the association with particular phenotypes of wheezing. There is also some evidence suggesting that caesarean birth increases susceptibility to common childhood infectious diseases, although the scope of studies available is limited. The aim of this DPhil research was to elucidate whether mode of birth is associated with an increased risk of childhood asthma or infectious disease, including those affecting the upper and lower respiratory tract as well as the gastrointestinal tract. Comparisons are made between each type of medically interventional delivery - assisted vaginal delivery, planned and emergency caesarean sections - and unassisted vaginal deliveries.

Methods: Two data sources from the UK were used to investigate these questions in children born singleton at term and without major health problems at the time of birth. The first, the Millennium Cohort Study, is a nationally representative sample of children born in 2000-2002. The second is linked administrative datasets of the population of Wales including the children born in 2002-2016. Cox regression was used to calculate hazard ratios of hospital admission for respiratory and gastrointestinal infections and asthma. Multinomial logistic regression was used to estimate the relative risk ratio for experiencing various wheezing phenotypes during childhood.

Findings: Having adjusted for confounders, planned and emergency caesarean sections were found to be risk factors of small magnitude (10-40% increase in risk) for various adverse child health outcomes. Planned caesarean sections were associated

with an elevated risk of upper and lower respiratory tract infections during infancy and early childhood and persistent wheezing throughout childhood. Emergency caesarean sections were associated with increased risk of infectious diseases of the upper respiratory tract or gastrointestinal tract during infancy, and an increased risk of severe or poorly controlled asthma in later childhood. Assisted vaginal deliveries were not found to be associated consistently with any of the outcomes under study.

Conclusion:

This thesis provides modest strength of evidence to suggest that caesarean sections, whether planned or emergency, may increase the risk of infections of the respiratory or gastrointestinal tract requiring hospital admission during infancy. It also provides evidence to suggest the increased risk of respiratory morbidity such as severe asthma or persistent wheezing carries on into later childhood.

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Abbreviations and key terms

ACOG	American College of Obstetrics and Gynaecologists
ADDE	Annual District Death Extract
ALF	Anonymous Linking Field
CARIS	Congenital Anomaly Register & Information Service for Wales
CI	Confidence Interval
CLS	Centre for Longitudinal Studies
CS	Caesarean Section
EDDS	Emergency Department DataSet of Wales
GA	Gestational Age
GBS	Group B Streptococcus
HES	Hospital Episode Statistics
HR	Hazard Ratio
ICD	International Classification of Diseases
ISAAC	International Study of Asthma and Allergies in Childhood
LGA	Large for Gestational Age
LLCA	Longitudinal Latent Class Analysis
LRTI	Lower Respiratory Tract Infection
mat_ALF	Maternal Anonymous Linking Field
MCS	Millennium Cohort Study
NCCHD	National Community Child Health Database
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NPEU	National Perinatal Epidemiology Unit
NVQ	National Vocational Qualifications
NWIS	NHS Wales Informatics Service
OPCS	Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures
OR	Odds Ratio
PEDW	Patient Episode Dataset for Wales
RR	Relative Risk
RRR	Relative Risk Ratio
RSV	Respiratory Syncytial Virus
SAIL	Secure Anonymized Information Linkage Databank
SD	Standard Deviation
URTI	Upper Respiratory Tract Infection
VD	Vaginal Delivery
WDS	Welsh Demographic Service
WHO	World Health Organization
WIMD	Welsh Index of Multiple Deprivation

‘Birth’ and ‘delivery’ are used synonymously

‘Medically interventional birth’ refers to caesarean or assisted vaginal delivery

‘Infection’ and ‘infectious disease’ are used synonymously

Chapter 1: Introduction

1.1 Topic and scope

The research presented in this thesis addresses the penultimate stage of pregnancy and labour – the baby's birth[1]. In the past, all humans were born by vaginal delivery (VD), with only occasional manual assistance by a female supporter/midwife. The emergence of the field of obstetrics introduced medical instruments such as forceps to facilitate delivery in complicated labour. Later on, the development of surgical techniques, hygienic understanding, antibiotics and safe anaesthesia, facilitated caesarean sections (CS) – delivery of the fetus by surgical incisions through the abdomen and uterus [1]. Caesarean sections can be a life-saving procedure for mother and fetus. However, their practice has increased markedly in the past few decades, so much as to be referred to as 'the caesarean epidemic' [2].

The paradigms of 'Developmental Origins of Health and Disease' [3] or 'Primal Health' [4] point to the early developmental stage of life, particularly the prenatal and postnatal stages, as a critical time when exposures may affect long-term susceptibility to disease. During childbirth, dramatic physiological changes that accommodate the transition from fetal to extra-uterine life take place in a short timeframe. According to these paradigms, a medically interventional delivery interferes with these processes and might carry risks of long-term effects to the offspring.

The following chapter reviews the essential background of the research topic: mode of birth and its possible long-term effect on the child's health. My focus is on two distinct, but inter-related outcomes: infectious diseases and asthma.

[1] The ultimate stage being delivery of the placenta

1.2 Mode of birth

1.2.1 Etymology of the term caesarean

The word ‘caesarean’ is thought to have originated from the Latin word *caedere* meaning “to cut”. Historically, caesarean delivery was carried out to remove a fetus prior to the burial of a mother who had died while pregnant. During the time of the Roman Empire, the ‘Lex Caesarea’ law grounded this procedure legally.

An abdominal delivery of a fetus has been recognized in historic texts of numerous other societies [5]. For example, an abdominal birth is mentioned in the ‘Mishnah’, a compilation of Jewish law and oral traditions from 200 AD. The Mishnah discusses the legal rights of a child that had been born ‘*Yotze Dofen’,* a term whose literal meaning is “exit through the body wall”. Interestingly, in modern Hebrew, the term ‘*Yotze Dofen’* is used to denote an event that is out of the ordinary.

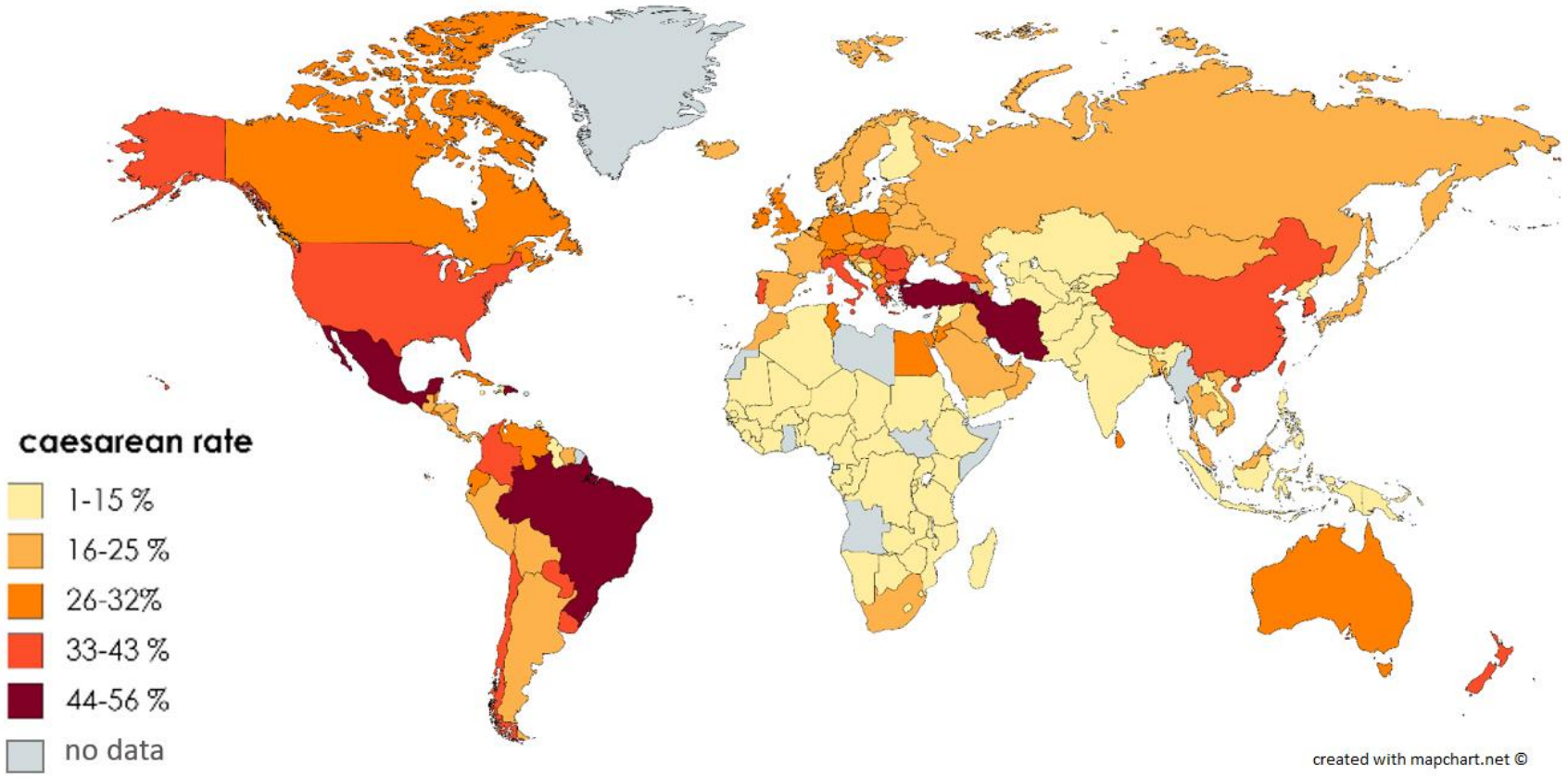
1.2.2 Global caesarean rates

Today, caesarean section is not at all out of the ordinary. Indeed, it is the most frequently performed surgical procedure worldwide [6]. Global data shows that 18.6% of the world’s births in 2014 were delivered by caesarean section [7], reflecting the steep rise during the recent decades in caesarean section in most countries, especially high- and middle-income countries. A regional perspective reveals the large variability among world regions in caesarean section rates. The highest caesarean rates are found in Latin America and the Caribbean (40.5%), followed by North America (32.3%), Oceania (31.1%), Europe (25%) and Asia (19.2%) [7]. As might be expected, the lowest rates are in Africa (7.3%). Figure 1-1 portrays recent global data about country-level caesarean rates [8]. Several large and highly populated countries stand out with more than 1 in 3 births by caesarean section. These include the USA, Brazil and China. Regarding the latter, there are recent reports of trend reversal following the relaxation

of the one-child policy [9]. In England, the 2018 rate of caesarean was 28.8% [10] compared with 9% in 1980 [11], indicating more than a three-fold increase in less than 4 decades.

For a long time, the ideal population-level caesarean rate was regarded as 10-15% of births, based on the recommendation of an expert panel of the World Health Organization (WHO) from 1985 [12]. In recent years, the WHO has re-visited the question of the optimal caesarean rate at the population level. They carried out a systematic review of ecological studies that had investigated population-level caesarean rates and maternal and offspring adverse outcomes [13]. In addition, the WHO conducted a new world-wide ecological study investigating the association between country-level caesarean rates and maternal and neonatal mortality [8]. The conclusion of both studies remained the same as previously: a caesarean rate above 10% at the population level is not associated with lower maternal or neonatal mortality. In light of this new information, and with acknowledgment of its limitations, the WHO issued a statement about caesarean section rates [14]. The new statement does not recommend striving for any particular population-level caesarean rate. Instead the new statement recognizes the importance of caesarean sections in saving lives but stresses that caesareans can cause significant complications and should ideally be undertaken only when medically necessary. The statement further highlights the substantial knowledge gap regarding the effect of caesareans on important outcomes other than mortality, such as maternal and perinatal morbidity, psychological well-being of the mother and paediatric outcomes.

Figure 1-1: Global rates of caesarean section, 2000-2012*



* Country-level rates derived from recent WHO publication [8]; missing rates for Greece and Taiwan derived from other publications [15,16]; rate for UK updated from NHS maternity statistics [10]

1.2.3 Indications for caesarean delivery

Indications that mandate surgical birth ('absolute indications') include conditions such as a prior classical caesarean section (vertical scar), complete placenta praevia[2], umbilical cord prolapse[3], vasa praevia[4], and prior or current uterine rupture. These obstetric complications would likely lead to an adverse outcome for baby and/or mother if a caesarean is not performed. All the same, absolute indications for caesarean surgery are rare, especially in industrialized countries. On the other hand, 'relative indications' are responsible for the vast majority of caesareans. These represent potentially modifiable conditions that may or may not call for caesarean delivery depending on the circumstance [6].

Although relatively dated, insight into the reasons caesarean are undertaken in the UK can be gained through 'The National Sentinel Caesarean Section Audit' [17]. The sentinel audit included all caesarean sections conducted in England, Wales, and Northern Ireland over the course of three months in the year 2000. The researchers surveyed clinicians regarding the main indication for the operations they had performed during the course of the audit. The most common indications reported were 'presumed fetal compromise' (including intrauterine growth restriction or abnormal recording of fetal heart rate), which accounted for 22.0% of caesareans, and failure to progress in labour, which accounted for 20.4%. Other relatively common indications were a previous caesarean section (13.8%) and the fetus in breech presentation (10.8%). Less common indications were maternal request[5] (7.3%) and fetal malpresentation or unstable lie (3.4%).

[2] Placenta covering the cervix
[3] Umbilical cord proceeding presenting part of the fetus
[4] Fetal blood vessels running proximate to cervix
[5] Not necessarily maternal request in the absence of any maternal or fetal medical complications

1.2.4 Determinants of rising caesarean rates

The determinants of the rising caesarean rates are multi-factorial and not fully understood [6]. However, the increased permissiveness in the use of caesarean delivery rides on the fundamental fact that caesareans are a safe operative procedure [1]. Additional features that likely influence the rising rates in high- and middle-income countries include changes in maternal, fetal, obstetric, healthcare organizational factors and cultural norms.

For example, in recent years, maternal demographics have changed, with a higher proportion of nulliparous mothers and a higher average maternal age. In parallel there has been an increase in maternal adverse health conditions such as obesity, diabetes and hypertension as well as in multiple pregnancies [14]. Fetal characteristics such as prevalence of macrosomia (co-morbid with gestational diabetes) also influence the caesarean rates.

Changes in the pattern of use of various medical practices are another important factor affecting caesarean rates. These include the pervasive practice of routine continuous fetal monitoring, which increases the risk of in-labour caesarean delivery [6,18] as well as the shift away from vaginal breech deliveries. The rise in practice of defensive medicine resulting from fear of litigation is an additional factor sometimes regarded as driving obstetricians to recommend caesareans. Cultural norms and women's preferences regarding childbirth have also changed in recent years [14], as these are not detached from the overall medicalisation of birth in Western societies. Magnifying the problem, is the fact that a rise in the rate of primary caesarean sections drives an increase in secondary caesareans in subsequent pregnancies. The extent to which this occurs depends on the practice of vaginal delivery after caesarean. In an attempt to constrain the rising caesarean rates, various professional groups such as the American College of Obstetrics and Gynaecologists (ACOG) have issued recommendations

aimed towards prevention of the primary caesarean delivery [19]. Conversely, some of the guidelines regarding childbirth issued by the UK's National Institute for Health and Care Excellence (NICE) became more permissive of maternal request for caesarean [20].

1.2.5 Classification of caesarean sections

Traditionally, caesarean sections were classified as either 'elective' or 'emergency' procedures. However, since not all non-elective caesareans are due to an immediate medical emergency, these terms are sometimes replaced by 'planned' and 'unplanned'. NICE clinical guidelines for performing caesarean sections [20] recognises this potential ambiguity of terms and therefore proposes a categorization depending on the urgency for the procedure [21,22]. The proposed categories are as follows:

1. Immediate threat to life of mother or fetus
   For example: severe fetal heart decelerations, cord prolapse, uterine rupture
2. Maternal or fetal compromise which is not immediately life-threatening
   For example: antepartum haemorrhage, failure to progress in labour with maternal or fetal compromise
3. No maternal or fetal compromise but needs early delivery
   For example: woman with a planned caesarean that is admitted during labour or failure to progress in labour without compromise
4. Delivery timed to suit woman or staff
   Includes all caesarean sections carried out 'electively' at a planned time

Categorization by degree of urgency exemplifies the ambiguity in the classic dichotomization of elective/emergency. For example, not all unplanned caesareans are due to an immediate emergency and on the other hand a scheduled caesarean may occasionally require a more urgent delivery than planned (category 3 urgency). An additional characteristic of caesarean section is the timing of surgery in relation to labour

onset. An elective caesarean would generally (although not necessarily) be carried out pre-labour. However, an emergency or unplanned section would usually take place in-labour, yet it may sometimes be required antenatally. Lastly, the term ‘elective’ may lead to confusion outside of medical circles, since it implies choice concerning the procedure, when in fact, choice may have been limited due to medical necessity [23]. Rather, the term indicates the timing of the procedure. An additional classification commonly used in publications from Scandinavian countries is elective vs. ‘acute’ caesarean sections.

Nevertheless, despite the ambiguous terminology, the various classifications generally distinguish between an elective, planned caesarean undertaken pre-labour and an emergency (or acute) unplanned one undertaken in-labour.

1.2.6 Caesarean sections – risks and benefits for mothers

As mentioned previously, the advancements in caesarean section technique and accompanying medical procedures have become a generally safe method of birth. However, as any medical procedure, and in particular major surgery, caesarean sections do still carry with them added risks. For example, in the short term, caesarean sections are associated with increased risk of haemorrhage and need for blood transfusion; elevated risk of infection of the uterus or surgical wound; possible damage to neighbouring organs; post-operative pain; and difficult mobility [24]. In future pregnancies, caesarean sections are associated with an increased chance of infertility or ectopic pregnancy and complications including abnormal placentation, uterine rupture, prematurity, stillbirth and subsequent caesarean [25,26].

Alongside added risks in comparison to vaginal delivery, birth by caesarean section also carries benefits. First and foremost, it facilitates delivery in cases that might otherwise lead to morbidity or mortality. Additional benefits include, for example, a lower chance of future incontinence or urogenital prolapse [25]. Furthermore, a caesarean may be a

suitable solution for women experiencing tokophobia (severe fear of childbirth) despite access to appropriate antenatal mental healthcare [27].

1.2.7 Caesarean sections – risks for offspring

Caesarean sections also carry risks to the offspring, both in the neonatal period and in the longer term. A pre-labour caesarean section increases the risk of newborn respiratory morbidity, including retained fluids in the lung (transient tachypnea of the newborn, i.e. abnormally rapid breathing) as well as respiratory distress syndrome. If the caesarean takes place at earlier gestational age, even within the window of term gestation (≥37 weeks), this risk increases further [28]. Additional immediate adverse effects include impairment of maternal-newborn bonding processes as well and lower breastfeeding rates [24].

Various paediatric long-term adverse health outcomes of caesarean delivery on the child have been documented as well, although with varying degree of robustness of the evidence. Using systematic reviews and meta-analyses of observational studies, which aid in synthesizing study findings, researchers have aggregated results and highlighted childhood conditions potentially associated with caesarean delivery. These include overweight/obesity [29–31], juvenile diabetes [32], autistic spectrum disorder [33], Crohn's disease [34], wheeze at school age [29] and asthma (see section 1.6.6). Further observational evidence has shown an association of caesarean delivery with metabolic disorder [35] and various infectious diseases (see section 1.6.2-1.6.5). Additionally, several studies have identified an association with inflammatory bowel disorder [34,36], allergies [29] wheeze at preschool age [29] and leukaemia [37]. However, for the latter outcomes, when the various findings were collected into a meta-analysis, these associations were no longer evident.

1.2.8 Assisted vaginal delivery – indications and risks

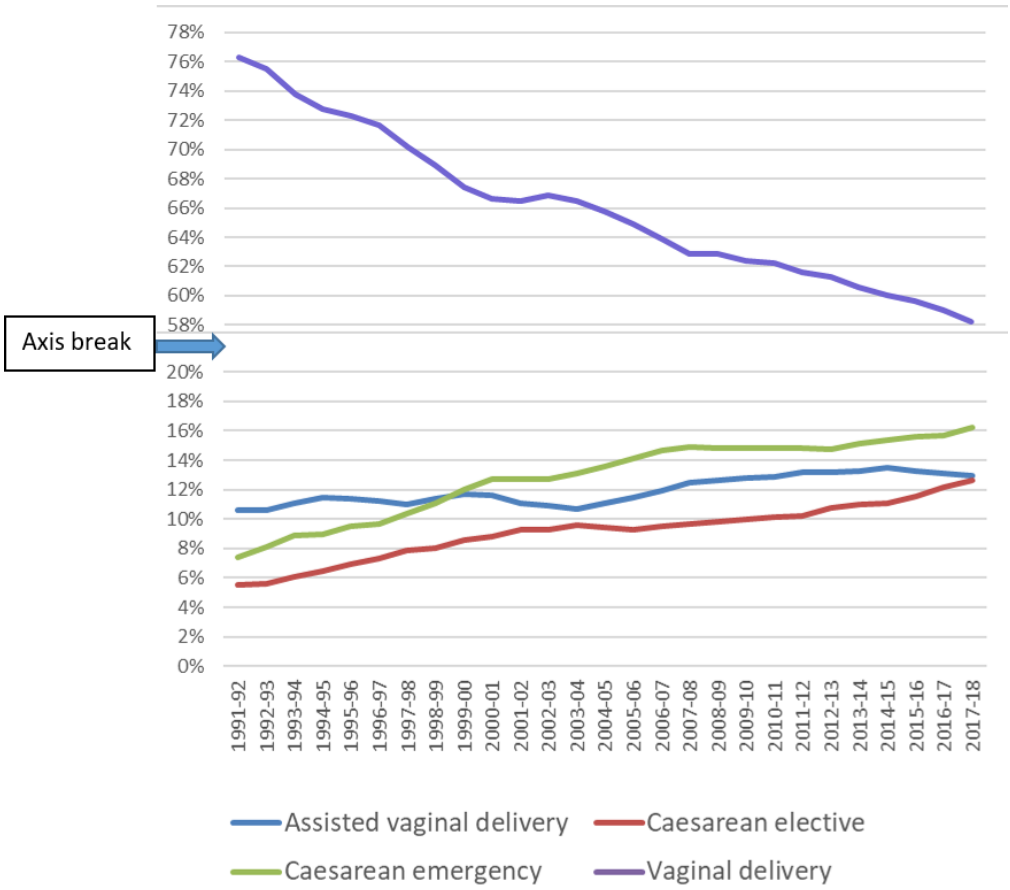
A vaginal delivery is sometimes medically facilitated by instrumental delivery such as ventouse for vacuum extraction or forceps. Such deliveries may be referred to as 'assisted', 'instrumental' or 'operative' vaginal deliveries [38]. The indications for assisted vaginal delivery partly overlap with those of caesarean section, but are usually performed only at an advanced stage of fetal descent when a caesarean is undesirable due to the risk of an entrapped head. These indications include presumed fetal compromise, the need to shorten the second stage of labour due to maternal medical conditions (e.g. cardiac problems), inadequate fetal progress or maternal fatigue [39]. An assisted vaginal delivery carries some potential risks. For the mother, these include perineal tears, postpartum haemorrhage and anal sphincter dysfunction. For the newborn, risks include haematoma, intracranial haemorrhage, facial nerve palsy, temporary marks or lacerations on the face or scalp and neonatal jaundice [39,40].

1.2.9 Modes of birth in England – time trends

In just a few decades, the use of all medically interventional modes of birth in England has increased at the expense of unassisted vaginal delivery. During the 27-year period depicted in Figure 1-2, the rate of assisted vaginal delivery increased from 10.6% to 13.1%, the rate of emergency caesarean increased from 7.4% to 15.7% and that of elective caesarean increased from 5.5% to 12.4%.

Due to this increasing trend and because of the potential risks to the child detailed previously, it is important to investigate whether these interventional modes of birth, particularly caesarean section, have any additional adverse health effects on the child. The health outcomes on which this research is focused – infectious diseases and asthma (as well as wheezing symptoms in general), are therefore introduced hereafter.

Figure 1-2: Time trends in mode of birth, England, 1991-2017*



* Source: NHS Maternity Statistics 2017-18;
methodology was updated in 2005 and 2011 (but led to only minor changes in rates) [41]; includes deliveries at NHS hospitals in England; excludes homebirths and private facilities; assisted vaginal delivery includes ventouse, forceps and breech.

1.3 Paediatric infectious diseases

The following section is an overview of some common infectious diseases in childhood, including those affecting the lower respiratory tract, the upper respiratory tract, the gastrointestinal tract and other body system. Note that the terms 'infection' and 'infectious disease' will be used interchangeably throughout this thesis and both refer to a symptomatic pathogenic infection.

1.3.1 Lower respiratory tract infections (LRTI)

1.3.1.1 Bronchiolitis

Bronchiolitis is an extensive inflammatory condition of the bronchioles - the small airways of the lungs. It is an acute viral lower respiratory tract illness that occurs during the first two years of life, with a peak incidence at ages 3 to 6 months and higher frequency during winter months [42]. This common illness is characterized by symptoms and signs of upper respiratory viral infection such as nasal discharge that later progress to the lower tract with persistent cough, excessive respiration, wheezing and crackles heard from the lungs. A hallmark presentation of bronchiolitis is the fluctuation in clinical findings while mucus is cleared from the bronchioles through coughing [43].

There are several main means of transmission of a pathogenic agent for bronchiolitis or other respiratory infections. These include direct contact with respiratory secretions of an infected individual (e.g. contaminated hands), indirect contact via intermediate objects or airborne transmission by coughing or sneezing [43]. The most common pathogenic agent causing bronchiolitis is Respiratory Syncytial Virus (RSV), responsible for about three quarters of cases [44]. The differential diagnosis of bronchiolitis in toddlers includes viral-induced wheezing and asthma, which could manifest itself similarly in young children so that it is not possible to distinguish between the two in the course of a single episode [42]. Research has linked hospital admission for bronchiolitis at a young age with development of recurrent wheezing and asthma later in life [42].

However, it is still unclear if the infection causing bronchiolitis predisposes the child to asthma by altering lung function, or if alternatively, it is due to shared risk factors such as altered immune response or airway function [42]. In the USA, bronchiolitis is the most common reason for hospitalisation during infancy [42,45].

1.3.1.2 Pneumonia

Pneumonia is an infection of the lungs which can present as symptoms of fever, cough, sounds of crackles or wheeze from the lungs or respiratory distress. Pneumonia is usually the result of a viral infection from RSV, Influenza, Parainfluenza or Adenovirus and is commonly preceded by a viral upper respiratory tract infection. Numerous other pathogens may cause pneumonia, including bacteria such as Streptococcus Pneumonia or Group B Streptococcus (GBS), as well as fungi and protozoa [46–48].

Pneumonia is not a common severe infection in children living in high-income countries. For example, the incidence of pneumonia in English pre-schoolers was reported to be 29 per 10,000 children per year [49]. In low and middle income countries, lower respiratory tract infections such as pneumonia are the 2nd leading cause of death in children age 0-14 (following perinatal conditions) [50].

1.3.1.3 Influenza

Influenza is a highly infectious virus that may cause fever, muscle pain and headache followed by cough, rhinitis, sore throat, and sometimes gastrointestinal symptoms. Influenza virus infection increases susceptibility to secondary bacterial pneumonia [51]. A vaccine for the pervasive strains of Influenza is developed annually and since 2013, the vaccination of children has been introduced as part of the UK routine vaccination programme [52].

1.3.2 Upper respiratory tract infections (URTI)

1.3.2.1 Common cold

The common cold is a viral infection of the upper respiratory tract that may involve the nasal passages, sinuses, eustachian tubes, middle ear spaces, conjunctivae and the nasopharynx. It is a common paediatric infection, in particular at preschool age and during autumn and winter time. Many infectious agents may cause cold symptoms, with rhinoviruses implicated most frequently. Complications of a viral cold may include acute otitis media, bacterial sinusitis and on rare occasions also secondary pneumonia [53].

1.3.2.2 Pharyngitis and tonsillitis

Acute pharyngitis, an inflammation of the throat, is one of the most common diagnoses in children. When the tonsils are also affected the diagnosis would usually be acute tonsillitis. The majority of cases are due to a viral infection such as adenovirus or Epstein Barr Virus, but such infection may also be caused by a bacteria [54].

1.3.3 Gastrointestinal infection

Gastroenteritis presents clinically with acute-onset vomiting and/or diarrhoea, abdominal pain and sometimes fever and may lead to dehydration. It is usually caused by a viral infection, mainly Rotavirus and Norwalk virus (i.e. Norovirus). The transmission of pathogenic agents may occur through direct or indirect contact with vomit or faeces from an infected individual. For example, indirect transmission may occur when an infected person handles food or drink without prior sufficient handwashing. Gastroenteritis may also be caused by bacteria such as Salmonella or E.coli potentially transmitted through contaminated food or drink [55]. In the UK, a vaccine for Rotavirus has been part of the routine vaccination programme since 2013 [52]. Unlike high income countries, in low and middle income settings, gastrointestinal infection is the 3rd leading cause of death in children age 0-14 [50].

1.3.4 Other infections

Many additional body systems can be potential targets of paediatric infection, and often a viral or bacterial agent may cause symptoms and signs in various other areas of the child's body. Some examples are ear infections such as otitis media, urinary tract infections, infected skin lesions and disease that manifest as rashes along with other symptoms such as Measles, Rubella and Chickenpox [47]. Some of these diseases are preventable by vaccination as part of the UK routine vaccination programme or privately.

1.4 Wheezing

In the previous section I introduced some of the common infectious diseases of childhood. Wheezing deserves special focus because it is a prevalent sign of both respiratory infection and of chronic respiratory morbidity such as asthma. Wheezing is a high-pitched continuous whistling sound heard in the chest while breathing, and is most prominent during expiration. The sound results from turbulent airflow due to narrowing of the airways and partial obstruction. Wheezing is most commonly associated with viral infection causing bronchiolitis or asthma; however, it may be the result of other factors as well. The majority of viral-induced wheezing in children is caused by RSV, Rhinovirus or Influenza virus infection [56]. When wheezing is caused by a viral infection, it is often preceded by upper respiratory symptoms and fever [57]. Conversely, wheezing associated with asthma exacerbation may be initiated by a variety of triggers, including physical activity, weather change, URTI or exposure to an allergy-triggering antigen.

1.4.1 Wheezing trajectory phenotypes

Longitudinal studies have been utilized to study the trajectories of wheezing throughout childhood and classify them into different wheezing phenotypes. The aim of this phenotypic categorization is to describe the different early life risk factors for each

phenotype, to study the varying risk of each phenotype for subsequent development of asthma and to understand their aetiology better.

A pioneer study [58] for phenotypic classification of wheezing was carried out in the USA – the 'Tucson Children's Respiratory Study'. The study followed children from infancy up to six years of age. Repeated clinical observations of these children led to identification of four different phenotypes based on wheezing trajectories: never wheezing, transient-early (in first 3 years), persistent (in first 3 years and at age 6) and late-onset wheezing (reported wheezing solely at age 6). Similar wheezing phenotypes were later described and characterised in additional cohorts, although with varying definitions of age-cut between phenotypes [59,60].

More recent studies have taken data-driven approaches to the identification of wheezing trajectories. Longitudinal Latent Class Analysis (LLCA) is such a method utilizing data from cohort studies. Based on the pattern of answers to a repeated question at several time points, in this case, whether the child experienced wheezing in the past year, each individual is assigned to their most probable latent (unobserved) sub-type. The sub-types derived are mutually exclusive and exhaustive [61,62] (include all options of answer sets). Table 1-1 presents the various phenotypes of wheezing trajectories identified using LLCA. There is noticeable variability in the ages of children included in each cohort from which the phenotypes were derived, in the number of phenotypic classes identified as well as variability in the specific trajectory of each phenotype. Nevertheless, the four trajectories described initially in the Tucson study – none, transient, persistent and late-onset wheezing - come up repeatedly using this data-driven method.

The various wheezing phenotypes have been shown to have different risk factors. For example, smoking is a risk factor for the phenotypes of wheezing commencing at early

life, but not for the late-onset wheezing phenotype. Day care attendance is associated with the transient-early wheezing phenotype more than others [63].

1.4.2 Wheezing trigger phenotypes

In addition to classifying wheezing by its trajectory through childhood (a classification useful for research purposes), another means of phenotyping wheezing is by type of trigger. This classification distinguishes 'episodic viral wheeze' from 'multiple trigger wheeze'. The first is characterized by intermittent seasonal episodes of wheezing less often associated with atopy and usually presenting with close to normal pulmonary function. These children's symptoms tend to resolve by late childhood. The latter phenotype shows discrete exacerbations of wheezing, but also symptoms in between episodes. Wheezing triggers of this phenotype include allergens, exercise, mist, crying, laughter and also respiratory viral infection [62,64].

Overlap exists between the various classification systems of wheezing phenotypes. For example, children that experience persistent wheezing are also substantially more likely to be atopic as in the multiple trigger wheeze phenotype [62]. Likewise, the late-onset phenotype is more highly associated with atopy [65].

1.4.3 Viral-induced wheeze and subsequent asthma

Wheezing induced by viral infection in early childhood is associated with subsequent development of asthma. The mechanism of this association is potentially through airway inflammation leading to airway hyper-responsiveness and remodelling (airway structural changes). However, it is still unclear whether viral infections of the lower respiratory tract are on the causal pathway of development of asthma. Alternatively, there may be shared risk factors between experiencing repeated incidents of LRTI at early childhood with development of asthma in later childhood [56].

Table 1-1: Wheezing phenotypes identified in cohort studies*

Study	Country, year of birth	Age queried about recent wheezing	Wheezing phenotypes identified
MAAS (Manchester Asthma and Allergy Study) [66]	UK, 1995	1,3,5,8 years	• Never • Transient early • Persistent controlled • Persistent troublesome • Late-onset
ALSPAC (Avon Longitudinal Study of Parents and Children) [67]	UK, 1991-1992	0.5 – 6.5 years in 1 year intervals	• Never/infrequent • Transient early • Prolonged early • Intermediate-onset • Persistent • Late-onset
PASTURE (Protection against Allergy Study in Rural Environments) [68]	Europe, 2002-2005	1-6 years in 1 year intervals	• Never/infrequent • Transient • Intermediate-onset • Persistent • Late-onset
PIAMA (Prevention and Incidence of Asthma and Mite Allergy) [69]	The Netherlands, 1996-1997	1-8 years in 1 year intervals	• Never • Transient early • Intermediate-onset • Persistent • Late-onset
CCCHE (Columbia Center for Children's Environmental Health) [70]	US, 2000	3 months to age 9 in extending intervals from 3 months to 2 years	• Never/infrequent • Early-transient • Early-persistent • Late-onset
MCS (Millennium Cohort Study) [71]	UK, 2000-2002	Ages 3,5,7,11 years	• Never/infrequent • Early • Persistent • Late
MCS (Millennium Cohort Study) [72]	UK, 2000-2002	Ages 3,5,7,11 years	• Never/infrequent • Early • Persistent • Late

* listed in several reviews of asthma phenotypes [62,73,74]

1.5 Asthma

1.5.1 Pathophysiology

Asthma is a chronic inflammatory condition of the airways. It is often described as a lung disease that includes three main features:

1. Episodes of airway obstruction reversible by bronchodilator, a substance that dilates the bronchi (the two main airways) and bronchioles (the smaller airways) and increases airflow.
2. Airway hyper-responsiveness to a variety of external stimuli such as those mentioned previously - viral respiratory infection, exercise, cold air, irritants (e.g. tobacco smoke) and allergens (e.g. dust mite, pollen and pets).
3. Chronic inflammation of the airways.

The three features together lead to structural changes in the airways and recurrent episodes of wheezing, shortness of breath, chest tightness and/or coughing [75,76].

Asthma has a strong genetic component, and therefore a child's risk of developing the condition is substantially elevated if one or more parents have asthma [77]. Often, asthma goes hand in hand with other atopic conditions such as atopic dermatitis (eczema) or allergic rhinitis (hay fever) [76].

The specific causes of childhood asthma are unknown as it is most likely due to a complex gene-environment interaction. A variety of pathophysiological processes which all result in airway inflammation and reversible airway obstruction are currently aggregated under the diagnosis of asthma. This results in a very clinically heterogeneous and multifaceted disease [76,78]. For this reason there is currently a shift away from the concept that asthma is a single disease entity; instead it is considered an umbrella term for distinct phenotypes or conditions that share common clinical features [62].

1.5.2 Epidemiology and time trends

Asthma is the most common chronic condition in childhood in high income countries, with prevalence estimates ranging from 8% to 13% [76,78]. In the UK, the estimated prevalence is 9-10% and is amongst the highest in Europe [79]. Since the 1950s, the prevalence of paediatric asthma in high-income settings has risen 2-3 fold. This has occurred concomitantly with a rise in other allergic diseases. Reassuringly, there are indications that the rise in asthma prevalence may have plateaued since the start of the 21st century [80,81].

1.5.3 Classification by severity and symptom control

Asthma severity is the intrinsic intensity of the disease and is best classified before measures of symptom control are applied. The two general categories of severity are "intermittent" and "persistent" asthma. A child with intermittent asthma would experience symptoms no more than 2 days per week and would not necessarily require daily medication [76,82]. A child with persistent asthma may be further classified as having a mild, moderate or severe form of persistent asthma. Asthma control can also be classified into several categories - well controlled, not well controlled and very poorly controlled [76].

These classifications of asthma help describe the varying presentations of the disease. For example, a child with intermittent asthma may not require daily medication based on the initial examination, but might still suffer a severe exacerbation triggered by viral infection and require hospital admission [76].

1.5.4 Medication for prevention and treatment of asthma

Asthma medications can be categorized as those for fast relief of acute symptoms and those for prophylaxis (prevention). Quick relief medication include short-acting beta2 agonists such as 'Salbutamol' that function as bronchodilators, as well as

systemic corticosteroids taken orally. Prophylactic medications are used to control the underlying pathophysiologic mechanism and include inhaled corticosteroids such as ‘Beclomethasone’ and long-acting beta2 agonists [76].

1.5.5 Challenges in the diagnosis of asthma

As explained, asthma has sign and symptom overlap with bronchiolitis, viral induced wheeze, and additional respiratory conditions that cause wheezing. This is especially true at preschool age and creates a challenge to accurately distinguish asthma from other wheezing illnesses. Furthermore, it is difficult to achieve objective measurements of pulmonary (lung) function to support clinical observations in such young children [82]. These features make it difficult to reliably diagnose asthma in children of preschool age. Moreover, some clinicians would feel cautious about assigning a chronic disease label so early in childhood [78].

Some researchers therefore strive to distinguish between the varying wheezing phenotypes, as described previously. The persistent or late-onset phenotypes are candidates for a valid asthma diagnosis, while the transient wheezing phenotype is less so, implying other underlying causes for the child’s wheeze.

1.6 The association between mode of birth and childhood infectious disease, wheezing and asthma

To understand the current state of knowledge about mode of birth and its association with subsequent infectious disease, wheezing illnesses and asthma in childhood, I reviewed the existing evidence using a structured literature search strategy.

1.6.1 Literature search strategy

Periodic searches of the 'PubMed' database were carried out starting December 2015 and ending January 2019. The search included three concepts appearing as a 'text word', i.e., in the title, abstract, author supplied keywords or 'Medical Subject Heading'. The concepts searched were as follows:

- Caesarean, mode of birth, mode of delivery, vaginal birth, assisted birth, natural birth, normal birth
- Infection, infectious, gastroenteritis, gastritis, respiratory, diarrhoea, asthma, wheezing, bronchiolitis, bronchitis, RSV, pneumonia, influenza
- Infant, child, baby, offspring, long

A detailed account of the search, including synonyms used, can be seen in appendix I. The reference list of the relevant research papers retrieved was interrogated to gather additional relevant research articles.

In addition to this periodic search, a broader, one-off, literature search aimed specifically at identifying articles about mode of birth and upper respiratory infections was carried out in January 2019. This was a rigorous structured search including the three concepts of mode of birth, URTI and children. The search was conducted with the assistance of a Population Health Subject Librarian. See appendix I for details.

My focus was on large cohort studies (including record linkage studies) with a sample size of approximately n>2,000, as well as on meta-analyses. The studies retrieved were those where mode of birth was the main exposure or one of the main determinants of interest and categorised into at least two types of caesarean delivery. Furthermore, one of the main outcomes was LRTI, URTI, gastroenteritis, any infection, wheeze or asthma, and measured in infants or children. Only studies in English were included with a focus on high-income settings.

The following information was extracted from the retrieved studies: publication title, author's surname, journal, year of publication, country where data was collected, study design, eligible years of birth, sample size, inclusion and exclusion criteria, mode of birth classification, outcome measurement including age when measured, covariates, statistical analysis model, relative risks of the main results (hazard ratios, odds ratio, relative risk ratios, etc.) and their confidence intervals, and results of relevant sub-group analyses. For meta-analyses the measure of heterogeneity was also extracted.

Following is a summary of the findings from relevant studies identified per each outcome of interest: LRTI, URTI, any respiratory illness, gastroenteritis, asthma and wheezing phenotypes.

1.6.2 Mode of birth and its association with LRTI

The association between mode of birth and severe lower respiratory tract infections has been studied, although not extensively. I was unable to identify a meta-analysis describing this relationship and therefore present the six individual published studies that have investigated it (Table 1-2).

Among the studies identified, the relative risk of planned caesarean section was moderately increased compared to the reference group of vaginal delivery in almost all the studies identified. The magnitude of increase in risk ranges from 10% to 30% *(*i.e. RR=1.1-1.3) [83–86]. In all studies apart from one, which had focused on mild infections

that did not necessarily require hospitalisation [87], this effect was statistically significant. In an additional study, only one of two outcomes related to LRTI was found associated with mode of birth [88].

Unlike planned caesarean, emergency caesarean was not consistently found to be a risk factor for LRTI. Several studies have described an elevated risk of 10-20% when compared to vaginal delivery [83,84] but most studies found a relative risk of about one [85–88].

An additional large study of births from the 1970-80s highlighted caesarean delivery (any type) as a risk factor for LRTI with a RR=1.35 (statistically significant) [89].

There is little research about assisted vaginal delivery. Only a few of the studies differentiated this mode of birth from unassisted vaginal delivery. Of those that had, this mode of birth was not generally found to be a risk factor for LRTI in the child.

1.6.3 Mode of birth and its association with URTI

My search strategy identified only one study that investigated the association between mode of birth and URTI in detail. This study [86] examined solely laryngitis as an URTI outcome and is presented in Table 1-3. The study described a small increased risk of 10-20% associated with elective and acute caesarean sections for this type of infection.

The scarcity of studies examining the potential association between mode of birth and URTI is presumably due to these illnesses not generally being regarded as causing serious morbidity in children. The additional detailed literature search carried out with the aid of a Librarian failed to find any additional relevant recent studies.

1.6.4 Mode of birth and its association with any respiratory infection

Some studies have investigated the association between perinatal factors and a broad outcome of any respiratory illness, aggregating infections of both the upper and lower respiratory tract and sometimes also asthma.

One such study [35] carried out after completion of the analyses presented in this thesis and utilizing Australian data identified a 30-40% increase in risk of hospitalisation for severe respiratory infections in children born by planned or emergency caesarean section. In this study, however, instrumental vaginal delivery and labour induction or augmentation were also identified as risk factors for any respiratory infection admission (Table 1-3).

Another study by Paranjothy et al [90] examined gestational age and birthweight and its association with hospital respiratory admission using Welsh data. The study did not examine mode of birth as one of the main determinants, but included it in multivariable models. The authors identified caesarean delivery (any type) as one of the risk factors for hospital admission due to respiratory infection, with a small (10%) statistically significant increase in risk compared to vaginal delivery.

1.6.5 Mode of birth and its association with gastroenteritis

Similar to previously mentioned outcomes, there have been few published studies examining the association between mode of birth and the child's risk of gastrointestinal infection in detail. No meta-analysis aggregating the results of the few available studies was found. However, the findings of the four studies identified that are presented in Table 1-4, were consistent. These studies concluded that both elective and emergency caesarean section are risk factors for subsequent gastroenteritis (RR=1.2-1.3) when compared with vaginal delivery [84,86,91,92].

Table 1-2: Studies of mode of birth and LRTI

Author, publication year, country, study design	Sample size, birth year, inclusion criteria, child age (years)	Exposure	Outcome (definition)	Adjustments	Analysis (effect measure)	Results: adjusted effect measure (95% CI)
Moore, 2010, Western Australia, Population register linkage study [83]	n=245,249 1996-2005 Singleton, age 0-2	VD Instrumental VD Elective CS Emergency CS	LRTI (Pneumonia, Bronchiolitis, Influenza, Whooping cough, Bronchitis, unspecified LRTI hospital admission ICD)	Maternal age, area socioeconomic index, parity, GA*, proportion of optimal BW, smoking, maternal asthma, sex, season of birth, year of birth	Logistic (OR)	The reference group was Instrumental VD: Elective CS 1.34 (1.22, 1.48) Emergency CS 1.20 (1.09, 1.33)
Magnus, 2011, Norway, Longitudinal cohort study [87]	n=37,171 1999-2008 singleton, age 0-3	VD Elective CS Acute CS	LRTI (≥3 episodes of RSV, pneumonia or bronchitis by parental report)	Maternal age, education, marital status, BMI, smoking, atopic status, chronic conditions, previous CS, parity, BW, GA, sex, daycare, breastfeeding at 6 months	General-ized linear model (RR)	Elective CS 1.19 (0.95, 1.48) Acute CS 1.01 (0.83, 1.22)
Moore, 2012, Western Australia, Population register linkage [88]	n=212,068 1996-2005 non-aboriginal, singleton, term GA Age 0-1, 1-2	VD Instrumental VD Elective CS Emergency CS	LRTI (Pneumonia or Bronchiolitis hospital admission ICD)	Maternal age, area socioeconomic, smoking, asthma, diabetes, preeclampsia, parity, breech, GA, proportion of optimal BW, sex, season of birth, year of birth	Negative binomial (IRR)	Bronchiolitis 0-1: Instrumental VD 0.96 (0.85, 1.08) Elective CS 1.11 (1.01, 1.23) Emergency CS 1.00 (0.89, 1.13) Pneumonia age 0-1: no significant effect

Author, publication year, country, study design	Sample size, birth year, inclusion criteria, child age (years)	Exposure	Outcome (definition)	Adjustments	Analysis (effect measure)	Results: adjusted effect measure (95% CI)
Roberts, 2012, New South Wales Australia, Population register linkage study [84]	n=626,700 2001-2008 singleton, term GA, age 0-1	VD Instrumental VD Planned CS Emergency CS	LRTI (hospital admission for bronchiolitis ICD)	Maternal age, socioeconomic status, parity, sex, preeclampsia, diabetes, breech, maternal asthma, smoking, GA, SGA, LGA, season and year of birth	Logistic (OR)	LRTI Instrumental VD 0.91 (0.86, 0.97) Planned CS 1.12 (1.08 , 1.17) Emergency CS 1.13 (1.07, 1.18)
Kristensen, 2015, Denmark, Population register linkage study [85]	n=399,175 1997-2003 Without congenital anomaly chronic condition, age 0-1, 1-2	VD Elective CS Acute CS	LRTI (hospital admission for RSV infection)	GA, asphyxia, BW, multiple births, single parenthood, smoking, older siblings, child's asthma, year of birth, sex	Cox (HR)	Age 0-1: Elective CS 1.29 (1.20, 1.39) Acute CS 1.02 (0.94, 1.11)
Kristensen, 2016, Denmark, Population register linkage study [86]	n=750,569 1997-2012 Singleton, term GA, without congenital anomaly, age 0-14	VD Elective CS Acute CS	LRTI (patient registry ICD)	Maternal age, smoking, pregnancy complications, sex, BW, GA, year of birth	Cox (HR)	LRTI: Elective CS 1.20 (1.16, 1.24) Acute CS 1.01 (0.97, 1.04)

* GA gestational age; BW birthweight; SGA small for gestational age; LGA large for gestational age; ICD International Classification of Diseases

Table 1-3: Studies of mode of birth and URTI or any respiratory infection

Author, publication year, country, study design	Sample size, year of birth, inclusion criteria, age of children in years	Exposure	Outcome (definition)	Adjustments	Analysis (effect measure)	Results: adjusted effect measure (95% CI)
Kristensen, 2016, Denmark, Population register linkage study [86]	n=750,569 1997-2012 singleton, term GA, without congenital anomaly, age 0-14	VD Elective CS Acute CS	URTI (patient registry ICD)	Maternal age, sex, smoking, pregnancy complications, GA*, BW year of birth	Cox (Hazard Ratio)	Laryngitis: Elective CS 1.19 (1.14, 1.25) Acute CS 1.14 (1.09, 1.20)
Peters, 2018, New South Wales Australia, Population register linkage study [35]	n=491,590 2000-2008 singleton, term GA, without congenital anomaly, healthy pregnant mother, age 0-5	VD Induced VD Instrumental VD Induced instrumental VD Elective CS Emergency CS Induced emergency CS	Any respiratory infection (hospital admission ICD)	Maternal age, country of birth, area socioeconomic index, pain medication, parity, GA, BW, SGA, LGA, birth trauma, sex	Logistic (OR)	Any respiratory infection: Induced VD 1.11 (1.08, 1.13) Instrumental VD 1.25 (1.20, 1.31) Induced instrumental VD 1.31 (1.27, 1.36) Elective CS 1.35 (1.31, 1.40) Emergency CS 1.39 (1.32, 1.46) Induced emergency CS 1.29 (1.23, 1.34)

* GA gestational age; BW birthweight; SGA small for gestational age; LGA large for gestational age; ICD International Classification of Diseases

Table 1-4: Studies of mode of birth and gastroenteritis

Author, publication year, country, study design	Sample size, year of birth, inclusion criteria, age of children in years	Exposure	Outcome (definition)	Adjustments	Analysis (effect measure)	Results: adjusted effect measure (95% CI)
Hakansson, 2003, Sweden, Population register linkage study [91]	n=863,846 1984-1996 singleton, term GA, Apgar≥9, without SGA, maternal asthma, congenital anomaly, perinatal complication, age >1	VD Instrumental VD Elective CS Acute CS	Gastroenteritis (hospital admission ICD)	Maternal age, education level, parity, smoking, GA*, sex	Mantel Haentzel (Odds Ratio)	Gastroenteritis: Instrumental VD 1.07 (1.00, 1.14) Elective CS 1.30 (1.20, 1.41) Acute CS 1.31 (1.23, 1.40)
Roberts, 2012, New South Wales Australia, Population register linkage study [84]	n=626,700 2001-2008 singleton, term GA, age 0-1	VD Instrumental VD Planned CS Emergency CS	Gastroenteritis (hospital admission ICD)	Maternal age, socioeconomic status, parity, smoking, preeclampsia, diabetes, breech, maternal asthma, GA, SGA, LGA, season of birth, year of birth	Logistic (Odds Ratio)	Gastroenteritis Instrumental VD 1.02 (0.96, 1.10) Planned CS 1.22 (1.15, 1.29) Emergency CS 1.26 (1.18 , 1.34)

(table continues on next page)

Author, publication year, country, study design	Sample size, year of birth, inclusion criteria, age of children in years	Exposure	Outcome (definition)	Adjustments	Analysis (effect measure)	Results: adjusted effect measure (95% CI)
Kristensen, 2016, Denmark, Population register linkage study [86]	n=750,569 1997-2012 singleton, term GA, without congenital anomaly, age 0-14	VD Elective CS Acute CS	Gastroenteritis (ICD in patient registry)	Maternal age, sex, smoking, pregnancy complications, BW, GA, year of birth	Cox (Hazard Ratio)	Gastroenteritis: Elective CS 1.18 (1.13, 1.23) Acute CS 1.22 (1.17, 1.27)
Bentley, 2016, New South Wales Australia, Population register linkage study[92]	n=893,360 2001-2011 singleton, ≥33 GA, without congenital anomaly, age 0-1 ,0-2	Spontaneous onset VD Induced VD Induced CS Spontaneous onset CS Planned CS + GA and breastfeeding	Gastroenteritis (hospital admission ICD)	Maternal age, parity, country of birth, socioeconomic, smoking, diabetes, hypertension, Apgar<7, perinatal infection, BW (sex and GA standardized), NICU stay	Cox (Hazard Ratio)	Gastroenteritis age 0-1: Elective CS 1.24 (1.18, 1.31) Spontaneous CS 1.25 (1.17, 1.34) Induced CS 1.33 (1.23, 1.43)

* GA gestational age; BW birthweight; SGA small for gestational age; LGA large for gestational age; ICD International Classification of Diseases

1.6.6 Mode of birth and its association with asthma

An elevated risk of asthma is one of better known long-term adverse effects of caesarean section on the offspring that is often cited by health organizations. For example, the WHO and the Royal College of Obstetricians and Gynaecologists list asthma as being a potential adverse outcome of caesarean section [26].

Indeed, a large number of studies identified an elevated risk of asthma in children born by caesarean delivery. The temporal trends in asthma and other allergic conditions probably play a part in the scientific community's interest in this relationship. As mentioned previously, an increase in the incidence of asthma and other atopic conditions has been documented in industrialized countries. This trend coincides with a rise in caesarean rates in these settings in corresponding years.

At least five meta-analyses of observational studies that address the association between caesarean delivery and subsequent wheeze or asthma have been carried out to date (Table 1-5). These studies have all consistently concluded that caesarean delivery is associated with a 20% increase in the odds of asthma or wheeze. However, some of these meta-analyses reported substantial heterogeneity between studies and all but one did not distinguish between the various types of caesarean. Huang et al [93] reported on a sub-group of 9 studies differentiating elective and emergency caesarean, and concluded that both types of caesarean are associated with 20% increased risk of asthma. However, the heterogeneity for emergency caesarean was large (I^2=85%).

One of the challenges in reviewing the literature on mode of birth and asthma and/or wheezing is the variability in outcome definitions and in the age of children when outcomes are examined. This is evident in the heterogeneity found in the meta-analyses as described above.

For example, the range of outcome definitions include the following:

- wheezing [87,94,95]
- asthma diagnosis (through parental report or medical records) [86,87,102,94–101]
- asthma medication use [96,100,103–106]
- asthma hospital admission [91,104–109]
- composite outcomes such as:
    - active asthma (asthma diagnosis and recent wheezing [95,110,111]
    - asthma diagnosis or medication use [100,112]

The age of children studied also varies substantially. Some researchers focused on preschool age [87,97,102,103,112], others on school-age [94–96,98,105,110,111] or broad age groups starting from young children up to early adolescence or later [86,91,99–101,106–108,113].

Table 1-6 focuses on large studies that have examined mode of birth and the association with asthma in detail which were published later than the meta-analyses in Table 1-5. All these studies differentiated between two types of caesarean. In general, the association found in these studies between each type of caesarean section with asthma seems to be different. For children born by elective caesarean the relative risk ranged from 20-30% [86,105,106,111], while only a single study did not find any association [35]. On the other hand, regarding emergency caesarean, one of these studies did not report an increased relative risk [111], and those that have reported an increase in risk identified a smaller relative risk than that of elective caesarean. Furthermore, as mentioned previously, additional studies that have contributed to the meta-analysis by Huang et al [93] showed particularly high heterogeneity in the emergency caesarean group. Therefore, although the potential effect of elective caesarean on childhood asthma is relatively broadly reported, it is less clear whether this association also appears in emergency caesarean section as well.

1.6.7 Mode of birth and its association with wheezing phenotypes

Although extensive research has been carried out on the potential effect of mode of birth on childhood asthma, very few studies have differentiated between the various childhood wheezing phenotypes. As explained previously, these phenotypes have been shown to be associated with different risk factors and are thought to have different aetiologies. I was only able to identify one study which investigated in detail the association of mode of birth with a range of wheezing phenotypes classified as wheezing trajectories [97]. The study, carried out on a Dutch birth cohort, concluded that caesarean section is relatively strongly associated with early and persistent wheezing (OR=1.36; 95% CI 1.06, 1.75 for early; OR=1.73; 95% CI 1.24, 2.40 for persistent) but not for late-onset wheeze (OR=1.06; 95% CI 0.59, 1.90). Similar effect sizes were found for elective and emergency caesarean.

Other research exploring various risk factors for wheezing phenotypes gave conflicting results regarding caesarean sections (any type). Most of these studies did not highlight caesareans as a risk factor for any of the examined phenotypes [114,115]. However a recent study (published after finalizing the analyses for this thesis) found an association between caesarean section and persistent wheezing phenotype only [72].

