Impact of childhood health and household experiences on educational attainment: Analysis using administrative data

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Summary

Inequalities in health and educational attainment continue to be observed in UK school children. The aim of this thesis was to address gaps in our knowledge about health and social factors that may impact on education in childhood. This thesis investigated the effects of unplanned hospital admissions, severity of a chronic condition (asthma) and Adverse Childhood Experiences (ACEs) on children's educational attainment.

A total population birth cohort of children born 1998-2005 in Wales was record-linked to administrative health and education data. Over 40,000 children were analysed using multilevel logistic regression and time-to-event analyses allowing adjustment for multiple socio-demographic, birth, neighbourhood, pupil mobility and school-level factors.

This thesis found emergency inpatient hospital admission during childhood was associated with an increased risk for lower education attainment at Key Stage 1 (KS1; age 6-7 years), particularly in the pre-school period or for injuries or external causes.

Children with an asthma (or wheeze) hospital admission rather than chronic asthma severity (or wheeze; using primary care prescriptions data) experienced increased risk of not attaining KS1. In addition, primary care consultations for lower respiratory tract infection were an independent predictor for children's education failure.

Adverse childhood experiences (ACEs) were also associated with increased risk for not attaining KS1 and Key Stage 2 (age 10-11 years): living with household members with common mental disorder or an alcohol problem, childhood victimisation, death of a household member and low family income. These effects were substantially greater for children with multiple ACEs.

Further, ACEs increased the risk for recurrent emergency hospital admission for asthma or all-causes in children. A first asthma or all-cause admission in childhood was not an important mediator between ACEs and KS1.

This thesis provides new evidence about these risk factors on educational attainment, where intervention could help children achieve their academic potential.

Manuscripts arising from the work in this thesis

1. **Evans A**, Dunstan F, Fone DL, Bandyopadhyay A, Schofield B, Demmler JC, Rahman MA, Lyons RA, Paranjothy S. The role of health and social factors in education outcome: A record-linked electronic birth cohort analysis. PLoS ONE 2019;14(8): e0220771.

2. **Evans A**, Farewell D, Demmler J, Bandyopadhyay A, Powell CVE, Paranjothy S. Association of asthma severity and educational attainment at age 6–7 years in a birth cohort: population-based record-linkage study. Thorax 2020;0:1–10.

3. **Evans A**, Hardcastle K, Bandyopadhyay A, Farewell D, John A, Lyons RA, Long S, Bellis MA, Paranjothy S. Adverse childhood experiences during childhood and academic attainment at age 7 and 11 years: an electronic birth cohort study. Public Health 2020;189:37e47.

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Abbreviations

ACE	Adverse Childhood Experience	MACRAL	Matching Algorithm for Consistent Results in Anonymised Linkage
ADHD	Attention deficit hyperactivity disorder	MAR	Missing at random
AHRQ	Agency for Healthcare Research and Quality	MCAR	Missing completely at random
ALF	Anonymised Linking Field	MCMC	Markov chain Monte Carlo
aOR	Adjusted Odds Ratio	MHI-5	5-item Mental Health Inventory
BMA	British Medical Association	MNAR	Missing not at random
BMJ	British Medical Journal	MOR	Median odds ratio
BTS	British Thoracic Society	NHLBI	National Heart, Lung and Blood Institute
cHR	Conditional hazard ratio	NHS	National Health Service
CI	Confidence interval	NPD	National Pupil Database
CMD	Common mental disorder	NRES	National Research Ethics Service
DAG	Directed Acyclic Graph	NWIS	National Health Service Wales Informatics Service
DIC	Deviance information criterion	ONS	Office of National Statistics
DRL	Deterministic record linkage	OR	Odds ratio
ED	Emergency Department	PAF	Population Attributable Fraction
ELAStiC	Electronic Longitudinal Alcohol Study in Communities	PEDW	Patient Episode Database Wales
EOTAS	Education other than at school	PICU	Paediatric intensive care unit
ERIC	Educational Resources Information Center	PLASC	Pupil Level Annual School Census
EU	European Union	PRL	Probabilistic record linkage
GDPR	General Data Protection Regulations	PRU	Pupil Referral Unit
GLM	General linear model	RALF	Residential Anonymised Linking Fields
GP	General Practitioner	RD	Risk difference
HDR UK	Health Data Research UK	RR	Relative risk / Risk ratio
HIRU	Health Information Research Unit	RTI	Respiratory tract infection
HES	Hospital Episode Statistics	SAIL	Secure Anonymised Information Linkage
HMO	Houses in Multiple Occupation	SDQ	Strengths and Difficulties Questionnaire
HPA	Hypothalamic-pituitary-adrenal	SEM	Structural Equation Modelling
HR	Hazard ratio	SEN	Special Educational Needs
ICD-10	International Classification of Disease 10th Revision	SIGN	Scottish Intercollegiate Guidelines Network
IgE	Immunoglobulin E	SQL	Structured Query Language
IGRP	Information Governance Review Panel	TF-CBT	Trauma focussed cognitive behavioural therapy
IQ	Intelligence quotient	UK	United Kingdom
IQR	Interquartile range	UKCRC	UK Clinical Research Collaboration
IRR	Incidence rate ratio	UKPRN	UK Provider Reference Number
KS	Key Stage	URTI	Upper respiratory tract infection
KS1	Key Stage 1	USA	United States of America
KS2	Key Stage 2	WDS	Welsh Demographic Service
LEA	Local Education Authority	WECC	Wales Electronic Cohort for Children
LRTI	Lower respiratory tract infection	WHO	World Health Organisation
LSOA	Lower super output area	WIMD	Welsh Index of Multiple Deprivation
		WLGP	Welsh Longitudinal General Practice

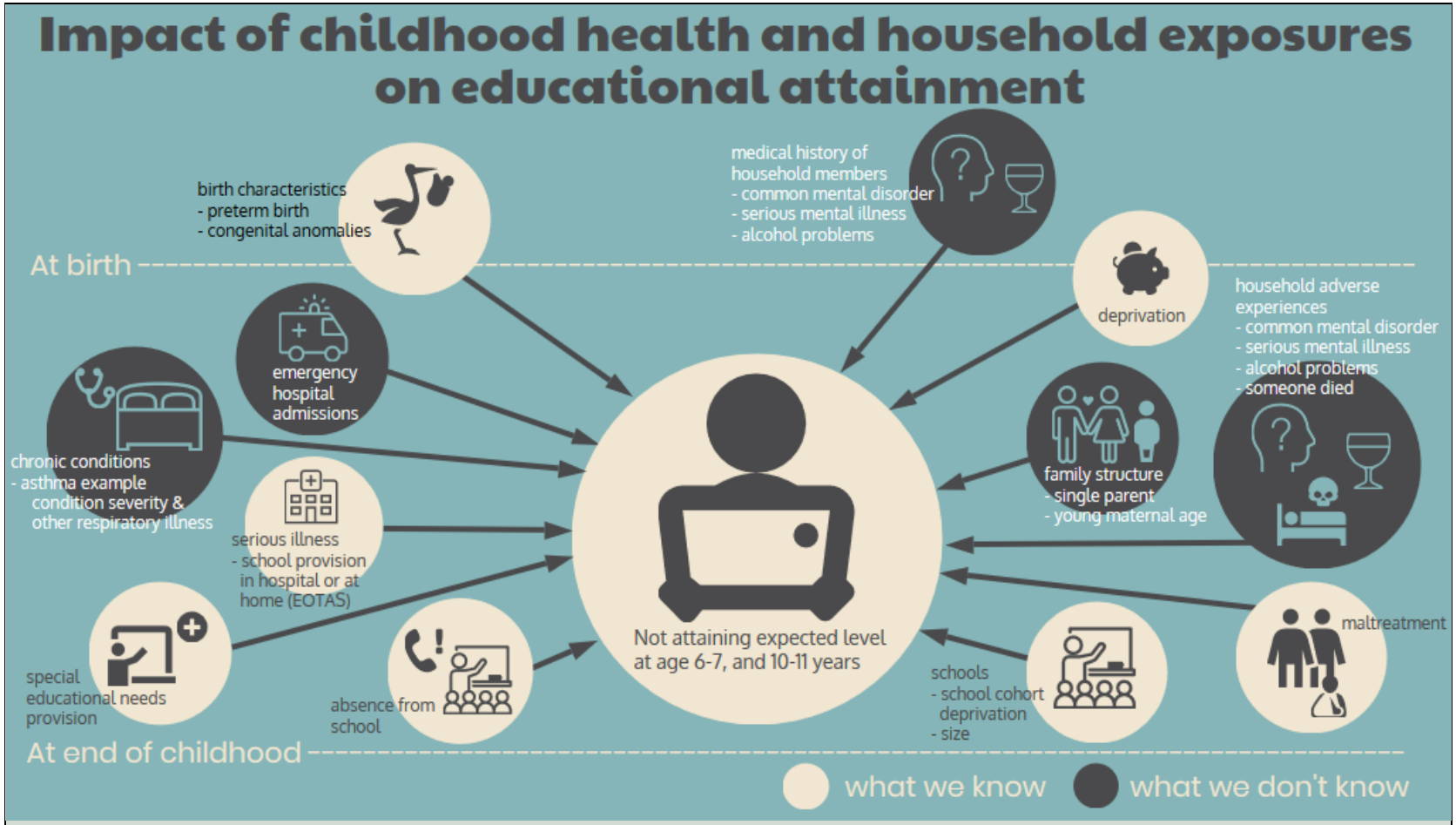
Note to the reader

This thesis uses the Vancouver referencing style as recommended by the School of Medicine at Cardiff University. I have chosen to include a reference list at the end of each chapter where references are numbered locally within the chapter rather than globally. I include a section title in the table of contents for the reference list in each chapter to aid navigation of the thesis.

Chapter 1 : Introduction

1. Overview

This thesis investigates the impact of childhood health and social factors on educational attainment in childhood, especially where limited previous research exists, using large record-linked administrative data sets. In this first chapter, I describe the background and importance of this research to Public Health, society and education policymakers. I provide an overview of the research gaps associated with both health and social factors on educational attainment, Figure 1.1. Then, I describe the rationale for this thesis; the use of new opportunities to analyse complex problems afforded by the availability of large administrative data sets. At the end of this chapter, I present the thesis aims and research questions.



This research will study the impact of the combination of these social and health factors on educational attainment in children.
EOTAS=education otherwise than at school.

Figure 1.1: Infographic of the overarching hypothesis of this thesis: childhood health and household exposures have a negative impact on educational attainment.

1.1 Background

In 2012, the chief medical officer for England stated in her report on children, that efforts to narrow health inequalities in children should be complemented with efforts to narrow the attainment gap in education.(1) The report highlighted the need to understand the effects of children's early years and key developmental stages on their life course because of the known link between early years and adult health and wellbeing. The aim of this thesis was to provide new evidence about the complex relationships between childhood health and social factors on educational attainment during childhood.

In the United Kingdom, statistics show that 75-85% of children attained the minimum reading level at the end of primary school in 2007-2013 (2,3,4) where compulsory schooling starts at age 5 years. It is known that children with serious illness where a child cannot attend school, or those with high school absence are more likely to not achieve educationally.(5) Moreover, it is established that educational attainment is socially patterned where children living in greater deprivation are more likely to have poorer academic achievement.(6) Health and social policies have been designed to aid improvement in educational outcomes for these children through out of school teaching or hospital schools for children too unwell to attend school,(7) fines for parents for child truancy issues (8) and extra funding for schools in deprived areas.

1.1.1 Importance of this research to Public Health and society

The published literature shows evidence of the benefits to health from academic education and additional time in education. Education is associated with improved adult health (9) due to enhanced knowledge of health issues and better cognitive skills. Individuals who have invested in education are more likely to aspire to better employment, which can lead to a better standard of living. Further, people with higher earnings from employment, are more likely to have a greater ability to use their income on health expenditure for private healthcare or supplementary therapies. The long-term effects of improved education are manifold and have a positive influence on the intergenerational effects of poverty (10); the characteristics of poverty mean poor parents have poor children, who are more likely to become poor adults.

1.1.2 Evidence of need for this research from school settings

It is known that when children have unplanned absence from school, where homework and schooling cannot be provided in advance, that children fall further behind than when absences are planned. Teachers indicate that they prefer children to have absences from school in blocks of time rather than one day a week for many weeks.(11) They provide evidence that some children are distracted at school (12) or have high school absence due to illness.(13) In addition there is evidence that teachers have witnessed children who have problems at school that may be explained by household dysfunction in their home.(14) Previous research shows children with poor nutrition related to poverty were found to lack concentration, had poorer cognitive development and were at greater risk of infection.(11) To mitigate these effects, there is growing support for schemes such as those to improve school engagement of both the child and parents, for example parents helping with homework, to aid children in achieving their potential.(15) Although there is evidence that teachers report disruption to learning from childhood health and social factors, the magnitude and potential cause of these effects on children's educational attainment remains unclear.

This thesis investigates whether or not there were other vulnerable groups of children in society not reaching their full potential in education where national intervention programmes do not already exist. A review of current evidence from the field led to the identification of three research gaps: unplanned hospital admissions, severity of a chronic condition using asthma and Adverse Childhood Experiences (ACEs) for effects on educational attainment outcomes in children.

1.2 Childhood health and educational attainment

1.2.1 Emergency hospital admissions

In the chief medical officer's report from 2012, a call was made for research to improve the understanding of the effects on children from childhood injury (reported to have high societal costs).(1) The published literature shows there is limited research about the effects of injury that required an emergency hospital admission on educational attainment in childhood. The unplanned nature of these admissions can potentially cause disruption and absence from school (the latter known to be related to poorer educational achievement).(5) Further, there is little evidence about the impact of other acute or

unforeseen conditions common in the first few years of life (e.g. infections) on educational attainment.

Few studies have examined how childhood health impacts on educational outcomes whilst considering the effects of health status at birth. Children in their early years of life can often experience hospital admissions, particularly for respiratory illness in those born late preterm and early term.(16,17) These acute conditions that can lead to unplanned hospital admission in children, may have a role on a potential causal pathway in the well-recognised relationship between preterm birth and lower educational attainment, Figure 1.2.

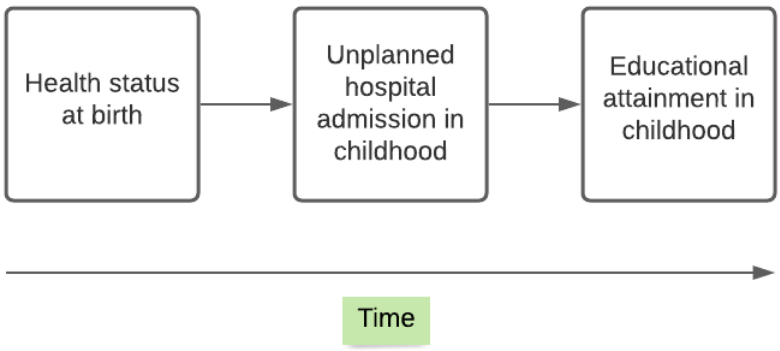


Figure 1.2: Potential causal pathway from birth health status to childhood health and educational attainment in childhood.

The effects on a child's education may be through influences on brain function from infection or injury,(18,19) or injuries that may potentially cause children to miss school.(20) No previous study has looked at the combined contribution of emergency hospital admissions, health status at birth (e.g. gestational age and birthweight), socio-economic and school level factors (e.g. school attended, percentage of deprived children at a child's school, and pupil mobility). This thesis investigates how the collective impact of pregnancy, perinatal factors, and emergency hospital admissions may impact on educational attainment.

1.2.2 Chronic disease: asthma and co-occurring respiratory infection

The report by the chief medical officer also called for research into the management of chronic disease (sometimes described as long-term conditions) in childhood so that appropriate interventions could be designed to optimise children's outcomes.(1) In the UK there are few studies about chronic health conditions and educational attainment in

childhood. During an initial review of the literature I concluded it was crucial to consider the severity of a disease on educational attainment.(21,22) For this reason, I chose to focus on one relatively common chronic disease as an exemplar in this thesis (asthma) to investigate the potential effects on children's educational attainment.

Asthma is a chronic disease whose aetiology is not fully understood. A clinician will often diagnose viral induced wheeze in young children when presented with wheeze symptoms (without diagnosing asthma), as symptoms resolve in many children as they grow older. The prevalence of current asthma diagnosis in children at age 7 years is estimated to be 12% in the UK (23) and the cumulative prevalence of wheeze is between 15-26% from yearly estimates during the first seven years of childhood.(24) Respiratory tract infections are also common in primary or pre-school children with upper respiratory tract infections (URTI) found to occur between three and eight times in a year.(25,26) Children with asthma may experience more severe symptoms when they acquire a respiratory infection.(27)

The findings from evidence in the published literature of the effects of asthma from birth on educational attainment in childhood is mixed, with some studies suggesting that well managed asthma had little effect on educational attainment(13,28,29,30,31,32) Moreover, the severity of asthma a child experienced had conflicting educational outcomes in previous research.(13,33,34)

This thesis investigates whether asthma severity is associated with educational attainment at age 7 years after taking account of perinatal factors and social deprivation (as described in Section 1.2.1). Additionally, it explores the role of respiratory infections, to see whether the effect of asthma interacts with respiratory infection on children's educational outcomes.

1.3 Social factors and educational attainment

1.3.1 Adverse Childhood Experiences

Public Health Wales have recently reported strong associations in Wales between ACEs and incarceration, health-harming and anti-social behaviour in adults, when comparing those with four or more ACEs (with estimated prevalence of 14%) to those with no ACEs.(35) ACEs included in this study were exposure to verbal, physical or sexual abuse, mental illness, alcohol abuse, parental separation, domestic violence, drug use and incarceration, but bullying and financial difficulties or deep poverty are included by other authors.(36) For

research in children, where collecting sensitive data from minors is problematic (because disclosure of information would need to be reported to Social Services) administrative data sets are an alternative resource that captures data on several ACEs.

Previous research in adults shows ACEs were associated with poorer adult health, leaving school without qualifications and unemployment.(36,37,38) Felitti et al's original theory was developed from an investigation of abuse and household dysfunction in childhood and associations with poorer adult health.(37) They hypothesised that if a child had exposure to multiple ACEs it caused mal-adaptive coping mechanisms that led to poorer adult outcomes. In further development of this theory, researchers speculate that the effects of ACEs in children create long-term or acute stress to a child that may affect their health and brain development (39) from exposure to family dysfunction or chaos in the household. These children who may have social, emotional or cognitive impairment related to exposure to ACEs may then go on to adopt health-risk behaviours such as cigarette smoking to cope in certain situations in adult life. These theoretical relationships are described in the Adverse Childhood Experiences Pyramid in Figure 1.3. ACEs are thought to influence education, health and wellbeing across the lifespan of the individual and may ultimately lead to an early death.

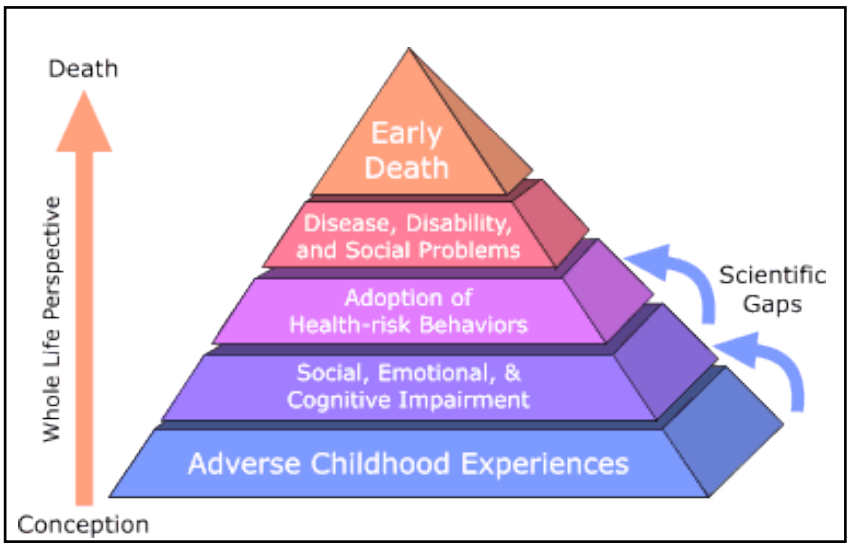


Figure 1.3: Adverse Childhood Experiences (ACEs) Pyramid: Theoretical mechanism about how ACEs influence health and wellbeing during a person's lifespan.
Charles Whitfield, M.D., Centers for Disease Control and Prevention, Public domain, via Wikimedia Commons. https://commons.wikimedia.org/wiki/File:The_ACE_Pyramid.gif All structured data from the file namespace is available under the Creative Commons CC0 License.

The published literature provides some evidence about the potential mechanisms for the effects of ACEs on children's educational attainment outcome. Children exposed to maternal depression were found to have higher levels of salivary cortisol, which could be a potential mediator in the pathway between chronic stress and lower executive functioning (e.g. working memory).(40) Differences in brain activity and hippocampal volume have been observed between children that have experienced maltreatment or neglect compared to those that have not, but the reasons for this are unclear.(41,42) Further work is needed to understand the associations between ACEs and educational outcomes in childhood.

One previous study investigated the association of multiple ACEs on school reading ability in children.(43) and found parental alcohol use, parental mental health issues and maltreatment increased risk for children's poorer reading attainment. However, this analysis was adjusted for absence from school and therefore the total effect (excluding mediator effects of absence from school) of ACEs on educational attainment is not known. Moreover, the impact of ACEs on academic attainment in childhood taking account of deprivation, birth and socio-demographic characteristics and school factors including school concentration of poverty remains unknown. In addition, the published literature shows maltreatment increased the risk for children receiving special educational needs (SEN) provision.(44) There is also evidence that ACEs such as maternal depression may mean support for homework is suboptimal when a child reaches later childhood.(45)

This thesis investigates whether there is a negative impact from multiple ACEs on educational attainment in childhood at age 7 and 11 years after taking account of a wider range of known important confounders than seen in previous research. The analyses in this thesis adjust for neighbourhood measures of multiple deprivation, single parent households, socio-demographic characteristics, birth characteristics and school factors. This thesis also investigates whether there is increased SEN provision for children who have ACEs and explores which ACEs are more strongly associated with this outcome in children. The analysis hopes to give insight into observed inequalities in educational outcomes in children, in order to better understand the pathways that lead to poor educational attainment. The findings should help to inform the design of interventions to mitigate the effects of adverse experiences on childhood education.

1.3.2 The role of poverty and deprivation

Young people (age 0-19 years) are disproportionately disadvantaged in the UK, 26.9% are in or at risk of poverty or social exclusion, compared to the overall population rate of 22.6%, markedly greater than the lowest European rate of 15.7% in the Netherlands.(1,46) Poverty is known to be associated with poorer academic attainment in children (11) and may potentially cause food insecurity and related psychological distress that may contribute to their failure in education.(46) A child who lives in a clean and dry home because caregivers can afford house repairs and maintenance can mean that children have a greater probability of reaching their potential in education.(48)

It is known there is social patterning in child health, educational attainment and ACEs in children.(49,50) In understanding the relationships between these factors, interventions could be designed to improve the lives of all children and determine how to allocate a greater proportion of these resources towards the most disadvantaged (proportionate universalism).(1) This thesis attempts to address these gaps in the evidence base to aid understanding and inform the development of interventions, using large administrative data sets.(51)

1.4 The complex interplay of health and social factors on educational attainment

This thesis examines part of the complicated interplay between risk factors on children's education outcomes. Firstly, it investigates the effects of ACEs on recurring all-cause and asthma emergency inpatient admissions in children. Secondly it determines whether or not emergency hospital admission explains (specifically, acts as a mediator of) any increased risk from ACEs on poorer educational attainment in childhood.

1.5 Rationale for this thesis

1.5.1 Current interest in chronic disease and adverse experiences in childhood

Areas that are currently of interest to health and education policy are the effects from chronic disease and adverse experiences in childhood. This thesis focusses on one common chronic disease (or long-term condition), asthma in childhood, as an exemplar. Previous research also highlights there is little evidence about the effects of unplanned inpatient hospital admissions on educational attainment. These questions do not cover all gaps in

the body of evidence of the complex associations between health and social factors on educational attainment in childhood. However, this thesis hopes to illuminate any problems in these areas using a very large population-based prospective cohort from birth to teacher assessment at age 7 and 11 years of age.

1.5.2 The potential to use administrative data to examine these questions

This thesis uses the Wales Electronic Cohort for Children (WECC), a cohort of nearly 1 million children born in Wales between the years 1990 to 2013. Its continuing aim is to transform information on demographics, health and education from routinely collected data into child population health policy and practice in Wales, whilst adding insight to the body of evidence of international research. These anonymised administrative data sets are accessed and analysed in the Secure Anonymised Information Linkage (SAIL) databank. The availability of record-linked General Practice data that can be linked to WECC means that chronic disease that are managed mainly in Primary Care (e.g. asthma, diabetes) can be investigated and clinical classifications developed through coding. These conditions may not present as hospital inpatient admissions or may only have a consultant specialism in outpatient data, so may be undetected in other health data sets.

Availability of these linked routine data sets for research provides a tantalising prospect for epidemiological research at the total population level into disease, social determinants, education and interventions across the life course. Although randomised controlled trials are the gold standard for medical research it is not always ethical to withhold the newest interventions designed to help children attain in education such as those needed in this thesis to create comparator groups. Additionally, long-term outcomes over 12 years from birth to Key Stage 2 used in this thesis are too expensive to fund in a trial and not practical to provide the advice needed today. In these situations, administrative observational data is the best and most cost-effective way to access this information, particularly at a total population level.

For statisticians and researchers, access to secondary health care data sets has allowed new knowledge to enter the public domain. The work in this thesis creates coding that captures childhood health categories and clinical groupings for asthma to use in analyses. The administrative data sets have permitted the inclusion of numerous variables in the analyses contained in this thesis that smaller samples would not allow, including multiple known important confounders. This thesis uses advanced statistical strategies to gain some

insight into the complex interplay between childhood health, socio-demographic characteristics, household exposures and composition, birth characteristics and school factors on childhood educational attainment. In schools, the published literature on educational progress showed neighbourhood deprivation, school-level factors and pupil mobility helped to explain variation in children's educational achievement.(52,53,54) Previous studies investigating the effects of child health and social factors on educational attainment have not accounted for these important confounders and effect modifiers that are included in the statistical modelling of this thesis.

This thesis provides further understanding about the effects of health and social factors on educational attainment in childhood. The potential identification of new groups of children vulnerable to academic failure mean health and education policymakers have a better understanding about how to help children reach their potential. The analysis in this thesis contains multiple measures of deprivation and poverty so that the effects on the most disadvantaged can be compared to other groups.

1.6 Thesis aims, objectives and scope

1.6.1 Aim

The overall aim of this thesis is to investigate the complex interplay of the effects from childhood health and social factors on educational attainment in childhood, especially where limited previous research exists (Figure 1.1).

1.6.2 Research question

What is the impact of childhood health and household exposures on educational attainment during childhood?

1.6.3 Hypothesis

Among children who experience childhood illness or ACEs preceding examination or assessment, a smaller proportion will achieve the expected level of educational attainment for their age compared to children who do not experience childhood illness or ACEs.

1.6.4 Objectives of thesis

1. To understand the coding of administrative data sets and externally validate these data sets against other data sources.
2. To write syntax to derive variables to create epidemiological cohorts.
3. To investigate and apply appropriate statistical techniques and causal inference diagrams to complex health, social and educational systems.
4. To review the literature and quantify the impact of unplanned hospital admissions on educational attainment in childhood.
5. To review the literature and explore the effects of respiratory illness including asthma (a common chronic disease) on educational attainment in childhood.
6. To review the literature and quantify the effects of ACEs on educational attainment in childhood.
7. To review the literature and investigate the impact of ACEs on recurrent all-cause or asthma emergency inpatient hospital admissions outcome.
8. To review the literature and determine whether or not either all-cause or asthma emergency inpatient hospital admission acts as a mediator between ACEs and educational attainment outcome.

1.6.5 Scope

The scope of this thesis is to focus on under-researched areas of health and social factors on educational attainment in childhood where interventions do not already exist.

1.7 Thesis synopsis

This chapter described the background and research questions of this thesis. Chapter 2 describes the development of WECC, data linkage to health and education data sets, and validation methods. Chapter 3 describes the causal diagram approach taken and statistical techniques employed to analyse these complex research questions. Chapter 4 presents the literature review, results and discussion from analyses of unplanned hospital admissions and social factors on educational attainment. Chapter 5 presents the literature review, results and discussion from asthma severity, common respiratory illness and social factors on educational attainment. Chapter 6 presents the literature review, results and discussion of ACEs on educational attainment in childhood. Chapter 7 presents the literature review, results and discussion of ACEs, all-cause or asthma emergency inpatient admissions and educational attainment. It presents the investigation of ACEs on recurrent all-cause or asthma emergency inpatient hospital admissions outcome. Subsequently, it determines whether these emergency hospital admissions explain the association between ACEs and educational attainment outcome in childhood. Chapter 8 provides a summary of the main findings, strengths and limitations of the work in this thesis, implications for policy makers and practitioners and the conclusions of this thesis.

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Chapter 2 : Methods

2. Overview

In this chapter I describe the design of the Secure Anonymised Information Linkage (SAIL) databank and the considerations in its conception. I describe the methods to anonymise individual data records in the SAIL databank, record-linkage between data sets at the individual level and linkage of individuals through their residential addresses. Then, I describe the processes to harmonise and merge variables from different data sources to create the Wales Electronic Cohort for Children (WECC). I carried out part of this work by cleaning and harmonising variables about week of birth, date of death, house moves, several birth characteristics and the education data. I describe the other data sources that were record-linked at the individual level to WECC and how children's exposures relating to household members were captured through the child's address. These data sets were inpatient hospital admissions, General Practice data and education data. Finally, I discuss the quality of the data sources, validity of the data for analyses, including the work I carried out on specific variables, and implications for the analyses within this thesis.

2.1 Data sources

2.1.1 Background

From the mid-1980s there has been speculation about the possibility of a secondary use for healthcare administrative databases to further medical research in larger samples and even at population level (1,2) as computer technology develops. The UK and other countries are now classifying data from healthcare systems such as from hospitals as assets for use in medical research and evaluation where previously data was collected through survey questionnaires. This has involved the creation of the UK Clinical Research Collaboration (UKCRC) and other collaborations to promote and support the use of healthcare system data sets.(3)

The design of medical research studies using healthcare administrative data sets as a secondary use need to consider the way data is recorded by clinicians, medical coders, and health administrators. Researchers should consider the reasons why information has been recorded in relation to payment recovery schemes and whether information is recorded systematically and by whom. Additionally, patient diagnoses or symptoms may have ambiguous definitions and advice from clinicians may be required on the reasons why conditions are classified in that way and how to interpret and use the information. For example in hospitals, historically electronic databases have recorded information using NHS coders for costing purposes, where money is claimed from health boards for each patient for beds, procedures and equipment.

Advances in computer technology has enabled anonymised databases to be held in 'safe havens', for example the Secure Anonymised Information Linkage (SAIL) databank at Health Data Research (HDR) UK, Swansea University,(4) and accessed either onsite or through remote computer desktops. Other registries on birth and deaths, demographic information and health registries have been record-linked for each individual person with the de-identified databases. These databases are accessible for analysis in the SAIL databank under stringent governance and anonymisation rules.(5)

2.1.2 SAIL databank: technology

2.1.2.1 The platform

The SAIL databank operates on a DB2 platform (Data Warehouse Edition on AIX) running on an IBM 'P' series Supercomputer: Blue-C.(4) The platform is held in buildings at the Health Information Research Unit (HIRU), Swansea University, Wales, UK. In 2009 the databank held over 500 million individual-level records on health and wellbeing and continues to expand as additional refreshes of data update records and with new linkage to other administrative data sets. These linked data sets currently include specific provider-level health data sets, education, social care data sets and survey data from other research. The databank holds multiple national Welsh data sets (a population of over 3 million people). It provides the opportunity to evaluate national health and social policies as well as inform policy development using data from the total population of Wales.

Development of the SAIL databank included a pilot project in the local authority area of Swansea.(4) The results of the pilot helped to develop the processes underpinning the databank. These are:

- that the data was transported by splitting data sets at source and transporting personal data and clinical data separately
- a reliable matching algorithm between data sets and anonymisation of commonly recognised identifiable variables by a third party, NHS Wales Informatics Service (NWIS) e.g. NHS number
- an algorithm to control the risk of disclosure in data views for researchers using the data that shows 'week of birth' instead of 'date of birth', (date of birth is recoded to the previous Monday and is potentially only 6+ days after the 'week of birth' date in SAIL data sets)
- data access control methods with both physical and permission restrictions and authorisations
- a collaboration review system; review by the HIRU team for data availability and feasibility and an Information Governance Review Panel to assess appropriateness of requests to use the data and results before publication

- an independent internal audit to assess compliance with Information Governance.

Currently a second stage encryption is used by the SAIL databank to store the data and a third stage encryption is used to create project-specific data sets and linkage between data sets.

2.1.2.2 Record-linkage

Individual record-linkage

There is no unique national identity number in the UK in contrast to other countries such as Sweden where a personal identity number is issued to every person resident in the country from the Tax Agency as part of the population register. However, in the UK each person who has registered or accessed health services within the UK is assigned a unique 10-digit NHS number that is used as a personal identifier across different NHS organisations. In Wales, the Welsh Demographic Service (WDS) assigns this unique NHS identification number to each person and this database can be used as a proxy for the Welsh population. The WDS contains anyone who is registered with a Welsh General Practitioner (GP) and includes those who currently reside in Wales, and may include those who live in close proximity to Wales. Record linkage between data sets within the SAIL databank use a combination of deterministic record linkage (DRL) and probabilistic record linkage (PRL).

DRL is based on the NHS number or on an exact match (usually where NHS number is not held in the database) between forename, surname, gender, postcode of residence and date of birth. Probabilistic matching allows similar but not identical query strings to be accepted as possible matches, which includes Lexicon matching (a list of alternative forename variants e.g. Betty, Liz for Elizabeth) and Soundex matching (phonetic spelling of forename and surname). For each individual, a probability score is assigned to each pair of variables to be matched using Bayesian likelihood ratios. Prior probabilities in the Bayesian modelling are based on distributions of the variables in the WDS database of the Welsh population. This allows the likelihood of a match between two variables to take account of common surnames like Jones in deriving the likelihood ratio that creates a weight assigned to each match. It also recognises non-independence between for example, female gender and recognised female first names. Posterior odds from the analyses are calculated for the five variables and a cumulative probability of a match is produced.(5)

Each individual in the WDS is assigned a unique Anonymised Linking Field (ALF) and matched to other data sets through the use of the SQL-based matching algorithm designed for HIRU, the MACRAL (Matching Algorithm for Consistent Results in Anonymised Linkage).

The optimum matching technique now used in the MACRAL was found to yield specificity values > 99.8% and sensitivity values >94.6% with PRL at the 50% threshold (for the five matching pairs of variables), with error rates of < 0.2%.(5) All person-identifiable matching is conducted at NWIS, a trusted third party.

Residential record-linkage

Residential Anonymised Linking Fields (RALFs) are created by encrypting postal addresses at NWIS. Individuals are linked to addresses by date through the WDS. This does mean that there may be some delay between the date when an individual moves address and when they register the change of address through contact with the NHS, and may lead to a delay in the date of change of address in the WDS database.(5) The recorded address in the WDS is based mainly on registration with a GP.

2.1.3 Wales Electronic Cohort for Children (WECC)

The Wales Electronic Cohort for Children (WECC) was created from harmonising and combining multiple demographic and health administrative data sets for each individual through record-linkage. These data for children were anonymised through encrypted anonymised linking fields (ALFs) for all children across Wales. As data access became available to researchers in Wales during the mid-2000's, a team of researchers in Cardiff and Swansea University (of which I was a member) worked together to create the cohort and data variable definitions. The linked routine data sets were accessed through the SAIL databank platform. Two phases of data extraction took place from the administrative data sets provided by NWIS, the Office of National Statistics (ONS) and Public Health Wales. The first data extraction was done in March 2011 and included children born or living in Wales between 1990 and 2008. The second, a complete data refresh was extracted in October 2013 and included children born or living in Wales between the years 1990-2012.

The WECC consists of 981,404 children born from 1st January 1990 to 7th October 2012. Children included in the cohort were those with a record in the WDS with an ALF assigned through the MACRAL matching algorithm. This meant that each child could be record-linked (based on their NHS number as described in Section 2.1.2.2) between the health and

demographic data sets held in the SAIL databank. WECC contains data from seven administrative databases in Wales as described in Table 2.1.

Table 2.1: WECC Data sources

Data source	Description	Data controller / owner
Welsh Demographic Service (WDS) – previously the NHS Administrative Register (NHSAR), from 1960	Data for each person who registers or accesses health services in Wales. A unique 10-digit NHS number is assigned as a personal identifier to be used across different NHS organisations	NHS Wales Informatics Service
Public Health Birth files from the Office for National Statistics (ONSB) - from 2003	Data on all births in Wales and to mothers who are usually resident in Wales	Local Registration Service in partnership with the General Register Office (GRO), monthly statistics.
National Community Child Health Database (NCCHD) - from 1987	A national database of all children resident in Wales or born in a Welsh hospital, containing data collected at birth such as parity, mode of delivery, gestation, birth weight, gender, breastfeeding, and Apgar Score	NHS Wales Informatics Service
Public Health Mortality Files from the Office for National Statistics (ONSM) - from 2002	Data on all deaths in Wales or of individuals who are usually resident in Wales	Local Registration Service in partnership with the General Register Office (GRO), monthly statistics.
Patient Episode Data set for Wales (PEDW) - from 1998	Demographic and clinical data on all inpatient and day-case admissions in National Health Service Wales hospitals and all Welsh residents treated in other UK countries	NHS Wales Informatics Service
All Wales Perinatal Survey (AWPS) - from 1993 to 2012	A database of perinatal and infant mortality in Wales including infants from 20 weeks' gestation to 1 year of age, who die in a Welsh hospital or whose mother is usually resident in Wales	Cardiff School of Medicine / NHS Wales Informatics Service
Congenital Anomaly Register and Information Service (CARIS) - from 1998	A population-based register of any foetus or infant who has a congenital anomaly whose mother is usually resident in Wales at the time of birth; congenital anomalies are defined by the European network of population-based registries for the epidemiologic surveillance of congenital anomalies	Public Health Wales

Several of the administrative data sets held data on the same information that needed to be cleaned and harmonised e.g. date of birth. The WECC development team discussed the

best way to combine these variables to create the highest quality of data for the cohort. For each data variable, the team made decisions about which databases contained more reliable data based on knowledge of the quality of the individual databases (understanding of the conception of the database, data collection methods, data holders and use of the data). This led to the creation of prioritisation rules, ordering the databases by quality and reliability, that were used where there were multiple entries for a child or to minimise their missing data. Additionally, the team considered the reliability of these individual databases in previous peer reviewed research.

For individual databases the team investigated missing data in the variables (by year and if of concern by unitary authority), the comparability in the way a question was asked, and the rate of agreement between data sources. As the cohort was concerned with epidemiological questions for babies and children, the variables were examined for any differences between those born in Wales and those who moved into Wales at a later date. The variables were investigated with particular attention to missing data, because children who moved into Wales at an older age may not have data on birth characteristics in the databases.

Table 2.2 describes the algorithms that were developed in WECC for harmonising and combining variables. It also shows the rate of agreement between variables from different data sources and the remaining levels of missing data after combining data sets, for those variables clinically relevant to analyses within this thesis. I investigated the data variables of week of birth, date of death (including neonatal death), maternal cigarette smoking in the first trimester, breastfeeding at birth and at 6-8 weeks, month and season of birth (derived from week of birth), residential moves, educational outcomes and characteristics (including free school meals and school moves).

Table 2.2: Algorithms in WECC for combining variables from different data sources, for children born between years 1990-2008.

Variable	Data sources	Proposed method[a]	Minimum rate of match	Maximum percentage of missing data
Week of birth (WOB) derived from 'date of birth'	WDS, NCCHD, ONSB, ONSM, AWPS.	1. Use the WDS week of birth if present. 2. If that is absent, use instead the NCCHD week of birth. 3. Where discrepancies occur between WDS and NCCHD versions of the WOB, when either match the ONSB WOB, change to ONSB WOB. 4. Additional cases from AWPS data source; backfill blank data with AWPS WOB but do not overwrite information from points 1-3.	99.7%	0%
Born in Wales	ONS, NCCHD, AWPS.	1. The ONS data is only available from 2003. As a consistent definition is wanted throughout the cohort it is agreed the data will be analysed using the definition of Welsh birth from the NCCHD Welsh birth flag to have a complete and simple definition. Most analyses will be restricted to these children as they will require data to be available from birth for immunisations or hospital admissions. 2. For the additional deaths in first year of life from AWPS, these children are all coded to Born in Wales as the AWPS is for all Wales so the majority will be Welsh born. Validation of baby and infant death rates has been done using the ONS. 3. Children with first contact with the NHS up to 4 months after birth are assumed born in Wales.	91.2%	0%
Gender	WDS, ONSB, ONSM, NCCHD.	1. Use the WDS. 2. If gender is missing fill with data sources in the following order: ONSB, ONSM, NCCHD. 3. If there are two sources, the same hierarchy is used to select the gender. 4. When three sources or more are present, the majority rules.	99.7%	0.005%
Gestation	NCCHD.	Cleaning removes gestational age less than 24 weeks and greater than 43 weeks.	NA	4.9% born in Wales, 84% not born in Wales
Birth Weight	NCCHD, ONSB.	For the NCCHD and the ONSB data sources after removal of stillbirths (6): 1. Exclude those gross outliers from a newly created variable defined as less than 660g and greater than 7000g. 2. Divide the data into males and females and by gestational age 3. Apply the Tukey method with k=2 to each sex-gestational age group. That is define fences to be Upper quartile + 2× IQR and Lower quartile - 2× IQR 4. If the NCCHD value has not been removed in the cleaning process then use this. 5. If there is not an acceptable value from the NCCHD but there is an acceptable value from the ONSB then use this one. (Therefore priority is given to NCCHD over ONSB in cases where both are present in the data set and neither was excluded as being implausible).	99.4% are within 100g	1.8% born in Wales, 90.7% not born in Wales

[a]AWPS only available in WECC phase 1.

Table 2.2: Algorithms in WECC for combining variables from different data sources (cont).

Variable	Data sources	Proposed method[a]	Minimum rate of match	Maximum percentage of missing data
Migration	NCCHD, WDS, ONSB.	Migration in: 1. Children removed from Swansea data extraction who are not born in Wales (no NCCHD Welsh birth flag) and never had a Welsh address (no Welsh LSOA in NCCHD at birth or WDS registration) within WECC timeframe. 2. Calculate children migrating into Wales who have a Welsh LSOA in the 'WDS first register' variable when move into Wales and do not have a Welsh LSOA at birth in the 'NCCHD LSOA at birth' or 'ONSB LSOA at birth'. Migration out: 1. Compare the date when a child leaves the WDS in Wales with the end of the WECC, the 7/10/2012, to decide whether a child was in or out of Wales at the end of the WECC timeframe, ie. if at this time the WDS LSOA is Welsh or not.	NA	NA
Maternal age	NCCHD, WDS.	1. Maternal age at time of birth removed if under age 12 and over 55. 2. NCCHD maternal age augmented by WDS.	75.2%	0.5% born in Wales, 21.7% not born in Wales
Stillbirths	NCCHD, ONSB, AWPS.	1. Records listed as stillborn from NCCHD or ONSB. 2. Or listed as stillborn in the AWPS outcome categories i. 4 'stillbirth – antenatal macerated' ii. 5 'stillbirth – antenatal fresh' iii. 6 'stillbirth in labour' 3. Or on the AWPS annual report outcome variable category 3 'stillbirths'.	95.1%	Data on stillbirths is only validated as the right magnitude from 1993.
Date of death including neonatal deaths	AWPS, ONSM, NCCHD, WDS.	1. Include additional Neonatal deaths identified in the AWPS records. 2. If only one date of death from one data source use this. 3. If more than one Date of Death and different dates use priority order for inclusion of date of death: AWPS, ONSM, NCCHD, WDS.	71.1%	NA
Maternal cigarette smoking in first trimester of pregnancy	NCCHD.	Only one data source with data available from 1998.	NA	84.9% overall, data improves in later years only 57.3% missing in 2008.
Breastfeeding at birth or at 6-8 weeks	NCCHD.	Only one data source. As there are high amounts of missing data, propose to combine breastfeeding recorded at either birth or at 6-8 weeks.		57.5% overall, only 12.9% missing in 2008.

[a]AWPS only available in WECC phase 1.

2.1.4 Identifying household members for WECC children

Children in WECC were linked through anonymised linking fields to residential addresses (using RALFs) and then to individuals living in the same household. To reduce the complexity of the record-linkage between data sets WECC children were linked through their address to their household members at four time points when the child was age 1 year, 5, 8 and 12 years. These time points were chosen to coincide with children's developmental stages i.e. infancy and key school years. In earlier work, each child in WECC was found to move residence more than 15 times by the time they reached their seventh birthday. These higher numbers of residential address changes only affected a small minority of children and their household members. Most children who change address move residence with an adult from their previous household. In addition, when a person changes residential address their past health records such as GP records transfer to their current address. This means household members' past health records can be included in analyses when they are linked to a child through a RALF at a particular time point. The research questions for this thesis look at common problems and health issues in children and because of the added database preparation time for statistical analyses to look at all residential changes the extra time could not be justified.

2.1.5 Hospital inpatient admissions data

Hospital inpatient admissions data was taken from the Patient Episode Database Wales (PEDW) and follows a similar format to the Hospital Episode Statistics (HES) database in England. Hospital admissions data is recorded by the healthcare provider during the patient's time in hospital and the data is used to claim back money for patient healthcare and treatment from the NHS using national tariffs.

The format of the PEDW data relates to each person's admission and care. A person admitted to hospital as an inpatient is assigned to a consultant in a particular type of ward with the relevant speciality. For instance, a person admitted to an orthopaedic ward who needs a knee replacement. This inpatient admission ward stay creates a row of data in the PEDW called a consultant episode. Each row of data relates to a specific person, and has an admission date, discharge date and fourteen diagnosis codes that use the WHO International Classification of Disease and related health problems version 10 codes (ICD-10).(7) If a patient then requires different treatment they are assigned to another consultant. For instance, if a patient has a myocardial infarction whilst in hospital they may

require care from a consultant cardiologist. The patient is then re-assigned to a cardiology ward, and another row of data is created in the database for the same stay in hospital. Other patients may move to another hospital instead of another ward for specialist care, for example to see a consultant in a specialist burns unit, this again creates another row of data in the database. For epidemiological purposes, consultant episodes that are part of the same spell of treatment within one or more hospitals, and transfers of up to two days between hospitals are counted as the same stay. They are described in this thesis as a 'person-spell' and defined by the Dr Foster definition.(8) This definition was developed at the Dr Foster Unit, Imperial College, London to compare adjusted mortality rates between hospitals.

Children who are admitted to hospital are assigned to a paediatric consultant. For analyses in this thesis, emergency inpatient hospital admissions were used as an indicator of child health because theoretically they could be a more sensitive measure than a pre-planned elective inpatient admission. There may be greater disruption to a child's life from an unplanned hospital admission, and a child's illness that causes a hospital intervention is likely to be more extreme than one that requires a GP appointment. Investigation of the PEDW diagnosis coding for children was found to be mainly limited to the first diagnosis code (or the first three codes) in emergency inpatient hospital admission data within the first consultant episode. Previous research using PEDW has highlighted there were some exceptions to this general rule, in particular all diagnoses codes were needed for injuries.

For this thesis, emergency hospital inpatient admissions for children were mainly defined using the first diagnosis in the first consultant episode for each person spell but any exceptions are described alongside the results in their relevant chapters. For injury and external causes in children a combination of diagnosis codes was required to describe the reason for admission and therefore all diagnosis coding positions were used.

For the WECC project, various emergency inpatient hospital admission categories have been created from groups of codes by clinical researchers and clinicians working in the WECC development group. In the WHO ICD-10 there are two chapters, R and Z, that contain more general descriptive codes rather than a diagnosis. The ICD-10 chapter that labels all diagnosis codes with an R in the first character of the 4-character alpha-numeric contains symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified. The chapter with a Z as the first character in the alpha-numeric contains factors that influence health status and contact with health services (e.g. contact to donate an

organ, or a problem that influences health status but is not the current illness). To create derived variables for categories of diagnoses for a patient, for instance for any respiratory admission, the first non-R or Z code was chosen from the potential 14 diagnosis variables in the first consultant episode in the PEDW data. Further exclusions from diagnoses lists were a set of U codes that related to maternal problems during childbirth that were recorded in the baby's record, and therefore were not appropriate in the coding of diagnoses of a child's health status (Appendix Table A2.1).

2.1.6 General Practice (GP) data

The Welsh Longitudinal General Practice (WLGP) database contains details on all contacts with a General Practice, including nurse appointments, and comprises information on symptoms, diagnoses, procedures and prescriptions. GP data available in the SAIL databank contains only coded data and not additional typed notes from consultations.

General practice routine data across Wales had approximately 40% coverage from 2007-2012 available for record-linkage to WECC, that is over 195 practices signed up out of 474 practices in Wales, and a population of over 1.9 million. The WLGP database, linked through the SAIL databank to WECC is area specific, with all children registered to a particular practice included in the available data. In 2012, areas in south-west Wales and parts of mid-Wales had over 89% of General Practice data uploaded to the SAIL databank that were used in the analyses of this thesis. The number of General Practices signing up to add their administrative databases to the anonymised SAIL databank continues to increase.

In analyses for this thesis, household members of children in WECC were record-linked to their GP data. The SAIL databank holds GP data for both adults and children. This thesis used GP data diagnosis, symptoms, procedures and prescriptions in its investigations.

2.1.7 Education data

WECC has been record-linked to the Pupil Level Annual School Census (PLASC) and the National Pupil Database (NPD) that contains information on children who attend Local Education Authority (LEA) schools. PLASC contains yearly information on what school a child attends, whether they are eligible for free school meals and what special educational needs provision they receive (recorded in January but also in May in Key Stage years). The NPD records information on exam and teacher-based assessments at the Key Stages.

In Wales, children have a statutory assessment at age 6-7 years called Key Stage 1 (KS1). This is one of four stages of compulsory education taught normally at ages 5-7 years, 7-11 years, 11-14 years and 14-16 years.(9) For the years of the analyses in this thesis, Key Stage 1 and 2 were mainly teacher-based assessments to attainment targets using the national curriculum, and included only a language (English or Welsh), mathematics and science at KS1 with the same core subjects assessed at Key Stage 2 (KS2). Children were given an overall classification of attaining the expected level (an average of level two or above in each subject at KS1, and of level four or above at KS2) or that they did not attain the expected level. Other children were defined as not attaining the Key Stage by the Department of Education if they were classed as working towards the assessment level (but had not completed enough of the curriculum to take the test) or were dis-applied (either due to special educational needs or in-migration where the language being tested was not currently spoken). Additionally, those unable to provide an assessment (usually due to physical difficulties) did not attain the Key Stage. In Wales formal tests were administered for KS1 in years 2003-05 and at KS2 in 2003-07 with a change to teacher-based assessments in subsequent years. In 2012 there was a change to the Foundation phase for KS1 with a curriculum change. Formal tests are administered after 1st May of the year the child usually takes the Key Stage, assessment can be done throughout the school year from September to July but is mainly focussed on work done by the child after the end of May. Therefore, this assessment is approximately at the same time as when a formal test would have taken place. Children coded as absent were excluded from the analysis in the years when formal tests were administered.