Table 1-5: Meta-analyses of mode of birth and childhood asthma

Author, publication year	Number of studies included, sample size, study design criteria	Exposure	Outcome (age range)	Results OR (95% CI) Heterogeneity (P-value)
Thavagnanam, 2008 [116]	23 studies; (n not reported) No restriction on study design	VD CS	Asthma or wheeze	1.22 (1.14, 1.29); I^2=46% (P<0.001) Sub-group age ≤ 18: 1.20 (1.14, 1.26); I^2=32% (P=0.08)
Bager, 2008 [117]	13 studies for asthma; 7 studies for asthma hospital admission; (n not reported) No restriction on study design	VD CS	Asthma Hospital admission for asthma	Asthma: 1.18 (1.05, 1.32); Q=31.38 (P<0.01) Asthma hospital admission: 1.21 (1.12, 1.31); Q=18.58 (P<0.01)
Mamluk, 2013 (doctorate thesis) [118]	35 studies; (n not reported) No restriction on study design	VD CS	Asthma or wheeze (≤ 18 years)	1.23 (1.13, 1.34) I^2=89% (P-value not recorded)
Huang, 2015 [93]	26 studies; (n not reported) No restriction on study design	VD Instrumental VD Elective CS Emergency CS	Asthma (≤ 18 years)	Total CS 1.16 (1.14, 1.29); I^2=25% Elective CS 1.21 (1.17, 1.25); I^2=25% Emergency CS 1.23 (1.19,1.26); I^2=85% (P-value not recorded)
Keag, 2018 [29]	13 studies for asthma; (n=887,960) 5 studies for wheeze age ≤5 years; (n=53,686) 4 studies for wheeze age 6-15 years; (n=20,815) RCT or large cohort	VD CS	Asthma or wheeze (≤ 12 years)	Asthma: 1.21 (1.11,1.32); I^2=75% Wheeze up to 5 years: 1.10 (0.96, 1.26); Heterogeneity not reported Wheeze 6-15 years: 1.18 (1.05, 1.33); Heterogeneity not reported

Table 1-6: Studies of mode of birth and childhood asthma not included in published meta-analyses

Author, publication year, country, study design	Sample size, birth years, inclusion, age in years	Exposure	Outcome (definition)	Adjustments	Analysis (relative risk measure)	Results: adjusted relative risk (95% CI)
Mamluk, 2013 UK, cohort (doctorate thesis) [118]	n=13,681 age 3 n=15,041 age 5 n=15,681 age 7 2000-2002 all inclusive, age 3, 5, 7	VD Instrumental VD Elective CS Emergency CS	Ever asthma, ever wheezing, recent wheezing, sleep disturbed by wheezing, speech disturbed by wheezing (parental report)	marital status, socio-economic status, fertility treatment, smoking in the same room as baby, GA*, BW	Logistic regression (Odds Ratio)	Statistically significant associations identified: Elective CS: speech disturbed age 3, ever wheezing age 5, recent wheezing age 5, Emergency CS: recent wheezing age 3, sleep disturbed age 3, recent wheezing age 7, speech disturbed age 7 No significant association in other 38 analyses
Kristensen, 2016, Denmark, Population register linkage study [86]	n=750,569 1997-2012 singleton, term GA, without congenital anomaly, age 0-14	VD Elective CS Acute CS	Asthma (ICD in patient registry)	Maternal age, sex, smoking, pregnancy, complications, BW, GA, year of birth	Cox (Hazard Ratio)	Elective CS 1.24 (1.20, 1.28) Acute CS 1.06 (1.02, 1.10)
Sevelsted, 2016, Denmark, Population register linkage study [106]	n= 864,049 1997-2010 age 0-15	VD CS before membrane rupture CS after membrane rupture	Asthma (Long-term medication)	Maternal age, education, employment, parity, smoking, asthma, BW, multiple birth, antibiotics, GA	Poisson (Incidence Rate Ratio)	Total CS 1.16 (1.13, 1.19) Pre-rupture CS 1.20 (1.16, 1.23) Post-rupture CS 1.12 (1.09, 1.16)

Author, publication year, country, study design	Sample size, birth years, inclusion, age in years	Exposure	Outcome (definition)	Adjustments	Analysis (relative risk measure)	Results: adjusted relative risk (95% CI)
Black, 2016, Scotland, Population register linkage study [105]	n=40,145 1993-2007 singleton, term GA, second delivery to mother with history of caesarean	VD following prior CS Planned repeat CS Unscheduled repeat CS	Asthma (hospital admission ICD and medication age 5)	Maternal age, socioeconomic, diabetes, sex, asthma, GA, BW, smoking, year, BF 6 weeks	Cox (Hazard Ratio)	Asthma hospital admission: Planned repeat CS 1.21 (1.09, 1.42) Unscheduled repeat CS 1.18 (1.05, 1.33) Asthma medication: Planned repeat CS 1.04 (0.88, 1.24) Unscheduled repeat CS 1.08 (0.88, 1.31)
Rusconi, 2017, Europe, meta-analysis of cohorts [111]	n=67,613 1996-2006 age 5-9	VD Operative VD Elective CS Emergency CS	Asthma (Current asthma = parental report on ever asthma and wheezing in past year)	Maternal age, country of birth, education, asthma, BMI, smoking, sex, hypertension, diabetes, parity, GA, BW for GA, year	Poisson (Risk Ratio)	Total CS 1.22 (1.02, 1.46) Operative VD 0.97 (0.84, 1.12) Elective CS 1.33 (1.02, 1.75) Emergency CS 1.07 (0.94, 1.22)
Peters, 2018, New South Wales Australia, Population register linkage study [35]	n=491,590 2000-2008 singleton, term GA, without congenital anomaly, healthy pregnant mother age 0-5	VD Induced VD Instrumental VD Ind. instrumental VD Elective CS Emergency CS Ind. emergency CS	Asthma (Hospital admission ICD)	Maternal age, country of birth, area socioeconomics, pain medication, parity, GA, BW, SGA, LGA, birth trauma, sex	Logistic (Odds Ratio)	Asthma No association in any group

* GA gestational age; BW birthweight; SGA small for gestational age; LGA large for gestational age; BMI body mass index; ICD International Classification of Diseases; Ind Induced; BF breastfeeding

1.7 Breastfeeding, mode of birth and child health

As mentioned previously, one of the adverse outcomes of caesarean delivery, is reduced levels of breastfeeding of the infant. Studies have reported lower initiation rates and/or shorter duration of breastfeeding after caesarean section, especially elective caesareans [119]. A global meta-analysis found lower odds of being breastfed at birth or at discharge in babies born by caesarean section compared to those born vaginally (OR=0.57). At 6 months, this effect was reduced to OR=0.81 but the effect was still statistically significant. Another study [120] found that women that had an elective caesarean were more likely to discontinue breastfeeding early, even after adjusting for sociodemographic and birth characteristics. NICE guidelines therefore [20] recommend offering additional support for breastfeeding initiation following caesarean birth.

Reduced levels of breastfeeding have been shown to be a risk factor for infant infectious disease, including LRTI and gastroenteritis [121] as well as any infection or any respiratory infection [122]. These studies have shown that breastfeeding, especially when exclusive, is a substantial protective factor against infectious disease, but its defence wears off soon after cessation. A meta-analysis investigating breastfeeding and asthma during school-age also concluded that breastfeeding is a risk factor for asthma at this age [123].

1.8 Gestational age at delivery, mode of birth and child health

Similar to breastfeeding, gestational age at birth is also associated with mode of birth in a way that is strongly dependent on degree of prematurity. For example, vacuum extraction is avoided in deliveries earlier than 34 weeks gestation [40]. Also, planned caesarean sections prior to term (37 weeks) are avoided when possible as it is considerably better for the fetus to mature in-utero.

Preterm birth is a substantial health risk for the neonate, but it is also a risk factor for a range of adverse outcomes in childhood. These include increased rate of hospital admission during infancy, higher risk of respiratory morbidity (bronchiolitis, asthma and other chronic conditions) as well as behavioural and neuropsychiatric problems [124,125]. The risk for these outcomes is elevated, even in late preterm gestation (34-36 weeks) [124], the largest group of premature births.

Gestational age is an important perinatal factor, not only in preterm deliveries, but also within the window of term gestation (37-41 weeks [126]). NICE guidelines about caesarean sections published in 2011 [20] recommend that caesareans not be routinely scheduled for earlier than 39 weeks gestation. This recommendation arose from research showing that neonates born by planned caesarean at early term gestation (37-38 weeks) suffer from respiratory morbidity more frequently that those scheduled for delivery at week 39 or later [28].

There is growing evidence showing that delivery at early term gestation compared with gestational weeks 39-40 is associated with respiratory illness during early childhood, independent of other perinatal factors [127–129]. The study by Paranjothy et al [90] showed that a child's risk of hospital admission due to a respiratory illness increases with earlier gestational age at birth, even within term gestation. For example, the risk of

respiratory admission at 37 weeks was 32% higher (aHR=1.32 (95% CI 1.28, 1.37) than the risk for children born at gestational weeks 40-42. A further study [130] examining elective inductions of labour at early term compared to 39-41 weeks (excluding planned caesarean) also found an increased risk of hospitalisation for lower respiratory tract infection up to age 5. In addition to respiratory illness, evidence also suggests that the risk of any infection-related admission may be increased in early term deliveries. Miller et al [131] found that for every week reduction in gestational age less than 39-40 weeks, this risk increased by 12%.

When fetal or maternal factors call to plan a caesarean delivery, this decision leads to scheduling the time of delivery (i.e. gestational age at birth) according to the currently acceptable practice. Therefore, in the case of planned caesarean, gestational age at delivery is the result of the plan to perform a caesarean section and may be on the causal pathway between mode of birth and child health outcomes. Almost all previously published studies on mode of birth and childhood infectious disease or asthma have adjusted the effects for gestational age at birth. It is thus unclear whether the scheduled delivery exerts an added effect to that of the potential effect of caesarean.

1.9 Possible long-term biological effects of mode of birth

In the previous sections, I summarised the evidence from epidemiological studies on the association between mode of birth and child infectious diseases, wheezing and asthma. Caesarean sections are risk factors for infections of the gastrointestinal tract and for adverse health outcomes of the lower respiratory tract such as LRTI, wheezing and asthma, with stronger evidence for planned caesarean in the latter.

Several hypothesized biological mechanisms may explain how the mode of birth of a child might directly affect their longer term health. These include the stress levels

experienced during labour, epigenetic modifications taking place during labour which affect gene expression levels, and the transmission of microbiota from mother to newborn [132]. To date, the mechanism most studied, is the third: aberrant composition of the microbiota - the microorganisms that naturally inhabit the human body. When a fetus passes through the birth canal, he or she is exposed to their mother's vaginal microbiota flora and these become the pioneering species to inhabit the newborn's body. Babies born by caesarean section have been shown to have an altered microbiota colonisation pattern [133]. The homeostasis of the microbiota, in turn, has been linked to various health risks such as obesity [134], allergic disease, asthma [135] and infection [136,137].

1.10 Rationale for the study

In recent years, the fundamental process of childbirth has been transformed in a profound manner. The steep rise in caesarean rates has evoked the urgent need to better understand the potential long-term effects that this mode of birth might have on child health. Evidence that the mode of birth impacts the development of the child's microbiota joins accumulating indications that children born by caesarean section may be susceptible to various chronic diseases and adverse health conditions.

Observations that the rate of asthma - the most common chronic disease in childhood – has also increased over the past few decades have led researchers to ask whether asthma might be affected by mode of birth. Recently, however, there is increasing understanding that asthma may not be a single disease entity. This understanding calls for exploration of how mode of birth might affect the various phenotypes of wheezing, only some of which would develop into asthma. Other phenotypes may be more representative of respiratory infections during preschool age, and these, too, need be investigated in relation to mode of birth.

Although infectious diseases are very common during childhood, it is still not known whether birth by caesarean section increases the susceptibility to severe infection, as only a few studies have examined this relationship. Furthermore, it has yet to be explored whether breastfeeding, which commences shortly after delivery and is tied both to mode of birth and to risk of infection and asthma, explains these associations.

Observational studies are still the only feasible means to better understand whether caesarean birth has a direct effect on the child's risk of asthma or infectious diseases. This is because it is unethical to randomize women with uncomplicated pregnancies to plan a caesarean section instead of a vaginal delivery. Observational studies face a challenge to properly address factors that may confound or bias the association. For this reason, and since medically interventional deliveries - caesarean or instrumental - are undertaken for a broad array of indications, it is important to differentiate well between various types of delivery. Furthermore, in order to shine a spotlight on the possible longer-term effects of mode of birth, it is of value to focus on the group of healthy children at the start of life and investigate any emerging illnesses. By analysing a large birth cohort, one can benefit from detailed adjustment of explanatory factors and gain a longitudinal perspective necessary for examining wheezing phenotypes. The use of administrative records of a complete population would reduce bias and enable detection even of small effect sizes to describe associations. Investigating mode of birth and its association with infectious disease and asthma can help to understand whether there are any long-term effects to how we are born.

1.11 Research aim and objectives

1.11.1 Research aim

The overarching aim of this thesis is to investigate the potential effect of mode of birth on the child's health in terms of their risk of infectious disease, wheezing phenotypes and asthma.

1.11.2 Research objectives

1. To investigate the association between mode of birth (vaginal delivery, assisted vaginal delivery, planned caesarean, emergency caesarean) and severe infectious disease during infancy. The following types of infectious disease will be investigated:
    - lower respiratory tract infection (LRTI)
    - upper respiratory tract infection (URTI)
    - any respiratory infection
    - gastrointestinal infection
    - any infection
2. To investigate whether breastfeeding plays a mediating or moderating role in any association found between mode of birth and infant infection.
3. To investigate the association between mode of birth and childhood wheezing phenotypes in the context of asthma indicators.
4. To investigate the association between mode of birth and severe respiratory infection during early childhood.
5. To investigate the association between mode of birth and severe or poorly controlled childhood asthma.
6. To investigate whether gestational age indirectly adds to any association between planned caesarean and childhood infectious disease or asthma.

Chapter 2: An investigation of the association between mode of birth and infant infectious disease in the Millennium Cohort Study

2.1 Introduction

The previous chapter summarized the current knowledge about the relationship between mode of birth and the child health outcomes that are the focus of this thesis. To address the aims of this thesis research, I commenced my investigation with a study examining common severe infectious diseases of infancy using the Millennium Cohort Study.

2.1.1 Study aims

The aim of this study was to investigate the relationship between mode of birth and the risk of severe infectious diseases during infancy. The diseases investigated included lower respiratory tract infection, gastroenteritis and a combined outcome of any infectious disease. A further particular aim was to elucidate whether breastfeeding plays a role in explaining such an association, if indeed one was found.

The research questions were:

1. Is mode of birth associated with hospital admission due to LRTI during infancy?
2. Is mode of birth associated with hospital admission due to gastroenteritis during infancy?
3. Is mode of birth associated with hospital admission due to any infectious cause during infancy?

4. Is breastfeeding a mediator of the potential effect of mode of birth on the risk of infectious diseases?
5. Does breastfeeding modify the potential effect of mode of birth on the risk of infectious diseases?
6. Does earlier gestational age indirectly add to any effect of planned caesarean on infectious disease during infancy?

2.2 Methods

The dataset used in this study was the “Millennium Cohort Study” (MCS).

2.2.1 Millennium Cohort Study

The MCS is a UK nationally representative longitudinal cohort study conducted by the Centre for Longitudinal Studies (CLS) based at the Institute of Education of University College London. The population from which individuals were sampled for the MCS included the following: all babies born between 1 September 2000 and 31 August 2001 in England and Wales and those born between 24 November 2000 and 11 January 2002 in Scotland and Northern Ireland, who were alive and living in the UK at age 9 months and eligible to receive Child Benefit provision [138]. At the time when the MCS was conducted, this provision was virtually universal. It excluded only a small proportion of families that did not have permanent resident status such as overseas students, members of foreign armed forces or recent immigrants, including asylum seekers. The MCS is a disproportionately stratified cluster sample. The study population was stratified by UK country and each country was further stratified by type of electoral ward. Electoral wards were stratified into ‘disadvantaged’ (amongst the poorest 25% of wards according to the Child Poverty Index) or ‘non-disadvantaged’. In England, a third stratum was included: an ‘ethnic minority’ ward, where at least 30% of the population were designated ‘Black’ or ‘Asian’ in the 1991 Population Census. The sampling method was

thus a cluster stratified one, with the basic sampling unit being an electoral ward[6], and employing stratification by country and ward type (9 strata in total). This allowed the MCS to oversample the smaller UK countries as well as wards with high proportions of disadvantaged and ethnic populations.

The initial interview of parents in sampled families was carried out by trained interviewers when the babies were approximately 9-10 months of age[7]. The overall response rate for recruitment to the MCS was 72% from eligible families (85% out of those where contact was achieved) [138]. Potential selection bias arising from non-response was addressed by weighting using information derived from the Child Benefit Register[8]. This cohort thus included 18,852 families and 18,818 children[9]. The main respondent was usually the child's mother. Partners, when available, were interviewed as well. The information collected encompassed the following topics: household structure, pregnancy, birth, baby's nutrition and health, and parent's health.

The MCS was linked to the hospital records[10] from the delivery episode of the cohort child [139]. Ninety percent of mothers consented to their interview data being linked to their hospital delivery records, and a matching record was found for 75% of MCS babies. Mothers less likely to consent were those living in disadvantaged or ethnic wards, from minority ethnic groups, single parents and those with higher degrees or no qualifications [140].

[6] Small wards were combined to 'superwards' with ≥24 expected births per year

[7] The age of the baby during interview ranged from 6-12 months with mean 9.2 months. Only 1 child was interviewed at 6 months, 3% interviewed at 8 months, 75% at 9 months, 19% at 10 months, 3% at 11 months and a handful at 12 months.

[8] This information was: method of benefit payment, claimant title, age of claimant, number of children in household and ward. The overall weights which include non-response weighting in addition to sampling weights are very similar to the sampling weights alone [138].

[9] The number of cohort members recruited was 18,819 but one family removed their consent.

[10] These were derived from the 'Hospital Episode Statistics' (HES) in England, 'Patient Episode Dataset for Wales' (PEDW) and the equivalent datasets for Scotland and Northern Ireland.

The study described in this chapter uses data collected in the first MCS interview conducted when most children were 9-10 months of age, and thus represents a cross sectional analysis. Information about the MCS, including the relevant questionnaires, can be found on the CLS website [141].

2.2.2 Inclusion criteria

The inclusion criteria for the current study were singleton babies born at term which did not exhibit severe health problems at the time of birth, and where the birth mother was the main survey respondent. Several groups of infants from the original 18,818 MCS sample did not meet the inclusion criteria and were thus excluded – see Figure 2-1.

Babies that were part of a multiple birth (twins or triplets) were excluded. This was due to 15% of mothers of multiples reporting more than a single mode of birth. Since it was not possible to differentiate which method or methods were relevant to each sibling, all multiples were excluded from the study (2.8%). Preterm babies (born before completing 37 weeks gestation) comprising 7.0%[11,12] of singletons were excluded as well. As mentioned in section 1.8, prematurity has a major influence on the type of delivery and is also a risk factor for various adverse health outcomes and could therefore be a strong confounding factor. Singleton babies born at week 43 or above were also excluded due to the potential for misclassification of gestational age[13] and because of increased rates of offspring morbidity [142]. For similar reasons, observations with missing gestational age were excluded too (2.1%). Newborns that had been admitted to the neonatal intensive care unit (NICU)[14], those that had unknown admittance status[15], had a major

[11] Percentages are non-sequential and are calculated from the number of singletons in the cohort = 18,296

[12] The proportion is validated by comparing to 6.7% of singleton births being preterm in England in 2000-01 [11].

[13] 84% disagreement between MCS and linked hospital records for gestational age 43 or above

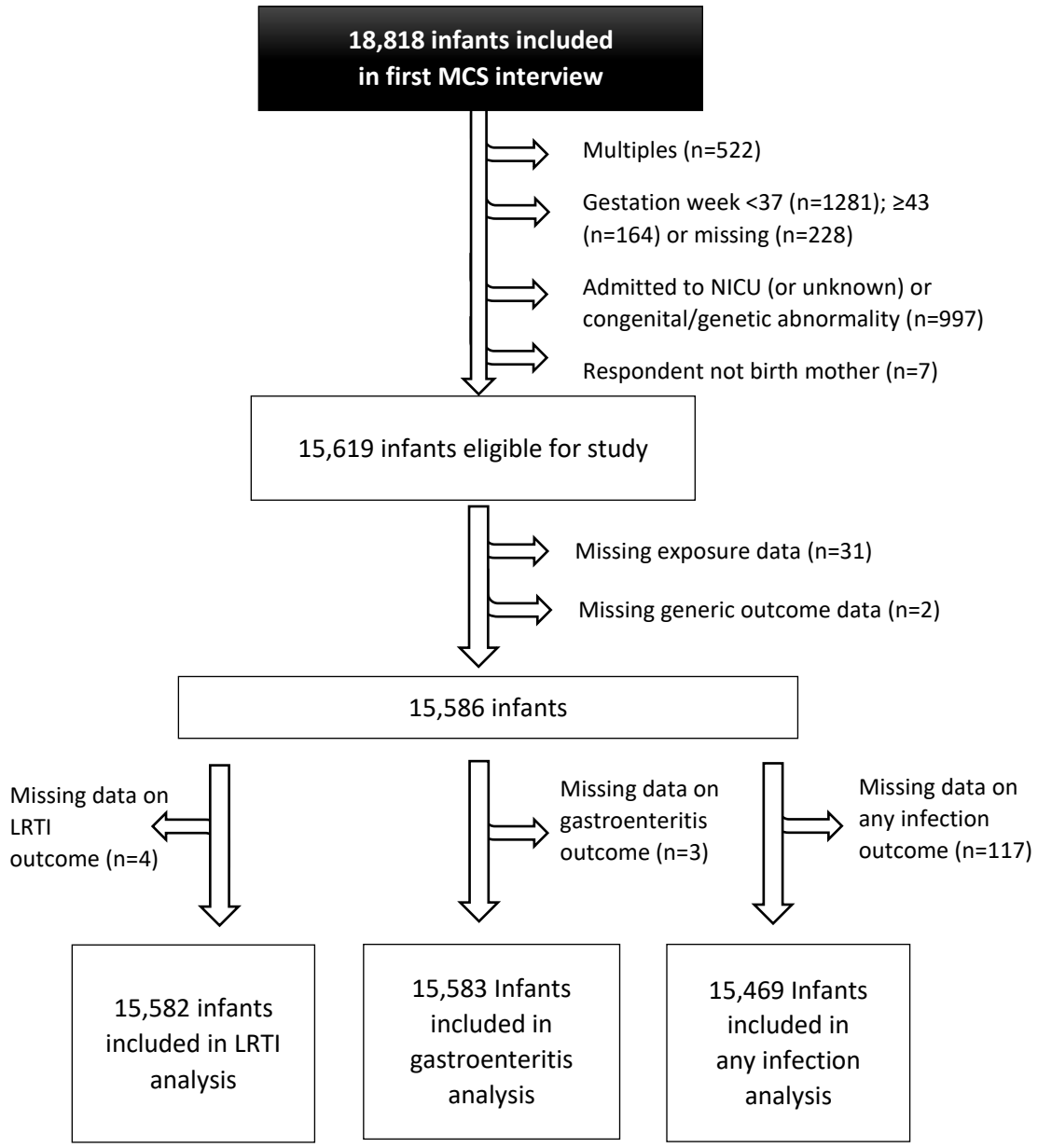
[14] Ascertained from question on whether baby was taken to the special care or neonatal or intensive care unit after birth

[15] A handful of babies with unknown NICU status were excluded. They were reported to have had 'something wrong with them at the time of birth or during the first week of life'.

congenital anomaly, a congenital heart disease or a genetic abnormality, were also excluded (9.1%). A complication arising during pregnancy or labour may not only indicate a medically assisted delivery but may also lead to major neonatal health problems with potential long-term adverse health effects. In order to reduce the influence of confounding by indication on the association at study, the most seriously ill neonates – those admitted to NICU or with serious congenital abnormalities – were excluded from the sample. Further exclusions were families where the main respondent was not the child's birth mother (0.3%) in order to avoid using invalid secondary reports of the exposure and other perinatal variables.

In total, 15,619 infants (83% of original cohort participants) met these inclusion criteria and were eligible for the study. Further exclusions of participants with missing data about exposure or outcome left over 99% of the eligible sample as the final study sample with roughly 15,500 participants for each outcome analysis.

Figure 2-1: MCS infants included in infectious diseases study sample



2.2.3 Exposure – mode of birth

2.2.3.1 Maternal report

Each infant's mode of birth was ascertained through the mother's answer to the question "What type of delivery did you have. Was it…" and the following multiple-choice options were read out by the interviewer: a normal delivery, assisted with forceps, assisted vacuum extraction, assisted breech, a planned caesarean, an emergency caesarean,

or - another type of delivery. The open text responses for another type of delivery were later coded into ‘other assisted breech’ or ‘waterbirth’.

The above mentioned categories of modes of birth were re-categorised into four:

1. Vaginal delivery (VD)
2. Assisted vaginal delivery (Assisted VD)
3. Planned caesarean section (Planned CS)
4. Emergency caesarean section (Emergency CS)

The types of birth included in each category are specified in Table 2-1 under ‘Maternal report in MCS’.

There were 298 infants (1.6% of cohort) where the mother of a singleton baby reported more than a single mode of birth. In these deliveries the higher medically interventional method was chosen as the final mode of birth. Namely emergency caesarean was selected over planned caesarean which was selected over assisted vaginal delivery and over vaginal delivery [143]. There was a handful of infants for which the mother refused to answer, did not know, gave an irrelevant response or declared another method of delivery which was non-codable. In these cases, the exposure was regarded as missing.

2.2.3.2 Hospital delivery record

The linked hospital record includes codes for medical procedures from the ‘Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures’ (OPCS), 4th revision. One of the OPCS codes indicates the mode of birth. Some maternity units also provide supplementary information through a ‘maternity tail’ (supplementary information about the delivery sometimes attached to hospital records) which has a specific variable for delivery method [144]. The codes for these two hospital record variables and their corresponding name in the study are detailed in Table 2-1 - section ‘Hospital delivery records linked to MCS’. In 3.4% of the cases there were some

internal inconsistencies within the two variables of the hospital record data. The hospital delivery record codes were used for validation of the exposure variable.

Table 2-1: Mode of birth classification from MCS report and hospital delivery records

Mode of birth classification for analysis	Maternal report in MCS	Hospital delivery records linked to MCS	
		Operational codes	**Maternity tail codes**
Vaginal delivery	Normal delivery Waterbirth	R24 Normal delivery R23 Cephalic vaginal delivery with abnormal presentation of head at delivery without instrument	Spontaneous vertex Spontaneous other cephalic
Assisted vaginal delivery	Forceps Vacuum Assisted breech Other assisted delivery	R19 Breech extraction delivery R20 Other breech delivery R21 Forceps cephalic delivery R22 Vacuum delivery	Low forceps, not breech Other forceps, not breech Ventouse, vacuum extraction Breech Breech extraction
Planned caesarean	Planned caesarean	R17 Elective caesarean delivery	Elective caesarean section
Emergency caesarean	Emergency caesarean	R18 Other caesarean delivery	Emergency caesarean section
% of sample available for validation	100	76.4	
% validated from available*	95.1		

* Agreement between 4-category mode of birth variable from maternal report and 4-category variable from delivery record (either operational codes or maternity tail code) (section 2.2.7.1)

2.2.4 Outcomes – hospital admission for an infectious disease

Infant's hospital admission episode for an infectious cause was ascertained through the mother's answer to the question "Has (baby's name) ever been admitted to a hospital

ward because of an illness or health problem?". Interviewees that responded positively were asked how many times this had happened and were requested to select the reason for each admission from a pre-defined list. The list included two options that were used as outcomes in this study: First - 'Chest infection or pneumonia', was defined as 'Lower respiratory tract infection (LRTI)' and second - 'Gastroenteritis'. A third outcome - 'Any infection' - was defined as including the following:

- Lower respiratory tract infection
- Gastroenteritis
- Meningitis

And the following causes when provided as an open text response [141]:

- High temperature / acute viral infection unspecified
- Chicken pox
- Measles or whooping cough
- Urinary tract infection
- Infection of nose, ear or throat, croup, flu or severe cough
- Other severe infection
- Other mild infection
- Severe or persistent vomiting

The mother was further asked for her baby's age in months at the time of each hospital admission. When multiple admissions were reported for a specific outcome, the time of the earliest admission was used in the study.

2.2.5 Potential explanatory variables

When assessing the association between mode of birth and infection, the following variables were adjusted for. These include variables that were previously found to be associated with the exposure [143,145,146] or the outcome [89,147–149] and that are

plausible confounders, risk factors for the outcome, mediators or moderators. All information was collected from parental report. See Figure 2-2 for a diagram of the explanatory variables examined and how they might affect the relationship between mode of birth and infant infectious disease.

2.2.5.1 Sociodemographic variables:

- Mother's marital status: married, cohabiting or single.
- Mother's education level using National Vocational Qualifications (NVQ): NVQ 4&5 equivalent to university degree; NVQ 3 equivalent to A level (exams completed prior to university); NVQ 1&2 equivalent to secondary school (exams typically completed at the end of compulsory schooling at age 16); other qualifications including from overseas; and no formal qualifications.
- Mother's age at birth: <20, 20-29, 30-39, ≥40 years.
- Household socioeconomic status defined using the last known occupation of the mother or her partner, if higher: managerial & professional, intermediate, routine & manual, or never worked & long-term unemployed[16].
- Child's ethnicity: White or Other.

2.2.5.2 Maternal, prenatal and postnatal variables:

- Firstborn: mother's first biological child yes/no[17]
- Sex
- Maternal atopic condition (eczema, hay fever or asthma)
- Diabetes or gestational diabetes
- Hypertensive condition during pregnancy
- Birthweight of the baby

[16] Variable derived by the CLS from various survey questions

[17] Variable derived from information on other resident biological children to the cohort member's mother and their date of birth as well as other non-resident biological children
The code used to generate this variable was written by Chris Hockley, Claire Carson and Gry Poulsen from the NPEU based on the code originally developed by the CLS

- Gestational age at delivery
    - Observations with implausible birthweight for gestational age were cleaned. Babies with an incompatible pairing of these variables were identified using a sex and parity-specific centile chart for singleton births [150]. Tukey's rule for outliers was used to flag those with extremely low or high reported birthweight for their gestational age. Outliers were defined as birthweight less than the 25th percentile for their gestational age minus twice the interquartile range or more than the 75th percentile plus twice the interquartile range (provided the mother did not report having diabetes in the latter case) as previously described [151]. Both birthweight and gestational age variables were recoded into missing in the rare extreme case[18] when observations were found to be implausible[19].
    - Gestational age (complete weeks) was categorized according to the American Congress of Obstetricians and Gynaecologists (ACOG) [126] to early term (37-38); full term (39-40); late term (41); post term (42)).
- Mother's smoking status: 'non-smoker', 'ex-smoker' who quit during pregnancy, 'relapsed smoker' who quit during pregnancy but took up again postnatally, 'postnatal quitter' who smoked throughout pregnancy but ceased smoking later, 'took up smoking postnatally' and 'smoker' who smoked both throughout pregnancy and postnatally.
- Breastfeeding duration – partial and/or exclusive breastfeeding based on age when last received breastmilk: none, <2 months, 2-3 months and ≥4 months[20].

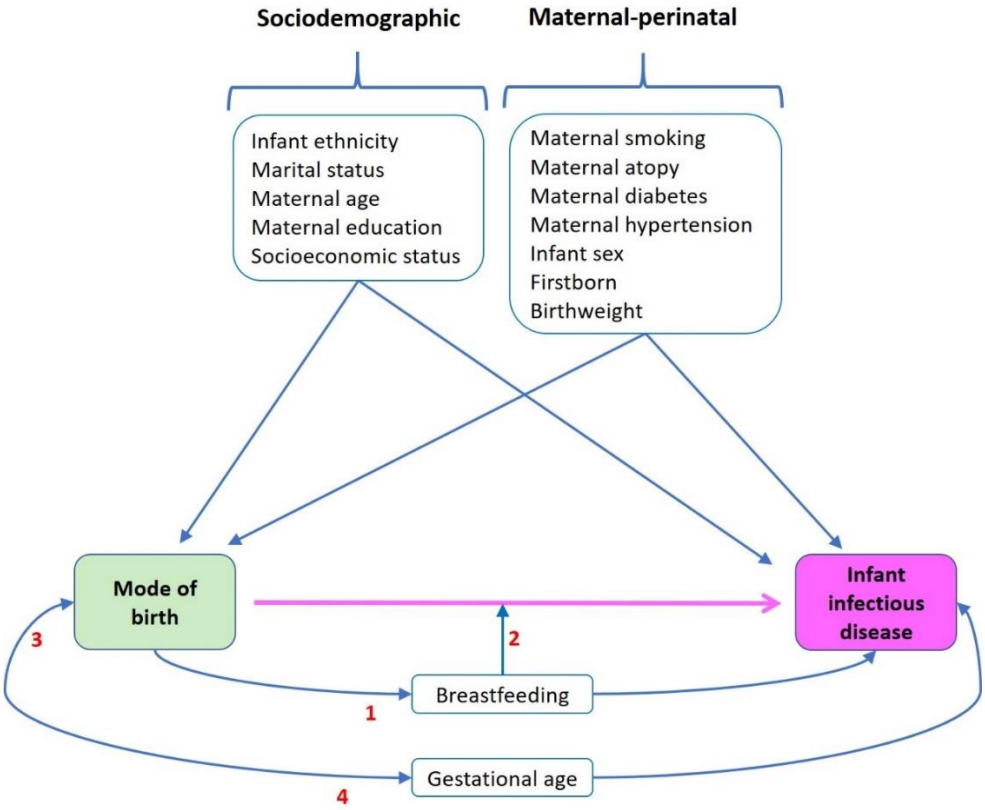
[18] Only 32 observations in the inclusion group had implausible birthweight for gestational age and were updated to be missing values
[19] The code used to generate this variable was based on that developed by Gry Poulsen (NPEU).
[20] The code used to generate this variable was based on that developed by Maria Quigley (NPEU).

- Exclusive breastfeeding duration based on age when last received breastmilk and age when first received formula, other liquids and solids: none, <2 months, 2-3 months and ≥4 months.

Breastfeeding was also examined as a potential mediator of the association between mode of birth and infant infection (see section 2.2.6.4). As explained in section 1.7, breastfeeding rates and duration may be diminished as a result of birth by caesarean section and this, in turn, may increase the infant's susceptibility to infection. Breastfeeding was also examined as a potential effect modifier of the association (see section 2.2.6.6). The aberrant microbiota composition of infants delivered by caesarean may be more strongly affected by formula feeding, as opposed to breastfeeding, compared with the microbiota of infants delivered vaginally [152]. This might lead to a modification of the level of risk. See Figure 2-2.

I further investigated whether birth at earlier gestation mediates some of the effect of mode of birth on infant infection in a way which is masked when adjusting for this variable (see section 2.2.6.4). As explained in section 1.8, planned caesareans are usually scheduled for a time to suit the woman or staff (grade 4 urgency) and the gestational week for which they are set is often determined by common clinical practice. For example, a repeat caesarean delivery following a prior caesarean birth was in the past often scheduled for early-term gestation (37-38 weeks) in order to precede the onset of labour. As mentioned, current guidelines, recommend against routinely scheduling the delivery to earlier than 39 weeks [20]. Gestational age at birth may therefore be the result of the scheduled caesarean and adjustment for this variable would conceal any added effect on susceptibility to infectious disease arising indirectly from birth at earlier gestation.

Figure 2-2: Conceptual framework of explanatory variables potentially affecting an association between mode of birth and infant infectious disease



Notes:

- The main research question investigated is the effect of mode of birth on infant infectious disease.
- Sociodemographic factors and maternal-perinatal factors are considered potential confounders, as they are associated with both the exposure and the outcome and may bias the effects identified if unaccounted for.
- Breastfeeding is considered a possible mediator **(1)** since it may be directly affected by a medically assisted birth and reduced breastfeeding is a risk factor for the outcome. Breastfeeding is also considered a possible effect modifier **(2)** since the biological effect of formula feeding may interact with the biological effect of caesarean birth and lead to different effects of mode of birth on infectious disease dependant on breastfeeding status.
- Gestational age is considered a confounder **(3)** similarly to other maternal-perinatal factors. Gestational age is also considered a potential mediator **(4)** for planned caesarean since it is the result of scheduling the delivery of the fetus by caesarean. Earlier gestational age at delivery, in turn, is a risk factor for infant adverse health outcomes.
- The conceptual framework presented here is relevant to all chapters of the thesis

2.2.6 Statistical analyses

All statistical analyses took the clustered stratified study design of the MCS into account by incorporating variables of electoral wards (the primary sampling unit), strata and weights provided by the CLS (see 2.2.1) using the 'svy' command in Stata version 13.

2.2.6.1 Univariable analyses

First, the association between mode of birth and each potential explanatory variable listed above, was assessed. The Chi-square test for proportions was employed for binary/categorical explanatory variables and the F-test for comparing means was used for continuous explanatory variables. Second, the association between each outcome and each explanatory variable was assessed using an overall Wald test of significance for the variable (using Stata's 'testparm' command for multiple coefficients) derived by Cox regression analysis. A cut-off P-value of <0.10 was used as the threshold to be included in the multivariable modelling process.

2.2.6.2 Multivariable analyses

The datasets were reshaped to have each row represent a month of follow-up of the infant's life from birth up until the month of interview. Cox regression was used to estimate the crude and adjusted hazard ratios, as well as 95% confidence intervals, of age at first hospital admission for each outcome for each mode of birth.

Follow-up began at the reported time at which the baby came home from hospital, as this length of stay was differential between the various modes of birth. The median number of days ranged from 1 day after a vaginal delivery to 5 days after an emergency caesarean (Table 2-4 – page 83). For the small proportion of babies born at home (2%), follow-up time began at the day of birth. The age at interview was the point of right-censoring for following up babies that had not experienced the outcome analysed.

The model building strategy was as follows: sex was selected for inclusion in all models a priori. Covariates associated with exposure (using the Chi-square or F-test) as well as outcome (using Wald) at P-value <0.1 were assessed for inclusion in the multivariable model in a two-stage process. Firstly, covariates were assessed in a 'socio-demographic block' (as listed in 2.2.5.1) or in a 'maternal-perinatal block' (as listed in 2.2.5.2) and a backwards method of selection was employed. The effect of each variable removal was examined individually until all covariates left in the block made a statistically significant contribution to the fit of the model (Wald <0.1). Next, the statistically significant variables from both blocks were combined and the same backwards method run once more. When assessing whether a mode of birth is associated with a given outcome, vaginal delivery was used as the reference group and hazard ratios with a P<0.05 were considered statistically significant.

The multivariable model utilized a time-dependent breastfeeding variable defined dichotomously as whether or not the infant was breastfed per each month of follow-up (as previously described by Quigley et al [121]) [21].

2.2.6.3 Testing of the proportional hazards assumption

The Cox model's assumption that the hazard ratio is constant throughout time was verified by two means: The first, using interaction of the exposure variable with time (P<0.05) and the second, using log-log plots (-ln(-ln(survival) vs. ln(analysis time)).

2.2.6.4 Analysis of potential mediation

The potential of breastfeeding to act as a mediator in the relationship between mode of birth and infection was examined by comparing the final adjusted Cox regression models with and without this variable included. If removing breastfeeding resulted in an increase

[21] For the purpose of the covariate selection process, a time-fixed breastfeeding variable was utilized.

in hazard ratio, this would have indicated a potential for mediation of the association through this variable (section 2.2.5.2).

Gestational age may also have a mediating effect in planned caesarean deliveries, in addition to its confounding effect on mode of birth. In order to obtain an effect of caesarean delivery that also incorporates the potential indirect effect of gestational age (if it indeed is also a mediator), fully adjusted multivariable models were run a second time without adjustment for gestational age. Hazard ratios and 95% confidence intervals were estimated.

2.2.6.5 Duration of breastfeeding by mode of birth

To explore the difference in breastfeeding duration between the various mode of birth types, quantification of the association between mode of birth and time until breastfeeding cessation was conducted using Cox regression analysis. This Cox model was fitted three times: once with adjustment for the explanatory variables appearing in the LRTI model, once for those appearing in the gastroenteritis model, and once with adjustment for the explanatory variables appearing in the any infection model.

2.2.6.6 Analysis of effect modification

Analysis of the role of breastfeeding as an effect modifier was examined by adding an interaction term between the time-dependent breastfeeding variable and mode of birth to the final adjusted models. Statistical significance of the interaction term was tested using the Wald test with $P<0.01$ as the threshold level considered significant (section 2.2.5.2).

2.2.7 Sensitivity analyses

The crude and adjusted Cox models were repeated for the following sensitivity analyses.

2.2.7.1 Restriction to observations with validated mode of birth

Validation of the mother's reported mode of birth was carried out using linked hospital records as described in section 2.2.3.2. The mother's reported mode of birth was considered valid if consistent with either one of the hospital record variables (OPCS or maternity tail). The sensitivity analyses were conducted on a sub-group of 73% of the sample, which included the observations that had a hospital record with a validated mode of birth variable (Table 2-1).

2.2.7.2 'Wheezing or asthma' indication included in LRTI and any infection outcome

'Wheezing or asthma' was listed as one of the reasons for hospitalising the infant from which respondents could choose. Wheezing could be the main presenting symptom in an infant with LRTI. Thus, this indication was added to the LRTI outcome and to the 'any infection' outcome.

2.2.7.3 Vomiting indication removed from any infection outcome

Vomiting in infants may be due to a non-infective cause such as reflux, motion sickness or eating too much or too fast. In this sensitivity analysis, cases with this reported indication were excluded from the 'any infection' outcome.

2.2.7.4 Infants with a history of perinatal infection excluded from study

An underlying infection during pregnancy or labour could lead to the need to medically intervene during birth and could also potentially lead to developing a severe infection after the newborn has been discharged home. To rule out such reverse causality, a sensitivity analysis was conducted excluding all babies with a report of infection during

the prenatal period, labour or immediate postnatal period. These infections include the following:

- Maternal urinary tract infection during pregnancy
- Early rupture of amniotic membranes (prior to labour) which increases risk of infection
- Other maternal infection during pregnancy or labour
- Infection or suspicion of infection in the neonate during first week after birth

2.2.7.5 Breastfeeding during previous month of follow-up

Illness and hospital admission of an infant could potentially lead to discontinuation of breastfeeding. To properly adjust for the effect of breastfeeding without the possible influence of the outcome event on this factor, a sensitivity analysis using a time dependant variable of whether or not the infant received breastmilk during the previous month of follow-up (contrary to the current month) was conducted.

2.2.8 Power calculation

The study's power to detect an association between exposure[22] and outcomes was estimated by comparing two independent proportions using the Chi-square test. The size of the reference group (vaginal delivery) in the study sample was 11,000 and the size of the exposed groups was 1,365 for planned caesarean and 1,578 for emergency caesarean. The expected proportion of LRTI hospital admissions was estimated at 3.6% and that for gastroenteritis was estimated at 1.2%. These proportions were extrapolated from the rates published in a study based on the MCS cohort [121]. The expected proportion of hospital admission due to any infectious disease in this age group was estimated at 7% [122].

[22] Planned or emergency caesarean only compared with vaginal delivery

The study had at least 80% power to detect a relative risk of 1.4-1.5 for LRTI, 1.8-1.9 for gastroenteritis and 1.3-1.4 for any infectious disease. However, if the effect sizes were as low as those found in some of the published studies then the power would be much lower. For example, the effect size for LRTI and gastroenteritis outcomes in planned and emergency caesarean ranged from 1.1 [84,88] to 1.3 [89,91]. No estimate for the effect size for any infection was found in the literature, so the same relative risk estimates were used to calculate the power for this outcome. The estimated power to detect the expected effects in the LRTI or gastroenteritis outcomes was low, ranging from 8% to 52% (see Table 2-2). The power for any infectious disease was higher (up to 76%) especially when the expected relative risk was estimated at 1.3. Note that these estimations do not account for the clustered study design which reduces the study's power to detect a statistically significant association.

Table 2-2: Power to detect associations in the MCS infectious diseases study by estimated effect size

	Power (%)					
Estimated effect size	**LRTI** (3.6%)		**Gastroenteritis** (1.2%)		**Any infection** (7.0%)	
	Planned CS	**Emergency CS**	**Planned CS**	**Emergency CS**	**Planned CS**	**Emergency CS**
1.1	11	11	8	8	15	16
1.2	26	29	14	14	42	46
1.3	48	52	23	24	71	76
1.4	69	74	34	37	**90**	**93**
1.5	**84***	**88**	46	50	98	99
1.6	93	95	58	62	100	100
1.7	97	98	68	73	100	100
1.8	99	100	77	**81**	100	100
1.9	100	100	**84**	88	100	100

* The smallest effect size for which a power of ≥80% is achieved is highlighted in bold

2.2.9 Data management

The Millennium Cohort Study data is held by the UK Data Service and is freely and publicly available.

All relevant datasets from the first sweep of the MCS were downloaded in Stata format. These include:

- Parent interview dataset (main respondent and partner)
- Longitudinal family dataset
- Derived variables dataset (coded by the CLS)

Also downloaded was linked hospital record data of the delivery episode of cohort members for each UK country. These datasets were then merged together based on the 'MCSID', an identification number unique to each family recruited to the MCS.

2.2.10 Ethics committee approval

Ethics committee approval for the Millennium Cohort Study was granted by an NHS Research Ethics Committee. Parents were given the opportunity to opt-out of the study at any point. Consent for linkage to mother's health records and child's birth registration data was obtained separately. The current study is a secondary data analysis of this anonymized dataset and therefore further ethical committee approval was not required.

2.3 Results

2.3.1 Study group and mode of birth – descriptive results

The number of cohort members eligible for inclusion in the study was 15,619 infants and the final study sample included 15,582 for LRTI analysis, 15,583 for gastroenteritis and 15,469 for the analysis of any infection outcome. The proportion of each of the four modes of birth was: 10.1% assisted vaginal delivery, 8.7% planned caesarean, 10.1% emergency caesarean and the remaining 71.0% by vaginal delivery. The most common

diagnostic codes within each mode of birth that appear in linked hospital records were collected through ICD codes (International Classification of Diseases - 10th revision) (Table 2-3). These diagnostic codes generally represent the indications for a medically interventional delivery. The distribution of codes is similar in the two unplanned interventions – emergency caesarean and assisted vaginal delivery - but those of planned caesarean are clearly different. The emergency caesarean and assisted vaginal delivery had high proportion of codes for fetal distress and long labour while planned caesareans were carried out predominantly due to the presence of a pelvic abnormality, the vast majority probably being a uterine scar from a prior caesarean. Furthermore, the planned caesarean section had high rates of fetal malpresentation such as breech.

Table 2-3: Three most common diagnostic codes* per mode of birth and their proportion in linked hospital record data of MCS infectious disease study

	VD (%)*	***Assisted VD (%)***	***Planned CS (%)***	***Emergency CS (%)***
Most common diagnostic code	Labour and delivery complicated by fetal stress [distress] (*O68)* **13.8**	Labour and delivery complicated by fetal stress [distress] (*O68)* **49.8**	Maternal care for known or suspected abnormality of pelvic organs (including uterine scar) (*O34)* **50.5**	Labour and delivery complicated by fetal stress [distress] (*O68)* **48.1**
2nd most common diagnostic code	Prolonged pregnancy (O48) **7.0**	Long labour (including prolonged 1st and 2nd stage) (*O63)* **49.1**	Maternal care for known or suspected malpresentation of fetus (including breech) (*O32)* **24.7**	Long labour (including prolonged 1st and 2nd stage) (*O63)* **32.3**
3rd most common diagnostic code	Other maternal diseases complicating pregnancy, childbirth and puerperium (O99) **6.1**	Other complications of labour and delivery, not elsewhere classified (O75) **13.6**	Other maternal diseases complicating pregnancy, childbirth and puerperium (O99) **12.5**	Other maternal diseases complicating pregnancy, childbirth and puerperium (O99) **14.4**

* A delivery record might not have an ICD code and could have more than a single code; listed from codes beginning with 'O' not including O80-O84 for mode of delivery, O70 for perineal lacerations or O72 for postpartum haemorrhage

** Percentages per each mode of birth are calculated from the sub-sample of observations with validated mode of birth data (see 2.2.7.1) and are weighted

2.3.2 Study group characteristics

Study group participants were found to have a statistically significant difference in all examined characteristics between the various mode of birth groups. A Chi-square test gave P-value<0.001 for all characteristics apart from maternal atopy, which had P=0.0245 (Table 2-4).

Mothers who had given birth by caesarean section (both planned and emergency) tended to be older, married, more highly educated and of higher socioeconomic status compared to the vaginal delivery reference group. These mothers were less likely to smoke or report atopic conditions (eczema, hay fever or asthma). They also experienced more complications of pregnancy: the mothers that had undergone a planned caesarean were more often diabetic and those that had undergone an emergency caesarean had higher rates of hypertensive conditions.

Mothers who had given birth by assisted vaginal delivery were of roughly similar age and had a slightly higher proportion of marriage than the reference group. These mothers were relatively highly educated and of higher socioeconomic status, smoked less frequently and reported more atopic conditions. In terms of complications of pregnancy, the mothers that had undergone assisted vaginal delivery did not exhibit higher rates of diabetes, but experienced slightly more hypertensive conditions compared to mothers that had undergone vaginal delivery.

Infants born by planned caesarean birth were slightly less often male and more often of white ethnicity as well as substantially less commonly the firstborn child in comparison to the babies born vaginally. The majority of these caesarean sections were scheduled for early-term (while ‘full term’ was the most frequent gestation in the vaginal delivery group) and had lower birthweights accordingly. The percentage of babies that received any breastmilk was similar in the planned caesarean group but at 4 months the

percentage of those still breastfeeding was slightly lower compared to the reference vaginal delivery group.

Infants born by emergency caesarean showed a different pattern of characteristics to those born by planned caesarean. They were more often male and slightly less often of white ethnicity, and were substantially more commonly the firstborn child compared to the vaginal delivery group. The babies born by emergency caesarean were also more likely than vaginally delivered babies to be born late or post term and had correspondingly higher birthweights. They had higher rates of breastfeeding initiation but similar rates of breastfeeding by 4 months.

Infants born by assisted vaginal delivery tended to be male, of white ethnicity and were much more commonly their mother's firstborn child. They were more likely to be born late and post term but were not notably heavier than the vaginal delivery group. These babies also experienced higher breastfeeding initiation rates compared to the vaginal delivery infants but the proportion at 4 months was similar.

Infants born vaginally and their mothers had very similar characteristics to the total study group, as these comprised the majority (71.0%) of the inclusion group

Table 2-4: Characteristics of infants and their mothers included in the MCS infectious diseases study by mode of birth

	VD n (%)	Assisted VD n (%)	Planned CS n (%)	Emergency CS n (%)	Total n (%) [a]
Mode of birth n (%)	**11,080 (71.0)**	**1,528 (10.1)**	**1,382 (8.7)**	**1,596 (10.1)**	**15,586 (100.0) [c]**
Maternal characteristics					
Maternal age group (years)					
<20	1,020 (8.3)	151 (8.1)	35 (1.9)	108 (5.1)	1,314 (7.4)
20-29	5,408 (46.5)	730 (45.3)	508 (33.9)	683 (39.3)	7,329 (44.6)
30-39	4,446 (43.3)	629 (45.6)	783 (60.2)	757 (52.2)	6,615 (45.9)
≥40	204 (1.9)	18 (1.0)	56 (4.1)	48 (3.4)	326 (2.2)
Marital status					
Married	6363 (58.6)	924 (62.6)	963 (71.8)	972 (64.4)	9,222 (60.8)
Cohabiting	2,708 (25.9)	393 (26.4)	254 (18.7)	388 (24.0)	3,743 (25.1)
Single	2,009 (15.5)	211 (11.1)	165 (9.5)	236 (11.6)	2,621 (14.1)
Education					
Higher	2,966 (30.4)	581 (41.0)	469 (37.5)	566 (40.4)	4,582 (33.1)
Intermediate	1,588 (14.6)	234 (15.1)	171 (11.9)	228 (14.0)	2,221 (14.3)
Lower	4,204 (38.6)	543 (35.4)	507 (37.4)	559 (33.8)	5,813 (37.7)
Overseas or other	362 (2.6)	35 (2.2)	37 (2.1)	49 (2.7)	483 (2.5)
None	1,940 (13.8)	134 (6.5)	198 (11.1)	190 (9.2)	2,462 (12.4)
Household socioeconomic class					
Managerial/ Professional	4,015 (42.5)	744 (53.9)	600 (48.2)	740 (53.7)	6,099 (45.3)
Intermediate	2,182 (19.8)	284 (18.6)	286 (22.8)	313 (18.4)	3,065 (19.8)
Routine/Manual	4,118 (32.5)	438 (24.4)	436 (26.3)	474 (24.4)	5,466 (30.3)
Never worked / long unemployment	765 (5.2)	62 (3.1)	60 (2.7)	69 (3.6)	956 (4.6)
Smoking					
Non-smoker	6,940 (63.2)	991 (65.9)	913 (67.2)	1,077 (69.2)	9,921 (64.5)
Ex-smoker	510 (5.0)	107 (7.4)	56 (3.4)	93 (6.1)	766 (5.2)
Relapse smoker	750 (7.0)	125 (8.3)	114 (8.3)	124 (8.4)	1,113 (7.4)
Postnatal quitter	179 (1.7)	36 (2.4)	20 (1.6)	24 (1.4)	259 (1.7)
Took up postnatally	190 (2.0)	27 (1.6)	32 (2.7)	23 (1.5)	272 (1.9)
Smoker	2,501 (21.1)	240 (14.5)	246 (16.8)	254 (13.5)	3,241 (19.3)
Maternal atopy	4,362 (42.2)	668 (46.2)	543 (40.6)	642 (40.7)	6,215 (42.3)
Diabetes	144 (1.5)	20 (1.7)	51 (4.6)	34 (2.3)	249 (1.9)
Hypertensive condition	574 (6.0)	125 (8.5)	96 (7.2)	173 (13.0)	968 (7.0)

	VD n (%)	Assisted VD n (%)	Planned CS n (%)	Emergency CS n (%)	Total n (%)
Infant characteristics					
Male	5,509 (49.5)	836 (55.1)	667 (47.9)	889 (55.4)	7,901 (50.5)
White ethnicity	9063 (86.7)	1356 (91.2)	1192 (89.2)	1301 (85.9)	12912 (87.3)
Firstborn	3,782 (34.1)	1,201 (78.2)	343 (23.1)	1,078 (68.5)	6,404 (41.1)
Gestational age in weeks					
37-38 (early term)	1,969 (17.7)	193 (12.1)	703 (54.2)	285 (17.8)	3,150 (20.3)
39-40 (full term)	6,230 (56.3)	813 (53.3)	574 (39.3)	746 (46.8)	8,363 (53.6)
41 (late term)	2,499 (22.6)	444 (29.5)	78 (4.9)	461 (28.8)	3,482 (22.4)
42 (post term)	364 (3.5)	75 (5.2)	20 (1.7)	100 (6.5)	559 (3.8)
Birthweight in kg, mean (SD) [b]	3.44 (0.6)	3.49 (0.6)	3.39 (0.5)	3.54 (0.7)	3.45 (0.6)
Breastfed					
Never	3,909 (31.5)	454 (24.8)	480 (30.5)	456 (25.3)	5,299 (30.1)
Up to 2 months	2,817 (25.2)	456 (30.3)	389 (28.6)	506 (31.3)	4,168 (26.6)
2-3 months	973 (9.4)	153 (10.6)	130 (9.6)	141 (9.6)	1,397 (9.5)
4 months or more	3,380 (33.9)	465 (34.3)	383 (31.3)	493 (33.8)	4,721 (33.7)
Exclusively breastfed					
No	4,664 (37.5)	551 (31.2)	577 (36.8)	628 (34.8)	6,420 (36.6)
Up to 2 months	3,105 (29.0)	522 (35.6)	451 (34.9)	539 (35.3)	4,617 (30.8)
2-3 months	1,571 (15.9)	223 (16.5)	163 (12.9)	209 (15.1)	2,166 (15.6)
4 months or more	1,739 (17.5)	232 (16.7)	191 (15.5)	220 (14.7)	2,382 (17.0)
Neonatal hospital stay in days, median (IQR [b])	1 (1-2)	2 (1-4)	4 (3-5)	5 (4-5)	2 (1-4)

a P-value for all characteristics was <0.001 except maternal atopy P=0.0245
b IQR Interquartile range; SD standard deviation
c Percentages do not accumulate to 100% due to rounding error

2.3.3 Hospital admission for an infectious disease

Thirteen percent of the cohort infants were reported to have been admitted to hospital for an illness or health problem up to the time of interview at ~9 months. The majority required such admission only once, however 14% of those hospitalized were admitted more than once and 5% more than twice. The prevalence of hospital admission for infectious disease was as follows:

- LRTI - 3.4% (95% CI 3.1, 3.8); 575 events[23]
- Gastroenteritis - 1.4% (95% CI 1.2, 1.6); 217 events[24]
- Any infectious disease - 7.6% (95% CI 7.0, 8.2); 1,235 events
    - 555 first hospital admission for LRTI (45% of admissions)
    - 208 first hospital admission for gastroenteritis (17% of admissions)
    - 472 first hospital admission for other infections (38% of admissions)

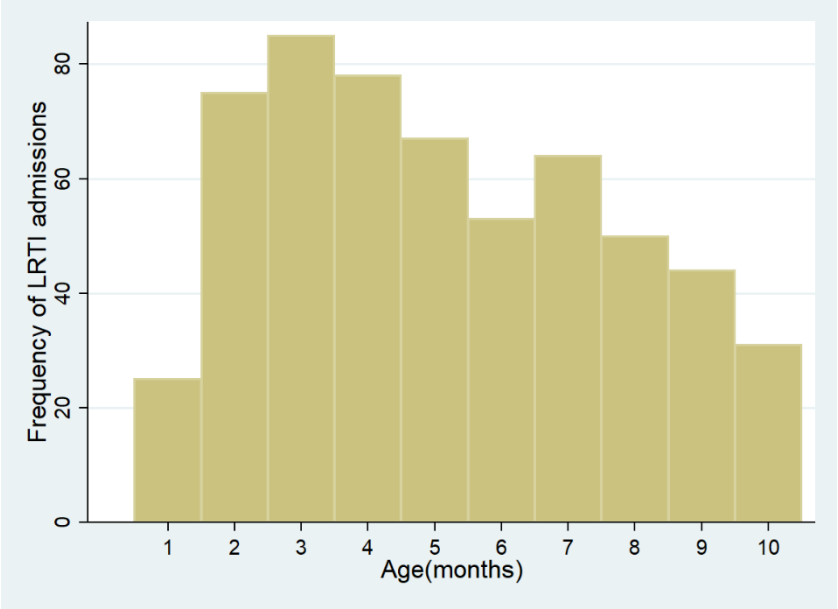
The trend in the timing of first hospital admission for each study outcome within the first 10 months is represented in Figure 2-3 to Figure 2-5 (note different Y axis scales). The frequency of admissions was lowest in the first month after birth for all outcomes. Notably, during this period the infant experienced a shorter time at risk for hospital admission, since admission in the immediate postnatal period before discharge home is not possible (Table 2-4).

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[23] In Wales only the prevalence of LRTI admission was 5.3% (95% CI 4.5, 6.3) weighted using CLS designed country-level weights (see Chapter 4)

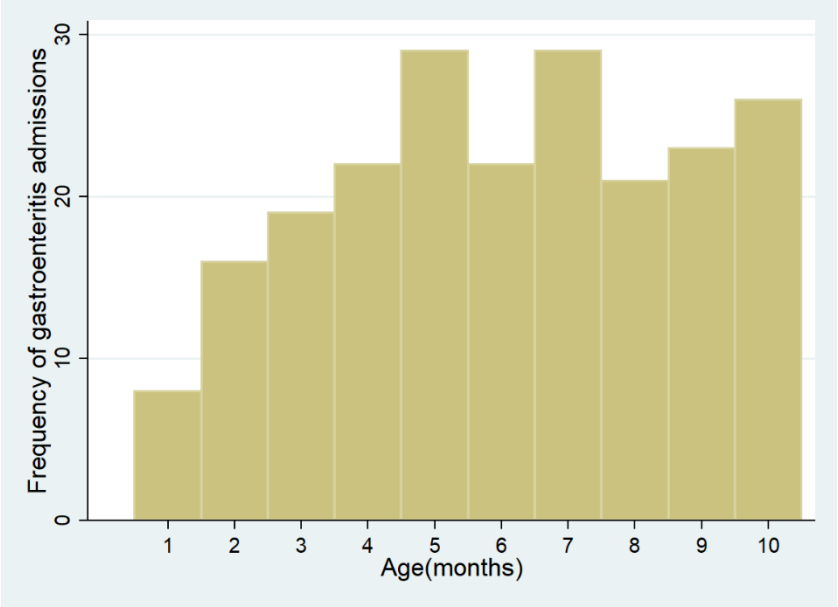
[24] In Wales only the prevalence of gastroenteritis admission was 1.4% (95% CI 0.9, 2.1) weighted using CLS designed country-level weights (see Chapter 4)

Figure 2-3: Frequency of hospital admissions (first spell) for LRTI by infant age



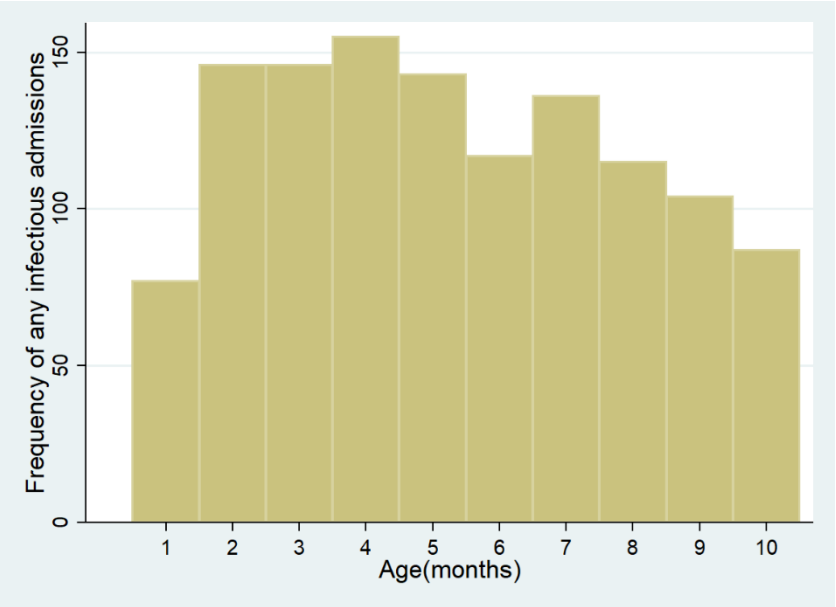
* follow-up complete until 8th month

Figure 2-4: Frequency of hospital admissions (first spell) for gastroenteritis by infant age



* follow-up complete until 8th month

Figure 2-5: Frequency of hospital admissions (first spell) for any infectious disease by infant age



* follow-up complete until 8th month

2.3.4 Mode of birth and hospital admission for LRTI

Overall, 3.4% of babies were admitted for LRTI, and this proportion varied across mode of birth groups from 2.8% in the assisted vaginal delivery group to 5.1% in the planned caesarean group (Table 2-5).

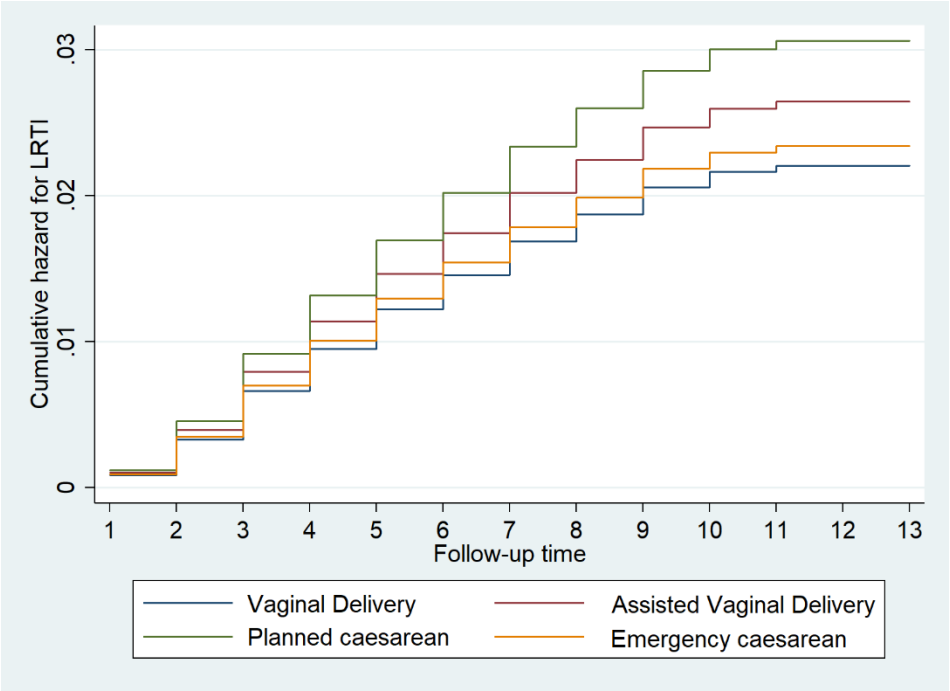
Assisted vaginal delivery was associated with a lower hazard than the vaginal delivery group in the crude model and a higher one after adjustment, however both were not statistically significant. Planned caesarean section was associated with HR=1.51; (95% CI 1.13, 2.03; P=0.006) in the crude model and after adjustment the hazard ratio was slightly attenuated to aHR=1.39; (95% CI 1.03, 1.87; P=0.030) and was statistically significant. Emergency caesarean section was associated with a lower hazard compared with vaginal delivery in the crude model and a higher one following adjustment, but in neither case were these effects statistically significant. A graphical presentation of the cumulative hazard can be seen in Figure 2-6 .

Table 2-5: Association between mode of birth and hospital admission for LRTI in the MCS study

	Main analysis					Sensitivity analysis - validated mode of birth [c]				
	No. of events	**n**	**% [a]**	**Crude HR (95% CI)**	**Adjusted HR [b] (95% CI)**	**No of events**	**n**	**% [a]**	**Crude HR (95% CI)**	**Adjusted HR [b] (95% CI)**
LRTI total	**575**	**15,582**	**3.44**			**429**	**11,330**	**3.53**		
VD	420	11,078	3.41	1.00	1.00	315	8,156	3.46	1.00	1.00
Assisted VD	43	1,528	2.81	0.82 (0.57,1.19)	1.18 (0.79, 1.75)	32	1,129	3.04	0.88 (0.57, 1.35)	1.29 (0.82, 2.03)
Planned CS	61	1,381	5.13	1.51 (1.13, 2.03)	1.39 (1.03, 1.87)	49	929	6.07	1.77 (1.27, 2.48)	1.60 (1.15, 2.23)
Emergency CS	51	1,595	2.86	0.83 (0.58, 1.20)	1.14 (0.79, 1.65)	33	1,116	2.46	0.71 (0.45, 1.12)	0.99 (0.63, 1.56)

a Percentages are weighted.
b Results are adjusted for maternal age, firstborn, baby's sex, mother's smoking, gestational age and time-dependent breastfeeding.
c Sensitivity analysis was conducted on a sub-sample with validated mode of birth data

Figure 2-6: Cumulative hazard of LRTI hospital admission by mode of birth in the MCS study



2.3.5 Mode of birth and hospital admission for gastroenteritis

Overall, 1.4% of babies were hospitalised for gastroenteritis, and this proportion was highest in the planned caesarean (1.7%) and emergency caesarean (1.8%) groups (Table 2-6).

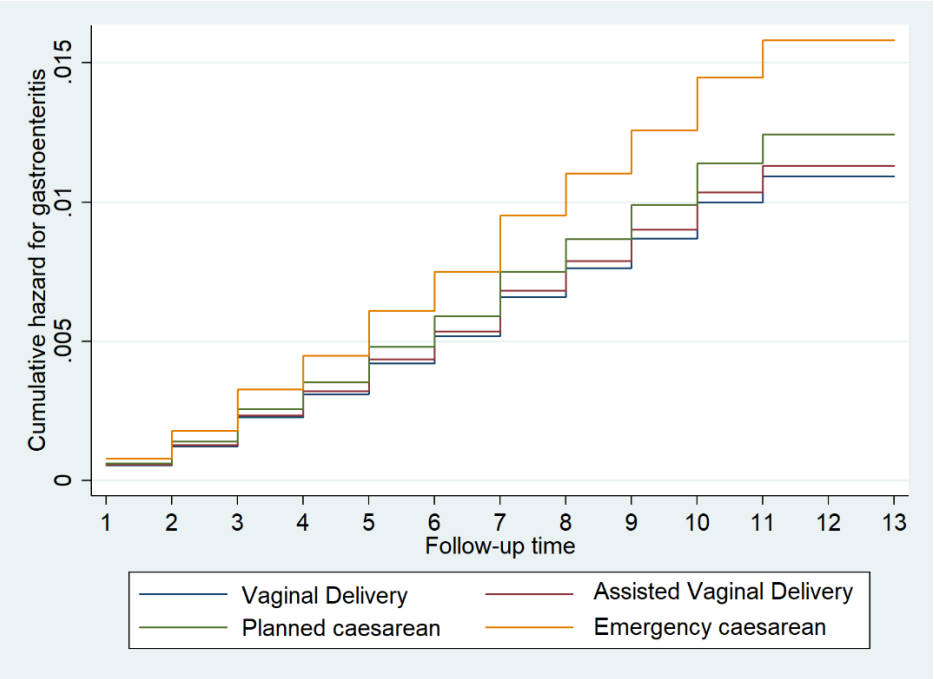
The hazard ratio of the assisted vaginal delivery group was no different from the reference group either before or after adjustment. The hazard ratio for planned caesarean was 1.32, but not statistically significant, and this effect was attenuated after adjustment for other explanatory factors (aHR=1.15; 95% CI 0.68, 1.94). The hazard ratio for emergency caesarean was 1.40 in the crude model. After correcting for explanatory variables the hazard ratio increased to aHR=1.52; (95% CI 0.96, 2.39; P=0.072) but was not statistically significant. See Figure 2-7 for a graphical presentation of the cumulative hazards for gastroenteritis by mode of birth (note different Y scale than in Figure 2-6).

Table 2-6: Association between mode of birth and hospital admission for gastroenteritis in the MCS study

	Main analysis					Sensitivity analysis – validated mode of birth [c]				
	No. of events	**n**	**% [a]**	**Crude HR (95% CI)**	**Adjusted HR [b] (95% CI)**	**No. of events**	**n**	**% [a]**	**Crude HR (95% CI)**	**Adjusted HR [b] (95% CI)**
Gastroenteritis	**217**	**15,583**	**1.38**			**161**	**11,330**	**1.33**		
VD	148	11,078	1.30	1.00	1.00	112	8,156	1.26	1.00	1.00
Assisted VD	19	1,528	1.22	0.94 (0.55, 1.60)	1.05 (0.62, 1.78)	14	1,129	1.20	0.96 (0.52, 1.77)	1.09 (0.59, 2.00)
Planned CS	22	1,382	1.70	1.32 (0.78, 2.22)	1.15 (0.68, 1.94)	14	929	1.66	1.33 (0.70, 2.50)	1.20 (0.63, 2.27)
Emergency CS	28	1,595	1.82	1.40 (0.89, 2.21)	1.52 (0.96, 2.39)	21	1,116	1.76	1.40 (0.83, 2.34)	1.56 (0.93, 2.63)

a Percentages are weighted.
b Results are adjusted for household socioeconomic class, baby's sex, gestational age and time-dependent breastfeeding.
c Sensitivity analysis was conducted on a sub-sample with validated mode of birth data

Figure 2-7: Cumulative hazard of gastroenteritis hospital admission by mode of birth in the MCS study



2.3.6 Mode of birth and hospital admission for any infection

Overall, 7.6% of babies were admitted for any infectious cause (first admission episode due any infectious cause). Amongst the different mode of birth groups, the proportion of infants hospitalized for any infection was highest in the emergency caesarean (8.1%) and planned caesarean (9.7%) groups (Table 2-7).

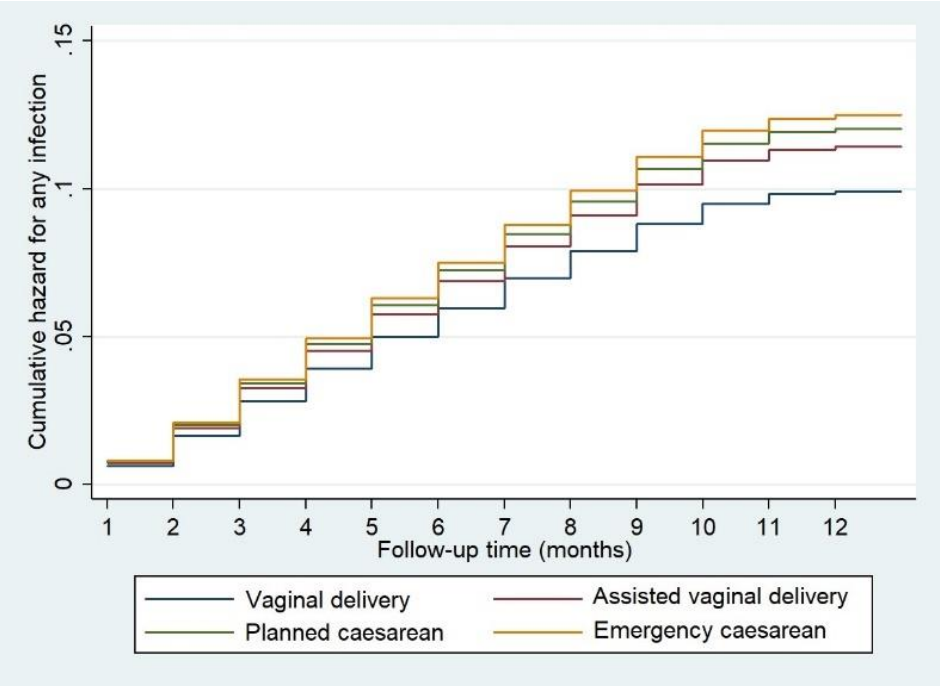
The hazard ratio of the assisted vaginal delivery group was the same as that of babies born vaginally. After accounting for explanatory variables, a small increased hazard was observed, although it was not statistically significant (aHR=1.14; 95% CI 0.91, 1.42). The crude hazard ratio for planned caesarean was 1.33 (95% CI 1.06, 1.66). After adjustments, the increased hazard was attenuated to aHR=1.23 (95% CI 0.97, 1.55; P=0.081). The crude hazard ratio for emergency caesarean was 1.10 and following adjustments the effect increased to 1.29 (95% CI 1.01, 1.65; P=0.039). See Figure 2-8 for a cumulative hazard graph (note different Y scale than in Figure 2-6 and Figure 2-7).

Table 2-7: Association between mode of birth and hospital admission for any infectious disease in the MCS study

	Main analysis					Sensitivity analysis – validated mode of birth [c]				
	No. of events	**n**	**% [a]**	**Crude HR (95% CI)**	**Adjusted HR [b] (95% CI)**	**No. of events**	**n**	**% [a]**	**Crude HR (95% CI)**	**Adjusted HR [b] (95% CI)**
Any infection	**1,235**	**15,469**	**7.60**			**930**	**11,256**	**7.77**		
VD	867	11,001	7.33	1.00	1.00	659	8,102	7.42	1.00	1.00
Assisted VD	107	1,519	7.25	0.99 (0.81, 1.22)	1.14 (0.91, 1.42)	78	1,124	7.41	1.00 (0.78, 1.28)	1.18 (0.90, 1.54)
Planned CS	127	1,370	9.69	1.33 (1.06, 1.66)	1.23 (0.97, 1.55)	95	924	11.01	1.50 (1.18, 1.92)	1.36 (1.05, 1.74)
Emergency CS	134	1,579	8.06	1.10 (0.87, 1.39)	1.29 (1.01, 1.65)	98	1,106	8.05	1.08 (0.81, 1.45)	1.30 (0.97, 1.75)

a Percentages are weighted.
b Results are adjusted for household socioeconomic class, maternal age, maternal atopic condition, firstborn, baby's ethnicity, baby's sex, gestational age and time-dependent breastfeeding.
c Sensitivity analysis was conducted on a sub-sample with validated mode of birth data

Figure 2-8: Cumulative hazard of any infection hospital admission by mode of birth in the MCS study



2.3.7 Testing of the proportional hazards assumption

The underlying assumption of a Cox model is that the hazard ratio is constant throughout time. This was examined in the final models by two means: a visual examination of a log-log plot, and interaction of the exposure variable with time. The log-log plots showed parallel survival curves for the medically interventional modes of birth compared to the reference group in all three fully adjusted models. This suggests that the proportional hazards assumption is not violated. Similarly, the interaction of mode of birth with time was not statistically significant in any of the outcomes studied: P=0.17 in LRTI, P=0.74 for gastroenteritis and P=0.06 for any infectious disease. Thus, there was no strong evidence that the proportional hazards assumptions of the Cox models were violated in these analyses.

2.3.8 Sensitivity analyses

2.3.8.1 Restriction to observations with validated mode of birth

Within the study group, 76.4% of cohort members had a linked hospital record (n=11,914). The mother's report of mode of birth could not be validated or was found to be invalid, i.e. in disagreement with hospital record, in 581 hospital records (4.9% of observations). (Table 2-1 page 67). The following sensitivity analyses focused solely on the cohort members with validated mode of birth data, including 11,330 for LRTI and gastroenteritis and 11,256 for any infectious disease outcome. These analyses showed a similar overall prevalence of outcome to the main analyses – 3.5% for LRTI (Table 2-5), 1.3% for gastroenteritis (Table 2-6) and 7.6% for any infection (Table 2-7).

The results of the Cox regression in the validated sub-sample were similar to the main findings of all outcomes, but generally showed slightly higher hazard ratios. For example, the adjusted hazard ratio for LRTI in the planned caesarean group was 1.60 as compared to 1.39 in the main analysis and the adjusted hazard ratio of gastroenteritis in the emergency caesarean group was 1.56 compared with 1.52 in the main analysis.

2.3.8.2 'Wheezing or asthma' indication included in LRTI and any infection outcome

Wheezing is a symptom that might indicate a respiratory infection. In this sensitivity analysis, 136 babies reported to have been admitted to hospital due to 'wheezing or asthma' were added to the LRTI outcome and 127 to the any infection outcome. The results of the analysis showed a similar trend to that seen in the main effects. The adjusted hazard ratio for hospital admission due to this extended definition of LRTI in the planned caesarean group was aHR=1.4 (P=0.026), which was the same as in the main analysis (Table 2-5). The adjusted hazard ratio for admission due to any infection was also similar to the main analysis with aHR=1.2 in both caesarean groups (P=0.076

in planned caesarean and P=0.078 in emergency caesarean) compared with 1.2/1.3 in the main analysis respectively (Table 2-7).

2.3.8.3 Vomiting indication removed from any infection outcome

Vomiting in infants may be due to non-infectious causes. In this sensitivity analysis 39 cases of reported 'severe or persistent vomiting' were excluded from the any infection outcome. The results of the adjusted model were almost identical to the main analysis findings.

2.3.8.4 Infants with a history of perinatal infection excluded from study

To account for possible reverse causality of perinatal infection leading to later infection in the infant, a set of sensitivity analyses excluding these infants (9.3% of study group) were conducted. These infections included mother's urinary tract infection during pregnancy, maternal infection during labour, experiencing a risk factor for infection (prolonged rupture of membrane) or neonatal infection shortly after birth. The results of these sensitivity analyses were very similar to the main analyses (Table 2-8).

Table 2-8: Sensitivity analyses of exclusion of babies with history of perinatal infection in the MCS infectious diseases study

	Adjusted HR (95% CI)	
	Main analysis	**Sensitivity analysis**
LRTI [a] **n**	15,533	14,092
VD	1.00	1.00
Assisted VD	1.18 (0.79, 1.75)	1.04 (0.69, 1.58)
Planned CS	1.39 (1.03, 1.87)	1.40 (1.03, 1.89)
Emergency CS	1.14 (0.79, 1.65)	0.99 (0.66, 1.50)
Gastroenteritis [b] **n**	15,550	14,106
VD	1.00	1.00
Assisted VD	1.05 (0.62, 1.78)	1.06 (0.60, 1.86)
Planned CS	1.15 (0.68, 1.94)	1.07 (0.60, 1.89)
Emergency CS	1.52 (0.96, 2.39)	1.48 (0.91, 2.41)
Any infection [c] **n**	15,410	13,984
VD	1.00	1.00
Assisted VD	1.14 (0.91, 1.42)	1.07 (0.84, 1.36)
Planned CS	1.23 (0.97, 1.55)	1.20 (0.94, 1.54)
Emergency CS	1.29 (1.01, 1.65)	1.27 (0.98, 1.65)

a LRTI results adjusted for maternal age, firstborn, baby's sex, mother's smoking, gestational age and time-dependent breastfeeding
b gastroenteritis results adjusted for household socioeconomic class, baby's sex, gestational age and time-dependent breastfeeding
c any infection results adjusted for household socioeconomic class, maternal age, maternal atopic condition, firstborn, baby's ethnicity, baby's sex, gestational age and time-dependent breastfeeding

2.3.8.5 Breastfeeding during previous month of follow-up

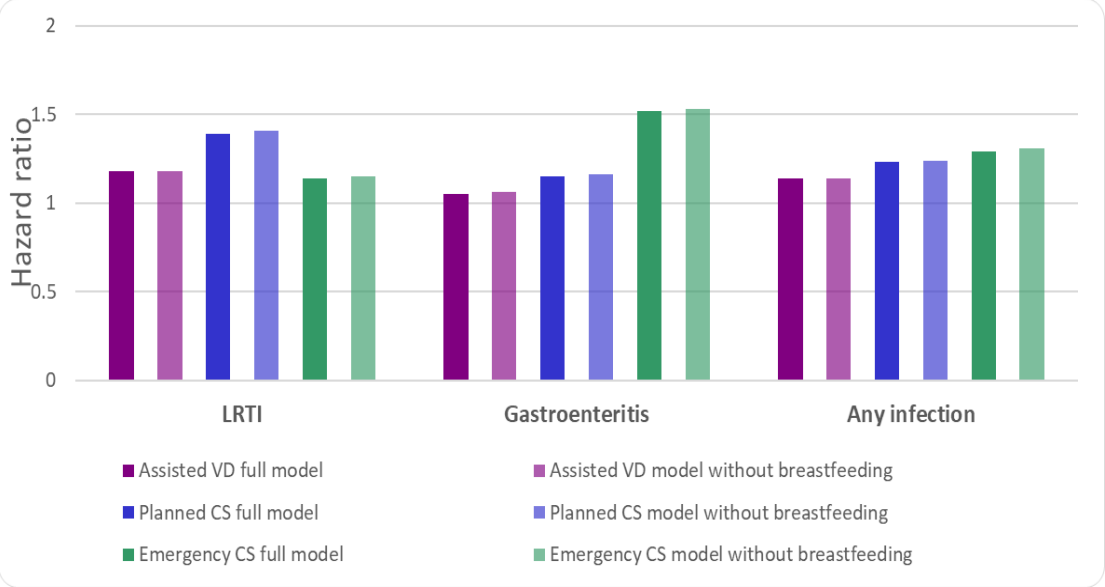
A sensitivity analysis using a time-dependent variable of breastfeeding during the previous month of follow-up was carried out. This was done in order to account for breastfeeding cessation being due to the infant's infection, and not vice versa. These sensitivity analyses gave almost identical results to the main analyses for all three outcomes (results not shown).

2.3.9 Breastfeeding as a potential mediating factor

One of the study aims was to test whether breastfeeding plays a mediating role in the association between mode of birth and subsequent risk of infection. To investigate whether breastfeeding is potentially a mediator, the time-dependent breastfeeding variable was removed from the fully adjusted models and the impact on hazard ratios was examined. Hazard ratios were unchanged, thus there was no evidence of a mediating effect of breastfeeding (see Figure 2-9).

The potential effect of 'exclusive breastfeeding' was also explored in order to investigate whether it had a different effect from 'any breastfeeding', which includes both exclusive and mixed feeding. Fully adjusted models using the time-fixed breastfeeding variable (any breastfeeding) were compared to a model using a time-fixed 'exclusive breastfeeding' variable. The hazard ratios associated with exclusive breastfeeding were very similar to those found with any breastfeeding (results not shown).

Figure 2-9: Hazard ratios of models for LRTI, gastroenteritis and any infection adjusted or unadjusted for breastfeeding



2.3.10 Breastfeeding as a potential effect modifier

An additional study aim was to investigate whether breastfeeding modifies the extent of risk associated with mode of birth on infectious disease outcomes. To test this, an interaction variable was included in the fully adjusted models. A Wald test of overall significance of the interaction term between a time-dependent breastfeeding variable and mode of birth was not statistically significant for any of the outcomes. The results showed P=0.341 for LRTI, P=0.279 for gastroenteritis and P=0.022 for any infectious disease. The P-values are all higher than the threshold for significance of the interaction term set at P<0.01.

2.3.11 Association between breastfeeding and mode of birth

The association of breastfeeding with mode of birth was investigated initially using a univariable analysis of mode of birth and a time-fixed breastfeeding variable (no breastfeeding, up to 2 months, 2-3 months, ≥4 months) and a P<0.001 was found (Table 2-4 page 83). However, a more refined means of examining this association is to compare breastfeeding duration amongst the various modes of birth. A Cox regression model was used to examine the association between mode of birth and duration of breastfeeding. The results showed no association (HR=1.0) between mode of birth and breastfeeding duration in all medically interventional modes of birth compared to the reference group of vaginal delivery. The model was re-run three additional times, each time while adjusting for the variables appearing in the final model of an outcome. This was performed in order to mimic the exploration of potential mediation conducted by removing the breastfeeding variable from the fully adjusted models. The results showed a 3-10% shorter duration of breastfeeding in the interventional modes of birth after adjustment for final models' covariates (see Table 2-9). For a graphical presentation of the duration of breastfeeding by mode of birth (adjusted hazard of time until breastfeeding cessation), see Figure 2-10.

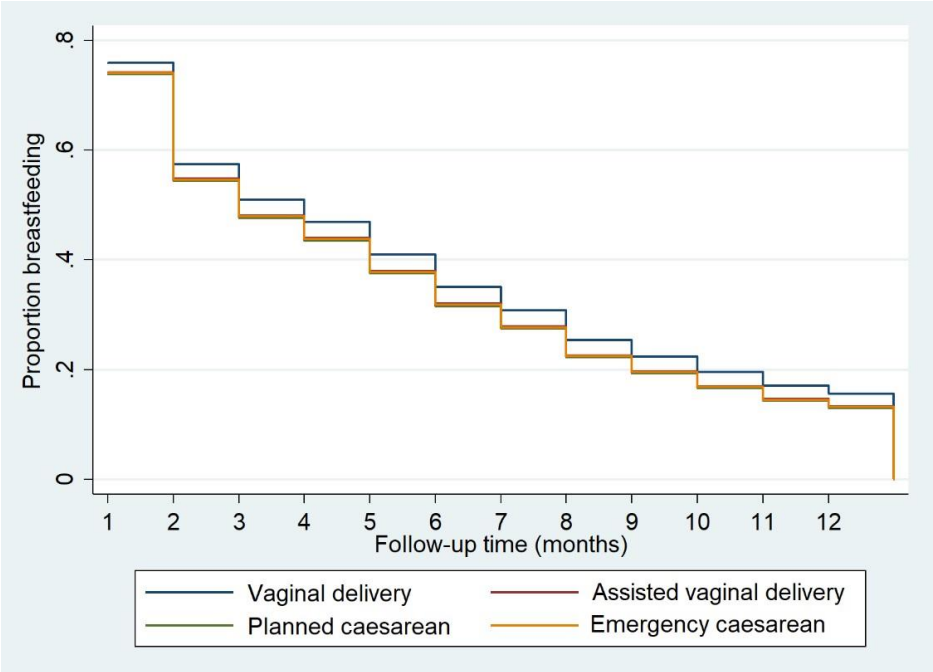
Table 2-9: Association between mode of birth and duration of breastfeeding in the MCS infectious diseases study

	Crude HR (95% CI)	HR adjusted to LRTI variables [a] (95% CI)	HR adjusted to gastroenteritis variables [b] (95% CI)	HR adjusted to any infection variables [c] (95% CI)
VD	1.00	1.00	1.00	1.00
Assisted VD	1.01 (0.95, 1.08)	1.09 (1.02, 1.15)	1.07 (1.01, 1.14)	1.08 (1.02, 1.15)
Planned CS	1.03 (0.97, 1.10)	1.10 (1.02, 1.18)	1.05 (0.98, 1.12)	1.10 (1.02, 1.18)
Emergency CS	0.98 (0.93, 1.04)	1.09 (1.03, 1.16)	1.03 (0.98, 1.10)	1.10 (1.04, 1.17)
P-value [d]	0.620	0.001	0.073	0.000

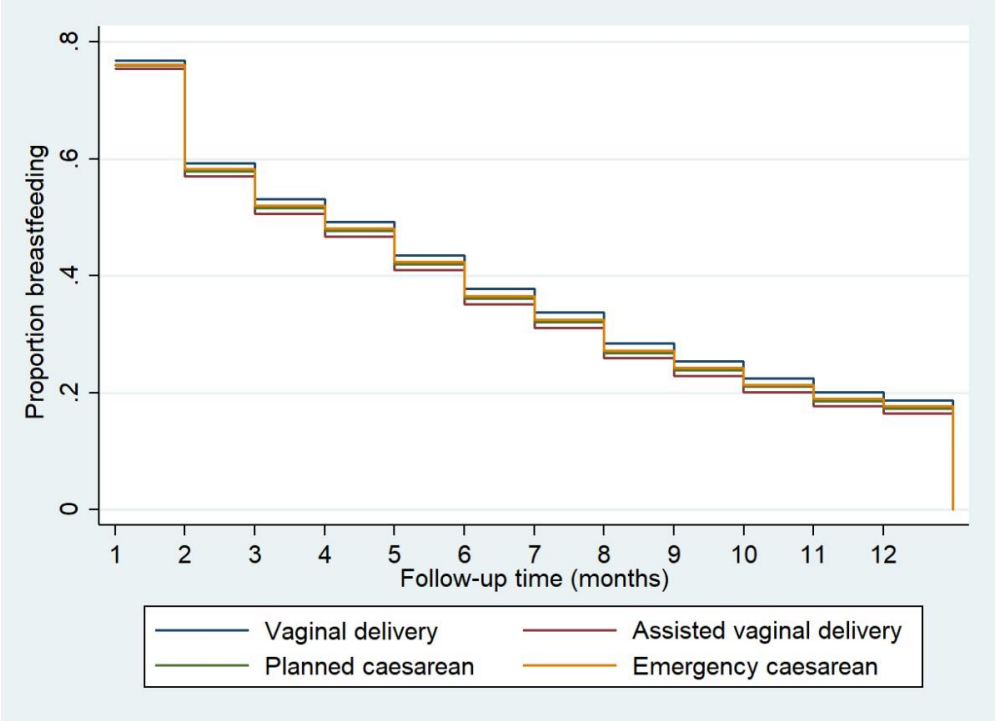
a LRTI variables of fully adjusted model include maternal age, firstborn, baby's sex, mother's smoking, gestational age and time-dependent breastfeeding
b gastroenteritis variables of fully adjusted model include household socioeconomic class, baby's sex, gestational age and time-dependent breastfeeding
c any infection variables of fully adjusted model include household socioeconomic class, maternal age, maternal atopic condition, firstborn, baby's ethnicity, baby's sex, gestational age and time-dependent breastfeeding
d Wald test of the association between mode of birth and duration of breastfeeding

Figure 2-10: Duration of breastfeeding by mode of birth adjusted for covariates of LRTI, gastroenteritis and any infection final models in the MCS study

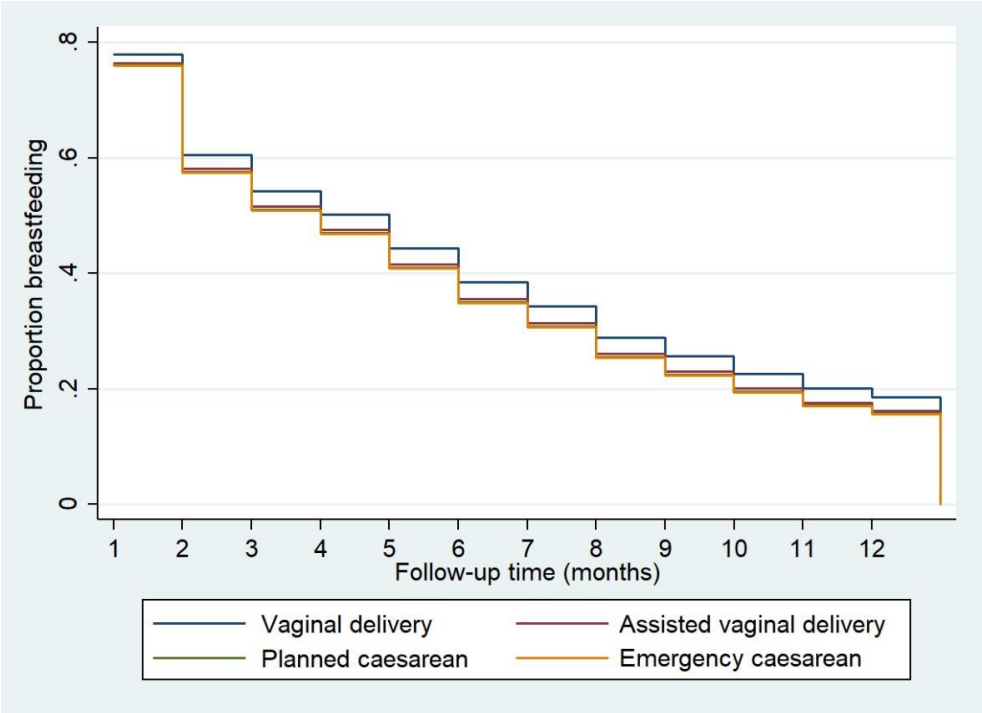
(A) Adjusted for LRTI model covariates



(B) Adjusted for gastroenteritis model covariates



(C) Adjusted for any infection model covariates



2.3.12 Added indirect effect through earlier gestational age at delivery

The majority of planned caesareans in the current study were undertaken at early term gestation while the majority of vaginal deliveries were carried out at full term gestation. I therefore investigated the potential added (unadjusted) effect of delivery at earlier gestation on the association between mode of birth and infectious disease by removing the variable from fully adjusted models. The hazard ratios for assisted vaginal delivery and emergency caesarean changed only slightly when gestational age was not adjusted for. However, the hazard ratios of planned caesarean consistently increased in all outcome analyses Table 2-10 . The hazard ratio for LRTI increased from 1.39 to 1.65 and that for gastroenteritis increased from 1.15 to 1.37 although it remained not statistically significant. The hazard ratio for any infectious disease increased from 1.23 to 1.41 and became statistically significant.

Table 2-10: Multivariable models for the association between mode of birth and LRTI, gastroenteritis and any infection in the MCS study adjusted or unadjusted for gestational age

	LRTI		Gastroenteritis		Any infection	
	Fully adjusted [a] **HR (95% CI)**	**Unadjusted for gestational age [b]** **HR (95% CI)**	**Fully adjusted [c]** **HR (95% CI)**	**Unadjusted for gestational age[d]** **HR (95% CI)**	**Fully adjusted [e]** **HR (95% CI)**	**Unadjusted for gestational age[f]** **HR (95% CI)**
VD	1.00	1.00	1.00	1.00	1.00	1.00
Assisted VD	1.18 (0.79, 1.75)	1.15 (0.78, 1.71)	1.05 (0.62, 1.78)	1.01 (0.60, 1.71)	1.14 (0.91, 1.42)	1.13 (0.91, 1.41)
Planned CS	1.39 (1.03, 1.87)	1.65 (1.24, 2.19)	1.15 (0.68, 1.94)	1.37 (0.82, 2.30)	1.23 (0.97, 1.55)	1.41 (1.14, 1.76)
Emergency CS	1.14 (0.79, 1.65)	1.16 (0.80, 1.68)	1.52 (0.96, 2.39)	1.51 (0.96, 2.37)	1.29 (1.01, 1.65)	1.29 (1.01, 1.64)

a Results are adjusted for maternal age, firstborn, baby's sex, mother's smoking, gestational age and time-dependent breastfeeding.
b Results are adjusted for maternal age, firstborn, baby's sex, mother's smoking and time-dependent breastfeeding
c Results are adjusted for household socioeconomic class, baby's sex, gestational age and time-dependent breastfeeding
d Results are adjusted for household socioeconomic class, baby's sex and time-dependent breastfeeding
e Results are adjusted for household socioeconomic class, maternal age, maternal atopic condition, firstborn, baby's ethnicity, baby's sex, gestational age and time-dependent breastfeeding
f Results are adjusted for household socioeconomic class, maternal age, maternal atopic condition, firstborn, baby's ethnicity, baby's sex and time-dependent breastfeeding

2.4 Discussion

2.4.1 Summary of results

The study described in this chapter aimed to examine whether mode of birth is associated with hospital admission for LRTI, gastroenteritis or a composite measure of any infectious disease in singleton term infants that were healthy at the time of birth.

The findings provide support to the hypothesis that mode of birth is associated with an increased risk of severe infectious disease. However, the results did not provide evidence that breastfeeding explains this association or modifies its effect in different modes of birth.

The findings show that following adjustment for explanatory variables, infants born by planned caesarean have a 39% increased risk of hospital admission for LRTI. This increased risk rises to 65% when the indirect effect of planning the caesarean for an earlier gestational age is added. These infants also have a 23% increased risk of admission due to any infectious disease, although this finding was not statistically significant (P=0.08). When the effect of earlier gestational age is added, this increased risk rises to 41% and is statistically significant.

The findings further show that infants born by emergency caesarean have a 52% increased risk of hospital admission for gastroenteritis, although the results were borderline statistically significant (P=0.07). These infants also exhibited a marginally significant 29% increase in the risk of admission for any infectious disease.

The babies born by assisted vaginal delivery were not found to have a statistically significant higher risk of any of the infectious disease outcomes investigated compared with vaginal delivery.

The results in relation to caesarean section were independent from the effect of breastfeeding, as it was shown that breastfeeding does not act as a mediator or moderator of the studied association in this population. In addition, the effect was independent of the influence of prematurity or neonatal morbidity, as infants with these complications were not included in the study.

An array of sensitivity analyses addressing the validity of the exposure, alternative outcome definitions and additional variables that may confound the association, all gave a similar pattern of results and support the findings of the main analyses.

2.4.2 Risk of LRTI by mode of birth – comparison with other studies

The prevalence of infants requiring hospital admission due to LRTI in this sample is 3.4%. Bases on this, a rough estimate of LRTI admission up to the 1st birthday can be extrapolated to be 4.4%[25]. The calculated proportion can be compared to previously published estimates from Hospital Episode Statistics (HES) in England of 3% of infants admitted annually with bronchiolitis during the years 2001/02 [153] and 3.4% of infants admitted in New South Wales, Australia [84]. Since infant infections of the lower respiratory tract are commonly located in the bronchioles [154], this proportion is comparable to the one estimated in the current study. Further validating the outcome is the trend in frequency of reported hospital admission, which was highest in infants younger than 6 months of age, as previously described [45].

Confidence in the validity of the LRTI outcome is enhanced owing to a sensitivity analysis of the outcome's definition, combining 'asthma or wheezing' with 'chest infection or pneumonia' that gave similar results as the main analysis. Wheezing is a common symptom of respiratory infection, but it may also be triggered by other factors

[25] Calculated as 3.4% / 9.2 (mean age at interview) X 12 (note that the extrapolation does not account for change in risk by age)

such as allergens, exercise, emotional state etc. Additionally, asthma is not typically diagnosed in infancy. For these reasons this reported cause for hospital admission was investigated as part of a sensitivity analysis, but not as part of the main analysis. This sensitivity analysis provides supporting evidence to the study's main findings.

The finding of an increased risk of lower respiratory tract infection in babies delivered by planned caesarean, but not as much by emergency caesarean, is in line with previously published literature. A large study conducted in Denmark [85] investigated infant hospitalisations for RSV infection, an infective agent responsible for three-quarters of bronchiolitis cases [44]. The study found a statistically significant hazard ratio of 1.29 for elective caesarean but a hazard ratio of 1.02 for acute caesarean compared to vaginal delivery, results which are generally consistent with mine. The same authors also investigated diagnosis of various diseases associated with immune function, including pneumonia and lower respiratory tract infection in Danish children up to the age of 14 [86]. The results of the present study are consistent with this Danish study too. Their findings showed a hazard ratio of 1.20 for elective caesarean compared with 1.39 in the current one and 1.01 in children born by acute caesarean compared with a non-statistically significant aHR=1.14 in my study.

A different population-based study conducted in Western Australia found a relative risk of 1.11 (95% CI 1.01, 1.23) for bronchiolitis in infants born by elective caesarean, which is smaller than the risk found in the present study, and no association in those born by acute caesarean [88], as found here. However, the authors found no association between caesarean and recurrent admissions for pneumonia. The same dataset was used for another study aimed at identifying target areas for prevention of lower respiratory infections up to age two, and this time the authors found a relative risk of 1.3 for elective and 1.2 for emergency caesarean, both statistically significant. Of note is that in the latter study, the reference group was instrumental birth, and not vaginal delivery, since the risk of LRTI in that group was found to be the lowest [83].

A similar magnitude of risk and pattern of association as in the current study was also demonstrated in a Norwegian cohort study examining the risk of recurrent episodes of LRTIs (illnesses that did not necessarily lead to hospitalisation) up to age three [87]. The authors found a relative risk of 1.19 (95% CI 0.95, 1.48) in the elective caesarean group and no association in the acute caesarean group. Notably, these findings were adjusted for a binary variable of whether the child was breastfed at 6 months.

An additional study utilizing undetailed information about breastfeeding examined risk factors for hospital admission due to bronchiolitis during infancy in the Oxford Record Linkage Study [89]. Caesarean delivery (any type) was found to have an odds ratio of 1.35 (95% CI 1.03 to 1.53) compared to any vaginal delivery. This elevated risk was found to be independent from a binary definition of whether the neonates received breastmilk at the time of discharge from hospital of birth. The results of this study, although based on only a binary categorization of mode of birth, are in line with the finding of the present study.

To summarize, the results of my study, showing planned caesarean is a risk factor for LRTI with little evidence of an effect of emergency caesarean, reinforce the findings of most previous studies. There are several possible explanations for this interesting finding, both non-causal and causal.

The different effect in relation to planned caesarean compared to emergency caesarean might be due to unmeasured confounding factors. For example, mothers consenting to a planned caesarean or requesting one (though the latter accounted for only 7% of caesarean deliveries in the UK at the time [17]) might also be more inclined to seek and agree to hospital care for their sick child. With that said, hospital admission is dependent on medical professionals' opinion and is not generally subject to the influence of parents' health seeking behaviour. It is also possible that an excess risk for LRTI was not observed in the emergency caesarean group solely due to low study power and not

owing to the different characteristics of these births compared to planned caesarean. The potential of confounding to explain my findings, as well as additional possible methodological and biological explanations for this pattern of risk will be discussed in the overarching discussion (Chapter 7).

2.4.3 Risk of gastrointestinal infection by mode of birth – comparison with other studies

The proportion of infants requiring hospital admission due to gastroenteritis in this sample was 1.4%. An extrapolated estimate of gastroenteritis admissions during the full first year after birth would therefore be 1.8%[26]. This proportion is of comparable magnitude to a study conducted in Finland that found a national average annual rate of 1.8%[27] of infants admitted to hospital due to acute gastroenteritis [155]. Likewise, a proportion of 1.7% was reported in a record linkage study in New South Wales [84].

The findings of this thesis contribute to a handful of previous studies that investigated the association between mode of birth and childhood gastroenteritis and diarrhoea. These studies found that both planned and emergency caesarean pose an increased risk for such an infection of the order of 20-30%. The current study found an elevated risk of 52% for emergency caesarean births, although the finding was only marginally statistically significant in the adjusted models. However, the increased risk for planned caesarean was only 15% (independent of gestational age) and was not statistically significant.

A study using Swedish national health registry data found a hazard ratio of 1.3 for hospitalisation due to gastroenteritis for both types of caesareans, although it focused on children over one year of age [91]. A further Scandinavian study using Danish data

[26] Calculated as 1.4% /9.2x12
[27] Rate calculated from the reported average annual hospital admission at 0-5 and 6-11 months and Finnish average number of live births per year during 1985-1995

also found a hazard ratio of 1.2 for each type of caesarean [86], although the age range at diagnosis was very wide. Two record linkage studies conducted in New South Wales also described both types of caesarean as risk factors. The first of these studies [84] found an effect size of RR=1.2-1.3 for gastroenteritis admission during infancy, whereas effect size of emergency caesarean in the current study is stronger, although only marginally significant. A further study by Bentley et al [92] from New South Wales examining the association of mode of birth and induction of labour on acute gastroenteritis, also partially agrees with the findings of the present study. The published study reported a hazard ratio of 1.2-1.3 for hospitalisation of infants born by caesarean following spontaneous labour or an induction (emergency caesarean), but also following a pre-labour caesarean (planned caesarean). Notably, these results were found to be independent of the effect of whether the neonate received breastmilk at the time of discharge at birth.

It is important to note that the raised risk of gastroenteritis found in babies born by emergency caesarean in the present study was not statistically significant, though the P-value was close to 0.05. In addition, there was no substantial increased risk in the planned caesarean group compared to vaginal delivery in adjusted models. It is possible that the lack of statistically significant associations is due to insufficient statistical power. The prevalence of hospital admissions due to this outcome in the investigated group was very low, with as few as 22 cases of gastroenteritis in babies born by planned caesarean. This low disease prevalence led to very low power (estimated at 14-24% for RR=1.2-1.3) and particularly wide confidence intervals. It is thus conceivable that the risk in both caesareans is actually elevated compared to vaginal delivery, as other research has shown, but this association was not detected as a statistically significant effect in this study sample due to a type 2 error.

2.4.4 Risk of any infectious disease by mode of birth – comparison with other studies

The overall prevalence of reported hospital admissions due to an infectious cause in the MCS was 7.6%. This prevalence is comparable to the prevalence reported in the 2010 UK Infant Feeding Survey where 7% of participating mothers reported their infants had been admitted to hospital due to an infection up to age 8-10 months [122].

The current study found an increased risk of hospital admission due to an infection of 23% in planned caesarean and 29% in emergency caesarean, both of borderline statistical significance. I was not able to identify any relevant published studies examining the association between mode of birth and the broad outcome of any infectious disease in detail. Very recently, though, a study using data from a large tertiary hospital in Israel [156] investigated the risk of admission due to any infectious disease up to the age of 18 in children born by elective caesarean compared to vaginal delivery. In a sub-group analysis of term births, the authors reported a 10% increased risk (statistically significant) for hospital admission due to any infection. The reported risk in this wide age range is broadly similar to the risk found in the current study for planned caesarean in term-born babies.

The outcome of any infectious disease was examined in the current study for several reasons. The first, was to explore whether there is a general effect of mode of birth on susceptibility to infection, plausibly through an effect on development of the immune system [157]. The second reason was to benefit from larger statistical power than that achieved for an infectious disease outcome focused on a single body system. However, it is important to consider that this outcome portrays a very heterogeneous group of symptoms and illnesses, some of which are not a highly reliable measure of infectious disease.

Examples are:

- Vomiting may be caused by a non-infectious reason (though this limitation was addressed through a sensitivity analysis where this condition was excluded).
- Some of the infections included in this outcome, such as measles and whooping cough (Pertussis), can be prevented by immunisations offered as part of the routine national vaccination programme. Families of infants that acquired one of these infections due to being unvaccinated might be distinct from the broader population in additional, unmeasured aspects.
- Some infections included are poorly specified or of mild severity.
- The infections that comprise this outcome apart from LRTI, gastroenteritis and meningitis were derived from the respondent's open text answers. They are therefore subject to an additional stage of post-field coding, a process which may adversely affect reliability as a measure of true infection.

The third reason for inclusion of the 'any infection' outcome was to help address misclassification of parental report of the indication for admission. For example, an answer of 'fever' is probably indicative of an infectious disease, but the admission would not be captured in any of the more specific, but narrow, outcome definitions.

The limitations of this outcome call for caution when interpreting the 'any infection' outcome results. Nevertheless, the validity of the findings is reinforced by the fact that the pattern of associations resemble those found for LRTI and gastroenteritis (though leaving in mind that they comprise the majority of the 'any infection' outcome).

2.4.5 The role of breastfeeding in explaining the relationship between mode of birth and infectious disease

Breastfeeding is a key variable in this study as it is the first time its effect on infant infections has been differentiated from the effect of caesarean section in an in-depth manner. An infant's risk of infection increases once other sources of nutrition are

introduced and also once breastfeeding is discontinued entirely [121]. Therefore, it was important to investigate the effect of breastfeeding in a nuanced approach.

A time-dependent variable of breastfeeding per month of follow-up was used instead of a time-fixed, ordinal variable, in order to minimize dilution of the effect of breastfeeding. For example, breastfeeding post-hospitalisation can no longer affect the infant's risk of infection, since only the first admission is measured. By using a time-dependent variable, any breastfeeding is appropriately censored at the time of admission. As an example of the opposite case is an infant hospitalised later than the point of breastfeeding cessation. In this case, the length of time when there was no exposure to breastmilk and no infection episode would be more accurately accounted for by using a time-dependent variable.

Breastfeeding may potentially act as a collider, which is a variable affected by both exposure and outcome. Collider bias is the distortion of effects which may take place when conditioning on a collider (e.g. through adjustment in multivariable models) [158]. Breastfeeding during the current month of follow-up may be the result of both the mode of birth and the state of the child being ill with an infection. It is thus a potential collider and controlling for it might bias effects. Contra to breastfeeding during the current month, breastfeeding during the previous month of life cannot be the result of current infection, and therefore is not a potential collider. A set of sensitivity analyses using breastfeeding during the previous month was carried out and findings were similar to the main analyses. This minimises any concern from collider bias arising from conditioning on breastfeeding.

It is plausible that breastfeeding would mediate an association between caesarean section and infectious disease, at least in part. For a variable to act as a mediator, it would need to be associated with both exposure and outcome and be on the causal pathway. Previous studies have found a lower prevalence of breastfeeding following

caesarean birth [119,120]. Indeed, caesareans may exert a challenge on establishing successful long-term breastfeeding. For example, deficiency of the hormonal surge during labour, post-operative pain, difficult mobility or maternal-newborn separation, might pose a challenge on initiating breastfeeding. The reported lower rates of breastfeeding in previous studies may well be caused by the caesarean surgery, at least to some extent. The univariable association between breastfeeding duration category (none, <2 months, 2-3 months, ≥4 months) and mode of birth in the current study showed a highly statistically significant association (P<0.001). However, it is noteworthy that when using a large dataset of >15,000 observations, even minute differences in breastfeeding rates between the modes of birth give rise to very small P-values. Breastfeeding was also previously reported to be associated with hospital admission for infant infectious disease [121,122]. One of these studies was even carried out on virtually the same sub-group of the MCS as the current one [121]. Although breastfeeding is a potential mediator of the association under study, there was no evidence of an actual mediating effect since the exclusion of breastfeeding from the models did not affect the strength of association observed. The effect of mode of birth on infant's risk of infection was thus shown to be independent from breastfeeding.

I further examined whether breastfeeding may modify any association between mode of birth and infant infection. Breastmilk is a source of nutrition, not only for the infant, but also for the microbes residing in the infant's body [159]. Hence it is plausible that an interaction might occur between the deficiencies in natural prebiotics (non-digestible nutrients that feed the microbiota) when formula feeding and the modified classes of microbes colonising caesarean-born babies. Breastfeeding may thus theoretically affect the risk of infection in a different manner in babies born by caesarean and those born vaginally. However, a recent study did not find evidence of an interaction between mode of birth and feeding method on the intestinal microbial composition in 6 week old infants

[160]. Likewise, the current analysis did not identify a statistically significant interaction between breastfeeding and mode of birth with regards to the risk of infection.

A possible explanation of the lack of evidence of mediation or modification by breastfeeding was unveiled when a nuanced exploration of the association of breastfeeding with mode of birth was conducted. A survival analysis of the duration of breastfeeding by mode of birth showed that when adjusting for the covariates included in each outcome's final model, there appears to be only a 10% increase in the risk of early breastfeeding cessation in the medically interventional modes of birth compared to vaginal delivery. Thus, the reason for absence of evidence of an intervening role for breastfeeding could be lack of a strong association between mode of birth and the extent of subsequent breastfeeding in this population. The conclusion that caesarean is an independent risk factor from breastfeeding still holds. However, it is possible that an additional effect of caesarean is theoretically exerted through lower uptake or duration of breastfeeding, but this effect cannot be observed in this population where breastfeeding behaviour tends to be similar following a caesarean or a vaginal birth.

2.4.6 Strengths and limitations of the study

The study's primary strengths are mainly a consequence of the data source used, which is a large population-based birth cohort. Participants were interviewed extensively and this allowed for a broad range of detailed information about potential confounders and other explanatory variables to be included in the analyses. Particularly, the ability to account for the extent of breastfeeding, and in a novel, in-depth manner, progresses the understanding of the effect of mode of birth on infection in infancy.

An additional strength of this study is the relatively high validity of the exposure variable used in a sensitivity analysis. It has been shown that it is very rare (less than 0.5%) for women in the MCS to misreport their type of birth when two options are given – caesarean or vaginal delivery. However, misclassification between planned and

emergency caesarean is more common and occurred in 10.7% of cases where a caesarean birth was reported [161]. At the same time, errors in routinely collected hospital record data occur as well. This was demonstrated in the MCS linked data as 3.4% internal disagreement between two variables for mode of birth within hospital records. Thus, the ability to employ a combination of sources of information – the mother's report and the hospital records, substantially increases the validity of this variable. However, it should be noted that mothers consenting to linkage to hospital records are not representative of the full cohort, and this could have led to selection bias in the sub-sample of the sensitivity analysis.

A further strength of the study and the thesis in general is the inclusion solely of babies born at term that were healthy at the time of birth. This focus helps disentangle the effect of mode of birth from the potentially major confounding effects of prematurity and complications during pregnancy and birth (see Chapter 7 for a detailed discussion).

An additional strength of this work is the fact that the study had accounted for confounding by perinatal infection. One of the sensitivity analyses conducted was a restriction to cases that had no report of an underlying perinatal infection in the mother or fetus. This issue is of importance, since an infection that originated before the time of birth may have led both to a medically interventional delivery and to later presentation with a serious infection. The sensitivity analysis that addressed the potential for confounding by perinatal infection is therefore a unique strength of this study.

The study had some limitations that should be discussed, the main one being the low statistical power, particularly for the gastroenteritis outcome. It is possible that both types of caesarean delivery actually pose a risk of infant infection. One should consider the published literature showing an elevated risk of gastroenteritis after both types of operations as well as the fact that some of the study's results are marginally significant. It is therefore possible that an elevated risk of gastrointestinal infection exists in the

studied population but was not detected because of the low power. The LRTI analysis also suffered from lower statistical power than the commonly accepted threshold of 80%.

Another potential limitation of this study is the fact that outcomes were derived from parental report and recalled at 9 months. However, the compatibility of the reported prevalence of LRTI admissions with that from HES (Hospital Episode Statistics of NHS hospitals in England) from the corresponding years [153] as well as the similarity of the prevalence of gastroenteritis to that reported for another European country [155] lends support to the validity of these particular outcomes. Moreover, it has been shown that parents, especially mothers, generally recall child hospitalisation events well, even over long time periods [162]. Furthermore, the LRTI and gastroenteritis outcomes were presented to the mother as a list from which to choose the appropriate condition. It thus seems plausible that they would generally be able to select the most suitable option. It is also reasonable to assume that mothers recalled the age of their baby at the time of hospital admission fairly accurately too. The child's lifespan up to the time of interview was short and baby's developmental stages change rapidly during this phase of life, which may assist in accurate recollection of age at admission.

Another limitation is the inability to account for URTIs, which in some cases progress to the lower respiratory tract. A study in Wales reported that hospital admissions due to URTI were the most common respiratory indications for hospitalisation, and were more frequent than for acute bronchiolitis [90]. However, the MCS collected information about URTIs only as an open text response with post-field coding, and the data was thus not reliable enough to be included as a separate outcome.

As is the case in all observational studies, the current research has potential for bias resulting from residual confounding. In the case of mode of birth, the indication for the medically interventional delivery may potentially confound results. I partially addressed this limitation by differentiating between planned and emergency caesareans, whose

indications were generally distinct from one another. In addition, the exclusion of neonates requiring special medical care helps minimize this potential bias. These limitations will be discussed in further detail in Chapter 7.

Lastly, due to the sampling scheme in the MCS, I was unable to adjust models for season of birth. Some of the outcomes investigated (mainly LRTI) have seasonal trends as well as a change in risk level by age of infant (Figure 2-3), therefore including season of birth as a potential explanatory variable would have been desirable. However, I had not included this variable since I detected an artifactual association between mode of birth and season of birth, probably due to the timing of sampling in different areas of the UK and their different demographic characteristics. Regardless, season of birth is not expected to be one of the key confounders in the study.

2.4.7 Conclusions

The current study presents some evidence of an elevated risk of severe infectious disease in singleton infants that were born at term by caesarean section and that were healthy at the time of birth. There is moderate strength of evidence for an association between planned caesarean and LRTIs and further evidence of a possible association between emergency caesarean and gastroenteritis. Both types of caesarean section might also be associated with any type of serious infectious disease, though the evidence for this outcome is not strong. This possible adverse effect of caesareans is not mediated through lower breastfeeding rates. Any effect of planned caesarean on infection admission is stronger when it is not adjusted for gestational age at delivery.

Chapter 3: An investigation of the association between mode of birth and childhood wheezing phenotypes in the Millennium Cohort Study

3.1 Introduction

Caesarean sections, and especially planned caesarean, were shown in previous studies and in the study presented in Chapter 2 to be a risk factor for lower respiratory tract infections during infancy. Other studies have shown caesareans to be a risk factor for various wheezing phenotypes as well as asthma in childhood. Wheezing is a respiratory sign that may represent asthma, but may alternatively be triggered in children that do not necessary currently have asthma. A common trigger in early childhood is LRTIs. In order to disentangle the possible effect of mode of birth on these respiratory illnesses, an investigation of the relationship between mode of birth and various wheezing phenotypes was carried out.

3.1.1 Study aims

The aim of this study was to investigate the relationship between mode of birth and the child's risk of wheezing during childhood. Various phenotypes of wheezing were examined: a transient, persistent and late-onset wheezing trajectory. To support this investigation, a further aim of this study was to examine the association of mode of birth with additional asthma-related outcomes at various time points from infancy to early adolescence.

The research questions were:

1. Is mode of birth associated with the child's wheezing phenotypes defined as transient, persistent or late-onset?
2. Is mode of birth associated with recent wheezing or severe wheezing at different time-points throughout childhood?
3. Is mode of birth associated with report of asthma at different time-points throughout childhood?
4. Is mode of birth associated with regular intake of prescription medication for asthma at different time-points throughout childhood?
5. Does earlier gestational age indirectly add to any effect of planned caesarean on wheezing phenotypes?