Information on schools was obtained from PLASC where data had been aggregated to a School level census from pupil level information. The School Census data is reported on the Statistics Wales website.(10) (Statistics Wales is a website containing aggregated tables of official data on Wales that allows the public to view and download information on population, health, education, and government departments like councils). Tables taken from Statistics Wales were edited into a format to allow record-linkage using a combined unique identifier from School and LEA identifiers. The concentration of pupils eligible for free school meals at a school, and school size were added to the education data sets through use of the SAIL databank. The average percentage of total pupils eligible for free school meals at the school was derived across the years when Key Stages were taken in the cohort. Similarly, the average school size was created from the total number of pupils at the school across Key Stage assessment years.

2.2 Discussion of data quality and validation to external data sources

2.2.1 WECC

Approximately 30,000 children are born in Wales each year. Nearly one million children were living in Wales between January 1990 and October 2012, of these children 78% were born in Wales, Figure 2.1.

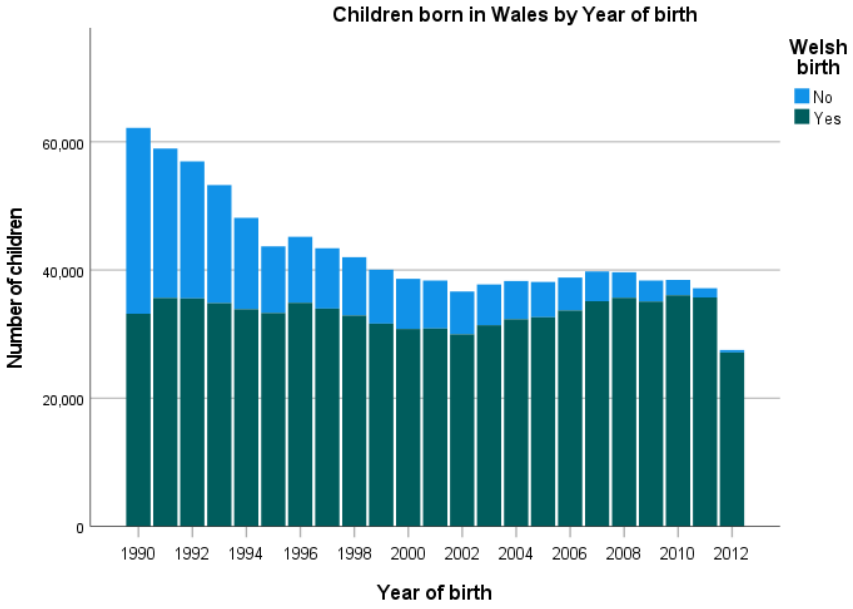

Figure 2.1. Children born or moved into Wales in the WECC birth cohort January 1990 - October 2012.

The administrative data sets used in WECC analyses have been cleaned for typographical and data entry errors and assessed and to be within plausible clinical ranges (e.g. birth weight). Each variable has been validated by comparing it to associated variables (e.g. for birth weight to gestational age and sex) and to other data sources. Other data sources were ideally other administrative data sets of similar populations or when no other information was available survey data in the published literature was used. The WECC data set produced from the cleaning and validation process should be reliable in analyses across Wales but the usual statistical checks for outliers, influential cases and any anomalies will be examined. This will be investigated by using frequency histograms, statistical model diagnostics and goodness of fit tests for the specific types of analysis. Individual or groups of cases will be investigated in the data (including review of their other related variables) for inclusion or exclusion from analyses.

The WECC data set from 1990-2012 contains nearly 1 million children and therefore syntax rules must be set up for errors rather than cleaning at the individual level. Data errors have been minimised with merger rules that pertain to previous knowledge of the quality of each database, levels of agreement for each variable between different data sources and normal statistical cleaning practises. The likelihood of statistical error in results for analyses on the full cohort are thought to be minimal due to the size of the cohort. For example, an error of 1000 children attributed to the wrong maternal age at childbirth, a 0.125% data error, will have little impact on the overall results of analyses. Small sub-group analysis (e.g. maternal age at childbirth of under 18 years) will be checked for the potential impact on results of data errors using cross-tabulations. For specific statistical analyses further cleaning and checking will be done especially when sub-samples are used.

The WECC development team thought examination of the data in tabulations and the distribution of the missing data provided evidence of very good agreement between data sources (where data set time frames overlapped). The team concluded the methods for merger were rational and provided satisfactory data for analysis.

The percentage of missing data was substantial for only two variables, breastfeeding and maternal cigarette smoking in the first trimester. Cross-tabulations of year and unitary authority for these two variables showed missing data had a relatively uniform pattern across Wales. It was surmised that missing data might relate to administrative and organisational differences in collection (such as incentives to collect data) and collation of data between hospitals in Wales rather than differences in the collected variables. This investigation suggested that these data can be reasonably assumed to be missing at random.(11)

2.2.2 Hospital inpatient admissions data

Data on hospital inpatient admissions is recorded by NHS coders from clinician records on patients for costing purposes. Interpretation of the clinical records may mean that information bias may arise due to any systematic differences from the truth in collection, recall, recording or data manipulation including how missing data is handled. This also may occur through detection bias for a particular disease or condition, that is systematic differences between groups in how diagnoses are determined. In PEDW, the WECC team found little variation in the ICD-10 codes used for similar causes of admission in childhood emergency admissions. As the same codes were mainly used for each admission the

likelihood of misclassification was thought to be minimal and unlikely to have any major effect on results of analyses.

There may be variation in the rates of admission to hospital in different hospital or health boards for several reasons. For borderline cases, at the clinician level the decision to admit an individual child may produce different results from training and past experience. Secondary data analyses from coded hospital data does not provide information on whether the need for admission is high or whether the reason for admission is variation in medical practice.(12,13) There may be differences in admission policies for different hospitals or health boards. Supply side factors may influence the decision to admit a child based on the organisation of out of hours primary care services,(14) or general access and availability of primary care in that area. Admission rates may be higher in localities close to a hospital or where there is easy access to the hospital via transport.(14) It may be that some parents have a lower threshold for contacting health services than others. Parental ability to look after a child outside of hospital, special educational needs or other complicating health problems, and quality of accommodation for recovery may also play a part in the clinician's decision to admit a child. The potential bias in any of the analyses in this thesis are discussed within the context of each of the results chapters and include speculation on the direction and likely magnitude of these effects.

2.2.3 GP data

The purpose of recorded coded data in General Practice is to treat a patient and is usually based on the symptoms presented within the consultation. For GP data it is therefore important to consider whether symptoms and / or diagnoses should be used to ascertain cases of exposure or outcome for research studies.

Children classified as born in Wales, those with first contact with the NHS within the first four months of life are assumed to have complete GP data from birth. Analyses showed counts were too high for children who were not born in Wales (in the NCCHD) to realistically have moved into Wales during these months.

The risk of selection bias from the inclusion of only 40% of General Practices at the time of analyses is thought to be low as the distribution of sociodemographic characteristics were similar to the Welsh population and included area-level deprivation. There may be other unmeasured differences but with over 1.9 million people with GP data within the SAIL

databank, the data is thought to be representative of the Welsh population. GP data is only available for all registered patients from 1998 (excluding those who have opted out from the SAIL databank, numbers are very few). If a patient has electronic records prior to 1998 these have been included in the SAIL databank and can be used in analyses (median 5·65 years, IQR (2·61–9·79)).(15, Appendix Table A2.2)

2.2.4 Education data

The education data sets included all children who attended a school maintained by the LEA. Children who did not have a KS1 assessment (who were excluded from the analyses in this thesis) included those attending independent schools (approximately 2% of children), severely disabled children and children with some major congenital anomalies (approximately 4.3% of children in Wales). Additional exclusions were children outside administrative systems, such as travellers, and children who took KS1 later than the normal time of age 6-7 years. This thesis considers educational attainment outcomes at the total population level in all analyses throughout this thesis. it is possible that these exclusions introduced some selection bias but it may be difficult to compare those children that are severely disabled to the general population concerning educational outcomes. Also fewer than 2% of primary school children attend independent schools in Wales and so any resulting bias is unlikely to be large.

There may be some selection bias in those children who do not attain the Key Stage because definitions for not attaining KS1 by the Department of Education include children unable to take the test or who were dis-applied. In 2008, approximately 20% of children in Wales who did not attain KS1 were awarded level 1, 4.8% were working towards the level, 0.1% were not able to take assessment, and 0.2% were dis-applied.(16) As the percentage of children who were not able to take the test or dis-applied was only 0.3% there should be little impact on results of statistical analyses in this thesis. A further discussion of selection bias where systematic differences may occur between those selected for the cohort in analyses and the total population of Wales is found within each results chapter.

2.2.5 Household data: RALF

The SAIL databank standardly defines children as less than 18 years of age. Types of household composition have been compared to the Census 2011 from figures produced by the ONS.

The definition of a household in the Census 2011 is the same as in 2001:

- 'one person living alone or a group of people (not necessarily related) living at the same address with common housekeeping – that is, sharing either a living room or sitting room or at least one meal a day'. The household definition has been updated to reflect recent social changes and is more pertinent to modern living conditions. It is also a more objective definition that is easier for people to interpret (the 2011 Census dwelling count (17)).

It also includes:

- sheltered accommodation units in an establishment where 50 per cent or more have their own kitchens should be defined as households (irrespective of whether there are other communal facilities), and all people living in caravans on any type of site that is their usual residence. It includes anyone who has no other usual residence elsewhere in the UK (the 2011 Census dwelling count (17)).

The 2011 Census defines a dependent as a child aged under 16 years of age who lives with at least one parent, or aged 16 to 18 years in full-time education, excluding all children who have a spouse, partner or child living in the household. In 2013, the overall proportion of 17-year-olds in education and work-based learning was 84.4% (18) so a plausible comparison can be made between the SAIL databank's standard definition of a child and the definition in the 2011 Census.

Household data from Geographical Information System (GIS) locations was investigated by the SAIL databank but showed low accuracy to ONS 2011 Census for households that contained a least one child with more than five household members. The SAIL databank has now developed record-linkage to postal addresses using the UK Provider Reference Number (UKPRN).(19) Using the UKPRN in the SAIL databank household size and composition are thought to match well to the ONS data for those up to 11 household members. Houses that may not accurately reflect those who live with children are those where an individual address has not been set up for each part of the house (e.g. for flat A and B, and for some Houses in Multiple Occupation (HMO)). Residences with more than 11 people in the household will exclude living accommodation like private schools (where children live at the school) and hospitals. This exclusion would probably not remove

children in out-of-home care such as residential homes because they are usually small in size.

The data on households within the SAIL databank is not able to differentiate the relationship of household members. The household data is not able to distinguish maternal or paternal relationships with children or whether household members are more distant relatives or lodgers. The effects on children from direct caregivers may be more relevant to their educational attainment outcomes than a lodger staying in the home.

2.3 Data set linkage for analyses in this thesis

The WECC data set was record-linked through ALFs to the health and pupil-level education data sets, and also health data on household members through RALFs. School-level data sets were linked through a combined school and LEA unique identifiers. Figure 2.2 shows the record-linkage between databases.

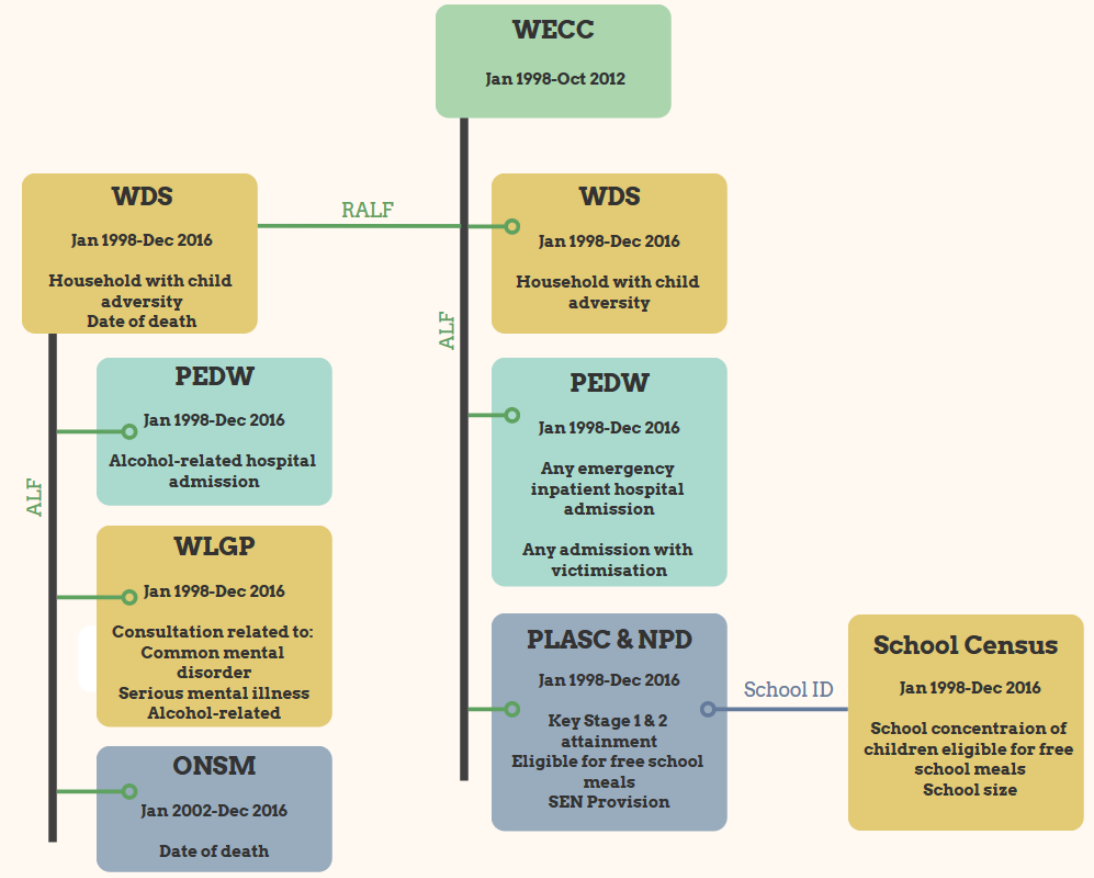

Figure 2.2. Diagram of linkage between data sets.
WECC=Wales Electronic Cohort for Children; WDS=Welsh Demographic Service; PEDW=Patient Episode Database for Wales; WLGP=Welsh Longitudinal General Practice; ONSM=Office of National Statistics Mortality database; ALF=Anonymised Linking Field; RALF=Residential Anonymised Linking Field; School ID=School and LEA combined unique identifier.

2.4 Ethics

Approval for the use of anonymised data in this study, provisioned within the Secure Anonymised Information Linkage (SAIL) Databank was granted by an independent Information Governance Review Panel (IGRP). The membership of this panel comprised of senior representatives from the British Medical Association (BMA), the National Research Ethics Service (NRES), Public Health Wales and NWIS. The use of anonymised data for research is outside the scope of the EU General Data Protection Regulations (GDPR) and the UK Data Protection Act.

The Research Ethics Committee for Wales judged WECC to be an anonymised research database that does not require ethical review, in line with National Ethics Committee guidance.

2.5 Implications for thesis

The WECC database and record-linked administrative data sources create a large whole population cohort that will facilitate the longitudinal examination of detailed data with large sample sizes for exposure and outcome groups of interest. Routine data sets are generally not subject to the selection bias that can arise in surveys due to non-response and sampling bias in recruitment of participants. Administrative data sets mean many of the variables to be used in analyses were collected in a standardised way and will allow better comparison of the data across Wales. The large data sets allow for multiple confounders to be included in the model, that cannot be individually included in smaller samples, and statistical design that can accommodate the temporal order of the data to examine potential cause-and-effect relationships of exposure on outcome. In all observational studies further unmeasured confounding should be considered because randomisation of the exposure cannot be achieved, that is as found in a randomised control trial.

The routine data sets may have potential for misclassification in the coding of diagnoses for exposures or outcomes of interest. It requires analysts to thoroughly investigate and validate variables to other data sources. However, misclassification is likely to be at random, and not related to other variables in the model, partly because variables were collected from separate data sources.

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Chapter 3 : Statistical methods

3. Overview

In this chapter I describe the statistical methods I used in this thesis and explain why they are appropriate to answer the research questions, given the type and structure of data sets I was working with. Firstly, I describe the use of Directed Acyclic Graphs (DAGs) used to visualise causal relationships. DAGs aid the choice of the minimal sufficient adjustment set of potential confounders and allow transparent assessment of assumptions underlying causal inference in statistical modelling. I then describe frequentist and Bayesian statistical approaches and their advantages and disadvantages for the analyses of this thesis. Finally, I outline other statistical methods I used in this thesis, where I made the most up-to-date 'standard choice' in epidemiological research. I outline why these choices are advantageous; to reduce bias and improve estimate precision.

3.1 Causal inference and use of Directed Acyclic Graphs

3.1.1 Background

Causal inference

This thesis investigates whether or not childhood health and social factors impact on a child's educational attainment where there are gaps in the published literature. A central aim of epidemiology is causal inference and moves beyond the investigation of association or correlation between risk factors and disease. Causal inference enables us to make conclusions about the presence and size of cause-and-effect relationships.(1,2) The knowledge of the cause of a disease or detrimental outcome means that interventions can be designed either to prevent exposure to that risk or to mitigate the effects of the exposure through their mechanisms.

In statistics the philosophy of causation can be expressed using probability theory. It can help when investigating theories about potential causal associations between exposures and outcomes. In probabilistic interpretation all else being equal, causes raise the probabilities of their effects.(3) This differs from a deterministic interpretation of causation where if A causes B, then A must always be followed by B. This thesis investigates whether childhood health or social factors cause an increase in the probability for poorer educational attainment, but may not observe that every child who has poor health or adverse social factors has poorer educational attainment.(4,5,6) That is, for those with poor health or adverse social factors, all else being equal, the probability of poorer educational attainment would be greater than otherwise.

To draw causal conclusions from data, Pearl uses a counterfactual approach to define causal inference with the notion 'had the exposure differed, the outcome would have differed.' (4 p.1) That is, the outcome would have differed for the exposed group in an alternate world where they had not been exposed. In the real world it is not possible to obtain these two measures at the same point in time. Alternatively, two groups of participants can be compared where the first group has the same risk of the outcome from the exposure as the second group had they been exposed, an assumption called exchangeability. For causal contrasts (risk ratios, rate ratios, odds ratios) under this assumption of exchangeability, the observed risk equals the counterfactual risk and associations between exposure and outcome can be interpreted as causal.(7,8)

Randomised control trials (RCTs) are the gold standard for testing cause-and-effect relationships and have strong assumptions with the central assumption of exchangeability. 'In probability, random variables are said to be exchangeable (under a given joint distribution) if they can be interchanged (permuted) in any statement without altering the probability of the statement'.(9,10) In RCTs, participants are randomly assigned to exposed and non-exposed groups, usually unconditionally unless study designs such as cluster or stratified randomisation are used. The assignment to treatment is independent of participant characteristics and neither confounding nor unmeasured confounding is expected, although confounding may still occur on the effect of taking the treatment. The interpretation of a trial's causal conclusions may be threatened if bias occurs within the trial from problems such as differential loss to follow-up, selection bias or treatment adherence.(7,11) For observational studies as in this thesis (that are closer to real life scenarios), statistical models try to move closer to the results of a randomised control trial design by controlling for confounding variables. Observational studies may be more generalisable to the population of interest when compared to trial results. A confounding variable is defined as a variable that can cause the outcome of interest (poorer academic attainment) and can also cause (or is at least directionally associated with) the exposure of interest (childhood health) Figure 3.1 a). Statistical models are adjusted for confounders to prevent distortion from bias or spurious results to make sure that the estimate is of the causal effect. In this thesis, by adjusting models for confounding, it will be possible to estimate the true effects of childhood health on educational attainment.

The traditional or classical approach to confounding uses only three variables in a diagram to identify a confounder or a variable on the causal pathway (mediator) between an exposure and outcome. With the availability of large administrative data sets there is an opportunity to explore more complex relationships between variables using the principles of causal inference. Statistical modelling can take account of numerous confounders, effect modifiers and mediators in longitudinal data analyses. Traditional methods to adjust for potential confounders in statistical modelling may introduce conditional associations and bias rather than their aim to minimise it due to accidental adjustment for variables misclassified as confounders.(12) Using more complex causal diagrams may find a potential confounder identified through the traditional approach is not actually a confounder after all, and therefore should not be adjusted for in statistical modelling.

There are several methods for developing causal diagrams for complex epidemiological problems to visualise causal relationships. The Directed Acyclic Graph (DAG) that uses counterfactual theory is becoming increasingly popular in epidemiology.(2,13) Pearl's review of the causal theory behind other techniques, Structural Equation Modelling (SEM) and Graphical Causal Models (causal diagrams using set theory notation and Boolean propositions) found they translated directly to counterfactual theory.(4,8) DAGs are also known as 'Bayesian networks', a term coined by Pearl for belief of causation. The advantage of a DAG in comparison to modelling such as SEM is that it is a graphical technique and is typically non-parametric so parametric assumptions such as linearity are not required.(14)

3.1.2 Directed Acyclic Graphs

DAGs visualise causal relationships between variables to aid choice of the minimal sufficient adjustment set of potential confounders for analyses of causal contrasts (risk ratios, rate ratios, odds ratios).(8) Theoretical relationships between variables from previous research and clinical knowledge can be investigated with the exposure and outcome of interest. DAGs help to decide what variables should be adjusted for in regression modelling, and also what variables should not be adjusted for in the models. A key point is 'adjusting for all variables' as an approach in statistical modelling may risk an investigator not finding a theoretical causal effect because estimates were accidentally conditioned on colliders (defined below).

DAGitty software can now be used to produce a DAG,(15) multiple variables can be drawn and connected with directional arrows to show any theoretical cause to effect relationship. Colour coding is applied to the DAG in DAGitty using causal inference and probability theory to help identify confounders, effect-modifiers, mediators, colliders and selection bias. The temporal order of variables is usually drawn from left to right of the diagram. The causal structures of DAGs are described in Figure 3.1 and specific language is used.

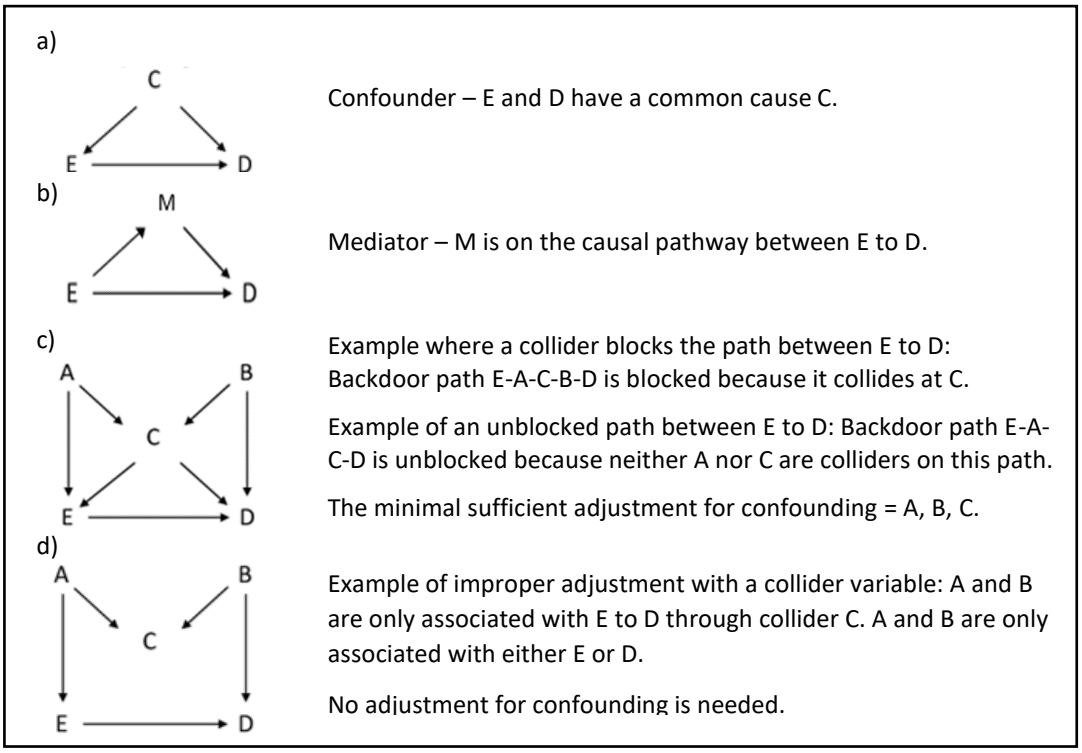

Figure 3.1 Directed Acyclic Graphs: Examples of causal structures for consideration of confounding variables when exposure and outcome variables have no descendants.
Adapted from Greenland et al (14) and Daniel R.(2) E=exposure; D=disease/outcome; A,B,C,M=potential predictor variables; directional arrow=theoretical cause-and-effect relationship. DAG assumption: Causal Markov assumption = Conditional on its parents, a variable is independent of its non-descendants.(7) (Terminology associated with DAGs variable=node; directional arrow=edge).

The arrow in a DAG represents a theoretical direct causal effect from one variable to another variable. Using these arrows in a DAG confounders that create conditional probabilties between the exposure and outcome can be identified; conditional probabilities can be described as equivalent to adjusting or controlling for confounders in statistical models. They can identify mediators that explain the relationship between exposure and outcome and may also include effect modifiers. Effect modifiers such as participant characteristics provide additional information because the magnitude of the effect of exposure on outcome varies according to the subgroups of this variable. That is, the variable is associated with the outcome but not the exposure. The DAGitty software can be used to design total causal effects analysis where potential mediators (such as school absence between child health and educational attainment) are excluded from analyses, or alternatively direct causal effects analysis that include identified mediators. Both types of analysis are found in this thesis.

DAG terminology says a variable is a parent / ancestor with any theoretical causal effect on another variable if a directed arrow / chain of arrows leads from it to another variable, and no arrow represents no causal effect.(7) It says a variable is a child / descendent if an arrow / chain of arrows is drawn to it from another variable that affects it. The terminology does not represent a biological association. The theoretical causal effect should apply to at least one individual in the population and should be included if a person is not willing to assume there is no potential causal association (Figure 3.1).

The aim of a DAG is to identify variables that are marginally independent, or that have marginal (or crude / unadjusted) associations where one causes the other. Further, potential confounding variables can be added to the DAG and conditional independence can be explored (with use of the Causal Markov assumption Figure 3.1). It is important to consider whether or not observations are independent when using statistical modelling techniques because many methods such as linear or logistic regression assume independent observations.

There are several advantages to DAGs compared to the traditional causal diagram that contains only three variables. The DAG allows multiple relationships to be drawn on the same diagram across all variables. Theoretical causal associations can be drawn to an exposure or outcome from parents or earlier ancestors and to children of those variables. It identifies collider variables including those that may cause selection bias. The published literature shows methodologists have improved access to DAGs through variable selection processes and the DAGitty software so that complex epidemiological scenarios can be examined.(12,14,15)

According to Greenland et al, to identify the minimal sufficient adjustment for confounders Figure 3.1 a) a DAG should be drawn with all potential causal relationships and then any arrows emanating from the exposure should be removed. (In practise it is preferrable to draw causal relationships for the total population rather than for exposed or unexposed groups and only separate temporal nodes are drawn over time if of particular interest).(16) If all paths are blocked between exposure to outcome Figure 3.1 (c , then there is no confounding of the net exposure effect on the outcome.(14) A path is blocked when it has one or more colliders; a collider is a variable with two parents (it has conditional association between the two parents), Figure 3.1 (c . Where paths are not blocked the confounding variables are included in statistical models to investigate the conditional associations between exposure and outcome. A collider may lead to improper adjustment.

If exposure and disease share no common cause (no confounder) but are associated through the strata of a third variable and each parent of that variable is only associated with either the exposure or the disease Figure 3.1 (d. In this case the model should not be adjusted for the strata variable or its parents.(14) The choice of variables can be confirmed using Shier's six-step process.(12)

A collider variable may create selection bias, for example when a collider variable is a child of the outcome variable and of an exposure variable. For example, testing folic acid supplements (exposure) in pregnant women for foetus cardiac malformation (outcome) where only those with foetuses who survived until birth (collider) were included in the study. Folic acid also reduces the risk of mortality from congenital malformations that are not cardiac. Some foetuses in the study with cardiac malformations would not survive until birth, Figure 3.2. Other scenarios of selection bias are described by Hernan and Robins.(7,8)

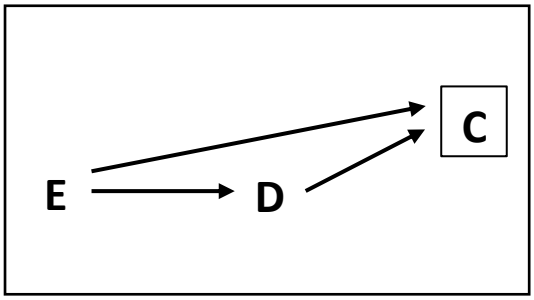

Figure 3.2. Example of a DAG where a collider may create selection bias.
E=Exposure of the foetus to folic acid supplements taken by the mother shortly after conception; D=Disease outcome: foetus cardiac malformation in the first 2 months of pregnancy; C=Collider: study was conditioned (represented by the box) on only children who survived until birth.

As Greenland et al has described how to check the DAG represents relations among exposure, disease, and potential confounders Pearl et al has extended the theory with d-separation for a set of variables and variable subsets of potential confounders.(17) This concept is useful as it implies stratum-specific independence across a set of potentially confounding variables. Each variable (or node) in a DAG now represents a set (collection of elements) or categories of a variable between exposure and outcome.(14) Greenland et al finds when there are no descendants of exposure or outcome their method still obtains a sufficient set of variables to control for confounding. There are many further epidemiological scenarios described in the literature (4, 7,14) where once the DAG is drawn comparisons can be made to these causal diagrams and are beyond those needed for this thesis. Figure 3.3 shows a DAG with colour coding from Chapter 5.

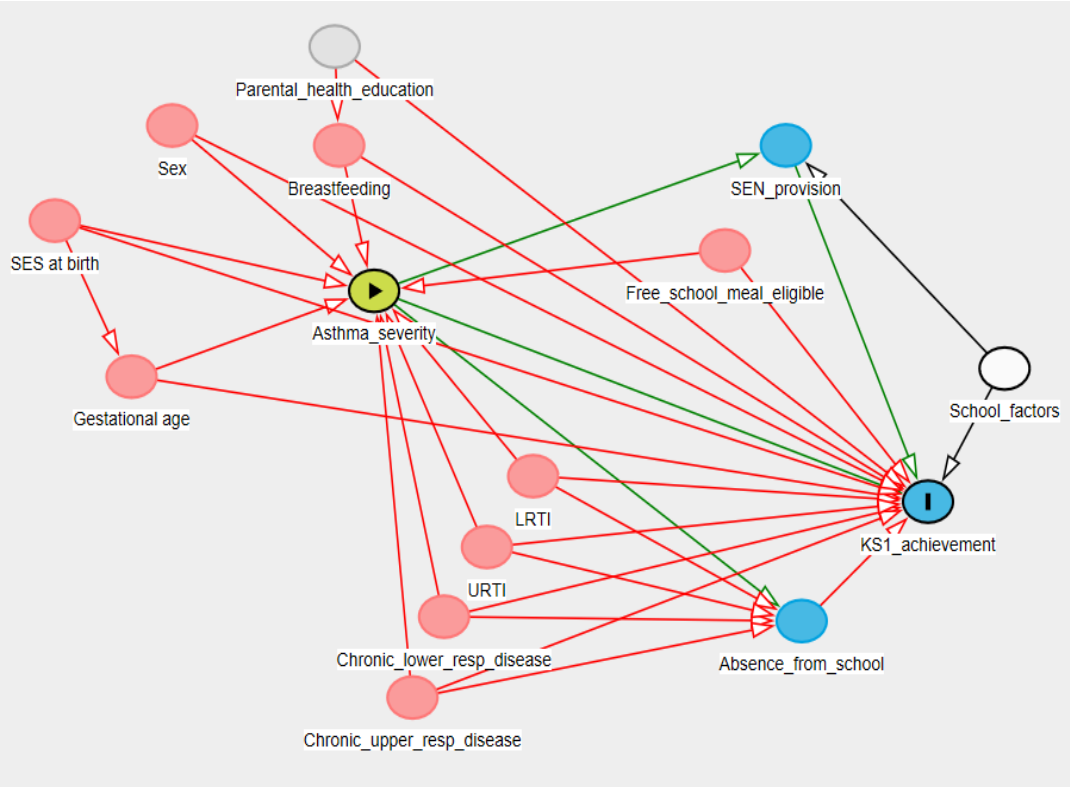

Figure 3.3. Example of a Directed Acyclic Graph (DAG): visual diagram of potential causal relationships to aid selection of confounder variables.
SES=Socio-economic status; Green circle with black triangle – exposure; Blue circle with vertical black line – outcome; Pink circle – ancestor of exposure and outcome (confounder); Pink arrow – directional biasing path; Plain blue circle – ancestor of outcome; Green arrow – directional causal path; White circle – adjusted variable; Black arrow – directional relationship; Grey circle – unobserved variable; Exposure=asthma severity; Outcome=KS1 attainment; Example of a potential confounder between exposure and outcome=LRTI; Example of a potential mediator between exposure and outcome=SEN provision.

3.1.3 Implications for thesis

DAGs offer a way to strengthen causal inference within complex epidemiological studies. They aid discussion between clinicians, researchers and statisticians using easy to explain visual diagrams. DAGs help improve the choice of variable selection in statistical modelling and avoid potential sources of bias. Confounding variables can be identified by using processes and software that apply counterfactual and probability theory. This thesis uses DAGs to add these visual diagrams to other approaches such as the Bradford-Hill criteria to strengthen causal inference.(18,19,20)

This thesis suggests potential causal interpretation between exposure and outcome that includes potential theoretical mechanisms to explain these results because epidemiological

study centres on the search for the cause of disease or social outcome. It is acknowledged in observational studies such as prospective cohorts that measures of association between exposure and outcome can be obtained and potential causal inference suggested under the assumption of no unmeasured residual confounding. In observational studies there is of course the possibility that there may still be some unmeasured confounding. In addition, this thesis uses terminology to describe results from logistic regression by stating that children with an exposure have an increased risk for poorer educational attainment outcome. This should be interpreted as a higher odds, risk or likelihood in children who are exposed for poorer educational attainment outcome compared to their unexposed peers. A similar interpretation applies to hazard ratios, children with an exposure that increased risk for poorer health outcomes should be interpreted as having a higher risk or hazard compared to those unexposed.

3.2 Statistical modelling methods

3.2.1 Background

As described in Section 3.1.1 causation can be expressed using probabilistic interpretations. In probabilistic interpretation all else being equal, if childhood health and social factors cause poorer educational attainment then they will raise the probability for not attaining in education. In epidemiology and evidence-based medicine there are two main competing philosophies for inferential statistics, although others exist. The two philosophies have different theories, assumptions and beliefs that have two different interpretations of probability. These are the frequentist and Bayesian statistical approaches. In 1998, almost all analyses that appeared in the BMJ used the frequentist methods, but with the development of increasingly powerful computers Bayesian analysis is becoming used more widely.(21)

3.2.2 Frequentist approach

The frequentist statistical approach uses empirical data and is a physical (objective or frequency) interpretation of probability.(22) These probabilities are associated with random events in physical systems that tend to have a persistent rate in long run independent trials e.g. a die scoring a one, a roulette wheel. For example, the classical approach gives probability of 1/6 of a four from a die, the frequentist approach counts the actual outcomes (relatively frequency) in finite frequentism.(22) In an ideal world,

frequentists would want to run an infinite number of experiments but instead draw conclusions about statistical inference from observed sample data taken from a population of interest.

In statistical inference collected observed sample data is used to infer the properties of the underlying distribution of probability for a population of interest by deriving estimates or testing hypotheses between for example an exposure and outcome. This is usually a frequentist idea. In frequentist statistics conclusions are drawn about possible mechanisms between in our example an exposure and outcome from observed sample data. The uncertainty of sample-to-sample variation in the estimates from the use of an observed sample of data is reported using confidence intervals (that contain the true parameter in repeated sampling) and may result in rejection of a hypothesis.

3.2.3 Bayesian approach

The Bayesian statistical approach is an evidential interpretation of probability.(22) Statisticians who use Bayesian statistics accept the importance of physical probabilities, but also consider evidential probabilities to be valid and necessary. Evidential probabilities give the notion of subjective probability as a degree of belief from an assessment of a situation with uncertainty.(23) The subjective probability, or credence as opposed to being called chance, is measured by each individual e.g. gambling odds from bettors' beliefs in horse racing, how probable a suspect committed a crime from evidence presented in court. Both frequentist and Bayesian statistics sample from a larger population where the samples are assumed to be independent and identically distributed with unknown distribution.(23) This is the basis for the assumption of exchangeability (Section 3.1.1) and is discussed further by Kreps et al.(23) Bayesian inference uses degrees of belief of a hypothesis to consider the *a priori* unknown distribution (i.e. before the event is observed) and includes this information as more evidence in statistical modelling.

In the Bayesian approach to statistical inference, random variables from sample data are considered to be conditionally independent given an *a priori* distribution of probabilities. A posterior probability distribution is calculated by updating the prior probability with data sampled from the population of interest using Bayes' Theorem (Figure 3.4).

Bayes' theorem, expressed in terms of probability distributions:

$$P(\vartheta \mid x) = \frac{P(x \mid \vartheta) \times P(\vartheta)}{P(x)}$$

x = data sample
ϑ = parameters describing the data distribution

$P(\vartheta)$ = prior probability distribution
$P(x)$ = marginal sampling distribution averaged over the prior
$P(\vartheta \mid x)$ = posterior probability distribution
$P(x \mid \vartheta)$ = conditional sampling distribution of the data given a particular value of theta (sometimes called the likelihood function)

Figure 3.4. Bayes' theorem.

The posterior probability distribution from Bayes' theorem is the resulting probability distribution from Bayesian modelling and is interpreted as degrees of belief. A 95% credible interval can be calculated from this distribution and reported as a probability of 0.95 that the unknown population value lies between the two estimates.(21) In Bayesian statistics the prior probability distribution is the degrees of belief from notions about possible mechanisms between for example an exposure and outcome. These beliefs may be based on the previous experience of an individual, previous research from the published literature or a previous posterior distribution from Bayesian modelling.

3.2.4 Advantages and disadvantages of the approaches in epidemiology

The advantage of Bayesian when compared to frequentist statistics is that the modelling does not ignore prior information and takes account of this information in the posterior probability distribution. Parameters are most often estimated iteratively using Markov chain Monte Carlo (MCMC) methods that sample from the posterior distribution.(24) In frequentist analyses, confidence intervals are often based on theoretical approximately normal distributions of estimators, unless bootstrapping (repeated random sampling with replacement) is used.(21) Additional processing time is needed for bootstrapping. Frequentist and Bayesian analyses usually give similar results, but Bayesian estimates depend on and are nearer to the prior distribution and give a narrower interval for estimates.(21) The 95% credible interval from a Bayesian analysis is analogous to the 95% confidence interval that can be calculated in frequentist analysis, but the interpretation is

different. In Bayesian statistics it is possible to report a 95% probability that the true population value is between two estimates. In frequentist statistics we can only say if multiple samples were taken from the same population the true population value would lie between the estimates 95% of the time. The true population value is a fixed unknown value that lies either inside or outside the confidence interval and is known with complete certainty.(25)

The disadvantage of Bayesian statistics compared to frequentist statistics is how to decide on the prior distribution where subjective probabilities could lead to different conclusions from the same sample data. Bayesian analyses depend on the subjective *a priori* distribution from synthesis of information and this may differ between research teams.(21) Where there is little previous research a uniform prior distribution (uninformative prior) can be used as an estimate of the variance for the random effect in a hierarchical model with an increased number of burn-in iterations to obtain model convergence. However, it should be noted that even a uniform distribution used as an uninformative prior gives some information about a distribution. These models still tend to have narrower intervals for estimates than frequentist methods.(26,27) Nonetheless, computational complexity is increased when using Bayesian statistics and there may be issues with compatibility with other software, for example the practical application of multiple imputation. It has been reported that similar results were found between Bayesian and frequentist methods for sample data of only 1000 survey participants,(21) for large population-based data sets of 40,000 children there may be little discernible improvement in precision. Results from frequentist and Bayesian approaches will gives similar estimates unless very informative priors, or a parameter about which the data doesn't provide much information are available to include in Bayesian analyses.

3.2.5 Implications for thesis

Bayesian analyses are advantageous because an *a priori* probability distribution adds more information to the model than just evidence from sample data alone. There is potential for increased precision in estimate intervals of unknown values in the population of interest by using estimates from available previous research. The computing power needed for large data sets and Bayesian methods, and the incompatibility of the latter with other statistical software is a disadvantage to using this technique.

In Chapter 4 of this thesis, second order penalised quasi-likelihood estimates were used from a hierarchical logistic regression (frequentist methods) as starting values for the Bayesian analysis to investigate emergency hospital admissions on educational attainment in childhood. This is the recommended method in the MCMC Estimation in MLwin manual.(24) This estimate was used as the *a priori* distribution for the Bayesian analysis because there was no similar measure of the association between all-cause emergency admissions and educational attainment outcome at age seven years in the literature. Bayesian analysis was used to estimate the posterior distribution so it was possible to reach inferences from the estimated unknown parameters of the research question in this thesis.

Briefly, Bayesian analysis MCMC methods were used to circumvent the need for many-dimensional integration to produce the exact form of the posterior distribution and instead created simulated draws from this distribution. Both likelihood-based methods and Bayesian analysis are iterative, but the former looks for convergence until consecutive parameter estimates are sufficiently close together, the latter uses the last iteration estimate to produce new estimates. Bayesian analysis was used to create accurate interval estimates from the sample of the posterior distribution, similar to bootstrapping.

The results of the analyses showed little difference between the precision of estimates for Bayesian and frequentist modelling (only Bayesian estimates are reported in Chapter 4) when using the very large population-based data sets. Further, no *a priori* distribution that was very informative nor other parameters were found in the published literature that might improve estimates for Bayesian analyses for the other research objectives of this thesis. Therefore in later chapters of this thesis the analyses are modelled with more widely used frequentist methods that have lower computing power and shorter run-times (i.e. fewer days). In the analyses of this thesis a pragmatic approach was chosen where methods are stable and efficient even though they are not always philosophically consistent.

3.3 Other standard statistical methods

3.3.1 Statistical models

For other statistics used within this thesis the most up-to-date standard choice acceptable in the field of epidemiology has been used. As these are well-known techniques, the detail is not regurgitated in the statistical methods section of this thesis but is outlined and

referenced within each project chapter. This thesis used multilevel modelling as it calculates the variation attributable to differences between schools. Children of the same school may be more correlated in their educational outcomes as for example they experience the same teachers and headmaster compared to children from different schools.(26) In Chapter 5, analyses used a random child from each household (because clusters were too small to use hierarchical modelling) when investigating asthma and children's educational attainment. This mitigated the potential for spuriously small standard errors arising from correlation between outcomes for children born to the same mother. Asthma has been associated with a combination of genetic risk factors.(27)

In Chapter 7 where both social factors and health factors were included in analyses on educational attainment outcome in childhood, Cox regression was used to first estimate the effects of social factors on time to first emergency hospital admission. The advantage of Cox regression is that it makes no assumption about the underlying distribution of survival time, the baseline hazard function is taken from the sample data. Additionally, Andersen Gill models were used, an extension to the Cox model for time-to-event data for recurrent events (emergency hospital admissions) to obtain estimates.(29) The Andersen Gill model assumes that the within-person correlation for event times can be explained by measured covariates of past events. It implies given the covariates, increments of time between events are conditionally uncorrelated with previous events (30) and is suitable for investigating the hazards of social factors for unplanned hospital admissions in Chapter 7. The correlation between events is captured by appropriate time-dependent covariates, that is the number of previous events or a function of previous events.(30)

3.3.2 Multiple imputation

The multiple imputation used in this thesis is reported as suggested by Sterne et al.(31) The exposures in this thesis did not contain missing data because they were measured from a child attending a GP consultation or from records of an inpatient hospital admission. Therefore, it is possible there may be misclassification of exposures due to coding procedures but there was no missing data. Children who did not have educational attainment data were excluded from the cohort analyses in this thesis because imputation of outcome data adds noise to model estimates.(32) Approximately 4-8% of children did not have educational attainment data in the cohorts and were thought to attend private schools, were severely disabled children unable to enter schooling and Special Educational Needs provision, or those outside administrative systems e.g. travellers. The participant

selection flowcharts in each chapter provide further details of the cohorts (Figures 4.3, 5.3, 6.4). Confounders and covariates in the analyses of this thesis had missing data of less than 6% in all variables apart from breastfeeding and maternal smoking during the first trimester. These latter two binary variables had a range of 16-50% missing data for breastfeeding and 49-80% missing data for maternal smoking in the first trimester in the cohorts of this thesis. Descriptive analyses of these missing data by Unitary Authority (county or county borough councils) and year showed a fairly uniform pattern of missingness throughout Wales, and for reasons that are likely unconnected to true breastfeeding or smoking status. The distribution of missing data for these covariates and children's educational attainment outcome is tabulated in Tables 4.3, 5.3, 6.4 and 7.1.

Missing data in this thesis was imputed using multiple imputation by chained equations, (32) where all variables including the outcome were used in the imputation models to generate five imputed data sets. The results of statistical modelling using these imputed data sets were then combined into pooled estimates using Rubin's rules.(33) Data was assumed to be missing at random (MAR) where the probability of missingness depends on observed but not missing data (e.g. older children are less likely to be weighed than babies in the GP surgery). A special case of MAR is missing completely at random (MCAR) when the probability of missingness does not depend on observed or missing data and it is the same for all individuals or observations. Or it could be missing not at random (MNAR), where the probability depends on missing data values (e.g. people with low IQ not taking an IQ test).

Stata Version 13 was used to produce the multiple imputation by chained equations with each imputation drawn after 10 iterations. Continuous versions of birthweight, gestational age and maternal age variables were used to obtain valid predictions and converted to categorical variables before analyses. The mean, standard deviation, minimum and maximum values of variables were compared between imputed data sets and the original unimputed data set and showed very little difference between these measures. The evidence from these results provide knowledge of the data and suggest the variables included in the imputation model make the missing at random assumption plausible.

For Bayesian analyses statistical models were run individually in MLwin for each of the five imputed data sets and results were then combined using Rubin's rules due to limitations in the MLwin software. Several pragmatic decisions were made when imputing the data. Firstly, the multilevel structure of the analyses was ignored in the multiple imputation

because Stata does not currently offer this option (it is available in R). Some of the primary schools in the analyses of this thesis were small (in mid-Wales) and created small clusters preventing the possibility of easily adding this variable to modelling as a fixed effect. As the main focus of analysis in this thesis was not on clustering from schools previous research suggests adequate estimates may be obtained when the clustering is ignored in the imputation if it is included in the analysis model.(32) In addition, although no interactions were found between the exposures and main confounders in this thesis interactions between other covariates were found to improve model fit statistics. Where present, interactions were not important because they failed to show consistent, monotonically increasing or decreasing patterns of adjustment to the main effects of interest. Further, they did not alter any of the substantive findings and consisted of changes to a third or fourth decimal place. Consequently, interactions were excluded in subsequent modelling and interpretation. These interactions were not included in the imputation model but it is noted that an imputation approach that ignores these interactions will likely underestimate the interactions in the analysis model, typically towards zero.(32) Other post estimations such as the Population Attributable Fraction may also be less precisely estimated because of the pragmatic approach to the multiple imputation in this thesis. Further information on missing data observed in this thesis is discussed in the context of the analyses within each chapter.

3.3.3 Implications for thesis

The advanced multivariable techniques described improve the precision of estimates and reduce bias to better understand the relationships between children's health and social factors on educational attainment. These statistical techniques provide the opportunity to gain better insights for the research questions of this thesis by helping to estimate more difficult to measure potential causal effects in complex scenarios rather than easier to estimate associations.

3.4 References

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Chapter 4 : Investigation of the effects of unplanned hospital admissions on educational attainment in childhood

4. Overview

In this chapter, I investigate the extent to which unplanned hospital admissions in childhood impact on educational attainment at Key Stage 1 (KS1), the teacher-based assessment taken at 6-7 years in Wales. First, I describe rates of KS1 failure in Wales and England, and potential reasons for non-attainment found in the literature surrounding health status in childhood beyond health status at birth. Then I describe which children are currently recognised as having healthcare needs regarding their education and the available interventions that have been designed and implemented across Wales (i.e. education other than at school (EOTAS)). Then, I describe the rates and types of common emergency hospital admissions in childhood, which by their nature are unplanned, and why these admissions could fall outside the current universally implemented interventions that already exist to support children with healthcare needs in their education.

I investigate the published literature for evidence of previous research into child health measured using unplanned hospital admissions, beyond established birth characteristics, for effects on educational attainment or on absence from school. I describe the aims and objectives for the analysis of this chapter. The literature review and the observational study conducted in this chapter, consider articles and analyses that include a measure of deprivation (or as a proxy maternal education) where possible as this is an important confounder between health and educational attainment in childhood. I describe the methods used to design and implement a cohort analysis using routine data to ascertain if there is an association between any emergency inpatient hospital admission from birth to KS1 and children's poorer educational attainment. The analyses will look at the most common types of unplanned hospital admissions in children and see if the impact differs between types of conditions. I include a flowchart of the participant selection, a brief description of the linkable data available from data sources (a full description is found in Chapter 2) and cohort exclusions. I introduce definitions for exposures and outcomes, and

confounders such as social factors both at the individual child level and those associated with schools. I then illustrate the relationships between these variables using a Directed Acyclic Graph (DAG).

I present the results, and conclude the chapter by summarising my results, discussing the strengths and limitations of this work in comparison to the published literature. The insights gained from this work will help to inform clinicians and educationalists on whether children do not attain their expected level of educational attainment due to emergency hospital admissions. This knowledge will enable further work on extending current interventions to include a potential new group of children who are vulnerable to KS1 failure.

4.1 Background

In children, the determinants of educational outcomes are multifactorial, with complex interactions between many biological, social and environmental factors. Nearly 1 in 5 children do not attain the expected level the Department of Education has agreed all children should aim to reach at age 6-7 years in Wales,(1) with only slightly lower rates in England.(2) These high proportions of children failing educationally warrant further investigation of potential reasons from aspects of their health, that are not currently recognised and supported by government interventions (i.e. teaching other than at school). Previous research has indicated that birth characteristics such as gestational age and birthweight are associated with poorer educational outcomes in childhood.(3) It is postulated in this chapter that other health problems, on the pathway from birth to the time when children are formally tested in education, may have detrimental effects.