3.2 Methods

The dataset used for the study presented in this chapter is the "Millennium Cohort Study" (MCS) surveys 1 to 5 from age 9 months to 11 years. Details of the cohort design and of the first survey are given in section 2.2.1.

3.2.1 Millennium Cohort Study – age 3, 5, 7 and 11 surveys

Table 3-1 details the number of cohort member participating in each of the MCS surveys and the percentage of the initially recruited sample. Overall, 10,550 children participated in all five MCS interviews from infancy to age 11 (56.1% of the original sample of babies). The number of families participating in the MCS had undergone attrition for various reasons. Some families were not approached for a repeated survey due to the child's death, sensitive family conditions or emigration. Other families were approached but not able to be contacted due to change of address or not responding to the surveyors' contact attempts, or due to refusal to continue to participate. Families in the disadvantaged and ethnic minority strata were more likely to be lost to follow-up

compared to the non-disadvantaged stratum [163]. This non-differential attrition was accounted for in the analysis by the application of non-response weights as will be detailed in section 3.2.6.1.

Table 3-1: Number of participants per each MCS survey

MCS Survey	Number of participants *	Percentage of original MCS sample (%)**
9 months (1st)	18,818	100.0
3 years (2nd)	15,109	80.3
5 years (3rd)	14,887	79.1
7 years (4th)	13,543	72.0
11 years (5th)	12,913	68.6
All surveys 1 to 5	10,550	56.1

* That were part of original MCS sample
** Unweighted percentage

3.2.2 Inclusion criteria

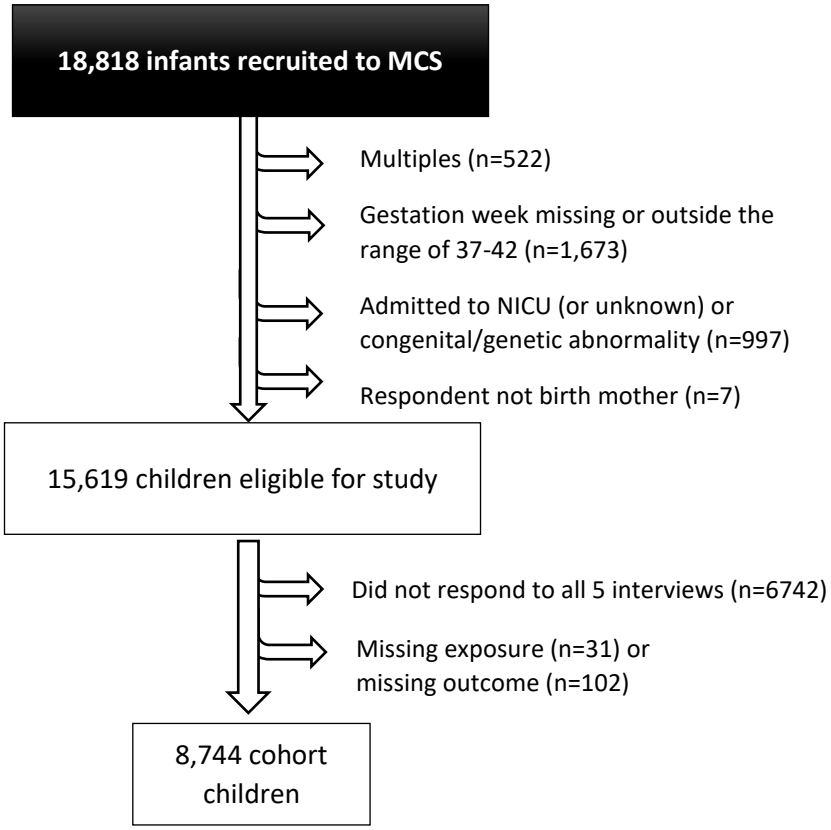
The inclusion criteria for this analysis were the same as those detailed in section 2.2.2. In brief, the following children were included:

- Singleton
- Born at term (37-42 weeks)[28]
- Not admitted for neonatal intensive care or diagnosed with a serious congenital anomaly or genetic abnormality
- The main respondent at the first survey was the birth mother

The number of children eligible to be included in the study according to these criteria was 15,619 (Figure 3-1). Cohort members who did not take part in all five interviews (43.8%)[29], had missing exposure data (0.5%) or missing responses for recent wheezing in one or more of the surveys (1.8%) were further excluded. Thus, 8,744 cohort members were included in this study (46.5% of original cohort participants).

[28] The classical definition of term pregnancy is 37-41 weeks but the current definition includes 42
[29] Percentages are non-sequential and calculated from all singletons of 18,296

Figure 3-1: Children included in the MCS wheezing phenotypes study sample



3.2.3 Exposure – mode of birth

Mode of birth was the exposure variable of interest and was classified as described in section 2.2.3 to four categories: vaginal delivery, assisted vaginal delivery, planned caesarean section and emergency caesarean section.

3.2.4 Outcomes – asthma-related indicators

The outcomes were various indicators related to wheezing and asthma. The primary outcome was wheezing phenotypes based on longitudinal wheezing trajectories. The secondary, age-specific outcomes, were recent wheezing symptoms, severe wheezing symptoms, 'ever asthma' and asthma medication use.

Most of the study outcomes were based on data items derived from the 'core questionnaire wheezing module' for ages 6-7 of 'ISAAC' (The International Study of

Asthma and Allergies in Childhood). ISAAC is a widely used validated instrument for investigating the epidemiology of wheezing illnesses and other atopic disorders in children [164,165]. Additional outcomes were derived from other questions included in various MCS surveys. Box 3-1 to Box 3-3 list the various questions included in the different MCS surveys and how they were used to derive the variables for the analyses reported here.

3.2.4.1 Survey questions and derived variable definitions

Box 3-1: MCS questions from ISAAC questionnaire (survey at ages 3, 5, 7 and 11)

Has (child's name) ever had asthma?
'Ever asthma'

Has (child's name) ever had wheezing or whistling in the chest at any time in the past?
'Ever wheezing'
If answered positively =>

Has (child's name) had wheezing or whistling in the chest in the last 12 months?
'ISAAC recent wheezing'
If answered positively =>

How many attacks of wheezing has (child's name) had in the last 12 months?

- None
- 1-3
- 4-12
- >12

In the last 12 months, how often on average has (child's name)'s sleep been disturbed due to this wheezing?

- Never woken with wheezing
- Less than one night per week
- One or more nights per week

In the last 12 months, has wheezing ever been severe enough to limit (child's name)'s speech to only one or two words at a time between breaths?

- Yes
- No

'Severe wheezing' recorded if reported 4 or more wheezing attacks or woken one or more nights per week or answered positively to wheezing being severe enough to limit speech

* Items used to define variables are marked in red

Box 3-2: MCS questions on wheezing not included in ISAAC questionnaire (survey at age 9 month)

We would like to know about any health problems for which (child's name) has been taken to the GP, Health Centre or Health visitor, or to Casualty, or you have called NHS direct.
If any problems were reported, select the type of problem from the list =>

Chest infections
Ear infections
Feeding problems
Sleeping problems
Wheezing or asthma => 'GP (General Practitioner) recent wheezing'
Skin problems
Sight or eye problems
Failure to gain weight or to grow
Persistent or severe vomiting
Persistent or severe diarrhoea
Fits or convulsions
Other health problems

Box 3-3: MCS question on asthma medication use not included in ISAAC questionnaire (survey at ages 5, 7 and 11)

Is (child's name) currently taking any medicines on a regular basis that were prescribed by a doctor or hospital? By regular I mean every day for two weeks or more.
If answered positively =>

Please could you tell me the name(s) of the medicine(s)
=> 'Asthma medication' recorded if at least one of the following were mentioned:

03.01.01 – Bronchodilators, Adrenoceptor agonists (e.g. Salbutamol)
03.01.02 – Bronchodilators, Antimuscarinic bronchodilators
03.01.03 - Bronchodilators, Theophylline
03.02.00 - Inhaled Corticosteroids (e.g. beclomethasone dipropionate)
03.03.01 - Cromoglicate and related therapy
03.03.02 - Leukotriene receptor antagonists
03.04.02 - Allergen immunotherapy

3.2.4.2 Wheezing phenotypes - primary outcome

Wheezing phenotypes were based on wheezing trajectories constructed using both the 'GP recent wheezing' and the 'ISAAC recent wheezing' items (referred to generally as 'recent wheezing') as defined in section 3.2.4.1. As explained in section 1.4, various trajectories of wheezing phenotypes have been identified either by clinical definitions or using longitudinal latent class analysis (LLCA) in cohort studies [62,73,74], including in the MCS [71,72]. The phenotypes chosen for this study were the four trajectories that were consistently identified in all LLCA studies. Additionally, two prior studies [166] examining wheezing phenotypes in the MCS (but focusing on different exposures) have used similar definitions of these phenotypes [166,167].

The wheezing phenotypes were classified as the following trajectories:

- No wheezing – no report of 'recent wheezing' any time from 9 months of age up to 11 years.
- Transient wheezing – report of 'recent wheezing' at age 9 months, 3 years or both, but no report of 'recent wheezing' at ages 5, 7 and 11.
- Persistent wheezing – report of 'recent wheezing' at age 9 months, 3 years or both, and at least a single additional report of 'recent wheezing' at ages 5, 7 or 11.
- Late-onset wheezing – no report of 'recent wheezing' at ages 9 months or 3 years, but at least a single report of 'recent wheezing' at ages 5, 7 or 11.

See Table 3-2A for a summary of the phenotypic classification.

Table 3-2: Definitions and time of data collection of wheezing phenotypes and asthma-related outcomes

(A) Definitions of the primary outcome

<table>
<tr><td></td><td colspan="4">Primary outcome – wheezing phenotypes</td></tr>
<tr><td></td><td>None</td><td>Transient</td><td>Persistent</td><td>Late-onset</td></tr>
<tr><td>9 months</td><td rowspan="5">No report of recent wheezing</td><td>Report of recent wheezing</td><td>Report of recent wheezing</td><td>No report</td></tr>
<tr><td>3 years</td><td rowspan="3">No report</td><td rowspan="3">Report of recent wheezing</td><td rowspan="3">Report of recent wheezing</td></tr>
<tr><td>5 years</td></tr>
<tr><td>7 years</td></tr>
<tr><td>11 years</td></tr>
</table>

(B) Time of data collection of secondary outcomes

	Secondary outcomes			
	Recent wheezing	**Severe wheezing**	**Ever asthma**	**Asthma medication**
9 months	V			
3 years	V	V	V	
5 years	V	V	V	V
7 years	V	V	V	V
11 years	V	V	V	V

3.2.4.3 Recent wheezing – secondary outcome

Recent wheezing was defined in this study as a binary variable of whether the child experienced wheezing in the past year. Information about this variable was collected by two means: at age 9 months through the item of 'GP recent wheezing' and at ages 3, 5, 7 and 11 years through the item of 'ISAAC recent wheezing'.

3.2.4.4 Severe wheezing – secondary outcome

Severe wheezing was defined as a binary variable of whether the child exhibits recent wheezing that is recurrent or that disturbs the child's sleep or speech. The composite outcome was based on the 'severe wheezing' item collected when cohort members were 3, 5, 7 and 11 years old. This definition of severe wheezing was based on the definition used in a previous study by the ISAAC research group [168].

3.2.4.5 Ever asthma – secondary outcome

Binary information about whether the child has had asthma was collected at ages 3, 5, 7 and 11 through the question regarding 'ever asthma' in the ISAAC questionnaire.

3.2.4.6 Asthma medication use – secondary outcome

At ages 5, 7 and 11 parents were asked about regular use of prescribed medications. Medications for prevention and treatment of asthma were identified in the British National Formulary codes under "Chapter 3 (Respiratory System medications)" and reviewed by a clinician [169]. A binary outcome of whether the child regularly uses one of the listed medications was derived. See Table 3-2B for data collection times.

3.2.5 Potential explanatory variables

The following variables are associated with mode of birth [143,145,146] and with asthma-related outcomes [77,170–172] and were often included as potential confounders in previous studies [93].

3.2.5.1 Parental characteristics

- Mother's age at birth: <20, 20-29, 30-39, ≥40 years
- Mother's education level as described in 2.2.5.1: NVQ 4&5 equivalent to university degree; NVQ 3 equivalent to A level; NVQ 1&2 equivalent to secondary school; other qualifications including from overseas; and no formal qualifications.
- Mother's marital status: married, cohabiting or single
- Household socioeconomic status defined using the last known occupation of the mother or her partner, if higher: managerial & professional intermediate, routine & manual, or never worked & long-term unemployed.
- Maternal smoking status during pregnancy: none, ceased during pregnancy, and smoked.

- Parental asthma status: both parents reported they had never had asthma; mother reported never having asthma but father's status unknown; father reported asthma and mother reported never having asthma; mother reported asthma and father reported never having asthma; mother reported asthma but father's status unknown; both parents reported having asthma.
    - This variable was chosen due to being strongly correlated with the outcomes and because of a dose-response in risk magnitude for asthma when none, one or two parents have asthma [77]
- Diabetes or gestational diabetes
- Hypertensive condition during pregnancy

3.2.5.2 Child characteristics

- Child's ethnicity: White, Mixed, Indian, Pakistani, Bangladeshi, Black Caribbean, Black African, Other.
- Firstborn: mother's first biological child yes/no
- Sex
- Birthweight of the baby, cleaned as described in 2.2.5.2
- Gestational age at delivery, cleaned as described in 2.2.5.2 and categorized as early term (37-38), full term (39-40), late term (41) and post term (42).

All information about explanatory variables was collected through parental report.

3.2.6 Statistical analyses

Stata version 13 was used for all statistical analyses.

3.2.6.1 Weighting

All statistical analyses accounted for the clustered stratified study design of the MCS, non-response to the initial survey as well as loss to follow-up. Non-response weights to the age 11 survey were constructed by the MCS team at the Centre for Longitudinal

Studies using various predictors from prior surveys[30] [138,163] and implemented using inverse probability weighting.

3.2.6.2 Univariable analyses

The association between each potential confounder and mode of birth was assessed in a univariable analysis using the Chi-square test for proportions or the F-test for comparing means as detailed in section 2.2.6.1.

The association between each potential confounder and wheezing phenotypes was assessed using multinomial logistic regression and the Wald test of overall significance of variable coefficients. A cut-off P-value of <0.10 was used as the threshold to be included in the multivariable modelling process detailed hereafter.

3.2.6.3 Multivariable analyses

The primary outcome (wheezing phenotypes) was a categorical variable. Therefore, multinomial logistic regression was used to estimate crude and adjusted Relative Risk Ratios (RRRs) and 95% confidence intervals for the association between mode of birth[31] and wheezing phenotypes. In the multinomial model each wheezing phenotype was compared to no wheezing and each mode of birth compared to vaginal delivery.

The secondary outcomes were binary. Therefore, logistic regression was used to estimate the crude and adjusted odds ratios and 95% confidence intervals for the association of mode of birth with each of the secondary outcomes from the age-specific analyses (recent wheezing, severe wheezing, 'ever asthma' and asthma medication).

[30] The predictors utilized by the CLS to generate weights to account for non-response to the subsequent surveys were: cohort member's sex, mother's age at first live birth, ethnicity, housing tenure, accommodation type, education level, breastfeeding, main respondent's work status and income item non-response [253]

[31] This is the ratio of the OR for experiencing a wheezing phenotype compared to no wheezing in a medically interventional mode of birth with this OR in the reference vaginal delivery group.

The selection process for covariates to be included in multivariable models was as follows: First, a series of potential explanatory variables were selected a priori: maternal age, maternal education, smoking during pregnancy, parental asthma, sex of the child, firstborn status, gestational age and birthweight. The covariates selected were those previously shown to be associated with mode of birth and asthma-related outcomes. Additionally, they were either used frequently in previous studies [93], were previously found to confound the association between mode of birth and asthma or wheeze [106], or are causally associated with the outcome [77].

Second, the associations between a set of additional potential confounders and the exposure and wheezing phenotype outcome was assessed using univariable analyses as detailed in 3.2.6.2. These potential explanatory variables were selected due to their inclusion in a previous study of mode of birth and wheezing phenotypes [97]. These variables were: ethnicity, socioeconomic class, marital status, diabetes during pregnancy and hypertensive condition of pregnancy.

Third, the variables found to be associated with both exposure and outcome, and the ones selected a priori were examined in a multivariable multinomial regression model. A backwards method was employed until all covariates that had not been chosen a priori exhibited at least a single statistically significant coefficient for one wheezing phenotype category (Wald $P<0.05$). To aid comparability of results the covariates selected to be included in the wheezing phenotypes multivariable model were also used for modelling all of the secondary outcomes.

When assessing the association of mode of birth with a given outcome, $P<0.05$ was considered statistically significant.

3.2.6.4 Analysis of potential mediation

As explained previously, gestational age may have a mediating effect (especially for planned caesarean, when the timing of delivery is decided following mode of birth

decision) on the examined association. To investigate the association of mode of birth with wheezing phenotypes without controlling for this potential mediating effect, the fully adjusted multivariable model was run a second time without adjustment for gestational age.

3.2.7 Sensitivity analyses

3.2.7.1 Alternative definition of wheezing phenotypes

As detailed in section 1.4.1 (page 32), the specific age cut-offs classifying the various wheezing phenotypes identified in cohort studies are not universally agreed and indeed some studies have used a different age cut-off when defining the wheezing phenotypes in the MCS [167]. Therefore, a sensitivity analysis was carried out with an alternative definition for the trajectories of the major wheezing phenotypes, with a cut-off following the age 5 survey rather than prior to it.

- No wheezing – no report of recent wheezing from 9 months of age up to 11 years.
- Transient wheezing – report of recent wheezing at age 9 months, 3 years or 5 years, but no report of recent wheezing at ages 7 and 11.
- Persistent wheezing – report of recent wheezing at age 9 months, 3 years or 5 years, and at least a single additional report of recent wheezing at ages 7 or 11.
- Late-onset wheezing – no report of recent wheezing at ages 9 months, 3 years or 5 years, but at least a single report of recent wheezing at ages 7 or 11 years.

3.2.7.2 Restriction to observations with validated mode of birth

See section 2.2.7.1 for an explanation regarding this sensitivity analysis based on hospital records.

3.2.8 Extended-group analysis - inclusive of preterm and unwell neonates

Many of the studies of mode of birth and asthma or wheeze have included premature neonates and those requiring special medical care. To aid the comparison with prior publications, an additional analysis of an extended inclusion group was carried out. This group included participants who were born preterm, admitted to NICU, or were reported to have a congenital anomaly or genetic abnormality. This addition increased the size of the analysed study group from 8,744 to 9,971 children. Multinomial and logistic regression models were adjusted using the same variables as in the main analysis, with the exception that gestational age was extended to include the following sub-categories: <32 weeks, 32-33, 34-36, 37-38, 39-40, 41, and 42 weeks.

3.2.9 Power calculation

The study had at least 80% power to detect a relative risk of 1.3-1.4 for persistent and transient wheezing and 1.5-1.6 for late-onset wheezing.

The study's power to detect a crude association between mode of birth and wheezing phenotypes was estimated by comparing two independent proportions using the Chi-square test. For example, to compare the proportion of children experiencing transient wheezing within those born by planned caesarean vs. those born by vaginal delivery (the reference group). The size of the reference group in the study sample was 6,133 and the size of the exposed groups was 799 for planned caesarean and 916 for emergency caesarean. The expected proportions of each wheezing phenotype were estimated from a study using the MCS data [166] (although using a narrower age range). The estimated effect size used to calculate expected power were derived from a study on mode of birth and wheezing phenotypes by van Berkel et al [97].

The estimated power to detect a statistically significant effect was near the acceptable level of 80% for the transient and persistent wheezing phenotypes, even for the lower

effect size estimate of 1.3. For late-onset wheezing, the estimated power was only moderate when a lower effect size was predicted but was acceptable for an effect size of 1.6 (Table 3-3). Note that as mentioned previously, these power estimations do not account for the clustered study design.

Table 3-3: Power to detect associations in the MCS wheezing phenotypes study by estimated effect size

	Power (%)					
Estimated effect size	***Transient*** (17.1%)		**Persistent** (12.0%)		**Late-onset** (4.9%)	
	Planned CS	**Emergency CS**	**Planned CS**	**Emergency CS**	**Planned CS**	**Emergency CS**
1.3	79	**83**	68	73	40	43
1.4	**95***	96	**88**	**91**	59	63
1.5	99	99	97	98	75	79
1.6	100	100	99	100	**86**	**90**

* The smallest effect size for which a power of ≥80% is achieved is highlighted in bold

3.2.10 Data management

The Millennium Cohort Study data is held by the UK Data Service and is freely and publicly available. The parent interview dataset (main respondent and partner) and derived variables dataset were downloaded for each MCS survey from age 9 month to 11 years. The longitudinal family dataset of the age 11 survey, which includes non-response weights, was also downloaded. All datasets were then merged[32] based on the 'MCSID', an identification number unique to each family recruited to the MCS.

3.2.11 Ethics committee approval

See section 2.2.10 for details.

[32] MCS age 11 survey parent interview dataset required reshaping from long to wide format before merging as it was formatted by cohort member rather than by family

3.3 Results

3.3.1 Study group and mode of birth – descriptive results

After exclusions described in section 3.2.2, the final study sample included 8,744 children. The distribution of the sample characteristics by mode of birth is presented in Table 3-4.

3.3.2 Study group characteristics

The proportion of the measured characteristics of the study group and their distribution amongst the mode of birth categories was almost identical to those described previously using the age 9 months survey data alone (n=15,586; section 2.3.2). Therefore, the description of study characteristics will not be repeated here. In the current study, mode of birth was strongly associated with the various characteristics, as it was in the study focusing on infancy only. A Chi-square test gave P-value<0.001 for all characteristics except parental asthma (P=0.008) and ethnicity (P=0.002) (Table 3-4).

Table 3-4: Characteristics of children and their parents included in the MCS wheezing phenotypes study by mode of birth

	VD n (%)	Assisted VD n (%)	Planned CS n (%)	Emergency CS n (%)	Total n (%)
Mode of birth n (%)	**6,133 (71.7)**	**896 (10.0)**	**799 (8.5)**	**916 (9.9)**	**8,744 (100.0)**
Maternal characteristics					
Maternal age group (years)					
<20	380 (7.8)	63 (9.4)	15 (2.1)	42 (5.4)	500 (7.3)
20-29	2,807 (47.7)	402 (44.7)	281 (37.7)	353 (40.1)	3,843 (45.8)
30-39	2,819 (42.5)	416 (44.8)	464 (55.8)	490 (51.0)	4,189 (44.7)
≥40	127 (1.9)	15 (1.3)	39 (4.4)	31 (3.5)	212 (2.2)
Marital status					
Married	3,906 (59.5)	586 (63.1)	585 (70.8)	625 (66.6)	5,702 (61.6)
Cohabiting	1,421 (25.8)	231 (27.6)	148 (20.6)	203 (22.1)	2,003 (25.2)
Single	806 (14.6)	79 (9.3)	66 (8.6)	88 (11.3)	1,039 (13.3)
Education					
Higher	2,027 (29.7)	399 (40.8)	308 (35.6)	387 (39.2)	3,121 (32.3)
Intermediate	961 (14.9)	149 (15.9)	89 (10.5)	139 (15.2)	1,338 (14.7)
Lower	2,235 (39.3)	292 (35.9)	279 (38.6)	296 (34.6)	3,102 (38.4)
Overseas or other	154 (2.6)	14 (1.9)	22 (2.8)	24 (3.2)	214 (2.6)
None	753 (13.5)	41 (5.6)	101 (12.6)	69 (7.9)	964 (12.1)
Household socioeconomic class					
Managerial/ Professional	2,741 (43.2)	501 (52.9)	405 (49.7)	500 (53.0)	4,147 (45.7)
Intermediate	1,207 (19.6)	161 (19.2)	153 (19.5)	175 (18.2)	1,696 (19.4)
Routine/Manual	1,892 (31.9)	212 (25.6)	211 (27.7)	223 (25.7)	2,538 (30.3)
Never worked / long unemployment	293 (5.4)	22 (2.3)	30 (3.2)	18 (3.2)	363 (4.7)
Smoking					
Non-smoker	4,207 (65.7)	631 (68.6)	590 (71.5)	665 (72.7)	6,093 (67.2)
Ex-smoker (gave up)	655 (11.7)	123 (14.7)	84 (10.6)	118 (13.0)	980 (12.0)
Smoker	1,270 (22.6)	142 (16.7)	125 (17.9)	133 (14.3)	1,670 (20.8)
Diabetes	92 (1.9)	12 (1.6)	32 (5.1)	19 (2.1)	155 (2.1)
Hypertensive condition	352 (6.3)	71 (7.6)	59 (8.7)	111 (13.7)	593 (7.4)
Parental asthma					
Both parents no asthma	3,452 (53.4)	534 (57.0)	498 (61.7)	554 (58.9)	5,038 (55.0)
Mum no asthma	1,099 (19.7)	125 (15.5)	102 (12.5)	146 (17.9)	1,472 (18.5)
Dad asthma mum none	577 (9.2)	87 (10.4)	72 (9.1)	75 (7.9)	811 (9.2)
Mum asthma dad none	659 (11.3)	101 (11.6)	83 (10.5)	98 (10.8)	941 (11.2)
Mum asthma	233 (4.4)	28 (3.0)	32 (4.6)	28 (3.1)	321 (4.2)
Both parents asthma	111 (2.1)	21 (2.5)	12 (1.6)	14 (1.4)	158 (2.0)

	VD n (%)	Assisted VD n (%)	Planned CS n (%)	Emergency CS n (%)	Total n (%)
Infant characteristics					
Male	2,966 (48.8)	483 (55.8)	370 (46.0)	499 (55.5)	4,318 (49.9)
Ethnicity					
White	5,232 (86.6)	820 (92.1)	708 (89.7)	789 (86.4)	7,549 (87.4)
Mixed	156 (3.1)	19 (2.7)	13 (1.4)	26 (3.4)	214 (2.9)
Indian	155 (1.9)	19 (1.9)	10 (0.7)	15 (1.2)	199 (1.8)
Pakistani	267 (3.6)	16 (1.2)	31 (3.3)	29 (2.1)	343 (3.2)
Bangladeshi	101 (1.2)	7 (0.6)	12 (0.9)	11 (0.7)	131 (1.0)
Black Caribbean	52 (1.0)	3 (0.4)	6 (1.0)	10 (1.1)	71 (0.9)
Black African	81 (1.4)	5 (0.8)	7 (1.4)	17 (2.6)	110 (1.4)
Other	78 (1.3)	6 (0.4)	11 (1.6)	19 (2.5)	114 (1.4)
Firstborn	2,017 (33.0)	704 (77.7)	204 (24.6)	627 (68.7)	3,552 (40.3)
Gestational age in weeks					
37-38 (early term)	1,053 (17.4)	100 (11.0)	414 (54.4)	158 (18.0)	1,725 (19.9)
39-40 (full term)	3,456 (56.8)	474 (52.7)	319 (38.3)	426 (46.5)	4,675 (53.8)
41 (late term)	1,439 (22.7)	268 (30.9)	50 (5.7)	272 (28.8)	2,029 (22.7)
42 (post term)	174 (3.1)	52 (5.5)	10 (1.6)	57 (6.8)	293 (3.6)
Birthweight in kg, mean (SD)	3.43 (0.66)	3.51 (0.54)	3.39 (0.62)	3.55 (0.67)	3.45 (0.68)

* P-value<0.001 for all characteristics except parental asthma P=0.008 and ethnicity P=0.002

3.3.3 Mode of birth and wheezing phenotypes – primary outcome

A little over a third of the study group participants experienced wheezing at some stage during the follow-up period. Classification of the wheezing phenotypes resulted in similar proportions per each phenotype – roughly 11-13% for each phenotype (Table 3-5A).

Overall, 11.6% of the children experienced transient wheezing. Children born by assisted vaginal delivery were less likely to experience transient wheezing than children born vaginally, although the effect was not statistically significant (RRR=0.77; 95% CI 0.59, 1.01) (P=0.060) and was attenuated after adjustment (aRRR=0.87; 95% CI 0.65, 1.18) (Table 3-5B). Planned caesarean was not associated with transient wheezing, either before or after adjustment. Emergency caesarean was not associated with transient wheezing in the crude model, however, after adjustments the children born by

emergency caesarean were more likely to experience transient wheezing, but the effect was not statistically significant (aRRR=1.21; 95% CI 0.91, 1.61).

A total of 11.1% of the children experienced persistent wheezing. Children born by assisted vaginal delivery were more likely to experience persistent wheezing compared to children born by vaginal delivery, although the results were not statistically significant neither in the crude nor the adjusted model (aRRR=1.27; 95% CI 0.97, 1.67) (P=0.086). Children born by planned caesarean were 33% more likely to experience persistent wheezing compared to the reference group, and this effect remained the same after adjustments (aRRR=1.34; 95% CI 1.02, 1.76) (P=0.037). Children born by emergency caesarean were more likely to experience persistent wheezing in the adjusted model, although the effect was not statistically significant (aRRR=1.21; 95% CI 0.93, 1.59).

Overall, 12.9% of the children experienced late-onset wheezing. The risk of late-onset wheezing was not strongly associated with mode of birth in either the crude or adjusted models.

Table 3-5: Association between mode of birth and wheezing phenotypes in the MCS study

(A) Frequencies and percentages of wheezing phenotypes by mode of birth

	No wheezing		Transient wheezing		Persistent wheezing		Late-onset wheezing		Total sample	
	n	%	n	%	n	%	n	%	n	%*
VD	3,960	64.6	706	11.9	674	10.6	793	12.8	6,133	100.0
Assisted VD	592	65.8	85	9.4	101	12.1	118	12.7	896	100.0
Planned CS	480	61.5	88	11.3	109	13.5	122	13.7	799	100.0
Emergency CS	584	64.0	114	12.1	106	11.3	112	12.7	916	100.0
Total	5,616	64.4	993	11.6	990	11.1	1,145	12.9	8,744	100.0

* Percentages are weighted.

(B) Crude and adjusted relative risk ratios for the association between mode of birth and wheezing phenotypes

	Crude RRR * (95% CI)	Adjusted RRR ** (95% CI)
n sample size	8,744	8,697
Transient wheezing		
VD	1.00	1.00
Assisted VD	0.77 (0.59, 1.01)	0.87 (0.65, 1.18)
Planned CS	1.00 (0.72, 1.38)	1.04 (0.73, 1.47)
Emergency CS	1.02 (0.79, 1.33)	1.21 (0.91, 1.61)
Persistent wheezing		
VD	1.00	1.00
Assisted VD	1.12 (0.87, 1.44)	1.27 (0.97, 1.67)
Planned CS	1.33 (1.02, 1.75)	1.34 (1.02, 1.76)
Emergency CS	1.07 (0.82, 1.38)	1.21 (0.93, 1.59)
Late-onset wheezing		
VD	1.00	1.00
Assisted VD	0.97 (0.77, 1.24)	0.96 (0.74, 1.25)
Planned CS	1.13 (0.87, 1.46)	1.14 (0.88, 1.49)
Emergency CS	1.00 (0.79, 1.26)	0.99 (0.78, 1.26)

* RRR = Relative Risk Ratio
** Adjusted for household socioeconomic class, marital status, maternal age, maternal education level, parental asthma, firstborn, mother's smoking during pregnancy, child's sex, ethnicity, gestational age, birthweight

3.3.4 Added indirect effect through earlier gestational age at delivery

An additional model was run which included all covariates from the fully adjusted model apart from gestational age (Table 3-6). In this model, adjusted results for transient wheezing and late-onset wheezing were no different from the results described above. Similarly, results for persistent wheezing in the assisted vaginal delivery and emergency caesarean were no different. However, the relative risk ratio of planned caesarean increased from 1.34 to 1.43.

Table 3-6: Multivariable models for the association between mode of birth and wheezing phenotypes in the MCS study, adjusted or unadjusted for gestational age

	Fully adjusted [b] RRR [a] (95% CI)	Unadjusted for gestational age [c] RRR (95% CI)
Transient wheezing		
VD	1.00	1.00
Assisted VD	0.87 (0.65, 1.18)	0.87 (0.65, 1.17)
Planned CS	1.04 (0.73, 1.47)	1.04 (0.75, 1.45)
Emergency CS	1.21 (0.91, 1.61)	1.20 (0.90, 1.59)
Persistent wheezing		
VD	1.00	1.00
Assisted VD	1.27 (0.97, 1.67)	1.25 (0.95, 1.64)
Planned CS	1.34 (1.02, 1.76)	1.43 (1.09, 1.88)
Emergency CS	1.21 (0.93, 1.59)	1.21 (0.93, 1.58)
Late-onset wheezing		
VD	1.00	1.00
Assisted VD	0.96 (0.74, 1.25)	0.95 (0.73, 1.24)
Planned CS	1.14 (0.88, 1.49)	1.17 (0.89, 1.53)
Emergency CS	0.99 (0.78, 1.26)	0.98 (0.77, 1.24)

a RRR = Relative Risk Ratio
b Adjusted for household socioeconomic class, marital status, maternal age, maternal education level, parental asthma, firstborn, mother's smoking during pregnancy, child's sex, ethnicity, gestational age, birthweight
c Adjusted for the variables mentioned in (b) except gestational age

3.3.5 Mode of birth and asthma-related secondary outcomes

The study's secondary outcomes were recent wheezing, severe wheezing, 'ever asthma' and asthma medication use examined at each survey separately.

3.3.5.1 Recent wheezing

The proportion of children experiencing recent wheezing was lowest at infancy (6.3%), peaked at age 3 (18.8%) and decreased to 11.2% at age 11 (see Figure 3-2 page 140). Of note, there were some inconsistencies in the report of recent wheezing compared with 'ever wheezing' at different ages. One in five children that were not reported to have experienced recent wheezing in any of the MCS surveys, all the same had a positive answer to the question regarding 'ever wheezing' at one of the interviews. However,

there were also inconsistencies in the responses regarding ‘ever wheezing’, as almost a third of the children reported to have ever wheezed, were reported to have never wheezed in a later interview.

Overall, there were no strong or consistent associations between mode of birth and recent wheezing with adjusted odds ratios ranging between 0.79 and 1.30. Planned caesarean was associated with 30% increased risk for recent wheezing at age 5 (aOR=1.30; 95% CI 1.02, 1.65), but not at other ages. Assisted vaginal delivery and emergency caesarean were not consistently associated with recent wheezing either.

3.3.5.2 Severe wheezing

The proportion of children reported to suffer from severe wheezing was 6.8% when first measured at age 3 and decreased to 4.5% by age 11 (Figure 3-2). The proportion of children experiencing severe wheezing out of those experiencing any symptoms of recent wheezing ranged between 38% and 47% in each survey.

Assisted vaginal delivery was associated with severe wheezing at all ages examined (adjusted odds ratios 1.22-1.68), but the association was statistically significant only at age 3 (aOR=1.68; 95% CI 1.20, 2.34). Planned caesarean was associated with severe wheezing at age 3 in the crude model (OR=1.39; 95% CI 1.00, 1.94), however the association was no longer statistically significant after adjustment (aOR=1.28, 95% CI 0.91, 1.80) and did not persistent to older ages. Likewise, emergency caesarean was not consistently associated with severe wheezing.

3.3.5.3 Ever asthma

The proportion of children reported to have ever had asthma increased steadily from 11.7% at age 3 to 16.7% at age 11 (Figure 3-2). The proportion of ‘ever asthma’ report amongst participants with recent wheezing increased with age - from 42% to 70%. Likewise, the proportion of ‘ever asthma’ amongst those with severe wheezing increased with age as well - 59% to 83%.

Overall, there was an adjusted increased risk of 'ever asthma' for all medically interventional modes of birth from age 3 to 11 (odds ratios 0.98-1.45). However this association was only statistically significant for assisted vaginal delivery at age 5 (aOR=1.45; 95% CI 1.14, 1.84) (Table 3-9 page 143).

3.3.5.4 Asthma medication use

The proportion of children currently taking prescription asthma medication on a regular basis was low, ranging from 3.6% at age 5 to 5.1% at age 11 (Figure 3-2). Almost all prescribed medications were bronchodilators (i.e. Salbutamol) or inhaled corticosteroids (i.e. Beclometasone). Roughly a third of the children with a report of regular asthma medication were taking both. Almost all children (95-97%) that used asthma medication were also reported to have ever had asthma at the same interview.

No consistent trend in the association between mode of birth and asthma medication use was observed from age 5 to 11. Assisted vaginal delivery and planned caesarean were associated with an increased risk at age 5, a lower risk at age 7 and again an increase in risk at age 11, neither statistically significant. Emergency caesarean was associated with asthma medication use at age 5 (aOR=1.48; 95% CI 0.98, 2.24) (P=0.062) but the association was reduced at age 7 and no longer observed at age 11.

Figure 3-2: Prevalence of age-specific asthma-related outcomes in the MCS

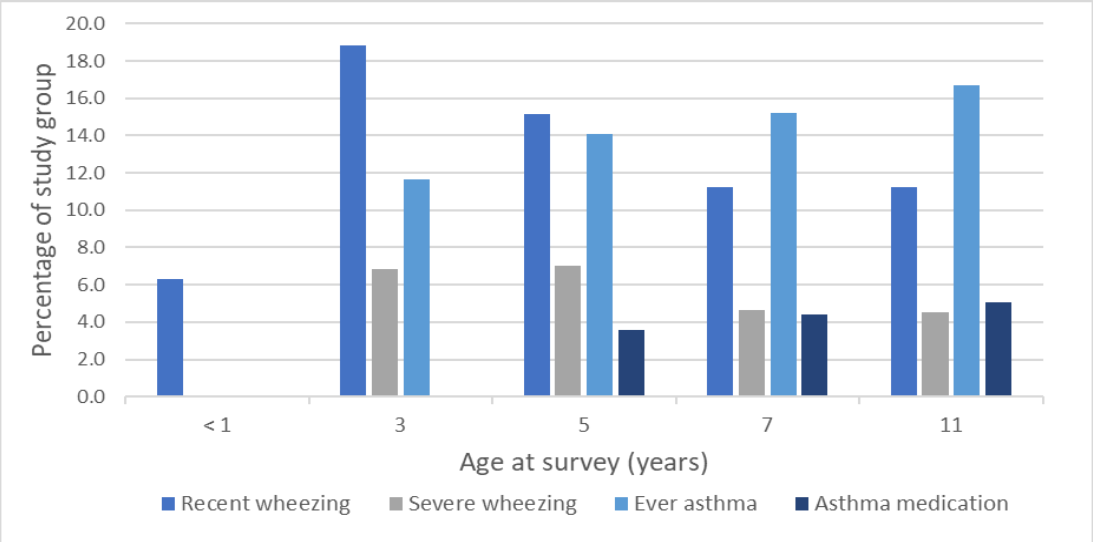


Table 3-7: Association between mode of birth and recent wheezing symptoms in the MCS at ages 9 months, 3, 5, 7, and 11 years

	Recent wheezing				
	No. of events	**n**	**% [a]**	**Crude OR (95% CI)**	**Adjusted OR [b] (95% CI)**
Age 9 months					
VD	386	6,133	6.6	1.00	1.00
Assisted VD	44	896	4.7	0.70 (0.49, 1.00)	0.79 (0.54, 1.17)
Planned CS	57	799	6.7	1.02 (0.71, 1.45)	1.14 (0.76, 1.69)
Emergency CS	54	916	5.7	0.86 (0.60, 1.24)	0.98 (0.68, 1.44)
Total	**541**	**8,744**	**6.3**		
Age 3 years					
VD	1,134	6,133	18.6	1.00	1.00
Assisted VD	157	896	18.5	0.99 (0.81, 1.22)	1.12 (0.90, 1.39)
Planned CS	164	799	20.7	1.15 (0.90, 1.46)	1.16 (0.90, 1.48)
Emergency CS	180	916	19.3	1.05 (0.85, 1.30)	1.21 (0.98, 1.51)
Total	**1,635**	**8,744**	**18.8**		
Age 5 years					
VD	923	6,133	14.9	1.00	1.00
Assisted VD	128	896	15.1	1.02 (0.81, 1.30)	1.11 (0.87, 1.43)
Planned CS	151	799	18.5	1.30 (1.04, 1.63)	1.30 (1.02, 1.65)
Emergency CS	136	916	14.5	0.97 (0.77, 1.22)	1.05 (0.83, 1.32)
Total	**1,338**	**8,744**	**15.2**		
Age 7 years					
VD	691	6,133	10.8	1.00	1.00
Assisted VD	110	896	13.1	1.24 (0.96, 1.60)	1.30 (1.00, 1.68)
Planned CS	98	799	11.9	1.11 (0.84, 1.46)	1.07 (0.81, 1.42)
Emergency CS	109	916	11.5	1.07 (0.84, 1.37)	1.11 (0.86, 1.43)
Total	**1,008**	**8,744**	**11.2**		
Age 11 years					
VD	714	6,133	11.1	1.00	1.00
Assisted VD	111	896	12.3	1.12 (0.86, 1.46)	1.04 (0.80, 1.35)
Planned CS	96	799	11.4	1.02 (0.77, 1.36)	1.07 (0.81, 1.43)
Emergency CS	104	916	11.0	0.98 (0.76, 1.26)	0.94 (0.72, 1.23)
Total	**1,025**	**8,744**	**11.2**		

a Percentages are weighted
b Results are adjusted for household socioeconomic class, marital status, maternal age, maternal education level, parental asthma, firstborn, mother's smoking during pregnancy, child's sex, ethnicity, gestational age, birthweight

Table 3-8: Association between mode of birth and severe wheezing symptoms in the MCS at ages 3, 5, 7, and 11 years

	Severe wheezing				
	No. of events	**n**	**% [a]**	**Crude OR (95% CI)**	**Adjusted OR [b] (95% CI)**
Age 3 years					
VD	414	6,088	6.4	1.00	1.00
Assisted VD	69	890	8.6	1.36 (1.00, 1.85)	1.68 (1.20, 2.34)
Planned CS	70	793	8.8	1.39 (1.00, 1.94)	1.28 (0.91, 1.80)
Emergency CS	57	907	6.2	0.96 (0.66, 1.41)	1.19 (0.83, 1.70)
Total	**610**	**8,678**	**6.8**		
Age 5 years					
VD	421	6,131	7.0	1.00	1.00
Assisted VD	61	896	7.7	1.11 (0.78, 1.56)	1.22 (0.86, 1.74)
Planned CS	62	798	7.4	1.07 (0.77, 1.48)	1.07 (0.76, 1.50)
Emergency CS	61	915	6.3	0.90 (0.63, 1.27)	0.98 (0.70, 1.37)
Total	**605**	**8,740**	**7.0**		
Age 7 years					
VD	297	6,131	4.5	1.00	1.00
Assisted VD	54	896	6.0	1.36 (0.93, 1.99)	1.36 (0.92, 2.00)
Planned CS	40	798	4.7	1.06 (0.68, 1.66)	1.10 (0.72, 1.68)
Emergency CS	49	916	4.9	1.10 (0.75, 1.61)	1.14 (0.76, 1.70)
Total	**440**	**8,741**	**4.7**		
Age 11 years					
VD	288	6,131	4.6	1.00	1.00
Assisted VD	53	896	5.9	1.31 (0.91, 1.89)	1.30 (0.90, 1.88)
Planned CS	28	799	3.6	0.78 (0.49, 1.25)	0.81 (0.51, 1.28)
Emergency CS	34	916	3.6	0.78 (0.49, 1.24)	0.81 (0.49, 1.32)
Total	**403**	**8,742**	**4.5**		

a Percentages are weighted.
b Results are adjusted for household socioeconomic class, marital status, maternal age, maternal education level, parental asthma, firstborn, mother's smoking during pregnancy, child's sex, ethnicity, gestational age, birthweight

Table 3-9: Association between mode of birth and 'ever asthma' in the MCS at ages 3, 5, 7, and 11 years

	Ever asthma				
	No. of events	**n**	**% [a]**	**Crude OR (95% CI)**	**Adjusted OR [b] (95% CI)**
Age 3 years					
VD	696	6,036	11.5	1.00	1.00
Assisted VD	90	883	11.4	0.99 (0.75, 1.31)	1.22 (0.90, 1.66)
Planned CS	101	792	13.4	1.19 (0.87, 1.61)	1.22 (0.89, 1.68)
Emergency CS	96	893	11.2	0.97 (0.74, 1.26)	1.19 (0.89, 1.59)
Total	**983**	**8,604**	**11.7**		
Age 5 years					
VD	829	6,110	13.5	1.00	1.00
Assisted VD	134	892	16.8	1.29 (1.03, 1.61)	1.45 (1.14, 1.84)
Planned CS	121	797	15.3	1.15 (0.87, 1.52)	1.21 (0.89, 1.63)
Emergency CS	125	913	14.3	1.07 (0.87, 1.35)	1.21 (0.95, 1.55)
Total	**1,209**	**8,712**	**14.1**		
Age 7 years					
VD	929	6,124	14.8	1.00	1.00
Assisted VD	144	895	16.9	1.17 (0.95, 1.44)	1.23 (0.99, 1.53)
Planned CS	131	794	16.0	1.09 (0.85, 1.41)	1.12 (0.86, 1.48)
Emergency CS	141	914	16.0	1.09 (0.88, 1.36)	1.18 (0.93, 1.49)
Total	**1,345**	**8,727**	**15.2**		
Age 11 years					
VD	1,036	6,132	16.3	1.00	1.00
Assisted VD	169	895	18.6	1.17 (0.96, 1.43)	1.15 (0.93, 1.42)
Planned CS	138	799	15.9	0.97 (0.76, 1.23)	0.98 (0.77, 1.26)
Emergency CS	162	915	18.2	1.14 (0.92, 1.41)	1.16 (0.93, 1.44)
Total	**1,505**	**8,741**	**16.7**		

a Percentages are weighted
b Results are adjusted for household socioeconomic class, marital status, maternal age, maternal education level, parental asthma, firstborn, mother's smoking during pregnancy, child's sex, ethnicity, gestational age, birthweight

Table 3-10: Association between mode of birth and asthma medication use in the MCS at ages 5, 7, and 11 years

	Asthma medication use				
	No. of events	**n**	**% [a]**	**Crude OR (95% CI)**	**Adjusted OR [b] (95% CI)**
Age 5 years					
VD	213	6,131	3.2	1.00	1.00
Assisted VD	39	896	4.2	1.31 (0.84, 2.03)	1.34 (0.84, 2.14)
Planned CS	32	799	4.4	1.40 (0.88, 2.22)	1.19 (0.73, 1.95)
Emergency CS	36	916	4.7	1.48 (0.95, 2.29)	1.48 (0.98, 2.24)
Total	**320**	**8,742**	**3.6**		
Age 7 years					
VD	277	6,126	4.5	1.00	1.00
Assisted VD	45	896	4.1	0.92 (0.62, 1.37)	0.89 (0.59, 1.34)
Planned CS	30	799	4.1	0.91 (0.61, 1.37)	0.89 (0.60, 1.32)
Emergency CS	45	914	4.9	1.11 (0.75, 1.64)	1.10 (0.73, 1.66)
Total	**397**	**8,735**	**4.4**		
Age 11 years					
VD	319	6,133	4.9	1.00	1.00
Assisted VD	58	896	6.5	1.36 (0.95, 1.94)	1.26 (0.87, 1.81)
Planned CS	41	799	5.1	1.04 (0.71, 1.51)	1.16 (0.80, 1.67)
Emergency CS	44	916	5.1	1.05 (0.73, 1.51)	1.00 (0.69, 1.45)
Total	**462**	**8,744**	**5.1**		

a Percentages are weighted
b Results are adjusted for household socioeconomic class, marital status, maternal age, maternal education level, parental asthma, firstborn, mother's smoking during pregnancy, child's sex, ethnicity, gestational age, birthweight

3.3.6 Sensitivity analyses

3.3.6.1 Alternative definition for wheezing phenotypes

A sensitivity analysis using an alternative definition for wheezing phenotypes was carried out: the cut-off for discriminating the various phenotypes was set after the age 5 survey, rather than before. The proportion of each phenotype was as follows: 18.8% transient wheezing, 10.8% persistent wheezing and 6.0% late-onset wheezing (Table 3-11A).

The results of this sensitivity analysis were broadly similar to those of the main analysis. Children born by planned caesarean sections were found to have a 28% increase in the

adjusted relative risk for persistent wheezing, although this was not statistically significant (Table 3-11B).

Table 3-11: Sensitivity analysis of the association between mode of birth and alternative definition of wheezing phenotypes in the MCS study

(A) Frequencies and percentages of alternative definition of wheezing phenotypes by mode of birth

	No wheezing		Transient wheezing		Persistent wheezing		Late-onset wheezing		Total sample	
	n	%	n	%	n	%	n	%	n	% [a]
VD	3,960	64.6	1,117	19.0	684	10.5	372	5.9	6,133	100.0
Assisted VD	592	65.8	143	15.8	94	11.6	67	6.9	896	100.0
Planned CS	480	61.5	164	20.4	103	12.6	52	5.5	799	100.0
Emergency CS	584	64.0	170	18.5	110	11.0	52	6.5	916	100.0
Total	**5,616**	**64.4**	**1,594**	**18.8**	**991**	**10.8**	**543**	**6.0**	**8,744**	**100.0**

a Percentages are weighted.

(B) Adjusted relative risk ratios for the association between mode of birth and alternative definition of wheezing phenotypes compared to main definition

	Adjusted RRR [b] (95% CI)	
	Main analysis	Sensitivity analysis
Transient wheezing		
VD	1.00	1.00
Assisted VD	0.87 (0.65, 1.18)	0.93 (0.73, 1.18)
Planned CS	1.04 (0.73, 1.47)	1.15 (0.88, 1.49)
Emergency CS	1.21 (0.91, 1.61)	1.14 (0.92, 1.43)
Persistent wheezing		
VD	1.00	1.00
Assisted VD	1.27 (0.97, 1.67)	1.13 (0.84, 1.51)
Planned CS	1.34 (1.02, 1.76)	1.28 (0.97, 1.68)
Emergency CS	1.21 (0.93, 1.59)	1.13 (0.87, 1.46)
Late-onset wheezing		
VD	1.00	1.00
Assisted VD	0.96 (0.74, 1.25)	1.09 (0.76, 1.55)
Planned CS	1.14 (0.88, 1.49)	1.03 (0.71, 1.49)
Emergency CS	0.99 (0.78, 1.26)	1.08 (0.75. 1.54)

b Results are adjusted for household socioeconomic class, marital status, maternal age, maternal education level, parental asthma, firstborn, mother's smoking during pregnancy, child's sex, ethnicity, gestational age, birthweight

3.3.6.2 Restriction to observations with validated mode of birth

A sensitivity analysis was carried out using solely observations where mode of birth was validated using hospital delivery records. The sample size in this analysis was smaller than that of the main analysis and included 6,537 children (Table 3-12A). The proportion of each wheezing phenotype was similar to that found in the main analysis. The results were not materially different to those of the main analysis, however the relative risk ratio for persistent wheezing in children born by planned caesarean was smaller compared to the main analysis (aRRR=1.18), and was not statistically significant (Table 3-12B).

Table 3-12: Sensitivity analysis of the association between validated mode of birth and wheezing phenotypes in the MCS study

(A) Frequencies and percentages of wheezing phenotypes within validated mode of birth categories

	No wheezing		Transient wheezing		Persistent wheezing		Late-onset wheezing		Total sample	
	n	%	n	%	n	%	n	%	n	% [a]
VD	2,967	64.0	556	12.3	506	10.7	606	13.0	4,635	100
Assisted VD	455	66.8	63	9.2	79	12.6	86	11.4	683	100
Planned CS	344	65.1	50	9.3	75	13.1	81	12.6	550	100
Emergency CS	419	62.0	84	12.7	76	11.1	90	14.2	669	100
Total	**4,185**	**64.2**	**753**	**11.8**	**736**	**11.1**	**863**	**12.9**	**6,537**	**100**

a Percentages are weighted.

(B) Adjusted relative risk ratios for the association between validated mode of birth and wheezing phenotypes compared to main analysis

	Adjusted RRR [b] (95% CI)	
	Main analysis	**Sensitivity analysis**
Transient wheezing		
VD	1.00	1.00
Assisted VD	0.87 (0.65, 1.18)	0.81 (0.57, 1.13)
Planned CS	1.04 (0.73, 1.47)	0.75 (0.46, 1.22)
Emergency CS	1.21 (0.91, 1.61)	1.24 (0.88, 1.74)
Persistent wheezing		
VD	1.00	1.00
Assisted VD	1.27 (0.97, 1.67)	1.29 (0.95, 1.74)
Planned CS	1.34 (1.02, 1.76)	1.18 (0.83, 1.68)
Emergency CS	1.21 (0.93, 1.59)	1.23 (0.91, 1.67)
Late-onset wheezing		
VD	1.00	1.00
Assisted VD	0.96 (0.74, 1.25)	0.79 (0.58, 1.09)
Planned CS	1.14 (0.88, 1.49)	0.98 (0.72, 1.33)
Emergency CS	0.99 (0.78, 1.26)	1.10 (0.84, 1.45)

b Results are adjusted for household socioeconomic class, marital status, maternal age, maternal education level, parental asthma, firstborn, mother's smoking during pregnancy, child's sex, ethnicity, gestational age, birthweight

3.3.7 Extended-group analysis – inclusive of preterm and unwell neonates

To enhance the comparability of this study with prior studies (including a cross-sectional study carried out on the MCS [118]), I undertook an additional sensitivity analysis where babies born preterm or known to have been unwell at birth (i.e. requiring NICU or having congenital or genetic abnormalities) were included in the study population (n=9,971).

All adjusted longitudinal and age-specific analyses that were found to have statistically significant associations in the main study group remained so in this extended inclusion study group. In addition to these risks found in the main inclusion group, the extended group consistently showed emergency caesarean to be a risk factor for various wheezing and asthma-related outcomes. In the analysis of wheezing phenotypes, the adjusted relative risk ratio of assisted vaginal delivery and planned caesarean remained

the same as in the main inclusion group (28% increase in risk for the former and a statistically significant 32% increase in risk for the latter). However, the adjusted relative risk ratio of emergency caesarean increased from 1.21 to 1.55 and became highly statistically significant in the extended study group (Table 3-13). Emergency caesarean was also found to be associated with age-specific asthma-related outcomes with adjusted odds ratios ranging from 1.24 to 1.52 in 8 out of 16 age-specific analyses conducted in this extended study group (Table 3-14).

Table 3-13: Extended-group analysis of study group inclusive of preterm and unwell neonates – adjusted relative risk ratios of the association between mode of birth and wheezing phenotypes in the MCS study

	Adjusted [a] RRR (95% CI)	
	Main analysis	**Sensitivity analysis**
n sample size	8,697	9,893
Transient wheezing		
VD	1.00	1.00
Assisted VD	0.87 (0.65, 1.18)	0.82 (0.62, 1.09)
Planned CS	1.04 (0.73, 1.47)	1.10 (0.80, 1.51)
Emergency CS	1.21 (0.91, 1.61)	1.08 (0.85, 1.38)
Persistent wheezing		
VD	1.00	1.00
Assisted VD	1.27 (0.97, 1.67)	1.28 (0.99, 1.66)
Planned CS	1.34 (1.02, 1.76)	1.32 (1.02, 1.72)
Emergency CS	1.21 (0.93, 1.59)	**1.55 (1.26, 1.91)** [b]
Late-onset wheezing		
VD	1.00	1.00
Assisted VD	0.96 (0.74, 1.25)	0.95 (0.73, 1.24)
Planned CS	1.14 (0.88, 1.49)	1.10 (0.85, 1.41)
Emergency CS	0.99 (0.78, 1.26)	1.01 (0.82, 1.25)

a Results are adjusted for household socioeconomic class, marital status, maternal age, maternal education level, parental asthma, firstborn, mother's smoking during pregnancy, child's sex, ethnicity, birthweight and gestational age category (<32, 32-33, 34-36, 37-38, 39-40, 41, 42 weeks).
b Statistically significant (P<0.05) associations that were not statistically significant in the main inclusion group are marked in bold

Table 3-14: Extended study group including preterm and unwell neonates – adjusted odds ratio of the association between mode of birth and age-specific asthma-related outcomes in the MCS study

	Adjusted OR (95% CI) [b]			
n=9,971 [a]	**Recent wheezing**	**Severe wheezing**	**Ever asthma**	**Asthma medication**
Age 9 months				
VD	1.00			
Assisted VD	0.75 (0.52, 1.08)			
Planned CS	1.07 (0.75, 1.52)			
Emergency CS	1.03 (0.75, 1.43)			
Age 3 years				
VD	1.00	1.00	1.00	
Assisted VD	1.11 (0.90, 1.37)	1.57 (1.16, 2.14)	1.11 (0.83, 1.47)	
Planned CS	1.18 (0.94, 1.47)	1.25 (0.91, 1.72)	1.25 (0.94, 1.67)	
Emergency CS	**1.35 (1.14, 1.60) [c]**	**1.39 (1.07, 1.81) [c]**	1.22 (0.96, 1.54)	
Age 5 years				
VD	1.00	1.00	1.00	1.00
Assisted VD	1.17 (0.94, 1.45)	1.19 (0.86, 1.65)	1.36 (1.08, 1.72)	1.29 (0.84, 1.98)
Planned CS	1.27 (1.02, 1.58)	1.17 (0.87, 1.58)	1.17 (0.90, 1.53)	1.25 (0.82, 1.92)
Emergency CS	1.16 (0.94, 1.42)	1.07 (0.79, 1.43)	**1.27 (1.02, 1.57) [c]**	**1.52 (1.03, 2.24) [c]**
Age 7 years				
VD	1.00	1.00	1.00	1.00
Assisted VD	1.32 (1.03, 1.69)	1.37 (0.95, 1.97)	1.18 (0.97, 1.45)	0.85 (0.58, 1.26)
Planned CS	1.08 (0.82, 1.41)	1.19 (0.81, 1.73)	1.13 (0.88, 1.47)	0.94 (0.65, 1.36)
Emergency CS	**1.34 (1.06, 1.68) [c]**	**1.47 (1.05, 2.07) [c]**	**1.24 (1.00, 1.52) [c]**	1.13 (0.80, 1.61)
Age 11 years				
VD	1.00	1.00	1.00	1.00
Assisted VD	1.07 (0.83, 1.37)	1.33 (0.93, 1.90)	1.15 (0.94, 1.41)	1.27 (0.90, 1.78)
Planned CS	1.13 (0.87, 1.48)	1.01 (0.67, 1.51)	0.98 (0.78, 1.24)	1.23 (0.88, 1.71)
Emergency CS	1.11 (0.89, 1.39)	0.99 (0.68, 1.42)	**1.29 (1.07, 1.56) [c]**	1.09 (0.79, 1.51)

a Sample size for unadjusted model
b Results are adjusted for household socioeconomic class, marital status, maternal age, maternal education level, parental asthma, firstborn, mother's smoking during pregnancy, child's sex, ethnicity, birthweight and gestational age category (<32, 32-33, 34-36, 37-38, 39-40, 41, 42 weeks)
c Statistically significant (P<0.05) associations not observed in the main inclusion group are marked in bold

3.4 Discussion

3.4.1 Summary of results

The study described in this chapter examined whether mode of birth is associated with wheezing and asthma throughout childhood in singleton children born at term that were healthy at the time of birth. The findings suggest that mode of birth is not strongly associated with transient or late-onset wheezing phenotypes, however there is some evidence to suggest that it is associated with persistent wheezing. In particular, there is evidence that planned caesarean is a risk factor for this phenotype and further evidence regarding emergency caesarean, especially if preterm and unwell neonates are included. No consistent trend of elevated risk for a particular mode of birth emerged for the secondary asthma-related outcomes studied at specific ages from infancy to age 11.

The findings show that children born by planned caesarean have a marginally significant 34% increase in risk of persistent wheezing following adjustment for explanatory variables. When gestational age is not adjusted for, this excess risk increases to 43%. A sensitivity analysis using an alternative definition for wheezing phenotypes confirmed this finding, however it was of a smaller magnitude (28%) and not statistically significant. An additional sensitivity analysis using validated mode of birth data supports the main findings, but with a smaller magnitude of effect (18%) and is also not statistically significant. The age-specific investigation of mode of birth with secondary asthma-related outcomes show a 30% statistically significant increased adjusted odds for recent wheezing in the planned caesarean group of children, but only at age 5. Planned caesarean was not found to be a risk factor for other age-specific outcomes in this study.

Emergency caesarean is associated with a 21% increased risk of transient and persistent wheezing, however not statistically significantly. Age-specific investigations did not reveal a consistent increased risk in asthma-related outcomes among children born at term by emergency caesarean. However, in the extended study group,

emergency caesarean consistently emerged as a risk factor for persistent wheezing (aRRR=1.55) and all other secondary asthma-related outcomes investigated (for example, 22-29% consistently increased risk for 'ever asthma').

Assisted vaginal delivery was not found to be a strong risk factor for any of the wheezing phenotypes studied, except for a 27% increased risk for persistent wheezing, not statistically significant. This mode of birth was found associated with some of the secondary asthma-related outcomes, especially severe wheezing and 'ever asthma', however not statistically significantly.

In summary, these findings suggest a possible association between any medically interventional birth on a particular wheezing phenotype (persistent). There is evidence especially on the association of planned caesarean with persistent wheezing, and the evidence is stronger when the earlier gestational age at birth for these children is unadjusted for. The evidence regarding emergency caesarean section is not as strong, except when preterm or unwell children are included.

3.4.2 Risk of asthma-related outcomes by mode of birth - comparison with other studies

3.4.2.1 Prevalence of asthma-related outcomes

One of the main challenges in researching asthma, is the absence of a consensus definition for the disease. A study by van Wonderen et al [173] found that 122 publications examining asthma in children aged 6-18 years used 60 different definitions for the condition. The researchers also found that different definitions result in a very wide range for the estimation of prevalence in children at risk of asthma - from 15% to 51%. For this reason, it is only useful to compare the outcome prevalence found in the current study to prior ones that have used the same outcome definition.

The prevalence of recent wheezing and 'ever asthma' identified in the MCS age 7 survey is validated internally by comparing with a study by Carson et al [169] carried out in the MCS. The study reported a prevalence of 11.9% for recent wheezing compared with 11.2%[33] in the current one and 16.5% for 'ever asthma' compared with 15.2% in my study. Furthermore, the prevalence found here can be compared to a prevalence previously reported in the UK in same-age children using the ISAAC questionnaire. This survey found higher rates of recent wheezing (18-19.5%) and asthma (22-24%) [174] than found here. The different rates might be due to methodological limitations of the prior study since the response rate was only 56%. It might also be due to real temporal changes in the prevalence of asthma during that time frame [175] since the published study took place several years prior to the MCS.

The proportion of children who experienced severe wheezing at age 7 (4.7%) is comparable to 5.3% reported recently in a study that used the complete MCS cohort [176]. The proportion of children with severe wheezing out of those that had any recent wheezing at age 7 years (41.5%) is roughly similar to the proportion reported in a previous study utilizing the same definitions in UK children of the same age (50.4%) [168].

The proportion of children using asthma medication (4-5%) is internally validated with the study by Carson et al [169]. This proportion, found in both studies, is lower than 10% reported in a study conducted in Welsh children 5-10 years of age [128]. However, the MCS defines asthma medication use stringently (daily for at least two weeks) and does not cover shorter duration or occasional use of asthma inhalers. The difference is probably also explained by an actual higher prevalence of asthma in Welsh children compared to the rest of the UK at the time of the MCS [79,177].

[33] The corresponding rates in an unselected study group in the MCS (including preterm and NICU admissions etc.) were only slightly higher

3.4.2.2 Association between mode of birth and asthma

As described in Chapter 1, previous studies found that caesarean section is a risk factor for childhood asthma. Meta-analyses have aggregated both types of caesarean section and consistently concluded that there is a 20% increase in risk in children born by caesarean compared to vaginal delivery. A thesis [118] that examined numerous asthma indicators in cross-sections of the MCS in relation to the child's mode of birth (see Table 1-6) found caesarean section to be a risk factor for some of these outcomes. Nevertheless, my findings using age-specific investigations of selected asthma-related outcomes did not identify planned or emergency caesarean as a consistent risk factor from infancy to age 11 (Table 3-7 to Table 3-10). Of note, is that as well as the mentioned thesis, many of the studies included in the meta-analyses and some of those published later, have included children born preterm and those requiring intensive medical care. No sub-group analysis of only term births is available in these meta-analyses, though. I therefore carried out an extended group analysis including singletons[34] of all gestations and those requiring special intensive care in order to enhance comparability with prior studies. The results of these analyses highlighted emergency caesarean as a risk-factor for asthma-related outcomes at ages 3, 5, 7, and 11, for example a 24-29% increase in risk of 'ever asthma' at ages 5-11. These findings are consistent with the meta-analysis of Huang et al [93] that examined emergency caesarean section separately.

Being born preterm, especially very preterm, is a known risk factor for neonatal respiratory morbidity and for later development of asthma [125]. When a baby is born preterm, this may be due to spontaneous premature labour or because of a serious health risk. The mode of birth would likely be either vaginal delivery or an emergency caesarean section. Indeed, the mode of birth of the children added to the sample in the

[34] The mode of birth per child born in a multiple birth cannot be determined in the MCS when more than a single mode of birth is reported. For this reason, multiples were still excluded from the extended-group analyses.

extended group analysis was dominated much more by emergency caesarean compared to the main inclusion group (data not shown). Furthermore, caesareans carried out prior to 37 weeks are plausibly of higher urgency than those carried out during term gestation (see section 1.2.5). It is thus reasonable to assume that prematurity modifies the effect of emergency caesarean on asthma, and therefore merely adjusting for gestational age in a sample including premature born children would not be sufficient. These premature children and their higher chance of urgent emergency caesarean and subsequent asthma may partially explain the results of some prior studies and meta-analyses that have included these births.

3.4.3 Risk of wheezing phenotypes by mode of birth – comparison with other studies

3.4.3.1 Prevalence of wheezing phenotypes

The wheezing phenotypes selected for this study were based on clinical phenotypes and informed by the trajectories identified in other studies using LLCA. The four wheezing phenotypes selected to be examined in the current study were those identified in all known studies using this method. Despite being consistently detected in different cohorts, there is much heterogeneity in the particular characteristics of these phenotypes between the various studies that had identified them. This heterogeneity may not be entirely due to different population characteristics, but is plausibly at least partially due to differences in methodology, and thus compromises the comparability between studies.

An internal validation of wheezing phenotypes can be made through comparison with a recently published study by Kotecha et al [72] that conducted a latent class analysis using MCS data from ages 3, 5, 7 and 11. The researchers identified four wheezing phenotypes with comparable trajectories to those defined here. Furthermore, the

proportions per each phenotype within a sub-group of term-born children[35] were roughly comparable to the proportions identified in the current study using the alternative definition of phenotypes. Early wheeze was found in 13.0% of the sub-group compared with 18.8% in my study, persistent wheeze in 9.2% compared with 10.8% in mine and late-onset wheeze in 3.1% compared with 6.0% in the current study. The Kotecha et al study therefore corroborates the validity of the phenotypes reported in this thesis, especially the alternative definition.

3.4.3.2 Association between mode of birth and wheezing phenotypes

A study by van Berkel et al [97] used the Generation R cohort in The Netherlands to examine the association of mode of birth with wheezing phenotypes and other asthma-related outcomes. The researchers investigated the effect of mode of birth on early, persistent and late-onset wheezing using the ISAAC 'recent wheezing' definition. The authors did not state the proportions of each of the wheezing phenotypes in the studied population, thus a comparison of the prevalence of each phenotype between the MCS and Generation R cannot be made. Since the Dutch study included preterm births, the findings are best compared with my extended-group analysis (Table 3-13).

Early wheezing was defined by van Berkel et al as wheezing in the first three years of life, but no wheezing between age 3 to 6. The researchers did not identify instrumental vaginal delivery as a risk factor for early wheezing compared to vaginal delivery (OR=0.97; 95% CI 0.76, 1.24)[36], which is consistent with the findings from my study for assisted vaginal delivery and transient wheezing. However, they found an increased risk of 43% in elective caesarean (OR=1.43; 95% CI 0.99, 2.05), whereas my results were of only a non-significant 10% increase in risk. Similarly, for emergency caesarean, van

[35] Note that the sample of the Kotecha study is different from mine since it included families that did not respond to all five surveys

[36] The authors referred to the relative risk ratios derived from multinomial logistic regression as OR

Berkel et al reported OR=1.31 (95% CI 0.95, 1.80), whereas no strong adjusted effect was found in my analysis.

Persistent wheezing was defined in the Generation R study as wheezing both before age 3 and between age 3 to 6. Again, the researchers found no difference in the odds for instrumental vaginal delivery (OR=0.99) which contrasts somewhat with the increased risk observed in my study (aRRR=1.28; 95% CI 0.99, 1.66). The Dutch study further found an increased risk of OR=1.56 in elective and emergency caesarean, which are consistent with my extended-group analysis (aRRR=1.32 for planned and aRRR=1.55 for emergency). However, the effect of emergency caesarean in the main inclusion group of healthy term-born children in my study was smaller (aRRR=1.21).

The definition for late-onset wheezing in the Generation R study was recent wheezing reported after age 3 but before age 6. Consistent with my results, the Generation R researchers also did not find a strong association between mode of birth and late-onset wheezing (instrumental OR=0.87; 95% CI 0.51, 1.48), (elective caesarean OR=0.81; 95% CI 0.31, 2.11), (emergency caesarean OR=1.08; 95% CI 0.55, 2.09). However, the Dutch study had only few children with this wheezing phenotype. With larger numbers of affected children, my study had greater power and confirmed the absence of strong association between mode of birth and late-onset wheezing.

Several additional studies have explored the association of mode of birth with wheezing phenotypes as one of various possible risk factors, but have used only a binary categorization of vaginal versus caesarean birth as a covariate included in multivariable models. Most of these studies did not identify caesarean as a risk factor for a particular wheezing phenotype. A study investigating environmental risk factors for six wheezing phenotypes identified in the ALSPAC cohort [114] found no association between caesarean section and any wheezing phenotype. Another study conducted on the PIAMA cohort in The Netherlands [115] examining various perinatal risk factors for

asthma found no association between caesarean section and five wheezing phenotypes, although the sample size was very small. Interestingly, an additional study [178] using the same group of children, but that was focused on a different outcome ('chronic asthma' defined as active asthma at both age 3-7 and at age 8) found caesarean to be a strong risk factor (aHR=1.77, P<0.001).

In the MCS, the recent study by Kotecha et al [72] mentioned previously examined the independent effect of caesarean section (any type) compared to vaginal delivery as one of several possible early life risk factors. Their results were consistent with mine. In term-born children, caesarean delivery was not found to be a risk factor for transient and late-onset wheezing, however there was a statistically significant 20% increased risk for persistent wheezing. The similarity in pattern of results between this study and mine, despite the different methodology for defining wheezing phenotypes, enhances confidence in the current study's findings.

3.4.4 Strengths and limitations of the study

This study is one of the first to examine the association of mode of birth with a full range of commonly identified wheezing phenotypes. Furthermore, it is the first to examine asthma-related outcomes both through a longitudinal perspective and through an age-specific perspective for various outcomes at multiple time points. Due to the complex natural history of asthma, such an approach that gives a thorough, extensive view of results, may be more appropriate compared to an approach examining the outcome only up to a single time-point.

An additional study strength is the lengthy follow-up period from infancy to early adolescence, which enables to better capture children experiencing the various phenotypes of wheezing. The only study I am aware of that has previously focused on mode of birth and a range of wheezing phenotypes (the Generation R cohort) [97] was limited by a short follow-up period (up to age 6 years) and small sample size (n=6,128).

A further strength of my study was the use of a validated, widely used instrument for measuring wheezing – the ISAAC questionnaire. Although the MCS did not include the final two questions of the core questionnaire concerning asthma[37], it included all the commonly used questions of the instrument. ISAAC was primarily developed to be a standardized cross-national tool for measuring the prevalence of asthma and other atopic conditions [164]. It thus allows better uniformity of the current study with prior studies, in contrast to outcomes such as asthma diagnosis, for which guidelines and practices vary considerably.

The focus of my study on wheezing phenotypes may help elucidate associations between mode of birth and asthma-related outcomes that cannot be otherwise properly described. This perspective highlighted a possible association of planned caesarean with persistent wheezing, which could not be detected in age-specific analyses based on the same question ('recent wheezing'). A study by Griffiths et al [177] from 2018 made use of data from MCS participants that has been linked to GP records to describe the relationship between ISAAC recent wheezing, and a diagnosis or a prescription indicating asthma. The study found that at ages 7 and 11 there was at least 91% agreement between parental report of recent wheeze and doctor diagnosis of asthma. However, agreement at age 3 was lower with more upper respiratory tract infections recorded instead of asthma. Therefore, a phenotypic perspective of recent wheezing, as carried out in the present study, enables a better account of the relevant clinical presentation.

An additional strength of the current study is the ability to account for attrition over time using inverse probability weighting. There was high concordance for all maternal and child characteristics between the study inclusion group in the first survey and those participating in all five surveys up to age 11 (section 3.3.2). This provides evidence that

[37] Question regarding wheeze during exercise and dry cough at night

the attrition that naturally occurs in longitudinal studies was appropriately accounted for by the non-response weights and did not introduce unaccounted for selection bias.

A further strength of the current study is the use of a second, alternative definition for the phenotypes of wheezing through sensitivity analyses. There is currently no gold standard cut-off point to differentiate between the various wheezing phenotypes. Thus, examining the research question using more than one possible definition enhances the study's validity.

As noted previously, the inclusion solely of healthy term neonates in the main analyses helps account for the potential major confounding effect of prematurity and is a study strength. At the same time, an 'extended-group' analysis that includes children born preterm enables comparison of this study with previous studies and meta-analyses and to explore premature births as a reason for discrepant findings.

The main limitations of the study arise from the heterogeneity of asthma and the difficulty to measure clear-cut outcomes for this condition. Due to the lack of gold standard for defining and diagnosing asthma, there was a need to analyse an array of outcomes at different time points and investigate any consistency across outcomes and throughout time. Furthermore, some of the questions used for these age-specific analyses are not well defined or validated. For example, the question regarding 'ever asthma' does not specifically imply a doctor diagnosis of asthma.

A further limitation of the study is likely misclassification of wheezing phenotypes. This was evident in the reference wheezing phenotype of children classified as non-wheezers that were nevertheless reported to have 'ever wheezed' at some point during follow-up. However, it is plausibly more likely for the errors to be in the 'ever wheezing' answers compared with the 'recent wheezing' answers. Further, the study by Kotecha et al [72] mentioned previously used a data-driven technique and identified similar trajectories of

wheezing in the MCS as those defined here, which therefore increases the confidence in the current definitions.

Although breastfeeding is potentially an important explanatory variable that has been shown to have a dose-response protective effect for transient wheezing [179], I had not adjusted for it or any other postnatal variable. All the same, the investigation described in Chapter 2 revealed that mode of birth is not strongly associated with breastfeeding duration in this population, and therefore adjustment would not be expected to have a strong effect.

Absence of objective tests of pulmonary function and asthma are an additional limitation of the study. These might have included airway inflammation measures, such as fractional exhaled nitric oxide, or lung function tests such as spirometry. Nevertheless, the ISAAC questionnaire has been previously validated against objective tests of lung function and found to be a valid tool for measuring the prevalence of asthma symptoms [180,181].

Lastly, my study was not able to incorporate measures of atopy. Atopic status is considered one of the means to clinically distinguish between asthma phenotypes [62]. Objective levels of atopy such as allergic sensitization measured through serum immunoglobulin E levels were not available for MCS children. Alternatively, report of rhinitis or eczema could have potentially been used as a proxy for atopic status. However, these were not incorporated in the current study since the ISAAC core questionnaire for measuring eczema and rhinitis was not included in the MCS, but instead a single, non-validated question about each condition was asked.

3.4.5 Conclusions

The current study presents some evidence to support the hypothesis that there is an association between mode of birth and the child's wheezing phenotypes from infancy to early adolescence. There is some evidence to suggest that children born by planned

caesarean have an elevated risk of persistent wheezing, but there is not enough evidence to support an increased risk of transient or late-onset wheezing. However, when the effect of gestational age is added to that of delivery by planned caesarean, there is stronger evidence of an increased risk of persistent wheezing. There is little evidence to suggest that emergency caesarean is implicated as a risk factor for wheezing phenotypes in children born at term, however it poses an increased risk in a population that includes those born preterm or unwell at the time of birth. There is no apparent consistent strong association between any mode of birth and the other age-specific asthma-related outcomes including severe wheezing, ‘ever asthma’ and asthma medication use.

Chapter 4: An investigation of the association between mode of birth and infant infectious disease in Wales

4.1 Introduction

Previous studies have highlighted caesarean sections as a risk factor for LRTI and gastroenteritis during infancy, whereas their possible effect on URTI has not been extensively researched. My study using the MCS (described in Chapter 2) corroborated the association of mode of birth with infectious diseases. However, since the MCS is limited by size and by the unavailability of reliable data on URTI, an additional investigation of these outcomes was carried out using linked administrative datasets of the population of Wales.

4.1.1 Study aims

The aim of this study was to investigate the relationship between mode of birth and the risk of severe infectious diseases during infancy. The infectious diseases investigated were gastroenteritis, lower respiratory tract infection and upper respiratory tract infection.

The research questions investigated were:

1. Is mode of birth associated with hospital admission for gastroenteritis during infancy?
2. Is mode of birth associated with hospital admission for lower respiratory tract infection during infancy?

3. Is mode of birth associated with hospital admission for upper respiratory tract infection during infancy?
4. Does earlier gestational age indirectly add to any effect of planned caesarean on infectious disease during infancy?

4.2 Methods

The data used in this study was derived from the Welsh Secure Anonymized Information Linkage Databank (SAIL).

4.2.1 SAIL – Secure Anonymized Information Linkage Databank

SAIL is a resource for storing anonymized linkable data for use as a research platform for Wales [182]. It was established by the Health Informatics Group in 2007 and is based at Swansea University Medical School [183]. The SAIL Databank hosts a range of datasets including several health and administrative datasets of the Welsh population. Person-level data undergoes anonymization and encryption by designating a unique person identification code - 'Anonymous Linking Field – Encrypted (ALF)'. ALF codes are generated based on the individual's NHS number, when available. These undergo a digit check to ensure they are a valid NHS number. When unavailable, NHS number is derived from other datasets by means of linkage on five personal identifiers - first name, surname, gender, date of birth, postcode [184]. The ALF code is consistent throughout SAIL datasets and thus enables linkage of person-level data. The integrity of this code is key for accurate matching and for the validity of any research carried out using the SAIL databank. Lyons et al [184] demonstrated that an accuracy of >95% is regularly attained, and >99% attained for the patient admission datasets used here.

The datasets included in the current study were provided to the SAIL databank by NHS Wales' Informatics Service (NWIS) and are described below.

4.2.1.1 National Community Child Health Database (NCCHD)

The National Community Child Health Database (NCCHD) is the all Wales child health surveillance dataset and includes records for all children born, resident or treated in Wales [185]. The dataset is used to track administration of child immunisation and other health programmes [186]. In addition to the ALF code, 95% of the records in the timeframe concerned include also a maternal ALF code (mat_ALF). These are derived by one of the following means:

- Using mother's valid NHS number
- Through linkage on five mother's personal identifiers
- Through linkage to external datasets using information about females of reproductive age cohabiting with the child[38]

Week of birth dates covered in the current study range from 07/01/2002 to the latest available – 11/07/2016.

4.2.1.2 Patient Episode Dataset for Wales (PEDW)

The Patient Episode Dataset for Wales (PEDW) is an analogous dataset to the English HES dataset. It includes all admitted patient episodes in NHS Wales as well as admissions of Welsh residents in English Trusts. The dataset contains information about hospital spells - a continuous period of time an admitted patient spends in the care of one NHS local health board provider. Each spell is composed of one or more consultant episodes. Episodes include ICD-10 diagnostic codes: a single primary diagnostic code (the diagnosis primarily driving the cost for the admission) and up to 19 secondary diagnostic codes. Each episode may also include up to 20 operation codes (coded using OPCS-4). The admission dates of PEDW entries covered in the current study range from 01/01/2002 to 28/02/2017.

[38] Unpublished, through email correspondence with SAIL Analyst Arfon Rees dating 22/11/2018

4.2.1.3 Welsh Demographic Service (WDS)

The Welsh Demographic Service (WDS) dataset consists of demographic information about individuals registered with a General Practice (GP) in Wales, including name, address, date of birth and NHS number [187]. Tracing of records from English GPs is also possible. The WDS dataset within SAIL includes a Residential Anonymous Linking Field based on address.

4.2.1.4 Congenital Anomaly Register & Information Service for Wales (CARIS)

The Congenital Anomaly Register and Information Service for Wales (CARIS) is a population-based registry that holds records of fetuses and babies of mothers normally resident in Wales that have a suspected or confirmed congenital anomaly [188].

4.2.1.5 Annual District Death Extract (ADDE)

The Annual District Death Extract (ADDE) is the Office of National Statistics death registry data relating to Welsh residents [189].

4.2.2 Study population

The study population was all births to mothers who were resident in Wales between January 2002 and July 2016 ascertained from the NCCHD. The data to be extracted for this study from each dataset was defined by myself (in consultation with the SAIL team) and extracted by a SAIL Analyst. Note that the first extract of the NCCHD included children of non-residents, however these were later excluded. See Figure 4-1 on page 169 for details.

4.2.3 Data extraction

All children recorded in the NCCHD born between 07/01/2002 and 11/07/2016 that include both an ALF code and mat_ALF code were selected. This dataset was the source of most of the variables used for the inclusion criteria and adjustments. Additional

information about the children included in the study population was derived from other datasets using the ALF code (or mat_ALF in the case of hospital birth spell).

The PEDW dataset was used to derive information about mode of birth, maternal age and diagnostic codes for the birth episode. All spells containing the previously identified mat_ALF codes with admission date spanning 60 days prior and 30 days after the child's week of birth as appears in the NCCHD were selected. A further prerequisite was that the selected spells include an episode with an operational code R17-R25 or a diagnostic code O80-O84, both indicating a childbirth delivery episode (Table 4-2).

The WDS dataset was used to derive socioeconomic data as quintiles of the 'Welsh Index of Multiple Deprivation' (WIMD) - a measurement of deprivation on a small area scale [190]. This measurement is derived from the first recorded 'Residential Anonymous Linking Field' in the WDS. The 2001 Lower Super Output Areas were used with the corresponding 2011 WIMD to categorize the residential linking fields. Information about date of emigration from Wales was derived for the purpose of censoring. The date of the last recorded Welsh address was used, although gaps of up to 90 days in recorded address were allowed and these individuals were not flagged for censoring.

The ADDE dataset was utilized to derive information about date and cause of death for children in the study population by searching for the relevant ALF codes.

The CARIS register was utilized to derive information about neonates included in the study population that had a major congenital malformation or a chromosomal abnormality, as defined per clinician advice (appendix II).

The PEDW dataset was further used to derive information about the various outcomes of interest, including type and date of admission and diagnostic and operational codes. Any hospital spell with the ALF code of a child included in the study population and with at least one of the ICD codes listed in Table 4-1 was extracted.

Table 4-1: Infectious diseases and corresponding ICD codes in child PEDW admissions

Study outcome	ICD code	Annotation
Gastroenteritis	A08	Viral and other specified intestinal infections
Gastroenteritis	A09	Diarrhoea and gastroenteritis of presumed infectious origin
Gastroenteritis	K52	Other noninfective gastroenteritis and colitis
LRTI	A37	Whooping cough
LRTI	J10	Influenza due to identified influenza virus
LRTI	J11	Influenza, virus not identified
LRTI	J12	Viral pneumonia, not elsewhere classified
LRTI	J13	Pneumonia due to Streptococcus pneumoniae
LRTI	J14	Pneumonia due to Haemophilus influenzae
LRTI	J15	Bacterial pneumonia, not elsewhere classified
LRTI	J16	Pneumonia due to other infectious organisms, not elsewhere classified
LRTI	J17	Pneumonia in diseases classified elsewhere
LRTI	J18	Pneumonia, organism unspecified
LRTI	J20	Acute bronchitis
LRTI	J21	Acute bronchiolitis
LRTI	J22	Unspecified acute lower respiratory infection
URTI	J00	Acute nasopharyngitis [common cold]
URTI	J01	Acute sinusitis
URTI	J02	Acute pharyngitis
URTI	J03	Acute tonsillitis
URTI	J04	Acute laryngitis and tracheitis
URTI	J05	Acute obstructive laryngitis [croup] and epiglottitis
URTI	J06	Acute upper respiratory infections of multiple/unspecified sites

4.2.4 Dataset merging

I merged the data extracted from the SAIL dataset as follows: first, each data file was cleaned separately (see appendix II for details) and next the NCCHD, WDS, and PEDW birth spell were merged on ALF code as illustrated in Figure 4-1.

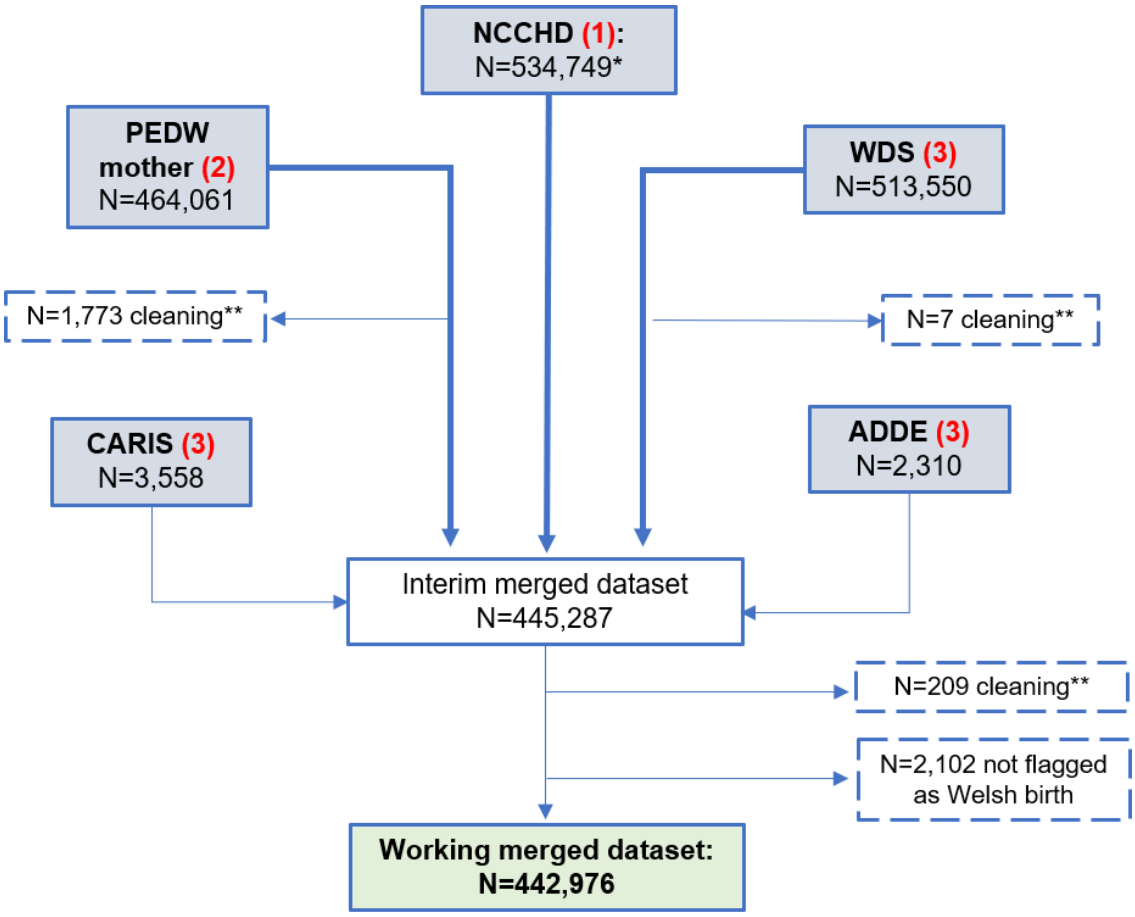
Out of the defined study population from the NCCHD, 96% (n=513,543) were matched to a WDS record; 86.5% (n=462,288) were matched to a PEDW delivery record and 83.3% (n=445,287) were matched on all three datasets (marked 'interim merged dataset'). The proportion matched amongst those flagged as a Welsh birth (i.e., child of

a Welsh resident) was higher - 90.3%. Around 30% of the unlinked records (~3% of original population) were homebirths that have no PEDW delivery admission. A further 5% of unlinked records were of stillborn babies. As anticipated, the unlinked observations had a higher proportion of vaginal deliveries than in the linked data, and most of this difference was explained by homebirths. The unlinked were similar to the linked observations in terms of child's sex, ethnicity and maternal smoking, but were slightly more likely to be of older, multiparous mothers. See appendix IV for a detailed comparison of the characteristics of linked and unlinked observations.

For babies, 77% of matches were achieved using a valid NHS number and 23% through personal identifiers. For mothers, 81% of matches were achieved through valid NHS number, 1% through personal identifiers and 18% through information derived from other SAIL datasets about females of reproductive age living at the same address as the child. Regarding the latter, note that all individuals included in the study sample were also linked to a PEDW delivery record, and therefore the female cohabitee identified is reliably the child's mother.

Children appearing in ADDE and CARIS datasets were merged for the purpose of censoring and exclusion. Further cleaning was carried out (see appendix III) and individuals not flagged as a Welsh birth in the NCCHD (not children of Welsh residents) were removed.

Figure 4-1: Data flowchart of merging SAIL datasets



(1) Cohort created from all children born week 07/01/2002 - 11/07/2016 with mat_ALF code
(2) Delivery spell identified by mat_ALF & admission date spanning week of birth & OPCS or ICD code indicating an admission for birth
(3) Entry identified by ALF
* Number flagged as Welsh birth (of a Welsh resident) in NCCHD = 490,826
** Data errors and duplicates (see appendix III)

NCCHD:	National Community Child Health Dataset
PEDW:	Patient Episode Dataset for Wales
WDS:	Welsh Demographic Service
CARIS:	Congenital Anomaly Register of Wales
ADDE:	Annual Death Dataset of Wales

4.2.5 Study inclusion criteria

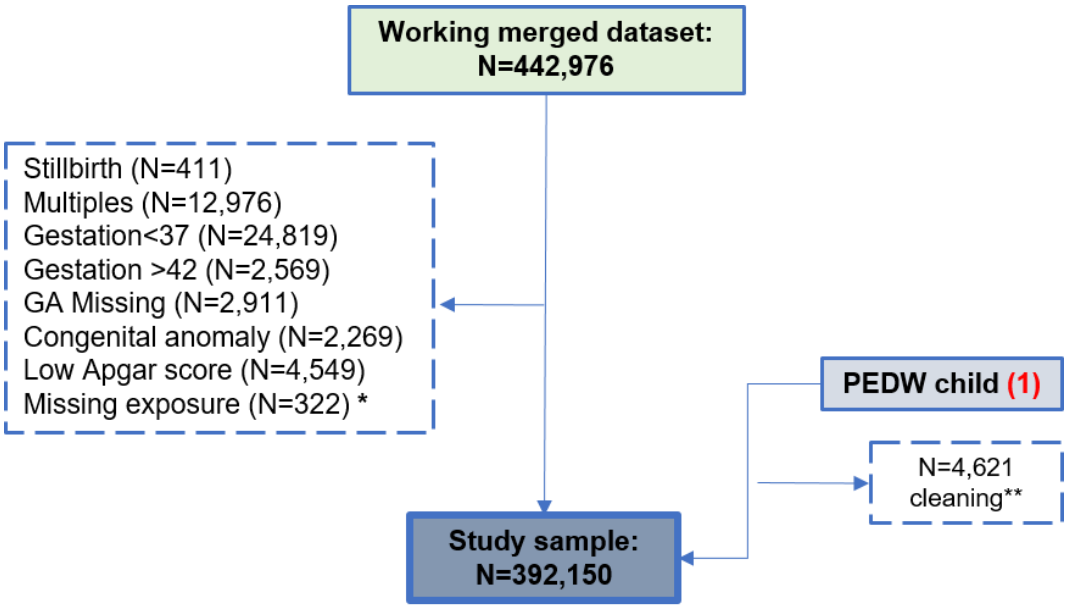
The inclusion criteria for the current study were consistent with the MCS studies (sections 2.2.2 and 3.2.2). The criteria were: singleton babies born alive at term in a Welsh hospital who did not have a major congenital anomaly, chromosomal abnormality or a low Apgar score (0-2 at 1 minutes or 0-6 at 5 minutes)[39]. The following babies were excluded from the study (percentage out of linked cohort[40] are shown in parenthesis) – see Figure 4-2.

- Stillborn babies (0.09%)
- Multiple births (2.96%)
- Preterm (7.16%), born beyond 42 weeks gestation (0.58%) or missing gestational age (0.68%)
- Severe congenital anomaly or genetic abnormality[41] (0.66%).
- Neonates with low Apgar score (1.37%) (Note that individuals missing information about both 1 and 5-minute Apgar scores - 9.8% of linked cohort - were not excluded).
- Missing exposure data (0.08%).

The number of babies eligible for the study that met the inclusion criteria was 392,150 (89% of the 'interim merged dataset').

[39] In addition to those not flagged as Welsh birth
[40] Percentages are calculated from the overall linked cohort sample ('working merged dataset') of 442,976 participants
[41] These were mainly ventricular septal defect of the heart

Figure 4-2: Infants included in SAIL infectious diseases study sample



(1) Child's admission spell identified by ALF and one of the ICD codes listed in Table 4-1
* Numbers are in sequential order of exclusion
** Data errors and merging of spells of the same admission (continuous inpatient spells)

4.2.6 Exposure – mode of birth

Mode of birth was ascertained from OPCS codes R17-R25 in maternal PEDW records of the child's delivery spell (Table 4-2). Note that these are the same codes used for MCS validation (Table 2-1). In the uncommon case of more than a single operation code for the delivery, the method of higher medical intervention was used (see section 2.2.3). When a spell did not include one of the operational codes for mode of birth, diagnostic codes were examined. However, the latter were available for only 13% of the dataset, hence their contribution to exposure data completeness was minor (336 PEDW spells) and these observations were marked as missing for mode of birth.

Consistent with the MCS analyses, mode of birth was classified into four categories:

- Vaginal delivery (VD)
- Assisted vaginal delivery (Assisted VD)
- Planned caesarean section (Planned CS)
- Emergency caesarean section (Emergency CS)

Table 4-2: Mode of birth classification from PEDW delivery spells and the NCCHD

Mode of birth classification	PEDW delivery spells	NCCHD
	Operational codes	**Delivery method**
VD	R24 Normal delivery R23 Cephalic vaginal delivery with abnormal presentation of head at delivery without instrument	Spontaneous vertex Spontaneous other cephalic
Assisted VD	R19 Breech extraction delivery R20 Other breech delivery R21 Forceps cephalic delivery R22 Vacuum delivery	Low forceps, not breech Other forceps, not breech Ventouse Breech Breech extraction
Planned CS	R17 Elective caesarean delivery	Elective caesarean section
Emergency CS	R18 Other caesarean delivery	Emergency caesarean section
Missing	R25 Other method of delivery	Other
% of sample available for validation	100	59
% validated from available*	96	

* Agreement between a 4-category mode of birth variable from operational codes and a 4-category NCCHD delivery method variable (section 4.2.11)

4.2.7 Outcomes – hospital admission for infectious disease

Hospital admission for infection was ascertained from the child's PEDW admissions. Adjacent hospital spells (when an admission date is identical to the prior spell discharge date) were joined into a single continuous inpatient spell (see appendix III for details).

Outcomes were categorized into the following:

- Lower respiratory tract infection (LRTI)
- Upper respiratory tract infection (URTI)
- Gastroenteritis

A separate dataset was created for the first admission per each outcome and each of these datasets was merged with the study sample (each designated PEDW in Figure 4-2).

A hospital admission event was defined as an emergency admission (based on an admission method variable and detailed in appendix III) that includes at least one of the diagnostic codes detailed in Table 4-1 for that particular outcome. Diagnostic codes were chosen based on those used in prior research about perinatal risk factors for childhood infectious diseases [83–85,89,90,92,131,191]. Codes could appear at either the primary or one of the secondary positions of any episode of the continuous inpatient spell. Age at admission was calculated by subtracting infant's week of birth from date of first admission for a particular outcome. The maximum number of days allowed in order to be considered an infant admission was 365. Note that for infants admitted more than once, only the first event was counted.

4.2.8 Potential explanatory variables

The variables used in Table 4-3 had previously been found to be associated with the exposure or the outcome (as detailed in 2.2.5) and are plausible confounders or other explanatory variables. The association between mode of birth and infant infection was thus adjusted for them. Additionally, year of birth was added due to the long eligible inclusion period and season of birth was included because of seasonal changes in infection risk (especially respiratory infections) and varying risk by infant age [192]. Potential explanatory variables, their sub-categories and datasets from which they were derived are detailed in Table 4-3, in addition to a comparison with potential explanatory variables used in the MCS infection analyses (Chapter 2). See also appendix III for details about the coding of these variables.

Table 4-3: Potential explanatory variables included in the SAIL study and corresponding variables from the MCS

Potential explanatory variable	Grouping	SAIL dataset	Outcome analyses in which included	Included in MCS infectious disease study
Maternal characteristics				
Mother's age at birth	<18, 18-19, 20-24, 25-29, 30-34, 35-39, ≥40	NCCHD	All	Yes
WIMD quintile	1st (most deprived), 2nd, 3rd, 4th, 5th (least deprived)	WDS	All	Yes – highest level of occupation of mother or partner; maternal education
Nulliparous	Yes, No (coded from previous live and stillbirth of child and siblings and from ICD codes indicating a prior birth)	NCCHD + PEDW deliveries*	All	Firstborn
Mother's smoking status	non-smoker, gave up in pregnancy, smokes 1-9 a day, smokes ≥10 a day, missing	NCCHD	LRTI & URTI	Yes
Maternal asthma	Yes, No (ICD for asthma in any of a mother's birth episodes included in sample)	PEDW deliveries*	LRTI & URTI	asthma / hayfever / eczema
Maternal diabetes (gestational or pre-gestational)	Yes, No	PEDW deliveries*	All	Yes
Maternal hypertensive condition	Yes, No	PEDW deliveries*	All	Yes

(table continues on next page)

Potential explanatory variable	Grouping	SAIL dataset	Outcome analyses in which included	Included in MCS infectious disease study
Infant characteristics				
Sex	Male, Female	NCCHD	All	Yes
Ethnicity	White, mixed, Indian/Pakistani/Bangladeshi, Black, other, missing	NCCHD*	All	Yes – white / other
Gestational age in weeks (implausible observations cleaned as described in 2.2.5.2[42])	37, 38, 39, 40, 41, 42	NCCHD	All	Gestational age category
Birthweight in Kg (implausible observations cleaned as described in 2.2.5.2)		NCCHD	All	Yes
Breastfeeding	any (at birth or at 8 weeks), none, missing	NCCHD	All	Breastfeeding per-month of follow-up
Year of birth	2002-2016	NCCHD	All crude and adjusted	No
Season of birth	January-March, April-June, July-September, October-December	NCCHD	All	No

* coding detailed in appendix III

[42] Number of observations with implausible gestational age for birthweight that were turned into missing were 974 in the study sample of 392,150 (0.25%)

4.2.9 Statistical analyses

Stata version 14 was used for all analyses.

4.2.9.1 Univariable analyses

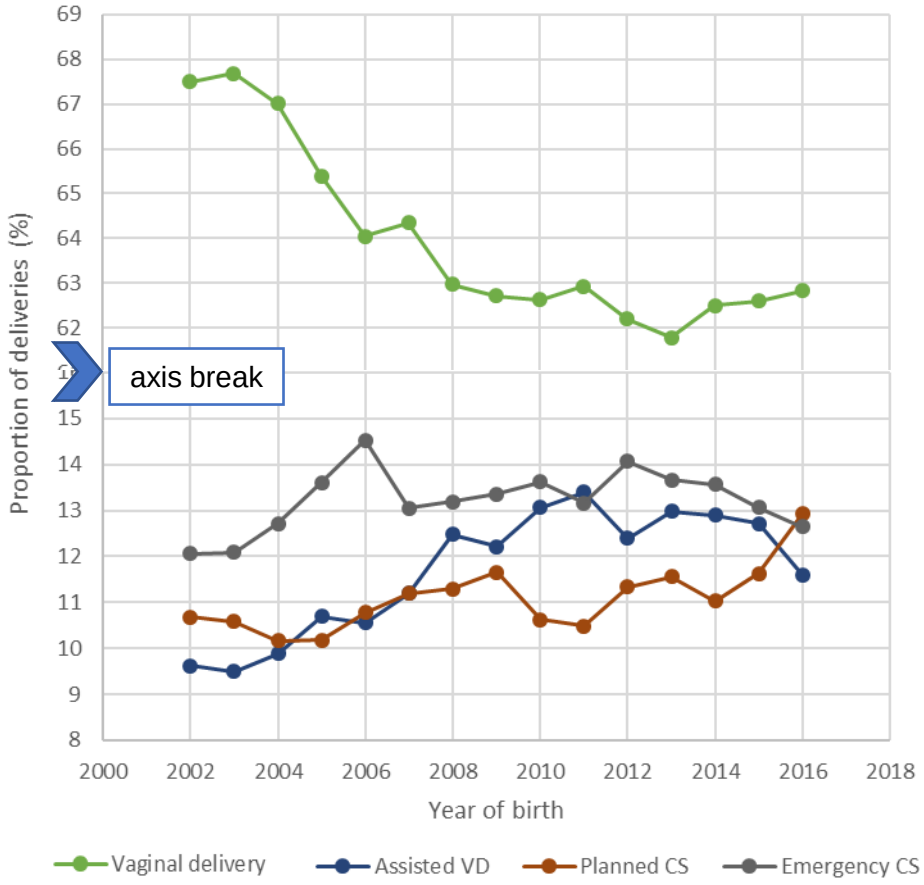
First, the association between mode of birth and each explanatory variable listed in section 4.2.8 was assessed using the Chi-square test for proportions or F-test for comparing means as detailed in 2.2.6.1. Next, the association between each explanatory variable and each outcome was assessed using a likelihood ratio test in univariable models using Cox regression analysis. A P-value of <0.10 was used as a cut-off for determining whether a variable would be included in the multivariable models.

4.2.9.2 Multivariable analyses

Cox regression was used to estimate the crude and adjusted hazard ratios as well as 95% confidence intervals for the first hospital admission for each outcome. The period of time eligible for inclusion in the cohort was 14 years and substantial shifts in rates of delivery methods occurred in that time – see Figure 4-3. Hence, crude analyses were also adjusted for year of birth, and the variable was also included in all multivariable analyses a priori. All analyses allowed for within-family clustering using mat_ALF since sixty percent of the cohort members had at least one sibling in the cohort.

Data was censored at date of death, time of emigration from Wales, or February 2017 when follow-up for hospital admission ended for infants who had not experienced the outcome of interest.

Figure 4-3: Time trends in distribution of mode of birth in the SAIL study sample, 2002 to 2016



4.2.9.3 Testing of the proportional hazards assumption

The proportional hazards assumption was examined using two methods. The first by using graphs of -ln(-ln(Survival) vs. ln(analysis time), referred to as log-log plots. The second involved splitting the follow-up time into two periods (0-6 months and 6-12 months), fitting separate models and evaluating whether the hazard ratios in the two periods are similar.

4.2.9.4 Analysis of potential mediation by gestational age

As detailed in section 2.2.6.4, final models were run a second time without adjustment for gestational age. Hazard ratios and 95% confidence intervals were estimated.

4.2.10 Missing data

Explanatory variables with <10% missing values were analysed using a complete case approach. Three of the study variables had higher levels of missing values, namely ethnicity (11.2%), breastfeeding (15.3%) and smoking (59.7%). Several approaches were employed to address the moderate to high level of missing values in these variables. In the main analyses, an additional sub-category of 'missing' was created for these three variables. Additional approaches were undertaken through sensitivity analyses described below.

4.2.10.1 Complete case analysis – sensitivity analysis

All multivariable models were repeated using complete case analysis for all variables, including ethnicity, breastfeeding and smoking.

4.2.10.2 Multiple imputation of smoking, breastfeeding and ethnicity – sensitivity analysis

The variables with >10% missing – smoking, breastfeeding and ethnicity – were imputed. I assumed the variables were missing at random dependent on the other variables used for my analyses, as well as hospital of birth and year of birth. I examined the smoking variable stratified by hospital and year of birth and found large variability in completeness levels, but roughly similar distribution amongst the sub-categories of smoking. This implied that the mechanism responsible for missing data is mainly due to hospitals or related health workers not collecting this information in certain years.

Chained imputations (80 sets) were carried out for each outcome's final model using the same variables as those found in the final adjusted model with the addition of the binary outcome variable [193]. Following imputation, the distribution of each imputed variable was compared to its original distribution in complete cases. For each of the three imputed variables, the distribution was found to be almost the same as the distribution prior to imputation.

4.2.11 Sensitivity analyses for exposure and outcome

4.2.11.1 Restriction to observations with validated mode of birth

Data about mode of child's delivery ascertained from PEDW operational codes was validated using the delivery code in the NCCHD (see Table 4-2 page 172). This variable was available for only 59% of the sample, out of which 96% were in agreement with the PEDW variable. Hence, the sensitivity analyses were conducted on a sub-group of 56% of the observations that had a validated mode of birth variable.

4.2.11.2 Gastroenteritis outcome including non-infective gastroenteritis

To address possible misdiagnosis or misclassification, an additional, broader definition of gastroenteritis was utilized which includes ICD code K52 "Other noninfective gastroenteritis and colitis". This code was included in a previous publication examining mode of birth and gastroenteritis [92]. The crude and adjusted models were repeated using this extended outcome definition.

4.2.12 Power calculation

The study's power to detect an association between exposure and outcomes was estimated by comparing two independent proportions using Chi-square test. The size of the reference group (vaginal delivery) in the study sample was 250,743 and the size of the exposed groups was 43,231 for planned and 52,090 for emergency caesarean.

The expected proportion of LRTI and gastroenteritis hospital admissions were extrapolated from the findings of the MCS analyses for the total UK population: 4.5% for LRTI and 1.9% for gastroenteritis. The proportion of infants admitted for URTI was expected to be the same as for LRTI (4.5%) on the basis of the findings of the study by Paranjothy et al [90] conducted on the same dataset.

The estimated relative risk of LRTI and gastroenteritis based on previous studies (as detailed in section 2.2.8) and on the findings from the MCS analyses (sections 2.3.4 and

2.3.5) ranged from 1.1 to 1.5. An estimate of the relative risk of URTI in babies born by each type of caesarean could not be found in the literature, and therefore the same relative risks as above were used to calculate the power for this outcome.

This study had high power to detect an association with LRTI and URTI, even for small effect size in the range of RR=1.1. For the gastroenteritis outcome the power to detect an RR=1.1 was adequate (73-79%) and for stronger effects it was high (Table 4-4).

Table 4-4: Power to detect associations in the SAIL infectious disease study analyses by estimated effect size

	Power (%)					
Estimated effect size	**LRTI** (4.5%)		**URTI** (4.5%)		**Gastroenteritis** (1.9%)	
	Planned CS	**Emergency CS**	**Planned CS**	**Emergency CS**	**Planned CS**	**Emergency CS**
1.1	**97 ***	**99**	**97**	**99**	73	79
1.2	100	100	100	100	**100**	**100**

* The smallest effect size for which a power of ≥80% is achieved is highlighted in bold

4.2.13 Data access and security

Data was stored within the SAIL servers at Swansea, accessed through SAIL's remote-access gateway and all analyses are carried out within the secure SAIL environment. Extensive measures are taken by SAIL to ensure that individuals' privacy and data security are maintained. Measures include anonymizing personal identifiers such as aggregation of date of birth into week of birth and recoding of address into area of residence [184]. SAIL's encrypted set of ALF codes are also produced uniquely per-project to prevent the ability to link between studies. Furthermore, access rights to the gateway are time-limited. Lastly, export of study results from the gateway requires an approval process that assures there is no disclosure risk (for example - no cells with ≤5 observations) and that analyses comply with the authorized study aims.

4.2.14 Ethics committee approval

I sought permission from the SAIL Information Governance Review Panel [182] to carry out this study. The use of ethnicity codes was given specific permission because of potentially sensitive use of this information. Furthermore, the use of CARIS data required special approval by the dataset owner as this is a restricted dataset in SAIL. A separate ethics committee approval was not required for this secondary analysis of anonymised data.

4.3 Results

4.3.1 Mode of birth – descriptive results

The distribution of mode of birth in the study sample is presented in the top row Table 4-5: assisted vaginal delivery occurred in 11.8% of births, planned caesarean in 11.0% and emergency caesarean in 13.3% while the remaining 63.9% of births were by vaginal delivery (unassisted). For the purpose of comparing with MCS results, the prevalence in 2002 was also calculated and compared to the equivalent distribution of Welsh births in the MCS. Results from the two studies were similar, differing by only 0.5-1.1%.

Table 4-5: Distribution of mode of birth in the SAIL study compared with MCS

Proportion	VD (%)	Assisted VD (%)	Planned CS (%)	Emergency CS (%)	Total (%) **
Total SAIL sample	63.9	11.8	11.0	13.3	100.0
SAIL sample 2002 only	67.6	9.6	10.7	12.1	100.0
MCS Welsh births only*	68.7	10.1	10.0	11.3	100.0

* Weighted using country-specific survey weights
** Percentages do not accumulate to 100% due to rounding error

The most common diagnostic codes per each mode of birth in PEDW delivery spells are presented in Table 4-6. As in the MCS analyses, births by emergency caesarean and assisted vaginal delivery had high proportion of codes for fetal distress and long labour.

Planned caesarean sections were carried out predominantly due to the presence of a uterine scar as well as fetal malpresentation.

The distribution of mode of birth in term singleton births in Wales changed substantially between the year 2002 and 2016 (Figure 4-3 page 177). Rates of vaginal delivery decreased and those of the medically interventional deliveries increased, although for emergency caesarean and assisted vaginal delivery the increasing trend shifted in more recent years. During this time, the proportion of births by planned caesarean ranged between 10.2% and 12.9%, those of emergency caesarean ranged between 12.1% and 14.5% and the proportion of assisted vaginal delivery ranged between 9.5% and 13.4%. The proportion of vaginal delivery varied during these years between 67.7% and 61.8%.

Table 4-6: Three most common diagnostic codes* per mode of birth and their proportion in the SAIL study

	VD (%)	**Assisted VD (%)**	**Planned CS (%)**	**Emergency CS (%)**
Most common diagnostic code	Labour and delivery complicated by fetal stress [distress] (O68) **9.6**	Labour and delivery complicated by fetal stress [distress] (O68) **52.1**	Maternal care due to uterine scar from previous surgery (O34.2) **52.9**	Labour and delivery complicated by fetal stress [distress] (O68) **44.7**
2nd most common diagnostic code	Prolonged pregnancy (O48) **8.5**	Long labour (including prolonged first stage and second stage) (O63) **44.0**	Maternal care for known or suspected malpresentation of fetus (including breech) (O32) **18.9**	Long labour (including prolonged first stage and second stage) (O63) **31.7**
3rd most common diagnostic code	Premature rupture of membranes (O42) **8.0**	Prolonged pregnancy (O48) **12.8**	Other maternal diseases complicating pregnancy, childbirth and puerperium (O99) **7.7**	Prolonged pregnancy (O48) **15.5**

* A delivery might not have an ICD code and could have more than a single code;
listed from codes beginning with 'O' not including O80-O84 for mode of delivery, O70 for perineal lacerations or O72 for postpartum haemorrhage

4.3.2 Study group characteristics

Study participants had a statistically significant difference in all examined characteristics by mode of birth (P-value<0.001) (Table 4-7).

Mothers who had given birth by caesarean section (both planned and emergency) tended to be older and living in a more affluent area compared to mothers who had a vaginal delivery. Mothers giving birth by planned caesarean were most often multiparous, while those giving birth by emergency caesarean were mostly nulliparous. Compared to the vaginal delivery group, mothers delivering by both types of caesarean tended to smoke less and were slightly more often recorded as having asthma and they also experienced more diabetes and hypertensive conditions (the latter only in emergency caesarean).

Mothers who had given birth by assisted vaginal delivery were of similar age to the vaginal delivery group, however they lived in more affluent areas and were much more often nulliparous. They smoked less frequently and had similar rates of recorded asthma. These mothers had similar rates of diabetes but were substantially more likely to have hypertensive conditions.

Infants born by planned caesarean had a similar distribution of sex and white ethnicity compared to those born vaginally. Planned caesarean sections were more likely to occur at early term but had similar rates of full term births and lower rates of late and post-term births. The birthweight of these infants was similar to that of vaginal delivery and the percentage of babies that were ever breastfed was similar to the reference group.

Infants born by emergency caesarean were more often male and of similar proportion of white ethnicity compared to those born vaginally. Emergency caesareans were less likely to occur at full term but more likely later, and the baby's birthweight was correspondingly higher than the reference group. Breastfeeding rates were slightly higher than following vaginal birth.

Infants born by assisted vaginal delivery were more likely to be male and slightly more likely to be of white ethnicity. They were more likely to be born at late term and post term but were not notably heavier than the vaginal delivery group. These babies also experienced higher breastfeeding rates compared to the infants born vaginally.

Table 4-7: Characteristics of cohort infants and their mothers included in the SAIL infectious diseases study by mode of birth

	VD %	Assisted VD %	Planned CS %	Emergency CS %	Total % [c]
Mode of birth n (%)	**250,743 (63.9)**	**46,086 (11.8)**	**43,231 (11.0)**	**52,090 (13.3)**	**392,150 (100.0)**
Maternal characteristics					
Maternal age group (years)					
<20	9.0	9.0	2.3	6.6	7.9
20-29	53.3	51.0	38.7	47.3	50.7
30-39	35.5	37.6	53.6	42.5	38.7
≥40	2.2	2.3	5.4	3.6	2.8
Area deprivation quintile (WIMD)					
1st (most deprived)	27.7	21.9	22.9	23.2	25.9
2nd	22.2	21.1	21.2	21.6	21.8
3rd	19.1	19.7	19.4	20.1	19.3
4th	16.3	18.3	17.2	18.3	16.9
5th (least deprived)	14.8	19.1	19.2	16.8	16.0
Nulliparous [a]	35.4	75.8	20.5	65.5	42.1
Maternal smoking [b]					
Non-smoker	30.0	31.4	33.3	33.6	31.0
Gave up in pregnancy	1.5	1.6	1.1	1.7	1.5
Smoker 0-9 a day	4.5	3.2	2.9	3.3	4.0
Smoker ≥10 a day	4.3	2.3	3.2	2.9	3.8
Missing	59.7	61.5	59.5	58.5	59.8
Maternal asthma	5.3	5.5	6.5	6.1	5.5
Diabetes	1.6	2.0	4.8	3.6	2.2
Hypertensive condition	4.4	8.3	4.1	10.4	5.6

(table continues on next page)

	VD %	Assisted VD %	Planned CS %	Emergency CS %	Total %
Infant characteristics					
Male	49.7	54.0	50.6	55.3	51.0
Child ethnicity [b]					
White	81.2	82.4	81.7	81.4	81.4
Mixed	2.0	2.1	1.7	1.9	2.0
Indian/Pakistani/ Bangladeshi	2.0	2.1	1.8	2.1	2.0
Black	0.9	0.5	0.9	1.0	0.9
Other	2.5	2.6	2.3	2.7	2.5
Missing	11.4	10.3	11.7	10.9	11.2
Gestational age					
37-38 (early term)	16.7	13.4	34.0	18.5	18.4
39-40 (full term)	56.5	51.4	58.8	44.6	54.6
41 (late term)	23.1	28.3	5.8	28.1	22.5
42 (post term)	3.7	7.0	1.4	8.8	4.5
Birthweight [a] **in kg,** mean (SD)	3.43 (0.47)	3.45 (0.46)	3.45 (0.50)	3.52 (0.54)	3.45 (0.48)
Any breastfeeding [b]					
Yes	48.3	54.7	47.2	51.7	49.4
No	36.7	31.0	35.9	31.9	35.3
Missing	15.0	14.3	16.9	16.4	15.3

a Variables with ≤10% missing - percentages are calculated from non-missing (97.7% for birthweight and 93.3% for nulliparity).
b Variables with >10% missing – percentages are calculated from total; missing category shown
c P-value<0.001 for all characteristics

4.3.3 Hospital admission for an infectious disease

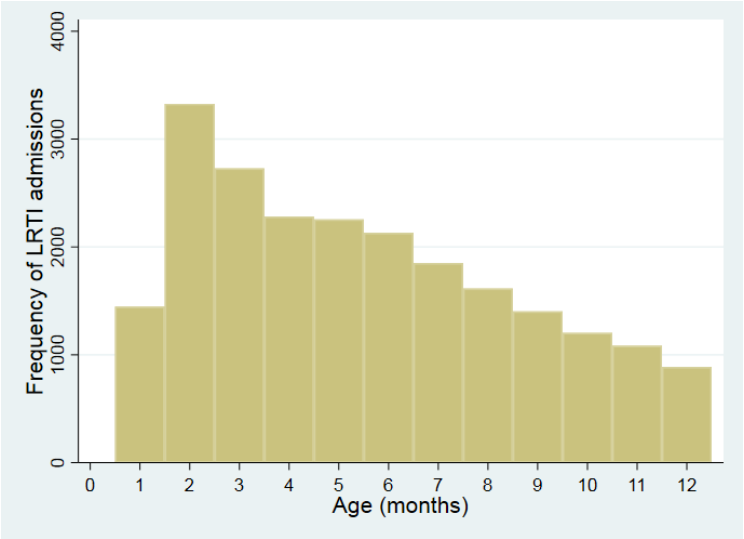
4.3.3.1 Lower respiratory tract infection (LRTI)

The proportion of children with an emergency admission to hospital for a LRTI during infancy was 5.6% (95% CI 5.6, 5.7) (22,154 events), with 95% as the primary indication for admission (first position for ICD code). For the purpose of comparison with the MCS study, the proportion of infants born in 2002 and admitted for LRTI up to age 9.2 months[43] in the current study was calculated and found to be 4.0% (95% CI 3.7, 4.2).