Previous research of health status and educational outcomes has used definitions of health status based on combinations of any hospital admission and self-reported ascertainment of chronic conditions (4,5) or separate specific chronic conditions (6,7,8) such as diabetes, sickle cell disease, cardiovascular disorders, asthma, ADHD, autism and seizure disorders. Chronic conditions vary in their severity and impact on daily life activities, therefore may have different impacts on a child's educational attainment.(6) Health problems in children could lead to hospital admissions, and this may give a better comparator of severity between conditions, for example the effects of cardiovascular disorders compared to asthma, for impact on a child's educational attainment.

For children who have stays in hospital that may be expected with their condition or accident (perhaps a related operation) there is potential for their teacher to plan their schoolwork in advance, where if it is possible, the child can do this work during their time away from school. Alternatively teaching outside of school through EOTAS services enable children to attend hospital school, have home tuition, online schooling (usually as a complement to face-to-face teaching) or attend a Pupil Referral Unit (PRU). These services become available to children through their local authority when they are not able to attend mainstream or special schools due to severe illness (e.g. very severe asthma, mental health disorders).(9)

A child is eligible for EOTAS services from the Local Authority, where the Local Authority should attempt to arrange alternative schooling if a child is expected to be away from

school for more than 15 school days (consecutively or cumulatively). This threshold was more than three times the average 3-5 days missed by primary school children or those of that age in special schools in 2011-12.(10,11) For such a child, the arrangements would be for full-time education if the child is of compulsory school age, with a temporary part-time timetable in exceptional circumstances (and not a long-term measure). Absence from school for these circumstances are treated as authorised absence.(9)

Children who have unplanned emergency hospital admissions are likely to fall outside these current universal interventions and it may mean there is a detrimental effect on their educational attainment. Emergency hospital admissions in children are common: in England around 30% of children under 1 year had an admission, 10% of children of age 1-4 years, and 3.5% of children age 5-9 years in hospital data from 2006-2016.(12) In previous research, emergency hospital admissions were used as a measure of health status because they are common and occur at short notice as a result of clinical need.(13) The primary reasons for emergency admission are respiratory and gastro-intestinal infections in younger children and due to injuries and external causes in older children.(13)

In Wales, children have their first teacher-based educational assessment at age 6-7 years (Key Stage 1, KS1) that creates an overall attainment (yes/no) of the expected level and differs from England where formal exams are taken. There is debate in the literature about what age children should start formal learning and educational assessments, although most countries provide play-based sometimes compulsory pre-schools from the age of 3 years.(14,15) Children who start school later tend to do better in their initial assessments most likely due to their age at the time of examination.(14) The additional effect of a child starting school at a later age is either fewer years of schooling that may reduce overall educational attainment or later entry into the labour market and lower initial salary due to less work experience for their age.(16) In contrast, previous research shows pre-compulsory education rather than pre-school nursery or playgroup improved long term educational attainment at age 16 years, although parents reported some adverse behavioural effects.(17) The debate continues because more recent research suggests possible benefits to children's mental health and self-regulation that may aid learning from starting school at a later age such as at age 6 or 7 years.(15,18)

Educational attainment in early childhood has been associated with better life trajectories in health and employment in adulthood.(19) Although a child's KS1 attainment may not be pivotal to their educational achievement when they leave school, earlier educational

assessments are strong indicators and predictive measures of future outcomes at age 16 years.(20,21,22) The progression children should make in education at each age is set out in the national curriculum, in guidance developed by practitioners in a network of schools, the Welsh Government, regional consortia, Estyn, Qualifications Wales and a range of key stakeholders and experts.(23) This thesis uses teacher-based assessment of children at KS1 and Key Stage 2 (KS2) as outcomes in analyses because of the availability of data follow-up from birth in the total population administrative data sets. In addition, KS1 assessment is in proximity to the exposure of childhood health and is used to investigate any immediate effects that at later ages are likely to be diluted.

Other measures could be used to describe children's cognitive ability such as IQ or child development such as the Strengths and Difficulties Questionnaire (SDQ) that investigates social, emotional or behavioural difficulties. The published literature shows that these difficulties are associated with poorer academic outcomes across all school years,(24,25) that difficulties can co-occur but may not persist,(26,27) and that they are more often found in those born preterm compared to children born at term.(28) Of children who had Special Educational Needs (SEN) provision during primary school in Wales in 2017, 15% needed support due to social, emotional or behavioural difficulties, 28% due to general learning difficulties and 23% for speech, language and communication difficulties.(29) In addition, children with neurodiversity, physical or sensory impairments or severe learning difficulties received SEN provision. In this thesis it has been chosen to investigate the average effects of health and social factors in a total population cohort for educational attainment outcome in childhood to determine if associations exist (and in Chapter 6 for SEN provision outcome). Children's educational attainment from teacher-based assessments were used as a measure of cognitive ability and potential cognitive impairment. Children's SEN provision was used as a measure of support the children required in their learning and will include some children who received support due to social, emotional or behavioural difficulties. In future work, further measures such as the SDQ (that are unavailable in routine data sets) may provide more specific insight about the effects of health and social factors on children's social, emotional or behavioural difficulties and the association between these difficulties and educational attainment in children.

This chapter hypothesises that children who have frequent unplanned hospital admissions may fall behind in their educational attainment in the long-term. These children may possibly need additional help at school through SEN provision, to try to offset the potential

negative impact of unplanned hospital admissions on their educational attainment trajectory.

4.2 Literature review

To begin to address the research question 'is child health, in particular unplanned hospital admission in childhood associated with failure to attain the expected level of education at age 6-7 years?', a review was undertaken of the existing published literature. The objective of this review was to assess the effects of unplanned hospital admissions from birth, on educational attainment at age 6-7 years (KS1). This section of the chapter summarises the evidence from the published literature and highlights gaps in the evidence. The results will give context to the findings and discussion later in this chapter.

4.2.1 Methods

Criteria for considering studies for this review

Eligible study designs for the review were cohorts (where all or some individuals in a defined population who have similar exposures or outcomes are followed over time). A cohort study can be described using the wider definition of prospective longitudinal studies but observe the same participants over a period of time. (Prospective longitudinal studies that collected data from regular random samples from a representative panel where children were not necessarily followed over time were not included in the review). A cohort is one type of prospective longitudinal study.(30) Cross-sectional and case-control studies were excluded from the review as they did not follow children over time, and therefore there was no information about the temporal order of health problems and educational attainment in childhood, which is necessary to investigate the potential causal association between these variables.

Participants of most interest were those up to the age of 7 years. Participants that were included in the search strategy were children up to age 7 years, children in wider age ranges that included ages 5 to 7 years when KS1 is taught, or included school aged children up to age 16 years.

The exposure was any admission to hospital that would be considered as an unplanned hospital admission. Outcomes were educational attainment at school, pre-school tests measuring cognition that were considered equivalent to tests in education and absence

from school. The primary outcome of the literature review was to determine whether there is evidence of a detrimental effect on educational attainment from unplanned hospital admissions.

Search methods for identification of studies

A search was conducted of electronic databases from conception to June 2019 in NHS evidence from 2009, TRIP database from 1997, Cochrane Library from 1993, Ovid Medline from 1946, EMBASE from 1996, Web of Science combined database that starts 1970-1990, Educational Resources Information Center (ERIC) from 1966, the British Education Index from 1986, and the University of Bristol Centre for Multilevel Modelling Gallery for peer reviewed systematic reviews, journal articles and grey literature (working papers). Backward snowballing was used to review the reference lists from relevant articles to identify additional articles. A further search was undertaken in Google and Google Scholar using the main terms for exposures and outcomes because relevant articles could be part of several silos of research (medicine, epidemiology, sociology, education, psychology). Table 4.1 shows the search strategy. The main search considered the types of study, participants, health exposures, educational outcomes and countries. Mediating factors, characteristics and confounders were included individually with health exposures removed, to identify any further papers of interest.

Table 4.1: Literature search word diagram on child health and educational outcomes*

Types of study	Participants	Exposure	Outcomes	Mediating factors	Characteristics and confounders	Countries
Systematic review	Child	Children health	Educational attainment	Learning disorders	School moves	High income countries
Cohort	Children	Chronic disease	Education attainment	Special educational need	Free school meals	Higher income countries
Prospective	Childhood	Health status	School	Absenteeism	Gestational age	Rich countries
Routine data	Student	Hospital admission	Education status	Repeated school year	Gestation	Europe
Retrospective		Hospitalisation	Academic performance		Deprivation	European
Multilevel		Hospitalization	Grades		Birth weight	USA
Multi level		Inpatient	School drop out		Neonatal admission	US
Multi strategy		Outpatient	Academic achievement		Maternal age	Japan
Propensity scores		General practice	School achievement		Gender	Australia
Longitudinal		Deprivation	Cognitive development		Congenital anomalies	New Zealand
Hierarchical		Comorbidities	Absenteeism			Organisation for Economic Co-operation and Development
		Multi morbidities	Repeated school year			World Bank's Economic classification
		Multi-morbidities				
		Multimorbidities	Repeat school year			

*words were combined in each column with a bitwise OR operation and columns in the double line box were combined with a bitwise AND operation.

Data collection and analysis

Study selection

Once duplicate references had been removed, the search records were screened against the predetermined inclusion criteria, excluding ineligible studies based on the title or abstract. For the remaining relevant studies, full text versions were obtained to determine whether they met inclusion criteria.

Data extraction and management

Information was extracted from articles about study design (setting / context), sample size, participants, exposures, outcomes and confounders (methods / quality). The methodological quality of studies was assessed using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (31) (because the criteria is specific to cohort studies and includes more relevant questions than other healthcare study quality assessment tools, and is recommended in the Cochrane handbook). Assessment scores from each article were graded as good, fair or poor using the recommended conversion to Agency for Healthcare Research and Quality (AHRQ) standards.(32) Guidance on the literature review methodology and presentation of results was adapted from the Cochrane review guidelines (33) and on conducting a narrative synthesis from Popay et al.(34) All types of analytical outcome measures were included. The strategies used for missing data were considered, that may produce bias in the results reported. This included looking for information on participant drop out from follow-up, as missing outcomes data for participants may not be 'missing at random' and could cause selection bias and lead to publication bias in research studies. It was considered whether any sensitivity analysis, or imputation of missing data was performed in these situations. Sensitivity of results can be tested by making reasonable changes to assumptions. The characteristics of included studies table was restricted to the exposure of unplanned hospital admissions and outcomes of educational attainment, pre-school tests measuring cognition that were considered equivalent to tests in education or absence from school as stated in the criteria of the review.

4.2.2 Results

The literature search found 9,825 articles. Seven articles were specifically related to unplanned hospital admissions and educational outcomes and eligible for inclusion. Figure 4.1 presents a flow diagram of the search and study selection process, Table 4.2 describes the characteristics of included studies.

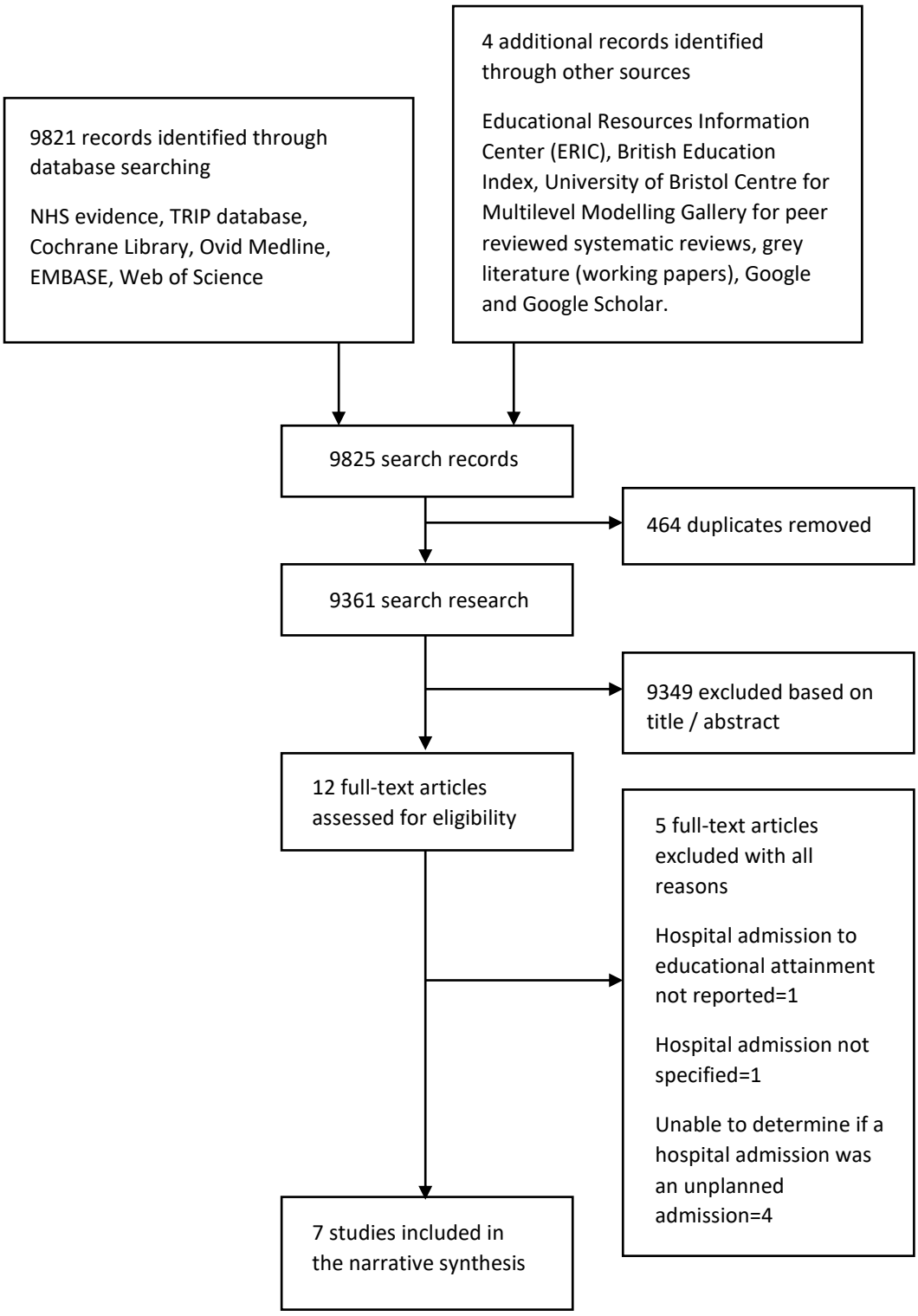

Figure 4.1: Flow diagram of the search and study selection process.

Characteristics of included studies

Table 4.2 shows the limited number of studies found in published literature for the effects of unplanned inpatient hospital admissions on educational attainment. Three studies combined different kinds of diagnoses in their definition for unplanned hospital admissions, and four studies focussed on a particular diagnosis. Four studies used administrative data population cohorts and were found to be of good quality.(35,36,37,38) The other studies were from cohorts using surveys and suffered from attrition bias, or the details were missing from the article so were scored as fair. One study used administrative data with a parental survey but did not adjust for deprivation (or proxy parental education) (39) (a known important confounder between health and education outcomes in children). Sample size was thought sufficient for all but one study, but as this study reported 95% confidence intervals indicating precision of estimates the study was included in the review.(39) Missing data was investigated in 6 of the 7 studies, it was reported as mainly of magnitude under 5%, or up to 17% in one study for gestational age.(37) The studies concluded that missing data was either not of concern because little difference was found in estimates in sensitivity analyses and bias was likely to be minimal, was included in modelling as a separate category, or did not directly relate to the exposure and outcomes of the research. One study did not report any information on missingness in the data set.(38)

Characteristics of excluded studies

Five studies were excluded from the main literature review that appeared to meet the eligibility criteria because they did not specify that the hospital admission was unplanned or that a hospital admission took place. The first study looked at educational outcomes for early adolescents who had required major neonatal surgery,(40) two studies measured any hospital bed days (in a UK 1970 birth cohort) (41) or for major illness.(42) The fourth study recorded number of hospital admission but did not report associations between hospitalisation and children's educational attainment.(43) The fifth paper was a parental survey of health occurrences before school entry and reported data on serious infections, accidents or injury, but did not report a definition of what conditions were considered serious or whether there was a hospital admission.(44)

Effects of unplanned hospital admission on educational attainment

Of the categories of results reported in the seven studies that were relevant to the research question, 9 of 14 suggested unplanned hospital admission had detrimental effects on children's educational outcomes, and 5 results showed no evidence for poorer educational attainment. In the good quality studies, that all adjusted for deprivation or parental education and birth characteristics, 5 of 8 relevant results reported unplanned hospital admission had a detrimental association on children's educational attainment. These differing results may be due to what exposure (diagnosis) was measured as an unplanned hospital admission (e.g. type of injury, chronic disease). Due to heterogeneity in exposures measured (variation in diagnoses considered for unplanned hospital admissions) and different measurement of educational outcomes (at different ages, split by subject, or using days absence from school) meta-analysis was not considered appropriate.

Table 4.2: Characteristics of included studies for unplanned hospital admissions and educational attainment in childhood.

Reference	Exposures	Participants	Settings / context	Outcomes	Results	Methods / quality	Newcastle-Ottawa quality assessment
(ref 4) O'Brien Caughy 1996 USA	Rehospitalisation after birth in first year of life 75% were for illness or accident	National longitudinal survey of youth, mother / child from 1979-1986, 54% impoverished, average maternal age at birth was 20 years	Longitudinal study with yearly waves: cohort	Peabody individual achievement tests in mathematics and reading recognition for children age 5-6 years old	Study size n=867 Linear regression coefficient (p value): Mathematics -0.061 (p<0.10) Reading recognition -0.082 (p<0.05)	Secondary analysis 83% of surveys had complete data for analyses Models were adjusted for income, mother's education, employment status, birth status, length of hospitalisation at birth, quality of home environment	Fair
(ref 5) Kull 2015 USA	Hospitalised for asthma or a respiratory infection	Early childhood longitudinal study birth cohort born in 2001 without severe disabilities and with 5 years follow-up	Nationally representa-tive longitudinal study with waves every one to two years: cohort	Children's school readiness at age 5 years using tests derived from PreLAS 2000, Peabody Picture Vocabulary Test 3rd Ed., Test of early mathematics ability and the Preschool comprehensive test of phonological and print processing	Study size n=5,900 Models using linear regression of item response scores coefficient (SE) p value: Mathematics -1.30 (0.50) p<0.05 Reading -1.40 (0.56) p<0.05 Learning -0.06 (0.05) p≥0.05	55% with 5 years follow-up to education survey tests Rating of child's general health had limited use for clinicians or early intervention programs Model adjusted for child age, gender, race, twins/triplets, kindergarten exposure, maternal age, parental education, income, health insurance stability, non-English speaking, neonatal risks, asthma diagnosis, acute conditions (e.g. otitis media), rating of general health	Fair
(ref 35) Bell 2016 Australia	Emergency hospital admission or morbidity for a chronic illness and cancer diagnosis from the cancer registry	Birth between 2003-2004 with Early Development Census record without special educational needs or developmental disorder diagnosed e.g. autism or cerebral palsy	Population-based administra-tive data prospective cohort	School readiness using the Canadian Early Development Instrument, lowest 10% are developmentally vulnerable/at risk	Study size n=22,890 Chronic illness n=2879 Developmentally vulnerable / at risk: OR (95% CI): Chronic Otis media 1.15 (1.04-1.28) Chronic respiratory disease 1.24 (1.05-1.47) Epilepsy 0.85 (0.49-1.48)	94% included after exclusions or no education outcome data Model adjusted for parental chronic illness, age and marital status, child ethnicity, local community deprivation, remoteness of community, English as a second language.	Good

Table 4.2: Characteristics of included studies for unplanned hospital admissions and educational attainment in childhood (cont).

Reference	Exposures	Participants	Settings / context	Outcomes	Results	Methods / quality	Newcastle-Ottawa quality assessment
(ref 36) Kohler-Forsberg 2018 Denmark	Hospitalisation from infection	Birth between 1987-1997 with education data available	Population-based administrative data prospective cohort	Ninth grade national tests at age 15-17 years	Study size n=547,805 Infection admission n=78,480 Mean decrease in grade score for children with infection admission (p value) -0.07 (<0.001)	91.5% of cohort had education outcome Models adjusted for birth characteristics or mental disorder, parental mental disorder and education	Good
(ref 39) Sesko 2005 USA	Received different treatments for acute orthopaedic injury recorded in clinical administrative data	Children aged 5-18 years who received treatment at the trauma and paediatric orthopaedic clinics at the New York Presbyterian Hospital, February to June 2002	Population of Manhattan and Bronx who attended the clinics	Parental survey about missing any days of school attributed to injury in the injury clinic sample	Study size n=73 Injury to extremity: Upper n=40, lower n=33 Mean (SD) days absence for those missing school without home tuition n=34, 35 (33) days Attending school compared to missing any days of school n, OR (95%CI): Crutches: 30, OR 0.22 (0.06-0.79) Cast (vs. splint): 48 (vs. 19), OR 1.99 (0.54-7.28) High-energy injury: 14, OR 0.65 (0.13-3.14) Operative status: 11, OR 0.12 (0.01-1.17)	96% filled in survey questionnaire Injuries were mainly not severe. Small sample leading to wide confidence intervals. Not adjusted for deprivation Models adjusted for gender, age, presence of cast or splint, use of crutches, high-energy injury, operative status	Fair

Table 4.2: Characteristics of included studies for unplanned hospital admissions and educational attainment in childhood (cont).

Reference	Exposures	Participants	Settings / context	Outcomes	Results	Methods / quality	Newcastle-Ottawa quality assessment
(ref 37) Gabbe 2014 UK	Head injury emergency admission for >24 hours with diagnosis of concussion, skull fracture or intracranial injury	Birth cohort September 1998 to August 2001 with no Special Educational Needs provision.	Population-based administrative data prospective cohort	Satisfactory performance (yes/no) in National curriculum assessment at age 6-7 years	Study size n=90,661 Head injury n=290 Attainment of KS1 n, OR (95% CI): Intracranial injury: 107, OR 0.46 (0.30-0.72) Concussion: 30, OR 0.87 (0.31-2.49) Skull fracture: 153, OR 0.79 (0.52-1.18)	89% of cohort had KS1 results for follow-up Education tests may be insensitive for intracranial injury, no severity of injury Models adjusted for deprivation, birth characteristics, siblings.	Good
(ref 38) Azzam 2018 Australia	Admission to hospital for a burn injury	Birth between 2000-2006 with education data available	Matched cohort for population-based administra-tive data burn injuries. Match 4:1 ratio on birth characteri-stics and deprivation	National standardised curriculum-based school tests in children aged 8-9 years	Burn injury n=1556 Failure to attain OR (95% CI): 1.41 (1.18-1.68) Effect most prominent in primary school children Severity of burns and shorter duration to tests gave worse results	Approximately 96% of cohort had education outcome Results from government and independent schools 2.6% of children with burn injury without test linkage compared to 0.5% without burns to age 13 years Models adjusted for city school, government school, parental: education, smoking in pregnancy, maternal mental and behavioural comorbidity, previous pregnancies and age.	Good

SE=standard error; OR=odds ratio; CI=confidence interval; SD=standard deviation.

4.2.3 Discussion

The literature review identified seven studies that specifically examined the impact of unplanned hospital inpatient admissions on educational outcome.(4,5,35,36,37,38,39) Three articles considered school readiness. O'Brien Caughy's analysis of secondary data in the USA for school readiness found mixed results because inpatient hospital admissions during the first year of life were associated with lower scores on children's reading recognition but not mathematics.(4) These results were thought to be partially explained by differences in levels of maternal education and the home environment.(4) Kull et al tested the associations between indicators of physical health during childhood (including acute conditions and unplanned hospitalisations) and child development at age five years in a large national birth cohort of children in Boston USA.(5) Their analyses showed that multiple aspects of child health, specifically, neonatal risk (prematurity and birth weight), poor general health and unplanned hospitalisation for asthma or respiratory infection independently predicted lower cognition in mathematics and reading at school entry, but not for learning skills.(5)

Bell et al examined the association between chronic illness and children's school readiness using population-based linked administrative data in Western Australia, adjusted for child, parent and community socio-demographic variables. They reported that chronic illness (chronic otitis media, chronic respiratory disease), measured using admission to hospital, emergency department attendance, or in cancer registry data, increased risk for children having developmental vulnerability and reduced school readiness,(35) but found no association for epilepsy.

In older children, Kohler-Forsberg et al showed that hospital inpatient admissions for infections were associated with subsequent decreased cognitive ability and lower educational outcomes at age 15–16 years.(36) This may be due to missed school days, or the confounding effects of socio-economic status, which are also associated with an increased risk of hospital admissions.

Three of the seven studies identified in the review focussed specifically on hospital admissions due to injuries. Sesko et al showed that paediatric orthopaedic injuries and their treatment contribute to long spells of school absence, suggesting the need for school policies that accommodate the needs of injured children.(39) Of the children who received

hospital treatment in this study, 47% were unable to return immediately to school, and on average these children had up to 40 days absence from school.(39) It is known that there is an association between missed school and poorer educational attainment in childhood. Gabbe et al quantified the impact of inpatient admission for head injury on academic performance using the same administrative cohort as used in the analyses of this thesis, the Wales Electronic Cohort for Children (WECC). The study showed sustaining an intracranial injury increased risk for children not attaining the expected level of attainment at age 6–7 years, but that there was no evidence of detrimental association with education for concussion or skull fracture.(37) This could be a direct effect of temporary or permanent brain damage or an indirect effect of time missed from school. Azzam et al examined the influence of burn injuries in national standardised curriculum-based school tests among children aged 8–14 years in Australia. They found that most childhood burn injuries occurred during the pre-school years, and children who were hospitalised had lower performance on academic assessments, suggesting that rehabilitation programmes for children with burn injuries should also include educational support.(38) These studies illustrate the detrimental effects on educational attainment from injury in childhood. Other types of injury that can occur in children have not been investigated in previous research for effects on educational attainment. An overall measure of injury or external causes in childhood warrants investigation for the impact on educational attainment in childhood.

4.2.3.1 Confounders and other important factors

A confounding variable is a variable that can cause the outcome of interest (poor academic attainment) and can also cause the exposure of interest (childhood health). Statistical models should be adjusted for confounders to prevent bias or spurious results. By adjusting models for confounding we move closer to the results we would obtain from a study design where children are randomly allocated to exposed and non-exposed groups, admission to hospital in this example, so that we can see the true effect on educational attainment. Figure 4.2 describes the theoretical causal pathway and potential confounding relationships from this literature review.

Birth characteristics

It is important to consider health status at birth because previous research shows being born with low birthweight,(3,45,46) or born before term,(43,47,48) is associated with higher risk of lower educational attainment in childhood. The risk for not attaining

academically appears to increase with each earlier week of gestation at birth,(50,51) and each decrease in kilogram of birthweight (adjusted for gestation).(45) These children are more likely to have poor long term cognitive and school outcomes across a range of measures,(52) reduced language abilities,(53) special educational needs,(54) and higher rates of morbidity, including emergency hospital admissions during childhood.(55) For example, children born preterm may have underdeveloped lungs that make them prone to more severe respiratory infection in childhood that lead to unplanned admission to hospital.(55)

Socio-demographics and school level factors

Socio-economic and school level factors (e.g. number of school moves, school attended, school size, proportion of deprived children who attend a school) are known to be important determinants of educational outcome. Socio-economic factors are also related to childhood health.

For children in the UK, the education system uses benchmarking to assess and set targets at each school for performance of the school, with published benchmarking reports available in Wales from 1997 onwards. The proportion of children who attain the expected level at KS1 differ due to many factors, but it is generally accepted that there are disparities due to economic differences in areas. Investigation of effects of childhood health on educational attainment should adjust for this important confounder, as many childhood health conditions such as asthma are also found to be associated with deprivation.

The National Assembly for Wales provides schools with information on school performance split out by the proportion of children who are eligible for free school meals (FSM), a measure of deprivation that is currently available to them in school data sets. School results are compared at a national and local level with separate benchmarks for schools with up to 8% of children eligible for free school meals, between 9% to 16% of children eligible, and further cut-points at 24% and 32%. Each school will set its own targets based on these benchmarks, recent school, Local Education Authority (LEA) and Wales wide results, national and LEA targets, and their pupil's performance.(56)

Multilevel research on educational progress has shown the importance of neighbourhood deprivation, pupil mobility, and school-level factors in explaining educational achievement.(57,58,59) Although moving schools and the learning environments created by teachers and schools may account for some of the unexplained variation in school

performance, previous studies investigating the relationship between child health and educational attainment have not adjusted for the influences of these important exposures. School factors, number of school moves, school attended, school size, proportion of deprived children who attend a school, are not considered to be confounders. However, they reduce residual variation in the outcome measure that can be of benefit in causal modelling, depending on the research question. For health exposures on educational attainment outcomes, adding these factors to the model reduces variation attributed to schools on educational attainment so that health status in childhood can more easily be modelled.

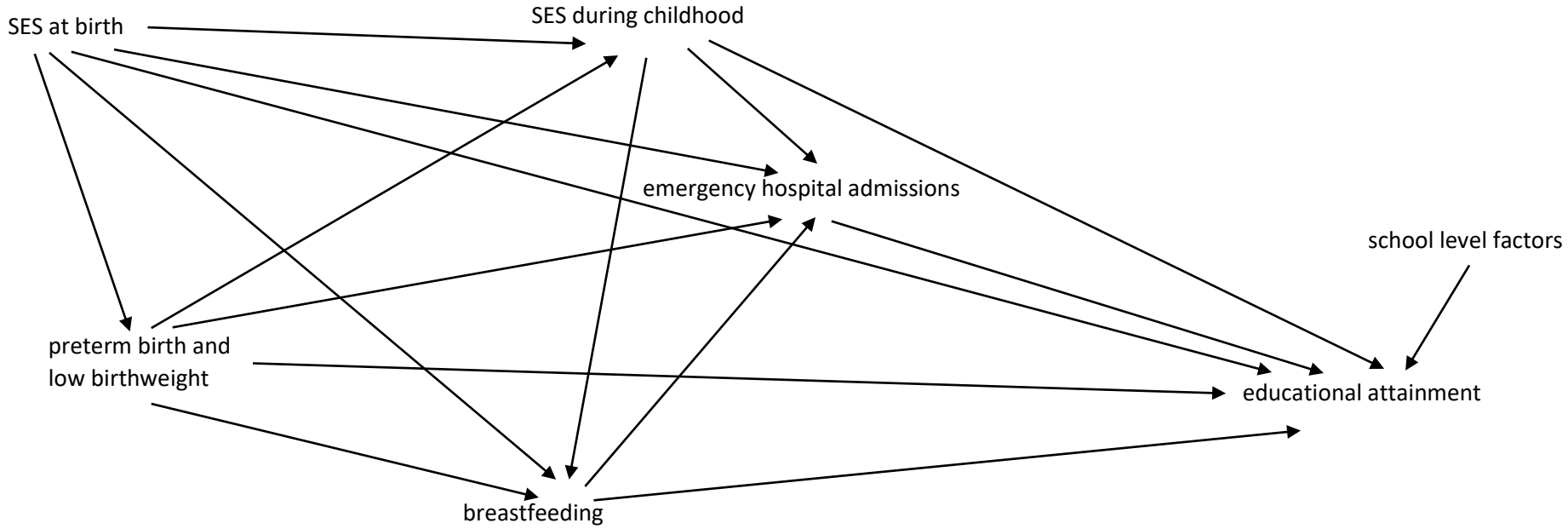

Figure 4.2. Directed Acyclic Graph (DAG): visual diagram of potential causal relationships to aid selection of confounder variables.
SES=Socio-economic status.

4.2.4 Conclusion

Implications for practice

From the literature review, the overall weight of evidence marginally supports an association between unplanned hospital admissions and poorer educational attainment in childhood but this is not conclusive. For all-cause admissions to hospital studies in the literature review consider school readiness rather than school attainment where a child has experienced some learning at school. The literature review showed previous research is limited for injuries to specific conditions finding detrimental effects on educational attainment in mostly smaller studies. Additionally, all positive associations for any emergency hospital admission on poorer educational attainment in childhood that are found in larger studies suffered from high attrition bias. None of the studies examined the combined contribution of confounders and other factors also known to be associated with health or education outcomes in children; health status at birth (e.g. gestational age and birthweight), socio-economic and school level factors.

The limitation of the review was that there were very few studies found from the literature search. The strength of the review was that it was exhaustive across multiple research silos and research databases. Also the methodological quality of the included studies, were deemed good to fair using the Newcastle-Ottawa assessment scale for cohort studies.

In the review, the studies considered of better quality varied in whether a detrimental association was found between admissions and childhood educational attainment due to what exposure (diagnosis) was measured as an unplanned hospital admission (e.g. type of injury, chronic disease). Those studies that instead looked at unplanned admissions, for any reason and educational attainment, scored lower in quality because they had much higher rates of attrition in follow-up surveys. Results of these larger studies mainly found an association between unplanned hospital admission and educational attainment in childhood, but cannot be fully relied upon due to missing outcomes. The review demonstrates that the use of administrative data had much lower attrition rates when compared to prospective cohort surveys (Table 4.2). The use of a measure of days in hospital for any reason can negate the disparities from the multitude of reasons for possible admission, to instead measure the impact on a child's life. From the review it is notable there is little evidence on infections, the most common reason for unplanned

admissions to hospital in early childhood and association with children's educational attainment.

Implications for research

There remains uncertainty from the evidence base about the effects of unplanned hospital admissions on educational attainment in childhood because previous studies look only at sub-sets of specific reasons for unplanned admission or use tests at school entry as their outcome. Although evidence leans towards the potential detrimental effect of unplanned hospital admission on educational attainment in childhood, there are conflicting results. These results may be explained by high attrition rates in some studies. Also, models in previous studies do not fully control for birth health status, socio-economic status and school factors and therefore may indicate greater association to poorer educational attainment than the true effect. Length of stay in hospital over multiple unplanned admissions, different reasons for common unplanned admissions such as infections and age of first admission on educational attainment in childhood also still remain unanswered.

4.3 Aim and objectives

Aim

To investigate the association between emergency hospital admissions and educational attainment in childhood.

Objectives

i. To investigate and quantify the association of emergency inpatient hospital admissions in children, for

    a. any cause

        i. number of admissions before Key Stage 1 (age 6-7 years)

        ii. age at first admission

        iii. number of bed-days before and after a child starts compulsory schooling (age 5 years)

    b. respiratory hospital admission

    c. external cause including injury hospital admission

    d. gastro-intestinal admission

    e. other admission

    on educational attainment at KS1 (age 6-7 years)

4.4 Participant selection

The study in this chapter analysed data from WECC,(60) a population-based birth cohort using anonymised health and education administrative databases as described in Chapter 3. The cohort for this analysis was held in the Secure Anonymised Information Linkage (SAIL) databank at Health Data Research, Swansea University, UK.(61,62)

For this study, record-linked data on babies born in Wales between 1st January 1998

and 31st August 2001 was used as this cohort of children had both educational data recorded at age 7 years and linked hospital admission data available from birth. The cohort for analysis was 64,934 children with KS1 assessment between three school years 2005/06 to 2007/08. Children born outside of Wales were excluded as these children did not have pregnancy or birth data available. The other main categories of exclusion were children who had moved out of Wales, children with SEN provision, missing birthweight or gestational age, stillbirths and deaths, and missing educational data. The flow chart defining the cohort for analysis is shown in Figure 4.3.

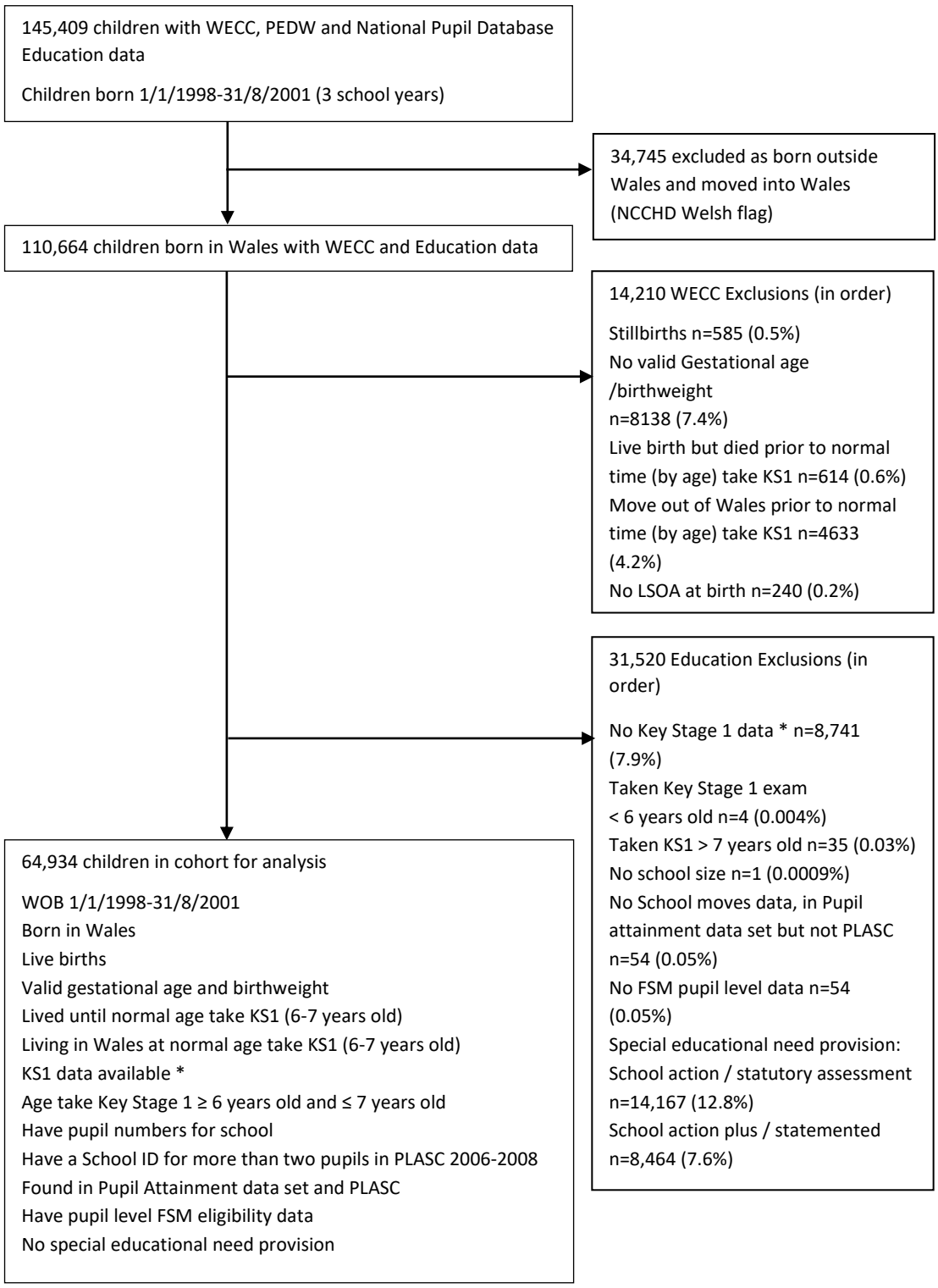

Figure 4.3. Anonymised participant selection for education and hospital admissions data within Wales Electronic Cohort for Children

WECC=Wales Electronic Cohort for Children, PEDW=Patient Episode Database Wales, NCCHD=National Community Child Health Database, KS1=Key Stage 1, LSOA=Lower Super Output Area, PLASC=Pupil Level Annual School Census, FSM=Free school meal. *Children with no Key Stage 1 data do not attend schools maintained by the Local Education Authority or do not have a KS1 assessment (private schools, severely disabled children who do not enter the Special Educational Needs status system, those outside administrative systems e.g. Travellers)

4.5 Exposure and outcome variables: definitions using coded data

Outcome: Educational attainment

The outcome for these analyses was KS1 teacher-based assessment to attainment targets for educational attainment at age 6-7 years. This is an assessment from the national curriculum that contains subjects of a language, science and mathematics (Section 2.1.7). WECC was linked to the National Pupil Database (NPD) and Pupil Level Annual School Census (PLASC) database, described further in Section 2.3. Children were normally assessed in the school year (1st September to 31st August) that included their 7th birthday. The range of scores that a child could attain for each of the three KS1 subjects is between 0-4. For overall KS1 attainment a child must attain the expected level with at least level 2 in all three KS1 assessments, otherwise they do not attain the expected level because they have less than level 2 in at least one assessment. The KS1 overall attainment variable is a binary (yes/no) variable. Not attaining KS1 is the primary outcome in the analyses of children in this chapter. KS1 scores are reviewed nationally by the Department of Education in Wales and thresholds set before a final outcome is given to school pupils.

Exposures: Emergency hospital admissions

Data on emergency inpatient hospital admissions were linked from the Patient Episode Data set for Wales (PEDW), which includes data on hospital beds used for daycases and inpatients to National Health Service (NHS) Wales hospitals and all Welsh residents treated in England from 1 January 1998. The emergency inpatient hospital admissions data used in this analysis included any unplanned hospital admission either through accident and emergency departments or a direct admission to a ward. Data was extracted on the International Classification of Disease 10th Revision (ICD-10) (63) diagnosis code in the first, subsidiary and second fields of the 14 coding positions for each individual child's emergency inpatient admissions. For each child, a binary variable was derived recording if there had been any emergency inpatient admissions between birth and the 1st of September (roughly, the first day of school) in the school year in which they were assessed for KS1. This date was chosen because work undertaken throughout the school year can be included in the teacher-based assessment of KS1, which usually takes place in the summer term, and enabled analyses to preserve the temporal order of exposure to outcome.

The most common causes of childhood emergency inpatient admissions variables were derived and classed as respiratory, injury and poisoning, gastro-intestinal using the ICD-10 Chapter headings J, S to Y and K respectively and 'other' including all other diagnosis codes. The total number of all emergency inpatient admissions was coded for each child and a second variable for the number of bed days, created by subtracting the date(s) of discharge from the date(s) of each admission for each child. Bed days is reported in multiples of 10 bed days compared to no bed days for ease of interpretation. This variable was calculated for two time periods: from birth to the start of school, and from starting school to the start of the school year in which KS1 was assessed, to examine whether or not the timing of emergency admissions had a differential effect on educational outcome. Finally, age at first admission was derived into categories of never admitted (reference category), under 1 year of age (period during which neonatal conditions are the biggest contributor to morbidity), pre-school (between 1 year and 4 years of age on 1st September of the school entry year, when community acquired infections are more prevalent) and school-age (age 4+ years between school entry date and the start of the school year in which KS1 attainment was assessed, during which time injuries and external causes are a major contributor to morbidity). These time periods were chosen because they reflect the different stages of the early life course to simplify reporting and because there may be different processes operating in these different life periods.

4.6 Confounders and covariates

Pregnancy and birth covariates

The date of birth was recorded to the nearest week by the data custodian in accordance with Information Governance policy (Section 2.1.2.1). Covariates derived from the WECC data sets were academic season of birth, sex, gestation, maternal age, parity, multiple births, congenital anomaly (coded as none, major or minor), whether the child was admitted in the perinatal period (<7 days), whether the child was born by caesarean section, was small for gestation (below the 10th centile of birthweight adjusted for gestation and sex), maternal smoking during pregnancy, and breastfeeding at birth or at 6-8 weeks of age. Data on maternal smoking during pregnancy and breastfeeding are collected by midwives and health visitors respectively and entered on to local electronic child health systems that are used for clinical management and administrative purposes.

Socio-demographic variables

The NPD was used to obtain data for each child's eligibility for free school meals, as a measure of socioeconomic status before age 7 years (defined as a family receiving income-based benefits, e.g. Income Support or Child Tax Credit, in 2007 classified as families with an income below around £15,000). This individual level of socio-economic status adds extra insight to modelling than previous research which usually only contains area level deprivation. Additionally, social deprivation of the area of residence the Welsh Index of Multiple Deprivation (WIMD) 2005 at Lower Super Output Area (LSOA) level was used, equivalent to a postcode area with a minimum of 1000 houses and mean 1500 houses.(64) The 1896 LSOAs in Wales were divided into five quintiles of approximately equal counts. WIMD 2005 uses geographical data from the 2001 census, and 8 domains of relative deprivation (income, employment, health, education, community safety, housing, physical environment and geographical access to services). This measure was chosen to include the broadest group of measures at the mid-point of the 1998–2005 cohort follow-up.

Guidance on the use of WIMD (65) states that valid comparisons can be made between deprivation deciles over time, and shows that reference periods for some of the domain measures stretch back over the last 10 years.

Previous research indicated that neighbourhood deprivation was an important determinant of educational attainment but did not measure individual socio-economic status. In order to assess the influence of moving house between neighbourhoods, each child's LSOA at birth was extracted from the data and also their LSOA at the usual age of taking KS1, at age 6–7 years. Each of these LSOAs was classified as being above or below the median of the WIMD score and four categories were defined, based on the initial WIMD score and the score at the time of taking KS1. Each child was placed in one of these categories: remained not deprived, moved from not deprived to deprived, moved from deprived to not deprived, or remained deprived. For simplicity only the deprivation quintile at birth and the last deprivation quintile before KS1 were used (some children had moved up to 30 times in the data and more than 15 times by age 7 years). In addition, each child was assigned their Office of National Statistics (ONS) urban/rural settlement classification for their neighbourhood at birth (66) because this was a factor associated with educational attainment in children in previous research.(67)

School-level variables

School-level data available from the Local Education Authorities were anonymously linked to the cohort. School size data was divided into bands of ≤100 pupils, 101–200, 201–300 and >300 for simplicity of reporting an interpretation. School-based measures of deprivation were calculated for each school catchment area using the annual percentage of children eligible for free school meal in each school and creating an average for each school over 2006 to 2008. This was categorised into ≤10%, 11–20, 21–30, 31–40, >40%.

The number of school moves was derived for each child during the reception year or school years 1 and 2 based on change in the school reference code assigned to the child and recorded in the PLASC in January of each year, and additionally in May in Key Stage years. This variable enhances the information on individual experiences during school years and is seen in few other studies.

4.7 Statistical analysis

Using MLwiN software (68) multilevel logistic regression models were fitted, for not attaining the expected level in KS1 outcome. Models were specified with the hierarchical structure of children nested within schools within LEAs. Firstly, a null random-effects model was fitted, quantifying the variation in the risk of poor educational attainment with random intercept terms for schools and LEAs.

In model 1 emergency inpatient hospital admission variables were estimated for the unadjusted risk of poor educational attainment associated with hospital admission. Model 2 was fully adjusted for all the individual level variables and estimated the associations between the outcome and hospital admission, pregnancy factors, birth characteristics and socio-economic status (using the free school meals variable). Then, the model was repeated using each of the cause-specific hospital admission variables to prevent possible effects of collinearity between hospital variables. Finally, in model 3 terms were added for area-level and school-level variables to adjust for associations between these and educational attainment.

Several pregnancy and perinatal variables had missing values for small numbers of children but there was a large proportion of missing data for breastfeeding (50.0%) and maternal smoking (49.0%) during pregnancy. Descriptive analyses of these missing data by year and Unitary Authority (county or county borough councils) showed a fairly uniform pattern of

missingness across Wales, and for reasons likely to be unconnected to true breastfeeding or smoking status. In fact, the highest percentages of recording were found to exist where incentives to collect data for the data gatherer were known about, and could relate to higher rates of lack of breastfeeding but as rates of breastfeeding were relatively similar across unitary authorities it was judged such administrative reasons for missingness to be ignorable.(69) When these variables are recorded, there is of course a risk of social desirability bias, whereby maternal smoking in pregnancy may be underestimated or breastfeeding overestimated. The effect of such measurement error, as usual, is to attenuate real differences between groups. The sample size with observed data for these two variables was sufficient to estimate the effect of their association with the outcome and their 95% credible intervals.

Multiple imputation using chained equations (70) was applied to models, with all variables included in the imputation models to generate five imputed data sets, and derived pooled estimates using Rubin's rules.(71) Parameters were estimated for the fully adjusted models using Markov chain Monte Carlo (MCMC) methods,(72) with second order penalised quasi-likelihood estimates as starting values. Chains of length 30,000 were run, based on the run-length diagnostics, and 95th credible intervals derived for each parameter (Bayesian analogues of confidence intervals that summarise the posterior distribution).

For binary outcome models, variation attributable to different hierarchical levels in a multilevel model are only approximated by intraclass correlation coefficients, and explained variation R^2 calculations are problematic. Therefore, model variation has additionally been described using the median odds ratio (MOR) for each hierarchical level and allows direct comparison to fixed effect odds ratios (ORs) on the outcome. The MOR quantifies the magnitude of the effect of clustering and is described as the median odds ratio from the repeated sampling at random of two subjects with the same covariates from different clusters (differences are quantified entirely by cluster-specific random effects).(73)

4.8 Results

4.8.1 Descriptive statistics

The cohort comprised 64,934 children in 1463 schools, nested within 22 LEAs. Overall, 4680 (7.2%) did not attain the expected educational level, when children with special

educational needs in the KS1 year are excluded from the cohort. About half of the children in the cohort (48.4%) had an emergency inpatient hospital admission (Table 4.3), with 11.4% having two admissions and 9.7% having three or more admissions between birth and before the normal time they take KS1 at age 6-7 years of age. The majority of these occurred during the first year of life.

Table 4.3: Emergency inpatient admissions, birth and socio-demographic characteristics, and school factors by not attaining Key Stage 1 in education at age 6–7 years.

Characteristic		Children in Cohort N=64,934 n (%)	Not attained KS1 n=4,680
Emergency inpatient admissions			
Any admission	No	33475 (51.6)	2143 (6.4)
	Yes	31459 (48.4)	2537 (8.1)
Any respiratory admission	No	52152 (80.3)	3593 (6.0)
	Yes	12782 (19.7)	1087 (8.5)
Any admission for external causes	No	59325 (91.4)	4144 (7.0)
	Yes	5609 (8.6)	536 (9.6)
Any gastro-intestinal admission	No	61042 (94.0)	4362 (7.1)
	Yes	3892 (6.0)	318 (8.2)
Any other admission	No	44782 (69.0)	3034 (6.8)
	Yes	20152 (31.0)	1646 (8.2)
Number of admissions	0	33475 (51.6)	2143 (6.4)
	1	17721 (22.3)	1331 (7.5)
	2	7420 (11.4)	620 (8.4)
	≥3	6318 (9.7)	586 (9.3)
Age at first admission	No admission	33475 (51.6)	2143 (6.4)
	<1	15778 (24.3)	1355 (8.6)
	1-4	12429 (19.1)	924 (7.5)
	>4	3256 (5.0)	248 (7.6)
Number of bed-days pre-school	10**	1.99(SD 5.57)^	
Number of bed-days at school	10**	0.25 (SD 1.68)^	
Birth characteristics			
Gender	Female	30239 (46.6)	2579 (8.5)
	Male	34695 (53.4)	2101 (6.1)
Gestational age	≤32	678 (1.0)	65 (9.6)
	33-36	3303 (5.1)	284 (8.6)
	37-39	24051 (37.0)	1821 (7.6)
	40-42	36902 (56.8)	2510 (6.8)
Maternal age	≤19	5754 (8.9)	702 (12.2)
	20-24	12124 (18.7)	1189 (9.8)
	25-29	19646 (30.3)	1263 (6.4)
	30-34	17631 (27.2)	930 (5.3)
	35-39	7024 (10.8)	399 (5.7)
	≥40	1122 (1.7)	74 (6.6)
	No answer	1633 (2.5)	123 (7.5)
Parity	0	28354 (43.7)	1731 (6.1)
	≥1	36477 (56.2)	2943 (8.1)
	No answer	103 (0.2)	6 (5.8)
Multiple births	No	63312 (97.5)	4576 (7.2)
	Yes	1622 (2.5)	1104 (6.4)
Perinatal/neonatal inpatient admission‡	No	60343 (92.9)	4309 (7.1)
	Yes	4591 (7.1)	371 (8.1)

**per 10 bed-days; ^SD=standard deviation; ‡emergency or elective.

Table 4.3: Emergency inpatient admissions, birth and socio-demographic characteristics, and school factors by not attaining Key Stage 1 in education at age 6–7 years (cont).