[43] The mean age of baby at interview in the MCS

The number of admissions for LRTI was highest at ages 2-3 months and declined later during infancy (Figure 4-4). Admissions were predominantly for acute bronchiolitis (83% of events) and much less frequently for unspecified LRTI (9%) and pneumonia with unspecified organism (3%). Admission due to one of the other ICD codes that comprise the LRTI outcome were rare. Only 3% of admissions for LRTI were found to also have a diagnostic code for URTI.

Figure 4-4: Frequency of hospital admission (first spell) for LRTI by infant age in the SAIL study

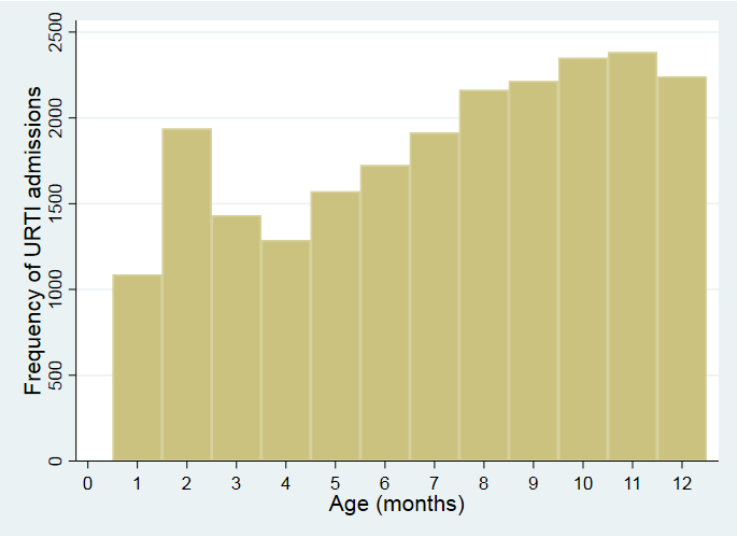


4.3.3.2 Upper respiratory tract infection (URTI)

The proportion of children with an emergency admission to hospital for URTI during infancy was 5.7% (95% CI 5.6, 5.8) (22,278 events), with 91% as the primary indication.

Unlike LRTI, for URTI there was a trend of higher frequency of admissions in older infants compared to younger ones (Figure 4-5). Admissions were predominantly for acute URTI of multiple or unspecified sites (72% of events) and much less frequently due to tonsillitis (12%), laryngitis (11%) and the common cold (3%). Other ICD codes for URTI were rare. Only 3% of admissions for URTI also had a code for LRTI (see section 4.3.3.1).

Figure 4-5: Frequency of hospital admissions (first spell) for URTI by infant age in the SAIL study

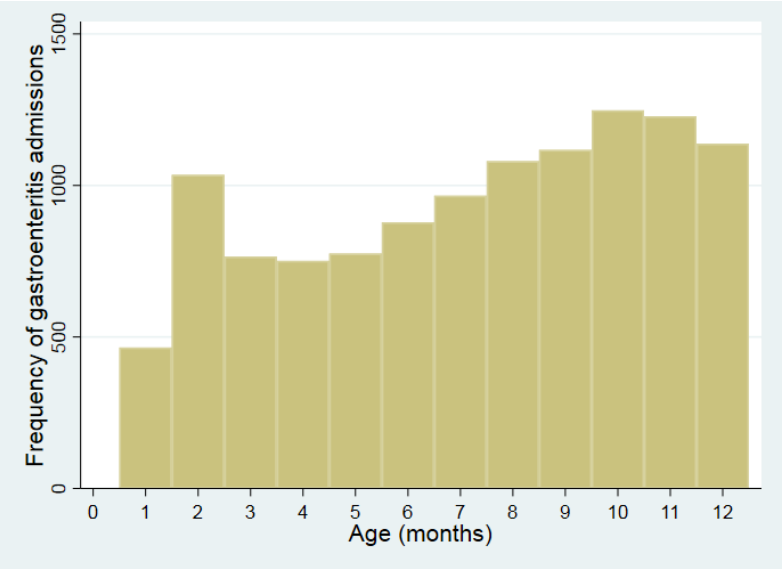


4.3.3.3 Gastroenteritis

The proportion of children with an emergency admission to hospital with gastroenteritis during infancy was 2.9% (95% CI 2.9, 3.0) (11,428 events), and for 91% this was the primary indication. For the purpose of comparing with the MCS study, the equivalent proportion in the current study of infants born 2002 and admitted for gastroenteritis up to age 9.2 months was calculated and found to be 2.1% (95% CI 1.9, 2.3).

There was a trend of higher risk of hospital admission as the infant grew older (Figure 4-6). Admissions were predominantly due to viral and other specified infection (78%) while the remaining admissions were due to unspecified infectious gastroenteritis and colitis.

Figure 4-6: Frequency of hospital admissions (first spell) for gastroenteritis by infant age in the SAIL study



4.3.4 Mode of birth and hospital admission for LRTI

Overall, the rate of hospital admission for LRTI (accounting for time until admission and censoring) was 5.9 per 100 child-years (Table 4-8). The rate ranged from 4.6 per 100 child-years in babies born by assisted vaginal delivery and 7.2 in those born by planned caesarean.

Assisted vaginal delivery had a statistically significantly lower hazard than the reference group of vaginal delivery, but there was no evidence of an association after adjustment. Planned caesarean was associated with higher hazard of admission in the crude model (HR=1.15; 95% CI 1.11, 1.20; P<0.001). Following adjustment, there was still a 10% increase in hazard of admission for LRTI in this group (aHR=1.10; 95% CI 1.05, 1.15; P<0.001). Emergency caesarean section was associated with a statistically significant lower hazard in the crude model compared to vaginal delivery, but after adjustments there was no longer an association. A graphical presentation of the cumulative hazard can be seen in Figure 4-7.

In order to address the problem of missing data, a complete case analysis and multiple imputation analyses were carried out. The results were consistent with those of the main

analysis. Only planned caesarean was found to be a risk factor for LRTI admission and the hazard ratios were of a similar magnitude as in the main analysis: aHR=1.12 (95% CI 1.04,1.22) in complete case and aHR=1.10 (95% CI 1.06, 1.15) in multiple imputation (Table 4-8).

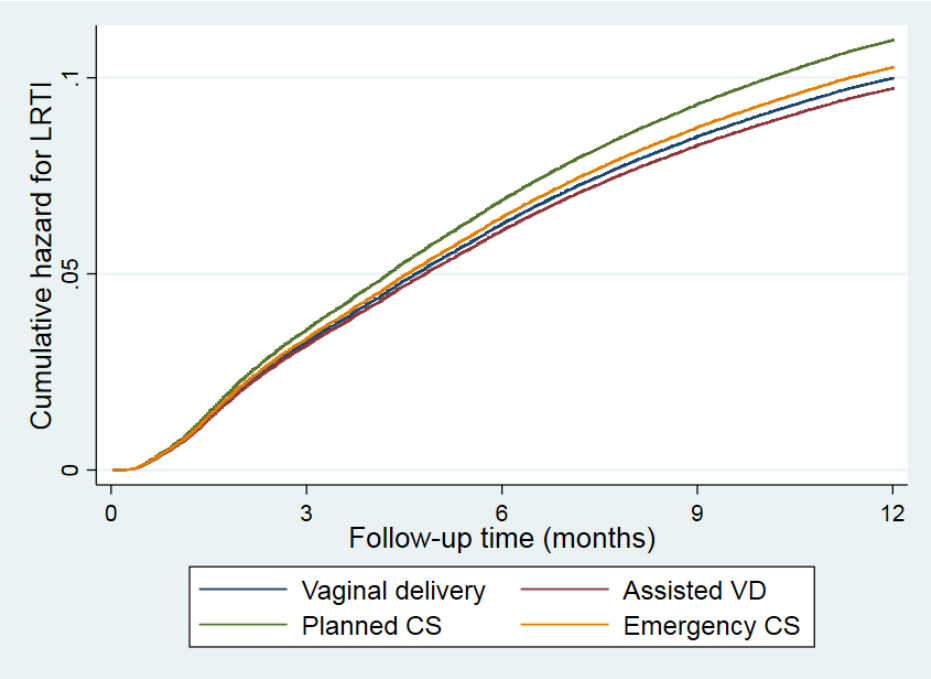
An additional sensitivity analysis using a sub-set of the data where mode of birth category has been validated again gave consistent results with the main analysis - only planned caesarean was a risk factor for LRTI with a similar magnitude as in the main analysis (aHR=1.08; 95% CI 1.01, 1.15).

Table 4-8: Association between mode of birth and hospital admission for LRTI in the SAIL study

	Main analysis					Sensitivity analyses		
						Adjusted HR (95% CI)		
	No. of events	Child-years	Rate per 100 child-years	Crude HR [a] (95% CI) n=392,145[b]	Adjusted HR [c] (95% CI) n=364,651	Complete case analysis [d] n=124,037	Multiple imputation [d] n=364,651	Validated mode of birth [c] n=198,765
Total	**22,154**	**374,489**	**5.9**					
VD	14,697	239,134	6.2	1.00	1.00	1.00	1.00	1.00
Assisted VD	2,024	44,348	4.6	0.73 (0.69, 0.76)	0.97 (0.93, 1.02)	0.93 (0.84, 1.02)	0.98 (0.93, 1.03)	1.01 (0.94, 1.08)
Planned CS	2,942	41,005	7.2	1.15 (1.11, 1.20)	1.10 (1.05, 1.15)	1.12 (1.04, 1.22)	1.10 (1.06, 1.15)	1.08 (1.01, 1.15)
Emergency CS	2,491	50,002	5.0	0.80 (0.77, 0.84)	1.03 (0.98, 1.08)	1.00 (0.92, 1.08)	1.02 (0.98, 1.07)	1.01 (0.95, 1.08)

a Adjusted for year of birth
b 5 observation excluded due to illogical time of outcome event
c Adjusted for maternal age, area deprivation quintile, nulliparity, smoking (with missing category), maternal asthma, hypertensive conditions, infant's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category), season and year of birth
d Adjusted for maternal age, area deprivation quintile, nulliparity, smoking, maternal asthma, hypertensive conditions, infant's sex, ethnicity, gestational age, birthweight, breastfeeding, season and year of birth

Figure 4-7: Cumulative hazard of LRTI hospital admission by mode of birth in the SAIL study



4.3.5 Mode of birth and hospital admission for URTI

The overall rate of admissions due to URTI was 5.9 per 100 child-years (Table 4-9) and ranged from 5.6 in babies born by assisted vaginal delivery to 6.6 in those born by planned caesarean.

Assisted vaginal delivery had a slightly lower hazard of hospital admission due to URTI compared with vaginal delivery (HR=0.95; 95% CI 0.91, 0.99), but following adjustments there was no significant effect. Planned caesarean was associated with a small, statistically significant increased hazard for URTI both in the crude and adjusted model (aHR=1.11; 95% CI 1.06, 1.16). Emergency caesarean was not associated with URTI in the crude model but had a 9% increased hazard in the adjusted model (aHR=1.09; 95% CI 1.05, 1.14). A graphical presentation of the cumulative hazard is presented in Figure 4-8.

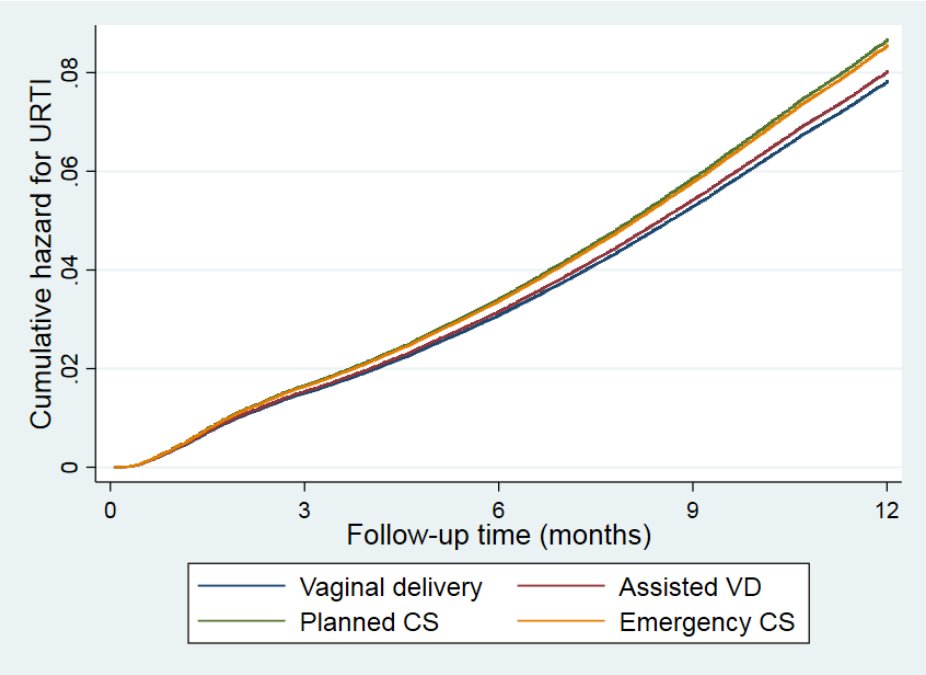
The sensitivity analyses of alternative methods to account for missing values had very similar findings to the main analysis. The results showed 9-11% higher adjusted hazard for URTI in the planned and emergency caesarean groups (statistically significant), but not in the assisted vaginal delivery group. Similar results were found when focusing only on observations where mode of birth has been validated (Table 4-9).

Table 4-9: Association between mode of birth and hospital admission for URTI in the SAIL study

	Main analysis					Sensitivity analyses		
						Adjusted HR (95% CI)		
	No. of events	Child-years	Rate per 100 child-years	Crude HR[a] (95% CI) n=392,145[b]	Adjusted HR[c] (95% CI) n=364,654	Complete case analysis[d] n=124,037	Multiple imputation[d] n=364,654	Validated mode of birth[c] n=198,765
Total	**22,278**	**377,422**	**5.9**					
VD	14,073	241,384	5.8	1.00	1.00	1.00	1.00	1.00
Assisted VD	2,495	44,425	5.6	0.95 (0.91, 0.99)	1.03 (0.98, 1.07)	0.98 (0.90, 1.07)	1.02 (0.98, 1.07)	1.04 (0.97, 1.11)
Planned CS	2,717	41,481	6.6	1.12 (1.07, 1.16)	1.11 (1.06, 1.16)	1.10 (1.02, 1.19)	1.11 (1.06, 1.16)	1.08 (1.01, 1.15)
Emergency CS	2,993	50,132	6.0	1.02 (0.98, 1.06)	1.09 (1.05, 1.14)	1.11 (1.03, 1.20)	1.09 (1.05, 1.14)	1.11 (1.04, 1.18)

a Adjusted for year of birth
b 5 observation excluded due to illogical time of outcome event
c Adjusted for maternal age, area deprivation quintile, nulliparity, smoking (with missing category), maternal asthma, infant's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category), season and year of birth
d Adjusted for maternal age, area deprivation quintile, nulliparity, smoking, maternal asthma, infant's sex, ethnicity, gestational age, birthweight, breastfeeding, season and year of birth

Figure 4-8: Cumulative hazard of URTI hospital admission by mode of birth in the SAIL study



4.3.6 Mode of birth and hospital admission for gastroenteritis

The overall rate of hospital admission for gastroenteritis was 3.0 per 100 child-years (Table 4-10). The lowest rate was found in babies born by planned caesarean (2.8 per 100 child-year) and the highest in those born by emergency caesarean (3.5 per 100 child-years).

Assisted vaginal delivery was associated with a higher hazard of gastroenteritis in the crude model compared to the reference group and following adjustment this risk was attenuated, but remained statistically significant (aHR=1.09; 95% CI 1.03, 1.16). Planned caesarean was not associated with gastroenteritis in the crude model, but after adjustment the hazard ratio was 1.07 (95% CI 1.00, 1.15; P=0.044). Emergency caesarean was associated with a 21% higher hazard than the vaginal delivery group both before and after adjustment (aHR=1.21; 95% CI 1.15, 1.29). A graphical presentation of the cumulative hazard can be seen in Figure 4-9.

The results of the complete case and multiple imputation sensitivity analyses mirrored the findings of the main analysis. Assisted vaginal delivery and planned caesarean were associated with 6-9% higher adjusted hazard compared to the reference group, while emergency caesarean was associated with 21-26% higher adjusted hazard. The sensitivity analysis using validated mode of birth data resulted in similar hazard ratios, but with a slightly smaller effect size in the emergency caesarean group (aHR=1.15; 95% CI 1.06, 1.25).

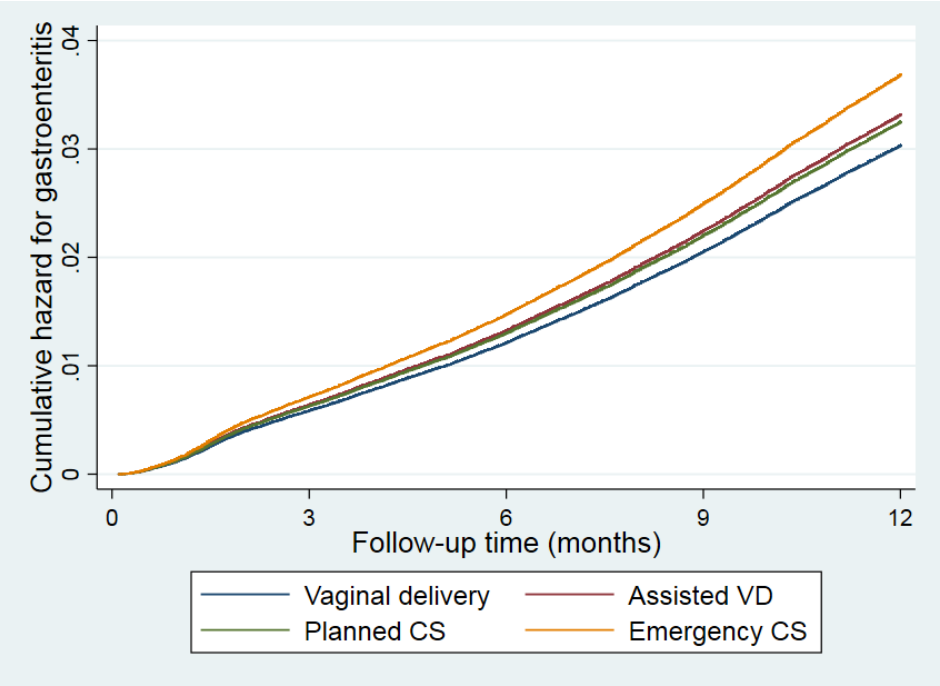
A sensitivity analysis using a broader definition of the outcome which includes non-infective gastroenteritis was also carried out. The proportion of infants admitted to hospital using this extended definition was 3.8% and results were broadly similar to those of the main analysis (Table 4-10).

Table 4-10: Association between mode of birth and hospital admission for gastroenteritis in the SAIL study

	Main analysis					Sensitivity analyses			
						Adjusted HR (95% CI)			
	No. of events	Child-years	Rate per 100 child-years	Crude HR [a] (95% CI) n=392,147 [b]	Adjusted HR [c] (95% CI) n=364,653	Complete case analysis [d] n=277,561	Multiple imputation [d] n=364,653	Validated mode of birth [c] n=198,764	Outcome including non-infective gastroenteritis [c] n=364,652
Total	**11,428**	**382,174**	**3.0**						
VD	7,007	244,532	2.9	1.00	1.00	1.00	1.00	1.00	1.00
Assisted VD	1,462	44,832	3.3	1.13 (1.07, 1.20)	1.09 (1.03, 1.16)	1.08 (1.00, 1.16)	1.09 (1.03, 1.16)	1.11 (1.02, 1.21)	1.10 (1.04, 1.16)
Planned CS	1,196	42,191	2.8	0.99 (0.93, 1.05)	1.07 (1.00, 1.15)	1.06 (0.98, 1.15)	1.07 (1.00, 1.14)	1.03 (0.94, 1.14)	1.10 (1.04, 1.17)
Emergency CS	1,763	50,619	3.5	1.21 (1.15, 1.28)	1.21 (1.15, 1.29)	1.26 (1.18, 1.34)	1.21 (1.15, 1.29)	1.15 (1.06, 1.25)	1.18 (1.12, 1.24)

a Adjusted for year of birth
b 3 observation excluded due to illogical time of outcome event
c Adjusted for maternal age, area deprivation quintile, nulliparity, hypertensive conditions, infant's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category), season and year of birth
d Adjusted for maternal age, area deprivation quintile, nulliparity, hypertensive conditions, infant's sex, ethnicity, gestational age, birthweight, breastfeeding, season and year of birth

Figure 4-9: Cumulative hazard of gastroenteritis hospital admission by mode of birth in the SAIL study



4.3.7 Testing of the proportional hazards assumption

Final adjusted models were examined to test whether the hazard ratios were constant throughout time. A visual examination of log-log plots showed that the plots for all modes of birth were parallel. Furthermore, a stratification of the follow-up time into two time periods did not lead to materially different hazard ratios in the first six months compared to the second. Thus, there was no strong evidence that the proportional hazards assumption of the Cox model was violated in these analyses.

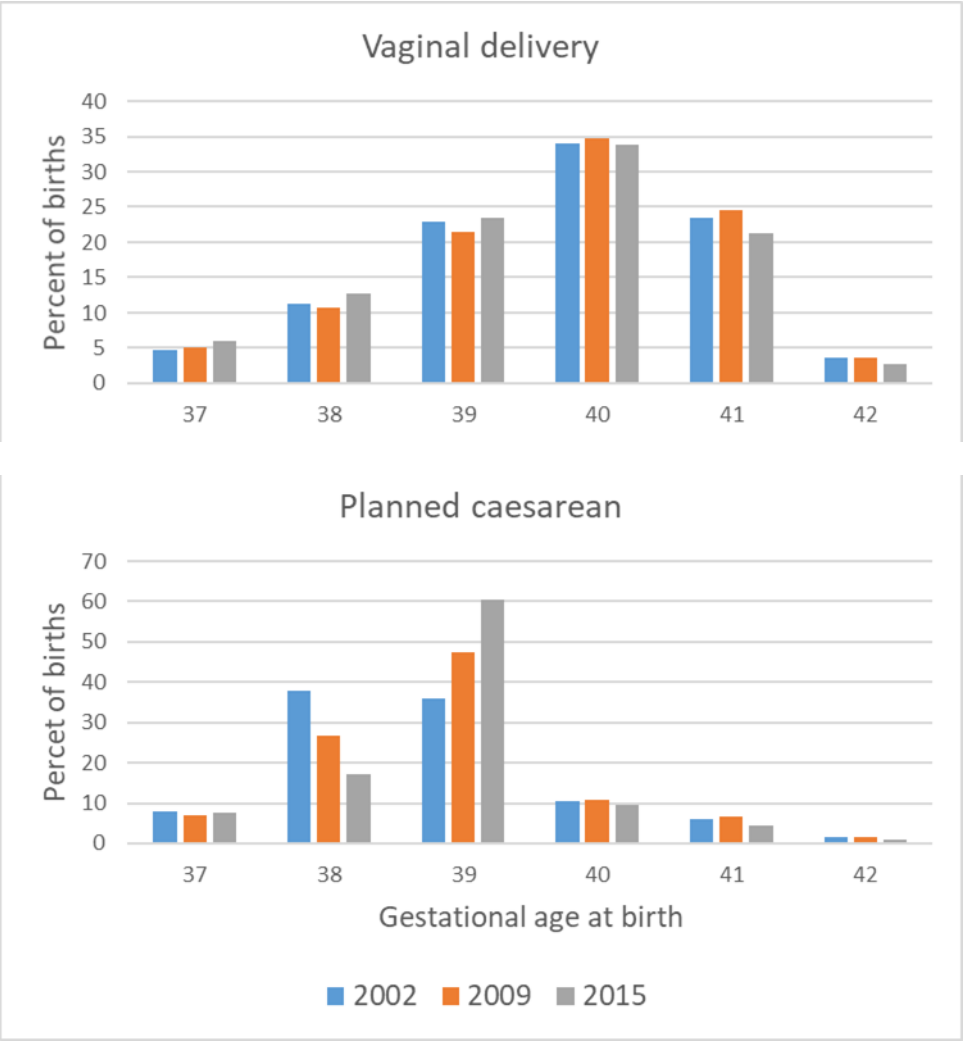
4.3.8 Added indirect effect through earlier gestational age at delivery

As explained previously, pregnancies that are scheduled in advance to be delivered by caesarean section are carried out, on average, at an earlier gestational age than vaginal deliveries. However, it is noteworthy that common practice regarding the timing for which caesarean delivery is scheduled has changed in Wales in recent years. In 2002, 38% of planned caesareans in the study sample were scheduled for week 38 and 36% for week

39, but common practice shifted and by 2015 only 17% were undertaken in week 38 and 60% at week 39. During these years the distribution of gestational age in vaginal deliveries did not change and 80% of term births (≥37 weeks) occurred at 39-41 weeks (Figure 4-10).

When gestational age was removed from final models, the hazard ratios and confidence intervals for the effect of assisted vaginal delivery and emergency caesarean remained unchanged or differed only slightly by 1%. On the other hand, the hazard ratio of planned caesarean increased when gestational age was removed from fully adjusted models for all infectious disease outcomes (Table 4-11). In babies born by planned caesarean, the hazard ratio for hospital admission for LRTI and URTI increased from 1.10/1.11 to 1.17 and that for gastroenteritis increased from 1.07 to 1.14 when the effect of gestational age was not controlled.

Figure 4-10: Distribution of gestational age at birth in the SAIL study sample during the years 2002, 2009 and 2015



* note different Y scale between vaginal delivery and planned caesarean

Table 4-11: Multivariable models for the association between mode of birth and LRTI, URTI and gastroenteritis in the SAIL study adjusted or unadjusted for gestational age

	LRTI		URTI		Gastroenteritis	
	Fully adjusted [a] HR (95% CI)	**Unadjusted for gestational age [b] HR (95% CI)**	**Fully adjusted [c] HR (95% CI)**	**Unadjusted for gestational age [d] HR (95% CI)**	**Fully adjusted [e] HR (95% CI)**	**Unadjusted for gestational age [f] HR (95% CI)**
VD	1.00	1.00	1.00	1.00	1.00	1.00
Assisted VD	0.97 (0.93, 1.02)	0.97 (0.92, 1.02)	1.03 (0.98, 1.07)	1.02 (0.97, 1.07)	1.09 (1.03, 1.16)	1.09 (1.02, 1.16)
Planned CS	1.10 (1.05, 1.15)	1.17 (1.12, 1.22)	1.11 (1.06, 1.16)	1.17 (1.12, 1.22)	1.07 (1.00, 1.15)	1.14 (1.07, 1.21)
Emergency CS	1.03 (0.98, 1.08)	1.04 (1.00, 1.09)	1.09 (1.05, 1.14)	1.10 (1.05, 1.14)	1.21 (1.15, 1.29)	1.22 (1.15, 1.29)

a Adjusted for maternal age, area deprivation quintile, nulliparity, smoking (with missing category), maternal asthma, hypertensive conditions, infant's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category), season and year of birth.
b Adjusted for the variables mentioned in (a) except gestational age
c Adjusted for maternal age, area deprivation quintile, nulliparity, smoking (with missing category), maternal asthma, infant's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category), season and year of birth
d Adjusted for the variables mentioned in (c) except gestational age
e Adjusted for maternal age, area deprivation quintile, nulliparity, hypertensive conditions, infant's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category), season and year of birth
f Adjusted for the variables mentioned in (e) except gestational age

4.4 Discussion

4.4.1 Summary of results

The current study aimed to examine whether mode of birth is associated with hospital admission for LRTI, URTI and gastroenteritis in singleton term infants who were healthy at the time of birth. The findings support the hypothesis that mode of birth is associated with risk of severe infectious disease during infancy, however, the effect size is small.

The results show that after adjustment for explanatory variables, infants born by assisted vaginal delivery have 9% higher risk of being admitted for gastroenteritis during infancy when compared to babies born vaginally. However, these infants do not appear to have a higher risk of admission due to either of the two respiratory tract infections studied. The risk of infants born by assisted vaginal delivery to be admitted for any of the infectious diseases studied is unchanged whether gestational age is adjusted for or not.

Infants born by planned caesarean have a 10-11% increased risk of being admitted for lower or upper respiratory tract infection when compared to babies born vaginally. When gestational age is not included in the model, this elevated risk increases to 17%. In addition, the findings show that these babies have a 7% increased risk of gastroenteritis, though this effect is only marginally statistically significant. The risk of gastroenteritis is, however, higher, when gestational age is not adjusted for and increases to 14%.

The findings further show that infants delivered by emergency caesarean are at a small increased risk of hospital admission for URTI (9%) and have a 21% elevated risk for gastroenteritis; both are statistically significant after adjustment. However, these infants do not appear to have a higher risk of LRTI compared to babies born vaginally. The effect of emergency caesarean on any of the infectious diseases studied is unchanged whether gestational age is adjusted for or not, as is the case for assisted vaginal delivery.

4.4.2 Risk of LRTI by mode of birth - comparison with other studies and with the MCS study

The proportion of study infants admitted to hospital due to LRTI was 5.6%. For infants born in Wales in 2002 and admitted up to the age 9.2 months, this proportion was 4.0% (95% CI 3.7, 4.2) which is similar to the MCS Wales proportion based on mother's report (5.3%; 95% CI 4.5, 6.3) (footnote 23 page 85). Although these estimates are not identical, their general similarity adds weight to the validity of the outcomes of both studies. Further validation of the outcomes of the present study was carried out by comparison with an English study by Cecil et al [194]. The study examined unplanned hospital admissions using HES data during similar years and used a slightly more limited outcome definition. The reported LRTI admission rate during infancy was 3.6 per 100 child-years, which is lower than the rate of 5.9 per 100 child-years found in the current study. Of note, however, is that the Cecil et al study is based on people registered in a sample of GP practices across England, while my study is based on the full population of Wales. The different rates of LRTI between England and Wales is potentially a genuine one, as there was higher prevalence of reported LRTI admissions during infancy in Welsh compared with English participants of the Millennium Cohort Study (results not shown). Furthermore, the trend in frequency of admission, being highest in infants younger than 6 months of age, is in line with that found through report by MCS mothers (Chapter 2) as well as in prior literature [45]. This, too, adds confidence in the validity of the current study's outcome.

The findings of an association between mode of birth and infant admission for LRTI are very similar to those found in the MCS study. The results again show planned caesarean is a risk factor for LRTI, that is moderately attenuated following adjustments (aHR=1.39 in MCS and aHR=1.10 in Wales), but do not provide sufficient evidence that emergency caesarean is a risk factor too. As discussed in detail in section 2.4.2, this pattern is in line with that found in many of the previously published studies using population health

datasets in Denmark [85,86], Western Australia [88] and using a Norwegian birth cohort [87]. The results are partially in line with other studies that have found both types of caesarean section to be a risk factor. A study using Western Australia data [83] found effects of the of magnitude 1.3 for elective and 1.2 for emergency caesarean, slightly larger than those described here. Another study using data from New South Wales [84] and examining bronchiolitis admission during infancy described a similar effect size to the current study - 12% for both types of caesarean.

The effect size for planned caesarean in the current study is relatively small (aHR=1.10) compared to most of the prior studies that found effects ranging from 10-35%. Potential non-causal and causal explanations for the findings that planned caesarean, but not emergency caesarean, is a risk factor for LRTI were discussed in section 2.4.2 and will be further discussed in Chapter 7.

4.4.3 Risk of URTI by mode of birth - comparison with other studies

The proportion of study infants admitted to hospital with an URTI was almost the same as that for LRTI – 5.7% and the rate was 5.9 per 100 child-years. The rate of this outcome can be internally validated by comparing to the previously described study by Paranjothy et al [90] that used data of PEDW emergency respiratory admissions in the years 1998 to 2008. The mentioned publication reported a very similar rate of admission for upper respiratory tract infections during infancy - 5.5 per 100 child-years. It is difficult to attempt to verify this outcome with the reports of the MCS mothers, since URTI was not given as one of the multiple-choice options of reason for the reported hospital admission. However, due to its high frequency during infancy (as shown in the current study amongst others) it is reasonable to presume that many of the MCS open text answers about reason for admission related to this type of infection. These may include

answers later coded as ‘high temperature’, ‘severe infection’, ‘mild infection’ and ‘infection of nose, ear, throat, coup, flu or severe cough’ (see section 2.2.4).

The study by Cecil et al [194] also reported rates of URTI admissions during infancy in an English sample, although including different ICD codes in the outcome definition. The reported rate was 2.7 per 100 child-years, which is lower than the rate of 5.9 per 100 child-years reported here. The different rates could be the result of the different outcome definition or the sampling method in England. Alternatively, it may represent a true difference in the rates between Wales and England.

With regards to the association of mode of birth with URTI, the results of the current study suggest that babies born by both types of caesarean section have a small increase in risk of hospital admission (9-11%). Kristensen et al [86] examined the association of mode of birth with various outcomes including laryngitis and concluded that children born by both types of caesarean delivery have a small increased risk for this infection up to the age 14. However, laryngitis comprised only 11% of my study’s outcome definition. A recent small study followed-up 334 children in Copenhagen and did not find an association between perinatal risk factors, including caesarean section, and upper respiratory infections from birth to age 3 [192]. As discussed previously, I could not identify additional published studies examining mode of birth and upper respiratory tract infection despite carrying out an additional literature search focused on this outcome.

Of note is the very small overlap in admissions coded for both LRTI and URTI. As there is a continuum from the nose to the alveoli in the lungs, some infectious agents such as RSV and influenza may reside in both loci [195], however the ICD codes for admissions did not show evidence of this. It is reasonable to assume that the infection in the locus most responsible for the infant’s morbidity and need for medical care would be the ICD code chosen. Thus, it is plausible that some of the infants analysed diagnosed with LRTI

also suffered from an URTI. This non-differential misclassification may lessen the degree of association of mode of birth with this type of infection.

4.4.4 Risk of gastroenteritis by mode of birth - comparison with other studies and with the MCS study

The proportion of infants admitted to hospital with gastroenteritis in this sample was 2.9%. For infants born in Wales in 2002 and admitted up to the age of 9.2 months, this proportion was 2.1% (95% CI 1.9, 2.3) and the corresponding proportion in the MCS Welsh births was 1.4% (95% CI 0.9, 2.1) (footnote 24 page 85). Other studies have reported the annual prevalence of gastroenteritis admission in infancy as 1.7-1.8% [84,155]. The Cecil et al study using HES data [194] reported a rate of 2.3 per 100 child-years (although including ICD codes K52 and others), that is only slightly lower than the rate of 3.0 per 100 child-years reported in this study. Therefore, the rate of gastroenteritis admission in the current study is slightly higher, but generally comparable, to those reported in the MCS and in previous studies.

The findings of the present research are that any medically interventional mode of birth is associated with a small elevated risk of gastroenteritis in infancy compared to vaginal delivery. Within the caesarean deliveries, the increased risk in infants born by planned caesarean was 7% and only marginally statistically significant, however the increase in risk in the group born by emergency caesarean was larger at 21%. This result is in line with the findings from the MCS analyses. Emergency caesarean was associated with a 52% higher risk of gastroenteritis (P=0.072) compared with vaginal delivery in the MCS, while other modes of birth were not identified as risk factors in the fully adjusted models. Other large population studies conducted outside of the UK [84,86,91,92] reported an increased risk of 20-30% in babies born by both types of caesarean section. Thus, the present study findings are in accord with these studies, highlighting both emergency and

planned caesarean as risk factors for gastroenteritis, although planned caesarean to a lesser degree.

4.4.5 Strengths and limitations of the study

The primary strength of the study presented here is the dataset used, which encompasses routinely collected data for the entire population of Wales. The large study size allowed for sufficient statistical power to identify small but important associations between mode of birth and infectious disease. A large study sample is especially important, since mode of birth is split into four sub-categories and since the outcomes studied are relatively uncommon (infectious disease severe enough to require hospital admission).

An additional strength of this study is the partial overlap with the MCS population, both geographically and by close timeline proximity. This allows cross comparison of important variables between the two parts of the thesis. Indeed, the exposure variable was validated by this means: the distribution of modes of birth amongst births in 2002 in the current study and births of Welsh MCS participants were found to differ by no more than ~1%.

The proportion of records of Welsh residents linked between the three main datasets of this study (NCCHD, PEDW and WDS) was 90.3% (see section 4.2.4). The proportion linked in the current study is comparable to 92% linkage achieved in a pilot linking birth registration, NCCHD and PEDW data from the years 2005-7 [196]. The study linkage rate will be discussed in more detail in Chapter 7.

An additional study strength is the outcome measurement using mandatory administrative records of hospital admissions, which minimizes the concern from missing cases.

The analysis of the association of mode of birth with infant upper respiratory tract infection is a novel one. Being one of the common reasons for infants to require hospital admission in Wales, the potential effect of mode of birth on this type of infection is thus of importance.

As discussed in Chapter 2, the sensitivity analyses focusing on a validated exposure variable substantially increase the internal validity of the study. There is high confidence in the validity of mode of birth when using solely records where PEDW operational codes agree with NCCHD delivery code (96% of observations that include both codes).

Lastly, the timeline for inclusion of births in the study is relatively long and ends with recent data from 2016. This portrays the current state of exposure and outcome variables in the population of Wales. Importantly, the rates of various modes of birth shifted substantially from 2002 onwards. It is unlikely that this change is explained solely by different maternal, fetal or labour characteristics, but instead implies that obstetric and midwifery practices have also changed over time. Due to these changing practices and the underlying conditions for which each mode of birth is undertaken, it is therefore of value to investigate the association of mode of birth and infectious disease using relatively recent data.

The study has several limitations that, too, arise from the data platform used. Because of the use of administrative datasets, some of the study's explanatory variables were only available at a relatively crude level and not in the degree of granularity more often achieved through questionnaires. For example, a family's socioeconomic status could not be accounted for at the individual level, but only at the area level. Furthermore, additional variables such as education level and marital status that were included in the MCS were not available through the SAIL databank. This leads to the potential for residual confounding in my results. Variables such as maternal diabetes, hypertension and asthma were only available through ICD codes from the delivery record and likely

do not include all women experiencing these conditions during pregnancy. With regards to asthma, which is a chronic condition and one where genetic susceptibility of the child is of interest, I was able to extend the coverage by including mothers with an ICD code for asthma in delivery records of siblings. All the same, the proportion identified is still a probable underestimation of the proportion of women with asthma during pregnancy. This is evident when comparing the proportion found in my sample - 5.5% - with that found using GP records of pregnant women in the UK, which has shown a higher prevalence of 8.3% [197]. Hypertension might also be somewhat under-measured, since the proportion found in the current sample (5.6%) is lower than that reported by MCS mothers (7.0%). For maternal diabetes, however, the proportion of the sample identified in the Welsh analyses through ICD codes (2.2%) is comparable to that found through maternal report in the MCS (1.9%) and in a previous report from the UK (2.4%) [198]. In addition to these variables, the study was also limited by inclusion of children admitted to NICU, as reliable information was not available. Alternative variables including Apgar scores or major congenital anomaly were used to exclude some of these infants.

The study was also limited in the quality of an important variable - breastfeeding. The information was only available at two time points – at birth and at 8 weeks postnatally and since there were high levels of missing data, a crude differentiation between any breastfeeding and none was used instead. This, too, leads to potential unaccounted confounding. The unavailability of nuanced information about breastfeeding prevented testing of whether it mediates or modifies the association between mode of birth and infant infectious disease, as was investigated in the MCS. In the MCS, the findings suggested that the excess risk of infectious disease experienced by an infant born by caesarean section is not mediated by being breastfed less. However, this lack of mediating effect needs to be investigated in additional populations, particularly in populations where there is a strong association between mode of birth and duration of breastfeeding. Such an association may depend, to some degree, on the hospital's

policy of encouraging breastfeeding following caesarean delivery (for example – facilitating early skin-to-skin contact post-surgery) as is recommended in NICE guideline [20]. Therefore, although it would have been beneficial to examine the potential of breastfeeding to mediate or modify the effect of mode of birth on the outcomes in an additional population to the MCS sample, this was not possible using the SAIL data.

The large amount of missing data for breastfeeding (despite re-categorising the variable into a binary one), ethnicity and especially smoking, is a limitation of the study. Nevertheless, the use of a missing category allowed these records to be included in final models and avoided losing the majority of the sample when adjusting for covariates. Two additional methods of handling missing data, i.e. complete case analysis and multiple imputation, were implemented in sensitivity analyses. Owing to the similarity between the findings from these sensitivity analyses to the main analyses, the large proportion of missing data is not considered a major weakness.

Lastly, the nature of the SAIL databank work model requires that the end-user does not have access to identifiable information. Therefore, the SAIL team and their associates have the task of assigning anonymized ALF codes that allow for matching of an individual between the various dataset. As an end-user of this data, I am not able to verify the quality of linkage of these datasets and must rely on the ALF codes given by the SAIL databank. All the same, the SAIL linkage method has been shown to be of high quality [184] and has been the platform for generating many research articles.

4.4.6 Conclusions

The current study presents evidence of a small elevated risk of subsequent severe infectious disease in healthy singleton infants born at term by caesarean section. There is evidence of an association between planned caesarean and respiratory infections and weaker evidence of an association with gastrointestinal infection. The effect of planned caesarean on infection risk is stronger when the added effect of gestational age is not

adjusted for. There is stronger evidence of an association between emergency caesarean and gastroenteritis, and evidence of a weaker association with URTI. There is also evidence of a small association between assisted vaginal delivery and gastroenteritis, but not other infection sites.

Chapter 5: An investigation of the association between mode of birth and childhood respiratory illness in Wales

5.1 Introduction

The study described in Chapter 4 has found a small increased risk of both URTI and LRTI during infancy following caesarean section. To better understand the possible effect of caesarean on general respiratory morbidity, the current chapter is therefore focused on hospital admissions for any respiratory illnesses (upper and lower respiratory tract infections and asthma) during infancy and further extends to early childhood.

5.1.1 Study aims

The aim of this study was to investigate the relationship between mode of birth and risk of any severe respiratory illness during infancy. The respiratory illnesses investigated were lower (LRTI) and upper respiratory tract infections (URTI) and asthma.

The research questions were:

1. Is mode of birth associated with hospital admission for a respiratory illness during infancy?
2. Is mode of birth associated with hospital admission for a respiratory illness at ages 1 to 4 years?
3. Does earlier gestational age indirectly add to any effect of planned caesarean on respiratory illness?

5.2 Methods

The methods used for this study are identical to those for the study in Chapter 4, except where indicated below.

5.2.1 SAIL

The SAIL databank and the datasets detailed in 4.2.1 was used for the study described in this chapter.

5.2.2 Study population

The study population was all births to mothers who were resident in Wales between January 2002 and February 2016 as ascertained from the NCCHD.

5.2.3 Data extraction

Data was retrieved from SAIL datasets as illustrated in section 4.2.3 and Figure 4-1. Extraction of relevant spells from PEDW was carried out using ICD codes for URTI and LRTI listed in Table 4-1 (page 167) in addition to codes J45 (“Asthma”) and J46 (“Status Asthmaticus”).

5.2.4 Dataset merging

The merging of datasets was carried out as detailed in section 4.2.4.

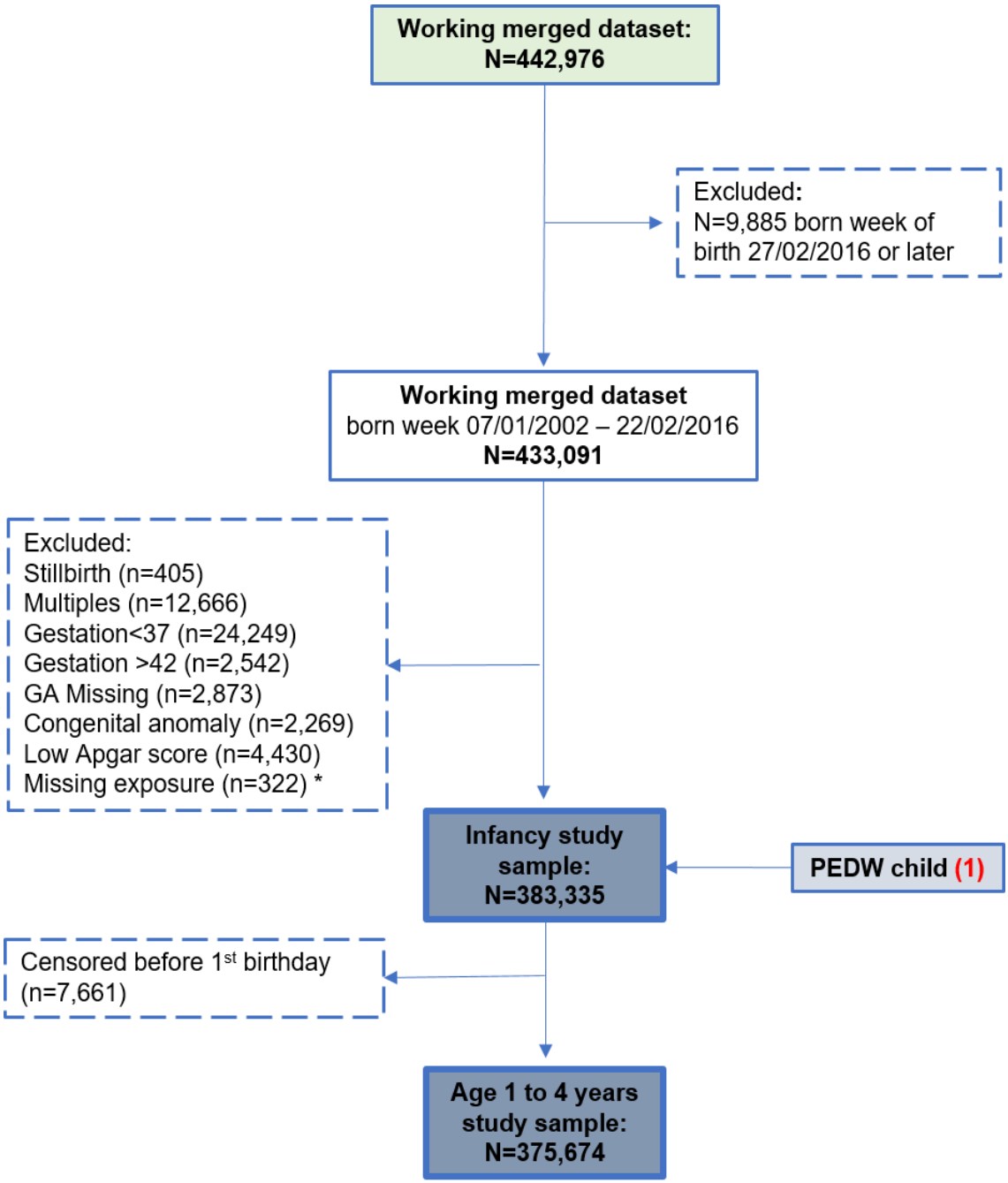
5.2.5 Study inclusion criteria

The inclusion criteria for the current study were the same as those specified in 4.2.5, with the further limitation that week of birth is no later than 22/02/2016 to ensure all infants had passed their 1st birthday before the follow-up ended on 28/02/2017. This criterion was put in place in order for a birth to be eligible for inclusion in the analysis of

any respiratory infection at ages 1 to 4[44]. Thus 9,885 children (2.2% of the 'working merged dataset') were excluded from the analyses presented here. Further exclusions of multiples, children born preterm or with congenial anomaly or low Apgar score were carried out as detailed in Figure 5-1. The percentages excluded according to each reason were very similar to those detailed in section 4.2.5 and are therefore not repeated here. The final sample size for the study of any respiratory illness during infancy was 383,335. The final sample size for the study of any respiratory illness from age 1 to 4 years did not include those censored prior to their 1st birthday (predominately due to emigration from Wales) and was therefore 375,674.

[44] To allow for comparability, this criterion was set for both analyses – that of ages 1 to 4 and that of infancy

Figure 5-1: Children included in the SAIL respiratory illness study sample**



* Numbers are in sequential order of exclusion
(1) Child's admission spell identified by ALF and one of ICD codes for asthma (J45 or J46) or one of the codes for URTI or LRTI listed in Table 4-1
** See Figure 4-1 for dataflow prior to 'Working merged dataset'

5.2.6 Exposure – mode of birth

Mode of birth was defined as described in section 4.2.6 and categorized into the four categories, as before.

5.2.7 Outcomes – hospital admission for a respiratory illness

A hospital admission event was defined as an emergency admission that includes at least one of the following:

- ICD codes for LRTI as detailed in Table 4-1 at any diagnostic code position
- ICD codes for URTI as detailed in Table 4-1 at any diagnostic code position
- ICD code J45 or J46 for asthma in the primary diagnostic code position

Outcomes were categorized as:

- Any respiratory admission during infancy: the time starting week of birth and until 365 days later
- Any respiratory admission during early childhood: the time starting 366 days after week of birth and up to 1825 days (four years of follow-up from age 1 to 4).

For children with more than a single hospital admission for a respiratory illness, only the first admission during the relevant timeframe (either infancy or early childhood) was counted. Children admitted both during infancy and between age 1 to 4 would be included in both analyses.

5.2.8 Potential explanatory variables

The explanatory variables eligible to be included in the final models were the same as those of the LRTI and URTI analyses, i.e., all variables detailed in Table 4-3 on page 174.

5.2.9 Statistical analyses

Stata version 14 was used for all analyses.

5.2.9.1 Univariable analyses

The association between mode of birth and each explanatory variable was assessed as described in section 4.2.9.1. The univariable association of each potential explanatory variable with the outcome was assessed separately for admission during infancy and for admission from age 1 to 4 years. The same cut-off of P<0.10 was used to determine whether a variable would be included in multivariable analyses.

5.2.9.2 Multivariable analyses

Cox regression was used to estimate the crude and adjusted hazard ratios and 95% confidence intervals for first hospital admission for each outcome. As detailed in 4.2.9.2, the variable of year of birth was included a priori and analyses allowed for within-family clustering. Data was censored at the earliest point in time out of the following: date of death, time of emigration from Wales or February 2017.

5.2.9.3 Testing of the proportional hazards assumption

The proportional hazards assumption was assessed by comparing the hazard ratios across the follow-up period. For the analysis of any respiratory admission in infancy, the follow-up was split into two equal time intervals: 0-5 and 6-12 months. For the analysis at ages 1 to 4 years, the follow-up time was split at the cut-off of age 2½ years. The second follow-up period was set to be longer than the first because of lower frequency of admissions at older ages. Separate models were fitted for each time period. The similarity of the hazard ratios between the models of the two time intervals was evaluated and log-log plots were generated and examined as detailed in section 4.2.9.3.

5.2.9.4 Analysis of potential mediation by gestational age

As detailed in section 4.2.9.4.

5.2.10 Missing values

The same approaches for addressing missing data described in section 4.2.10 were used in this study. Briefly, the main analysis included a sub-category of 'missing' for the three variables - ethnicity, breastfeeding and smoking - and two additional sensitivity analyses of complete case and multiple imputation for these variables were carried out.

5.2.11 Sensitivity analyses for exposure

5.2.11.1 Restriction to observations with validated mode of birth

These sensitivity analyses were carried out as described in 4.2.11.1.

5.2.12 Power calculation

According to the power calculations conducted separately for LRTI and URTI in section 4.2.12, the power to detect even a small association with a combined any respiratory admission outcome during infancy would be very high. The calculations are therefore not specified here.

For admission during early childhood, the power to detect a significant association for any respiratory cause was estimated. The estimated prevalence of this outcome during this age timeframe was 10.5% [90]. Therefore, the expected power was almost 100% even for the small effect size of RR=1.1.

5.2.13 Data access and security

As detailed in section 4.2.13.

5.2.14 Ethics committee approval

As detailed in section 4.2.14.

5.3 Results

5.3.1 Mode of birth – descriptive results

The study sample for the current analyses was only slightly smaller than the sample for the analyses of infectious diseases detailed in Chapter 4. The distribution of the mode of birth groups was almost the same as those detailed previously: 11.7% assisted vaginal delivery, 11.0% planned caesarean, 13.3% emergency caesarean and the remaining by vaginal delivery.

5.3.2 Study group characteristics

Characteristics of the study sample were almost identical to those described in section 4.3.2 and are therefore not repeated here.

5.3.3 Hospital admission for a respiratory illness

5.3.3.1 Any respiratory illness admission during infancy

The proportion of children with an emergency hospital admission for any respiratory illness during infancy was 10.6% (95% CI 10.5, 10.7) (40,450 events).

The monthly frequency of admissions for any respiratory illness was highest at age 2-3 months and declined later, remaining relatively constant until 12 months (Figure 5-2). The indications for admission are specified in Table 5-1. The most common indications were bronchiolitis and unspecified URTI. There were equally as many admissions for an infection in the upper respiratory tract as those of the lower respiratory tract.

Figure 5-2: Frequency of hospital admissions (first spell) for respiratory illness by infant age in the SAIL study



Table 5-1: Specific indications for hospital admission for any respiratory illness during infancy in the SAIL study

Respiratory illness type	ICD code	Annotation	Proportion of respiratory admissions (%)
LRTI	J21	Acute bronchiolitis	41.2
URTI	J06	Acute upper respiratory infections of multiple/unspecified sites	35.2
URTI	J03	Acute tonsillitis	5.6
URTI	J05	Acute obstructive laryngitis [croup] and epiglottitis	5.5
LRTI	J22	Unspecified acute lower respiratory infection	4.2
		Multiple respiratory ICD codes	3.2
LRTI	J18	Pneumonia, organism unspecified	1.8
URTI	J00	Acute nasopharyngitis [common cold]	1.3

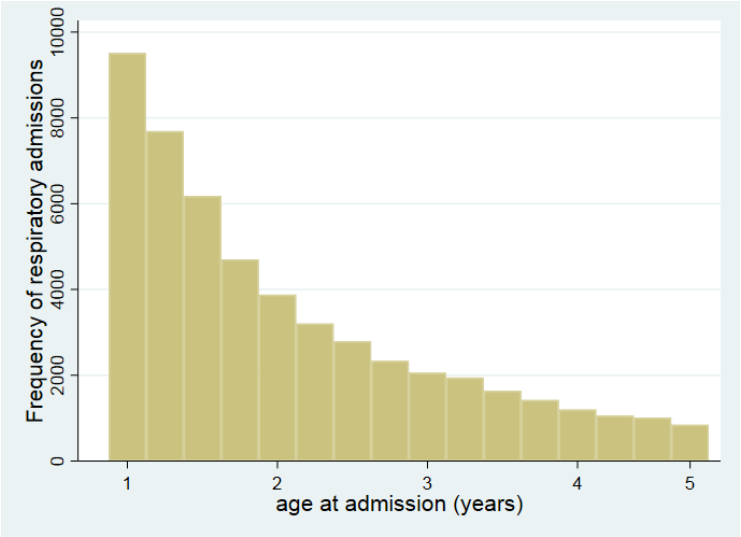
5.3.3.2 Any respiratory illness admission at ages 1 to 4

The proportion of children with an emergency hospital admission for any respiratory illness at age 1 to 4 was 13.7% (95% CI 13.6, 13.8) (51,480 events).

The frequency of emergency admissions for any respiratory illness decreased as the child grew older (Figure 5-3). The indications for admission are specified in Table 5-2,

the most common of which were unspecified URTI and acute tonsillitis. The majority of indications contributing to this outcome were infections of the upper respiratory tract.

Figure 5-3: Frequency of hospital admissions (first spell) for respiratory illness (age 1 to 4) by child age in the SAIL study*



* each bar represents a 3-month period

Table 5-2: Specific indications for hospital admission for any respiratory illness at age 1 to 4 in the SAIL study

Respiratory illness type	ICD code	Annotation	Proportion of respiratory admissions (%)
URTI	J06	Acute upper respiratory infections of multiple/unspecified sites	33.4
URTI	J03	Acute tonsillitis	21.7
LRTI	J22	Unspecified acute lower respiratory infection	11.8
URTI	J05	Acute obstructive laryngitis [croup] and epiglottitis	11.2
LRTI	J18	Pneumonia, organism unspecified	5.7
		Multiple respiratory ICD codes	5.4
Asthma	J45	Asthma	4.9
LRTI	J21	Acute bronchiolitis	2.3
URTI	J02	Acute pharyngitis	1.6
URTI	J00	Acute nasopharyngitis [common cold]	0.9

5.3.4 Mode of birth and hospital admission for respiratory illness during infancy

Overall, the rate of hospital admission for any respiratory illness during infancy was 11.3 per 100 child-years (Table 5-3). The rate ranged from 9.8 per 100 child-years in babies born by assisted vaginal delivery to 13.0 in those born by planned caesarean.

The assisted vaginal delivery group had a statistically significant lower hazard than the vaginal delivery group, but the association was no longer evident after adjustment. Planned caesarean was associated with a 13% higher hazard compared with vaginal delivery, and this was slightly attenuated to 10% following adjustments (aHR =1.10; 95% CI 1.07, 1.14). Emergency caesarean was associated with a lower hazard in the crude model, however, following adjustments these babies had a hazard ratio of 1.07 for any respiratory illness (aHR=1.07; 95% CI 1.03, 1.10). A graphical presentation of the cumulative hazard can be seen in Figure 5-4.

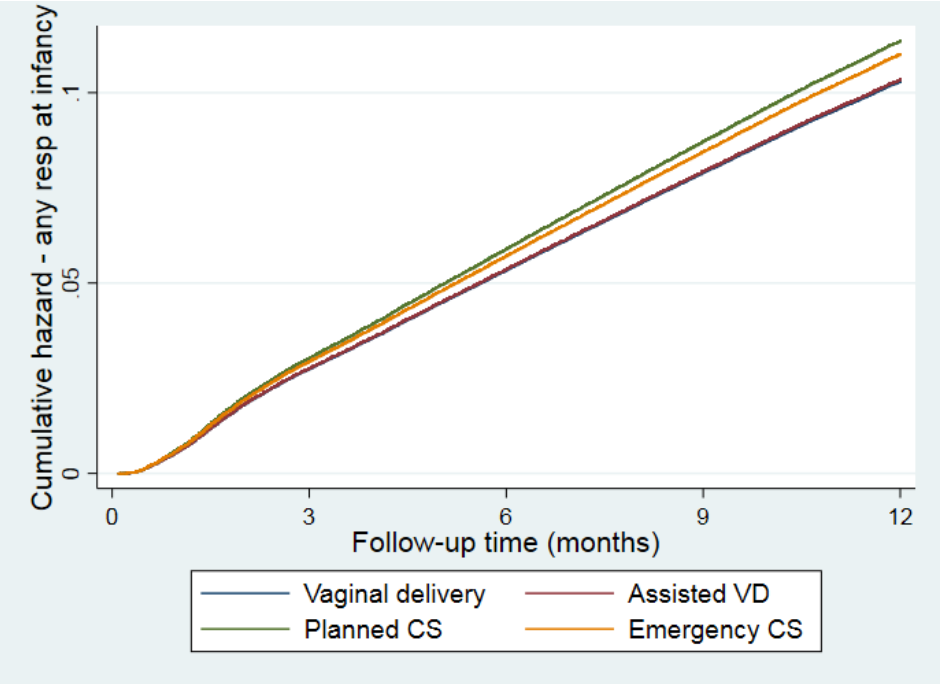
The results of three sensitivity analyses shown in Table 5-3 were consistent with the findings of the main analysis. Assisted vaginal delivery was not associated with any respiratory illness in any of these sensitivity analyses. Emergency caesarean was associated with a 7-8% increased hazard. Planned caesarean was associated with an 8-12% increased hazard.

Table 5-3: Association between mode of birth and hospital admission for respiratory illness during infancy in the SAIL study

	Main analysis					Sensitivity analyses		
						Adjusted HR (95% CI)		
	No. of events	Child-years	Rate per 100 child-years	Crude HR [a] (95% CI) n=383,312[b]	Adjusted HR [c] (95% CI) n=356,783	Complete case analysis [d] n=123,365	Multiple imputation [d] n=383,312	Validated mode of birth [c] n=194,354
Total	**40,450**	**359,166**	**11.3**					
VD	26,162	229,467	11.4	1.00	1.00	1.00	1.00	1.00
Assisted VD	4,174	42,625	9.8	0.84 (0.82, 0.87)	1.00 (0.97, 1.04)	0.96 (0.90, 1.02)	1.00 (0.97, 1.04)	1.02 (0.97, 1.07)
Planned CS	5,080	39,058	13.0	1.13 (1.10, 1.17)	1.10 (1.07, 1.14)	1.12 (1.06, 1.19)	1.11 (1.07, 1.14)	1.08 (1.03, 1.14)
Emergency CS	5,034	48,016	10.5	0.91 (0.89, 0.94)	1.07 (1.03, 1.10)	1.07 (1.01, 1.13)	1.07 (1.03, 1.10)	1.08 (1.03, 1.13)

a Adjusted for year of birth
b 23 observations were removed due to illogical time of outcome event
c Adjusted for maternal age, area deprivation quintile, nulliparity, smoking (with missing category), maternal asthma, hypertensive conditions, infant's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category), season and year of birth.
d Adjusted for maternal age, area deprivation quintile, nulliparity, smoking, maternal asthma, hypertensive conditions, infant's sex, ethnicity, gestational age, birthweight, breastfeeding, season and year of birth

Figure 5-4: Cumulative hazard of respiratory illness hospital admission during infancy by mode of birth in the SAIL study



5.3.5 Mode of birth and hospital admission for respiratory illness during early childhood

Overall, the rate of hospital admission for any respiratory illness at ages 1 to 4 was 4.6 per 100 child-years (Table 5-4). The rate ranged from 4.4 per 100 child-years in babies born vaginally to 5.0 in those born by emergency caesarean.

Assisted vaginal delivery was associated with 9% higher hazard for respiratory illness and this was slightly attenuated after adjustments (aHR=1.05; 95% CI 1.02, 1.08). Planned caesarean was found to have 13% higher hazard and the effect remained after adjustments (aHR=1.12; CI 1.09, 1.16). Likewise, emergency caesarean was associated with respiratory illness in the crude and adjusted models (aHR=1.10; 95% CI 1.07, 1.13). For a graphical presentation of the cumulative hazard see Figure 5-5.

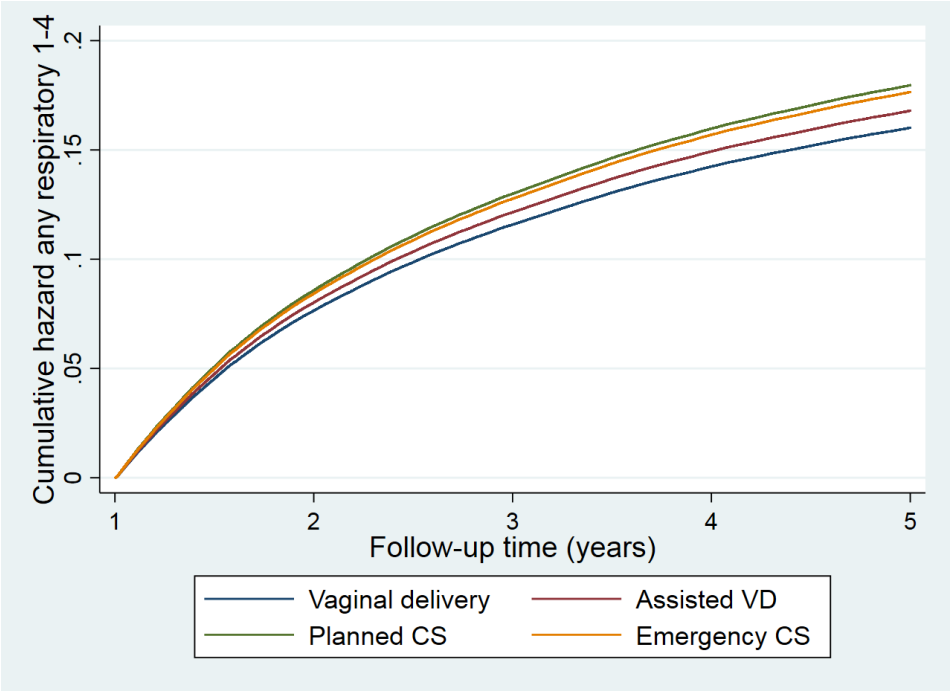
The findings from sensitivity analyses were very similar to the findings of the main analysis (Table 5-4).

Table 5-4: Association between mode of birth and hospital admission for respiratory illness at age 1 to 4 in the SAIL study

	Main analysis					Sensitivity analyses		
						Adjusted HR (95% CI)		
	No. of events	Child-years	Rate per 100 child-years	Crude HR [a] (95% CI) n=375,674	Adjusted HR [b] (95% CI) n=350,059	Complete case analysis [c] n=121,004	Multiple imputation [c] n=350,059	Validated mode of birth [b] n=190,188
Total	**51,480**	**1,131,292**	**4.6**					
VD	31,716	729,804	4.4	1.00	1.00	1.00	1.00	1.00
Assisted VD	6,285	129,651	4.9	1.09 (1.06, 1.12)	1.05 (1.02, 1.08)	1.03 (0.98, 1.08)	1.05 (1.01, 1.08)	1.03 (0.99, 1.07)
Planned CS	6,091	123,281	4.9	1.13 (1.10, 1.16)	1.12 (1.09, 1.16)	1.12 (1.07, 1.18)	1.12 (1.09, 1.15)	1.10 (1.06, 1.15)
Emergency CS	7,388	148,557	5.0	1.13 (1.10, 1.16)	1.10 (1.07, 1.13)	1.09 (1.04, 1.14)	1.10 (1.07, 1.13)	1.10 (1.06, 1.14)

a Adjusted for year of birth
b Adjusted for maternal age, area deprivation quintile, nulliparity, smoking (with missing category), maternal asthma, diabetes, hypertensive conditions, child's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category), season and year of birth
c Adjusted for maternal age, area deprivation quintile, nulliparity, smoking, maternal asthma, hypertensive conditions, child's sex, ethnicity, gestational age, birthweight, breastfeeding, season and year of birth

Figure 5-5: Cumulative hazard of any respiratory illness admission at ages 1 to 4 by mode of birth in the SAIL study



5.3.6 Testing of the proportional hazards assumption

Final adjusted models for the two analyses were examined to test whether the hazard ratios were constant throughout time. Log-log plots were parallel for all modes of birth and when the follow-up time was split into two, the hazard ratios were not found to be materially different. Thus, there was no strong evidence that the proportional hazards assumption of the Cox model was violated in these analyses.

5.3.7 Added indirect effect through earlier gestational age at delivery

The assessment of potential mediation of gestational age on the association between mode of birth and any respiratory illness gave similar results to those described in section 4.3.8. When gestational age was removed from fully adjusted models, the hazard ratios for assisted vaginal delivery and emergency caesarean remained unchanged, whilst the effect size for planned caesarean increased from 1.10 to 1.17 during infancy and from 1.12 to 1.18 during early childhood (Table 5-5).

Table 5-5: Multivariable models for the association between mode of birth and respiratory illness admission in the SAIL study, adjusted or unadjusted for gestational age

	Any respiratory illness infancy		Any respiratory illness 1 to 4 years	
	Fully adjusted [a] HR (95% CI)	Unadjusted for gestational age [b] HR (95% CI)	Fully adjusted [c] HR (95% CI)	Unadjusted for gestational age [d] HR (95% CI)
VD	1.00	1.00	1.00	1.00
Assisted VD	1.00 (0.97, 1.04)	1.00 (0.96, 1.03)	1.05 (1.02, 1.08)	1.04 (1.01, 1.07)
Planned CS	1.10 (1.07, 1.14)	1.17 (1.14, 1.21)	1.12 (1.09, 1.16)	1.18 (1.15, 1.21)
Emergency CS	1.07 (1.03, 1.10)	1.08 (1.04, 1.11)	1.10 (1.07, 1.13)	1.10 (1.07, 1.13)

a Adjusted for maternal age, area deprivation quintile, nulliparity, smoking (with missing category), maternal asthma, hypertensive conditions, infant's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category), season and year of birth
b Adjusted for the variables mentioned in (a) except gestational age
c Adjusted for maternal age, area deprivation quintile, nulliparity, smoking (with missing category), maternal asthma, diabetes, hypertensive conditions, child's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category), season and year of birth.
d Adjusted for the variables mentioned in (c) except gestational age

5.4 Discussion

5.4.1 Summary of results

The current study aimed to examine whether mode of birth is associated with hospital admission for any respiratory illness during infancy and early childhood in singletons born at term and healthy at the time of birth. The findings provide support for the hypothesis that mode of birth is associated with risk of severe respiratory illness both during infancy and during early childhood, however, the effect sizes are small.

The results show that babies born by assisted vaginal delivery have a similar risk of being admitted to hospital for a respiratory illness during infancy compared to those born vaginally. Later on, at ages 1 to 4 years, children exhibit a very small (5%) increase in risk of admission which was statistically significant.

Babies born by planned caesarean have a 10% increased risk of admission during infancy and a 12% increased risk during early childhood compared with those born by vaginal delivery. When results are not adjusted for gestational age, the risk associated with planned caesarean is higher - 17% during infancy and 18% during early childhood.

The findings further show that babies born by emergency caesarean are at a small increased risk of any respiratory illness during infancy (7%) and during early childhood (10%); both are statistically significant following adjustment for other factors.

5.4.2 Risk of hospital admission for respiratory illness by mode of birth – comparison with other studies

Paranjothy et al [90] investigated the association between gestational age and emergency respiratory admissions using the SAIL databank, however, with a sample slightly different from the current one, as it was based on earlier births (1990-2008) and included premature and unwell newborns. The outcome definition was very similar to

the definition used in the current study, but using the primary coding position only. The authors reported a respiratory admission rate of 12.2 per 100 child-years during infancy which is comparable to the rate found in the present study of 11.3 per 100 child-years. A slightly lower rate of admission would be expected in my sample, which is focused only on term babies healthy at the time of birth. Likewise, the rate at ages 1 to 4 is also internally validated through this comparison: 5.3 admissions per 100 child-years in the published study[45] compared with 4.6 admissions in the current study.

An external validation of the rate of emergency respiratory admission found here can be made with the study by Cecil et al [194] mentioned previously that had used a sample of English GP practices and examined unplanned HES admissions at ages 1 – 4 years. They reported a rate of 0.5 per 100 child-years for LRTI and 2.0 per 100 child-years for URTI. Although a combined rate was not reported by Cecil et al, it is clear that the rate of emergency respiratory admissions in the current study (4.6 per 100 child-years) is higher. This discrepancy is consistent with that found for admissions during infancy and as explained, may represent a real increased rate of hospitalisation for respiratory infection in Wales compared to England. Furthermore, a report on child health [79] using routinely collected data across UK countries showed that until recently, the asthma admission rate in Wales was higher than in England.

The association of mode of birth with respiratory admission during infancy is, as expected, in accord with the association found for each type of respiratory infection investigated separately in Chapter 4. Babies born by planned caesarean had a 10% increased risk for this outcome, which was also found separately for LRTI and for URTI. Babies born by emergency caesarean had a 7% increase in risk, which was intermediate between the effect of URTI (9%) and LRTI (no statistically significant association) identified separately.

[45] The age range is described as ‘between 1 to 5 years’

A direct comparison with results obtained through the MCS study investigating mode of birth and hospital admission for infectious disease during infancy (Chapter 2) is not possible, since an outcome of any respiratory infection could not be examined in the MCS data. However, the outcome of 'any infection' examined in the MCS study is composed of 45% LRTI and 38% other infection, with only 17% being due to gastrointestinal infection. It is plausible that many of the admissions due to other infections involved the upper respiratory tract, and therefore a cautious comparison between these studies can be made. The findings of the MCS study were an increased risk of planned caesarean (aHR=1.2) and of emergency caesarean (aHR=1.3), both marginally statistically significant (0.04<P-value<0.08). In the analyses using SAIL data, both types of caesarean section were identified as a risk factor for any respiratory infection during infancy (though with a smaller effect size of 7-10%), which is therefore generally similar to the findings of the MCS analysis.

The small increased risk associated with planned and emergency caesarean found during infancy remained essentially constant up to the child's 5th birthday. The study by Paranjothy et al [90] included a binary variable for any caesarean versus any vaginal delivery as a confounder in multivariable models. The excess risk was 10% (aHR=1.10, 95% CI 1.08, 1.12) which is in line with the excess risk found during early childhood in the current study.

Although some studies have examined the association of mode of birth and lower respiratory infections in children older than one year, only a few focused on any respiratory illness or upper respiratory infection in this age group. This distinction is important because of the shift in the type of respiratory illness between infants and older children, the latter being predominantly URTIs. Research published after my study was finalized used the New South Wales population registry [35] in Australia to investigate the effect of medical birth interventions (i.e. induction of labour, instrumental and caesarean delivery) on health risks for children up to 5 years. The researchers found

OR=1.3-1.4 for respiratory infection admission in children born by any medical delivery compared to spontaneous-onset vaginal delivery. The current study found an increased risk of 5-12%, which is a smaller effect size, however is consistent in its trend with the Australian study.

5.4.3 Strengths and limitations of the study

The study described here is one of the few that investigated the relationship between mode of birth and any respiratory infection (in contrast to solely diseases affecting the lower respiratory tract) and that explored the risks beyond infancy into early childhood.

The study has several strengths arising from the data platform used as detailed in section 4.4.5. These include the use of routinely collected population-level data, which minimizes the likelihood of selection bias. The large population size along with the broad outcome definition gives high power to detect even small effects. The focus on hospital admissions minimizes potential variability of disease severity and bias arising from parental health seeking behaviour.

The focus of the current study on a composite outcome of 'any respiratory illness' is an additional strength. An infection may spread from the upper to the lower respiratory tract and may coincide in different areas of the respiratory system at the same time. However, only the site of infection causing greater morbidity would be coded in hospital records. This was demonstrated with only 3% co-occurrence of codes for URTI and LRTI. Using a composite outcome helps address this misclassification. Furthermore, using such a composite outcome is especially important in the preschool age group. In this age group, it is difficult to distinguish between viral-induced wheeze and early stage of asthma development. This outcome, which includes ICD codes for asthma, addresses the challenging diagnostic classification of various wheezing conditions at preschool age.

A limitation of this study is the fact that the outcome does not include admissions that were coded solely for an abnormal breathing symptom such as ICD code R06.2 for

wheezing, but that did not include one of the ICD codes for respiratory disease listed. Inclusion of these admissions within the 'any respiratory illness' outcome could have extended the coverage of respiratory illnesses captured. All the same, most other epidemiological studies of perinatal risk factors for long-term respiratory health have not included ICD codes for respiratory symptoms in addition to codes for disease diagnoses. However, some earlier studies proposed a 'diagnostic transfer' in the UK: a process where admissions previously coded as asthma were being coded as a wheezing disease or wheeze symptom [199,200]. The latter case of asthma being coded as a wheezing symptom would have not been captured as a respiratory illness in the current study.

Additional limitations shared with the other analyses using SAIL data, including residual confounding and missing data, were explained in 4.4.5 and will be further discussed in Chapter 7.

5.4.4 Conclusions

The current study presents evidence of a small elevated risk of severe respiratory illness, of either the upper or lower respiratory tract for children born by emergency or planned caesarean section. Although of small magnitude (~10%), the excess risk persists not only in infancy, but also in early childhood. When gestational age at birth is not adjusted for, the relative risk of respiratory illness admission in children born by planned caesarean is stronger (17-18%)

Chapter 6: An investigation of the association between mode of birth and childhood asthma in Wales

6.1 Introduction

The literature review described in Chapter 1 highlighted asthma as a relatively broadly studied adverse health outcome in relation to mode of birth. My research pointed at persistent wheezing throughout childhood (described in Chapter 3) and hospital admission due to any respiratory illness in early childhood (Chapter 5) as potentially increased following caesarean delivery. The study described in the current chapter delves deeper in the investigation of the possible effect of mode of birth on asthma by examining routine administrative data from Wales and focusing on admissions starting age 5, when diagnosis is more reliable [78].

6.1.1 Study aims

The aim of this study was to investigate the possible effect of mode of birth on the risk of severe or poorly controlled asthma.

The research questions explored were:

1. Is mode of birth associated with hospital admission for asthma in children at ages 5 to 11?
2. Does earlier gestational age indirectly add to any effect of planned caesarean on asthma?

6.2 Methods

All methods used are identical to those specified in section 4.2 with the exceptions detailed below.

6.2.1 SAIL

The SAIL databank and the datasets detailed in 4.2.1 were used for the study described in this chapter too.

6.2.2 Study population

The study population was all births to mothers who were resident in Wales between January 2002 and February 2012 as ascertained from the NCCHD.

6.2.3 Data extraction

Data was retrieved from SAIL datasets as detailed in section 4.2.3 and in Figure 4-1. ICD codes J45 (“Asthma”) and J46 (“Status Asthmaticus”) were used to extract the relevant child admission spells from PEDW.

6.2.4 Dataset merging

The merging of datasets was carried out as detailed in section 4.2.4.

6.2.5 Study inclusion criteria

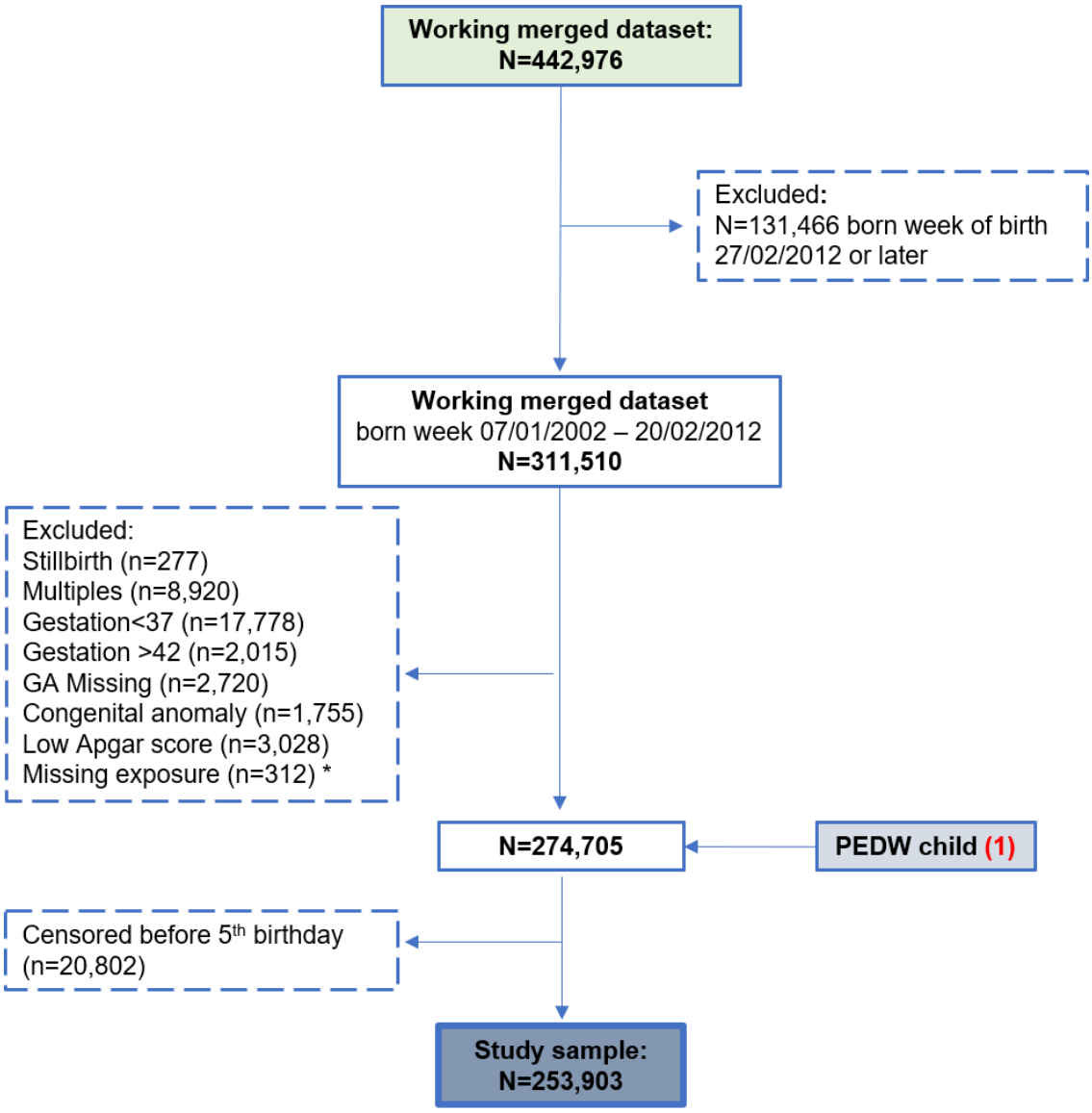
The inclusion criteria for the current study were the same as those specified in 4.2.5. However, since the analysis was focused on hospital admissions from age 5 onwards, a child was eligible for inclusion only if at least 5 years of follow-up were available. Thus, a further limitation of week of birth no later than 27/02/2012 was applied and 131,466 children (29.7% of ‘Working merged dataset’) were excluded. Further exclusions of multiples, children born preterm, with congenital anomaly or low Apgar score were carried out as specified in Figure 6-1. The percentages excluded for each of these

groups of children were very similar to those detailed in section 4.2.5 and are therefore not repeated here. The final sample size was 274,703.

6.2.6 Exposure – mode of birth

Mode of birth was defined as described in section 4.2.6 and categorized into the four sub-groups, as before.

Figure 6-1: Children included in the SAIL asthma study sample**



* Numbers are in sequential order of exclusion
(1) Child's admission spell identified by ALF and one of ICD codes for asthma (J45 or J46)
** See Figure 4-1 for dataflow prior to 'Working merged dataset'

6.2.7 Outcomes – hospital admission for asthma

A hospital admission event was defined as an emergency admission for asthma (ICD code J45 or J46) as the primary diagnosis. The time until a child's first admission for asthma beginning from the week of birth of the 5th birthday and ending just before the week of birth of the 12th birthday, was calculated (7 years of follow-up from age 5 to 11). For children with more than a single admission for asthma, only the first admission during this time frame was included as an outcome event.

6.2.8 Potential explanatory variables

The potential explanatory variables tested for inclusion in the final models were the same as those of the LRTI and URTI analyses, i.e., all variables detailed in Table 4-3.

6.2.9 Statistical analyses

Stata version 14 was used for all analyses.

6.2.9.1 Univariable analyses

As described in section 4.2.9.1.

6.2.9.2 Multivariable analyses

Data was censored at the earliest point in time out of the following: date of death, time of emigration from Wales or February 2017.

6.2.9.3 Testing of the proportional hazards assumption

To test the proportional hazards assumption, the follow-up time was split into two periods as described in section 4.2.9.3. The cut-off was placed at the child's 8th birthday and separate models were fitted for age 5-7 years and 8-11 years. The second interval was set to be longer than the first because of lower frequency of admissions at older ages. The similarity of the hazard ratios between the two models was assessed and log-log plots were generated and examined as detailed previously.

6.2.10 Missing values

The proportion of missing data about smoking in the current study sample was high (58.2%), and equivalent to the proportion of missing smoking data in the study focusing on infectious diseases (59.7%) (Chapter 4). The proportion of missing values for ethnicity (9.9%) and breastfeeding (7.8%) were lower than those for the study on infectious diseases (11.2% and 15.3% respectively). The same approaches for handling missing data described in section 4.2.10 were used here for these three variables here.

6.2.11 Sensitivity analyses for exposure

6.2.11.1 Restriction to observations with validated mode of birth

The sensitivity analysis was carried out as described in 4.2.11.1.

6.2.12 Power calculation

The study's power to detect an association between exposure and outcomes was estimated as described previously using Chi-square test for proportions. The size of the reference group used for these calculations was 177,562, and the size of the exposed groups was 29,672 for planned caesarean and 36,234 for emergency caesarean[46]. The estimated proportion with an outcome was 0.2% [79]. The study had adequate power (80%) to detect an effect size of 1.4. However, for the smaller effect size of RR=1.2 that has been frequently found in studies, the power was estimated at only 30%.

6.2.13 Data access and security

As detailed in section 4.2.13.

6.2.14 Ethics committee approval

As detailed in section 4.2.14.

[46] Calculated based on study sample size prior to left censoring

6.3 Results

6.3.1 Mode of birth – descriptive results

The distribution of mode of birth in the study sample is presented in the top row of Table 6-1 (page 239): assisted vaginal delivery occurred in 11.2% of births, planned caesarean in 11.0%, emergency caesarean in 13.1% and vaginal delivery took place in 64.7% of births.

6.3.2 Study group characteristics

The characteristics of the study groups are also described in Table 6-1. The current study sample includes births up to 2012, while the sample described in Chapter 4 extended until 2016. Nevertheless, the distribution of characteristics amongst the mode of birth groups was analogous to that described in section 4.3.2. The sole noteworthy divergence from the characteristics presented previously is a lower proportion of missing data in the breastfeeding and ethnicity variables. Nevertheless, the distribution within the non-missing data was the same as that described in Chapter 4.

6.3.3 Hospital admission for asthma

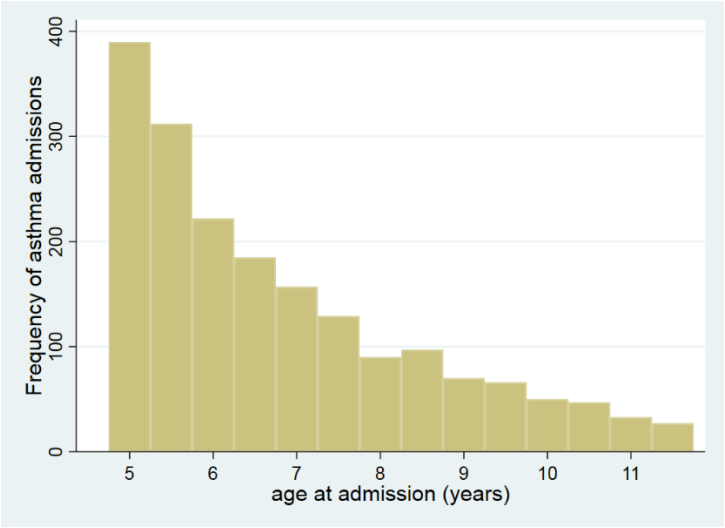
The proportion of children admitted for asthma as the primary indication of an emergency admission between the age 5 and 11 was 0.71% (95% CI 0.68, 0.75) (1,811 events). Almost all of these asthma admissions had an ICD code for ‘Asthma’ (J45) and only 3.2% had a code for ‘Status Asthmaticus’ (J46). A flowchart of the selection process of asthma admissions which met the definition of the outcome is shown in appendix V.

Note that only 43% of admissions that included a code indicating asthma were coded as the primary indication for hospitalisation. In the 57% of spells where asthma was coded as a secondary diagnosis, the most common primary diagnoses were the following:

- 20% - Injury, poisoning, other external causes (“S” ICD code)
- 19% - Diseases of the respiratory system (”J” ICD code)
- 18% - Symptoms, signs, abnormal clinical and lab findings (“R” ICD code)
- 9% - Certain infectious and parasitic diseases (“B” ICD code)
- 7% - Diseases of the digestive system (“K” ICD code)

The frequency of emergency admission for asthma as the primary indication was highest at age 5, fell to almost half a year later and continued declining as the child grew older (see Figure 6-2). Note, however, that not all children were followed up until their 12th birthday - the median age when follow-up ended was 9 years and 7 months.

Figure 6-2: Frequency of hospital admission (first spell) for asthma as the primary indication by child age in the SAIL study*



* each bar represents a 6-month period; follow-up was incomplete for some children

Table 6-1: Characteristics of cohort children and their mother included in the SAIL asthma study by mode of birth

	VD %	Assisted VD %	Planned CS %	Emergency CS %	Total %
Mode of birth n (%)	**164,231 (64.7)**	**28,539 (11.2)**	**27,793 (11.0)**	**33,340 (13.1)**	**253,903 (100.0)**
Maternal characteristics					
Maternal age group (years)					
<20	9.8	10.2	2.6	7.4	8.7
20-29	52.8	50.1	38.8	46.5	50.1
30-39	35.2	37.4	53.6	42.7	38.5
≥40	2.2	2.4	5.0	3.4	2.7
Area deprivation quintile (WIMD)					
1st (most deprived)	28.1	21.8	23.0	23.0	25.2
2nd	22.0	20.9	21.4	21.7	21.8
3rd	19.0	19.7	19.1	19.7	19.1
4th	16.0	18.3	16.9	18.1	16.7
5th (least deprived)	15.0	19.4	19.6	17.5	16.3
Nulliparous [a]	36.2	76.5	21.7	66.2	42.8
Maternal smoking [b]					
Non-smoker	31.2	32.8	35.1	34.9	32.3
Gave up in pregnancy	1.4	1.6	1.0	1.7	1.4
Smoker 0-9 a day	4.5	3.3	2.9	3.2	4.0
Smoker ≥10 a day	4.5	2.5	3.4	3.1	4.0
Missing	58.5	59.8	57.7	57.2	58.3
Maternal asthma	4.6	5.1	5.6	5.4	4.9
Diabetes	1.1	1.4	4.0	2.8	1.7
Hypertensive condition	4.4	8.2	4.5	10.5	5.6

(table continues on next page)

	VD %	Assisted VD %	Planned CS %	Emergency CS %	Total [c] %
Infant characteristics					
Male	49.8	54.1	50.8	55.1	51.1
Child ethnicity [b]					
White	82.3	83.7	83.8	83.9	83.6
Mixed	1.9	1.8	1.5	1.7	1.8
Indian/Pakistani/ Bangladeshi	2.0	1.8	1.6	2.0	1.9
Black	0.7	0.4	0.7	0.8	0.7
Other	2.1	2.2	1.9	2.4	2.1
Missing	10.1	9.1	10.6	9.2	9.9
Gestational age					
37-38 (early term)	16.1	13.1	37.0	17.9	18.3
39-40 (full term)	56.5	51.5	55.2	44.8	54.2
41 (late term)	23.5	28.4	6.3	28.6	22.9
42 (post term)	3.9	7.0	1.5	8.7	4.6
Birthweight [a] **in kg,** mean (SD)	3.43 (0.47)	3.46 (0.46)	3.45 (0.50)	3.52 (0.54)	3.44 (0.48)
Any breastfeeding [b]					
Yes	51.6	58.2	51.4	56.4	53.0
No	40.8	34.4	40.5	35.4	39.3
Missing	7.6	7.4	8.1	8.2	7.7

a Variables with ≤10% missing - percentages are calculated from non-missing (97.7% for birthweight and 93.3% for nulliparity).
b Variables with >10% missing – percentages are calculated from total; missing category shown.
c P-value for all characteristics was <0.001

6.3.4 Mode of birth and hospital admission for asthma during childhood

Overall, the rate of hospital admission for asthma at ages 5 to 11 was 0.16 per 100 child-years (Table 6-2) and ranged between 0.16 per 100 child-years in children born by vaginal delivery to 0.19 per 100 child-years in those born by emergency caesarean. The rate of admission in children with the potential for full follow-up until age 11 years (those born in 2002-2004) was comparable to that of the total sample – 0.15 per 100 child-years.

Children born by assisted vaginal delivery had a HR=1.08 for asthma, which was not statistically significant in both the crude and adjusted models. Children born by planned caesarean had a non-significant hazard ratio of 1.11, and following adjustments the risk remained the same (aHR=1.12; 95% CI 0.95, 1.32). Children born by emergency caesarean had a 22% increased risk of asthma admission (HR=1.22; 95% CI 1.07, 1.39) which remained similar following adjustments (aHR=1.20; 95% CI 1.04, 1.39; P=0.012). The cumulative hazard can be seen in Figure 6-3.

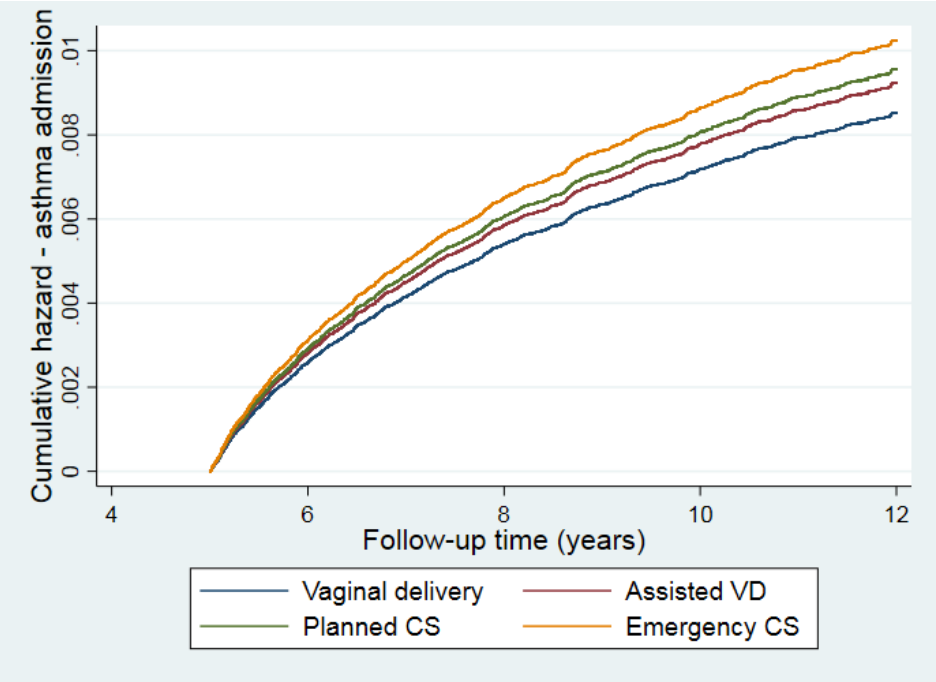
The results of the sensitivity analyses were not materially different from those of the main analysis. The hazard ratio for emergency caesarean was smaller than in the main analysis (aHR=1.07) when using a complete case approach, but similar (aHR=1.21) when using multiple imputation. The adjusted hazard ratio for planned caesarean in these sensitivity analyses was slightly higher than in the main analysis, but was not statistically significant. The results of the analysis using a validated mode of birth variable were not substantially different from the main analysis for emergency caesarean delivery, although with a smaller effect (aHR=1.15), but there was no association found with planned caesarean (Table 6-2).

Table 6-2: Association between mode of birth and hospital admission for asthma during childhood in the SAIL study

	Main analysis					Sensitivity analyses		
						Adjusted HR (95% CI)		
	No. of events	Child-years	Rate per 100 child-years	Crude HR (95% CI) n=253,903	Adjusted HR [a] (95% CI) n=236,817	Complete case analysis [b] n=90,705	Multiple imputation [b] n=236,817	Validated mode of birth [a] n=124,084
Total	**1,811**	**1,100,867**	**0.16**					
VD	1,127	721,823	0.16	1.00	1.00	1.00	1.00	1.00
Assisted VD	200	116,358	0.17	1.08 (0.93, 1.25)	1.08 (0.92, 1.28)	1.10 (0.85, 1.43)	1.08 (0.92, 1.28)	1.14 (0.90, 1.44)
Planned CS	210	119,691	0.18	1.11 (0.96, 1.29)	1.12 (0.95, 1.32)	1.16 (0.88, 1.51)	1.13 (0.96, 1.33)	1.01 (0.78, 1.30)
Emergency CS	274	142,995	0.19	1.22 (1.07, 1.39)	1.20 (1.04, 1.39)	1.07 (0.85, 1.36)	1.21 (1.04, 1.39)	1.15 (0.93, 1.42)

a Adjusted for year of birth
b Adjusted for maternal age, area deprivation quintile, nulliparity, smoking (with missing category), maternal asthma, hypertensive conditions, child's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category) and year of birth
c Adjusted for maternal age, area deprivation quintile, nulliparity, smoking, maternal asthma, hypertensive conditions, child's sex, ethnicity, gestational age, birthweight, breastfeeding and year of birth

Figure 6-3: Cumulative hazard of asthma hospital admission by mode of birth in the SAIL study



6.3.5 Testing of the proportional hazards assumption

As in Chapter 4, the proportional hazard assumptions were tested and there was no strong evidence that they were violated in these analyses.

6.3.6 Added indirect effect through earlier gestational age at delivery

When comparing a model adjusted for all variables with a model adjusted for all apart from gestational age, the findings were consistent with those shown in all previous chapters. The risk of asthma in the planned caesarean group strengthened (HR=1.18 versus 1.12), whereas the risk in children born by assisted vaginal or emergency caesarean did not change.

Table 6-3: Multivariable models for the association between mode of birth and asthma in the SAIL study, adjusted or unadjusted for gestational age

	Asthma admission age 5 to 11	
	Fully adjusted [a] **HR (95% CI)**	**Unadjusted for gestational age [b]** **HR (95% CI)**
VD	1.00	1.00
Assisted VD	1.08 (0.92, 1.28)	1.08 (0.92, 1.27)
Planned CS	1.12 (0.95, 1.32)	1.18 (1.01, 1.38)
Emergency CS	1.20 (1.04, 1.39)	1.21 (1.05, 1.40)

a Adjusted for maternal age, area deprivation quintile, nulliparity, smoking (with missing category), maternal asthma, hypertensive conditions, child's sex, ethnicity (with missing category), gestational age, birthweight, breastfeeding (with missing category) and year of birth
b Adjusted for the variables mentioned in (a) except gestational age

6.4 Discussion

6.4.1 Summary of results

The current study aimed to examine whether mode of birth is associated with hospital admission for asthma in primary school aged children. The results provide support for the hypothesis that mode of birth is associated with severe or poorly controlled asthma that required hospital admission.

Assisted vaginal delivery was not shown to be a risk factor for hospital admission for asthma. Planned caesarean had a 12% higher risk of asthma than vaginal delivery, but this was not a statistically significant association. When the effect of gestational age was not adjusted for, this risk increased to 18% compared vaginal delivery and was marginally statistically significant (P=0.038). Emergency caesarean was associated with a 20% higher risk of admission for asthma in children aged 5 to 11 (P=0.012).

6.4.2 Risk of asthma by mode of birth – comparison with other studies and with the MCS study

The prevalence and rate of asthma admission in this study was very low with only 0.71% of children age 5 to 11 admitted and a corresponding rate of 0.16 per 100 child-years. Paranjothy et al [90] reported a higher rate of asthma admissions of 0.7 per 100-child years using the same outcome definition in a cohort based on SAIL datasets, but for admissions at ages 1 to 5. The lower rate found in the current study is partially the consequence of the older age range since only 40% of the children ever admitted for asthma had an admission from age 5. A detailing of the process of deriving the relevant spells that address the asthma outcome definition is shown in appendix V. Furthermore, as discussed previously, the published study [90] included children born prematurely that were shown to have a higher risk of asthma admission. A report by the Royal College of Paediatrics and Child Health from 2017 [79] presented statistics about emergency asthma admissions in under 19s using data collected by NHS Wales Informatics Services through PEDW. The prevalence reported for the years 2003-2012 ranged between ~0.21% and ~0.29% and is thus roughly comparable to the rate of 0.71% described here for a narrower age range. The proportion of asthma admissions I had found is also comparable to the proportion of MCS participants recently reported to have had a hospital admission for wheeze or asthma between ages 5 to 7, which was also 0.7% [176]. Although the proportion is identical, the measurement is slightly different from mine: the MCS represents the entire UK, the timeframe for admission is shorter and no children were excluded. Furthermore, only the most severe case of hospital admission for each child was reported in the MCS.

As described in Chapter 1, several meta-analyses [93,116–118] concluded that caesarean section poses a 20% higher risk of asthma or wheeze outcomes compared with vaginal delivery. One meta-analysis [117] conducted a sub-group analysis including seven studies that reported asthma hospitalisation (as opposed to any asthma/wheeze

outcome), and the finding of a 20% increase remained the same. Likewise, another meta-analysis [118] reported on a sub-group analysis where studies measuring asthma hospitalisation were excluded, and results remained consistent with the main analysis.

Several additional studies not included in these meta-analyses and utilizing hospital records to investigate the association between mode of birth and asthma in children came to a similar conclusion. A large study using Danish population registry data [107] examined a binary variable of caesarean compared to vaginal delivery and its association with inpatient and outpatient admissions for asthma (primary or secondary diagnosis). The study excluded preterm babies by using a birthweight proxy. The results showed that caesarean delivery increases the risk of admission by 23%. Acknowledging the potential inaccuracy of a diagnosis at early ages, the authors conducted a sensitivity analysis of admission after age 5 and came to a similar conclusion, but with a slightly smaller risk (16%). The models were not reported to have been adjusted for gestational age and can therefore be compared with the analysis unadjusted for gestation in the current study. Thus, the findings from my study of an 18-21% increase in the risk of admission (Table 6-2) is comparable to the results of the Danish study.

As discussed previously, some studies have differentiated between planned and emergency caesarean, and one meta-analysis that inspected this distinction [93] concluded that both types of caesarean are risk factors with effect sizes of similar strength. However, this analysis also found a large degree of heterogeneity (I^2=85% P<0.001) in the association between emergency caesarean and asthma. Some studies that focused particularly on hospital admission for asthma and differentiated the two types of caesarean, found both types of caesarean to be risk factors. For example, a study using Scottish registries [105] examined mothers with a history of caesarean section and investigated the risk for asthma admission up to age 21 years in planned and unplanned repeat caesarean. The researchers reported a hazard ratio of 1.2 (statistically significant) in both types of caesarean compared to a successful vaginal

birth after caesarean. The same increase of 20% in risk was described in the Scottish population when focusing only on first births and comparing elective and emergency caesarean sections [104]. However, other studies highlighted planned caesarean as a stronger risk factor than emergency caesarean, unlike the findings of this thesis. A study using Danish population registries [86] examined diagnosis of asthma at ages 0-14 and reported that the increase in risk for acute caesarean was 6% (but statistically significant) and that of elective caesarean was higher – 24%. Another study utilizing the Swedish national registries [91] and focusing on hospital admission of term born children from 1 to 13 years of age identified that acute caesarean is associated with a 26% increase in odds, while elective caesarean with a 38% increase. The Swedish study examined this association further by comparing with a control group of children admitted to hospital for reasons other than asthma or gastroenteritis (the studied outcomes). The effect following acute caesarean was no longer statistically significant, however the effect of elective caesarean was only slightly attenuated to OR=1.23 and was still statistically significant. Conversely, a recent study based on the population of New South Wales [35] did not identify an association between mode of birth and hospitalisation for asthma in healthy pregnant woman giving birth at term. However, the study examined admissions only up to age 5, when diagnosis is less reliable.

Within studies relying on parental report of asthma and asthma symptoms, a recent large meta-analysis of nine European cohort studies concluded that elective caesarean is a risk factor for asthma, while emergency caesarean is not, and the findings were more pronounced within term-born children [111].

Therefore, my findings regarding emergency caesarean being a risk factor for asthma hospital admission with a magnitude of 20% increased risk, is aligned with some, but not all, of the prior research. My findings regarding planned caesarean of a non-statistically significant 12% increased risk (when adjusted for gestational age) do not fully agree with prior research, that generally identified somewhat higher relative risks.

A possible explanation for the absence of a statistically significant association between planned caesarean and asthma admission is the rarity of the outcome, as most exacerbations of asthma are prevented or managed in the community. This resulted in very low power, estimated at ~30% to detect an effect of RR=1.2. Therefore, there was a high chance of not detecting a statistically significant association when a true association is actually present.

The outcome definition in the current study is not directly comparable to the asthma-related outcomes investigated through the MCS, since it was not possible to measure hospital admissions for this indication in the MCS. After the initial survey carried out at 9 months, the question regarding hospital admission changed to focus only on the most severe reason for admission and the data quality was therefore not good enough to be used as an outcome. Nevertheless, the wheezing phenotypes examined through the MCS distinguish children with transient wheeze from those with persistent or late-onset wheeze, where a diagnosis of asthma may be more valid. The definition of the transient wheeze phenotype was children that had wheezed early on, however were not reported to wheeze in the past year when interviewed at ages 5, 7 and 11. Since the age range of outcome definition in my SAIL study commenced at 5, it would be unlikely for a child with transient wheezing to be counted as experiencing an event in this study. Those with persistent or late-onset wheezing would, in theory, be the pool of children from which some would have severe exacerbations that require hospital admission. These children would satisfy the outcome definitions of my SAIL study. Therefore, a broad comparison between the current study and that of the wheezing phenotypes would only be possible for the persistent and late-onset phenotypes. Both the MCS and the SAIL studies have highlighted caesarean sections as possible risk factors for an asthma-related outcome: planned caesarean was highlighted as a potential risk factor for persistent, but not late-onset wheezing, while emergency caesarean was highlighted as a risk factor for hospital admission for asthma within the population of Wales.

6.4.3 Strengths and limitations of the study

The study's main strength is its use of linked population-level routinely collected administrative datasets, as discussed in Chapters 4 and 5.

Further strengthening the study is the high validity of the outcome definition. Almost all prior studies examining the association between mode of birth and hospital admission due to asthma have used a less rigorous outcome definition. Many previous studies have not accounted for whether the primary indication for hospitalisation was due to asthma or alternatively, whether asthma was only a secondary indication. Since asthma is a chronic condition, a child might be given a secondary ICD code for asthma even when the reason for seeking medical help is unrelated. The drawback of studies defining the outcome as asthma at any diagnostic position is demonstrated in section 6.3.3: a large proportion of admissions where asthma is coded as a secondary indication were for reasons entirely unrelated to asthma. The proportion of admissions unrelated to asthma is at the very least 27% (injury or diseases of the digestive system) but is likely much higher. Further enhancing the validity of the study's outcome was the focus on admissions from age 5 onwards and not earlier. NICE guidelines for diagnosing and treating asthma acknowledge the difficulty of confirming an asthma diagnosis in children younger than 5 [82]. The reason that an asthma diagnosis is less reliable at preschool age, is the difficulty in distinguishing asthma from transient wheeze due to bronchiolitis, viral respiratory disease or exercise induced wheeze. Furthermore, some of the objective diagnostic tests for asthma are not generally performed in younger children. This limitation of diagnosis reliability in younger children is widely accepted and indeed some studies, such as that of Sevelsted et al [107], have addressed it through a sensitivity analysis. However, most studies examining mode of birth and hospital admission for asthma have measured admissions starting at birth or at age 1-2, thus compromising the outcome reliability. Therefore, the outcome used in my study, which

includes only emergency admissions for asthma as the primary diagnosis from age 5, is unique in its stringency.

The main limitation of the study also arises from the outcome definition. My focus was on hospital admissions due to asthma, which represent cases of severe or poorly controlled asthma (section 1.5.3). It is important to emphasise that these cases do not represent the full range of children suffering from asthma, since the majority of cases would not require secondary care, but rather be managed in primary care. A study examining GP records of Welsh children found that 10.7% of 11 year olds had a diagnosis of asthma [177], a prevalence markedly higher than that of children admitted to hospital for asthma in my study and others.

Furthermore, the study's definition of hospital admissions for asthma was a narrow one, focusing only on admissions with the primary ICD code for asthma and only starting at age 5. As explained in section 6.3.3, 57% of first asthma admissions were primarily for other reasons, and 60% of first primary asthma admissions actually took place at younger ages than 5. Thus, the outcome definition, although identifying highly reliable severe or poorly controlled asthma cases, defined a rare outcome. Therefore, although the population was large, the study had low power to detect real effects if in reality they exist.

As mentioned previously, further limiting the study is the potential for residual confounding arising from crudely estimated or unavailable variables which may give rise to an apparent association that is not a real one, and missing data that may lead to biased associations.

6.4.4 Conclusions

The current study provides evidence that singleton children born by emergency caesarean section at term and that did not experience major health problems at the time of birth have an estimated 20% increased risk of hospital admission for asthma at age

5-11. The evidence for an increased risk following planned caesarean section, independent from other variables, is weak, although the study's power was relatively low. However, the study provides evidence that delivery by planned caesarean at early gestational age may put the children born by this method at increased risk of asthma.

Chapter 7: Overarching discussion

7.1 Introduction

The overall aim of this thesis was to elucidate whether mode of birth is associated with infectious disease, wheezing illnesses and asthma during infancy and childhood. The findings of each study were summarized in the discussion section of each chapter and when applicable, the results arising from the SAIL and the MCS parts of the thesis research were compared.

In the current chapter I first summarize the thesis findings and then the indirect effect of mode of birth through gestational age. I then propose some methodological explanations for the findings as well as review the biological mechanisms that might provide an explanation of the findings, assuming the effect is causal. Next, I discuss the overall thesis findings. Finally, I highlight some recommendations for research, practice and policy arising from the findings.

7.2 Summary of thesis findings by mode of birth

The research carried out in the framework of this thesis investigated specific outcomes for singleton infants and children born in the UK at term with no major health problems at the time of birth.

The research provides very little evidence of an association between planned caesarean and hospital admission for gastroenteritis during infancy, but there is some evidence to suggest that the risk of admission due to any infectious cause is increased in these

infants (RR[47]=1.23) (Figure 7-1). Furthermore, my research provides fairly consistent evidence of a small increased risk of respiratory infections and wheezing illnesses during infancy and early childhood following planned caesarean. There is evidence of an increased risk of hospital admission for LRTI during infancy (RR=1.39 in the MCS and RR=1.10 in SAIL) as well as evidence of an increased risk of URTI (RR=1.11 in SAIL). Likewise, the risk of any respiratory hospital admission in infancy is slightly increased (RR=1.10 in SAIL) and persists up to age 4 (RR=1.12). There is also evidence that children born by planned caesarean are at increased risk of experiencing persistent wheezing during childhood (RR=1.34 in MCS), but there is not enough evidence to suggest the same regarding asthma admission (RR=1.12; 95% CI 0.95, 1.32).

The research provides evidence that emergency caesarean is associated with hospital admission for gastroenteritis during infancy (RR=1.21 in SAIL and RR=1.52 in MCS) although the finding from the MCS is of lower certainty (Figure 7-2). There is not enough evidence to suggest that emergency caesarean is associated with LRTI hospital admissions in infancy, however there is some evidence of a slight increased risk of URTI (RR=1.09) or any respiratory admission (RR=1.07) during infancy, which persists up to age 4 (RR=1.10). There is only little evidence to suggest that emergency caesarean is associated with wheezing phenotypes in childhood in term-born children (Figure 7-2), although there is stronger evidence of this association when preterm and unhealthy neonates are included. There is further evidence that emergency caesarean is a risk factor for asthma admission (RR=1.20) in term-born children.

This thesis provided very little evidence that assisted vaginal delivery is a risk factor for infectious disease, wheezing or asthma (Figure 7-3). There is only weak and inconsistent evidence of an association with gastroenteritis during infancy (RR=1.09) and any respiratory admission during early childhood (RR=1.05).