Characteristic		Children in cohort N=64,934 n (%)	Not attained KS1 n=4,680
Congenital anomaly	No	60885 (93.8)	4345 (7.1)
	Minor	1890 (2.9)	146 (7.7)
	Major	2159 (3.3)	189 (8.8)
Caesarean section	No	49861 (76.8)	3644 (7.3)
	Yes	13443 (20.7)	513 (6.8)
	No answer	1630 (2.5)	123 (7.5)
Small for gestational age	No	59014 (90.9)	4067 (6.9)
	Yes	5920 (9.1)	613 (10.4)
Breast feeding	No	14548 (22.4)	1329 (9.1)
	Yes	17925 (27.6)	1098 (6.1)
	No answer	32461 (50.0)	2253 (6.9)
Smoking	No	10628 (16.4)	620 (5.8)
	Yes	2800 (4.3)	361 (12.9)
	Missing	51506 (49.3)	3699 (7.2)
Academic season of birth	Sept-Dec	18312 (28.2)	896 (4.9)
	Jan-Apr	23724 (36.5)	1683 (7.1)
	May-Aug	22898 (35.3)	2101 (9.2)
Socio-demographic characteristics			
Free School meals	No	55587 (85.6)	3207 (5.8)
	Yes	9347 (14.4)	1473 (15.8)
Townsend deprivation quintile at birth / first 4 months	1 least deprived	12392 (19.1)	461 (3.7)
	2	11889 (18.3)	653 (5.5)
	3	12680 (19.5)	867 (6.8)
	4	13005 (20.0)	985 (7.6)
	5 most deprived	14968 (23.1)	1714 (11.5)
Deprivation status change, using the Townsend score at birth / first 4 months and at taking KS1	Stayed low, least deprived (below median)	26500 (40.8)	1119 (4.5)
	Low to high (below to above median)	4321 (6.7)	342 (7.9)
	High to low (above to below median)	6316 (9.7)	424 (6.7)
	Stayed high, most deprived (above median)	27797 (42.8)	2715 (9.8)
Living environment in birth / first 4 months	Urban (>10K population)	44879 (69.1)	3300 (7.4)
	Town & Fringe	10795 (16.6)	759 (7.0)
	Village, hamlet & isolated dwellings	9260 (14.3)	621 (6.7)
School factors			
Number of school moves	0	58795 (90.5)	3814 (6.5)
	1	5787 (8.9)	779 (13.5)
	2+	352 (0.5)	87 (24.7)
Average school size between 2006 and 2008	≤100	6459 (9.9)	544 (8.4)
	101-200	19983 (30.8)	1564 (7.8)
	201-300	19147 (29.5)	1261 (6.6)
	>300	19345 (29.8)	1311 (6.8)
Average percentage of children eligible for free school meals in school during 2006-8	≤10	26672 (41.1)	1336 (5.0)
	10-20	21212 (32.7)	1420 (6.7)
	20-30	9332 (14.4)	839 (9.0)
	30-40	4980 (7.7)	565 (11.3)
	>40	2738 (4.2)	520 (19.0)

4.8.2 Statistical modelling results

The fully adjusted odds ratio for a child who had at least one emergency inpatient hospital admission was 1.12 (95th credible interval 1.05, 1.20) when compared to those without an admission for not attaining KS1. Admission due to an injury or external cause or being admitted in infancy had the strongest associations with not attaining KS1 (Table 4.4). Children who had three or more inpatient hospital admissions had only slightly higher fully adjusted odds for not attaining KS1 1.13 (95th credible interval 1.01, 1.26) (Table 4.4). The number of bed days in the pre-school age group was associated with an increased risk for children not attaining KS1, but the number of bed days during school-age was not significant in the model.

The proportion not attaining KS1 was significantly higher in a number of groups, most notably in boys, those born extremely preterm, maternal age under 20 years, not being a first child (i.e. with parental attention shared with siblings in their early years), being small for gestational age and being eligible for free school meals.(Table 4.3) In addition, similar effects were seen for being born between January and August (meaning they were young for their school year), moving school, living in areas of higher social deprivation and attending a school with a high percentage of pupils eligible for free school meals.

The associations between emergency hospital inpatient admission variables and children's educational attainment were weaker than the observed effects associated with pregnancy, perinatal, social and school environment variables.(Appendix Tables A4.1 and A4.2) However, there remained an independent association between emergency inpatient hospital admissions and educational attainment in childhood in the adjusted models.

In the unadjusted multilevel null model for any emergency inpatient hospital admission, 2.3% of the unexplained variation in the educational outcome was attributable to the LEAs, 25.4% to schools and 72.3% to individual variation. The model fit statistic measured with the Bayesian deviance information criterion (DIC) was 29349.52 on average. In the fully adjusted models these percentages changed little, to 2.7%, 22.1% and 75.2%, respectively; average Bayesian DIC 27581.45. The variance attributable to the hierarchical levels on the outcome and fit statistics for the null model, and models 1 to 3 are reported in Table 4.5

The analyses were repeated for the outcome measures separately for not attaining the expected level in each of language, mathematics and science. For language 4.6% of children

did not attain the expected standard, in mathematics 3.9% and in science 2.8%. The ORs associated with any emergency inpatient hospital admission were 1.07 (0.98, 1.16) for language, 1.16 (1.06, 1.27) for mathematics and 1.06 (0.95, 1.19) for science, suggesting mathematics results were a key factor in the association between overall KS1 results and emergency inpatient hospital admission. For science, considerably more variation (31%) was attributable to differences between schools; for maths and language the results were comparable to those for the overall assessment.

Table 4.4: Multilevel logistic regression for not attaining Key Stage 1 at age 6–7 years and emergency inpatient hospital admissions (emergency hospital admission variables were entered individually into adjusted models), N = 64934.

Characteristic		Unadjusted OR (95% CrI)	Model 2 with partially adjusted OR* (95% CrI)	Model 3 with fully adjusted OR** (95% CrI)
Any admission	No	1.00	1.00	1.00
	Yes	1.23 (1.15, 1.31)	1.14 (1.07, 1.22)	1.12 (1.05,1.20)
Any respiratory admission	No	1.00	1.00	1.00
	Yes	1.23 (1.14, 1.33)	1.13 (1.04,1.22)	1.10 (1.01, 1.20)
Any admission for external causes	No	1.00	1.00	1.00
	Yes	1.31 (1.18, 1.45)	1.20 (1.08, 1.33)	1.19 (1.07,1.32)
Any gastro-intestinal admission	No	1.00	1.00	1.00
	Yes	1.09 (0.98, 1.21)	1.03 (0.90,1.18)	0.99 (0.87, 1.14)
Any other admission	No	1.00	1.00	1.00
	Yes	1.18 (1.10, 1.26)	1.11 (1.03,1.19)	1.09 (1.01, 1.17)
Number of admissions	0	1.00	1.00	1.00
	1	1.17 (1.08, 1.26)	1.12 (1.03, 1.21)	1.11 (1.02, 1.20)
	2	1.26 (1.14, 1.40)	1.18 (1.06, 1.31)	1.14 (1.02, 1.26)
	≥3	1.37 (1.3, 1.52)	1.17 (1.05, 1.31)	1.13 (1.01, 1.26)
Age at first admission	No admission	1.00	1.00	1.00
	<1	1.30 (1.20,1.41)	1.16 (1.06,1.25)	1.31 (1.04, 1.22)
	1-4	1.15 (1.06,1.26)	1.12 (1.03,1.22)	1.11 (1.01, 1.21)
	>4	1.18 (1.02,1.37)	1.16 (1.00, 1.35)	1.15 (0.99, 1.34)
Number of bed-days pre-school	10***	1.13 (1.08,1.18)	1.14 (1.07,1.21)	1.12 (1.05,1.19)
Number of bed-days at school	10***	1.09 (0.96, 1.25)	1.06 (0.91, 1.22)	1.05 (0.90, 1.22)

An emergency inpatient admission is a continuous inpatient spell of finished consultant episodes and includes transfers between hospitals using the Dr Foster superspells method (92; Section 2.1.5). Type of admission is derived from the first 3 diagnosis codes in the first consultation episode for each emergency inpatient admission. * Partially adjusted ORs are adjusted for gender, gestational age, maternal age, parity, multiple births at childbirth, congenital anomaly, perinatal/neonatal inpatient admission, caesarean section, small for gestational age (<10th centile), breastfeeding, maternal smoking in first trimester, academic season of birth, free school meal eligible (Appendix Table A4.1). ** Fully adjusted ORs are adjusted for all the variables in the partially adjusted model and area-level and school-level variables (Townsend deprivation quintile at birth, deprivation status change between birth and KS1, living environment at birth, number of school moves, average school size, average percentage of children eligible for free school meal at school; Appendix Tables A4.1 and A4.2). *** ORs shown correspond to a difference per 10 bed-days. OR=Odds ratio; CrI=Credible interval.

Table 4.5: Hierarchical variation and fit in multilevel logistic regression for any emergency inpatient hospital admission and not attaining Key Stage 1 at age 6–7 years, N = 64934.

	Null model	Model 1 with any hospital admission	Model 2 with any hospital admission and individual level characteristics	Model 3 with any hospital admission, individual level, area-level and school-level characteristics
Unexplained variance (SE)				
Child	3.29	3.29	3.29	3.29
School	1.119 (0.073)	1.113 (0.073)	0.972 (0.066)	0.934 (0.065)
Local Education Authority	0.101 (0.047)	0.106 (0.050)	0.092 (0.042)	0.092 (0.042)
Percentage of unexplained variance:				
Child	72.3	71.6	74.5	75.2
School	25.4	25.3	22.8	22.1
Local Education Authority	2.3	3.1	2.7	2.7
Explained variation (%)				
School	Reference	0.5	13.1	16.5
Local Education Authority	Reference	4.7	8.9	8.9
Median odds ratio (MOR)				
School	2.74	2.74	2.56	2.51
Local Education Authority	1.35	1.36	1.34	1.34
Model fit statistic				
Bayesian deviation information	29349.52	29313.83	28015.08	27581.45

4.9 Discussion

In this electronic birth cohort the analyses show that emergency inpatient admission to hospital in the first seven years of life is associated with poorer educational attainment in standardised teacher assessments at age seven years. This effect was greater for admissions due to injuries and external causes and for admissions in infancy. The effect increased with more bed days spent in hospital during the pre-school period, which may indicate that school absence is a mediator between unplanned hospital admissions and educational attainment in children. These observed increased risks are probably a conservative estimate as the analysis excluded children with special educational needs, some of whom may have had a higher number of emergency inpatient hospital admissions (75) due to more specialist care required or complications with their other conditions.(37)

Most previous studies have focussed on the association between education outcomes and various combinations of factors, such as health status measured at birth (gestational age,(3,43,47,48,49,50,51,52,53,54,55) birth weight (3,45,46) and Apgar score(75)), socioeconomic and school-level factors. Few studies have examined how health during

childhood, which is partially influenced by birth health status, impacts educational outcomes. Hospital admissions, particularly for respiratory diseases, which are more common in infants born late preterm and early term,(76,77) may have a role on a potential causal pathway in the well-documented relationship between preterm birth and lower educational outcome. Previous research shows pregnancy and perinatal factors such as maternal smoking during pregnancy, lower gestational age, low birthweight, and not breastfeeding are associated with increased rates of emergency admissions in children.(76)

Poor health due to chronic conditions can affect a child's daily activities, social interactions and school attendance, either due to the illness itself or the treatment associated with it.(6,44,77,79,80,81) The biological insults resulting in a child's health status may influence the neural connections required for optimal development affecting concentration, memory and general cognitive ability. Most previous studies have either measured health during childhood using self-reports of general health condition, duration of hospital admissions or studied disease specific cohorts. Few studies have examined the impact of acute conditions requiring unplanned hospital admission (such as infections and injuries) on education outcomes.

In previous research two studies found poorer school readiness in tests at school entry from common cause emergency inpatient admissions,(4,5) and emergency inpatient admissions due to chronic disease (35) rather than after some formal schooling. This study shows that even after two years of schooling some children who had an emergency inpatient hospital admission in the first seven years were unable to catch up on their learning and attain KS1 when compared to their peers. The published literature shows this effect is also seen in older children aged 15-16 years, those who had infections that led to hospital inpatient admissions had subsequent decreased cognitive ability and lower educational outcomes.(36)

An increased risk for poorer educational outcomes for those with hospitalisation due to infection may be because of days absent from school, days spent not learning prior to entering the school year, or confounding from socio-economic status associated with an increased risk of hospital admissions. There is also increasing recognition that a wide range of infections may impact on brain function via cytokines and / or inflammatory markers.(82) Infections are the most common cause of inpatient hospital admissions, particularly in younger children. The finding in this thesis of a larger effect size for the association between inpatient hospital admissions during the first year of life and lower

education outcomes at age 6–7 years may reflect the effects of infections or other insults on the developing brain. Pre-term birth is often associated with perinatal complications requiring hospital inpatient admission. It can also lead to compromise of the central nervous system increasing the risk of poor cognitive development and subsequent lower educational outcomes. The results of these analyses show an independent effect of emergency hospital inpatient admissions on education outcomes, over and above the increased risks associated with pre-term births. This suggests that unplanned hospital inpatient admissions, particularly during the first year of life, may be an early indicator of children who require early intervention to assess their health and potential educational support needs so that they achieve their academic potential.

Similar results to these analyses were found in three studies that looked specifically at hospital admissions due to injuries. Sesko et al showed children who received hospital treatment for paediatric orthopaedic injury had on average up to 40 days absence from school.(39) Injuries had the strongest association with not attaining KS1 in this thesis study. Evidence from large-scale robust studies in the USA have shown that school absence in the elementary years is associated with poorer educational outcomes in reading and mathematics.(82,84) This evidence suggests school policies need to accommodate the needs of the injured child.(78)

Gabbe et al found larger effects for intracranial injury than for the general injury categorisation used in this analysis in models adjusted for deprivation, birth characteristics but not school factors for attaining KS1 at age 6-7 years.(37). The study used the same cohort as this study, and academic performance measure. The study found no evidence of an association for concussion or skull fracture and poorer educational attainment,(37) indicating a measure of severity of condition through length of stay in hospital might help to differentiate conditions without listing each diagnosis. Intracranial injury could have a direct effect of temporary or permanent brain damage or an indirect effect of time missed from school on educational attainment. Azzam et al examined the influence of burn injuries in national standardised curriculum-based school tests among children aged 8–14 years in Australia, and found those hospitalised had lower performance on academic assessments. Most burn injuries occurred in the pre-school years and suggests rehabilitation programmes for children with burn injuries should also include educational support.(38)

To measure the time lost from school during an emergency inpatient hospital admission the number of bed days for each child was assessed and a significant association with non-

attainment was found in the pre-school period, but not during the three years of school in the KS1 period. This may potentially reflect the fact that neonatal and other chronic conditions that can have significant consequences for development during the life-course are most prevalent during the preschool years (before age 5 years). Whereas after age 5 injuries and external causes are more prevalent causes of morbidity.(85) However, there was no available data on days of absence post-discharge, nor on school absence generally. Not being able to include the full school absence from hospital admission in the analysis would tend to bias the results of this study towards the null, because we only know children are absent from school on days when they are in hospital. In reality, children who have a stay in hospital will probably need to recover further at home before they return to school, therefore this suggests the possible true effect of emergency inpatient hospital admission on KS1 attainment is stronger than was estimated.

Unplanned hospital inpatient admissions are easily identifiable events that are potentially disruptive to the lives of children and their families. This analysis adds to the body of evidence from previous studies that children who have been admitted to hospital before starting school, particularly in the presence of other socio-economic indicators may represent a group that need additional support to ensure they reach their academic potential. Injuries and external causes are a major cause of morbidity in school-aged children. These findings of increased risk of lower educational attainment associated with injuries and external causes, suggest rehabilitation programmes for these children should also address their educational needs. Effective injury prevention strategies are needed for school children, to reduce the incidence of these types of admissions and their consequences.

The effects associated with unplanned hospital inpatient admissions in the analysis of this chapter are rather less than those for many perinatal factors, particularly being extremely premature, being small for gestational age and for socio-economic measures, including eligibility for free school meals, living in deprived areas and attending a school with a high proportion of pupils eligible for free school meals.

Recent research provides evidence that children living in more deprived areas had higher levels of social, emotional and behavioural difficulties at school entry compared to those living in less deprived areas.(86) These children are likely to receive SEN provision because of these difficulties to help with their school education. Interestingly, these observed differences in children's social, emotional and behavioural difficulties using the SDQ were

found to widen during the first 3 years of schooling (86) and these findings may help to explain why inequalities exist in educational attainment in this age group. In addition, it could be postulated that children who live in greater deprivation may find it more difficult to catch up in their learning after an unplanned hospital admission because of the greater likelihood that they have behavioural difficulties that may hamper their ability to learn. Further work to investigate these complex relationships on children's educational attainment is warranted.

For other confounding variables in these analyses, it is unsurprising that moving schools is associated with lower levels of attainment. In line with previous studies,(87) there is a striking and strong association with being born late in the school year, with such a child being younger on school entry and also when being assessed. Analyses included the effect of school size and it showed that smaller schools were associated with an increased risk for not attaining KS1. Previous research has shown that while smaller schools may be favoured by parents for children with special educational needs (who may not be receiving SEN provision), larger schools may have more services to help all learners. However, lower reading scores were also observed for children from more deprived areas as school size became larger (88) and may be an effect of urban or rural residences. The models in this chapter adjust for urban or rural residences so risk found for different school sizes is more likely associated with school size rather than location.

Although the majority of the variation in the educational outcome was explained by differences between children, it is an important finding that over 20% of the variation in educational attainment may be explained by variation between schools. Children of the same school are more correlated, as for example they experience the same teachers compared to children in different schools. In contrast, only 2% of the variation was attributable to differences between LEAs.

This study has the important strength of record-linking longitudinal perinatal data on all 64,934 children born in Wales who satisfied the eligibility criteria over three school years. The cohort included complete data on educational attainment and inpatient hospital admissions, and a wide range of clinical and socioeconomic factors. Children were also linked to their school's information to investigate the potentially important school-level influences on educational achievement, as well as the effects of changes in small-area deprivation from moving house.

There are a number of limitations, primarily concerned with missing data or data quality. The measurement used for health status during childhood was emergency inpatient hospital admissions. Emergency admissions in younger children are most commonly due to respiratory and gastrointestinal infections, and in older children injuries and external causes. In addition to clinical need, hospital admissions may also reflect supply side factors such as availability and ability to access primary care, and other socially patterned factors. However, there was an increased risk of lower attainment at KS1 even after adjustment for all available measures of socio-economic status and social deprivation in the model. Children attending independent schools were not included as the education data sets were restricted to children in schools maintained by the LEA. It is possible that this introduced some selection bias but fewer than 2% of primary school children attend independent schools in Wales and so any resulting bias is unlikely to be large. Children with special educational needs were also excluded because they are considerably less likely to achieve the expected standard at KS1 and their inclusion would have introduced considerable heterogeneity.(2,89) However, it is acknowledge that head injuries can lead to learning difficulties, and hence this exclusion could have biased the estimate for the effect of head injuries towards the null. For children who have SEN provision more accurate indicators of progress and achievement may be provided by reviewing progress in individual education plans (IEPs) that relate to their individual starting points or personal goals. This progress may be captured in more recent measures of children's education such as in the area of learning about personal and social development, wellbeing and cultural diversity.(90,91)

Data on the cause of an emergency inpatient hospital admission depends on the accuracy of coding. A review of the codes used by NHS coders in the available data found little variation in the codes for similar causes of admission, so any misclassification was likely to be minimal and unlikely to have a major effect on the results.

Children without a valid birthweight or gestational age were excluded but other data were imputed using a standard method of chained equations. The percentage of missing data was substantial only for breastfeeding and smoking, due to organisational and administrative differences in data collation between hospitals in Wales, suggesting that these data can be reasonably assumed to be missing at random. However, the subset for which data was available was large enough to fit an imputation model for these covariates with sufficient precision. For the maternal smoking variable there were still over 13,000

children with data in the cohort and nearly 1,000 children who did not attain KS1. Using this maternal smoking data there was little variation in the estimates of associations between KS1 attainment and hospital admissions between imputations. This suggests the procedure was robust and able to successfully predict smoking status, with missing data most probably missing at random. It was chosen to impute these variables because they are key factors that are socially patterned and known determinants of child health status.

It is also possible that the relationship between emergency hospital inpatient admission and educational attainment is confounded by unmeasured factors associated with socio-economic status. Adjustment was done for as many of these as was possible to measure in this analysis of administrative health and education data sets, but there may be other measures of socio-economic status such as maternal education level or home environment it was not possible to control for. However, the analyses did adjust for eligibility for free school meals, defined by eligibility for means-tested income support benefit, as a measure of family socio-economic status, and small-area deprivation measured by the Welsh index of multiple deprivation.

4.10 Implications for this thesis

Emergency inpatient hospital admission during childhood, particularly during infancy or for injuries and external causes are associated with lower educational attainment at age seven years, even after allowing for the effects of pregnancy factors such as gestational age and birthweight, and school-level factors. These findings suggest that emergency inpatient hospital admissions can be used to measure an additional effect on educational attainment beyond birth health status, several measures of environment, deprivation and school factors. These children may need a review of their health and support networks, possible additional learning support in school to achieve their potential, and the results strengthen the case for more effective injury prevention strategies. This research points towards the reasons why some children do not fulfil their educational potential, that every child should attain the expected level at KS1.

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Chapter 5 : Investigation of the effects of asthma severity and respiratory infections on educational attainment in childhood

5. Overview

In the previous chapter, I found childhood emergency hospital admissions and in particular those for injuries and external causes were associated with poorer school attainment at Key Stage 1 (KS1) at age 6-7 years. Also, the timing of the admission was important for educational outcomes at age 6-7 years, with greater risk from admission during infancy, or the length of time spent in hospital during the pre-school years. These results from Chapter 4 were adjusted for birth health status, deprivation and school factors. The findings highlight that the health of children beyond birth resides on a pathway between birth and educational attainment and assume there are no other important unmeasured confounders between child health and educational attainment. This chapter considers whether chronic illness, using the long-term relatively common condition of asthma as an example, has associations with poorer education attainment in childhood, after adjustment for the same set of confounders and characteristics.

I investigate whether current (within the last year) chronic asthma severity and acute asthma exacerbations (attacks) impact on educational attainment at KS1 at age 6-7 years. I review the published literature and describe methods to implement an observational cohort study using administrative data to ascertain if asthma, measured from birth to before KS1 assessment, is associated with poorer educational attainment. I derive measures of current acute asthma and categories of chronic asthma severity that closely match current asthma management guidelines using General Practice (GP) diagnoses and prescriptions, and hospital admissions administrative data. I include wheeze in a second definition for asthma because often this is a preferred clinical diagnosis of symptoms in young children.

In addition to the main research question, I explore whether respiratory infections may act as an additional exposure and interact with the association of asthma on educational attainment. Also, I explore the role of school absences in the year when KS1 was taken

(when data was available) in the relationship between asthma severity and educational outcome. The findings of this chapter will give further insight to the investigation in Chapter 4 on unplanned hospital admissions and educational attainment. From these analyses clinicians and educationalists will be better informed about the burden of the chronic disease asthma on children's educational attainment. The analysis takes account of multiple important confounders (perinatal factors and social deprivation) and school factors not previously seen modelled together in other studies for this specific age group.

5.1 Background

As mentioned in Chapter 4, nearly 20% of children in Wales do not attain the expected level of education most children should reach at age 6-7 years.(1) Failure to achieve educational developmental stages in the early years can lead to a change in the trajectory of a child's education, and may result in poorer life chances surrounding tertiary education, employment and health.(2) In addition children's poorer academic attainment may influence later social outcomes, well-being and participation in society.

As described in Chapter 4, the published literature highlights parent-reported ascertainment of chronic conditions or separate specific chronic conditions in children have conflicting results on educational attainment. The reason why the literature may show different results for educational attainment from the same chronic condition in children may be the influence of the data collection method. These collection methods include data that is parent-reported, parent-reported from a previous clinical diagnosis, or reported by a clinician. This is particularly important for some conditions such as asthma where parents of children who hear terms such as 'pre-asthma symptoms' or 'asthma-like symptoms' may assume a diagnosis of asthma. Access to routine data gives the opportunity to investigate clinician diagnosed chronic conditions. Therefore, in this thesis it was chosen to investigate the effects of asthma on educational attainment in children, because it is a relatively common chronic disease in childhood.

There are challenges associated with asthma that can adversely affect a child's school experience.(3) A child's school functioning may be affected due to acute asthma exacerbations, iatrogenic effects of medication (e.g. oral steroids), poor medical management of asthma, and possible stress associated with a chronic disease, and this may also increase their absenteeism.(4) In addition through speaking to teachers about asthma and educational attainment comments such as 'pupils with asthma tend to have noticeably more days off school for respiratory tract infections than children without asthma' were noted. Both asthma and respiratory infections in children could be investigated using administrative data.

Asthma is a common childhood condition, with prevalence of current asthma (symptoms within the last year) at age 7 years estimated to be 12% in the UK,(5) and similar to Australia(6) and the USA.(7) Cumulative prevalence of wheeze was found to be between 15-26% during the first seven years of childhood in the UK,(8) with current wheeze at age

6-7 years from 7% in the Indian subcontinent to 21% in English Language centres (UK, Australia, Canada, New Zealand), and Oceania (22%).(9) Healthcare and societal burden of asthma in the UK was thought to be in excess of £1.1bn in 2011-12.(10)

Clinicians mostly follow asthma management guidelines that vary by age of the child (11,12) and advise step changes in medication or a hospital admittance. Decisions to step up or step down in the management plan are based on assessment usually after any hospital admission for acute asthma exacerbation and include consideration of previous hospital admission, PICU admission, recent steroids, psychological and family issues, compliance / adherence issues, response to initial treatment, distance from home and family preference. Chronic asthma is managed using regular reviews, and guidelines differ in their recommendations for a step change due to frequency of exacerbations ranging from no acute exacerbations to more than 2 to 3 exacerbations occurring in a year. These guidelines for asthma mention that clinicians should consider the ability to attend school in their assessment of symptoms when prescribing. The guidelines do not include evidence on the impact of hospital admissions for asthma or the burden of co-occurring respiratory infections on educational outcomes.

Asthma aetiology is multifactorial, diagnosed by a combination of symptoms of inflammation in the airways with reversible airway narrowing, and airway hyper-responsiveness. Asthma historically means shortness of breath, to breathe hard or pant. Acute asthma exacerbations present as the onset of wheeze and respiratory distress. In young children, clinicians often diagnose viral induced wheeze but do not diagnose asthma, as symptoms may resolve as the child grows older. Upper respiratory tract infections are also common during childhood, and found to occur between three and eight times a year in primary or pre-school children.(13,14) Children with asthma may experience more severe symptoms when they acquire a respiratory infection as was observed in a small study in adults.(15)

Asthmatic children who suffer frequent exacerbations that may require intervention by a General Practitioner or a hospital stay, may miss school days resulting in lower educational attainment compared to their peers. However, the evidence base shows there are mixed results for the effects of asthma on children's educational attainment between age 5 and 9 years.(16,17) Children may also experience respiratory tract infections more often when they have asthma and it is important to understand whether there is an impact on educational attainment during childhood.

5.2 Literature review

To begin to address the research question 'what is the prevalence of asthma or wheeze in the population in Wales and is a chronic disease such as asthma in childhood associated with not attaining the expected level of education at age 6-7 years?', a review was conducted of the existing published literature. The objective was to assess the effects of asthma from birth on educational attainment at age 6-7 years (KS1). This section of the chapter summarises the evidence of previous research and highlights gaps in the evidence. This review will give context to the findings and discussion of this chapter.

5.2.1 Methods

Criteria for considering studies for this review

Eligible study designs for the review were cohorts or cross-sectional studies. Case-control studies were excluded as prevalence of asthma could not be ascertained within the population of interest. Although cross-sectional surveys may suffer from reverse causality, they are useful to Public Health practitioners and educators to measure the prevalence of a disease such as asthma and its associations with education outcomes in the population of interest. This information may help practitioners tailor interventions depending on how common or rare the condition is in the population.

As in Chapter 4, participants of most interest were those up to the age of 7 years. Participants that were included in the search strategy were children up to age 7 years, or wider age ranges of children that included ages 5 to 7 years when KS1 is taught.

The exposure was any report of asthma or wheeze in children. Outcomes were educational attainment at school and pre-school tests measuring cognition that were considered equivalent to tests in education. The primary outcome of the literature review was to determine whether there is evidence of a detrimental effect on educational attainment from asthma or wheeze in childhood.

Search methods for identification of studies

The previous wider review of the published literature in Chapter 4 helped to inform the design of this search. A search was conducted of electronic databases EMBASE, Medline, and Web of Science for peer reviewed systematic reviews, journal articles and grey

literature (working papers) from January 1990 to June 2019. The literature was reviewed from 1990 onwards because the WECC birth cohort started from 1990 and children in these studies would have similar asthma treatment regimen. The search terms used were ('educational attainment' OR 'education attainment' OR 'academic achievement' OR 'school performance' OR 'education status' OR 'cognitive development' OR 'repeated a school year' OR 'repeat a school year' OR 'repeat school year' OR 'grade retention' OR 'school absence' OR 'absenteeism' OR 'school drop out') AND ('asthma' OR 'wheeze' OR 'wheezing') AND ('child' OR 'childhood' OR 'children') AND ('high income countries' OR 'higher income countries' OR 'rich countries' OR 'Europe' OR 'European' OR 'UK' OR 'USA' OR 'US' OR 'Australia' OR 'New Zealand' OR 'Organisation for Economic Co-operation and Development'). The country terms were used to identify studies in countries with high asthma prevalence, and relatively similar healthcare systems, asthma management guidelines, and school systems. The snowballing technique was used to identify additional papers from reviewing reference lists of relevant articles and article citations. An additional search of Google and Google Scholar was undertaken using the main terms for exposures and outcomes because relevant articles could belong to several silos of research.

Data collection and analysis

The same methods for study selection, data extraction and management were used as described in Chapter 4. For cohort studies, the methodological quality of studies was assessed using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies.(18,19) For cross-sectional studies an adapted version of the Newcastle-Ottawa Quality Assessment was used.(20) Both scales check articles for representativeness of the population, assess non-response, check main confounders are included in analysis and assess the outcome measure. The adapted scale for cross-sectional studies also checks whether an article has a validated tool to measure exposure, assesses justification of sample size and whether appropriate statistical tests are used and clearly described. Characteristics in the included studies table were restricted to the exposure of asthma or wheeze and outcomes of educational attainment and pre-school tests measuring cognition that were considered equivalent to tests in education as stated in the criteria of the review.

5.2.2 Results

The literature search found 681 articles. Twelve articles were specifically related to asthma or wheeze and educational outcomes and eligible for inclusion. Figure 5.1 presents a flow diagram of the search and study selection process.

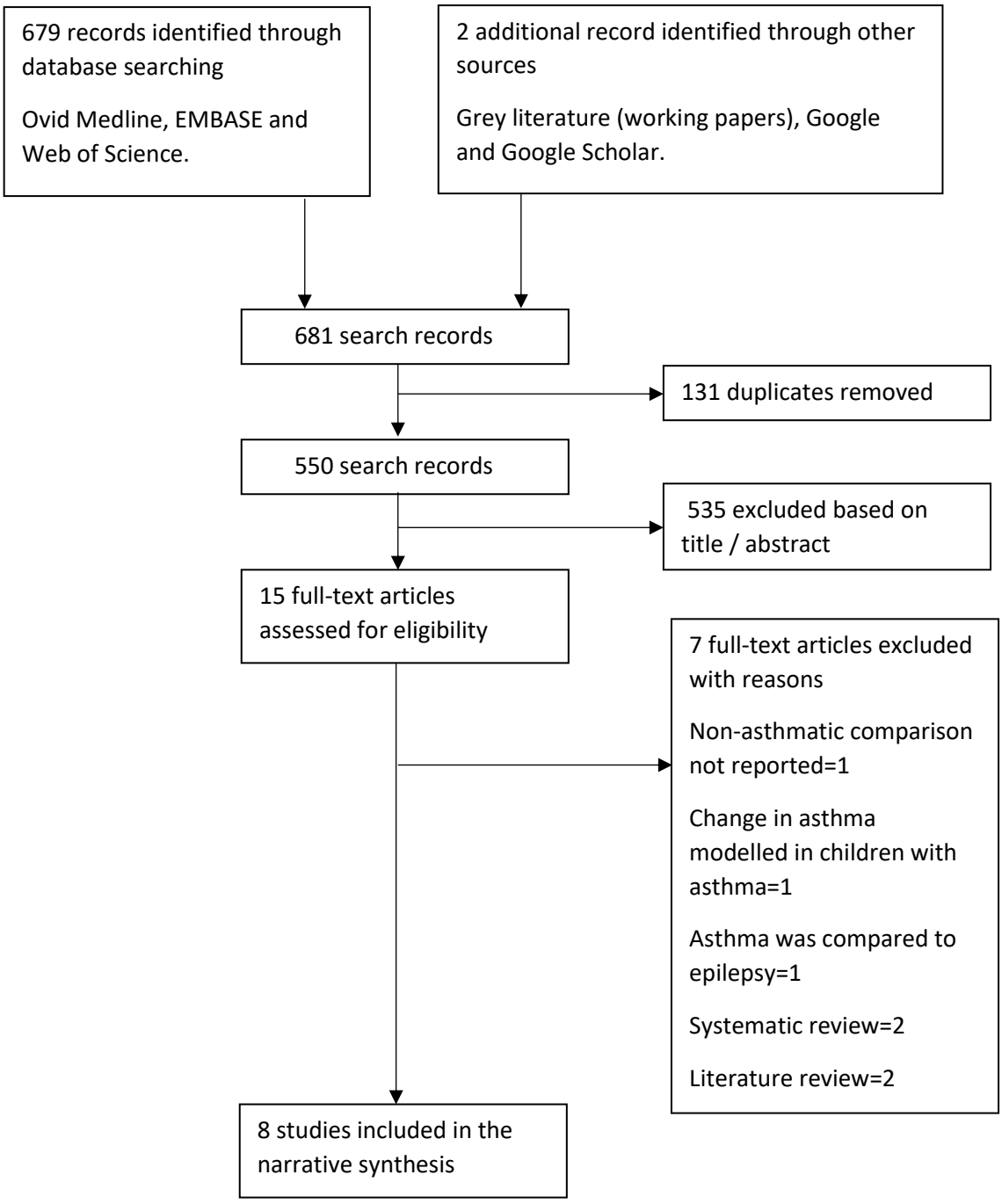

Figure 5.1: Flow diagram of the search and study selection process.

Characteristics of included studies

Table 5.1 shows the eight primary studies in the published literature that looked at the association between asthma or wheeze and educational attainment. The search of the published literature found two systematic reviews (21,22) and two reviews,(23,24) that

were excluded from the critical appraisal of this review but whose primary studies were included if they met the inclusion criteria.

Three studies were cohorts and considered of good quality.(17,25,26) Five studies were cross-sectional studies and therefore could only show associations between asthma and educational attainment where it was not possible to adhere to the temporal order of data collection of the exposure before knowledge of the outcome. One study used administrative data for all measures,(25) and three studies used administrative data for only educational outcomes from school records,(16,26,27) one a cohort study.(26) One cohort study (26) and two cross-sectional studies (16,27) suffered from potential attrition bias, but the cohort study included a sensitivity analysis that showed those excluded did not change the interpretation of results. All studies adjusted for a measure of deprivation or maternal education as a proxy for deprivation,(28) a known important confounder between asthma and education outcomes in children. Sample size was thought sufficient for all studies, one study had low counts for one analysis but the sample was adequate for the statistical analysis performed, and therefore the study was included in the review.(17) Two studies reported missing data in exposure or outcome measures of under 5%,(16,26) and one study had high levels of missing data in outcomes for non-asthmatics (27); other studies reported no information on missing data. The cross-sectional studies were thought to be of good to fair quality apart from one study where the most appropriate statistical analysis was not used.(16)

Characteristics of excluded studies

Seven studies were excluded from the main literature review that appeared to meet the eligibility criteria. The first study did not have non-asthmatic children as a comparison group,(7) similarly the second study only reported a change in asthma in children who had asthma and association with educational attainment.(29) The third study took children with asthma as a comparison group to investigate academic attainment in children with epilepsy.(30) Four studies were review studies and excluded from the main literature review.(21,22,23,24)

Effects of asthma or wheeze on educational attainment

In the eight studies of the review, 5 of 11 results showed asthma had a detrimental effect on educational outcomes (some studies reported separate results for mathematics and a language), with no evidence of an association found in the other studies. For asthma

severity measured in five studies, 6 of 13 results found asthma severity was associated with poorer educational attainment, and no evidence of an association was found in the other studies. In the good quality cohort studies, 5 of 8 relevant results for asthma reported a detrimental association on educational attainment, which is in contrast to the results when cross-sectional studies are included in the count of the review results. Due to heterogeneity in the measures of educational outcomes (at different ages, split by subject, or using grade retention) meta-analysis was not considered appropriate.

Table 5.1: Characteristics of included studies for asthma or wheeze and educational attainment in childhood.

Reference	Exposures	Participants	Settings / context	Outcomes	Results	Methods / quality	Newcastle-Ottawa quality assessment
Cohorts							
(ref 26) Crump 2013 USA	Asthma recorded from parental reports of chronic health conditions to school where at least first 2 years of school records exist	Children age 7-16 years at the San Jose Unified District School records, California from 2007-2010, 43% of cohort enrolled in free / reduced lunch program	Retrospecti ve cohort	California Standards test of English language arts (ELA) and math grades 2-11 "basic or below" ELA or math performance. Absence from school per year	Study size n=22,730 Logistic regression: OR (95% CI): English language arts 1.13 (1.01-1.26) Mathematics 1.11 (1.00-1.24) Negative binomial regression: IRR (95% CI) Absence from school 1.29 (1.23-1.35) (raw numbers not reported) Models additionally adjusted for absence from school Logistic regression: OR (95% CI): English language arts 1.09 (0.98-1.22) Mathematics 1.05 (0.94-1.16)	70% of children had complete data for analyses, (sensitivity analysis showed slightly weaker associations but with the same interpretation) Not clinically diagnosed asthma Models were adjusted for age, gender, ethnicity, language, grade level, special education, participation in free or reduced price lunch program, parental education 2% missing outcome data 5% missing exposure data No mention of wheeze	Good
(ref 17) Liberty 2010 New Zealand	Asthma diagnosed using the International Study of Asthma and Allergies in Children (ISAAC) questionnaire, if yes then physician sent a form to say whether current asthma (in last 12 months) based on a diagnosis of asthma or wheezing symptoms, if only cough symptoms children were not classified as asthma. All children classified with asthma had a doctor-prescribed medication for asthma.	Cohort of randomly selected schools in Christchurch age 5-6 years	Prospective cohort	School readiness at age 5 years: Wechsler Individual achievement test second edition (WIAT) in word reading and mathematical reasoning subtests (poor readiness >= 6 months lower than peers), School attainment at age 6 years: (low achievement >= 6 months behind). Wechsler Intelligence Scale for children 4th edition (WISC) oral reading school texts.	Study size n=278 Low achievement in word and text reading at age 6 years in adjusted models but not in mathematics in chi square analysis. Logistic regression: OR (95% CI) Word reading for current asthma: 2.20 (1.08-4.51) Text reading: 2.03 (1.01-4.07) No difference for school readiness at age 5 years in chi-square tests. No difference in absenteeism in first year of school in chi-square tests. Top quartile of absenteeism days mean 11.70 (SD 8.08), 29.4% in current asthma compared to 26.1% no asthma.	94% of children recruited, 93% of children had complete follow-up Quite small numbers in mathematics analysis. Models adjusted for poor readiness, low SES from deprivation decile score from participant address via 2006 census, single parent. Exclusions high or very high SEN provision for example children with cerebral palsy or severe intellectual disability, at least one parent whose own first language was English, Maori or a Pacific Island language. No mention of missing data study used face-to-face interviews.	Good

Table 5.1: Characteristics of included studies for asthma or wheeze and educational attainment in childhood (cont).

Reference	Exposures	Participants	Settings / context	Outcomes	Results	Methods / quality	Newcastle-Ottawa quality assessment
Cohorts (cont)							
(ref 25) Sturdy 2012 UK	H33 diagnosis code for asthma in GP data. Active asthma (one or more bronchodilator prescriptions in the previous year before take exam) or inactive asthma (diagnosis of asthma but no bronchodilator prescription in previous year before take exam). Asthma severity: BTS medication step in year prior to take exam in 2005. Comparison between step 1 and step 2 to 5 in two groups.	Children age 5-14 years in clinical administrative data linked to education and social care data sets in east London (2002-2005), contained ethnic diversity	Cohort	Key stages 1 - 3 exams or tests. Key stage 1 mean score for reading, writing and maths, for KS2 and 3 mean score of English, maths and science.	Study size n=12,136 Models adjusted for SEN: Linear regression: Coefficient (95%CI): Active asthma: 0.07 (0.01-0.12) Inactive asthma: 0.02 (-0.03 to 0.07) Asthma severity: No difference between defined BTS asthma severity groups, step 1 compared to steps 2-5, for children with active, or inactive asthma.	14/15 General Practices recruited. Using BTS step assumed severity for each child was stable over the study duration. Disappointing some markers of asthma severity including peak flow recording and asthma consultations were poorly recorded in general practice. All models adjusted for SEN provision – a potential mediator. Also adjusted for inactive asthma, ethnicity, sex, age, smoking household, council tax band, living in social housing, in receipt of benefits, free school meals, special educational needs, allergic rhinitis diagnosis, eczema diagnosis, mental health problems. Sensitivity analysis conducted. No information on missing data.	Good
Cross-sectional studies							
(ref 31) Byrd 1994 USA	Any asthma (a childhood chronic health condition) at the time of recording the survey	National Health survey 1988 of children age 7-17 years, population representative of the USA	Cross-sectional	Grade retention in Kindergarten or first grade (age 5-7 years)	Study size n=9,996 No evidence of an association found between asthma and grade retention. Univariable logistic regression: OR (95% CI) Grade retention: 1.3 (1.0-1.2), p-value=0.9	91% response rate Childhood chronic health conditions at the time of the survey not at age 5-7 years old. Other chronic diseases in models adjusted for poverty, gender, low mat age, less than 2 biological parents in home at age 6 years, low mat education, child age in the cohort 7-10yrs the ref, low birth weight, deafness in one or both ears, speech defects, enuresis, household exposure to cigarette smoke, frequent ear infections. Information unclear on missing data.	Fair

Table 5.1: Characteristics of included studies for asthma or wheeze and educational attainment in childhood (cont).

Reference	Exposures	Participants	Settings / context	Outcomes	Results	Methods / quality	Newcastle-Ottawa quality assessment
Cross-sectional studies (cont)							
(ref 28) Fowler 1992 USA	Child asked if they had asthma in the past 12 months (current asthma) Asthma severity defined as taking asthma medication	National Health survey 1988 of children age 7-17 years, population representative of the USA	Cross-sectional	Grade failure (retention) in grades 1-12 age 7 to 17 years	Study size n=10,362 No evidence of an association found between asthma and grade retention. Logistic regression: OR (95% CI) Asthma and grade retention: 1.3 (0.9-1.9) Adjusted for school absence: Asthma and grade retention: 1.2 (0.8-1.6) Stratified analysis: ≥$20,000 family income:0.9 (0.7-1.3) <$20,000 family income: 2.0 (1.1-3.4) Asthma severity taking medication: 2.7 (1.0-7.1) 11% of children with asthma had 16+ days absent from school in the last year compared to children without asthma.	91% response rate Analysis is adjusted for maternal education as a proxy for family income. Models adjusted for sex, age group (5-8yr, 9-11yr, 12-17yr), maternal education level, family income, race / ethnicity. A further model adjusts for school days absent. Non-response adjusted for in weighted analyses	Good
(ref 32) Halterman 2001 USA	Parental report of asthma in last 12 months that required attention or treatment Asthma severity defined as with limitation to child's activity, compared asthma without limitation.	School survey, Rochester, New York in 1998, age 5 years, 80% of the community from minority backgrounds.	Cross-sectional	Parent reported school readiness using developed questionnaire with an evidence-based and expert consultation model called PACED including factor analysis of question results into 4 domains: school readiness skills (read simple words, count objects, identify colours), language skills, motor skills, socioemotional skills. Scores between 0 – 4.	Study size n=1,058 Linear regression. Asthma with or without limitation no evidence of association with poorer language skills. Asthma without limitation no evidence of association with school skills. Asthma with limitation compared to no asthma and school skills: Average score 2.0 V 2.5, p<0.001	>90% response rate Parental reported data on observable behaviours of the child, subjective assessment of performance. Asthma not validated in a medical record. No information on medication use. Models adjusted for sex, medicaid insurance, caretaker education, participation in day care and preschool. No information on missing data.	Fair

Table 5.1: Characteristics of included studies for asthma or wheeze and educational attainment in childhood (cont).

Reference	Exposures	Participants	Settings / context	Outcomes	Results	Methods / quality	Newcastle-Ottawa quality assessment
Cross-sectional studies (cont)							
(ref 27) Kohen 2010 Canada	Past-year wheezing or whistling in the chest and regular use of inhalers. Asthma severity defined as diagnosed and: low (no wheezing or whistling and no use of medication), moderate (reported wheezing or whistling OR use of medication), severe (reported wheezing or whistling AND use of medication)	1998-99 National Longitudinal Survey of Children and Youth age 7-15 years	Cross-sectional	Grade 2 to 10 (age 7 to 15 years) low scores in standardized tests administered in the classroom.	Study size n=4,418 for asthma severity analysis Logistic regression: OR (95% CI) Low score maths test: low asthma: 1.39 (1.00-1.92) moderate asthma: 1.90 (1.34-2.68) severe asthma: 1.62 (1.17-2.25) Low score reading: low asthma: 0.82 (0.59-1.15) moderate asthma: 1.73 (1.28-2.32) severe asthma: 1.23 (0.91-1.67) Adjusted for school absence: Low score maths: low asthma: 1.36 (0.98-1.90) moderate asthma: 1.84 (1.30-2.62) severe asthma: 1.59 (1.14-2.22) Low reading scores: low asthma: 086 (0.62-1.20) moderate asthma: 1.83 (1.36-2.46) severe asthma: 1.36 (1.00-1.86)	No information on response rate but analysis weighted to national proportions. Approximately 50% attrition for asthma severity analysis. Models adjusted for parent reported maternal age, female-headed household, maternal education, mother in employment, income adequacy, child health status, chronic condition excluding asthma, child's mean age, sex, province. Additional models with absence from school High non-response in mathematics and English tests for children without asthma compared to children with asthma. No sensitivity analysis performed.	Fair

Table 5.1: Characteristics of included studies for asthma or wheeze and educational attainment in childhood.

Reference	Exposures	Participants	Settings / context	Outcomes	Results	Methods / quality	Newcastle-Ottawa quality assessment
Cross-sectional studies (cont)							
(ref 16) Moonie 2008 USA	Asthma reported to school nurse with physician signed asthma action plan or asthma medications by parent / guardian Asthma severity: National Asthma Education and prevention program standardised questions in first two months of school those with asthma: yes - mild intermittent, mild persistent, moderate persistent, severe persistent in the last 30 days. Kindergarten to grade 4 parental reporting, grades 5-12 self-report by children to the school nurse.	Missouri school cohort in greater St Louis Metropolitan region age 8-16 years, random sample across schools, 95% African American, from 2002-2003	Cross-sectional	Missouri assessment program (MAP) combined achievement (performing below Nearing proficiency in a 5 point scale) in combined educational outcome across all subjects. In grade 3 (age 8-9 years) only in subjects Communication arts and Science, in other years maths and social studies can be included (10-16 years) Absence from school	Study size n=3,812 No difference for asthma to those without on overall attainment in Fisher exact tests. Models with asthma severity Logistic regression: OR (95% CI) Asthma severity two group comparison:1.93 (0.93-4.01) (mild intermittent compared to persistent (mild, moderate, severe)). 1.5 days more absence on average for children with asthma compared to those without. Significantly higher days absent for children with severe persistent asthma (mean = 11.6 +/- 9.4 days) compared to mild intermittent asthma (mean = 8.5 +/- 9.5 days. No difference between mild and moderate persistent.	1.5% exclusions due to missing outcome data or ethnicity Models adjusted for gender, race, grade level, eligibility for free school Asthma severity not compared to 'no asthma' group and only collected for 175 children 44% of those with asthma 397 children. 1.0% missing outcome data.	Poor

OR=odds ratio; CI=confidence interval.

5.2.3 Discussion

The literature review identified eight studies that specifically examined the impact of asthma on educational outcome.(16,17,25,26,27,28,31,32) Of the studies that looked specifically at children between the age of 5 and 9 years the evidence of the review found mixed results for an association between asthma and poorer educational outcomes. Liberty et al found poorer educational outcomes in word and text reading but not in mathematics for current asthma within the last year.(17) This cohort had a relatively small sample of children entering school with asthma, and reading tests were direct tests and not parental or school reports. Halterman et al reported in their cross-sectional study of children age 5 years that asthma had no evidence of an association with poorer parent reported language skills, but did find an association between poor school readiness and asthma with limitations.(32) This may be explained by asthma preventing the children effectively participating in pre-school educational activities. The study contained 80% ethnic minorities that may mean the prevalence of asthma in the study is not generalisable to the UK population. However, this study does provide evidence for an association between asthma severity and poorer educational outcomes.