[47] All relative risks are adjusted

Figure 7-1: Summary of findings regarding the effect of planned caesarean on childhood infectious diseases, wheezing and asthma

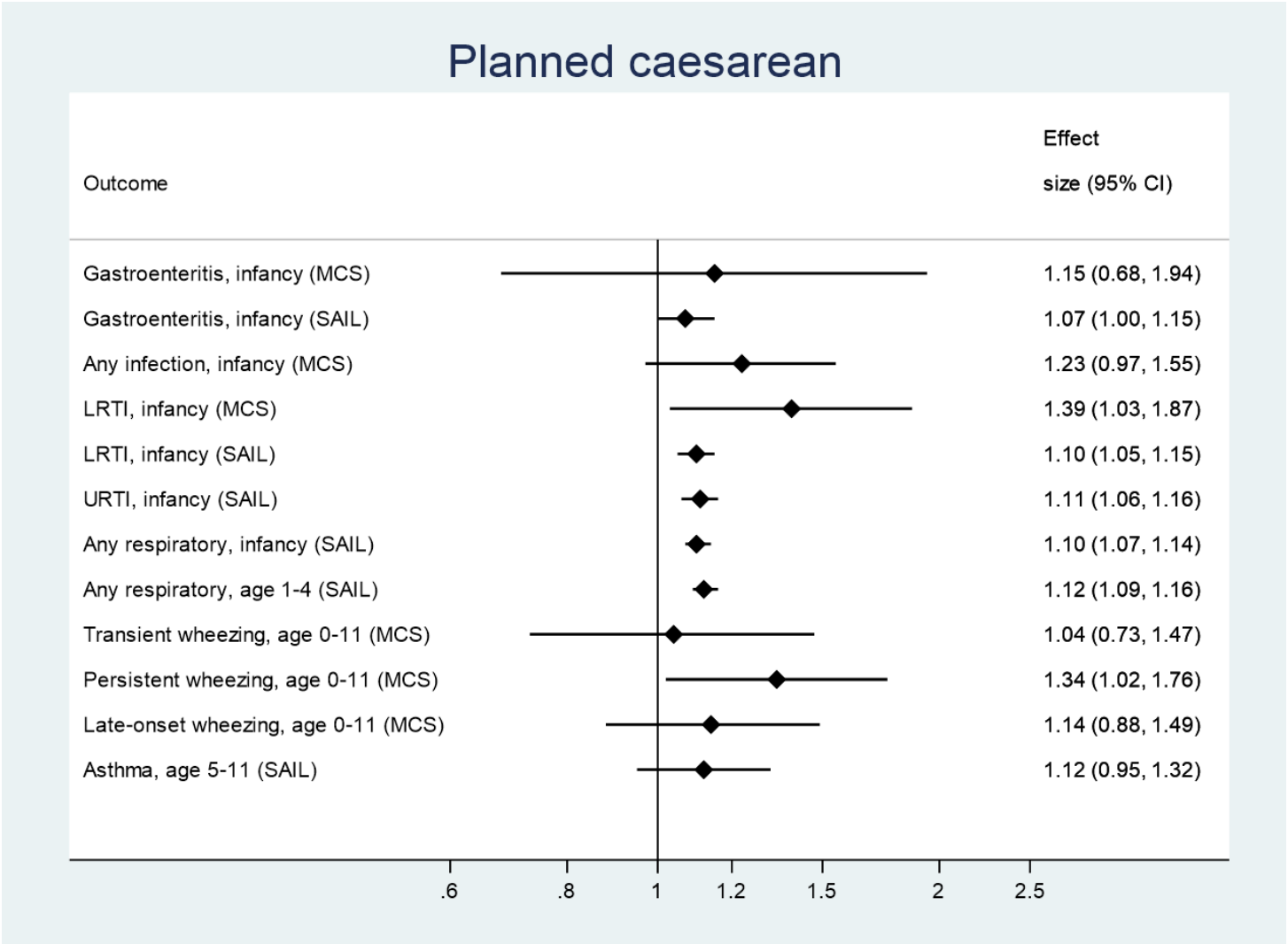


Figure 7-2: Summary of findings regarding the effect of emergency caesarean on childhood infectious diseases, wheezing and asthma

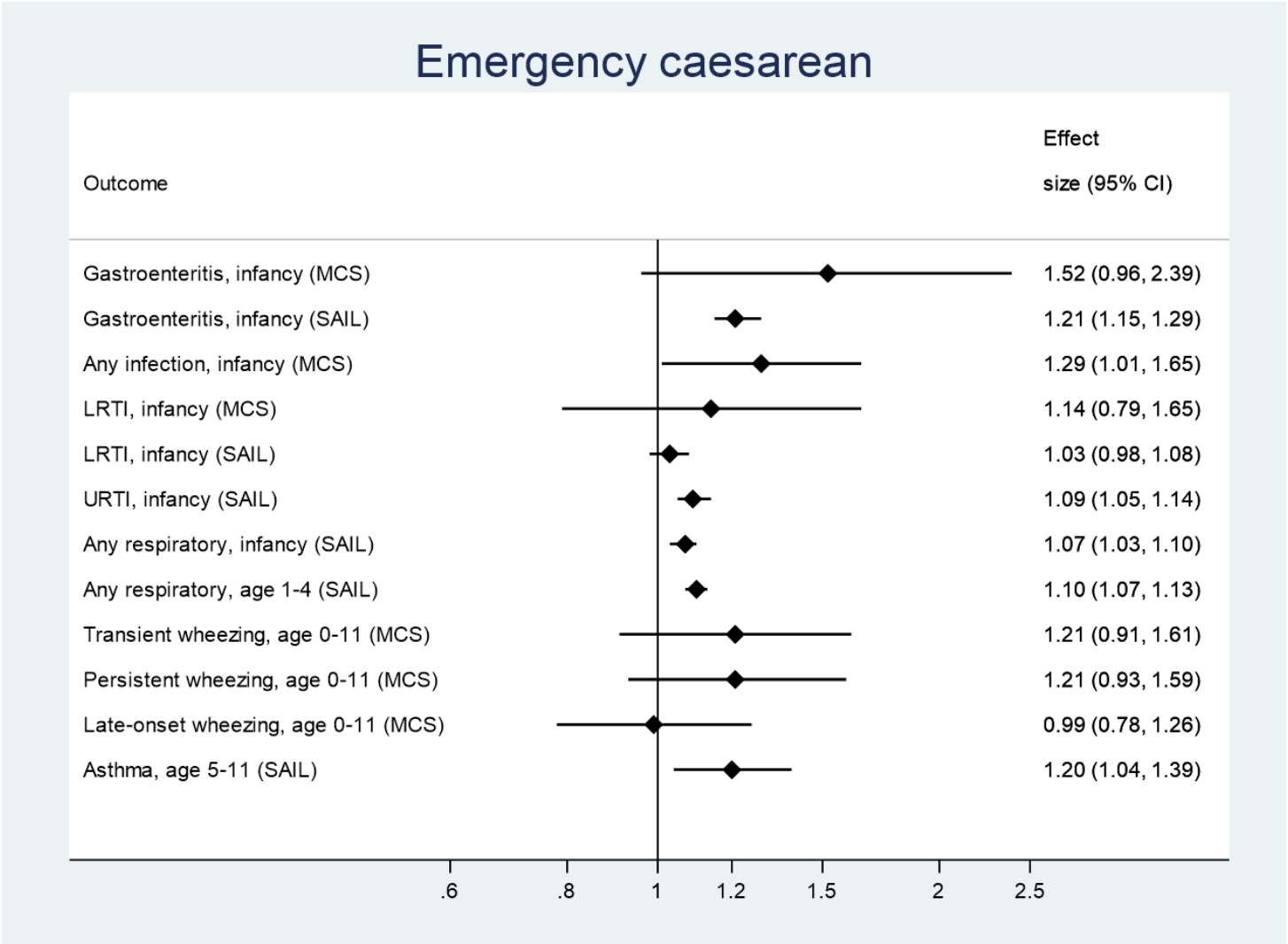
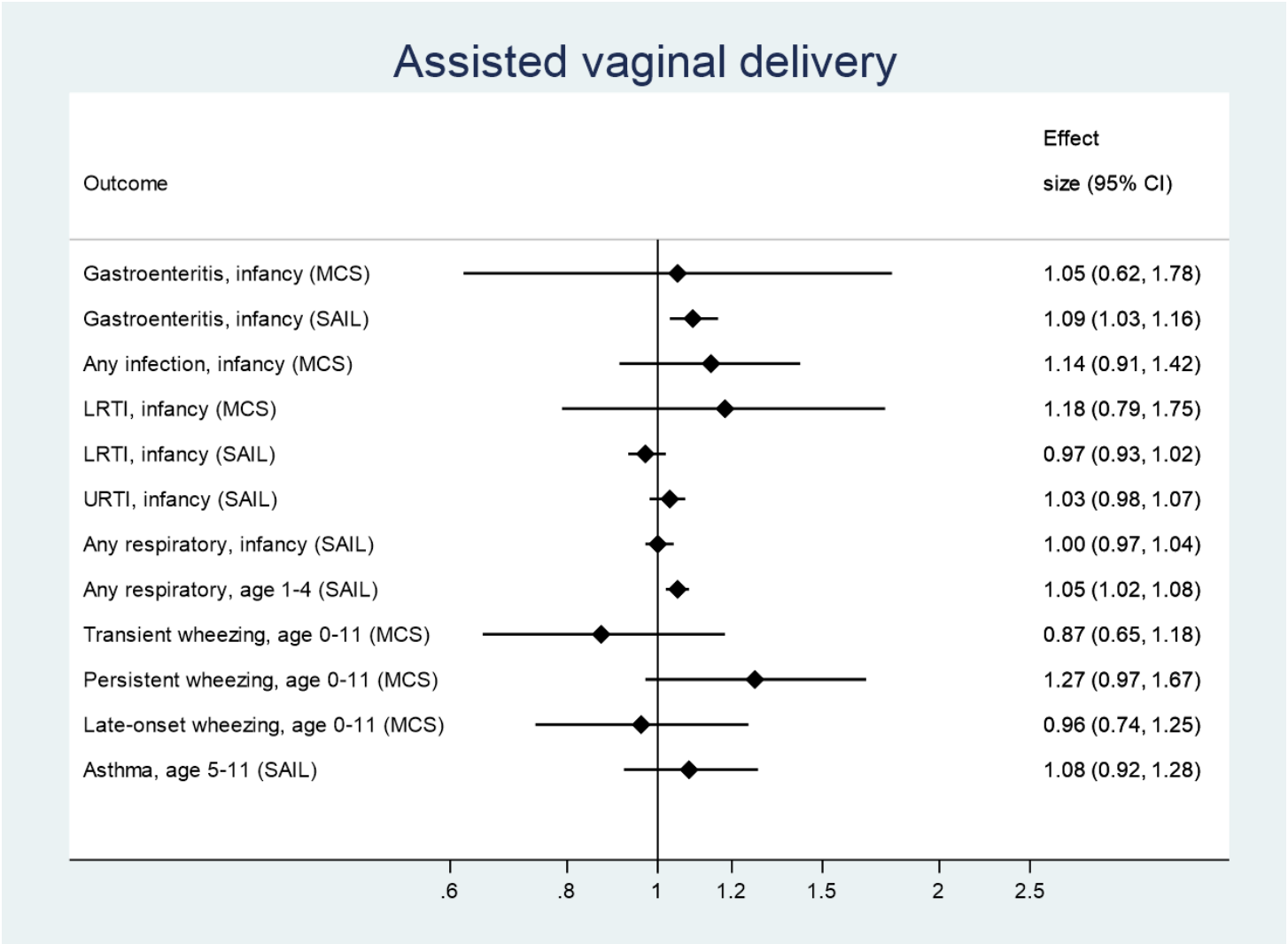


Figure 7-3: Summary of findings regarding the effect of assisted vaginal delivery on childhood infectious diseases, wheezing and asthma



7.3 Indirect effect of mode of birth through delivery at earlier gestational age

Gestational age is a potential confounder of the association between mode of birth and child health outcomes. In the case of planned caesarean section, the timing of delivery is the result of the decision to schedule a caesarean. In this type of delivery, therefore, gestational age may be on the causal pathway between mode of birth and childhood outcomes. Adjustment for gestational age would thus mask some of the added, indirect effect of mode of birth through delivery at earlier gestation.

NICE guidelines [20] recommend caesareans to be scheduled no earlier than 39 weeks gestation. However, in the years 2000-2002 when the MCS children were born, this was not common practice in the UK. Rather, the majority (54.2%) of planned caesareans in this sample, which is focused on births at 37-42 weeks, were performed at early term. In the Welsh sample, the average timing of birth for planned caesarean deliveries was earlier than that of vaginal deliveries. However, the difference became smaller over time as the timing in which caesareans were scheduled was gradually delayed. This change in practice likely reflects a gradual implementation of the NICE recommendation.

Indeed, the current study presents evidence suggesting that the increased risk of infectious disease, persistent wheezing or asthma experienced following planned caesarean section is higher when the earlier gestation for the scheduled delivery is not adjusted for. This added, indirect, effect was observed consistently for planned caesarean in all examined outcomes where this type of delivery was found to have an adverse effect. Such an added effect of gestational age was not observed for the other medically interventional modes of birth.

The added, indirect, effect of mode of birth through earlier delivery is more pronounced in the MCS analyses compared with the Welsh analyses. This is in line with generally

smaller relative risks associated with mode of birth identified in SAIL data compared with the MCS. Furthermore, the added effect is probably diluted because of the shift from planned deliveries at 38 weeks to deliveries at 39 weeks that had taken place over time in the Welsh population.

Although most prior studies investigating the long-term effects of mode of birth have simply included gestational age as a confounder, some have attempted to understand the effect of each factor separately. For example, Bentley et al [92] investigated the independent and combined effects of mode of birth, breastfeeding and gestational age on gastroenteritis. Similar to my results, the researchers found that each factor is a risk factor in itself and that the combined effect is greater than the individual effects. Edwards et al [128] investigated early compared to full term delivery as well as caesarean compared to vaginal delivery and their effect on childhood wheezing. They found that when holding gestational age constant, caesarean section was not a statistically significant risk factor, but when holding mode of birth constant, early term delivery was a risk factor. The authors later called for further studies of the independent effects of caesarean delivery and early term birth on child respiratory health [201].

It is noteworthy that my study is limited by the unavailability of reliable data about induction of labour. Roughly a fifth of births in the UK are induced, i.e., delivered earlier than their physiologically-determined timing [11,202]. To better understand the effect that delivery at an earlier gestational age has on the association between planned caesarean and child health outcomes, one must consider whether the onset of labour in the reference group of vaginal birth was spontaneous.

7.4 Possible non-causal explanations for the findings

The three main pillars of possible non-causal explanation of an association in epidemiology are: chance, bias and confounding. The likelihood that each one may explain the research findings is explained here.

7.4.1 Chance

7.4.1.1 Power

It is generally accepted that 80% is the threshold of adequate power for a study, where power is the chance of detecting an effect when it indeed exists in the population. However, in the studies using the MCS data and in the study of asthma hospitalization in Wales, the estimated power was much lower than 80%. The main concern arising from low power is a higher than acceptable likelihood of a type 2 error (mistakenly 'accepting' the null hypothesis). Although it is scientifically impossible to prove that an association does not exist, one can better trust that a null finding is not the result of such error when there is adequate power. This limitation was at least partially addressed by using the SAIL dataset (with high power) to investigate parallel outcomes to those investigated in the MCS. However, due to this limitation, some questions, such as the effect of planned caesarean on asthma hospital admission, where the power was low and no statistically significant association was found, were still left unanswered.

Underpowered studies might also suffer from inflated effect sizes leading to a spurious association when a true one does not exist in the population [203]. This limitation was also addressed by investigating duplicate or similar outcomes in different datasets and comparing findings.

Very high power also has its caveats. In such a case (for instance, in the analyses of any respiratory illness in SAIL), even a very small risk increase which is not clinically

important, may be statistically significant. The meaning of such a small effect to the individual may be of no consequence. Nevertheless, at the population level, especially when the prevalence of the exposure is high and continuously increasing, any effect (provided it is real) could be of interest.

7.4.1.2 P-value threshold

The P-value threshold set in this thesis for a result to be considered statistically significant was 5%. Some of the studies included in this thesis examined numerous outcomes in parallel. This was especially true for the analysis of wheezing phenotypes and the secondary outcomes that supported the study. Furthermore, because the exposure variable is divided into 4 sub-categories, each analysis inherently includes 3 relative risks. This increased the probability of finding a statistically significant association by chance, when a true one does not really exist in the population (type 1 error). Again, the fact that I had carried out parallel or similar investigations using two different datasets and found generally consistent results reduces the likelihood that significant effects are due to chance. Likewise, the general findings of a higher risk of infection, wheezing or asthma in infants and children born by caesarean section are in line with previously published research. In theory, publication bias could explain the associations described in the literature, however, at least with regards to asthma, the available meta-analyses did not find evidence of such bias [93,116,117]. This strengthens the confidence that the associations found here are genuine.

7.4.2 Bias

7.4.2.1 Selection bias

Selection bias is not a major concern for the studies reported in this thesis. In the MCS, families were sampled from child benefit records, which at the time of recruitment included almost the entire UK population of recently born infants. Although selection bias could have been introduced by the fact that only babies still alive at 9 months were

eligible for inclusion, this excluded only a very small percentage – 0.6% of all births [161]. The survey weights provided by the CLS corrected for bias resulting from non-response to the initial survey and thereby minimized any effects of potential selection bias. Furthermore, for the longitudinal investigation of wheezing phenotypes, the CLS weights also corrected for non-response to later surveys (loss to follow-up). As shown, the characteristics of the sample individuals who took part in all 5 surveys matched those of the first survey, suggesting that the weighting adequately corrected for any bias arising from loss to follow-up.

Being based on the complete population of Wales, the studies using SAIL data are not prone to substantial selection bias either. However, some bias might have been introduced through unlinked records (9.7%). Unsuccessful linkages were, to a large extent, the result of homebirths that do not have a PEDW delivery record and to a smaller extent due to stillbirths or other reasons. A comparison of key characteristics revealed that the linked population was only slightly less representative of vaginal births and of older, multiparous mothers. Most of the difference in characteristics was indeed explained by the homebirths in the unlinked records. Nevertheless, the unlinked records were similar to the linked sample in other characteristics such as sex, ethnicity, gestational age within term and smoking. It is therefore unlikely that major selection bias was introduced through unlinked records.

Additional bias could have been introduced through the emigration of families out of Wales. However, there was no evidence that the characteristics of the original population under study (Table 4-7) are different from the characteristics of those that had not emigrated by age 5 (Table 6-1). Furthermore, although missing data has the potential to introduce selection bias, this is not a major concern. In both the MCS and SAIL studies, missing values in exposure and outcome data were uncommon. In the MCS studies, missing data on confounders was also minimal. In the Welsh studies I

refrained from removing individuals missing confounder data and avoided the possible resulting selection bias by using a category for missing values in multivariable models.

Lastly, although the studies using Welsh data did not include homebirths (apart from transfers to hospital) or births in private facilities, these represent a very small percentage (~3%) of all births. Furthermore, homebirths were included in the studies using MCS data.

7.4.2.2 Information bias

Information bias arises from errors in measuring or recording variables, and is sometimes referred to as misclassification. Non-differential misclassification might take place when exposure, outcome or other variables are misclassified, but not in a manner linked with the exposure or the outcome. Inaccurate recall may be a source of non-differential misclassification. In the MCS, inaccurate recall may theoretically bias the exposure - maternal report of mode of birth. However, my results showed that mother's report of mode of birth disagreed with hospital records rarely - in less than 5% of cases. The mother's report of hospital admission for LRTI or gastroenteritis is also not likely to be very inaccurate for reasons discussed in 2.4.6. The outcome of 'any infection' may be more prone to this type of bias due to being comprised also of open text responses.

Non-differential misclassification may have also taken place within additional variables. For example, in the MCS, the ISAAC questionnaire focuses solely on wheezing and does not include cough, which is also a symptom of asthma [177]. Non-differential misclassification also takes place through ambiguity in the cut-off set between the wheezing phenotypes and in general inaccurate parental recall of recent wheeze. In the Welsh analyses, non-differential misclassification would take place if diagnoses for hospital admission are unclear. For instance, it may arise by not including ICD codes for 'wheezing' symptom as part of the 'any respiratory' outcomes. Misclassification would

have also been a potential problem for children admitted to hospital in England instead of Wales, however, as mentioned previously, PEDW includes HES admissions.

Differential misclassification of exposure or outcome may take place if the likelihood of misclassifying one depends on the value in the other. Parental recall bias is a theoretical source of differential misclassification, however, it is unlikely to have had a major influence on my analyses using the MCS. As explained previously, report of a dramatic event such as hospital admission is not likely affected by recall bias. Further, the sample did not include children born prematurely or those with serious illness postnatally, therefore the birth event is less likely to influence the parents' report of recent wheezing or hospital admission. In both the MCS and the Welsh analyses, the focus on children born at term also minimizes any potential physician bias when deciding whether to admit a child to hospital. Since the current state of knowledge does not tie the outcomes under investigation (apart from asthma) to mode of birth, the perinatal history of the child with regards to mode of birth would unlikely affect this decision. This is not necessarily true for children that had been born prematurely.

Until recently, it was common to assume that non-differential misclassification would always bias results towards the null. Although bias away from the null leading to a type 1 error is more serious, bias towards the null is also of concern. This is especially true regarding small effect sizes such as those found in the Welsh analyses. Some scientists are arguing that non-differential misclassification of a variable with more than two categories can bias the effect in both directions [204–207]. In my thesis I therefore dealt with potential information bias arising from possible misclassification by performing an array of sensitivity analyses. These analyses make use of an alternative definition for outcomes or a validated definition of the exposure. The results from sensitivity analyses did not differ substantially from the main findings, many of which were also in accord with prior publications. Therefore, information bias resulting from non-differential misclassification is unlikely to be of major concern in this thesis.

A potential additional source of outcome misclassification is unaccounted visits to Accident and Emergency (A&E) departments. The decision whether to provide treatment and discharge from A&E rather than admit a child to hospital may depend not only on disease severity, but also on additional factors such as departmental overload, time of day and level of senior support available, as well as the patient's support network and availability of community follow-up [208]. Child's age is an additional factor affecting the decision of whether to admit to hospital[48]. Estimates have been made that 19-40% of bronchiolitis visits to A&E result in hospital admission [45] and that only a third of paediatric non-trauma visits lead to admission [208]. Thus, A&E visits should have ideally been analysed, as they encompass an additional group of infants and children with a potentially severe illness. In the MCS, information about A&E visits was collected solely regarding injuries. In Wales, the SAIL databank holds information from the Emergency Department Dataset of Wales (EDDS) starting 2009 [209] and these data were retrieved for this research. However, 40% of recorded attendances were missing a code for diagnosis or coded as non-specified. This information was thus unusable. The unavailability of information about A&E visits is, therefore, a major limitation of the studies in this thesis, but it is not a unique problem as it is shared with most studies focusing on child hospital admissions.

7.4.3 Confounding

Confounding by indication is an important potential bias that is often mentioned in the critique of the findings from studies examining the long-term effects of mode of birth on child health. Ill health of the fetus arising from an adverse maternal health condition [210] (e.g. diabetes, hypertensive condition) or a situation arising prior to or during labour (e.g. premature rupture of membrane, fetal distress) may indicate the use of medical intervention to facilitate delivery. If this adverse health condition has potential long-term

[48] Personal communication with a Paediatrician

effects on the risk of respiratory morbidity or susceptibility to infection, this might explain the increased risk identified in the study. Although diabetes and hypertensive condition were included in multivariable models through maternal report or hospital ICD codes, it was difficult to fully account for the variety of indications for intervention. Firstly, clinicians probably attach diagnostic codes such as fetal distress or long labour more meticulously to births that ended up requiring medical intervention than to vaginal deliveries where the complication occurred but did not end in delivery intervention. This will result in substantial differential misclassification. Also, the potential influence of the different medical conditions or labour complications on the delivery and on the child's subsequent health is not well understood and is difficult to interpret. Furthermore, when the delivery is complicated by a medical intervention, this is sometimes due to multiple indications. Lastly, for the MCS study, the linked hospital record data including ICD codes for the birth episode was available only for a sub-set of the sample.

Dividing caesarean sections into two types, planned and emergency, lowers the potential for confounding by indication. Indication is unlikely to have such an effect in the planned caesarean category in a strong manner. In most cases, planned caesareans are carried out as a pre-emptive measure: either to avoid risk of uterine rupture following prior caesarean or to avoid a potentially complicated breech vaginal delivery. In certain cases, a caesarean may be carried out primarily due to the mother's request and without medical reason. The UK caesarean sentinel [17] reported on the primary indications of grade 4 caesareans, where there is no urgency and delivery is timed to suit woman or staff (the urgency level comprising 80% of elective caesareans) [17]. Only ~10% of these caesareans were indicated due to a maternal, fetal or obstetric condition[49] that has the potential to affect the fetus in a manner that may theoretically have long-term

[49] These indications include: presumed fetal compromise; cord prolapse; chorioamnionitis; other (fetal); placenta praevia, actively bleeding; haemorrhage; placental abruption; pre-eclampsia; maternal medical disease; uterine rupture; other (maternal) [17]

consequences. Therefore, the fact that planned caesarean was identified as a risk factor in many of my analyses implies the effect found in those analyses is unlikely to be due to confounding by indication. Furthermore, the indications for emergency caesarean are very similar to those of assisted vaginal delivery. Had confounding by indication been a strong source of bias, one might expect to also see parallel increased risks in the assisted vaginal delivery group. It is acknowledged, however, that the level of severity of the situation indicating medical intervention or the length of time the fetus was exposed to the situation may not be the same for emergency and assisted vaginal delivery. For example, a labour when the fetus experiences distress and where an instrumental vaginal delivery was possible, may have had a shorter exposure to distress compared with a labour ending with emergency caesarean. Nevertheless, the lack of consistent increased risk in babies and children born by assisted vaginal delivery reduces concern that confounding by indication substantially biased my results. Lastly, I excluded neonates requiring NICU or with low Apgar scores. This removes the extreme cases where a serious health condition indicates a particular mode of birth and also causes serious neonatal morbidity (and theoretical long-term health effects).

Residual confounding may explain some of the observed effects in this thesis. In the Welsh studies, this was one of the main limitations, since some demographic and perinatal factors were unavailable and other variables were available only in a crude level. Moreover, some of the variables included in my analyses were not well measured. For example, in the Welsh analyses, information about maternal conditions such as asthma were only available through ICD codes from the delivery record and did not capture all cases of maternal asthma in the sample (see section 4.4.5). Likewise, in both the MCS and the Welsh analyses, the firstborn and nulliparous variables were probably not highly accurate. Adjusting the models using variables that are not of high accuracy may lead to unaccounted residual confounding and to a biased effect estimate.

Furthermore, I had not adjusted for several variables that some previous studies included such as number of siblings, crowding in the household, damp housing conditions or attendance at childcare. In the Welsh analyses, these variables were not available, while in the MCS analyses, the low power limited the number of variables that could be included in multivariable models. Nevertheless, my analyses did include other similar variables: gestational age, birthweight, firstborn, maternal education and socioeconomic status or WIMD. The effect sizes found in this thesis are small, and therefore residual confounding is a potential non-causal explanation for the findings. However, the fact that my findings, showing that caesarean sections are a risk factor for infectious diseases and asthma, are in agreement with many of the previous studies, reduces this concern. Nevertheless, it is conceivable that many studies share the problem of unaccounted confounders, since the datasets used in research tend to rely on a similar variety of variables, especially when administrative records are concerned. Therefore, residual confounding is a potential limitation of this (and other) research.

Antibiotic use is an example of a potentially important confounding factor that was unaccounted for in the current study (as well as most other studies), as it could be associated both with mode of birth and with child health outcomes. Indeed, antibiotic use during pregnancy and early life has been shown to be a risk factor for childhood infection [211] and respiratory illness [212]. Prophylactic antibiotics are sometimes given during labour to prevent neonatal GBS infection. In the UK, routine screening for vaginal GBS infection is not carried out. Therefore the use of these prophylactic antibiotics would not be wide, but limited to women with risk factors such as preterm birth, pre-labour rupture of membranes or fever [213]. Furthermore, intrapartum antibiotics given to prevent caesarean scar infection may act as a mediating factor of the association between mode of birth and child health through disruption of microbiota homeostasis [214] (in which case effects should be examined without adjustment for it in any case). At the time when the MCS children were born, antibiotics were given in 86% of

caesarean sections [17]. However, common practice during that time was to administer the antibiotics only after cord clamping [215,216]. Therefore, no direct transfer to the fetus would have taken place. Nowadays, NICE guidelines recommend administration of antibiotics before incision [20] and as a result, common practice has changed in more recent years. In the Welsh studies, therefore, antibiotics may be a mediating factor that explains the effect of caesarean section on infection and respiratory illness. However, in the MCS studies, such a mediating effect is not likely, but residual confounding arising from inability to control for antibiotics use remains a potential limitation.

Induction of labour and the unavailability of reliable data was previously discussed as limiting the ability to understand the indirect effect of mode of birth through earlier gestational age. Induction of labour may also act as a confounder, as there is some evidence to suggest that induced or augmented labour (or their underlying indication) may be an independent risk factor for respiratory and other infections [35]. The inability to control for this potential confounder may therefore bias the effects found.

It is important to note, however, that by excluding preterm births, I have accounted for one of the potentially strongest confounding factors of the associations under investigation. Preterm births are strongly associated with mode of birth (e.g. over half of very preterm fetuses were delivered by emergency caesarean[50]). At the same time, premature delivery may lead to a range of adverse health conditions later in life. By excluding preterm births, I have not only restricted this potentially major confounder, but also avoided various possible biases arising from their inclusion. These biases include differential misclassification of the outcomes according to status of prematurity of the child (which is associated with the exposure). Further, as mentioned previously, the common indications per type of delivery are expected to be different in preterm delivery compared with term delivery and as a result, prematurity may modify the effect of

[50] Results from MCS regarding delivery <28 weeks - not shown

caesarean on child health. Lastly, inclusion of premature births would complicate and modify one of the proposed causal mechanisms: the maternal vaginal microbiota has been implicated in the pathophysiology of preterm birth [217]. These limitations were demonstrated in the extended group analysis of wheezing phenotypes in the MCS. The analyses showed a different, stronger effect of emergency caesarean on childhood wheezing and asthma-related outcomes when preterm babies were included in the sample compared to when they were excluded despite adjustment for gestational age. The restriction of births to term only is therefore a strength of my study.

7.5 Possible causal explanations for the findings

There are currently three main hypothesized biological mechanisms by which the mode of birth of a child might directly cause longer-term health effects. These include the altered transmission of microbiota from mother to newborn, epigenetic modifications resulting from intrapartum exposures and stress levels experienced during labour [132].

7.5.1 Dysbiosis of microbiota colonisation

Microbiota is the collective term for bacteria, fungi, viruses and other microorganisms residing in the human body. The development of high-throughput DNA sequencing techniques has opened the door to investigating the world of the microbiome, which is the collective genome of the microbiota [218]. This new knowledge is shaping our understanding of human health and susceptibility to disease.

The initial microbial colonisation of a newborn human takes place at the time of birth. Neonates born by the vaginal route benefit from the natural transmission of their mother's vaginal and faecal microbial flora. They have indeed been shown to have a colonisation pattern resembling their own mother's vaginal flora [219]. On the other

hand, neonates born abdominally have an altered colonisation pattern from those born vaginally [132,214].

The microbiota of newborn babies delivered by caesarean section is underrepresented in several bacterial taxa [133,220] and has been shown to have a microbial pattern similar to that generally found on human skin [219]. This alteration in microbiota composition following caesarean birth is thought to persist for at least 3 months [221], with some studies demonstrating differences up to 2 years of age [222], although a recent study reported no detectable difference by 6 weeks [223]. Additional perinatal factors other than mode of birth have been shown to strongly affect the microbial colonisation pattern of an infant. These include intrapartum antibiotics and formula rather than breastmilk feeding [214,220,224].

The microbiota has a ‘cross-talk’ with the immune system. During early life, the immune system is at its developmental stage and has the task of learning to differentiate friendly antigens from pathogenic insults [225]. Correct ‘education’ of the immune system during the window of time of the early years when it is still maturing, is of vast importance [226]. Indeed disruptions in the microbiota’s homeostasis have been linked to various adverse health conditions, including obesity [227], autoimmune diseases, respiratory infections [136,137] and asthma [228,229]. Experimental evidence about the potential beneficial effect of the microbiota on asthma susceptibility comes from germ-free mice [132,230]. These mice exhibit hyper-responsiveness of the airways and show altered lung immune cells composition that is reversed when they are re-colonised with commensal bacteria.

Further to aiding the function of the immune system, the microbiota also protects humans from infection of pathogenic bacteria by directly acting as a barrier [227]. The symbiotic bacteria colonise the mucosal sites of entry to the body and compete with pathogenic strains for adhesion sites and nutrients. Dysbiosis may therefore increase the risk of opportunistic infection.

The gut is the area most densely populated by bacteria and most thoroughly studied in relation to the connection between microbiota and health. The potential effect of these microbes is not limited to conditions relevant to the gastrointestinal tract, but also to other body systems, including the brain [231]. At the same time, the microbial colonisation of other areas of the body such as the airways, oral cavity and skin, has also been shown to be associated with mode of birth [232]. For example, the upper airway microbiota, was shown to have delayed development and reduced abundancy of some of the beneficial bacterial strains in 6 month old babies born by caesarean [231]. Skin microbiota of neonates delivered by caesarean was found to be different from vaginally delivered newborns [223] and oral microbiota was also found to be altered when examined at birth [233] and at 3 months postnatally [234].

It is important to mention that some studies have proposed that place of birth – home or otherwise – is one of the important determinants of microbial colonisation within vaginally delivered newborns [110,235]. When born at home, the initial exposure to the microbial world is limited to the predominant strains within the family, whereas babies born in hospital are initially exposed to additional strains, some of which are foreign to the family. My research, however, is focused almost entirely on hospital births.

Disruption of the normal microbiota development is a mechanism currently broadly studied, that might explain an effect of mode of birth on long-term adverse health outcomes such as allergy, asthma or susceptibility to infection.

7.5.2 Epigenetic modifications

Epigenetic modification is a tissue-specific chemical modification to the DNA that regulates gene expression. One type of epigenetic alteration is methylation: attachment of a methyl group to a Cytosine nucleotide that is followed by a Guanine nucleotide (CpG dinucleotide). Epigenetic modifications of DNA have been shown to regulate immune functions, amongst other biological functions [236].

Prenatal exposures such as maternal smoking, maternal prenatal stress and gestational age at delivery have been shown to alter the epigenetic profile of the newborn, sometimes in a manner lasting into adulthood [237–239]. With regards to mode of birth, although it is a brief event in comparison to other in-utero exposures, it is a process when extraordinary physiological changes take place. The term 'EPIIC' (Epi-genetic Impact of Childbirth) was coined to describe the hypothesis that epigenetic modifications arising from the birth process are responsible for long-term effects of mode of birth on health [240].

Only three studies that I am aware of have investigated the effect of mode of birth on the epigenetic map of the newborn's DNA. Two of these studies examined the global methylation level of cord blood DNA in fetuses delivered vaginally or by caesarean section and came to conflicting conclusions regarding whether the average methylation level is different [241,242]. A later study by Almgren et al [243] harvested haematopoietic stem cells derived from cord blood and examined locus-specific methylation levels. Using this more advanced and specific approach, the study identified altered levels of methylation in hundreds of sites throughout the DNA, including on genes implicated in antibody biosynthesis.

This hypothesized biological mechanism is currently at very early stages of research. However, if future research shows that caesarean delivery affects methylation levels and subsequent expression levels of immune genes, this mechanism might explain childhood susceptibility to serious infectious diseases and asthma.

7.5.3 Labour hormones and physical forces

Labour contractions cause rhythmic physical squeezing of the fetus that bring about intermittent hypoxia. This physiological stress exerted during labour and vaginal delivery leads to fetal secretion of stress hormones [132]. The term 'eustress' was coined to describe the physiological, healthy level of stress experienced by a fetus during normal

labour and delivery. This is in contrast to ‘dys-stress’ (fetal distress) that leads to abnormally high levels of stress hormones or ‘a-stress’ coinciding with pre-labour caesarean section with abnormally low stress levels [240,244]. Studies in humans and animal models have shown an altered stress response in newborns delivered by caesarean section as well as different hormonal levels which may mediate changes in immune function [132].

Labour contractions and descent through the birth canal physically squeeze amniotic fluid out of the lungs of the fetus, but this physical mechanism is reduced during in-labour caesarean and absent in pre-labour caesarean. Furthermore, delivery of the baby prior to spontaneous labour onset may mean the fetal lungs are not yet ‘mature’, i.e. lacking enough surfactant important for pulmonary function [245]. Importantly, the hormones secreted during labour itself also have a role in the physiology of rapid absorption of lung fluid [246]. Therefore, a delivery with diminished physical forces or hormone secretion (i.e. caesarean) might result in retained fluids, which may lead to transient tachypnea of the newborn (‘wet lung disease’) or in severe cases - respiratory distress syndrome. These conditions are more common following pre-labour caesarean (especially of earlier gestation) compared to other forms of birth [246,247] and may predispose to later pulmonary illness [248,249].

In this regard, note that my exclusion of neonates that were admitted to NICU has the potential to bias effects towards the null. If the caesarean delivery causally led to iatrogenic neonatal respiratory morbidity severe enough to require NICU admission, the exclusion of these individuals from the study group may dilute the effect size associated with caesarean section.

The mechanism of altered levels of stress hormones, either too high if fetal distress preceded an emergency caesarean, or too low in the case of pre-labour caesarean, may theoretically explain my findings through their possible effect on immune function.

Furthermore, the effect of labour on pulmonary function through both hormonal secretion and physical forces, may explain the increased susceptibility to respiratory conditions described in this thesis.

7.6 Overall findings - discussion and context

The overarching aim of my thesis was to investigate whether mode of birth affects the child's risk of subsequent infectious diseases, selected wheezing phenotypes or asthma. The first research objective was to investigate the effect of mode of birth on severe infectious diseases during infancy. To answer this objective, I examined hospital admissions for these causes using the MCS and SAIL datasets.

Lower respiratory tract infections were investigated using both datasets. The investigation provides evidence of an increased risk of LRTI admissions in infants born by planned caesarean, however there is insufficient evidence to suggest an increased risk following emergency caesarean section. This finding is in keeping with some of the prior research investigating this outcome which described a similar trend [85–88]. The parallel investigation of this outcome using both a longitudinal cohort and linkage of large administrative datasets improves confidence that the effects are real. The first provides rich data to adjust for multiple explanatory variables and the second benefits from size and thus high statistical power to detect an association. The two studies use different means of measuring the exposure and outcome – maternal report or routine hospital record – and still lead to a similar conclusion. This thesis therefore provides evidence that planned caesarean is a risk factor for LRTI during infancy, although the effect size is modest (RR=1.1-1.4).

Upper respiratory tract infections were investigated using the SAIL dataset. The findings add to the current state of understanding of the potential risk of caesarean (both planned and emergency) to later child health by pointing at severe URTI during infancy as

another possible adverse outcome. However, the effect found is small (RR=1.1) and the strength of evidence is limited as it was examined using only the SAIL dataset.

Any admission due to a respiratory illness during infancy was examined in the SAIL dataset. These admissions were equally due to LRTI and to URTI. Such hospital admissions were found to be slightly more likely after planned or emergency caesarean delivery than after a vaginal delivery (RR=1.1).

For gastroenteritis my findings were consistent in both datasets, providing evidence that emergency caesarean is a risk factor for gastroenteritis (RR=1.2-1.5), but there was not enough evidence to suggest the same for planned caesarean. Previously published studies investigating this outcome highlighted both types of caesarean as risk factors for gastroenteritis [84,86,91,92]. Possible explanations will be discussed later.

Any infectious disease leading to hospital admission was studied using the MCS. This investigation provides a moderate level of evidence suggesting that an infant's risk of any type of severe infection may be increased following either type of caesarean (RR=1.2-1.3).

The second research objective was to investigate breastfeeding and whether it explains the effect of mode of birth on infant infection. My research adds to the current state of knowledge by showing that the effect of mode of birth on infection is not necessarily explained by reduced levels of breastfeeding, but rather is an independent effect. Furthermore, there was no evidence that breastfeeding modifies the relationship between mode of birth and infant infection.

The third research objective was to investigate the association of mode of birth with childhood wheezing phenotypes, and to examine this relationship in the broader context of various indicators for asthma. This investigation was carried out using the MCS and provided some evidence suggesting persistent wheezing is more common following planned caesarean (RR=1.3), but only weak evidence regarding other modes of birth. A

persistent wheezing phenotype, unlike transient wheezing, may represent a child with genuine asthma. The strength of evidence is not high since the association was not corroborated through the secondary asthma-related indicators. Nevertheless, this result adds to the limited information regarding mode of birth and wheezing phenotypes available from previous studies.

The fourth research objective was to examine whether there is an effect of mode of birth on hospital admission for any respiratory illness that persists from infancy to early childhood. These admissions were mostly due to URTI, less so due to LRTI and infrequently due to asthma. This investigation adds to the current state of knowledge by providing evidence that children born by any type of caesarean are at a small increased risk of respiratory admissions not only during infancy, but throughout early childhood (RR=1.1).

The fifth objective was to investigate the association between mode of birth and severe or poorly controlled childhood asthma that leads to hospital admission. This investigation was carried out using the SAIL dataset at primary school age when the diagnosis of asthma is of higher reliability. The investigation provided evidence that emergency caesarean section is a risk factor for asthma, although the effect size is small (RR=1.2). I therefore contributed to the existing inconclusive evidence regarding the possible effect of emergency caesarean sections on childhood asthma by confirming that it is a risk factor, even within term gestation. However, my study did not provide sufficient evidence to conclude that planned caesarean is also an independent risk factor for asthma, although most prior research has linked planned caesarean with asthma. Since the current research has found planned caesarean to be associated with other respiratory outcomes (e.g. LRTI, any respiratory illness, persistent wheezing) it seems less likely that there is truly no excess risk of asthma following planned caesarean. It is quite possible that low power is the reason the effect identified for planned caesarean (RR=1.12) was not statistically significant.

The sixth and final objective was to investigate whether birth at earlier gestation adds to the effect of mode of birth on the outcomes under investigation. The findings consistently showed that any adverse effect of planned caesarean on child health is intensified when the indirect effect of scheduling the delivery to earlier gestation is added.

Most of the outcomes under investigation in this thesis were focused on the respiratory system. These include the acquisition of a serious infection of the respiratory tract or experiencing wheeze or asthma, the latter two involving also processes of allergy and inflammation. Almost all the respiratory outcomes studied were either found to be associated with planned caesarean or with both planned and emergency caesareans. This is true with the sole exception of the study on asthma admission using SAIL for which the power was very low. The only outcome under investigation in this thesis that is focused specifically on a different body system from the respiratory one, is gastroenteritis. Here the evidence of an association was substantially stronger for emergency caesarean section than for planned caesarean. There are several possible explanations for this pattern of risk factors for the various outcomes. Firstly, as explained previously, the microbiota helps protect the gut from opportunistic infection and any dysbiosis arising from the caesarean delivery might weaken the infants' immunity to gastrointestinal infection. It is plausible that this biological mechanism explains the increased risk seen in emergency caesarean, while methodological limitations such as insufficient power explain why a similar or stronger effect was not observed in planned caesarean. This suggested explanation is in agreement with prior studies that have examined gastroenteritis and identified also planned caesarean as a risk factor for such infection. Second, gastroenteritis might theoretically be affected more strongly than LRTI from factors other than mode of birth, such as familial hygiene habits surrounding infant feeding. As discussed in 1.3.3, a pathogenic agent causing gastroenteritis might be transmitted not only from one infected individual to another, but also through ingestion of contaminated milk or food or use of unsterilized feeding equipment. Third, it is

possible, in theory, that confounding by indication plays a more important role in susceptibility to gastrointestinal infection than to respiratory infection. As I was not able to fully adjust for indication for caesarean, such a mechanism would indeed lead to a stronger association of emergency caesarean with gastroenteritis compared to that of planned caesarean. However, the latter explanation is not consistent with the findings of prior studies, that although these are few, have all identified both types of caesarean section as associated with gastroenteritis.

The pattern of findings, where planned caesarean tended to be associated with respiratory, but not gastrointestinal outcomes, with a stronger association when adding the effect of birth at earlier gestation, may lend support to the mechanism of exposure to labour. As explained in section 7.5.3, labour hormones and physical forces of contractions may have a particular effect on neonatal pulmonary function. Therefore, this mechanism would presumably potentially adversely affect the child's respiratory system but have less of an effect on the gastrointestinal system. An additional possible mechanistic explanation for the outcomes that were found to be more consistently associated with planned caesarean compared with emergency caesarean, is the microbiota dysbiosis. A certain degree of fetal exposure to the mother's vaginal flora could occur in an emergency caesarean if the amniotic membranes have already ruptured during labour prior to surgery. Rupture of the amniotic membranes would rarely take place prior to a planned caesarean and therefore no such exposure would occur in planned caesareans. Needless to say that the effects found in this thesis, if indeed causal, may result from a combination and inter-play of several biological mechanisms.

7.7 Implications for research

The findings from this research suggest that both planned and emergency caesarean sections are risk factors for various infectious disease, wheezing and asthma during childhood. However, the two types of caesarean are not consistent in their effect in all

cases. Although one gains simplicity and statistical power when grouping together all caesareans and comparing with any vaginal delivery, any effects found by this means may be distorted. Future research would benefit from continuing the recent trend of differentiating mode of birth into four categories, as done in my thesis. Meta-analyses should also aim to differentiate these groups as a sub-group analysis at the least.

Some of the findings of this research are novel, with very few studies previously published on the topic. These include the association of mode of birth with severe infectious disease, and in particular URTI. The investigations carried out here need to be repeated in different populations and using large data sources. A meta-analysis aggregating the available findings on this association is also called for.

Ideally, future studies would include high quality data on potential confounders missing from the current studies. These include onset of labour (spontaneous/induced), indication for medically assisted delivery and labour complications, as well as the use of intrapartum antibiotics.

The role of breastfeeding as a mediator or moderator of the effect of caesarean delivery should be examined in other populations, preferably where rates of breastfeeding are affected more substantially by mode of birth.

'A plea to abandon asthma as a disease concept' is the name of the editorial piece for a 'Lancet' issue dedicated to Asthma published in 2006 [250]. The editors advocated a phenotypic approach to asthma research and the abolition of the unifying term altogether. Although this advocacy dates back several years, very few studies have assimilated the phenotypic approach in relation to the association with mode of birth, as my study has. Additional longitudinal studies examining trajectories of wheezing are required, as well as an approach differentiating allergic versus non-allergic asthma. These studies should also strive to include objective measures of pulmonary function, airway inflammation and atopy.

When a caesarean is planned, this consequently leads to scheduling the gestational week for the delivery. Future studies should not only report the independent effect of the caesarean birth on child outcomes, but rather also report the overall effect of the caesarean along with its timing (i.e. unadjusted for gestational age). This is especially important in studies using data where the majority of planned caesareans are carried out at early term (weeks 37-38).

In order to understand whether the observed increased risks of adverse childhood health outcomes are caused by the caesarean birth, it is crucial to set up large birth cohorts that incorporate the collection and analysis of biological samples. These should include infant faecal samples for measuring microbiota diversity and blood or saliva samples for measuring methylation levels. Several such cohorts already exist (e.g. 'CHILD' in Canada [3]) or are being set up (e.g. 'Baby Biome Study' in the UK [251].

7.8 Implications for practice and policy

The datasets used in the current research are both from the UK, but the findings and their implications for practice and policy are likely generalisable to other high-income countries. Indeed, similar relative risks were found in some of the previously published studies from Scandinavia, The Netherlands and Australia. It is recognized that the burden of serious infection during childhood is substantially higher in low and middle income countries compared to high income countries. Furthermore, some emerging economies such as China and Brazil have the highest caesarean rates globally. Nevertheless, my findings are not readily generalisable to these settings. Indications for caesareans and maternal demographics associated with them are likely different and additional risk factors for the outcomes that have not been accounted for in this thesis probably also play a part.

My research adds to the growing body of evidence suggesting caesarean sections may be a risk factor for long-term childhood morbidity, and therefore supports the paradigm

of ‘Developmental Origins of Health and Disease’ [3]. Of note, the relative risks identified in this research are small, and this could therefore be reassuring for parents of children that were born by caesarean delivery. However, because caesarean delivery is a very common mode of birth, the potential effect on the population (under the assumption that the effect is caused by the caesarean birth) is unlikely to be negligible. For example, compared with a caesarean rate of 15% [14], at the current rate in the UK (28.8%), even a small relative risk of 1.1 means an excess of 1,050 infants being admitted to hospital each year for respiratory illness[51]. Assuming the presumed causal risk persists into childhood and is shared with the other outcomes investigated here, this would result in an even larger number of annual paediatric admissions attributable to the caesarean birth. These findings therefore support the need for additional efforts to be made to stop, and then reverse, the increasing rate of caesareans in high-income settings. Healthcare system leaders should take extra measures to limit the scope of ‘unnecesareans’, a slang term denoting unnecessary caesareans, especially those without solid evidence-based indication. Guidelines similar to those produced by ACOG on ‘Safe Prevention of the Primary Cesarean’ [19] should be adopted more widely. At the same time, advances should be made in how healthcare facilities can enable the ideal conditions for women to have a physiological labour and birth [1], as the need for a caesarean to facilitate delivery is reduced when such conditions are met.

[51] Estimated based on 755,042 births in the UK in 2017 and 10.6% of infants admitted for respiratory illness (section 5.3.3.1), assuming the rate applies to the other UK countries

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Appendix I – Literature search

Periodical Pubmed search:

(cesarean [TW] OR caesarean [TW] OR cesarian [TW] OR caesarian [TW] OR "c-section" [TW] OR "mode of delivery" [TW] OR "mode of birth" [TW] OR "method of delivery" [TW] OR "method of birth" [TW] OR "birth mode" [TW] OR "method of delivery" [TW] OR "vaginal delivery" [TW] OR "vaginal birth" [TW] OR "assisted birth" [TW] OR "assisted delivery" [TW] OR "natural birth" [TW] OR "natural delivery" [TW] OR "normal birth" [TW] OR "normal delivery" [TW])

AND (infection [TW] OR infectious [TW] OR gastroenteritis [TW] OR gastritis [TW] OR respiratory [TW] OR diarrhea [TW] OR diarrhoea [TW] OR asthma [TW] OR wheeze [TW] OR wheezing [TW] OR bronchiolitis [TW] OR bronchitis [TW] OR rsv [TW] OR pneumonia [TW] OR influenza [TW]) AND

(infant [TW] OR infancy [TW] OR child [TW] OR childhood [TW] OR children [TW] OR baby [TW] OR offspring [TW] OR long [TW]) NOT (HIV [TI])

One-off database search focused on URTI:

Following is the search carried to identify studies focusing on mode of delivery and upper respiratory tract infections in childhood. The databases of Medline, Embase and Global Health were searched for studies in English published from 1st of January 2008 onwards.

#	Searches
1	birth/ or childbirth/ or caesarean section/
2	((mode? or method?) adj3 (deliver* or birth* or childbirth*)).ti,ab.
3	((vaginal or obstetric* or natural) adj3 (deliver* or birth* or childbirth*)).ti,ab.
4	(cesarean? or caesarean?).ti,ab.
5	1 or 2 or 3 or 4
6	laryngitis/ or laryngotracheitis/ or rhinitis/ or rhinotracheitis/ or sinusitis/ or tracheitis/ or upper respiratory tract infections/ or common cold/
7	(common cold or sore throat* or pharyngit* or nasopharyngit* or naso-pharyngit* or rhinopharyngit* or rhino-pharyngit* or sinusit* or nasosinusit* or naso-sinusit* or rhinosinusit* or rhino-sinosit* or rhinit* or tonsillit* or laryngit* or rhinolaryngit* or rhino-laryngit* or nasolaryngit* or naso-laryngit* or influenza or flu or respiratory tract infection? or urti or urtis).ti,ab.
8	6 or 7
9	exp children/ or exp infants/
10	(infan* or baby or babies or child* or schoolchild* or girl* or boy* or pediatric* or paediatric*).ti,ab.
11	9 or 10
12	5 and 8 and 11
13	limit 12 to yr="2008 -Current"

Appendix II – Congenital anomalies

Table II-1: ICD codes for major congenital anomalies retrieved from CARIS

ICD code	System	Annotation
Q00	Nervous system	Anencephaly and similar malformations
Q01	Nervous system	Encephalocele
Q03	Nervous system	Congenital hydrocephalus
Q05	Nervous system	Spina bifida
Q23.4	Circulatory system	Hypoplastic left heart syndrome
Q20.3	Circulatory system	Discordant ventriculoarterial connection
Q21.0	Circulatory system	Ventricular septal defect
Q33.8	Circulatory system	Other congenital malformations of lung (including Cystic adenomatoid malformation of lung)
Q60.1	Urinary system	Renal agenesis, bilateral
Q79.3	musculoskeletal system	Gastroschisis
Q79.0	musculoskeletal system	Congenital diaphragmatic hernia
Q90	Chromosomal abnormalities	Down Syndrome (Trisomy 21)
Q91	Chromosomal abnormalities	Edwards' syndrome (Trisomy 18) and Patau's syndrome (Trisomy 13)
Q96	Chromosomal abnormalities	Turner's syndrome (45X)

Appendix III – Cleaning process of SAIL datasets

Following is a description of the cleaning process applied to each dataset retrieved from the SAIL databank.

NCCHD n=534,749

- mat_smoking (maternal smoking)
    - Data contains code 4 which is not annotated in data dictionary => 1542 observations (0.3%) turned into missing
- tot_birth_number (number of babies delivered)
    - Observations marked as multiple birth corrected to singleton =>12
    - Observations marked as singleton birth corrected to multiple => 5
    - Observations duplicate for all analysis variables examined => all are multiples or addressed as mentioned above.
- Ethnicity (child ethnicity)
    - Two different formats of ethnicity coding are utilized in the dataset – 0-9 and A-Z. An error in the online data dictionary [252] led to wrongful labelling leading to most NCCHD records being marked as Black Caribbean instead of White. Following oral communication with NWIS Statistician the correct annotation was retrieved (below). Ethnicity coding was harmonised by recoding all 0-9 codes to the A-Z system (recoding methodology was corroborated by NWIS Statistician).

Table III-1: Ethnicity coding in the SAIL studies

Codes A-Z used starting April 2002	Codes 0-9 used before April 2002*	Classification in Study
A = White British	0 = Caucasian	White
	1 = White	
B = White Irish		White
C = Other White Background		White
D = Mixed White & Black Caribbean		Mixed
E = Mixed White & Black African		Mixed
F = Mixed White & Asian		Mixed
G = Any Other Mixed Background		Mixed
H = Indian (Asian or British)	5 = Indian	Indian/Pakistani/Bangladeshi
J = Pakistani (Asian or British)	6 = Pakistani	Indian/Pakistani/Bangladeshi
K = Bangladeshi (Asian or British)	7 = Bangladeshi	Indian/Pakistani/Bangladeshi
L = Any Other Asian Background		Other
M = Caribbean (Black or Black British)	2 = Black (Caribbean)	Black
N = African (Black or Black British)	3 = Black (African)	Black
P = Other (Black or Black British)	4 = Black (Other)	Black
R = Chinese	8 = Chinese	Other
S = Any Other Ethnic Group	9 = Other ethnic group	Other

* some health boards continued to use these codes in later years

PEDW deliveries n=464,061

- Records (spell) with duplicate ALF =>1518 identified
- Duplicate spell number =>
    - 118 observations deleted
- Identical values for wob (week of birth), admis_dt (admission date), oper_cd_1, oper_cd_2, oper_cd_3, oper_cd_4, (OPCS codes) diag_cd_1 (ICD code) =>
    - 236 observations deleted, 223 observations kept
- Unidentical values for admis_dt, oper_cd_1, oper_cd_2, oper_cd_3, oper_cd_4, diag_cd_1 =>
    - 942 observations deleted
- WOB earlier than admis_dt by more than a week =>
    - 297 observations deleted
- WOB later than disch_dt (discharge date) =>
    - 180 observations deleted
- Records with ≥ 20 diagnostic codes =>
    - 116 identified and examined. Later codes were found to be repetition of earlier ones =>
    - Variables DIAG_CD_21 - DIAG_CD_82 and DIAG_NUM_21 – DIAG_NUM_82 removed (the position of diagnostic code)
- Records with ≥ 15 operational codes

    - 20 identified and examined to make sure operational codes indicating mode of birth is in first 15 (2 moved to one of first 15) => Variables OPER_CD_15 - OPER_CD_24 removed
- Maternal asthma coded from ICD J45 or J46 appearing in any delivery spell with a specific mat_ALF (mother has code for asthma for any of her cohort children)
- Maternal diabetes (gestational or pre-gestational) coded from ICD O24 or E10-E14
- Maternal hypertensive condition coded from ICD O10-O16 or I10-I15

Total number of observations deleted: 1,773

WDS n=513,550

- Emigration date earlier than wob by more than a week =>
    - 7 observations deleted
- Date of death earlier than wob => 0 obs.
- Emigration date earlier than date of death by over a week => 27 observations kept

Total number of observations deleted: 7

CARIS n=3,558

ADDE n=2,310

- Death caused by the outcomes of interest was examined:
    - LRTI – 128
    - URTI – none
    - Gastroenteritis – 18
    - Asthma – <10

Cleaning and coding post merging (on 'Interim working dataset'):

- Gndr_cd = male or unknown in PEDW deliveries
    - 19 observations deleted
- Singleton siblings with unreasonable gap between birth dates (<24 weeks) according wob =>
    - 188 observations deleted
- Observations marked as tot_birth_number=1 but with same mat_alf, week of birth, maternal age, hospital code (duplicates or twins) =>
    - 680 observations changed to twins (will be excluded)
- Stillbirth diagnostic codes in PEDW delivery spells (O364, O362, Z371, Z373, Z376, Z377) were compared to the flag in NCCHD => all concordant
- Additional cleaning => 2 observations deleted
- Nulliparity (coded only for tot_birth_number=1. i.e. singletons)

Table III-2: Nulliparity coding in the SAIL studies

1 = nulliparous	0 = multiparous	Missing
Record with earliest wob of particular mat_alf and marked as having no previous still or live births	Not record with earliest wob of particular mat_alf and marked as having previous still or live births	Record with earliest wob of particular mat_alf and missing information about previous births in current or subsequent sibling records
	Record with earliest wob of particular mat_alf and marked as having previous still or live births (i.e. first child of a multiparous mother included in the cohort)	
	Not record with earliest wob of particular mat_alf and missing information about previous births.	
	Not record with earliest wob of particular mat_alf and marked as having no previous still or live births (presumed misclassification)	
Record with earliest wob of particular mat_alf and missing information about previous births with next sibling record marked as 1 previous live birth or one after next marked as 2 or two after next marked as 3	Record with earliest wob of particular mat_alf and missing information about previous births with next sibling record marked as >1 previous live birth or one after next marked as >2 or two after next marked as >3.	
	Record with earliest wob of particular mat_alf and missing information about previous births with matched PEDW delivery spell with one of the following diagnostic codes indicating a prior birth: Maternal care due to uterine scar from previous surgery (O342) Vaginal delivery following previous caesarean section (O757) Supervision of pregnancy with grand multiparity (Z354) Problems related to multiparity (Z641) Personal history of complications of pregnancy, childbirth and the puerperium (Z875) Personal history of certain conditions arising in the perinatal period (Z876)	

Total number of observations deleted: 209

PEDW child admissions n=263,840 (spells)

- Discharge date missing =>
    - 9 records (spells) deleted
- Admission date missing => none
- Admission method codes flagged as emergency admission (code number):
    - A&E or dental casualty department of the health care provider (21)
    - GP after a request for immediate admission has been made direct to a hospital provider (22)
    - Bed bureau (23)
    - Consultant clinic of this or another health care provider (24)
    - Domiciliary visit by Consultant (25)
    - Via NHS Direct Services (27)
    - Other means, including admitted from the A&E department of another provider where they had not been admitted (28)
    - (29) - not annotated, however seems to imply transfer of a patient admitted in an emergency
- Duplicates in ALF, gender, age, admission and discharge date and method, and diagnostic codes 1-18
    - 541 observations that have a duplicate record were deleted.
- Records that do not include diagnostic codes for any of the outcomes => 15 deleted
- Creating continuous inpatient spells (CIP) per outcome of spells where discharge date is same as next spell's admission date
    - CIPs of 3 spells with identical admission and discharge dates => 33 records deleted
    - CIPs of 3 continuous spells => 108 records (3rd spell) deleted
    - CIPs of 2 continuous spells => operational code of outcome moved to first spell if appeared in second and 3,915 records of 2nd spell deleted to create a CIP

Total number of observations deleted: 4,621

Appendix IV – SAIL unlinked observations

Using information from the NCCHD, I compared key characteristics of individuals linked on the three datasets NCCHD, PEDW and WDS compared with those unlinked. Table IV-1 presents the characteristics of the linked observations in comparison with the unlinked[52] as well as a comparison with the unlinked observations excluding 30% where place of birth was home.

The unlinked individuals were more likely to have been born by a vaginal delivery, but when focusing on non-homebirths only, there was not much difference from the linked individuals.

The unlinked observations were roughly similar to the linked observations in their distribution of sex, ethnicity, and maternal smoking. However, the unlinked were more commonly children of older, multiparous mothers and were more likely to be born preterm (although there was no major difference within term gestation). The linkage rate of births in 2015-2016 was lower (86.5%) compared with the overall linkage rate (90.3%). Stillborn babies accounted for 4.8% of the unlinked observations and would have been excluded if linked.

[52] Not including those missing a flag for 'Welsh birth'

Table IV-1: Characteristics of unlinked and linked observations in the SAIL study

	Linked on NCCHD, PEDW and WDS [a] (%)	Unlinked on one of the datasets NCCHD, PEDW and WDS (%)	
	All linked n=442,976	All unlinked [b] n=47,573	Unlinked excluding homebirths n=33,294
Mode of birth [c]			
VD	35.7	42.0	37.3
Assisted VD	6.6	4.5	6.4
Planned caesarean	6.4	4.0	5.7
Emergency caesarean	9.0	6.3	9.0
Missing	42.3	43.2	41.6
Maternal age			
<20	7.9	5.8	7.0
20-29	50.3	47.3	48.0
30-39	39.0	43.2	41.2
40 and above	2.9	3.7	3.8
Ethnic category			
White	80.9	78.1	76.2
Mixed	1.9	2.0	2.0
Indian/Pakistani/Bangladeshi	2.0	1.7	2.3
Black	0.8	1.0	1.3
Other	2.5	2.6	3.2
Missing	11.8	14.7	15.1
Parity [d]			
Nulliparous	40.9	32.1	37.3
Multiparous	44.7	51.0	43.2
Missing	14.5	16.9	19.5
Smoking			
Non-smoker	30.8	31.4	31.7
Gave up in pregnancy	1.5	1.2	1.3
Smoker 0-9 a day	4.0	3.9	3.9
Smoker ≥10 a day	3.9	4.3	4.3
Missing	59.9	59.3	58.8
Gestational age category			
<37 (preterm)	7.3	11.9	16.0
37-38 (early term)	18.2	16.1	17.4
39-40 (full term)	49.9	50.1	45.4
41 (late term)	20.5	18.7	17.7
42 (post term)	4.2	3.2	3.6
Male	51.3	51.3	51.8
Stillbirth	0	4.8	6.8

a Datasets used have undergone cleaning
b Not including those missing a flag for 'Welsh birth'
c Using NCCHD mode of birth variable
d Using NCCHD previous still and live births variable

Appendix V – SAIL asthma study outcome identification

Following is the process by which I identified the first emergency hospital admission at ages 5 to 11 for asthma as the primary indication