Other studies in the review contained children and adolescents in a much wider age range. Older children can manage their own asthma condition which may improve any impact on daily activities and learning. Also, asthma onset can occur in teenage years, particularly for teenage girls, so may not be generalisable across the age of the cohort as younger children with more severe asthma tend to be boys.(33) Two cohort studies found associations with current asthma and poorer educational attainment in children, a large study reported by Crump et al of children age 7-17 years that used only parent reports of asthma and wheeze,(26) and Sturdy et al for children age 5-14 years.(25) The latter study adjusted models for a child's Special Educational Needs (SEN) provision, a mediator between asthma and educational attainment, and the size of the total effect of the association of asthma and educational attainment was not reported.

In contrast, Byrd et al and Fowler et al both used the National Health Survey 1988 of children age 7-17 years, and found no evidence that asthma was associated with grade retention. Grade retention is a process where a child usually scores well below a given standard in learning and is required to repeat a school year. The first study looked at chronic asthma recorded at any time between age 7-17 years and grade retention between

age 5-7 years, and so asthma diagnosis could occur after the age of 7 years.(31) The second study showed no evidence of an association between current asthma in the past year and grade retention (28) for children between age 7-17 years (children and adolescents).

These results were supported by conclusions by Taras et al in their literature review who reported only a third of studies reviewed showed a significant association between asthma and poorer educational attainment,(23) this was echoed in the WHO report by Suhrcke.(24) Milton et al (22) and Lum et al (21) found no difference for children under 18 years for educational attainment with or without asthma. These reviews used all study designs in their selection criteria (i.e. included case-control studies) and did not consider the hierarchy of evidence in their interpretation and synthesis of these studies.

For asthma severity, Halterman et al measured severity in children as asthma with or without limitations to daily activities for children age 5 years in their cross-sectional study.(32) They found no evidence of a difference for children's language skills in the asthma severity groups compared to those without asthma. However, they did find an association between asthma with limitations to daily activities and children having poorer school skills when compared to non-asthmatic peers. The measurement of asthma with or without limitations was parental reported and could be subject to measurement bias.

In the broader age range of children age 5-14 years, Sturdy et al found no difference between asthma severity groups in their cohort study, defined as the British Thoracic Society asthma management guidelines step 1 compared to steps 2-5 in children with current asthma.(18) This result may be due to the choice of the comparator as the study did not compare asthma severity categories to children without asthma. Later in this chapter, these guidelines are used to create several categories of asthma severity in a total population cohort study. Two further cross-sectional studies showed some evidence of an association between asthma severity and poorer educational attainment, and differing results may be due to different definitions of asthma severity. Moonie et al found no difference between mild intermittent asthma and persistent (mild, moderate or severe) asthma and overall attainment.(16) Their study had over a 50% attrition rate for associations between asthma severity and educational attainment so their results may suffer from attrition bias. Children in the study were age 8-16 years, and 80% were from ethnic backgrounds and may mean prevalence of asthma may not be generalisable to the UK population. Kohen's cross-sectional study of asthma or wheeze in children age 7-15 years, found low scores in school tests were associated with increasing risk as asthma

severity increased.(27) Asthma severity was defined using symptoms and asthma medication (for the most severe category) from maternal reports. This study had large odds ratios for the associations reported in modelling, and this may be because the analysis did not adjust for important confounders such as birth characteristics e.g. gestational age and birthweight. The study ascertained asthma severity measures for only approximately half of the original sample recruited, and it also reported high non-response to mathematics and English tests for children without asthma that may have caused selection bias in results.

5.2.3.1 School absence

Five studies in the review measured absence from school in addition to children's educational attainment(16,17,26,32) where most reported two more days absence in a year for those with asthma compared to those without asthma, and higher absence for younger children.(23) Although absence from school is known to be associated with poorer educational attainment it is unlikely that two days absence from school from asthma would greatly impact on children's educational outcomes. For some children absence from school was higher if they had asthma. Liberty et al showed there were more children age 5-6 years who had 16+ days of absence from school in a year if they had current asthma compared to those without.(17) Moonie et al established worse performance for children with higher days absent from school, and higher days absent for children with asthma, but found no evidence of an association between asthma and poorer school test performance.(16) Kohen et al (27) and Fowler et al (28) had conflicting results for the association between asthma on poorer educational attainment or grade retention, and both found no change in their conclusions after adjusting for school absence. When more severe asthma was measured using reliever prescriptions, Emergency Department (ED) visits or hospitalisations, children had seven or more days absence from school in a year.(30,32) The latter study used ED visits or hospitalisations, > 3 bronchodilator prescriptions in 3 months or an asthma exacerbation within the last 12 months, as a measure of poor control of asthma symptoms for absence from school as an outcome.(34)

5.2.3.2 Confounders, other important factors

Figure 5.2 describes a theoretical causal pathway and potential confounding relationships from this literature review.

Respiratory infections, other respiratory disease or conditions

There was no evidence of the effects of respiratory infections in children on educational attainment from the review. Other research on absence from school for respiratory illness in children with diagnosed asthma showed higher levels of absence, compared to children classified as having a high or low probability of asthma at age 5 years.(35) However, the association with children's absence from school due to respiratory illness was no longer apparent for these asthma groups by the time they reached age 10-11 years, but the survey suffered from a low response rate (34%). An association between asthma diagnosis and higher absence from school due to respiratory illness was also found in a survey conducted in the Netherlands, when children age 4-15 years were compared to those without asthma.(36) Neither study explicitly categorised other respiratory illness beyond shortness of breath, asthma, wheeze or cough.

Birth characteristics

As mentioned in Chapter 4, previous research shows birth health status such as gestational age or birthweight was associated with higher risk of lower educational attainment. Children born preterm may have underdeveloped lungs that make them prone to more severe respiratory infection (37) and the incidence of asthma in young children is higher for boys than for girls.(33) Children who have other respiratory illness may have an increased burden on their respiratory system in addition to the effects of asthma, and therefore analyses should be adjusted for other chronic upper or lower respiratory disease, upper or lower respiratory tract infections and croup.

Socio-demographics and school level factors

As in Chapter 4, socio-economic and school level factors are included in the modelling. Asthma has been found to be associated with deprivation and this may relate to poor housing or less healthy diets.(9)

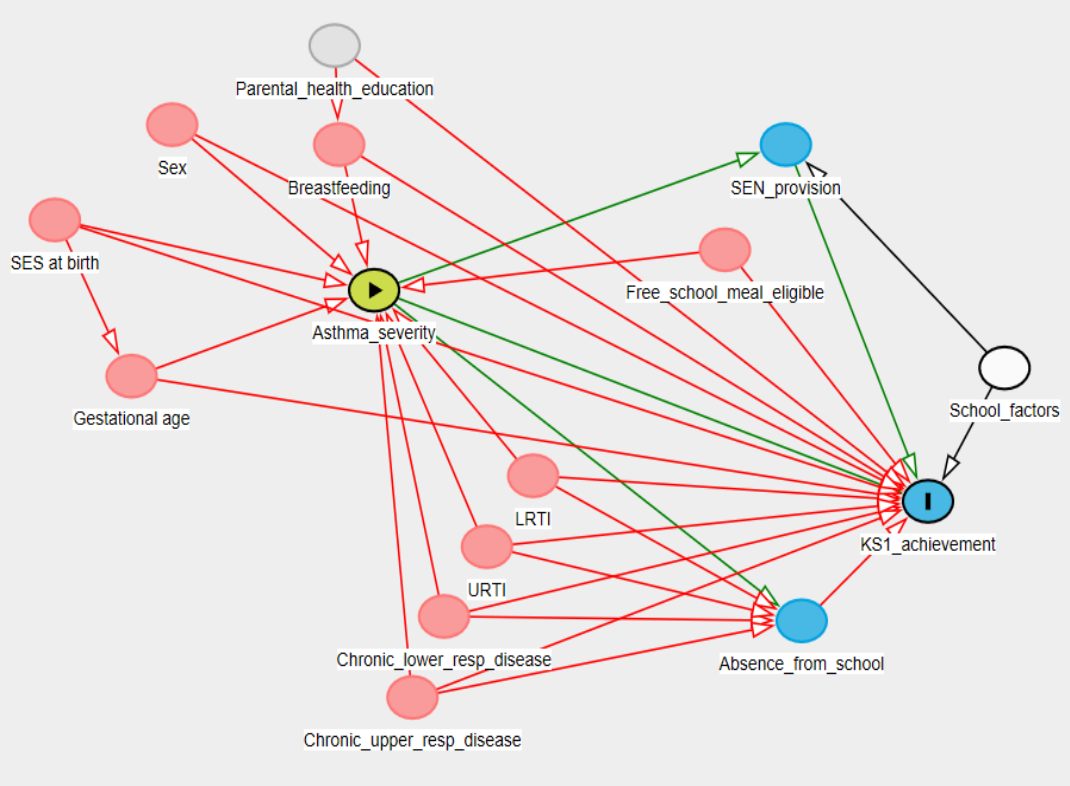

Figure 5.2. Directed Acyclic Graph (DAG): visual diagram of potential causal relationships to aid selection of confounder variables.
SES=Socio-economic status; Green circle with black triangle – exposure; Blue circle with vertical black line – outcome; Pink circle – ancestor of exposure and outcome (confounder); Pink arrow – directional biasing path; Plain blue circle – ancestor of outcome; Green arrow – directional causal path; White circle – adjusted variable; Black arrow – directional relationship; Grey circle – unobserved variable; Exposure=asthma severity; Outcome=KS1 attainment; Example of a potential confounder between exposure and outcome=LRTI; Example of a potential mediator between exposure and outcome=SEN provision.

5.2.4 Conclusion

Implications for practice

From the literature review the overall weight of evidence marginally supports no evidence of an association between asthma and poorer educational attainment in childhood, but when only cohort studies are considered the evidence marginally supports an association between asthma and poorer educational attainment. There was little evidence available that looked at asthma and educational outcomes in studies that were specific to children between age 5 and 9 years. In studies that looked at educational outcomes only in this age group, there was some evidence in both studies that asthma was associated with poorer school results, but not in all subjects or skills tested. It is important to focus on this age group at their first formal school assessment because illness may mean children miss early

developmental stages that may lead to poorer academic trajectories. The former study was a small cohort study, the latter a cross-sectional study in a specific community of children in the USA. Other studies, some of which were large, with wider age ranges of children found similar inconsistencies for associations between asthma and the results from different subjects tested with no clear pattern for those subjects.

Definitions of asthma and recording of asthma differed between studies, from clinical records, school nurse records and parental reporting. Two studies considered wheeze in their definitions of asthma and found inconsistent associations with educational attainment between different school subjects. One study showed poorer results for text and word reading but not mathematics, another study showed poorer scores across asthma severity categories for mathematics but not consistently across the categories for reading skills. It is possible these differences may be due to variations on the focus between mathematics and reading in education systems in different countries. In the studies that did not measure asthma severity in their design, it was recommended for further research.

Asthma severity was considered in five studies where 13 results between asthma severity and educational outcomes showed just under half were associated with poorer educational attainment. Severity of asthma was measured in different ways in these studies. Three studies incorporated any asthma medication in their definition of severe asthma. These studies found inconsistent results from asthma severity for overall attainment, specific subjects or grade retention in children. These results may be explained in part by the asthma severity category definitions, that may potentially be dominated by children who only use reliever medication (bronchodilator) occasionally for intermittent asthma that could have a low level of interruption to a child's life. Three studies analysed asthma severity categories between levels of severity rather than against children with no asthma, and this may have led to the findings of no difference in academic results. In addition, two studies had very high levels of attrition for their asthma severity variables that may mean results could potentially suffer from attrition bias. One study used parent reported limitations from asthma on a child's activities as a measure of more severe asthma, but results on educational attainment across subjects were again inconclusive.

Some of the studies in the review also looked at absence from school. Most studies agreed both in direction of effect and magnitude that children with asthma had on average two more days of absence compared to children without asthma. All studies agreed children

with more severe asthma had more days absent from school. This consistency in results from the review for absence from school in children with asthma does support the potential association between asthma and poorer educational attainment, as it is known that missed school days are associated with poorer school performance. However, the different results in the review highlight that the number of school days absent does not necessarily result in school failure, and that absence from school does not fully explain the association between asthma and educational attainment. Asthma may also potentially cause lack of concentration at school due to symptoms from the disease that may prevent a child from engaging fully in school learning.(38)

There was no evidence from the review about respiratory infections, asthma and educational attainment in children age 5 – 9 years. There was some evidence in the literature that looked at school absence from respiratory illness, it showed children with an asthma diagnosis had more days absent than those without when children were age 5-6 years, but conflicting results for older children.

Of the studies in the review only one study adjusted for birth characteristics, it used birth weight, which can be a surrogate for early birth and is known to be associated with poorer educational attainment. No studies adjusted for school factors that may explain the variance in educational outcomes. Absence of these confounders and effect modifiers from modelling may potentially cause associations between asthma and educational attainment to be higher or more variable than results if the combined contribution of these confounders and other factors were considered.

The strength of the review was that it adapted methods from the Cochrane Review Handbook for interventions to look instead at exposures. The review included both asthma disease, wheeze and severity of asthma as criteria for inclusion into the review for educational attainment outcomes in children and this has not been considered elsewhere. It is possible that some relevant research articles were missed but because multiple search engines were used and a Google search of the main search terms was included it is unlikely that any studies were missed.

Implications for research

The literature review highlights there is little evidence specifically for any association between asthma and educational outcomes in the UK for children age between 5-9 years. It

also shows the overall weight of evidence has conflicting outcomes between cohorts and cross-sectional studies that may be due to longitudinal designs of the data in cohorts. Cohort designs are known to give stronger evidence of potential causality than cross-sectional studies that can only measure associations between exposures and outcomes. A cohort study allows the researcher to respect the temporal order of the data where exposure is required to occur before the outcome. A review of only the cohort studies showed the balance of evidence only slightly supported a potential causal association between asthma and poorer educational attainment in children. Further, cross-sectional studies provided some evidence about asthma severity and educational outcomes even though cohorts are considered a superior research design. Measurement of educational outcomes differ between studies but the thresholds for poor attainment are probably relatively comparable for the general learning stages of a child in high income countries if they use school assessment. Asthma ascertainment varied within studies. Some studies included wheeze in their definition of asthma, but this is not universal and should be considered as younger children are often not diagnosed with asthma in case they grow out of the symptoms.

Asthma severity in children is imprecisely defined across all studies because the definitions give no measure of severe asthma beyond 'any medication' for asthma. One study asked parents to quantify their child's asthma as limitations to daily activities to try and capture a wider set of symptoms but could be subject to measurement bias because the classification did not come from a clinician. Asthma severity measured in studies looking at absence from school indicate asthma related ED visits, hospitalisations or high use of medication meant children had much higher days absent than their healthy peers. A combination of these measures from healthcare usage could be used to measure more severe asthma. ED visits or hospitalisations of children for asthma could measure acute asthma exacerbations and use of medications could define chronic asthma severity.

Although absence from school seems to provide more consistent results for asthma between studies, it is only thought to be a partial mediator between asthma and educational attainment in the literature reviewed. There was no evidence of the impact of respiratory infections or other respiratory illness in conjunction with asthma on educational outcomes. Studies investigating absence from school found higher days absent for respiratory illness in children with asthma compared to those without. The review highlights the need for further research using large cohort studies in the UK that include

wheeze in their definition of asthma. It also draws attention to the need for finer measurement of asthma severity potentially from the number of medications in a given timeframe, ED visits or hospitalisations (that could also be described as a measure of poor control). The review shows further research should consider other respiratory illness that a child may experience, particularly respiratory infections that may interact with the effects of asthma on educational outcomes.

5.3 Aim and objectives

Aim

To investigate the association between asthma or wheeze severity and educational attainment at age 6-7 years.

Objectives

ii. To investigate and quantify the association of acute asthma using inpatient hospital admissions in children, for

    a. asthma

    b. asthma or wheeze

iii. To investigate and quantify the association of chronic asthma severity using General Practice prescriptions, for

    a. asthma

    b. asthma or wheeze

iv. To investigate and quantify the role of other respiratory illness, for

    a. asthma

    b. asthma or wheeze

v. To assess if absence from school acts as a mediator between the association of acute asthma and chronic asthma severity, for

    a. asthma

    b. asthma or wheeze

on educational attainment at KS1 (age 6-7 years).

5.4 Participant selection

The study in this chapter used the Wales Electronic Cohort for Children (WECC) to create a population-based cross-sectional electronic cohort of all children born in Wales, from 1st January 1998 to 31st August 2005. This was a pre-planned record-linkage study consistent with the broad aims of the WECC cohort, with linkage to prospectively collected health and education administrative data as described in Chapter 2. Data was extracted for asthma, wheeze and other respiratory diagnosis from General Practice (GP) or inpatient hospital admissions data. Children were followed from birth to age 6-7 years when they have their first teacher-based educational assessment at KS1, through record-linkage between education and health routine data sets. The de-identified data was analysed in the Secure Anonymized Information Linkage (SAIL) databank, UK.(39,40)

For this project, children were excluded if they were not born in Wales (as these children had high levels of missing data for birth characteristics), born before 1st January 1998 (as electronic GP and hospital inpatient admissions data was not available from the data sources before this date) or after 31st August 2005 (as they would not have sufficient follow-up to age 6-7 years). Further exclusions were children who died or moved out of Wales before age 7 years, who did not attend a local education authority school, did not take KS1 at the normal age, or where the child's GP practice had not signed up to SAIL (Figure 5.3). At the time of data extraction, the WLGP database in the SAIL databank had over 40% of the 474 practices in Wales signed up, and over 1.9 million people.

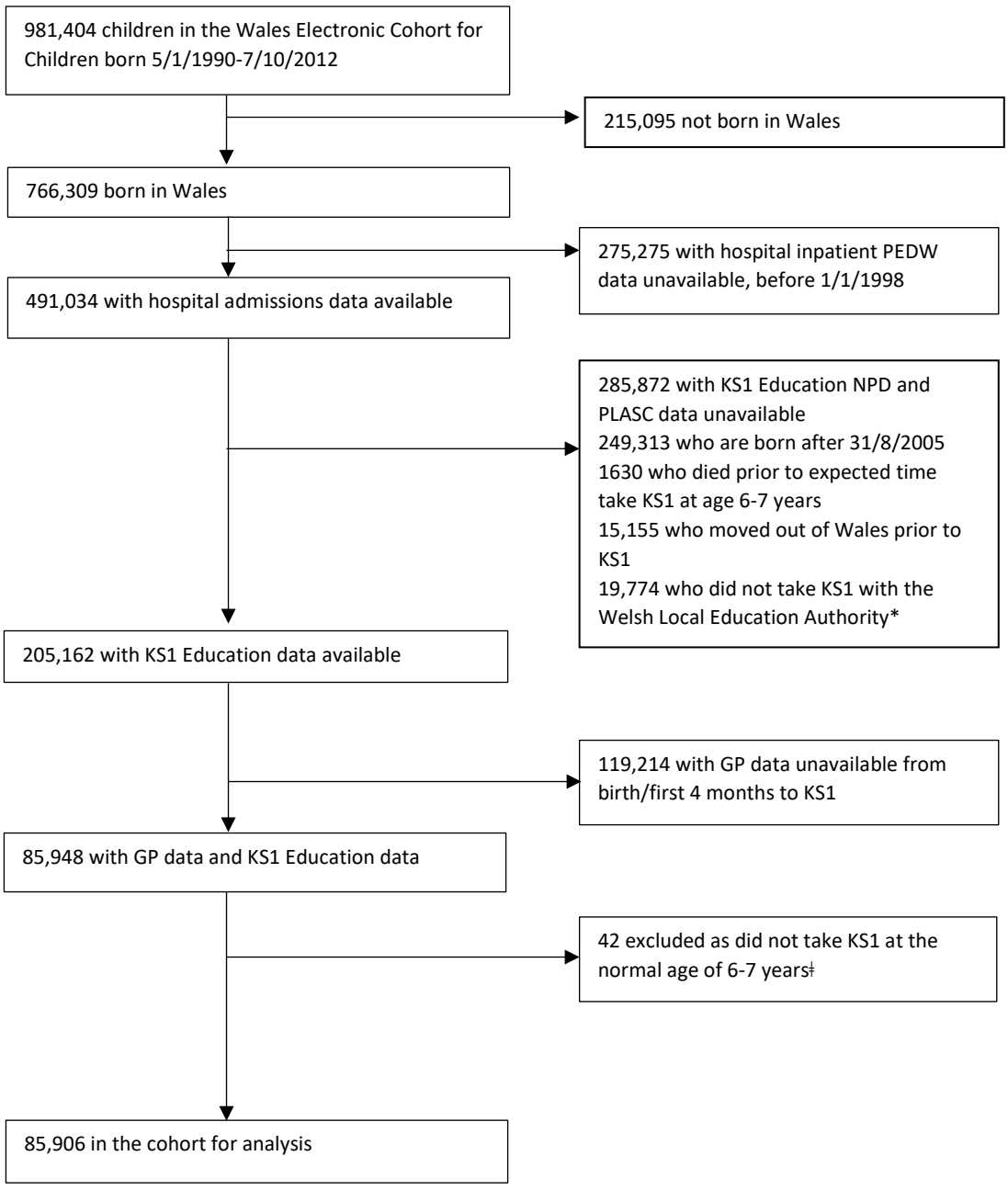

Figure 5.3 - Anonymised participant selection.
PEDW=Patient Episode Database Wales, KS1=Key Stage 1, NPD=National Pupil Database, PLASC=Pupil Level Annual School Census.
*private schools, severely disabled children who are not catered for by Special Educational Needs provision in the LEA school system, those outside administrative systems e.g. travellers; ‡ to adhere to no overlap between exposure and outcome time windows.

5.5 Exposure and outcome variables: definitions using coded data

Outcome: Educational attainment

The main outcome was attainment of the expected educational level (yes/no) in compulsory assessment in Wales at age 6-7 years (KS1), normally taught between age 5-7 years.(41) KS1 is a teacher assessment of a language, mathematics, and science with overall level awarded between 0 and 4, where below level 2 constitutes not attaining the expected level at KS1. Children who were dis-applied (either due to special educational needs or in-migration where the language being tested was not currently spoken), not awarded the level, unable to provide an assessment, or working towards the assessment level were coded as did not attain the expected level at KS1 in this study. These definitions agree with those of the Welsh Department of Education for children's educational attainment.

Exposures: Current asthma or wheeze severity, acute asthma exacerbations and respiratory infections

Variable categories were developed for current chronic asthma severity using coding and data on diagnoses, procedures and prescriptions, and for acute asthma from inpatient hospital admissions. Asthma or wheeze was ascertained in GP data (using a set of previously published Read codes in the WLGP database (42)) or ICD10 codes J45-46, R06.2 in the first coding position of any inpatient hospital admission (including hospital transfers) between birth and age 7 years. Two algorithms were developed to derive categorical variables that describe current chronic asthma severity: one excluded wheeze-only diagnoses (called the asthma severity algorithm), while the second, a broader algorithm included wheeze (called the wheeze severity algorithm). Chronic asthma severity was recorded for each year of the child's life, aligned to five levels of asthma management (based partly around yearly prescriptions) described in the National Heart, Lung and Blood institute (NHLBI) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma 2007 (USA).(11) An additional category was created where only a diagnosis was recorded. These guidelines were compared to current UK assessment and stepwise treatment guidelines for the clinical management of asthma(12,43) to create an algorithm that met both criteria, as described in Table 5.2 (coding lists in Appendix Tables A5.1-4; Appendix Figure A5.1). (The pharmacological guidelines were found to be very similar to those in the Global Strategy for asthma management and prevention 2020(44)). These two

algorithms enabled the study to compare analyses based on definitive diagnoses of asthma (from ongoing prescriptions of inhaled corticosteroid (ICS) or preventer medication, or tests like spirometry - usually only achievable from age 5 years), to those in a broader definition, i.e. children diagnosed with either wheeze or asthma.

To update the GP diagnosis and procedures codes from the previously published study (42) from 2009 to 2017, codes were extracted from the NHS Browser list of all Read codes Version 2 that contained the words 'asthma' or 'wheez' as a string within the descriptive text for each code. The string of text 'wheez' was used to capture both wheeze and wheezing. To update the asthma or wheeze prescriptions list, an extraction of all prescriptions that were classed for use for respiratory illness were taken from the data dictionary. Then, the previously published list of medications was used to guide the choice of any new codes. These lists were classified into types of medication for asthma using the websites listed in Appendix Table A5.5, and grouped into the asthma or wheeze chronic severity categories to match the asthma management guidelines (Appendix Table A5.2; Table 5.2). A list of prescriptions to define oral steroid use was also created from the endocrine drug medications in the NHS Browser 2017 (Appendix Table A5.3).

For simplicity in the main analysis, the most severe category of asthma was chosen from the yearly calculations as exposure status for each child between birth and age 7 years. In further analyses exposure status was split by the age of the child into less than 2 years, 2 to less than 5 years, 5 to less than 7 years to closely match the asthma guidelines and age when KS1 is taught. The current chronic asthma severity categories were labelled as 'none', 'diagnosis only', 'intermittent bronchodilator', 'persistent mild', persistent moderate', and 'persistent severe' to match the guideline categories (Table 5.2).

Table 5.2: Description of asthma severity using administrative health data sets.

Asthma or wheeze severity algorithms for this analysis (coding in Appendix Tables A5.1-4)	
Asthma severity algorithm	
Category	**Coding description**
None	No diagnosis of asthma between birth and KS1 (age 6-7 years).
Diagnosis only	Ever had an asthma diagnosis in either GP or hospital inpatient admissions data[a] between birth and age at KS1 (age 6-7 years)
Intermittent bronchodilator	> 1 and ≤ 12 prescriptions of asthma bronchodilator including nebulisers in any one year of life, and ever had an asthma diagnosis in either GP or hospital inpatient admissions data[a] between birth and age at KS1 (age 6-7 years).
Persistent mild	Inhaled corticosteroid including nebulised or > 12 bronchodilator prescriptions in any one year of life[b], and ever had an asthma diagnosis in either GP or hospital inpatient admissions data[a] between birth and age at KS1 (age 6-7 years).
Persistent moderate	Inhaled corticosteroid including nebulised or > 12 bronchodilator prescriptions in any one year of life[b], and at least one prescription of a preventer medication (e.g. long acting beta agonists), and ever had an asthma diagnosis in either GP or hospital inpatient admissions data[a] between birth and age at KS1 (age 6-7 years).
Persistent severe	Asthma injection prescription, immunosuppressant therapy prescription or > 3 oral corticosteroid prescriptions in any one year of life, and ever had an asthma diagnosis in either GP or hospital inpatient admissions data[a] between birth and age at KS1 (age 6-7 years).
Wheeze severity algorithm	
'No diagnosis of asthma or wheeze' replaces 'no diagnosis of asthma', and 'ever had a wheeze or asthma diagnosis' replaces 'ever had an asthma diagnosis' in the definitions for the asthma severity algorithm above.	

KS1=Key Stage 1; GP=General Practitioner; [a] Inpatient hospital diagnosis is first diagnosis code of first consultant episode of each person's continuous stay in hospital including transfers; [b] in this cohort no child had > 12 bronchodilator prescriptions in any one year of their life.

Two further variables for children were created for acute asthma or wheeze using inpatient hospital admissions in the Patient Episode Database Wales data set from birth to KS1. Acute asthma was defined with ICD10 codes J45-46, and acute asthma or wheeze included an additional code R06.2 for wheezing. Where children did not have a previous diagnosis, the initial hospital admission was excluded from these variables to allow for the possibility that prescribed medication following this admission may control symptoms.

Respiratory illness was ascertained from GP diagnosis codes, by a member of my supervisory team (Professor David Fone) and categorised as follows: lower respiratory tract infection (LRTI) including bronchiolitis when bronchitis was also coded, upper respiratory tract infection (URTI), influenza or pneumonia, bronchiolitis, chronic upper respiratory disease, chronic lower respiratory disease, croup, unspecified respiratory illness (Appendix

Table A5.4). GP contacts between birth and KS1 were categorised by frequency, for example: 0, 1, 2 or more, to give a measure of burden of disease. For URTI, GP contacts were grouped into 0, 1-4, 5-6, 7+ as they were more common.

5.6 Potential confounders, covariates and effect modifiers

Birth characteristics available from WECC were used for sex, gestation at birth, small for gestational birth (<10th centile) adjusted for gestation and sex, parity, major or minor congenital anomaly, maternal age and breastfeeding recorded at birth or at 6-8 weeks. Further, birth characteristics of maternal cigarette smoking in the first trimester, academic season of birth (relating to school year - autumn, spring or summer term) and urban or rural dwelling at birth were included in analyses. The study used deprivation at birth categorised into quintiles using Townsend deprivation scores of small area of residence Lower Super Output Area (LSOA) from the 2001 census. Variables were created from school data sets for each child on school attended at KS1 assessment, school moves, year a child took KS1, percentage of absence from school (in the school year when KS1 was taken where assessment usually starts in the final 2 ½ months) and free school meals eligibility in the school year KS1 was taken (used as a proxy for deprivation level beyond birth).

5.7 Statistical analysis

A Directed Acyclic Graph (DAG) (45) was used to inform variable selection for the analyses (Figure 5.2). Models were adjusted for school factors (46) because of the known association with variability in educational attainment. School factors were not needed for bias reduction when modelling asthma and educational attainment but instead were included to increase the precision of confidence interval estimates. SEN provision at school for each child was excluded from models due to its potential partial causal pathway between asthma and educational attainment (possibly occurring due to disruption to daily activities and missed school days), to investigate the impact of asthma rather than asthma after the effects of SEN provision. Likelihood ratio tests were used to investigate two-way interactions between chronic asthma severity and acute asthma, between these asthma variables and respiratory infections, sex or deprivation. The analyses tested if absence from school was a mediator between asthma and educational attainment using the difference method.(47)

Stata version 13 was used to analyse the data, hypothesis tests were two-sided and statistical significance was set at $p<0.05$. The clinical significance that asthma may prevent a child attaining the expected level at KS1, may lead to reduced life chances in later education and employment, with little comparative cost to update pre-existing guidance for asthma for clinicians and educators. Multilevel logistic regression (QR decomposition) was used to obtain odds ratios for not attaining the expected level at KS1. For the possibility of unobserved shared factors leading to correlation of educational outcomes within schools, school-level random effects were used.

The Hosmer-Lemeshow goodness of model fit test was used in analyses.(48) This test compares the observed outcome against expected counts (calculated via the probability of outcome from the model results) to assess the adequacy of a fitted model usually with groups based on deciles. It is an alternative to the Pearson $\chi 2$ goodness-of-fit test that compares observed and expected responses from cells defined by covariate patterns and is used when the number of patterns is near the number of observations. The goodness-of-fit statistic is calculated using the Pearson chi-square statistic from the groups(g) × 2 contingency table of observed and expected outcomes and has good approximation to the chi-square distribution with $g-2$ degrees of freedom, therefore $\chi 2(g-2)$. Model fit can be compared between observed and expected frequencies within these groups and may indicate where a model is not performing satisfactorily. Missing data was imputed using multiple imputation by chained equations of all the variables in the model (49) (five imputations). An investigation of the variables with missing data as described in Section 3.3.2 supports the theory that the variables in the imputation model make the MAR assumption plausible and therefore although possible missing data is unlikely to be MNAR.

Modelling was repeated for children for asthma or wheeze exposure split by age group for pairs of current chronic severity and acute asthma variables to prevent possible effects of collinearity between different age groups.

A sensitivity analysis was performed by including only one randomly selected child from each mother, to mitigate the potential for spuriously small standard errors arising from correlation between outcomes for children born to the same mother.

5.8 Results

5.8.1 Descriptive statistics

There were 85,906 children born in Wales between 1998-2005 with 7 years follow-up (Figure 5.3). Baseline characteristics (Table 5.3) of children were similar to those of the general population of Wales (Appendix Table A2.2). The prevalence of current chronic asthma (using the asthma severity algorithm) in this cohort of children between birth and KS1 (age 6-7 years) was 12.5%, with 0.6% categorised as diagnosis only, 2.7% with intermittent bronchodilator, 7.3% persistent mild, 1.6% persistent moderate, 0.3% persistent severe, and 4.1% of children had acute asthma classified from inpatient hospital admission (Table 5.4). For the wider definition that included wheeze (wheeze severity algorithm) the prevalence was 21.4% for children in the cohort, with noticeably higher proportions in categories of diagnosis only, intermittent bronchodilator, persistent mild, and acute asthma or wheeze inpatient hospital admissions (Table 5.4). As expected for children with asthma, there were higher proportions in males, lower gestational age at birth, no breastfeeding, maternal smoking in the first trimester, higher deprivation, and urban compared to rural dwelling at birth (Table 5.3).

Table 5.3: Demographics of the study population

	Asthma severity algorithm				Acute asthma
	No asthma	**Diagnosis only or intermittent bronchodilator**	**Persistent mild[a]**	**Persistent moderate or severe**	**Inpatient hospital admission[b]**
N	75156	2839	6247	1664	3487
Sex=male(%)	37906 (50)	1624 (57)	3767 (60)	1026 (62)	2284 (66)
Gestation at birth[c]					
≤ 32	990 (1)	73 (3)	180 (3)	56 (3)	152 (4)
33-36	3974 (5)	173 (6)	390 (6)	131 (8)	245 (7)
37+ weeks	65870 (88)	2429 (86)	5339 (86)	1389 (84)	2913 (84)
Small for gestational birth	6474 (9)	272 (10)	578 (9)	141 (9)	337 (10)
Parity ≥ 1	43284 (58)	1564 (55)	3572 (57)	947 (57)	2079 (60)
Congenital anomaly[d]=Yes(%)	3516 (5)	187 (7)	373 (6)	115 (7)	273 (8)
Maternal age at childbirth					
<18 (%)	1956 (3)	119 (4)	163 (3)	37 (2)	125 (4)
18-24 (%)	18713 (25)	878 (31)	1857 (30)	502 (30)	1126 (32)
25-29 years (%)	21072 (28)	802 (28)	1776 (28)	470 (28)	947 (27)
30-34 (%)	21750 (29)	696 (25)	1622 (26)	434 (26)	868 (25)
35+ (%)	11627 (16)	343 (12)	826 (13)	219 (13)	420 (12)
Breastfeeding[e]					
No (%)	28242 (38)	1138 (40)	2602 (42)	716 (43)	1540 (44)
Yes (%)	31996 (43)	1054 (37)	2282 (37)	661 (40)	1318 (38)
NA (%)	14918 (20)	647 (23)	1363 (22)	287 (17)	629 (18)
Maternal smoking in first trimester					
No (%)	18493 (25)	622 (22)	1351 (22)	382 (23)	729 (21)
Yes (%)	5448 (7)	243 (9)	491 (8)	130 (8)	308 (9)
NA (%)	51215 (68)	1974 (70)	4405 (70)	1152 (69)	2450 (70)
Townsend deprivation quintile at birth					
1 - least (%)	13723 (18)	424 (15)	920 (15)	218 (13)	460 (13)
2 (%)	14745 (20)	466 (16)	1102 (18)	307 (18)	593 (17)
3 (%)	15171 (20)	561 (20)	1244 (20)	340 (20)	676 (19)
4 (%)	15414 (21)	609 (22)	1414 (23)	390 (23)	824 (24)
5 - most (%)	15884 (21)	768 (27)	1547 (25)	403 (24)	921 (26)
Free school meals eligible[g]=yes(%)	12299 (16)	643 (23)	1270 (20)	338 (20)	796 (23)
School absence percentage[fg]					
<5 (%)	19867 (48)	608 (41)	1254 (39)	297 (31)	624 (33)
5-9 (%)	12776 (31)	476 (32)	1162 (36)	332 (35)	679 (36)
10-14 (%)	4473 (11)	196 (13)	462 (14)	174 (18)	300 (16)
15-19 (%)	1533 (4)	75 (5)	141 (4)	70 (7)	117 (6)
20+ (%)	922 (2)	60 (4)	111 (3)	44 (5)	92 (5)
NA (%)	1479 (4)	73 (5)	117 (4)	38 (4)	83 (4)

[a] Inhaled corticosteroid or alternative. [b] for asthma or wheeze; [c] 6% missing data evenly found across asthma groups; [d] major or minor; [e] at birth or 6-8 weeks; [f] in year preceding Key Stage 1 assessment proxy start date 1st May; [g] sub-sample due to availability of school absence data, births between Sept 2000-Aug 2004 N=46470.

Table 5.4: Asthma severity algorithms and acute asthma

	Asthma severity algorithm[a] n (%)	Acute asthma (hospital inpatient admission)[c]	Wheeze severity algorithm[b] n (%)	Acute asthma or wheeze (hospital inpatient admission)[c]
N	85906	3487 (4.1)	85906	4668 (5.4)
None	75156 (87.5)	0 (0)	67508 (78.6)	0 (0)
Diagnosis only	532 (0.6)	169 (32)	2237 (2.6)	683 (30.5)
Intermittent Bronchodilator	2307 (2.7)	474 (21)	6465 (7.5)	938 (14.5)
Persistent mild	6247 (7.3)	1978 (32)	7964 (9.3)	2164 (27.2)
Persistent moderate	1365 (1.6)	661 (48)	1407 (1.6)	673 (47.8)
Persistent severe	299 (0.3)	205 (69)	325 (0.4)	210 (64.6)

[a] developed with an asthma diagnosis
[b] developed with either a wheeze or asthma diagnosis
[c] excludes first admission if before first GP visit

Over 20% of children in each asthma severity category had an asthma inpatient hospital admission, with 69% of children in the persistent severe category with an admission; patterns were relatively similar for asthma or wheeze severity (Table 5.4). Multiple GP contacts for a child were found for respiratory infections, 11% of children had seven or more GP contacts for URTI, and 8% had three or more GP contacts for LRTI.

Children with higher asthma severity had more GP contacts for LRTI, 17% of children with intermittent bronchodilator and 50% with persistent severe asthma had three or more GP contacts for LRTI, compared to 6% for those without a diagnosis of asthma (Table 5.5). Similarly, the URTI GP contacts were higher for children with more severe asthma. The proportion of children with 7+ GP contacts for URTI was 17% for those with intermittent bronchodilator asthma and 32% for those with persistent severe asthma, compared to 10% in children without an asthma diagnosis. Similar proportions of children were found across the categories for the broader wheeze severity algorithm (data not shown). Of the 8% of children with three or more LRTI GP contacts, 31% also had seven or more URTI GP contacts, and greater numbers were found in the most deprived quintile and those eligible for free school meals (data not shown).

Table 5.5: Respiratory illness between birth and before Key Stage 1 assessment by asthma severity

	Asthma severity algorithm						Acute asthma
	No asthma	**Diagnosis only**	**Intermittent bronchodilator**	**Persistent mild[a]**	**Persistent moderate**	**Persistent severe**	**Inpatient hospital admission[b]**
N	75156	532	2307	6247	1365	299	3487
LRTI GP contacts[d]							
0 (%)	52170 (69)	346 (65)	1071 (46)	2515 (40)	445 (33)	71 (24)	1196 (34)
1 (%)	13361 (18)	94 (18)	520 (23)	1443 (23)	291 (21)	50 (17)	765 (22)
2 (%)	5336 (7)	48 (9)	319 (14)	863 (14)	207 (15)	30 (10)	511 (15)
3+ (%)	4289 (6)	44 (8)	397 (17)	1426 (23)	422 (31)	148 (50)	1015 (29)
URTI GP contacts							
0 (%)	20266 (27)	204 (38)	427 (19)	1022 (16)	169 (12)	25 (8)	598 (17)
1-4 (%)	39817 (53)	243 (46)	1195 (52)	3167 (51)	614 (45)	126 (42)	1663 (48)
5-6 (%)	7190 (10)	39 (7)	301 (13)	855 (14)	204 (15)	52 (17)	472 (14)
7+ (%)	7683 (10)	46 (9)	384 (17)	1203 (19)	378 (28)	96 (32)	754 (22)
GP contacts							
Influenza and pneumonia 1+ (%)	2067 (3)	20 (4)	82 (4)	304 (5)	113 (8)	16 (5)	242 (7)
Bronchiolitis 1+ (%)	3063 (4)	30 (6)	221 (10)	662 (11)	189 (14)	54 (18)	538 (15)
Chronic lower Respiratory disease 1+ (%)	465 (1)	6 (1)	28 (1)	96 (2)	32 (2)	6 (2)	89 (3)
Unspecified respiratory illness 1+ (%)	392 (1)	<5 (0)	24 (1)	39 (1)	15(1)	<5 (1-2)	20 (1)
Chronic upper respiratory disease GP contacts							
0 (%)	69704 (93)	490 (92)	2006 (87)	5250 (84)	1050 (77)	244 (82)	2907 (83)
1 (%)	4192 (6)	31 (6)	207 (9)	699 (11)	203 (15)	40 (13)	418 (12)
2+ (%)	1260 (2)	11 (2)	94 (4)	298 (5)	112 (8)	15 (5)	162 (5)
Croup GP contacts[e]							
0 (%)	69722 (93)	500 (94)	2077 (90)	5543 (89)	1146 (84)	239 (80)	3091 (89)
1+ (%)	5434 (7)	32 (6)	230 (10)	704 (11)	219 (16)	60 (20)	396 (11)

[a] Inhaled corticosteroid or alternative. [b] for asthma or wheeze; [c] excludes first admission if before first GP visit; [d] includes bronchiolitis if coded with bronchitis; [e] original categories 0, 1, 2+ changed due to small numbers concerning anonymity rules.

5.8.2 Statistical modelling results

Within the cohort, 14,935(17%) children did not attain the expected level at KS1 (Table 5.6), the average age at assessment was 7 years 1 month (SD 3.5 months). Unadjusted analysis showed children had increased risk for all categories in the asthma severity algorithm for not attaining the expected level at KS1; the highest risk was for diagnosis only (OR 1.58 (95% CI 1.29-1.95)) with similar size odds ratios for persistent severe, and acute

asthma from inpatient hospital admission. Over time there were increased numbers of children who became diagnosed with persistent mild or persistent moderate asthma (Appendix Figure A5.2).

Following adjustment for social deprivation, birth, and school characteristics, only asthma inpatient hospital admission remained associated with increased risk for children not attaining the expected level at KS1 (aOR 1.14 (95% CI 1.02-1.27)). Presenting to primary care for respiratory tract infections (RTIs) was also independently associated with increased risk for children not attaining the expected level at KS1, aOR 1.15 (95% CI 1.06-1.24) for three or more presentations for LRTI, and aOR 1.08 (95% CI 1.01-1.16) for seven or more URTI GP contacts (Table 5.6).

Table 5.6 – Multilevel multivariable models of asthma severity algorithm, respiratory illness and not attaining the expected level at Key Stage 1 (at 6-7 years).

	Not attained / Total (%)	Unadjusted OR (95% CI)	Asthma severity algorithm Multivariable[a] OR (95% CI)	Wheeze severity algorithm Multivariable[a] OR (95% CI)
N	14935 / 85906			
Asthma severity algorithm				
None (ref)	12733 / 75156	1.00	1.00	NA
Diagnosis only	134 / 532 (25)	1.58 (1.29-1.95)	1.21 (0.97-1.52)	NA
Intermittent bronchodilator	444 / 2307 (19)	1.11 (1.00-1.24)	0.90 (0.79-1.01)	NA
Persistent Mild	1260 / 6247 (20)	1.21 (1.13-1.30)	0.97 (0.89-1.05)	NA
Persistent moderate	298 / 1365 (22)	1.36 (1.18-1.55)	1.06 (0.91-1.24)	NA
Persistent severe	66 / 299 (22)	1.45 (1.09-1.93)	1.02 (0.75-1.40)	NA
Hospital inpatient admission (acute asthma)[b]=yes(%)	837 / 3487 (24)	1.48 (1.36-1.61)	1.14 (1.02-1.27)	NA
Wheeze severity algorithm				
None (ref)	11252 / 67508	1.00	NA	1.00
Diagnosis only	451 / 2237 (20)	1.24 (1.11-1.39)	NA	1.05 (0.94-1.19)
Intermittent bronchodilator	1271 / 6465 (20)	1.20 (1.12-1.28)	NA	1.01 (0.94-1.08)
Persistent mild	1582 / 7964 (20)	1.22 (1.14-1.29)	NA	0.97 (0.90-1.04)
Persistent moderate	306 / 1407 (22)	1.37 (1.20-1.57)	NA	1.06 (0.91-1.23)
Persistent severe	73 / 325 (23)	1.53 (1.16-2.00)	NA	1.08 (0.80-1.45)
Hospital inpatient admission (acute asthma or wheeze)[b]=yes(%)	1112 / 4668 (24)	1.48 (1.37-1.59)	NA	1.14 (1.04-1.25)
LRTI[c] GP contacts[d] (ref=None)				
1	2729 / 15759 (17)	1.05 (1.00-1.10)	1.01 (0.96-1.07)	1.01 (0.96-1.06)
2	1260 / 6803 (18)	1.14 (1.07-1.22)	1.05 (0.97-1.13)	1.04 (0.97-1.12)
3+	1421 / 6726 (21)	1.33 (1.25-1.43)	1.15 (1.06-1.24)	1.14 (1.06-1.23)
URTI[e] GP contacts (ref=None)				
1-4	7727 / 45162 (17)	0.98 (0.93-1.02)	1.00 (0.95-1.05)	1.00 (0.95-1.05)
5-6	1483 / 8641 (17)	1.00 (0.93-1.07)	1.01 (0.94-1.09)	1.01 (0.94-1.09)
7+	1842 / 9790 (19)	1.10 (1.03-1.17)	1.08 (1.01-1.16)	1.08 (1.00-1.16)
GP contacts				
Influenza and pneumonia 1+ (ref=None)	436 / 2602 (17)	0.96 (0.86-1.07)	NA	NA
Bronchiolitis 1+ (ref=None)	884 / 4219 (21)	1.26 (1.16-1.36)	1.01 (0.93-1.10)	1.00 (0.92-1.09)
Chronic lower respiratory disease 1+ (ref=None)	156 / 633 (25)	1.39 (1.15-1.69)	1.18 (0.96-1.45)	1.18 (0.96-1.45)
Unspecified respiratory illness 1+ (ref=None)	69 / 475 (15)	0.75 (0.57-0.98)	NA	NA
Chronic upper respiratory disease GP contacts (ref=None)				
1	914 / 5372 (17)	0.98 (0.91-1.06)	NA	NA
2+	308 / 1790 (17)	1.02 (0.90-1.16)	NA	NA
Croup GP contacts (ref=None)				
1	884 / 5247 (17)	0.98 (0.91-1.06)	NA	NA
2+	264 / 1432 (18)	1.14 (0.99-1.31)	NA	NA
Townsend deprivation quintile				
1 - least (ref)	1517 / 15285 (10)	1.00	1.00	1.00
2	2271 / 16620 (14)	1.27 (1.18-1.37)	1.16 (1.07-1.25)	1.16 (1.07-1.25)
3	2944 / 17316 (17)	1.53 (1.42-1.65)	1.28 (1.18-1.38)	1.28 (1.18-1.38)
4	3494 / 17827 (20)	1.84 (1.71-1.98)	1.42 (1.32-1.54)	1.42 (1.32-1.54)
5 – most	4668 / 18602 (25)	2.32 (2.16-2.49)	1.54 (1.42-1.67)	1.54 (1.42-1.67)

[a] adjusted for all variables in the table significant at the 5% level in unadjusted analyses, sex, gestation at birth, small for gestational age (<10th centile), parity, congenital anomalies, maternal age, breastfeeding, maternal smoking first trimester, free school meals eligible in year preceding Key Stage 1 assessment proxy start date 1st May (to approximate deprivation beyond birth), academic season of birth, school moves from start school to KS1 (1+), urban or rural dwelling at birth, year take Key Stage 1 (ref 2010); [b] excludes first admission if before first GP visit; [c] Lower respiratory tract infection; [d] includes bronchiolitis if coded with bronchitis; [e] Upper respiratory tract infection.

There was no evidence for interactions between the asthma severity algorithm GP categories or asthma inpatient hospital admissions at the 5% level of significance for children not attaining the expected level at KS1. Nor was there evidence of interaction between the asthma severity variables and other respiratory illness including LRTI and URTI, sex of the child or deprivation for children not attaining the expected level at KS1. Children's increased risk in unadjusted odds ratios in the asthma severity algorithm categories, fell to a third of its size when inpatient hospital admission was added to the model, and then became non-significant at the 5% level when a measure of deprivation, gender or LRTI was added to the model. Model goodness of fit tests found interactions between confounders were only adjustments to main effects (in opposing directions if significant at $p<0.05$ with no monotonic pattern) and therefore were not included in the final model interpretation (data not shown).

Very similar results were found for the wheeze severity algorithm and children's non-attainment of the expected level at KS1 (Table 5.6).

Further analyses using asthma variables divided by age of the child found no evidence of an association for current chronic asthma severity, but higher odds for not attaining the expected level at KS1 for three or more inpatient hospital admissions aOR 1.5 (95% CI 1.0-2.0) when children were age 2 - < 5 years, with similar results when children were age 0 -< 2 years, and 5- < 7 years. For wheeze or asthma, only 3 or more inpatient hospital admissions had an increased association for children not attaining the expected level at KS1 for children from age 2 years onwards (Appendix Table A5.6).

A sub-sample analysis of children born between 1st September 2000 to 31st August 2004 (where school absence data was available) showed after adjustment for school absence asthma inpatient hospital admissions were no longer associated with risk for not attaining the expected level at KS1 (aOR 1.05 (95% CI 0.90-1.24)), but LRTI remained an independent predictor (aOR 1.13 (95% CI 1.02-1.26)) (Appendix Table A5.7). Similar results were found for children for not attaining the expected level at KS1 for acute asthma or wheeze when absence from school was added to the model.

Models with only one child per mother in the cohort showed no substantial difference to the main results, indicating that there was no problematic underestimation of variances arising through correlation between children of the same mothers.

It was found that a small correction was required to the published article related to this chapter. There were 805 children excluded from the cohort that moved out of Wales or died between age 6-15 years after the outcome of interest (KS1) that should have been included in the cohort. This was less than a 1% addition to the 85,906 children in the original cohort; 779 children who moved out of Wales, 26 who died. A sensitivity analysis was performed to ascertain if there was a difference to the interpretation of findings described in this section, Section 5.8. No interpretable difference was found between the two cohorts as described in detail in Appendix A5.8 (Appendix Tables A5.8a-h, Appendix Figure A5.8).

5.9 Discussion

The results from this WECC cohort analysis show that an inpatient hospital admission for asthma was associated with an increased risk for children not attaining the expected level at KS1 at age 6-7 years after controlling for current asthma severity, deprivation, birth characteristics, other respiratory illness and school characteristics. Very similar results were obtained for children using a broader definition of asthma which included wheeze. For multiple admissions to hospital for asthma a dose-response association was found with poorer educational attainment, but the association only increased after age 2 years for children with asthma or wheeze. Presentations to primary care for respiratory infections, particularly LRTI, were independently associated with children not attaining the expected level at KS1, even after adjustment for school absence. No interaction was found for children between asthma and LRTI, or asthma and URTI for educational attainment outcome. School absence in the year a child takes KS1 assessment was found to be a potential mediator in the association between asthma hospital admissions and children not attaining the expected level at KS1.

This is the first study that explores the association of asthma and common respiratory ailments on educational attainment in childhood. The findings suggest that inpatient hospital admissions for asthma and recurring respiratory illness from birth to KS1 can have long-term effects on a child through their educational attainment.

The use of a second algorithm that included wheeze allowed the study to investigate potentially underreported asthma, particularly relevant to children under 5 years.(50) It highlights that being treated for only wheeze through hospital admission was associated with increased risk for children not attaining the expected level at KS1.

In previous research, GP data and parental surveys recording GP diagnosis of asthma (5,6,7) in the UK, USA and Australia, show similar results for this age group of children, which reassures the validity and classification of asthma in this analyses. For children with wheeze or asthma diagnosis, the measure of UK prevalence in this analysis matches a global survey,(9) but is slightly lower than other UK surveys,(8,23) most likely due to differences in cohort demographics.

In previous cohorts or surveys in population representative studies adjusted for confounding from deprivation (or proxy such as maternal education), a detrimental association of current asthma (defined as with a prescription) at age 6 years was found for reading (aOR 2.20 (95% CI 1.08-4.51))(17) (measured as ≥ 6 months behind), but with no evidence of a difference in mathematics in New Zealand. In the US asthma defined as requiring attention or treatment in the last year and limiting a child's activity found children less likely to be school ready, but no difference in language skills.(32) Another study found no significant difference ($p>0.05$) for children age 5-7 years in parental reporting for repeating a school year.(31) None of these studies separated chronic asthma severity and acute asthma or adjusted for the full range of respiratory illness, school or birth characteristics (the latter study only adjusting for birth weight).

Other cohorts that adjusted for deprivation used wider age bands (children 5 to 16 years) found no evidence of an association (16,25) with asthma, possibly due to adjustment for SEN provision,(25) or concluded lower marks were explained by higher days absent.(26) A Canadian study found severe asthma (defined as using asthma medication) was associated with poorer mathematics scores in children but not in reading.(27) None of these studies adjusted for birth characteristics or other respiratory illnesses and the smaller adjusted risks in the analyses of this project demonstrate the importance of controlling for confounding. At key developmental ages younger children may have greater risk of hospital admission for asthma or wheeze as they experience potentially more associated RTIs at younger ages,(51) and may be less able to communicate symptoms or manage their condition.

Studies measuring absence from school in addition to educational attainment(16,17,26,27) or as an outcome (34) mostly reported two more days absence in a year compared to those without asthma and this is unlikely to impact on educational outcomes. However, higher absence from asthma was found in younger children.(23) When more severe asthma was measured using reliever prescriptions or ED visits, children had seven or more days

absence from school in a year,(27,34) and this agrees with the higher proportions of absence found across the categories for asthma compared to having no asthma (Table 5.3). The average length of stay for an asthma emergency inpatient admission is reported to be 1-1.5 days for 0-24 year olds with 10% having a readmission within 30 days.(52) This may indicate children with asthma admissions have multiple admissions per year or that recuperation continues to occur post-discharge before a child returns to school. Other research provides evidence that the BTS/SIGN Guidelines may not be followed by all primary and secondary care clinicians or patients with asthma.(53) Closer adherence to these guidelines and patient education could improve control of children's asthma symptoms. The main areas where improvements to more closely match guidelines are that each patient should have a written asthma action (management) plan, yearly reviews and a follow up visit with the GP within two days after a hospital admission for asthma.(53)

Consistent with other studies,(25,54) this study found higher prevalence of asthma in children living in more deprived areas, possibly due to poorer housing conditions,(54) environmental factors or less healthy diets (9) that could also lead to more RTIs.

There were several strengths in the analyses of this study. This study used a clinical diagnosis in the asthma or wheeze algorithms: this means records of medications that sometimes have other uses, a bronchodilator medication trial over 6 weeks, or reversibility test at the clinician appointment are most likely excluded. General Practitioners indicated that symptoms used to classify severity of asthma or wheeze may not be fully recorded during GP consultations but inform prescribing, and this was echoed in one study in the review.(25) This study used prescriptions as well as diagnosis and therefore any selection or ascertainment bias should be minimised.

The use of routine data from clinical practitioners on diagnoses and prescriptions rather than parental reports, removes the potential impact of recall bias.

There were several limitations to this study's analyses. It may be that hospital admission policies differ across Wales, although testing models with LEAs (the same geographical areas as health boards before 2009) shows little correlation and minimal selection bias. Some families contact their GP more often than others; but any additional visits to the GP would bias risk for not attaining the expected level at KS1 towards the null (more visits would be required to show a significant association). Children in more deprived areas may be less compliant to asthma management plans. There was no interaction found between

chronic asthma severity or acute asthma and measures of deprivation for educational attainment, residual confounding may remain, but would only highlight barriers to health still exist.

This study does not include Accident and Emergency admissions data, and may underestimate the number of attendances for acute asthma exacerbations; an audit showed 86% of exacerbations were treated in General Practice in 1991.(55)

This study only investigated period prevalence, prevalence within the first seven years of life. A recent paper investigating worsening asthma in the previous year found an association with poorer educational attainment.(29)

Asthma in children under 8 years has been added to the quality outcomes framework in more recent years (excluded until at least 2011 in England), a voluntary monitoring scheme within the General Medical Services contract for General Practitioners (56) introduced in 2004. General practices record indicators about the management of chronic conditions, patient experience, the practice's organisation and specific services, and are awarded points for the number of indicators they meet to receive funding. This may mean that recording of asthma in children under age 8 years may increase in the years after the data extraction from SAIL used in this study due to improved recording practises. This study included both asthma and wheeze and was externally validated to other research for asthma, but any underreporting of asthma may change the prevalence of this study's results. However, the effect of an increased risk from asthma or wheeze on poorer educational attainment would only bias results towards the null from underreporting of the symptoms in GP administrative data.

This study uses a large population-based representative cohort with asthma or wheeze severity algorithms akin to asthma management guidelines found in the USA and UK. The study's data extraction from SAIL only contained 40% of GP practices in Wales but selection bias is thought to be low and the sample representative of the Welsh population as discussed in Section 2.2.3 (Appendix Table A2.2). Only 5% of children move out of Wales each year so most children can be followed in this cohort design. The results should be generalisable in the UK and other countries with similar socio-demographic and health systems.

5.10 Implications for this thesis

Clinicians and educators need to be aware that children who have inpatient hospital admissions for asthma or wheeze, or repeated LRTI GP visits, may need additional educational support for their educational outcomes. For children with asthma, the association between LRTI and not attaining the expected level at KS1 was not above that expected for children without asthma, but more children with asthma had multiple GP visits for LRTI (indicating accumulating risk).

This thesis so far has shown that unplanned hospital admissions are associated with poorer educational outcomes for children at age 6-7 years, and that admission to hospital for acute asthma exacerbations lead to poorer educational attainment rather than the level of asthma severity. From the literature review there is some evidence that home environment, stress and deprivation are confounders for childhood health on children's educational attainment, and the next chapter of this thesis looks at quantifying possible causes of childhood stress in the household. I then investigate whether these measures of adversity in childhood, described elsewhere as adverse childhood experiences impact on educational attainment and whether those children experience higher levels of special educational needs provision.

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Chapter 6 : Adverse childhood experiences and educational attainment in childhood

6. Overview

In Chapters 4 and 5 of this thesis I provided evidence that emergency hospital admissions for any cause and in particular for injury or external causes, first admission during infancy and length of stay of pre-school admissions increased the risk for not attaining the expected level at Key Stage 1 (KS1). In addition, hospital admission for acute exacerbation of asthma (a chronic condition) rather than asthma severity was associated with increased risk for not attaining KS1. The literature reviewed in the chapters also suggested academic achievement during childhood was influenced by a complex interplay between a range of biological, social and environmental factors including the home environment.

In this chapter, I investigate the potential influence of adversity experienced in the home on children's educational attainment. First, I describe the prevalence of adverse childhood experiences (ACEs) in the household easily identifiable by mainstream healthcare services and educationalists. I describe the theory of ACEs creating long-term stress reactions that influence brain development and lead to poorer educational attainment. I review the literature and identify the need to also investigate Special Educational Needs (SEN) provision. I design and implement a cohort analysis using administrative data to examine whether there is a potential causal association between ACEs and poorer educational attainment at age 7 and 11 years or if there is an increased likelihood of SEN provision at these ages. I present the magnitude of association of each ACE from statistical modelling of educational performance accounting for all ACEs measured, area-level deprivation, school factors, household composition and perinatal health indicators and discuss the implications of all the available evidence. The insights gained from this work will help to inform health, education and social care workers on whether there is immediacy in the impact of multiple ACEs on childhood educational attainment, known to be associated with poorer adult outcomes including economic participation.

6.1 Background

In society it is important to better understand the reasons for children not achieving their potential in education, as even small differences in educational attainment can have long term implications. In childhood social, environmental and biological factors interact to influence academic achievement. Children's lives may be characterised by the presence of chronic stressors from primary carers, such as mental disorders or alcohol related problems, or experience a death in their household, where long-term or acute stress could impact their development. Children who are exposed to these potential ACEs during childhood may grow up to have poorer health and economic outcomes in adulthood. (1,2)

The conceptual framework for the effects of ACEs throughout the life course is described using the ACE Pyramid in Figure 1.3. The theoretical context of the ACEs theory originates from a study by Felitti et al who investigated not only the association between child abuse and adult health-risk behaviours and disease, but also the co-occurring effects of household dysfunction in childhood. They suggested children who were exposed to multiple ACEs had mal-adaptive coping mechanisms that led to poorer adult health and social outcomes.(3) This theory has been developed into the ACEs pyramid, where ACEs are thought to affect children through chronic or acute stress reactions from these exposures that may affect their health and brain development.(4) These children who may have social, emotional or cognitive impairment related to exposure to ACEs may not adjust adequately to situations and use health-risk behaviours such as cigarette smoking to cope. These health-risk behaviours may subsequently lead to poorer adult outcomes. Previous research in adults show ACEs were associated with poorer adult health, and also leaving school without qualifications and unemployment.(1,2). Further insight may be gained in understanding the medical / Public Health investigations of the original ACEs study (3) by looking at theories from sociology and psychology. Bronfenbrenner's ecological systems theory about child development considers multiple levels of a child's surrounding environment to create a complex system of relationships from family, school, and broader cultural values, laws and customs.(5,6,7)

Children may also have positive experiences that may mitigate the effects of ACEs such as school engagement or one good quality parent-child relationship. With the availability of population-based linked anonymised administrative data from healthcare and education settings, children who experience adversity can be identified to investigate whether ACEs negatively affect their educational outcomes. Routine health and education services could

then easily identify these children and future households with ACEs and implement interventions for children.

Mental disorders and alcohol misuse are common in families. Although severe mental illnesses such as schizophrenia and bipolar disorder affect only 1–2% of adults in the UK (8,9) common mental disorders (CMD), including depression, anxiety, panic, and somatisation, can affect 16% of adults.(10) Alcohol misuse is also prevalent, affecting 9% of adults and a significant proportion also have co-occurring mental disorders.(11) In previous research it is estimated that 30% of infants lived with an adult with CMD and this rose to 48% of children by age 8 years.(12) Adult binge drinking in the household has been reported in up to 30% of children.(13)

Experience during childhood of chronic or acute stress has been shown to increase the risk of unplanned hospital admissions during childhood,(12) lead to poorer mental and physical health in adulthood (increased risk of cancer and cardiovascular disease),(3) as well as negative social outcomes (e.g. leaving school without qualifications, unemployment and incarceration).(2) The impact of these adverse experiences on education outcomes in school age children is unclear. Previous research mainly looks at individual ACEs rather than multiple ACEs and few studies report the magnitude of each ACE that may differ considerably in their effect on educational outcomes (e.g. CMD in the household compared to a maltreatment hospital admission). Other studies do not adjust models for potentially important confounders like household composition or school level effects.(14)

ACEs are thought to elevate glucocorticoid hormones (cortisol), with chronic stress impeding the regulation of stress physiology. Exposure to maternal depression has been shown to relate to higher levels of salivary cortisol in children, which could be a mediator in the pathway between chronic stress and lower executive functioning (e.g. working memory).(15) Differences in brain activity and hippocampal volume have been observed according to whether or not children have experienced maltreatment or neglect, but the reasons for this are unclear.(16,17) The pre-frontal cortex and executive functions of the brain are known to be sensitive to stress.(18) Therefore it is hypothesised that exposure to ACEs impact negatively on educational attainment during childhood, and contribute to the observed inequalities in education outcomes in children.

For children with a caregiver with schizophrenia the relationship between this ACE and their educational attainment may be more complicated. The exact cause of schizophrenia is

unknown but diagnosis in childhood or adolescence is characterised by an initial stable feature of impaired development or early deficits in cognitive function, and for some there may be a genetic link.(19) Although this genetic link may act as a confounder between a child's exposure to a household member with schizophrenia and their educational attainment this relationship remains unclear.

Previous research in children who were maltreated showed physiological differences in magnetic resonance imaging (MRI) scans of the brain at different ages of the child, the researchers suggest that stress during key developmental stages of the brain, during sensitive periods across childhood may mean opportunities for learning could be missed. (17) In Wales there are teacher-based assessments at age 7 and 11 years in childhood and it may be important to investigate the effects of ACEs at both Key Stages. Children followed to age 11 years may be exposed for a greater length of time to ACEs, or that ACEs such as maternal depression may mean support for homework is suboptimal when the child reaches later childhood.(20) It is therefore important to investigate whether there is an association between ACEs and not attaining the expected level at the Key Stages in childhood, and also when in the child's life is it most strongly associated, so that this may help to answer the question of when it is most beneficial to intervene.

6.2 Literature review

For the research question 'what is the prevalence of adverse childhood experiences among children in Wales and are they associated with not attaining the expected level of education during childhood?', a review was undertaken of the existing published literature. The objective was to assess the effects of adverse childhood experiences from birth, particularly those measurable by health services, on educational attainment at age 6-7 years (KS1) and at age 10-11 years (Key Stage 2, KS2). This section of the chapter summarises the evidence of previous research and highlights gaps in the evidence to give context to the findings and discussion in this chapter.

6.2.1 Methods

Criteria for considering studies for this review

Studies were eligible for inclusion if they were original research with designs that were cohorts or cross-sectional studies. Case-control studies were excluded because prevalence of ACEs could not be ascertained within the population of interest and outcomes were not

considered to be rare events. Although cross-sectional surveys may suffer from reverse causality, they are useful to Public Health practitioners in estimating the prevalence of different risk factors in the population so that they can tailor interventions accordingly.

Participants of most interest were those up to the age of 11 years, their childhood years. Participants included in the search strategy were children up to age 11 years, or wider age ranges of children that included children age 5 to 11 years when KS1 and KS2 are taught (KS1 from 5 to 7 years, KS2 from 8 to 11 years), or else children to age 16 years.

The exposure was any report of ACEs that could be observed (noticed or perceived) by mainstream healthcare services, educators or in population demographics. The exposures considered were household experiences of serious mental illness, common mental disorder, alcohol or financial problems (including low family income / eligible for free school meals), death of a household member or childhood maltreatment. This review is limited to previous research that considers multiple ACEs, measured individually in the study design, because ACEs frequently co-occur and a dose-response effect was found in adults for leaving secondary school with no qualifications.(2)

The ACEs considered are the most commonly listed in the published literature on adult outcomes.(1) Other ACEs were excluded from the literature review such as childhood bullying as they are not systematically recorded by schools or elsewhere. ACEs such as household criminality, parental separation or domestic violence are not routinely captured by healthcare professionals caring for children and were excluded from the review. Domestic violence is asked about during antenatal care and may be captured in court proceedings but is not currently data linked to other health and education data sets. ACEs such as domestic violence lead to inherent problems for researchers when interviewing children under 18 years in the general population as disclosures from minors need to be reported to social services. Household criminality or parental separation are potentially recorded elsewhere (prison and court databases) but may be beneficial to children because they could lead to the absence of a perpetrator. Outcomes were educational attainment at school and pre-school tests measuring cognition that were considered equivalent to tests in education.

Articles were selected for inclusion in the review if they reported a comparison to a non-exposed group and had risk estimates (odds ratios (ORs), relative risks (RRs)) or mean differences and confidence intervals (CI), p-values, or proportions between exposures and

outcomes. Studies that reported results from analyses using correlations or where latent constructs were created for multiple ACEs (to give a measure of for example 'parenting') were not included in the review because differences for individual ACE exposures on childhood educational outcomes were not quantified.(21)

Search methods for identification of studies

A search was conducted of electronic databases from their conception to July 2019 in Ovid Medline from 1946, EMBASE from 1947, Health Management Information Consortium (HMIC) from 1979, Web of Science combined database that started from 1970-1990, PsyINFO from 1806, Global Health from 1973, Social Policy and Practice from 1981 for peer reviewed systematic reviews, journal articles and grey literature (working papers). Relevant original studies were identified from review articles. The snowballing technique was used to identify further studies by reviewing reference lists of relevant studies and their citations. In addition, a search was undertaken on Google and Google Scholar using the main term for exposure and outcomes as relevant articles could be part of several silos of research. Table 6.1 shows the search strategy. The main search considered the types of study, participants, exposures and educational outcomes. Terms for financial problems, low family income and free school meal were included as an exposure in the search for articles. Review of the initial literature suggested there were different opinions on whether poverty could be an ACE but it is included in the search terms and is discussed later in the chapter. Measures describing the composition of the household e.g. single parent household were included individually with ACE exposures removed, to identify any further papers of interest.

Table 6.1: Literature search word diagram on child health and educational outcomes*

Types of study	Participants	Exposure	Outcomes	Characteristics (Household composition)
Cohort study	Children	Adverse childhood experiences	Educational attainment	Teenage mother
Cohort studies	Childhood	Maltreatment	Education attainment	Single parent
Longitudinal study		Victimisation	Education status	Sibling guardian
Longitudinal		Victimization	Education achievement	
		Psychosis	Academic performance	
		Serious mental illness	Academic achievement	
		Schizophrenia	School achievement	
		Bipolar	Cognitive development	
		Manic depression	Grades	
		Family mental health	Absenteeism	
		Parental mental health	Repeated school year	
		Adult mental health	Repeat a school year	
		Parental drinking	Repeated a school year	
		Family drinking	Grade retention	
		Adult drinking	School drop out	
		Household death	Key Stage 1	
		Death in household	Key Stage 2	
		Parental death		
		Death of a child		
		Sibling death		
		Family financial problems		
		Low family income		
		Free school meal		

*words were combined in each column with a bitwise OR operation and columns in the double line box were combined with a bitwise AND operation.

Data collection and analysis

The same methods for study selection, data extraction and management were applied as described in Chapters 4 and 5. The methodological quality of studies was assessed using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (22) and an adapted version for Cross-sectional studies.(23) The characteristics of included studies table was restricted to exposure to multiple ACEs and outcomes of educational attainment and pre-school tests measuring cognition that were considered equivalent to tests in education as stated in the criteria of the review.

6.2.2 Results

The literature search found 3437 articles. Nine articles were specifically related to ACEs and educational outcomes and eligible for inclusion. Figure 6.1 presents a flow diagram of the search and study selection process. Searching references and citations, and a Google search of the main search terms added relatively few articles to those identified from the main database search.

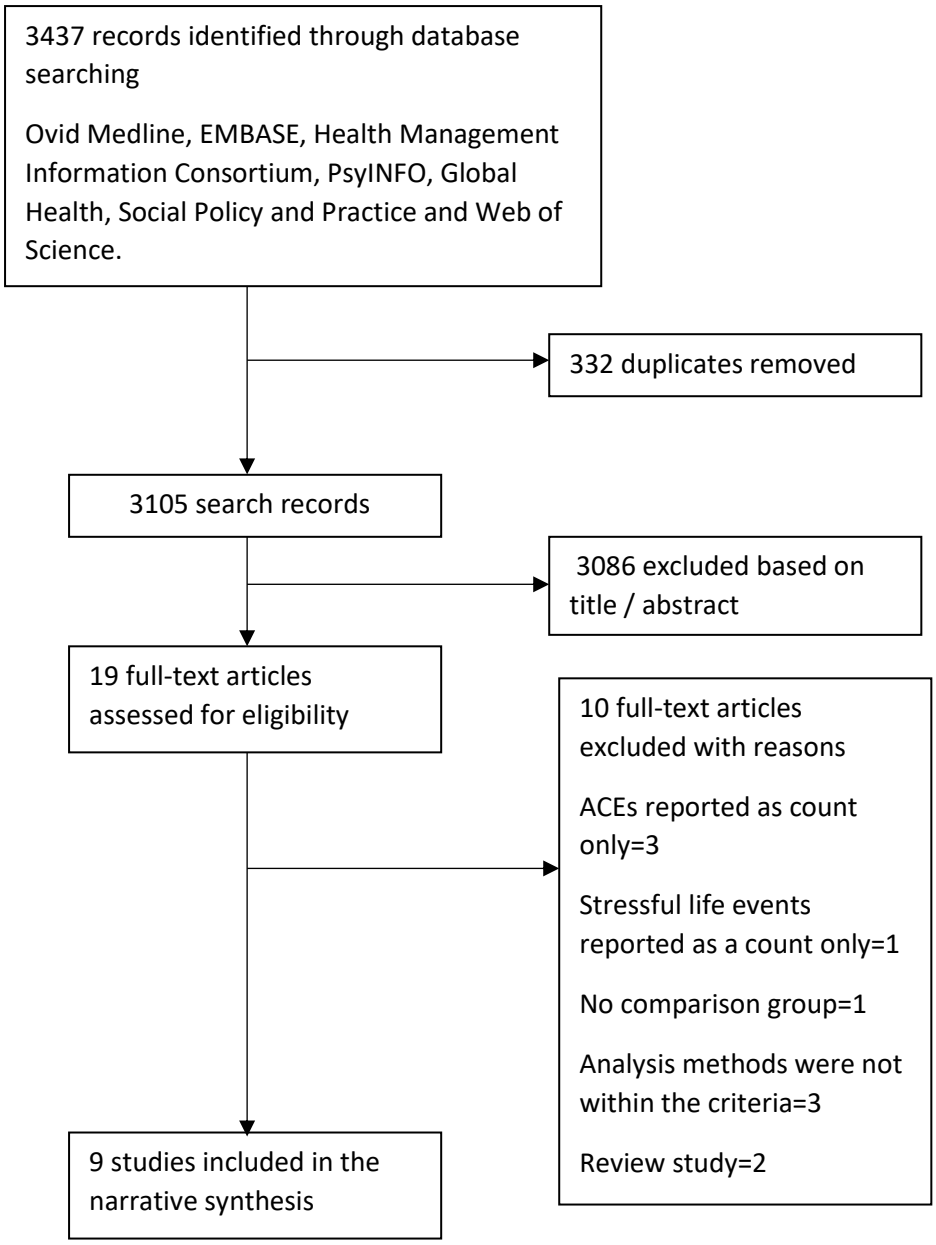

Figure 6.1: Flow diagram of the search and study selection process.

Characteristics of included studies

The search of the published literature found two reviews (24,25) and any relevant articles were included if they met the inclusion criteria of this review. Table 6.2 shows the nine primary articles in the published literature that looked at the association between multiple ACEs (where they were reported individually) and educational attainment.

Eight studies were cohorts, six considered of good quality (14,27,28,29,30,31) and two cohorts considered of poor quality (26,32) due to high attrition rates. Two studies included

children if they had at least two waves per child.(31,32) One very large cross-sectional study provided prevalence estimates for ACEs and educational outcomes but was considered of poor quality due to the limited statistical analysis performed.(33) Studies were of sufficient size, four studies used linked administrative data sets,(14,27,28,29) three of those at total population level. Three cohort studies (26,30,32) suffered from potential attrition bias, but reported the differences in their study compared to the general population and this will be considered when interpreting their results. Six studies adjusted models for low income / in receipt of social welfare payments (26,27,28,29,30,31) or reported extreme economic hardship.(33) The two remaining studies adjusted models for deprivation quintile,(14) or parental education as a proxy for deprivation (32) because deprivation is a known confounder (or upstream determinant) between ACEs and educational attainment in children. Five studies adjusted for parental or maternal education.(27,29,30,31,32) Missing data in the outcome measure was reported in five studies of under 5%,(28,29) under 15%,(27,30) or at 33%(14); other studies reported no specific information on missing data.

Characteristics of excluded studies

Ten studies were excluded from the main literature review that appeared to meet the eligibility criteria. Three studies used only a count of multiple ACEs in analyses on educational outcomes with no reporting of individual ACEs.(34,35,36) One study reported a count of stressful life events from the Holmes-Rahe life stress inventory, a substantially broader group of events than those described as ACEs.(37) Two review studies had relevant articles included in this review.(24,25) Two studies reported analyses using structural equation modelling (21,38) and one study used Latent Class analysis (39) where ACEs were combined to measure associations with childhood educational outcomes. One study had no comparison group.(40)

Effects of multiple ACEs measured individually on educational attainment

Children's educational outcomes were either for overall educational attainment, by academic subject or grade retention (repeating a school year). For children's educational outcomes reported in eight studies that adjusted results for multiple ACEs and a measure of deprivation 8 of 9 outcomes associated parental or sibling death with poorer outcomes. Living with a caregiver with alcohol problems (where some studies included illicit drugs in this category) 6 of 7 outcomes reported detrimental associations with children's

educational outcomes. Exposures of maltreatment (8 reports) and low income (5 reports) were associated with poorer educational outcomes in childhood in all analyses. Mental health problems in the household were found to only be associated with poorer educational outcomes in children in 2 of 14 outcomes reported. One large study did not model ACEs for effects on educational outcomes but it found higher proportions of ACEs in children who repeated a school year when compared to the national prevalence for alcohol or mental health issues in the household, parental death but not serious economic hardship. No studies considered all the ACEs in the criteria of this review in their modelling so that the most important ACEs could be ascertained or reported the combined impact of these individual ACEs for children's educational outcomes.

Several articles provided some evidence about the hierarchy of the increased risk for poorer educational attainment in childhood from each ACE in models that adjusted for some ACEs. Children's risk of being in the lowest 10% for reading at age 8 years if they experienced maltreatment was aOR 1.46 (95% CI 1.31-1.63), for household alcohol use that included drug use aOR 1.12 (95% CI 1.00-1.24) or mental health issues aOR 1.08 (95% CI 1.00-1.17) in adjusted models.(14) These models were adjusted for birth characteristics. A further study corroborated maltreatment was the highest risk aOR 1.6 ($p<0.0001$) for poorer reading skills at age 8 years with increased risk for low family income aOR 1.4 ($p<0.0001$) compared to children who did not experience these adversities.(27) At age 8 years the association of death or divorce of someone in the household changed children's cognitive scores by -0.26 (95% CI -0.52, 0.00), with a larger fall for poor home conditions -0.35 (95% CI -0.58, -0.12), compared to children without these experiences.(26)

As there was heterogeneity in how the educational outcomes were measured (at different ages, split by subject, or using grade retention) meta-analysis was not considered appropriate.

Table 6.2: Characteristics of included studies for adverse childhood experiences and educational attainment in childhood.

Reference	Exposures	Participants	Settings / context	Outcomes	Results*	Methods / quality	Newcastle-Ottawa quality assessment
Cohorts: outcomes age 5 to 11 years							
(ref 14) Maclean 2016 Australia	From birth to before year 3 school tests Main ACE: Maltreatment allegation 5.8% Other ACEs: Parental mental health (M 17%, F 9%), (inpatient hospital admissions or public outpatients), parental alcohol or drugs (M 9%, F 9%),	Population-based record linkage study, outcomes for children age 8 years, 2008-10	National representative cohort	Lowest 10% in Literacy and Numeracy (NAPLAN) reading test in school year 3 (taken in May)	Study size n=46,838 Logistic regression: OR (95% CI) Maltreatment allegation 1.46 (1.31-1.63) Maternal substance-related contact 1.12 (1.00-1.24) Maternal mental health 1.08 (1.00-1.17) Paternal mental health 1.11 (1.00-1.23)	67% with complete data, 30% had no attendance data available or were in private school, 3% did not sit the test severe disability, withdrawn by parent or absent on test day Models adjusted for birth characteristics, deprivation quintile, remoteness, parental education, marital status, maternal age at childbirth, absence from school Possible under ascertainment for maltreatment (more severe cases) and hospital contacts (higher socio-economic groups) for parental confounders, from routine data.	Good
(ref 26) Richards 2004 UK	Death or divorce 3.5% up to age 8 years Poor material home conditions quartile at age 4 years (possible measure of deep poverty: cumulative score for state of repair of house, crowding, age of house, cleanliness of house and child, condition of child's clothes and shoes) 6%	Birth cohort, born in 1 week 1946: 1 in 4 children of non-manual or agricultural workers and all other children	Cohort	Cognitive ability scores At age 8 years: 4 tests by the National Foundation for Educational research At age 15 years: Alice Heim Group ability test, Watts-Vernon Reading test	Study size n=1,339 Linear regression: Coefficient (95% CI): Death or divorce: At age 8 years -0.26 (-0.52, 0.00) between age 8-15 years change in cognition -0.33 (-0.53, -0.14) Poor material home conditions: At age 8 years -0.35 (-0.58, -0.12) between age 8-15 years change in cognition -0.28 (-0.45, -0.11)	24% with complete follow-up data and no missing data Models were adjusted for sex, paternal social class, maternal education, birth order, maternal management and understanding at age 4 years Cohort mostly UK representative except for overrepresentation among non-responders of the never married, least advantaged in terms of cognitive ability, educational attainment, and social class, the latter also with higher missing data	Poor

M=mother; F=father; * adjusted results presented with list of covariates in the methods column; OLS=ordinary least squares; SD=standard deviation.

Table 6.2: Characteristics of included studies for adverse childhood experiences and educational attainment in childhood (cont).

Reference	Exposures	Participants	Settings / context	Outcomes	Results*	Methods / quality	Newcastle-Ottawa quality assessment
Cohorts							
(ref 27) Rouse 2009 USA	From birth to child in 2nd grade Main ACE: Substantiated maltreatment by the Dept of Human Services 9% Other ACEs: Poverty in receipt of free or reduced lunch 62%	Municipal administrative data of children enrolled in second grade during 2002-3, age 8 years (Kids Integrated Data System), large city in the Northeast, high proportion of poverty in cohort	Cohort	School standardized reading and mathematics lowest quartile (Complete Battery Plus version of the TerraNova, 2nd Ed. / California Achievement Tests 6th Ed)	Study size n=10,349 Logistic regression: OR (p value) Child maltreatment: Reading 1.60 (p<0.0001) Mathematics 1.50 (p<0.05) 2nd grade retention 1.80 (p<0.05) Poverty: Reading 1.37 (p<0.0001) Mathematics 1.28 (p<0.0001) 2nd grade retention 1.62 (p<0.0001) Significant interaction between homelessness and maltreatment (p<0.05) for reading and mathematics	Less than 1% with false positive probability match between data sources 87% with no missing outcome data Models were adjusted for school location (multilevel model), age, gender, and race, homelessness, adequate pre-natal care (4+ visits), gestational age at birth, birthweight, low maternal education 80% of those who were maltreated were living in poverty Of those experiencing poverty 11% had been maltreated	Good
Cohorts: outcomes in adolescence							
(ref 28) Berg 2014 Sweden	Exposures up to age 15 years, mean age 9 years Main ACE: Death of a parent 2.9% Other ACEs: maternal and paternal alcohol or recreational drug abuse (M 3%, F 12%), mental health problem hospitalisations (M 8%, F 8%), social welfare 6%	Record linkage of all children born 1973-1981, living in Sweden at age 16 years with school performance information available Excludes children receiving disability benefits or retirement benefits who had no mean grades - 2.3% as assumed due to severe health problems	Nationally representative cohort	Mean grade points, school failure (i.e. having graduated without at least 1 grade in any subject) at age 15-16 years	Study size n=772,117 Logistic regression: OR (95% CI): Death of a parent: School failure 1.34 (1.26-1.42) Mean grade 2.95 (2.94-2.97) Vs 3.06 (95% CI 3.05-3.07) Linear regression: Coefficient (95%CI): Paternal death: Grade -0.11 (-0.12,-0.10) Maternal death: Grade -0.10 (-0.11,-0.08) Remaining parent psychosocial problems may be mediators and not confounders. Other ACEs not reported	2.2% with missing outcome data Models were adjusted for socioeconomic status (SES) of the household, criminal court convictions, parental birth country, geographic residency, gender. Paternal or maternal death only models adjusted for partner's highest education level rather than household SES Missing outcome data for children who lost a parent was higher 4.6% than those who did not Sensitivity analysis: Social welfare indicator added, no difference to results Children excluded with social service care had similar results (10.6% for death of a parent compared to 1.6% in the general population).	Good

M=mother; F=father; * adjusted results presented with list of covariates in the methods column; OLS=ordinary least squares; SD=standard deviation.

Table 6.2: Characteristics of included studies for adverse childhood experiences and educational attainment in childhood (cont).

Reference	Exposures	Participants	Settings / context	Outcomes	Results*	Methods / quality	Newcastle-Ottawa quality assessment
Cohorts							
(ref 29) Berg 2016 Sweden	From birth to 15th birthday of child Main ACE: Parental hospital admissions for alcohol-related disorders 2% Other ACEs: Parental mental health (M 4%, F 3%), social welfare 5%	Record linkage of all children born in 1990–96, living in Sweden at age 16 years with school performance information available	Nationally representative cohort	School performance using grade points (max 320), scores on national mathematics test scores (max 75) and eligibility for secondary education	Study size n=740,618 Linear regression: Coefficient (95% CI) Z-score for grades: Mother alcohol disorder (AD) -0.03 (-0.00 - 0.05) Father AD -0.10 (-0.12 - -0.08) Z-score for mathematics: Mother AD -0.08 (-0.11 - -0.05) Father AD -0.10 (-0.12 - -0.08) Logistic regression: OR (95% CI) Ineligible for secondary education: Mother AD 0.89 (0.81–0.96) Father AD 1.15 (1.09-1.22)	2.5% of children dropped out of school prior to grades at age 16 years (7% with maternal alcohol disorder, 5% with paternal alcohol disorder), 85-95% of diagnosis codes in hospital data are valid Models adjusted for year of birth, gender, parents' country of birth, geographic residency and parents' highest educational level, single parent, illicit drug abuse, criminality, placed in societal care Possible under ascertainment for alcohol disorders and mental health conditions from hospital admissions (more severe cases)	Good
(ref 30) Mills 2011 Australia	From birth to 14 years, records checked from 1981 to 2000 Notification of abuse or neglect, substantiated abuse or neglect Low family income before birth (<$10,399 per annum)	Birth cohort survey from mother's recruited in first antenatal visit 1981-83, singleton babies	Cohort	Wide Range Achievement Test (WRAT) reading test at age 14 years, standardized to mean 100 (SD 15)	Study size n=3,402 Linear regression: Coefficient (95% CI) Notification of: Neglect -5.1 (-7.7 - -2.4) Abuse -4.3 (-6.3 - -2.3) Substantiated: Neglect -4.4 (-8.5 - -0.4) Abuse -4.3 (-7.0 - -1.5)	47% with complete follow-up Models adjusted for maternal age, marital status, maternal education level, race, infant gender, birth weight z score, alcohol use, neonatal intensive care unit admission, breastfeeding, and infant medical symptoms (not unemployment, smoking, binge-drinking, anxiety, depression, attitude to pregnancy, or prematurity) and either abuse (neglect model) or neglect (abuse model)	Good

M=mother; F=father; * adjusted results presented with list of covariates in the methods column; OLS=ordinary least squares; SD=standard deviation.

Table 6.2: Characteristics of included studies for adverse childhood experiences and educational attainment in childhood (cont).

Reference	Exposures	Participants	Settings / context	Outcomes	Results*	Methods / quality	Newcastle-Ottawa quality assessment
Longitudinal surveys							
(ref 31) Fletcher 2018 USA	0-20 years, median 8 (IQR 4-14) Main ACE: Death of one sibling 5% Other ACEs: Welfare payments 1%	Births from 1986, families with 2 children, excludes children with disabilities with cognitive impairment, weighted to be nationally representative, results include multiple waves per child	Nationally representative longitudinal survey: cohort	Peabody Individual Achievement Test (PIAT) age 5-18 years, Peabody Picture Vocabulary Test (PPVT) 4-5 years, 10-11 years from 1996	Study size n=6,558 Linear regression: Coefficient (SE) Sibling death: Mathematics -5.4 (3.2) Reading -5.1 (3.9) Reading comprehension -8.4 (3.2) Picture vocabulary test -1.2 (4.3) Poorer scores reduce as years from sibling death increase	Approximately 89% without missing data used in analysis Models adjusted for age at assessment, sex, family income, parent's highest education, grandmother's years in education, number of children, family (multilevel model), urban/rural, disabled children, age of mother at first pregnancy, region Few families experienced sibling death that restricted sample size when obtaining precise fixed effects estimates of within-family effects	Good
(ref 32) Le 2017 Australia	Maternal and paternal self-reported depression or anxiety over last 4 weeks. Depressed for 2 weeks or more in the last year from birth to 12-13 years	Born Mar 1999-Feb 2000. Children living with both parents, separate analysis for single mothers. Biannual, 5 waves, children must be present in at least 2 waves. Data presented from multiple waves for each child	Nationally representative longitudinal survey: cohort	National Assessment Program - Literacy and Numeracy tests at 9-10 years, 11-12 years (reading, writing, spelling, grammar, numeracy), Peabody picture vocabulary test at 4-5 years	Study size n=1,893 Maternal depression: Significant results at the 5% level in adjusted fixed effects estimator modelling with parent ability for reading and writing but not once adjusted for multiple tests (results not statistically significant using OLS) Paternal depression: No difference in results.	38% with complete follow-up on all waves and without missing data Models were adjusted for sex, age, migration status, birth weight, school sectors, number of siblings, ethnicity, parent education, age and immigration status, local socioeconomic background variables, state or territory, year dummy, survey quarters Better educated healthier parents.	Poor

M=mother; F=father; * adjusted results presented with list of covariates in the methods column; OLS=ordinary least squares; SD=standard deviation.

Table 6.2: Characteristics of included studies for adverse childhood experiences and educational attainment in childhood (cont).

Reference	Exposures	Participants	Settings / context	Outcomes	Results*	Methods / quality	Newcastle-Ottawa quality assessment
Cross-sectional studies							
(ref 33) Bethell 2014 USA	ACEs age 0-17 years ACEs: Household alcohol or drug problem, household mental illness or suicide, death of a parent, extreme economic hardship	Survey of children age 0-17 years from 2011-12 (National Survey of Children's Health), weighted to represent non-institutionalised children	Nationally representative cross sectional	Repeated a school grade age 6-17 years	Study size n=95,677 Proportion of children with an ACE in children who repeated a school year %, National prevalence of ACE %: Household: Alcohol or drug problem 15%, 11% Mental illness or suicide 13%, 9% Death of a parent 18%, 3% Extreme economic hardship 14%, 26%	No information on missing data Modelling used an ACE count and did not report confidence intervals May suffer from recall bias	Poor

M=mother; F=father; * adjusted results presented with list of covariates in the methods column; OLS=ordinary least squares; SD=standard deviation.

6.2.3 Discussion

The literature review identified nine studies that specifically examined the impact of multiple ACEs on educational outcome.(14,26,27,28,29,30,31,32,33) Most studies investigated one ACE and adjusted analyses for other ACE exposures relevant to this review. No studies reported modelling educational outcomes in children for all the ACEs within this review's criteria but the review provides some evidence about the hierarchy of different ACEs on children's educational attainment outcomes. Only one study considered educational outcomes specifically at age 5 – 9 years and multiple individual ACEs but had relatively high missing data. This review finds limited evidence from previous research that multiple ACEs reported individually are associated with poorer educational outcomes in childhood and adolescence, but the evidence is not comprehensive. There were no reports on the cumulative effect of different combinations of ACEs. Additionally, interpretation of ACEs that were not the focus of a particular peer reviewed article may not have considered all possible confounding variables in analyses. However, all statistical modelling reported in the studies of the review adjusted for the main confounder, a measure of deprivation (or proxy maternal education).

In the published literature only one study looked specifically at educational outcomes in children between the age of 5 and 9 years and more than two individual adverse experiences. This may be because of the recent development in theories around maltreatment and poorer educational outcomes that are now considering co-occurring risk factors (ACEs) in addition to the experience of maltreatment. Maclean et al investigated three ACEs creating a cohort using record linked administrative data for school reading ability at age 8 years.(14) Children had poorer educational attainment with a hierarchy of decreasing risk if they had experienced maltreatment, household alcohol use that included drug use or mental health issues in adjusted models. The study's models adjusted for birth characteristics but not low family income or school factors. School factors such as school attended (to model variation between schools), school moves and the proportion of children living in higher deprivation may explain variability in reading outcomes and it is important to adjust for these variables when modelling educational outcomes. Their study used inpatient and outpatient hospital admissions to ascertain childhood adversity and may only identify the most serious cases of mental health conditions. Common mental disorders are often managed in primary care and therefore the proportion of children experiencing caregivers with mental health conditions may be underestimated. In addition,

Maclean et al adjusted models for children's absence from school, thought to be a mediator between ACEs and educational attainment using Directed Acyclic Graphs (DAGs), so associations with educational outcome may be lower than if total causal effect analysis was performed. Their analysis excluded 33% of children from the cohort because data on absenteeism was not available and may mean results suffer from selection bias.

Two other cohort studies looked at two ACEs and educational outcomes at age 8 years with low family income as a potential child adversity. Low family income was found to have a higher risk than death or divorce (26) but a lower risk than maltreatment (27) for children's poorer educational attainment compared to children without these experiences. These studies did not adjust analyses for other ACEs such as parental alcohol or mental health issues, school factors and only Rouse et al (27) adjusted analysis for birth characteristics. Without adjusting analyses for important confounders in modelling the effects of ACEs on educational attainment in childhood the results may be larger than the true association. The study by Richards et al (26) was considered of poor quality as only 24% of the original cohort was used in the analyses and attrition or selection bias from exclusion of those with missing data may be present. Rouse et al noted in children that were maltreated, those who had one good quality parent-child relationship had better outcomes than children who did not.

There is debate about whether low income in the household is an ACE, but deep poverty or extreme financial hardship could lead to stress within the household and for the child, including anxiety from food insecurity. Not all children who live in low income households experience adversity and some working class areas create strong community cohesion that may help to reduce the negative effects of poverty.(41) Policy makers may prefer to exclude low family income from the list of ACEs, as trauma-informed interventions may not be as appropriate as financial advice or debt management interventions. Low income is also caused by macroeconomic factors such as national income and policies rather than individual family structure or dysfunction. Rouse et al showed 80% of their cohort of children who had experienced maltreatment were living in poverty (27) and therefore low family income is an important consideration in ACEs research. It may be that a combination of childhood adversity and low family income lead to poorer educational attainment in childhood where adversity is more likely when the family is living in poverty.(42)

Other cohort studies looked at ACEs across childhood and educational attainment at age 14-16 years in good quality cohorts.(28,29,30) The cohort studies showed children had

poorer educational attainment from experience of parental death,(28,30) alcohol problems,(29) or maltreatment.(28,30) Berg et al commented that adjusting models for ACEs in the household attenuated the association of parental death for school failure, and authors surmise remaining parent psychosocial problems may become mediators and not confounders.(28) Differences may exist between the effects of ACEs on educational outcomes in children compared to teenagers. It is important to know if younger children's education is impacted in the same way from ACEs as has been found for teenagers. None of these studies looked specifically at educational outcomes at age 11 years, typically the age before children move to secondary school education in the UK. Interventions such as trauma-informed approaches (33) may need to be tailored to specific age ranges of the child, and also support for potential resilience factors such as school engagement of children or parents (33) would need to be suitable to the child's age.

Four studies looked at educational outcomes between age 5 and 17 years.(26,31,32,33) A similar increased risk for poorer educational attainment was found for death in the household including sibling death in this age range to that found for outcomes at age 8 years.(26,31) For parental mental health, results contrasted with those for children at age 8 years but the study was of poor quality because it did not report characteristics of the study sample but only differences between groups (32) and had high attrition or missing data across all survey waves (62%). Bethell et al found an increased proportion of children repeated a school year for all the ACEs considered in this review's criteria apart from extreme economic hardship in a large cross-sectional study.(33) No adjusted models were reported for individual ACEs in this study and it was classed as poor quality because without confidence intervals the results could not easily be interpreted. These studies contained outcomes for children as well as teenagers, children are more dependent on parents than teenagers, but teenagers may be more observant and sensitive to household problems so the effects of ACEs on educational attainment may be different in these two age groups.

6.2.3.1 Studies that investigated only prenatal alcohol exposure

Two studies investigated exposure to alcohol in the pre-natal period but did not look at exposure to alcohol in the household during childhood for effects on educational outcomes in childhood. These studies concluded that there were detrimental associations between maternal alcohol drinking and educational attainment during childhood and postulated this had occurred through inter-uterine mechanisms.(43,44)

6.2.3.2 SEN provision

Previous research shows maltreatment was associated with higher levels of specialised help with learning in addition to the standard teaching at school,(45) particularly for children who experienced neglect (and may relate to higher school absence). Poverty has also been associated with higher proportions of special education need provision.(46) This is of interest as SEN provision is an indication of a child's educational performance and a potential cost to the child and society of ACEs that could potentially be mitigated.

6.2.3.3 Confounders, other important factors

Figure 6.2 and 6.3 describe theoretical causal pathways and potential confounding relationships from this literature review with variables grouped as described in Table 6.3.

Table 6.3 – Variables grouped by theme in the causal diagrams.

Group variable name	Variables contained in the group
Pre-birth adverse childhood experiences (ACEs)	Household member with a historical common mental disorder (CMD), serious mental disorder, or alcohol problem
Post-birth ACEs to Key Stage	Household member with a CMD, serious mental disorder or alcohol problem between birth and Key Stage; victimisation recorded between birth and Key Stage; death in household birth to Key Stage
Pre-birth socio-economic status (SES)	Townsend deprivation quintile at birth, maternal cigarette smoking in first trimester of pregnancy, born to a mother under 18 years of age at childbirth**
Post-birth SES to Key Stage	Free school meals eligible in year take Key Stage* or single adult household between birth and Key Stage**
Perinatal factors	Gestational age at birth, small for gestational age, breastfeeding, academic season of birth
School factors at Key Stage	School mobility, school at Key Stage, average size of school at Key Stage, average proportion of children eligible for free school meals in the school at child's Key Stage

*free school meals eligibility may be classed as an ACE see Section 6.2.3; **although not a direct measure of socio-economic status these variables may give some indication of potential differences in income due to household composition.

Socio-demographics and household composition

As in Chapter 4 and 5, socio-economic factors are included as confounders in the DAG. Low family income may be an ACE as discussed in section 6.2.3.

In previous research studies showed living in a single parent household was associated with poorer preschool preparedness (47) and lower mean grade points (29) in children but it is suggested this is partly explained by socio-economic differences.(47) Interventions to help populations with low educational attainment and low earnings to improve human capital: a measure of skills, education, capacity and attributes that influence productive capacity and earning potential can reduce socio-economic inequalities. These interventions could be adapted to include opportunities for single parents that include consideration of their childcare responsibilities.(47) Further, there is evidence that teenage mothers were associated with poorer school attainment in their offspring (48) that may also relate to socio-economic status. Children of adolescent mothers were also found to have a higher proportion of SEN support at school compared to those not born to a teenage mother.(49) It is important to adjust analyses for these potential confounders when investigating ACEs, in particular low income and maternal depression, and educational attainment outcomes in children.(47,49)

Birth characteristics

As mentioned in Chapters 4 and 5, the published literature shows birth characteristics such as gestational age, birthweight and small for gestational age were associated with higher risk of lower educational attainment in childhood. Congenital anomalies may cause parents anxiety and distress both in the perinatal period and in later childhood due to increased caring responsibilities if there are associated disabilities. Previous research shows associations between childhood disability and poorer maternal mental health.(50) Children with congenital anomalies may have lower attainment in educational outcomes either through direct intellectual deficits or challenges surrounding senses or physical capacity.

School factors

As in Chapter 4 and 5, school factors were considered important to include in the DAG for educational outcomes. Concentration of school poverty (the proportion of children eligible for free school meals in the school) was described in Section 4.6. School-level economic hardship was found to contribute to lower reading and mathematics scores in children age 8 years, but school-level maltreatment was not associated with lower scores.(51)

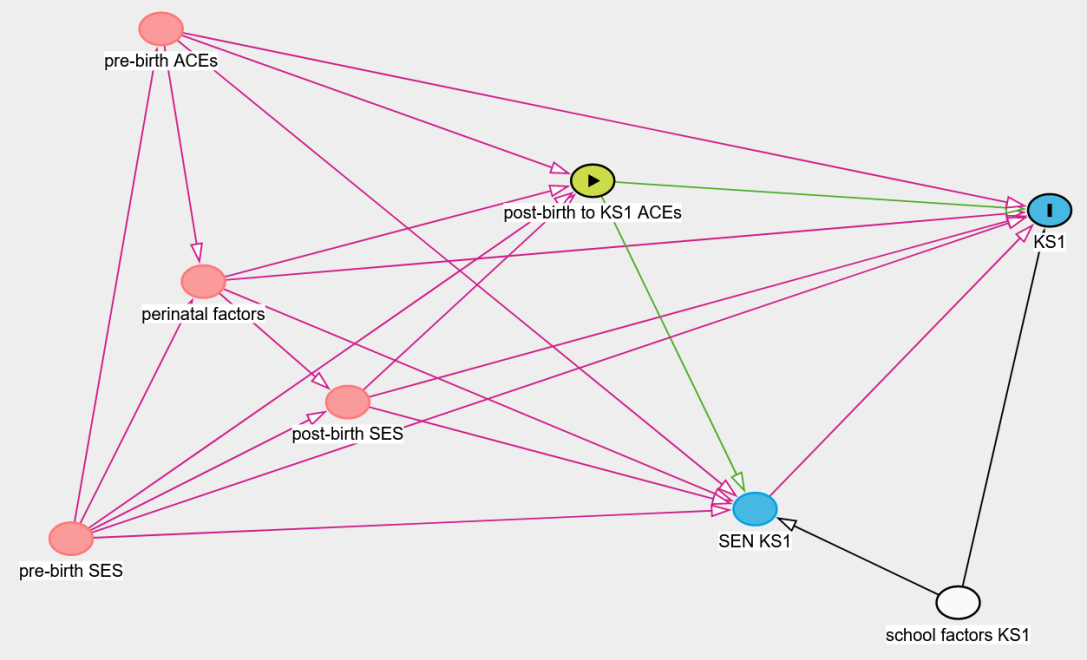

Figure 6.2. Directed acyclic graph (DAG): visual diagram of causal relationships to aid selection of confounder variables in analysis of exposure to post-birth adverse childhood experiences and KS1 attainment outcome.

The minimal sufficient adjustment set for total effects analysis was pre-birth SES, pre-birth ACEs, perinatal factors, post-birth SES and school factors at KS1 (an adjusted factor and not a confounder). ACE=adverse childhood experience; SES=Socio-economic status; SEN=Special Educational Needs provision; KS=Key Stage; Green circle with black triangle – exposure; Blue circle with vertical black line – outcome; Pink circle – ancestor of exposure and outcome (confounder); Pink arrow – directional biasing path; Plain blue circle – ancestor of outcome; Green arrow – directional causal path; White circle – adjusted variable; Black arrow – directional relationship; Exposure=post-birth to KS1 ACEs; Outcome=KS1 attainment; Example of a potential confounder between exposure and outcome=post-birth SES; Example of a potential mediator between exposure and outcome=SEN provision at KS1.

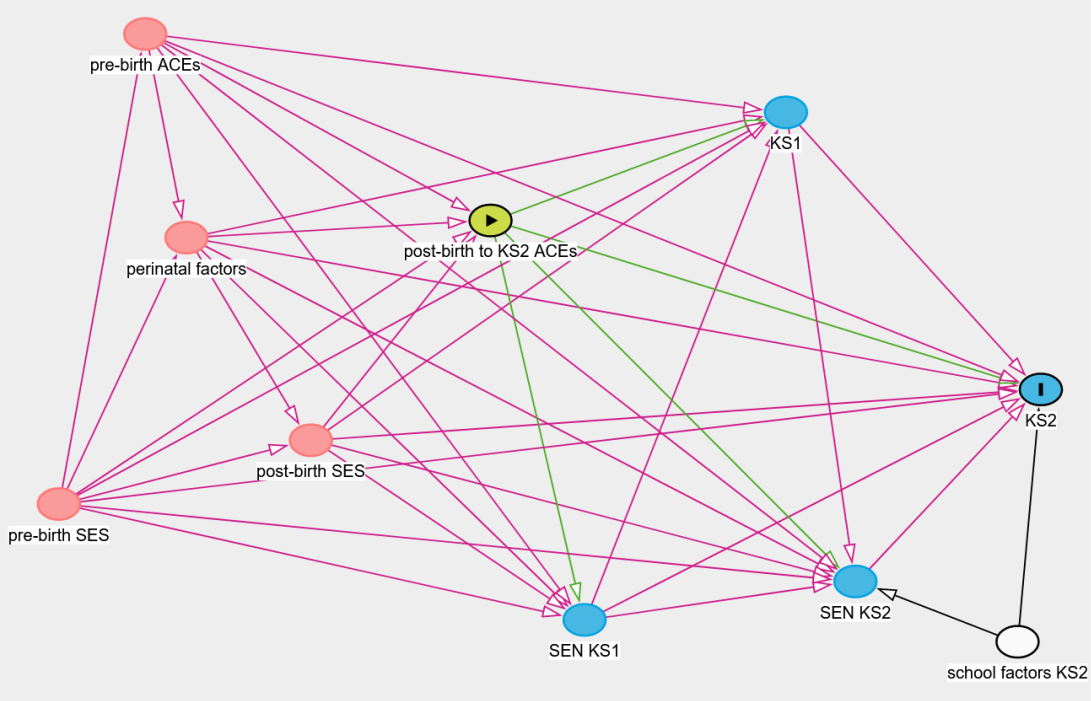

Figure 6.3. Directed acyclic graph of exposure to post-birth adverse childhood experiences and KS2 attainment outcome.
The minimal sufficient adjustment set for total effects analysis was pre-birth ACEs, prebirth SES, perinatal factors, post-birth SES and school factors at KS2 (an adjusted factor and not a confounder); Green circle with black triangle – exposure; Blue circle with vertical black line – outcome; Pink circle – ancestor of exposure and outcome (confounder); Pink arrow – directional biasing path; Plain blue circle – ancestor of outcome; Green arrow – directional causal path; White circle – adjusted variable; Black arrow – directional relationship; Exposure=post-birth to KS2 ACEs; Outcome=KS2 attainment; Example of a potential confounder between exposure and outcome=post-birth SES; Example of a potential mediator between exposure and outcome=SEN provision at KS2.

6.2.4 Conclusion

Implications for practice

From the literature review the overall weight of evidence supports that there is a potential causal association between certain ACEs that can be observed by healthcare or teaching professionals and educational attainment in children and adolescents. The review shows there is a lack of evidence between the association of multiple individual ACEs and educational outcomes for children specifically between the ages of 5 – 11 years. Only one cohort study looked at more than two individual ACEs for educational outcomes at age 8 years, but estimates were adjusted for absence from school, found to be a mediator using DAGs and therefore did not report the total effects of ACEs on educational attainment. Low family income was found to be an important potential ACE in the literature and this study did not adjust models for this important measure.

Other cohort studies highlighted that adjusting models for multiple ACEs reduced the association between each individual ACE and poorer educational attainment in adolescence. It was suggested that death of a parent could lead to alcohol problems and mental health issues in the household, but further investigation is needed. There is evidence in wider age groups of children between 5-17 years for educational outcomes that showed detrimental associations with education, but the effects of ACEs may have different impacts on younger children who are less independent than adolescents. The review found detrimental associations for maltreatment, alcohol problems in the household, death of a parent and low family income on educational attainment during childhood and adolescence. However, it was difficult to make comparisons between ACEs as most studies only reported the results of modelling for one ACE and educational attainment outcome. The review did not find any association between maternal and paternal mental health and educational attainment in children or adolescents, but findings were partly dependent on one poor quality study that had high attrition.

All the studies in the review adjusted models for a measure of deprivation or maternal education, but only three studies adjusted for birth characteristics, known to be associated with poorer educational attainment. None of the studies adjusted for school factors known to be associated with variability in school attainment. The absence of these variables from modelling may cause associations between ACEs and educational attainment to be higher than if the combined contribution of these confounders and other factors were considered in the results.

The strength of the review was that it used adapted methods from the Cochrane Review Handbook for interventions applied to exposures. The search for relevant articles was wide ranging across multiple silos of research (through choice of databases searched) to try to capture as many articles as possible with a search criterion specific to my research question. It is possible that some relevant research articles were missed in the search but because multiple search engines were used and a Google search of the main search terms was included it is unlikely that any studies were missed. This review was unable to include a small number of articles that reported only a count of ACEs or combined ACEs with other demographics for any association with educational attainment, as described in the excluded studies section. These studies could not be investigated further due to time and resource constraints.

Implications for research

The literature review highlights a research gap in the evidence base about the potential causal association between ACEs and educational outcomes for children aged between 5-11 years. It shows although the overall weight of evidence finds individual ACEs were associated with poorer educational outcomes for children and adolescents the importance of each individual ACE compared to other ACEs in this review remains unanswered. It is notable in the review that adjustment for other ACEs, than the one of particular interest in a study, can reduce the association of that ACE on educational attainment. Research is needed using large data sets so that multiple individual ACEs can be modelled together to help to understand the overall association of ACEs on poorer educational attainment and to clarify which ACEs have more risk than others. Also, no previous studies report the combined effects of multiple ACEs on children's education. Previous research has not uniformly included low family income and adjusted models for birth characteristics and school factors, these are important confounders and factors (that effect the variability of school outcomes). These measures should be included in statistical modelling to better understand the associations between ACEs and educational outcomes in children.

6.3 Aim and objectives

Aim

To investigate the association between multiple ACEs measured individually and educational attainment in childhood.

Objectives

vi. To investigate and quantify the association between adverse childhood experiences identifiable by health practitioners or educators, specifically

   a. common mental disorder in a household member

   b. serious mental illness in a household member

   c. alcohol problems in a household member

   d. victimisation (maltreatment: neglect, sexual, emotional or physical abuse)

   e. death of a household member

   f. free school meals eligibility

   on educational attainment at KS1 (age 6-7 years)

vii. To assess the association between ACEs identifiable by health practitioners or educators on educational attainment at KS2 (age 10-11 years)

viii. To assess the association between ACEs identifiable by health practitioners or educators on SEN provision in the year when KS1 is taken

ix. To assess the association of ACEs identifiable by health practitioners or educators on SEN provision in the year when KS2 is taken

x. To assess the association of a combination of multiple individual ACEs and educational attainment at KS1 (age 6-7 years).

6.4 Participant selection

The study in this chapter used the Wales Electronic Cohort for Children (WECC) to create a total population cohort of all children born in Wales, from 1st January 1998 to 31st August 2005. This was a part of the Electronic Longitudinal Alcohol Study in Communities (ELAStiC) study, with linkage to prospectively collected health and education administrative data as described in Chapter 2. Data was extracted for ACEs from General Practice (GP) or inpatient hospital admissions data and low family income through free school meals eligibility recorded in education data sets. Children were followed from birth to age 6-7 years, to their first teacher-based educational assessment at KS1, and to age 10-11 years to assessment at KS2 through record-linkage between education and health routine data sets. De-identified data was analysed in the Secure Anonymized Information Linkage (SAIL) databank, UK.(52,53) To enable individuals living in the same household to be anonymously linked, residential anonymised linking fields (RALFs) were created by encrypting individual's addresses for the study period.(54,55)

Children were included in the analysis if they were born in Wales, because there was enough data to adjust analyses for a comprehensive number of confounding birth characteristics for this group. Due to the way the administrative data is collated, data on birth characteristics are unavailable for children who were not born in Wales. The cohort was restricted by availability of inpatient hospital admissions data from 5th January 1998 to 7th October 2012.

For the KS1 cohort, children were included if they were present in the data at birth until the normal time they take the KS1 teacher-based assessment (proxy date 1st May) in a local education authority school and they had education data available. This excluded children who attended private schools or who did not attend school (e.g. travellers) as described in Chapter 4.9. Children were excluded if they were stillborn or died (identified from the Public Health mortality files) before the normal time they take the Key Stage, who moved out of Wales (identified from the Wales Demographic Service), or if they took the KS1 outside the expected age (6-7 years) to make sure exposure preceded outcome in analyses (Figure 6.4). Similar exclusions were made for follow-up to age 10-11 years for the KS2 cohort.

Children were included if there was a valid RALF obtained from postal address (see Section 2.1.2.2 for more details), an adult (age 16+ years) in the household and household

members for whom there was linked GP data available in the SAIL Databank. Household members that were included in this analysis were defined as those who were living with the child on any of their 1st, 3rd, 5th and 8th birthday. The household members were then linked to their inpatient hospital admissions and GP data, and variables were derived for the exposures for the WECC child's age before birth, birth to less than 1 year, 1 to less than 5 years, 5 years to less than the normal time they take KS1 that represented key times in the child's life. These key times were the first year of life when a child is most dependent on household care, the remaining pre-school years from age 1 to less than 5 years, and 5 years to just before KS1 assessment when the KS1 syllabus is taught. At least six months of data was required for household members in each of the key times of the child's life so that common mental disorder (anxiety or depression) could be captured (recommended by clinicians who developed the common mental disorder algorithm (56) in the SAIL databank). This approach was used to capture patients who present to a GP but are not diagnosed for a period of time or who delay seeing their GP for a period of time. For KS1 school data sets were available for years of birth 1998-2005, for KS2 these were years of birth 1998-2001 (to have sufficient follow-up to age 10-11 years).

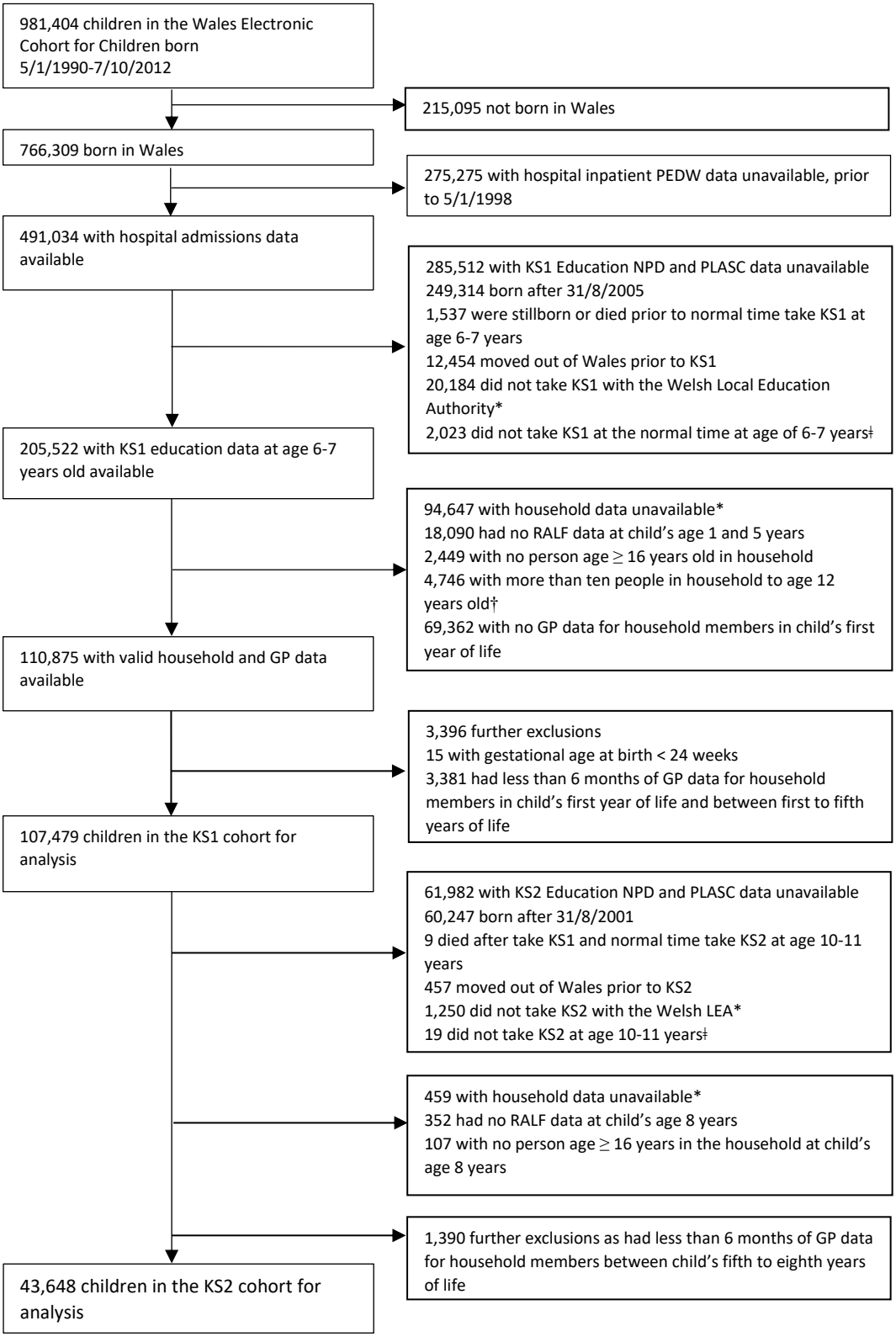

Figure 6.4: Anonymised participant selection for analyses.

PEDW=Patient Episode Database Wales, RALF=Residential Anonymous Linking Field, GP=General Practice, KS=Key Stage, NPD=National Pupil Database, PLASC=Pupil Level Annual School Census, LEA=Local Education Authority. *private schools, severely disabled children who are not catered for by Special Educational Needs provision in the LEA school system, those outside administrative systems e.g. travellers; ‡ to adhere to no overlap between exposure and outcome time windows.

6.5 Exposure and outcome variables: definitions using coded data

Outcomes: Educational attainment

Children in Wales have two statutory assessments during compulsory education that are normally undertaken between ages 5-7 years and 8-11 years(57) (two further assessments are taken at age 13-14 and age 15-16 years). In this analysis the education outcomes were the expected level in statutory assessment at (i) age 6-7 years (KS1) and (ii) age 10-11 years (KS2). KS1 and KS2 are teacher assessments rather than formal tests in three core subjects (a language, mathematics and science) where an overall binary measure is derived to indicate whether the expected standard is met or not. The definitions for attaining the expected level at KS1 or KS2 were described in the methods in Section 2.1.7.

A third outcome about provision of extra learning support for a child at school (SEN provision) was also investigated as an indicator of impaired academic performance. This was coded as a yes/no binary variable, indicating any help received by a child, which may include one to one help or support through external provision to the school (described in UK local educational authority schools as School action, School action plus and Statemented).

Exposure: Adverse Childhood Experiences (ACEs)

Children's exposure to ACEs were measured (i) between birth to age 6-7 years (KS1) and (ii) between birth to age 10-11 years (KS2). Exposure to ACEs in the household were ascertained using health records of adults living with the child on their first, fifth and eighth birthday as described in Section 6.4.

Six measures of potential childhood adversity were defined using the routine data sets. Three of these related to living with an adult household member with any of: (i) serious mental illness diagnosis (e.g. bipolar disorder, schizophrenia);(58) (ii) CMD (e.g. depression, anxiety)(56) and (iii) an alcohol problem defined by a record of heavy drinking in primary care records(59) or an alcohol-related hospital admission,(60) dating back to 1998. The fourth measure was childhood victimisation defined as an inpatient hospital admission of the child where victimisation was a contributing reason for admission.(61) The fifth measure was death of a household member and the sixth measure was low family income, defined as eligibility for free school meals in the year the Key Stage assessment was taken.

Validated algorithms were used to ascertain cases of CMD using diagnosis, symptoms and treatments (56) (validated via the 5-item Mental Health Inventory (MHI-5) questionnaire) and lifetime diagnosis of psychotic disorders(58) recorded in GP data sets. Problematic alcohol use among household members was ascertained using a set of GP symptoms, diagnosis and procedures (Read Version 2) codes that we had previously defined.(59) This category included current or past heavy alcohol drinking (anything above the recommended limit), alcoholic disease (liver or other), poisoning or treatment evidence and/or any alcohol-related emergency hospital admission during the exposure period.(56) Childhood victimisation was ascertained using a defined set of ICD-10 codes in any position of a first consultant episode of an inpatient hospital admission.(61; Section 2.1.5) For adult household members living with the child at age 1 year, the presence of alcohol related problems, CMD or serious mental illness were separated according to whether they were recorded before the birth of the child (pre-birth) or during the first year of life.

In previous analysis a medical history of common mental disorder (anxiety or depression) or alcohol problems in GP data for children's household members were associated with increased risk in children for inpatient hospital admissions.(12) For this analysis variables for ACEs were derived for pre-birth exposure of ACEs up to birth, and then between birth and the Key Stage where data availability in the SAIL databank allowed. A history of either CMD, serious mental illness or alcohol problems were defined using data from 5th January 1998 when hospital inpatient admissions and GP data were available. The period of retrospective data varied between individuals depending on when the child was born and whether their GP practice was in the SAIL databank.

6.6 Special educational needs provision

The child's SEN provision was used for the year when the child takes the Key Stage and was derived as a binary variable of any of provision (school action, school action plus or statemented), compared to no provision.

6.7 Potential confounders, covariates and effect modifiers

Birth characteristics available from WECC were used as described in Section 4.6 for sex, gestation at birth, small for gestational birth (<10th centile) adjusted for gestation and sex, parity, major or minor congenital anomaly, maternal age, breastfeeding recorded at birth or at 6-8 weeks, maternal cigarette smoking in first trimester and academic season of birth

(school terms September-December, January-April, May-August). Deprivation at birth was used and categorised into quintiles using Townsend deprivation scores of small area of residence Lower Super Output Area (LSOA) from the 2001 census (each containing 400-1,200 households). A variable was created for living in a single parent household (16+ years) from linkage of children to household member week of birth. Variables were constructed from the education data sets for each child on school attended at each Key Stage assessment, school moves (from start school at age 5 years to KS1 and between KS1 and KS2) and free school meals eligibility in the school year each Key Stage was taken as a measure of low family income beyond birth.

6.8 Statistical analysis

As in Chapters 4 and 5 multilevel logistic regression was used to model exposure to ACEs and (i) not attaining the expected level at KS1 and KS2 separately and (ii) receipt of SEN provision. Likelihood ratio tests were used to test two-way interaction terms between exposures, and between each exposure and each of maternal age, single adult household, and small area deprivation. The analysis was repeated to estimate ORs for any SEN provision allocated in the year the Key Stage assessment was taken, adjusted for maternal and perinatal characteristics. Models were adjusted for the calendar year in which Key Stage teacher-based assessments were completed (May-July), as there was some variation in the results of attainment over the years of the cohort for KS2. The effect across the years for KS1 results was much smaller than at KS2, but the year when the child took the Key Stage was added to the KS1 models for consistency. The first full school year of data (Sept-Aug) was used as the reference category.

A Direct Acyclic Graph (DAG) (62) was drawn to visualise confounding relationships and obtain a minimal sufficient adjustment set of potential confounders for analyses (Figure 6.2 & 6.3). The DAG for total causal effects analysis from exposures to ACEs on educational outcomes excludes SEN provision as it is a potential mediator between ACEs and educational attainment. Theoretically SEN provision could be provided if a child falls behind in schooling from an ACE. Children may also theoretically receive SEN provision because maltreatment such as neglect may have altered their brain activity and development. SEN provision gives additional insight into a child's school performance and the associated cost to the child and society from ACEs and is therefore investigated in this study as a secondary outcome. The analysis in this study will try to ascertain whether there is an association

between ACEs and educational attainment, rather than include any remediation that may be occurring for this or other reasons.

Small-area deprivation Townsend score incorporates unemployment, non-car ownership, non-home ownership and household overcrowding as an area level measure of social deprivation.(63) For this study the Townsend score was chosen instead of the Welsh Index of Multiple Deprivation (WIMD) because the WIMD includes education and health indicators and therefore may be weakly circular as the exposure and outcome measures were related to health and education domains. Perinatal factors (such as gestational age, academic season of birth, and breastfeeding at birth or 6–8 weeks (when the NHS collects such data)) were adjusted for as the DAG confirmed these factors were on the potential causal pathway but were not mediators between adverse childhood experiences and educational attainment.

Data were missing for breastfeeding (22% and 42%) and maternal smoking (70% and 80%) in the KS1 and KS2 cohorts respectively. The slightly higher proportions in the KS2 cohort were due to lower data completeness in the earlier years of the cohort. Tabulations by year and unitary authority showed that these could be reasonably assumed to be missing at random and thought to be due to organisational and administrative differences in data collection between hospitals. There was little difference between statistical model imputations for these variables, so we concluded that the cohorts were large enough to give sufficient precision. All other variables had less than 5% missing data. Multiple imputation with chained equations (64) was used to account for missing data with all covariates and the outcome variable included in the imputation model as described by White and Royston.(65) An investigation of variables with missing data as described in Section 3.3.2 supports the theory that the variables in the imputation model make the MAR assumption plausible.

For exposure to ACEs and educational attainment outcome average risk ratios (RR) and average risk differences (RD) were estimated from logistic regression using the 'adjrr' Stata command with one imputed data set.(66) For logistic regression, Rubin's rules to combine estimates after multiple imputation are not currently supported for use with the adjrr command (because it is based on the margins command and adjusted for non-linear predictions).(67) These measures were also investigated using general linear models using 'mi estimate:glm' for comparison.(68) The Population Attributable Fraction (PAF) was

estimated using the formula $PAF = \frac{P\,(RR-1)}{1+P\,(RR-1)} \times 100\%$,(69) where *P* is the prevalence of exposure in the cohort and *RR* is the risk ratio. The PAF estimates the proportion of cases of the outcome that can be attributed to a certain exposure (risk factor) in the population of interest. If the exposure was eliminated it is the proportion of cases of the outcome that could be prevented (assuming causality and absence of bias).

6.9 Results

6.9.1 Descriptive statistics

There were 107,479 and 43,648 children in the cohort between 1998 and 2012 who were included in this analysis, with follow-up to 6-7 years (KS1) and 10-11 years (KS2) respectively (Figure 6.4). Sociodemographic characteristics of the children were representative of national population statistics in both cohorts (Appendix Table A2.2). About 3% of children (n=3,313) were born to a mother who was under 18 years of age at childbirth, and 35,651 (33.2%) had lived in a single adult household (16+ years of age) between birth and age 6-7 years.

Overall 19,508 (18.2%) of children did not attain the expected levels at KS1, 8,462 (19.4%) did not attain the expected level at KS2, 27,393 (25.5%) and 11,910 (27.3%) had some SEN provision in the year they took KS1 and 2 (Table 6.4). There were 15,553 (14.5%) children aged 1 year who lived with an adult who had a history of CMD, and 41,257 (38.4%) children who lived with an adult who had a CMD between birth and age 6-7 years (Table 6.4). Less than 1% of children had lived with an adult who had a serious mental illness.

Table 6.4: Characteristics of adverse experiences in childhood, household composition, socio-demographics.

		Key Stage 1 cohort						Key Stage 2 cohort					
		Total		Not attained KS1		Special Education Need provided at KS1†		Total		Not attained KS2		Special Education Need provided at KS2†	
		N=107,479		n=19,508		n=27,393		N=43,648		n=8,462		n=11,910	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Household adverse experiences													
Common mental disorder GP code for a household member													
before birth of child	No	91926	(85.5)	15987	(17.4)	22431	(24.4)	40602	(93.0)	7770	(19.1)	10897	(26.8)
	Yes	15553	(14.5)	3521	(22.6)	4962	(31.9)	3046	(7.0)	692	(22.7)	1013	(33.3)
birth to Key Stage	No	66222	(61.6)	10735	(16.2)	15290	(23.1)	23001	(52.7)	3898	(16.9)	5657	(24.6)
	Yes	41257	(38.4)	8773	(21.3)	12103	(29.3)	20647	(47.3)	4564	(22.1)	6253	(30.3)
Serious mental illness GP code for a household member													
before birth of child	No	107051	(99.6)	19399	(18.1)	27230	(25.4)	43568	(99.8)	8446	(19.4)	11881	(27.3)
	Yes	428	(0.4)	109	(25.5)	163	(38.1)	80	(0.2)	16	(20.0)	29	(36.3)
birth to Key Stage	No	106550	(99.1)	19247	(18.1)	27052	(25.4)	43074	(98.7)	8308	(19.3)	11703	(27.2)
	Yes	929	(0.9)	261	(28.1)	341	(36.7)	574	(1.3)	154	(26.8)	207	(36.1)
Alcohol problem GP code for a household member													
before birth of child	No	101695	(94.6)	17853	(17.6)	25225	(24.8)	42487	(97.3)	8130	(19.1)	11453	(27.0)
	Yes	5784	(5.4)	1655	(28.6)	2168	(37.5)	1161	(2.7)	332	(28.6)	457	(39.4)
Alcohol problem GP code or alcohol-related hospital admission for a household member													
birth to Key Stage	No	95225	(88.6)	16198	(17.0)	23035	(24.2)	36168	(82.9)	6379	(17.6)	9222	(25.5)
	Yes	12224	(11.4)	3310	(27.1)	4358	(35.7)	7480	(17.1)	2083	(27.8)	2688	(35.9)
Victimisation hospital admission code from	No	106407	(99.0)	19095	(17.9)	26847	(25.2)	43284	(99.2)	8316	(19.2)	11730	(27.1)
birth to Key Stage	Yes	1072	(1.0)	413	(38.5)	546	(50.9)	364	(0.8)	146	(40.1)	180	(49.5)
Household composition and socio-economic status													
Household member died from	No	104015	(96.8)	18726	(18.0)	26312	(25.3)	42223	(96.7)	8107	(19.2)	11431	(27.1)
1 year to Key Stage	Yes	3464	(3.2)	782	(22.6)	1081	(31.2)	1425	(3.3)	355	(24.9)	479	(33.6)
Ever in a single parent household	No	71828	(66.8)	11878	(16.5)	16929	(23.6)	26664	(61.1)	4591	(17.2)	6643	(24.9)
from birth to 5 or 8 years	Yes	35651	(33.2)	7630	(21.4)	10464	(29.4)	16984	(38.9)	3871	(22.8)	5267	(31.0)

†Any code of school action, school action plus or statemented.

Table 6.4: Characteristics of adverse experiences in childhood, household composition, socio-demographics (cont).

		Key Stage 1 cohort						Key Stage 2 cohort					
		Total		Not attained KS1		Special Education Need provided at KS1†		Total		Not attained KS2		Special Education Need provided at KS2†	
		N=107,479		n=19,508 n (%)		n=27,393 n (%)		N=43,648		n=8,462 n (%)		n=11,910 n (%)	
Household composition and socio-economic status (cont)													
Maternal age at childbirth	<18	3313	(3.1)	1001	(30.2)	1289	(24.1)	1461	(3.3)	431	(29.5)	569	(38.9)
	18-24	30226	(28.1)	7150	(23.7)	9683	(20.3)	11976	(27.4)	2972	(24.8)	3964	(33.1)
	25-29 years old	29782	(27.7)	5014	(16.8)	7169	(22.1)	13017	(29.8)	2397	(18.4)	3378	(26.0)
	30-34	29095	(27.1)	4032	(13.9)	5910	(38.9)	11691	(26.8)	1767	(15.1)	2665	(22.8)
	35+	14998	(14.0)	2289	(15.3)	3318	(32.0)	5470	(12.5)	881	(16.1)	1321	(24.1)
	Missing data	65	(0.1)	22	(33.8)	24	(36.9)	33	(0.1)	14	(42.4)	13	(39.4)
Townsend deprivation quintile at birth or first 4 months	1 - least deprived	18383	(17.1)	1869	(10.2)	3027	(16.5)	7180	(16.4)	811	(11.3)	1257	(17.5)
	2	19475	(18.1)	2723	(14.0)	3983	(20.5)	7912	(18.1)	1233	(15.6)	1908	(24.1)
	3	21090	(19.6)	3681	(17.5)	5217	(24.7)	8582	(19.7)	1549	(18.0)	2319	(27.0)
	4	22126	(20.6)	4418	(20.0)	6246	(28.2)	8932	(20.5)	1922	(21.5)	2665	(29.8)
	5 - Most deprived	26078	(24.3)	6762	(25.9)	8851	(33.9)	10820	(24.8)	2900	(26.8)	3705	(34.2)
	Missing data	327	(0.3)	55	(16.8)	69	(21.1)	222	(0.5)	47	(21.2)	56	(25.2)
Maternal cigarette smoking at booking in	No	24634	(22.9)	3646	(14.8)	5625	(22.8)	6375	(14.6)	991	(15.5)	1555	(24.4)
	Yes	8163	(7.6)	2203	(27.0)	3004	(36.8)	2366	(5.4)	627	(26.5)	904	(38.2)
	Missing data	74682	(69.5)	13659	(18.3)	18764	(25.1)	34907	(80.0)	6844	(19.6)	9451	(27.1)
Free school meal in year take KS1	No	87206	(81.1)	12536	(14.4)	18730	(21.5)	36048	(82.6)	5673	(15.7)	8506	(23.6)
	Yes	20273	(18.9)	6972	(34.4)	8663	(42.7)	7600	(17.4)	2789	(36.7)	3404	(44.8)
Free school meal in year take KS2	No	-	-	-	-	-	-	35908	(82.3)	5608	(15.6)	8499	(23.7)
	Yes	-	-	-	-	-	-	7740	(17.7)	2854	(36.9)	3411	(44.1)

†Any code of school action, school action plus or statemented.

Table 6.4: Characteristics of birth (cont).

		Key Stage 1 cohort						Key Stage 2 cohort					
		Total		Not attained KS1		Special Education Need provided at KS1†		Total		Not attained KS2		Special Education Need provided at KS2†	
		N=107,479		n=19,508 n (%)		n=27,393 n (%)		N=43,648		n=8,462 n (%)		n=11,910 n (%)	
Birth characteristics													
Sex	Male	55234	(51.4)	12423	(22.5)	17815	(32.3)	22249	(51.0)	5199	(23.4)	7615	(34.2)
	Female	52245	(48.6)	7085	(13.6)	9578	(18.3)	21399	(49.0)	3263	(15.2)	4295	(20.1)
Gestational age at birth	24 - < 28 weeks: extremely preterm	263	(0.2)	117	(44.5)	152	(57.8)	104	(0.2)	49	(47.1)	56	(53.8)
	28 - < 33 weeks: v preterm	1379	(1.3)	407	(29.5)	561	(40.7)	549	(1.3)	163	(29.7)	226	(41.2)
	33 - < 37 weeks: moderately	6060	(5.6)	1393	(23.0)	1907	(31.5)	2370	(5.4)	555	(23.4)	769	(32.4)
	37+ weeks: term	93817	(87.3)	16403	(17.5)	23225	(24.8)	37832	(86.7)	7132	(18.9)	10107	(26.7)
	Missing data	5960	(5.5)	1188	(19.9)	1548	(26.0)	2793	(6.4)	563	(20.2)	752	(26.9)
Small for gestational age	No	91145	(84.8)	15706	(17.2)	22467	(24.6)	36646	(84.0)	6799	(18.6)	9643	(26.3)
	Yes	9836	(9.2)	2491	(25.3)	3206	(32.6)	3960	(9.1)	1053	(26.6)	1436	(36.3)
	Missing data	6498	(6.0)	1311	(20.2)	1720	(26.5)	3042	(7.0)	610	(20.1)	831	(27.3)
Breastfeeding at birth or 6-8 weeks	No	40191	(37.4)	9043	(22.5)	12295	(30.6)	13064	(29.9)	3111	(23.8)	4083	(31.3)
	Yes	43664	(40.6)	6136	(14.1)	9177	(21.0)	12173	(27.9)	1841	(15.1)	2835	(23.3)
	Missing data	23624	(22.0)	4329	(18.3)	5921	(25.1)	18411	(42.2)	3510	(19.1)	4992	(27.1)
Parity	No	46311	(43.1)	7150	(15.4)	10347	(22.3)	18660	(42.8)	3164	(17.0)	4560	(24.4)
	Yes	60935	(56.7)	12318	(20.2)	16972	(27.9)	24920	(57.1)	5287	(21.2)	7331	(29.4)
	Missing data	233	(0.2)	40	(17.2)	74	(31.8)	68	(0.2)	11	(16.2)	19	(27.9)
Congenital anomalies	None	102339	(95.2)	18087	(17.7)	25406	(24.8)	41514	(95.1)	7861	(18.9)	11056	(26.6)
	Major/minor	5140	(4.8)	1421	(27.7)	1987	(38.7)	2134	(4.9)	601	(28.2)	854	(40.9)
Academic season of birth	Sept-Dec	33044	(30.7)	4379	(13.3)	6837	(20.7)	11659	(26.7)	1730	(14.8)	2833	(24.3)
	Jan-April	36522	(34.0)	6485	(17.8)	9050	(24.8)	15953	(36.5)	3108	(19.5)	4331	(27.1)
	May-August	37913	(35.3)	8644	(22.8)	11506	(30.3)	16036	(36.7)	3624	(22.6)	4746	(29.6)

†Any code of school action, school action plus or statemented.

Table 6.4: School characteristics (cont).

		Key Stage 1 cohort						Key Stage 2 cohort					
		Total		Not attained KS1		Special Education Need provided at KS1†		Total		Not attained KS2		Special Education Need provided at KS2†	
		N=107,479		n=19,508 n (%)		n=27,393 n (%)		N=43,648		n=8,462 n (%)		n=11,910 n (%)	
School factors													
School moves start school to Key	0	101580	(94.5)	17743	(17.5)	25383	(25.0)	41532	(95.2)	7812	(18.8)	11095	(26.7)
Stage 1	1+	5899	(5.5)	1765	(29.9)	2010	(34.1)	2116	(4.8)	650	(30.7)	815	(38.5)
School moves from KS1 to KS2	0	-	-	-	-	-	-	31554	(72.3)	5447	(17.3)	8144	(25.8)
	1	-	-	-	-	-	-	8883	(20.4)	2203	(24.8)	2776	(31.3)
	2	-	-	-	-	-	-	3003	(6.9)	732	(24.4)	905	(30.1)
	3+	-	-	-	-	-	-	208	(0.5)	80	(38.5)	85	(40.9)
School average size at Key Stage^	> 0 - 100 pupils	10150	(9.4)	2076	(20.5)	2425	(23.9)	3967	(9.1)	793	(20.0)	1222	(30.8)
	> 100 - 150 pupils	12175	(11.3)	2679	(22.0)	3589	(29.5)	4584	(10.5)	1039	(22.7)	1453	(31.7)
	>150 - 200 pupils	18875	(17.6)	3632	(19.2)	4975	(26.4)	7310	(16.7)	1526	(20.9)	2120	(29.0)
	> 200 - 300 pupils	32621	(30.4)	5816	(17.8)	8674	(26.6)	12956	(29.7)	2561	(19.8)	3502	(27.0)
	> 300 pupils	33658	(31.3)	5305	(15.8)	7730	(23.0)	14831	(34.0)	2543	(17.1)	3613	(24.4)
School mean percent of children eligible for	<=5%	16316	(15.2)	1630	(10.0)	2531	(15.5)	5808	(13.3)	649	(11.2)	1109	(19.1)
free school meal at Key Stage^	>5-10	21668	(20.2)	2752	(12.7)	4110	(19.0)	7860	(18.0)	1106	(14.1)	1714	(21.8)
	>10-15	19312	(18.0)	3163	(16.4)	4277	(22.1)	6960	(15.9)	1182	(17.0)	1731	(24.9)
	>15-20	15647	(14.6)	***	(18.1)	4165	(26.6)	6427	(14.7)	1161	(18.1)	1698	(26.4)
	>20-30	18799	(17.5)	4117	(21.9)	6018	(32.0)	8409	(19.3)	1828	(21.7)	2501	(29.7)
	>30	15728	(14.6)	5013	(31.9)	6287	(40.0)	8183	(18.7)	2535	(31.0)	3156	(38.6)
	Missing data	9	(0.01)	<5	(33.3)	5	(55.6)	-	-	-	-	-	-
Year take Key Stage	2005	8174	(7.6)	1702	(20.8)	2110	(25.8)	-	-	-	-	-	-
	2006	12475	(11.6)	2351	(18.9)	3019	(24.2)	-	-	-	-	-	-
	2007	12841	(12.0)	2439	(19.0)	3248	(25.3)	-	-	-	-	-	-
	2008	13742	(12.8)	2558	(18.6)	3645	(26.5)	-	-	-	-	-	-
	2009	14236	(13.3)	2518	(17.7)	3662	(25.7)	7641	(17.5)	1806	(23.6)	2068	(27.1)
	2010	14666	(13.7)	2552	(17.4)	3705	(25.3)	11523	(26.4)	2377	(20.6)	3075	(26.7)
	2011	14980	(14.0)	2376	(15.9)	3750	(25.0)	11827	(27.1)	2235	(18.9)	3211	(27.2)
	2012	16365	(15.2)	3012	(18.4)	4254	(26.0)	12657	(29.0)	2044	(16.2)	3556	(28.1)

†Any of school action, school action plus, statemented; ^For years take Key Stage in cohorts; ***raw count not shown for to prevent identifiability for category with less than 5 counts.

6.9.2 Statistical modelling results

Living with an adult household member with CMD was associated with an increased odds for not attaining both KS1 (aOR 1.13 (95% CI 1.09-1.17)) and KS2 (aOR 1.13 (95%CI 1.07-1.19)). A record of serious mental illness in a household adult between birth and KS1 was also associated with increased odds of not attaining KS1 (aOR 1.21 (95% CI 1.02-1.42)) but not at KS2 (aOR 0.97 (95% CI 0.79-1.19)). The magnitude of association for these two exposures at KS1 are similar because the majority of children in this cohort (67.6%) who lived with an adult who had a serious mental illness were also exposed to CMD in the household (Table 6.5, Table 6.6).

Eleven percent of children in the KS1 cohort (n=12,224) and 17.1% (n=7,480) in the KS2 cohort had lived with an adult with an alcohol related problem. These children had an associated increased odds for not attaining KS1 (aOR 1.16 (95% CI 1.10-1.22)) and KS2 (aOR 1.16 (95% CI 1.09-1.24)), after adjusting for perinatal, socio-demographic, other adverse experiences and school factors.

One percent of children were admitted to hospital with a record of victimisation during the study period, and this group were also less likely to attain KS1 (aOR 1.58 (95% CI 1.37-1.82)) and KS2 (aOR 1.88 (95% CI 1.52-2.33)) and more likely to have received SEN provision at KS1 (aOR 1.90 (95% CI 1.66-2.17)) and at KS2 (aOR 1.79 (95% CI 1.46-2.20)).

About three percent of children in the cohort experienced a death of a household member and this was associated with an increased odds for not attaining KS1 (aOR 1.14 (95% CI 1.04-1.25)) and KS2 (aOR 1.13 (95% CI 1.03-1.25)). Low family income (measured as eligibility for free school meals in the year of taking KS1 or KS2) was also associated with an increased odds of not attaining KS1 (aOR 1.92 (95% CI 1.84-2.01)) and KS2 (aOR 1.65 (95% CI 1.53-1.78)).

The effects of socio-economic deprivation were similar for attainment at KS1 and 2, with lower levels of attainment associated with higher levels of deprivation. Young maternal age and the percentage of free school meals in the school attended in the Key Stage year, were both associated with lower educational attainment, although the magnitude of these associations was slightly smaller at KS2 compared with KS1. Children born to older mothers 30+ years were more likely to receive SEN provision at KS1, while children born to younger mothers (under 24 years) were more likely to receive this at KS2.

The inclusion of the two-way interaction terms between exposures, and between exposures and each of maternal age, single adult household, and small-area deprivation did not improve the fit of the model to the data in likelihood ratio tests at the 5% level. Where present, interactions were not important because they failed to show consistent, monotonically increasing or decreasing patterns of adjustment to the main effects of interest. Moreover, they did not alter any of the substantive findings, consisting of changes to the third or fourth decimal place. Consequently, interactions were excluded in subsequent modelling and interpretation.

Table 6.5: Multilevel logistic regressions of adverse household experiences and Key Stage 1 attainment, and Special Educational Needs provision.

		Key Stage 1 cohort (N=107,479)											
		Not attained KS1						Special Education Need provided KS1†					
		Univariable OR (95% CI)			Multivariable OR (95% CI)*			Univariable OR (95% CI)			Multivariable OR (95% CI)*		
Adverse experiences in the household													
Common mental disorder GP code for a household member before birth of child	No	1.00			1.00			1.00			1.00		
	Yes	1.35	1.29	1.41	1.08	1.03	1.14	1.40	1.35	1.45	1.11	1.06	1.16
Common mental disorder GP code for a household member from birth to Key Stage	No	1.00			1.00			1.00			1.00		
	Yes	1.32	1.28	1.37	1.13	1.09	1.17	1.32	1.28	1.36	1.14	1.10	1.18
Serious mental illness GP code for a household member before birth of child	No	1.00			1.00			1.00			1.00		
	Yes	1.41	1.13	1.77	0.92	0.72	1.18	1.74	1.42	2.13	1.15	0.92	1.44
Serious mental illness GP code for a household member from birth to Key Stage	No	1.00			1.00			1.00			1.00		
	Yes	1.66	1.42	1.93	1.21	1.02	1.42	1.62	1.41	1.86	1.20	1.03	1.40
Alcohol problem GP code for a household member before birth of child	No	1.00			1.00			1.00			1.00		
	Yes	1.70	1.60	1.81	1.17	1.09	1.25	1.67	1.58	1.77	1.14	1.07	1.22
Alcohol problem GP code or alcohol-related hospital admission for a household member from birth to Key	No	1.00			1.00			1.00			1.00		
	Yes	1.63	1.56	1.71	1.16	1.10	1.22	1.57	1.51	1.64	1.18	1.12	1.23
Victimisation hospital admission code from birth to Key Stage	No	1.00			1.00			1.00			1.00		
	Yes	2.49	2.18	2.84	1.58	1.37	1.82	2.78	2.45	3.16	1.90	1.66	2.17
Household member died from 1 year to Key Stage	No	1.00			1.00			1.00			1.00		
	Yes	1.27	1.17	1.39	1.14	1.04	1.25	1.32	1.23	1.43	1.21	1.11	1.31
Free school meal in year when take KS1	No	1.00			1.00			1.00			1.00		
	Yes	2.70	2.60	2.81	1.92	1.84	2.01	2.41	2.32	2.49	1.77	1.70	1.84
Family characteristics													
Ever in a single parent household from birth to 5 or 8 years	No	1.00			1.00			1.00			1.00		
	Yes	1.26	1.22	1.31	1.05	1.01	1.09	1.25	1.21	1.29	1.07	1.04	1.11
Maternal age at childbirth	<18	1.84	1.69	2.00	1.56	1.42	1.72	1.72	1.59	1.86	1.52	1.39	1.66
	18-24	1.40	1.34	1.46	1.23	1.18	1.29	1.36	1.31	1.42	1.22	1.18	1.28
	25-29 years old	1.00			1.00			1.00			1.00		
	30-34	0.84	0.80	0.88	0.90	0.86	0.95	0.84	0.81	0.88	0.88	0.85	0.92
	35+	0.95	0.90	1.00	1.00	0.95	1.06	0.96	0.92	1.01	0.99	0.94	1.04
Maternal cigarette smoking at booking in	No	1.00			1.00			1.00			1.00		
	Yes	1.93	1.79	2.08	1.34	1.22	1.47	1.65	1.57	1.74	1.19	1.11	1.28
Parity	No	1.00			1.00			1.00			1.00		
	Yes	1.35	1.31	1.40	1.47	1.41	1.53	1.32	1.28	1.36	1.44	1.40	1.49

*adjusted for variables in the table significant in univariable regression at the 5% level and confounders visualised in DAGs, sex, gestational age at birth, small for gestational age (<10th centile), parity, congenital anomalies, academic season of birth, school moves from start school to KS1, school average size at Key Stage, school mean percent of children eligible for free school meals at Key Stage, Year take Key Stage; OR=odds ratio;
†Any of school action (SA), SA plus, statemented.

Table 6.5: Multilevel logistic regressions of adverse household experiences and Key Stage 1 attainment, and Special Educational Need provision (cont).

		Key Stage 1 cohort (N=107,479)											
		Not attained KS1						Special Education Need provided KS1†					
		Univariable OR (95% CI)			Multivariable OR (95% CI)*			Univariable OR (95% CI)			Multivariable OR (95% CI)*		
Area/School measures of social deprivation													
Townsend deprivation quintile at birth or first 4 months	1 - least deprived	1.00			1.00			1.00			1.00		
	2	1.28	1.19	1.37	1.13	1.05	1.21	1.21	1.14	1.28	1.10	1.04	1.17
	3	1.56	1.46	1.66	1.22	1.14	1.31	1.46	1.38	1.54	1.20	1.13	1.27
	4	1.84	1.72	1.96	1.32	1.23	1.41	1.72	1.63	1.82	1.31	1.23	1.39
	5 - Most deprived	2.37	2.23	2.53	1.43	1.33	1.53	2.11	1.99	2.22	1.35	1.27	1.43
School mean concentration of children eligible for fresh school meals at KS1	≤5%	1.00			1.00			1.00			1.00		
	>5-10	1.21	1.10	1.35	1.10	0.99	1.23	1.32	1.20	1.45	1.16	1.05	1.29
	>10-15	1.63	1.48	1.81	1.30	1.17	1.45	1.62	1.48	1.79	1.28	1.15	1.42
	>15-20	1.89	1.70	2.10	1.33	1.19	1.48	1.97	1.79	2.18	1.40	1.26	1.56
	>20-30	2.27	2.05	2.51	1.40	1.26	1.55	2.65	2.42	2.90	1.71	1.54	1.89
	>30	4.09	3.71	4.51	1.93	1.73	2.15	4.11	3.75	4.51	2.09	1.88	2.32

*adjusted for variables in the table significant in univariable regression at the 5% level and confounders visualised in DAGs, sex, gestational age at birth, small for gestational age (<10th centile), parity, congenital anomalies, academic season of birth, school moves from start school to KS1, school average size at Key Stage, Year take Key Stage; OR=odds ratio;

†Any of school action (SA), SA plus,statemented.

Table 6.6: Multilevel logistic regression of adverse household experiences and Key Stage 2 attainment, and Special Educational Need provision.

		Key Stage 2 cohort (N=43,648)											
		Not attained KS2						Special Education Need provided KS2†					
		Univariable			Multivariable			Univariable			Multivariable		
Adverse experiences in the household													
Common mental disorder GP code for a household	No	1.00			1.00			1.00			1.00		
member before birth of child	Yes	1.19	1.09	1.31	0.99	0.89	1.09	1.33	1.23	1.45	1.02	0.94	1.12
Common mental disorder GP code for a household	No	1.00			1.00			1.00			1.00		
member from birth to Key Stage	Yes	1.34	1.27	1.41	1.13	1.07	1.19	1.29	1.23	1.35	1.11	1.06	1.16
Serious mental illness GP code for a household member	No	1.00			1.00			1.00			1.00		
before birth of child	Yes	1.02	0.58	1.81	0.79	0.43	1.45	1.51	0.94	2.43	1.06	0.63	1.76
Serious mental illness GP code for a household member	No	1.00			1.00			1.00			1.00		
from birth to Key Stage	Yes	1.36	1.12	1.66	0.97	0.79	1.19	1.39	1.16	1.67	1.05	0.87	1.27
Alcohol problem GP code for a household member before	No	1.00			1.00			1.00			1.00		
birth of child	Yes	1.54	1.34	1.77	1.13	0.97	1.31	1.65	1.46	1.88	1.13	0.98	1.29
Alcohol problem GP code or alcohol-related hospital	No	1.00			1.00			1.00			1.00		
admission for a household member from birth to Key	Yes	1.65	1.55	1.75	1.16	1.09	1.24	1.52	1.44	1.61	1.11	1.05	1.19
Victimisation hospital admission code from birth to Key	No	1.00			1.00			1.00			1.00		
Stage	Yes	2.79	2.29	3.41	1.88	1.52	2.33	2.39	1.92	2.97	1.79	1.46	2.20
Household member died from 1 year to Key Stage	No	1.00			1.00			1.00			1.00		
	Yes	1.32	1.20	1.45	1.13	1.03	1.25	1.30	1.15	1.46	1.13	1.03	1.24
Free school meal in year when take KS1	No	1.00			1.00			1.00			1.00		
	Yes	2.78	2.62	2.95	1.51	1.40	1.63	2.41	2.28	2.55	1.50	1.40	1.62
Free school meal in year when take KS2	No	1.00			1.00			1.00			1.00		
	Yes	2.82	2.66	2.99	1.65	1.53	1.78	2.33	2.20	2.46	1.40	1.30	1.51
Family characteristics													
Ever in a single parent household from birth to 5 or 8	No	1.00			1.00			1.00			1.00		
years	Yes	1.32	1.26	1.39	1.04	0.99	1.10	1.26	1.20	1.32	1.05	1.00	1.11
Maternal age at childbirth	<18	1.62	1.43	1.84	1.30	1.13	1.49	1.64	1.46	1.85	1.42	1.24	1.61
	18-24	1.36	1.27	1.45	1.18	1.10	1.26	1.34	1.26	1.42	1.20	1.12	1.27
	25-29 years old	1.00			1.00			1.00			1.00		
	30-34	0.83	0.77	0.89	0.90	0.83	0.97	0.88	0.83	0.94	0.93	0.87	0.99
	35+	0.89	0.82	0.98	0.95	0.86	1.04	0.95	0.88	1.02	0.96	0.89	1.05
Maternal cigarette smoking at booking in	No	1.00			1.00			1.00			1.00		
	Yes	1.73	1.62	1.85	1.18	1.09	1.28	1.81	1.63	2.01	1.32	1.13	1.55
Parity	No	1.00			1.00			1.00			1.00		
	Yes	1.29	1.23	1.36	1.37	1.29	1.46	1.26	1.21	1.32	1.36	1.29	1.43

*adjusted for variables in the table significant in univariable regression at the 5% level and confounders visualised in DAGs, sex, gestational age at birth, small for gestational age (<10th centile), parity, congenital anomalies, academic season of birth, school moves from start school to KS1, school average size at Key Stage, school mean percent of children eligible for free school meals at Key Stage, Year take Key Stage; OR=odds ratio; †Any of school action (SA), SA plus,statemented.

Table 6.6: Multilevel logistic regression of adverse household experiences and Key Stage 2 attainment, and Special Educational Need provision (cont).

		Key Stage 2 cohort (N=43,648)											
		Not attained KS2						Special Education Need provided KS2†					
		Univariable OR (95% CI)			Multivariable OR (95% CI)*			Univariable OR (95% CI)			Multivariable OR (95% CI)*		
Area/School measures of social deprivation													
Townsend deprivation quintile at birth or first 4 months	1 - least deprived	1.00			1.00			1.00			1.00		
	2	1.38	1.24	1.53	1.23	1.11	1.37	1.35	1.23	1.47	1.22	1.11	1.34
	3	1.55	1.40	1.72	1.23	1.11	1.37	1.50	1.37	1.63	1.25	1.14	1.37
	4	1.93	1.75	2.13	1.38	1.25	1.54	1.74	1.60	1.90	1.34	1.22	1.46
	5 - Most deprived	2.40	2.18	2.65	1.45	1.31	1.61	2.03	1.86	2.21	1.35	1.23	1.48
School mean concentration of children eligible	≤5%	1.00			1.00			1.00			1.00		
	>5-10	1.24	1.06	1.45	1.11	0.94	1.30	1.10	0.96	1.27	1.06	0.91	1.22
	>10-15	1.58	1.35	1.84	1.21	1.03	1.42	1.32	1.14	1.53	1.11	0.96	1.30
	>15-20	1.69	1.44	1.99	1.18	1.00	1.39	1.46	1.26	1.70	1.13	0.97	1.33
	>20-30	2.20	1.90	2.56	1.26	1.07	1.48	1.74	1.52	2.00	1.15	0.99	1.34
	>30	3.89	3.36	4.49	1.69	1.44	1.98	2.79	2.43	3.19	1.44	1.24	1.68

*adjusted for variables in the table significant in univariable regression at the 5% level and confounders visualised in DAGs, sex, gestational age at birth, small for gestational age (<10th centile), parity, congenital anomalies, academic season of birth, school moves from start school to KS1, school average size at Key Stage, school mean percent of children eligible for free school meals at Key Stage, Year take Key Stage; OR=odds ratio; †Any of school action (SA), SA plus,statemented.

Multiple adversities had substantially increased odds associated with children not attaining the expected level at each educational assessment as shown in Figure 6.5, Table 6.7. For example, the odds associated with not attaining KS1 are 3.59 times higher (aOR 3.59 (95% CI 3.25-3.96)) for a child who lived in an area with the highest level of social deprivation, was eligible for free school meals, and lived with an adult who had a common mental disorder and alcohol related problems, compared with a similar child who lived in a household in an area with the lowest level of social deprivation (Table 6.7). These data signal a clear need for early identification of this group and intervention to mitigate the impacts of multiple childhood adversities on education and consequent longer-term social and economic outcomes. Further, the PAFs for each individual ACE showed of those who did not attain KS1 there were different proportions of children who could attain the expected level at KS1 if that ACE was eliminated (Table 6.8). A summation of the PAFs across all ACEs including poverty illustrates approximately 1 in 10 children who do not attain KS1, could attain KS1 if these ACEs were entirely prevented or mitigated.

It was not possible to estimate a similar adjusted RR, RD and PAFs using general linear models (GLM) for comparison to the logistic regression estimates because the models failed to converge. Output from the models where convergence was not achieved showed potentially more than half the variables were preventing convergence (large standard errors) and would need to be removed to produce estimates. In this cohort, the model output suggests a combination such as death in the household, household alcohol problems, born in the academic summer term, being male, being small for gestational age (<10th centile), a gestational age of 33-36 weeks and household CMD may perfectly predict that a child does not attain the expected level at KS1.

Table 6.7: Likelihood of poor school performance associated with combinations of exposures and socio-demographic characteristics (based on linear combinations of adjusted model in Tables 6.5).

Reference category: Least deprived quintile of area-level deprivation, not eligible for free school meals in year preceding KS1 assessment (proxy start date 1st May), never exposed to child adversity measured, maternal age at childbirth between 25-29 years old, ≤5% mean of number of children eligible for free school meals in school when take the Key Stage 1 assessment.	**Not attained KS1 at age 6-7 years**		**Received SEN provision at age 6-7 years**	
	OR[a]	**(95% CI)**	**OR[a]**	**(95% CI)**
Household member with common mental disorder[b] AND household member with alcohol problems[b]	1.31	(1.23-1.39)	1.34	(1.27-1.41)
Most deprived quintile at birth/first 4 months AND eligible for free school meals in year preceding KS1 assessment AND household member with common mental disorder[b] AND household member with alcohol problems[b]	3.59	(3.25-3.96)	3.20	(2.94-3.49)
Most deprived quintile at birth/first 4 months AND eligible for free school meals in year preceding KS1 assessment AND household member with common mental disorder[b] AND household member with alcohol problems[b] AND victimisation	5.67	(4.80-6.71)	6.08	(5.19-7.12)

a=Odds ratio; b=between child's birth and age 6-7 years (KS1); KS1=Key Stage 1; SEN=Special Educational Need provision.

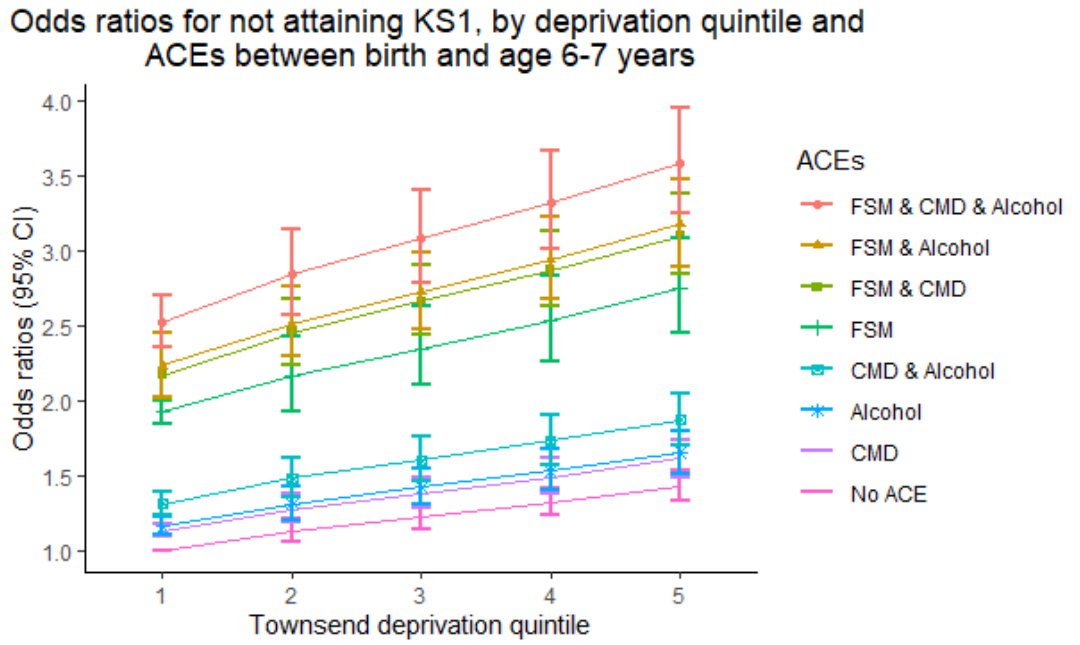

Figure 6.5: Likelihood of not attaining KS1 associated with combinations of exposures and sociodemographic characteristics (based on linear combinations of adjusted model in Table 6.5).

ACE=adverse childhood experience; CMD=household common mental disorder; Alcohol=household alcohol problem; FSM=free school meals eligible in year preceding KS1 assessment (proxy start date 1st May). Townsend deprivation quintiles for small area of residence Lower Super Output Area (LSOA) from the 2001 census=400-1200 households.

Table 6.8: ACE exposures and educational attainment outcomes adjusted average risk differences, ratios and population attributable fractions (one imputed data set for missing data).

	Percentage of exposed participants (%) N=107,479	Not attained KS1 n=19,508		
		Adjusted Risk Ratio (95% CI)	Adjusted Risk Difference (%) (95% CI)	Population attributable fraction (PAF)* (%)
Living with someone with CMD birth to KS1	38.4	1.10 (1.07-1.13)	1.7 (1.2-2.2)	3.61
Living with someone with SMI birth to KS1	0.9	1.12 (1.00-1.25)	2.1 (-0.1-4.4)	0.11
Living with someone with an alcohol problem (GP heavy drinker or alcohol related hospital admission) birth to KS1	11.4	1.10 (1.07-1.14)	1.9 (1.2-2.6)	1.18
Child victimisation birth to KS1	1.0	1.38 (1.26-1.51)	6.9 (4.7-9.1)	0.38
Death in the household child age 1 year to KS1	3.2	1.10 (1.03-1.17)	1.8 (0.5-3.0)	0.31
Single parent household birth to KS1	33.2	1.04 (1.01-1.06)	0.7 (0.2-1.1)	1.22
Free school meals eligible (FSM) in year take KS1	18.9	1.59 (1.54-1.64)	9.4 (8.7-10.0)	10.04
All potential ACEs				15.35
All potential ACEs excluding FSM				6.52
Living with someone with CMD birth to KS1 AND Living with someone with an alcohol problem (GP heavy drinker or alcohol related hospital admission) birth to KS1 AND FSM in year take KS1				13.86

* PAF is the percentage of children who do not attain the expected level at KS1 that could attain KS1 if ACEs (or the potential ACE of poverty) were eliminated, assuming causality.

6.10 Discussion

This study shows that children exposed to adverse experiences during childhood were less likely, compared to non-exposed peers, to attain the expected level of education at age 6-7 years (KS1) and age 10-11 years (KS2) after controlling for socio-demographic characteristics, perinatal health indicators, household composition and school factors. The magnitude of this potential causal association varied according to the type and timing of exposure. For example, exposure of a child during the first year of life to adults with a history of CMD had a lower magnitude of effect on KS attainment compared to exposure during the years leading up to taking the KS assessments. This may be due to the proximity of the exposure nearer the time when a child takes the KS assessment. The observed effect sizes of the associations for exposure to mental disorder or alcohol problems in the household were in addition to those observed for living in areas with high levels of deprivation. The results of this thesis agree with the conceptual framework in the ACEs Pyramid where ACEs are thought to be associated with cognitive impairment (Figure 1.3, Section 6.1). These results suggest that reducing the prevalence of these household exposures, ensuring children who are exposed are identified early and supported appropriately could make a difference to their educational outcomes. Public Health

practitioners may find it difficult to reduce the prevalence of children's ACEs in the household and therefore direct support for children's educational attainment may help to mitigate the effects of these ACEs.

The effects of the ACEs in this chapter's study were cumulative, such that children who had multiple exposures had even higher likelihood for not attaining the expected level at KS assessments. This result supports Felitti et al's ACEs theory of a cumulative risk from co-occurring ACEs for poorer adult outcomes,(3) and theories about ACE exposures and cognitive impairment outcomes in the ACEs Pyramid (Figure 1.3, Section 6.1). Childhood victimisation and low family income had the biggest associations for children not attaining the expected level at Key Stages, possibly reflecting the severity of these exposures. This study used hospital admissions as a measure of victimisation and is therefore likely to underestimate the true impact of victimisation on education outcomes. These findings provide compelling evidence of the need for trauma-informed services for early detection and intervention of affected children and additional educational support to mitigate future impact on educational outcomes. Death of a household member was also associated with an increased risk for not attaining the expected level at KS assessments. This study did not have sufficient data to explore this effect according to the relationship between the child and household member who had died or age at which this occurred. Further work is needed to fully understand how and in what circumstances death in the household impacts on a child's health and wellbeing.

The relationship between socio-economic deprivation and ACEs is debated in the literature. This study used data that provided two socio-economic measures (i) area-level deprivation and (ii) individual level eligibility for Free School Meals, the latter a measure of low family income that is not often available for analyses at population level. Area-level deprivation was included in statistical modelling as a confounder between ACEs and educational attainment. A confounder is, by definition, a shared common cause of both exposure and outcome, and consequently is specific to the choice of exposure of interest. Adjusting for a confounder therefore makes implicit causal inferences about hypothetical interventions on the exposure (ACEs) while holding confounders constant. The main exposure of interest were specific ACEs and potential for interventions on these ACEs, it is therefore entirely appropriate to consider area-level deprivation as a confounder.

Only one previous study has investigated the association of more than two individual adverse experiences during childhood on educational outcome.(14) The Australian study

reported that alcohol use, mental health issues and death of a parent increased the risk for poorer reading attainment at age 8 years but their analyses did not include low family income, did not take account of differences in school factors, or examine the cumulative effects of child adversity on educational outcome. This study adjusted analyses for school absence that may be a potential mediator between ACEs and educational attainment and therefore did not give a measure of the total causal effect of the exposures of interest. Two other studies considered two ACEs where one potential ACE was a measure of low family income (welfare payments, free school meals eligible), they highlighted the strength of this association with poorer educational outcomes and the importance of including this measure in modelling.(26,27) Other studies included wider age ranges of children between 5 to 17 years, they reported detrimental effects on educational attainment for household alcohol misuse,(29) death in the household,(26,28,30,31) victimisation of the child,(28,30) and low family income.(26,27,28,29,30,31) Most of these studies examined the impact of single adverse exposures adjusting models for other ACEs. None of these studies adjusted for the multiple confounders of deprivation, birth and socio-demographic characteristics, and school factors including school concentration of poverty that were used in this chapter's analyses.

Previous research shows that some ACEs are socio-economically patterned occurring more often in those more deprived and that these rarely occur in isolation.(2,12) This study adds to the current body of evidence by considering the collective impact of a range of adverse exposures in the household, in addition to socio-economic indicators on children's educational outcomes.

The key strength of this study is that it measures adverse exposures in the household using administrative and healthcare data sets. This addresses the limitation of some previous studies which have relied on self-reported data to ascertain exposure during childhood. It also uses data on a wide range of perinatal, socio-demographic and school level data, to take account of these complex relationships and the association between ACEs and educational outcomes. One of the limitations of this study is the reliance on coding in administrative data because of the potential for misspecification and the inability to liaise directly with data collectors in real-time about any anomalies. However, any misclassification is unlikely to disproportionately affect one group over another and so is unlikely to have created a bias in any particular direction.

Further limitations in this study were there was no data available on parental education or IQ (as a proxy for variation in school engagement) nor on contact with social care and therefore the role of these variables could not be explored. The data showed that 27% of children had SEN provision, however there was not sufficient data to explore any unmet need or the appropriateness of this provision for individual children. Further research is needed to explore how SEN provision is implemented and whether or not there is appropriate SEN provision to support young children and how this is accessed.

The study in this chapter investigated the potential causal direction of ACEs on children's educational attainment outcome and suggested a theoretical mechanism of chronic stress in children leading to cognitive impairment and poorer outcome. It is acknowledged that ACEs and cognitive ability in children may also have potential reverse causation for children who are neurodivergent (e.g. autism, attention deficit hyperactivity disorder, dyslexia, dyspraxia) or who have congenital anomalies because these children may be more difficult to parent. Previous research shows child maltreatment discordant twins at age 9 years had somewhat higher levels of neurodivergent symptoms in the maltreated twin even after adjustment for genetic factors and environment.(70)

There may also be complexity between parents and children from neurodiversity in children's educational outcomes. The link between genetic factors and neurodiversity in families may mean some parents and children both have symptoms of neurodiversity.(71,72,73) In addition, studies show neurodiversity in adults such as mild autistic spectrum disorder have previously been misdiagnosed as common mental disorder or that these disorders quite often co-occur.(74,75) Approximately 15% of the population in the UK are neurodivergent(76) so it is possible CMD measured in adults in the analyses of this thesis may include caregivers in the household with milder undiagnosed neurodiversity. A key feature of neurodivergence is problems with executive functioning,(76) and therefore children with neurodivergent symptoms may be more likely to not attain the expected level at KS1. Moreover, children's milder neurodivergence may not be diagnosed in childhood but at a later age (74) and so they do not receive SEN provision. The analyses in this thesis adjusted for confounding from congenital anomalies but had no information on neurodiversity in children or caregivers. It is likely that some neurodivergent children will be receiving SEN provision, however it is acknowledged there may be some residual confounding from milder neurodivergence in children and parents.

At a population level, this study demonstrates how the educational potential of many children may not be achieved due to exposure to adversity in childhood. Although the distribution of ACEs are socially patterned, these results suggest that the impact of ACEs on educational outcomes are in addition to those related to social deprivation. Thus, a combination of poverty in addition to childhood exposure to household mental disorders and alcohol related problems increases the likelihood of failing the basic educational tests in language and maths by over 350% for children living in the most compared to least deprived areas.

Critically, a poor start in education has been strongly linked with poorer educational outcomes across all schooling years, poorer employment prospects and consequently a poor economic outlook across the life course.(2,30,77,78) Consequently, exposure to ACEs increases the chances that children develop into adults with poor economic prospects; contributing to a cycle of hardship that fuels inequalities and potentially locks families into deprivation and ill health across generations. There are already a range of evidence-based interventions that provide parent and caregiver support for children's behavioural problems (79,80) and to improve self-regulation.(33) There are interventions for pre-school enrichment to improve school readiness and advance health equity in the economically disadvantaged.(81,82) Increasingly, there are trauma-informed educational services for post-traumatic stress responses in children (83,84) to build positive environments, develop social-emotional learning, coping and support systems. For those with more serious trauma from maltreatment, trials mainly in the USA show interventions such as trauma focussed cognitive behavioural therapy (TF-CBT) for a child and non-offending caregiver can be of benefit. Improvements in child symptoms were observed for post-traumatic stress disorder, anxiety, depression or mild to moderate behavioural outcomes from traumatic events.(85,86,87) These interventions coupled with services that can provide financial advice and debt management strategies mean it is no longer a lack of effective interventions for children or sound economic arguments that prevent safe and secure childhoods. There is compelling evidence from research into ACEs for political investment into these interventions to ensure subsequent generations of children achieve their full potential individually and live in communities that prosper.

6.11 Implications for this thesis

This study shows that children living with adults who have mental disorders or alcohol problems, who experienced victimisation or a death in the family are at increased risk for

not achieving their educational potential. As these experiences are relatively common, it is important that appropriate conversations are initiated when affected children come in to contact with health, education and social care services. This relevant information should be shared between health and care services and schools to facilitate a coordinated approach to tackle ACEs such as alcohol misuse and family violence as early as possible, whilst supporting affected families and children. It is also important that schools are adequately resourced to provide the additional support needed for children from affected families through onsite counsellors or social workers. This investment will help to reduce their risk of lower educational outcomes so they fulfil their educational potential, and subsequent economic and social participation.

This thesis finds unplanned hospital admissions for both any cause or from the long-term condition of asthma rather than asthma severity are associated with poorer educational attainment at age 6-7 years and that ACEs in the household environment easily observed by health, social care workers or educators have detrimental effects on educational attainment throughout childhood. This thesis provides new evidence on the magnitude of combinations of ACEs and their associations with children's educational attainment previously only measured in adults. The next chapter with investigate the interplay between these health and social factors for children's educational attainment at age 7 years (KS1).

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Chapter 7 : Adverse childhood experiences, emergency hospital admissions and educational attainment

7. Overview

In Chapters 4 to 6 of this thesis I determined that emergency inpatient hospital admissions for any cause or for asthma (rather than asthma severity), or adverse childhood experiences (ACEs) increased the risk for a child not attaining Key Stage 1 (KS1) at age 6-7 years. These effects were found to be stronger when more proximal to educational outcomes for ACEs, or at a younger age for exposure to emergency hospital admissions. For all-cause unplanned hospital admission, children had greater risk for not attaining KS1 if their admission was in the pre-school period, particularly for longer duration of stay in hospital. Moreover, children had increasing risk for not attaining the expected level at KS1 from asthma emergency admission as the number of admissions rose. These chapters provide new knowledge for current gaps in the research literature but the interplay between health and social factors on educational attainment outcomes remains uncertain. In this chapter I investigate part of this complex interplay between these risk factors by assessing whether or not childhood health is on a potential causal pathway (a mediator) between ACEs and poorer educational outcomes. To answer this research question, I initially determine whether ACEs have a potentially causal effect on emergency hospital admissions (for asthma or all-cause admissions) in childhood. I review the literature for previous evidence of a potential causal pathway between ACEs and emergency admissions and whether that relationship explains poorer educational attainment at KS1 (at age 6-7 years). I then examine the effects of these health and social factors using the administrative data cohort of children described in Chapter 6 and asthma hospital admissions defined in Chapter 5, and discuss the implications of all the evidence. This investigation will add to the understanding of the interplay between health and social factors for children's educational attainment at age 7 years so that the most appropriate interventions can be used.

7.1 Background

There is little evidence in the literature about ACEs and emergency hospital admission outcomes in children. In exposures prior to birth, prenatal maternal stress has been associated with increased susceptibility in offspring for asthma,(1,2,3) infections (4,5) and injuries. The exposure to prenatal alcohol is causative for foetal alcohol spectrum disorders and associated with impaired early lung development and more respiratory illnesses during childhood.(6) For exposure to adversity after birth, studies tend to focus on one ACE and emergency hospital admission outcomes in childhood.(7) The published literature for ACEs and asthma hospital admission outcome shows research is mainly limited to cohorts of children with asthma or those with susceptibility (e.g. family history, atopy).(8,9) A person with atopy has an immune system that overreacts to allergens and this effect is caused by their genetics. When these people come into contact with substances that are normally harmless their body produces too many antibodies (called immunoglobulin E, or IgE) leading to further cell reactions that cause symptoms of allergy such as allergic asthma. Emerging evidence using administrative data indicates children with ACEs were more likely to present earlier for first all-cause hospital admission (10) or for viral gastroenteritis.(11) Emergency hospital admissions are by their nature unpredictable, occur at short notice as a result of clinical need (10) and may reoccur in cases such as chronic disease in children.

In Chapter 6, this thesis provided evidence that ACEs are associated with poorer educational attainment in childhood. In Chapters 4 and 5, this thesis determined that all-cause emergency hospitalisations and asthma inpatient hospital admissions rather than childhood asthma severity impacted on children's educational attainment.(12) A feature of children's hospital admissions for asthma were that they occurred in even the least severe asthma severity categories. It is notable that previous research shows asthma exacerbations are most common in children under 5 years.(13)

In previous work I carried out, it was found that ACEs increased the risk for children's first all-cause emergency hospital admission in follow-up from birth.(10) However, the effects of ACEs on children's first asthma admission or recurrent (all-cause or asthma) emergency inpatient admissions in childhood remains unaddressed. In this chapter it is hypothesised that children exposed to ACEs have higher risk for emergency admission for asthma, or for recurrent admissions for asthma or all-causes. In addition, it is hypothesised that emergency hospital admissions are on the potential causal pathway between ACEs and poorer educational attainment outcome in childhood.

7.2 Literature review

For the research question 'do emergency hospital admissions explain the association between ACEs and not attaining the expected level of education at age 7 years?', a review was undertaken of the existing literature. The objectives of the review were to assess the potential causal association of ACEs from birth, particularly those measurable by health services, on emergency admissions, and to assess whether this relationship explains educational attainment at age 6-7 years (KS1). Two examples of emergency inpatient hospital admissions in childhood were chosen for the study in this chapter. Firstly, children with asthma admissions (acute attacks from a chronic condition) and secondly, those with all-cause admissions (a measure of general emergency admission, most often for reasons such as respiratory infections, gastroenteritis or injury in this age group). This section of the chapter summarises previous research and highlights gaps in the evidence to give context to findings and discussion later in this chapter.

7.2.1 ACEs and asthma emergency hospital admissions

Search strategy

For exposure to ACEs and asthma emergency hospital admissions outcome in children search terms for ACEs and asthma from Chapters 5 and 6 were used and the databases listed in those chapters (see Sections 5.2.1 and 6.2.1). The search found three comprehensive systematic reviews that summarised the results of asthma onset (7,8,9) and the course of asthma (acute asthma exacerbations) (7,9) throughout childhood. The reviews looked at individually measured ACEs rather than cumulative scores and the effect on asthma hospital admission outcome in children.

These reviews were supplemented with a further search of the same databases in two phases. The first search was for all ACEs excluding household mental health, bereavement, and child maltreatment and asthma from database conception to May 2021 for prospective cohorts. The second search was for the remaining ACE terms including the term 'common mental disorder' and asthma from January 2008 to May 2021 so that there was sufficient overlap to prevent any articles being missed. The reference lists of relevant studies and their citations were reviewed to identify any further studies. Two studies were not included in the review because they only reported ACEs or negative life events as a count rather than each individual experience and asthma outcomes in children.(14,15)

Overview

Few studies looked specifically at ACEs and asthma hospital admission outcome in children. There was a substantial literature surrounding prenatal maternal stress from stressful life events and asthma in offspring. For ACEs and asthma there were several systematic reviews that mainly centred on maternal mental health and first diagnosis of asthma (asthma onset) in childhood. Three cohort studies investigated ACEs and acute asthma exacerbations (elsewhere described as the course of asthma) using asthma hospitalisations or Emergency department (ED) visits as an outcome, mainly in cohorts of children diagnosed with asthma.

ACEs and acute asthma exacerbations

As mentioned, previous research of ACEs and acute asthma exacerbation outcome was found mostly in cohorts of children who already had a diagnosis of asthma. The literature showed that different ACEs had different effects on the likelihood of a child having an asthma exacerbation. Caregiver mental health conditions (psychological stress or distress) increased the risk for acute asthma exacerbation hospitalisations (7,9,16,17) or ED visits (18) in asthmatic children, when compared to children whose caregivers did not have mental health conditions. Other studies measured children's mental health and stress up to age 18 years, thought to be on the pathway (a mediator) between parent / guardian stress and children's asthma exacerbations. These studies showed mixed results, children with acute or chronic stress had increased risk for acute asthma exacerbation within 2-6 weeks,(19) increased wheeze and poorer general function but not asthma hospitalisations.(20) Only one study investigated children who were exposed to a guardian with an alcohol problem and no evidence was found of an increased risk for hospital admission for acute exacerbation in asthmatic children.(17) None of these studies looked at more than three ACEs (only two ACEs if poverty was excluded) or multiple hospital admissions for asthma (i.e. multiple acute asthma exacerbations) in children.

One study looked at all children in the general population, children's exposure to maltreatment and time to first asthma hospital admission in adolescence. Children who experienced maltreatment recorded in state records prior to age 12 years had increased risk for time to first asthma hospital admission in adolescence cHR 1.73 (95% CI 1.47-2.04) (21) compared to children without this experience. It is also notable that the hazard ratio was relatively large for children exposed to maternal mental ill health and the time to first

admission for asthma in adolescence cHR 1.47 (95% CI 1.03-2.09) in this study compared to those not exposed. However, the effect of poverty in childhood was small for time to first asthma hospital admission in adolescence cHR 1.04 (95% CI 1.001-1.08) likely because the study was set in a low-income cohort.

ACEs and first diagnosis of asthma (asthma onset)

The search of the published literature revealed several reviews for ACEs beyond birth and a new diagnosis of asthma (asthma onset). The reviews showed 11 of 18 studies found an association between exposure to ACEs and a new diagnosis of childhood asthma.(8,9) Interestingly, two further studies in these reviews found an effect between ACEs and a new diagnosis of childhood asthma but only in areas where there was high traffic air pollution ($p<0.05$). Three of the studies in the reviews were cohorts of children with a family history of atopy and these studies all showed an increased risk between ACEs and asthma onset. Exclusion of these studies from the review findings shows there is no evidence of an association between ACEs and asthma onset in healthy children without a family history of atopy, or for those from the general population. Importantly, most of these studies adjusted their analyses for socio-economic status, a known confounder.

The review by Oh et al and more recent research (22,23) weights the overall evidence towards an increased risk from exposure to parental psychological stress or mental health problems and a new diagnosis of asthma outcome in childhood.(7,16,21,22,23) However, this result is not decisive because most of these studies were of relatively small size (<2000 children). One of the studies in Oh et al's review was large, and found children who were exposed to maternal physician diagnosed anxiety or depression had an increased risk for asthma onset at age 7 years (aOR 1.25 (95% CI 1.01-1.55)).(24) A contrasting result was observed for childhood stress, thought to be a mediator between parental stress or distress and a new diagnosis of asthma. Tibosch et al's review concluded that there was no compelling evidence of an association between child-specific psychological conditions and asthma onset in childhood.(9) Conversely, three studies looked at poverty in childhood and found it increased risk for a new diagnosis of asthma.(8,21,25,26)

ACEs and asthma mechanisms

Three studies of children who were exposed to ACEs found changes in blood tests for asthma-relevant inflammatory markers, immune response markers for allergy,(9,17,27) or serum cortisol (7,28) compared to those who were not exposed. These findings lend support to the theory that exposure to parental stress causes biological changes in the child through disturbance of the hypothalamic-pituitary-adrenal (HPA) axis and this may interact with the child's predispositions for disease. A study that found a link between high traffic air pollution and ACEs for risk of an new diagnosis of asthma in childhood suggested a diathesis-stress explanation between ACEs and asthma.(8)

Maternal prenatal distress and asthma in offspring

The published literature shows there is accumulating evidence to establish a link between prenatal maternal psychological stress and the development of asthma or wheeze in their offspring in early childhood.(1,2,3) Exposure of children to prenatal maternal stress (in utero exposure) showed an increased risk for asthma or wheeze outcome in children in most (3,29,30,31) but not all studies.(32) Potential biological pathways between prenatal maternal stress and asthma in offspring are suggested.(1,29,33)

7.2.2 ACEs and all-cause emergency hospital admissions

In previous work (10) I investigated children who experienced ACEs and time to first all-cause emergency inpatient admission. This study found living with someone with a common mental disorder (e.g. anxiety, depression) had increased risk for an all-cause emergency admission in childhood, cHR 1.17 (95% CI 1·16–1·19) but found no evidence of increased risk if they lived with someone with an alcohol problem.(10) The findings used both measurement of children's prenatal exposure to ACEs and ACEs beyond birth for risk of all-cause emergency admission in childhood. For emergency admission, children's risk from living with someone with a common mental disorder was strongest in the first year of life when compared to up to age 8 years. Models were adjusted for all ACEs measured (household common mental disorder, serious mental illness, alcohol problems), maternal age, birth characteristics, deprivation and single parent. Prior to this study in 2018, to my knowledge there was no evidence in the published literature about children's exposure to ACEs and all-cause emergency inpatient hospital admission outcomes.

Recent literature shows evidence to support these findings in other administrative data cohorts.(11,34,35,36,37) Living with parents with mild mental health conditions (use of antidepressants or psychologists) increased number of hospital admissions for children in the first year of life IRR 1.25 (95% CI 1.24-1.27)(34) but these analyses were not adjusted for birth characteristics, poverty or other ACEs. Also, living with parents with psychiatric disorders was associated with children having an earlier hospital admission for viral gastroenteritis (11) in analyses adjusted for birth characteristics but no other ACEs, and an elevated risk for injury hospitalisation.(36) These studies showed similar results for children exposed to these ACEs and ED visits.(11,34) These results for children with a parent who had a psychiatric disorder contrast with the findings of the previous study I carried out (10) that found no evidence that living with someone with a serious mental illness increased risk for any hospital admission in childhood. This striking difference in effects may be due to adjustment for other ACEs in these analyses particularly common mental disorder (anxiety or depression are found to accompany 70% of serious mental illnesses when measured in the household in the UK),(10) or caregiver alcohol problems. These studies may also have differences in the definitions of parental psychiatric disorder although all were captured from medical records. The study I carried out (10) had a lower proportion of parents with serious mental illness in the population (1%) compared to these other studies (5-17%) in Sweden and Denmark.(11,34)

One further study looked at children with several ACEs and their ED visits (35) from Medicaid insurance records. Their study found children exposed to a parent with mental illness had an increased risk for the number of visits to the ED IRR 1.21 (95% CI 1.19-1.24). The study also found increased risk for ED visits for children if they had been exposed to a parent in the criminal justice system, experienced child abuse / neglect IRR 1.08 (95% CI 1.06-1.10), homelessness or poverty IRR 1.25 (95% CI 1.23-1.28). Conversely, this study found children exposed to parent domestic violence or parental death did not have a higher number of ED visits compared to children not exposed. The effect sizes of the results of this study for children exposed to abuse or neglect seemed particularly low when compared to poverty, also it did not consider the effects of parents with alcohol problems but did report a cumulative impact from several ACEs. None of the studies in the literature considered the effect on children from ACEs for time to next admission for multiple hospital admissions.

7.2.3 Emergency hospital admissions as a potential mediator between ACEs and educational attainment

The existing literature shows no studies have looked at individually measured ACEs, asthma and educational attainment outcomes in childhood in cohort studies. One study investigated potentially traumatic life events (e.g. family death, job loss) as a cumulative score from 46 yes / no questions.(38) There was no previous research for all-cause emergency admissions as a mediator between ACEs and educational attainment outcome in children.

Pattemore et al found no evidence of an association in univariate analysis between negative life events (scores ranged from 0-7) in the year prior to starting school and reading scores from standard national reading books at age 6 years in a cohort of children with asthma.(38) (Additionally a case-control design between those with and without an asthma diagnosis showed no evidence that negative life events were associated with poorer reading scores.) Further, for asthmatic children there was no change in the effect of negative life events when a variable comparing persistent versus improved asthma groups was added to a multiivarlable model for educational attainment outcome.

Consistent with findings in Chapter 5, a higher proportion of children were found in the lowest quartile for reading who had an asthma diagnosis compared to those without (cases versus controls). In the cohort of asthmatic children reading scores improved if asthma symptoms had improved over the year.(38)

The list of negative life events used by this previous study may not easily be compared to the 15 ACEs commonly seen in previous research.(39) The negative life events questionnaire is broader with 46 (yes/no) questions and may have a less severe impact on the child than ACEs, because they may be perceived as negative but may be positive (e.g. moving house).(40) In this study the negative life events showed no evidence of a detrimental effect on educational outcomes in children and contrasts with the results of Chapter 6, this may also be because the life events were only measured for one year compared to over several years from birth.

Figure 7.1 describes the hypothesised theoretical causal pathways and potential confounding relationships from this literature review.

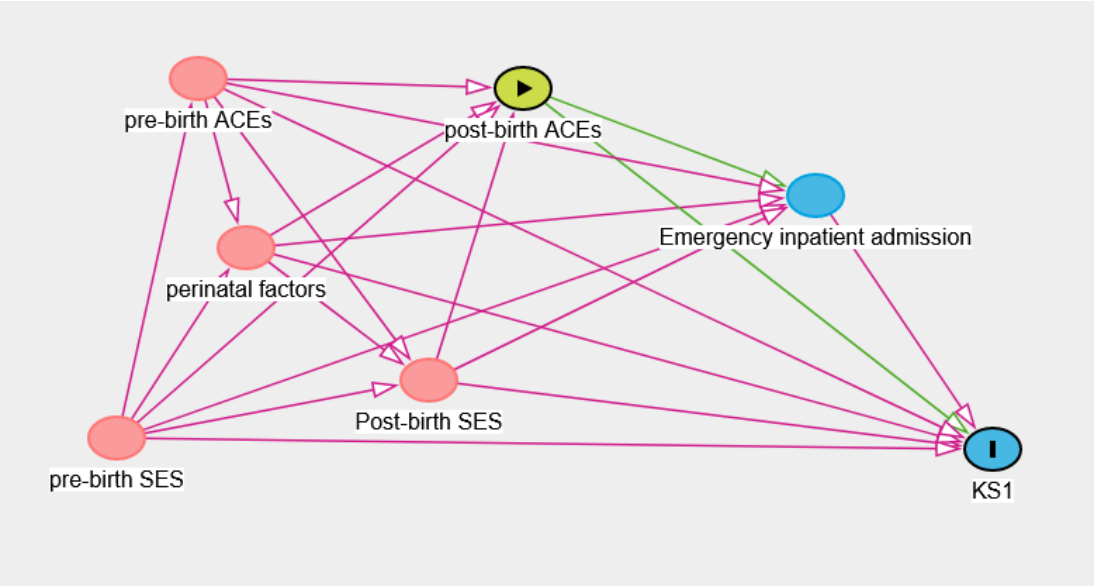

Figure 7.1. Directed acyclic graph (DAG): visual diagram of potential causal relationships to aid selection of confounder variables and identify potential mediator relationships in analysis of exposure to post-birth adverse childhood experiences and KS1 attainment outcome.
The minimal sufficient adjustment set for direct effects analysis was pre-birth SES, pre-birth ACEs, perinatal factors, post-birth SES and emergency hospital inpatient admissions. ACE=adverse childhood experience; SES=Socio-economic status; SEN=Special Educational Needs provision; KS1=Key Stage 1. Green circle with black triangle – exposure; Blue circle with vertical black line – outcome; Pink circle – ancestor of exposure and outcome (confounder); Pink arrow – directional biasing path; Plain blue circle – ancestor of outcome; Green arrow – directional causal path; Black arrow – directional relationship; Exposure=post-birth ACEs; Outcome=KS1 attainment; Example of a potential confounder between exposure and outcome=post-birth SES; Potential mediator between exposure and outcome=Emergency inpatient admission.

7.2.4 Summary and evidence gaps

In previous research of cohorts of children with asthma, children had increased risk for acute asthma exacerbations from exposure to parental mental health or distress. One study found no evidence of an association for living with someone with an alcohol problem and asthma exacerbations in childhood. None of these studies looked at more than three ACEs (that included poverty) or multiple hospital admissions for asthma (from multiple acute asthma exacerbations) in children. For children in the general population only one study investigated exposure to maltreatment, maternal mental health or low income and the timing of first hospital admission for asthma in adolescents. As mentioned in Chapter 5, the characteristics of children with asthma differ between childhood and adolescence (e.g. boys and girls) and therefore there is a gap in the research knowledge for outcomes in childhood.

The published literature shows no evidence of an association between children's exposure to ACEs beyond birth (including maternal mental health) and a new asthma diagnosis (asthma onset) for healthy children (no asthma symptoms at birth). For children with a family history of atopy, three studies of children who were exposed to ACEs found an increased risk for asthma onset. These studies from the literature about exposure to ACEs in children mainly relate to self-reported psychological stress and mental health issues in caregivers and therefore may suffer from reporting bias. In previous research, only up to three ACEs (including poverty) were statistically modelled together to investigate asthma onset in childhood and no studies looked at children living with someone with an alcohol problem. Further, these studies found children living in poverty had an increased risk for a new asthma diagnosis. It should be noted that there is growing support in the literature that prenatal maternal stress or distress is associated with asthma onset in childhood and biological pathways are suggested.

For children exposed to ACEs and all-cause emergency inpatient hospital admissions in childhood there is little previous literature, but studies use large administrative data sets. Two studies support an increased risk of inpatient admission for children whose caregivers have common mental disorders, but for caregivers with serious mental illness the association remains unclear. One study found no evidence of an association between living with someone with an alcohol problem and any emergency admission in childhood. Multiple ACEs were only statistically modelled together in one study for any emergency hospital admission in childhood but this study did not include a measure for poverty. None of the studies in the literature investigated ACEs and repeated inpatient hospital admissions in childhood.

Few studies in the literature have investigated emergency admissions to hospital as a potential mediator between ACEs and educational attainment in childhood. Only one study measured a broader list of potentially negative life events in the year prior to school reading tests and found no effect on education outcomes for children at age 6 years in univariate analyses. Further research is required to understand the potential pathway from ACEs to asthma or all-cause hospitalisation and a child's later educational attainment.

The strengths of this review were the use of the search terms from previous chapters of this thesis that were found to be comprehensive for these related research questions and therefore it is unlikely that any studies were missed. The review shows there are several gaps in the evidence from the published literature where new knowledge could be

obtained from investigations using large national administrative data sets from healthcare services rather than self-completion surveys.

7.3 Aim and objectives

Aim

To investigate to what extent emergency hospital admissions explain the relationship between multiple ACEs measured individually and educational attainment in childhood.

Objectives

i. To investigate and quantify the association of potential ACEs identifiable by health practitioners or educators, specifically

    a. common mental disorder in a household member

    b. serious mental illness in a household member

    c. alcohol problems in a household member

    d. victimisation (maltreatment: neglect, sexual, emotional or physical abuse)

    e. death of a household member

    f. free school meals eligibility (see Section 6.2.3 for debate on this definition)

    and asthma emergency inpatient admission

ii. To assess the association from potential ACEs identifiable by health practitioners or educators and recurrent asthma emergency inpatient admission

iii. To assess the association from potential ACEs identifiable by health practitioners or educators and recurrent all-cause emergency inpatient admission

iv. To evaluate whether asthma emergency hospital admission mediates the effect of ACEs identifiable by health practitioners or educators on educational attainment at KS1 (age 6-7 years)

v. To evaluate whether all-cause emergency hospital admission mediates the effect of ACEs identifiable by health practitioners or educators on educational attainment at KS1 (age 6-7 years)

7.4 Participant selection

For the analyses in this chapter the data set created for the ACEs and educational attainment at KS1 (age 6-7 years) was used and is described in Chapter 6. Participant selection from the administrative databases is detailed in Section 6.4. In addition, the cohort for this analysis included only those children who had GP data from birth to KS1. Where a child did not have a previous primary care diagnosis of asthma, the initial hospital admission was excluded if it occurred prior to a first GP visit to allow for prescribed medication following this admission to control symptoms. Figure 6.4 in Chapter 6 shows the anonymised participant selection of 107,479 children in the KS1 cohort, after exclusion of those children without GP data 77,093 children were eligible for inclusion in this cohort for analysis.

7.5 Exposures and outcomes

The educational outcome was attainment of the expected level in KS1 statutory assessment at age 6-7 years (see Section 2.1.7 for further details). Six potential childhood ACE exposures were defined as found in Section 6.5. Three exposures of potential childhood adversity were defined as living with an adult household member with any of: (i) serious mental illness diagnosis (e.g. bipolar disorder, schizophrenia); (ii) CMD (e.g. depression, anxiety) or (iii) an alcohol problem recorded as heavy drinking in primary care records or an alcohol-related hospital admission. Three further potential ACE exposures were defined as (i) childhood victimisation taken from a child's inpatient hospital admissions where victimisation was a contributing reason for admission, (ii) the death of a household member, and (iii) low family income, defined as eligibility for free school meals in the year the KS1 assessment was taken.

To include a medical history of CMD, serious mental illness or alcohol problems in children's household members, variables were derived from the date when these data were available in the SAIL databank, from the 5th January 1998 up to the child's birth. These variables were derived using GP and hospital inpatient admissions data. For further details on these exposures see Section 6.5.

7.6 Potential mediators

Asthma and all-cause emergency inpatient admissions are used as both an outcome and a potential mediator in the investigations of this chapter of the thesis. Asthma inpatient admissions described in Section 5.5 have been restricted to the first emergency admission for asthma (ICD-10 codes J45-46), where previously approximately 73% of admissions were categorised as emergency admissions from the PEDW data. As mentioned in Section 7.4, if the child had no previous diagnosis for asthma, the initial hospital admission was excluded from the definition to allow for the possibility that prescribed medication following this admission may control symptoms. All-cause emergency inpatient admissions were any entry into the PEDW admissions data classed as an emergency as described in Section 4.5.

7.7 Potential confounders, covariates and effect modifiers

Models were adjusted for birth characteristics including deprivation quintiles at birth / first 4 months of life as described in Section 4.6. For a measure of poverty beyond birth eligibility for free school meals was used as described in Section 4.6. These measures were also used in analyses in Chapters 5 and 6 of this thesis. For consistency between the models within the mediation analysis for both health and education outcomes of this chapter, statistical models were adjusted for variables that were applicable to all analyses. For this reason, models were not adjusted for school moves or school level eligibility for free school meals that were included in models in Chapter 4. For educational outcomes it was chosen to retain the hierarchical model so that variation attributable to schools was included in the model to prevent the potential for spuriously small standard errors arising from correlation between outcomes. Furthermore, the variable for year of KS1 assessment was kept in the adjusted models to take account for any trend effects in KS1 results.

7.8 Statistical analysis

To investigate whether emergency admission was a mediator between ACEs and educational attainment at KS1 in children, firstly there was a need to establish whether ACEs were associated with first and recurrent asthma admissions in childhood. A previous study I carried out provided evidence about the association between ACEs and first all-cause emergency admission in children (10); this chapter undertakes further analysis for recurrent all-cause admissions in childhood. Cox regression was used to estimate the effects of ACEs for time to first emergency hospital admission in children as a measure of

asthma incidence (that may occur at asthma onset) reporting hazard ratios (HRs) with 95% confidence intervals (CI). Additionally, Andersen Gill models were used, an extension to the Cox model for time-to-event data for recurrent events to model children's multiple emergency hospital admissions. These models used time-dependent covariates for a child ever being exposed to each ACE that varied depending on their follow-up time (e.g. exposures pre-birth to birth, pre-birth to 1 year, pre-birth to 5 years).(41) This analysis provides evidence about ACEs and the regularity of asthma exacerbations in children, elsewhere described as the course of asthma. For ACEs and all-cause recurrent emergency admissions in children, the analysis provides evidence about the periodic hazard from ACEs for first and subsequent emergency admissions. The Andersen Gill model assumes that the within-person correlation for event times for hospital admissions can be explained by the number of past events. The correlation between events is captured by appropriate time-dependent covariates, that is the number of previous events or a function of previous events.(42) For further information on these techniques see Section 3.3.

As in Chapters 4, 5 and 6 multilevel logistic regression was used to model children's exposure to ACEs and not attaining the expected level at KS1, grouped by schools. To test asthma emergency admission as a potential mediator the difference method was used.(43) (In this method the asthma emergency inpatient admission variable was added to the model to assess if there was any change (a reduction in the risk effect) between ACEs and educational attainment outcome. This was repeated for the all-cause emergency admission variable). Testing mediation using the difference method can provide evidence of mediation, but it has conservative inferences for logistic regression. If the difference method shows there is mediation then it is definitely present. However, if the difference method shows there isn't mediation it is a conservative test and may not detect small effects, but any substantial mediation would be detected.

A Direct Acyclic Graph (DAG, see Section 3.1.2) was drawn to visualise confounding and potential mediator relationships and obtain a minimal sufficient adjustment set of potential confounders for analysis (Figure 7.1). The DAG with direct causal effect adjustment was used to obtain the set of confounders needed for investigation of whether emergency inpatient admissions were on the potential causal pathway from ACEs to educational attainment outcomes in childhood. The direct (ACEs to KS1) and indirect effects (ACEs to hospital admissions and hospital admissions to educational attainment) were included in statistical modelling.

In this cohort, variables that contained missing data had similar proportions of missing data to those in the cohort in Chapter 6. This cohort had less than 6% of missing data for several birth characteristics, 20% missing data for breastfeeding at birth or at 6-8 weeks and 70% missing data for maternal smoking in the first trimester described in Table 6.4. In statistical modelling, multiple imputation with chained equations was used with five imputations as seen previously (see Section 6.8 for further details). An investigation of variables with missing data as described in Section 3.3.2 supports the theory that the variables in the imputation model make the MAR assumption plausible and missing data is unlikely to be MNAR.

7.9 Results

7.9.1 Descriptive statistics

There were 77,093 children in the cohort between 1998 and 2012 who were included in this analysis with follow-up to 6-7 years (KS1). With this cohort definition sociodemographic, ACEs and KS1 attainment were similar to those found in Chapters 4, 5 and 6 and were deemed representative of national populations (Table 7.1 & 7.2; Sections 4.10, 5.8.1, 6.8.1). For emergency asthma inpatient admissions 2,286 (3%) of children had experienced an admission before KS1 assessment and 40,474 (56%) had experienced an all-cause emergency admission (Table 7.3). Rates of hospital admissions were higher for children after age 1 year for a diagnosis of asthma, and highest for children in the first year of life for all-causes. Children in the most deprived quintile were found to have higher occurrences of ACEs and KS1 failure compared to children in the least deprived quintile. By contrast, children who had an asthma hospital admission were more often characterised by being born prematurely or they were small for gestational age when compared to children without an asthma hospital admission. Interestingly, children who had an asthma hospital admission were found only slightly more often in the most deprived quintile than the least deprived quintile.

There was a much higher rate of admission per 1000 person-years of risk for recurrent admissions compared to a first admission in age groups 1 - < 5 years and 5 years to KS1 for asthma or for all-cause emergency admissions (Table 7.3). However, in the first year of life there was little difference between the rate of recurrent admissions and first admission and this shows most children only had one admission in the first year of life for asthma or all-cause emergency admission.

Table 7.1: Demographics of the study population.

		Ever experienced				
	Total	**A household member with a common mental disorder in GP data before age 5**	**A household member with an alcohol problem in GP data or alcohol-related hospital admission before age 5 years**	**A victimisation hospital admission before age 5 years**	**An asthma emergency hospital admission before KS1**	**Did not attained the expected level at KS1**
N	77093	31720	7916	543	2286	13280
Sex=male(%)	39726 (52)	16440 (52)	4094 (52)	296 (55)	1514 (66)	8479 (64)
Townsend deprivation quintile at birth						
1 - least (%)	14017 (18)	4876 (15)	725 (9)	36 (7)	289 (13)	1370 (10)
2 (%)	14628 (19)	5332 (17)	1075 (14)	82 (15)	384 (17)	1958 (15)
3 (%)	15430 (20)	6204 (20)	1462 (19)	101 (19)	447 (20)	2620 (20)
4 (%)	15880 (21)	6971 (22)	1905 (24)	129 (24)	537 (24)	3073 (23)
5 - most (%)	16910 (22)	8273 (26)	2734 (35)	193 (36)	619 (27)	4221 (32)
Free school meals eligible[a]=yes(%)	12793 (17)	7683 (24)	2865 (36)	230 (42)	532 (23)	4323 (33)
Gestation at birth[b]						
24-32	1173 (2)	554 (2)	165 (2)	25 (5)	87 (4)	374 (3)
33-36	4189 (5)	1832 (6)	472 (6)	53 (10)	146 (6)	870 (7)
37+ weeks	67317 (87)	27483 (87)	6779 (86)	443 (82)	1938 (85)	11211 (84)
Small for gestational birth	6683 (9)	2897 (9)	909 (12)	90 (17)	205 (9)	1615 (12)
Parity ≥ 1	44633 (58)	18663 (59)	4439 (56)	306 (56)	1371 (60)	8525 (64)
Multiple births e.g. twins=yes(%)	2402 (3)	1018 (3)	231 (3)	12 (2)	76 (3)	457 (3)
Congenital anomaly[c]=yes(%)	3761 (5)	1606 (5)	419 (5)	53 (10)	169 (7)	972 (7)
Maternal age at childbirth						
<18 (%)	1951 (3)	1031 (3)	511 (7)	34 (6)	76 (3)	568 (4)
18-24 (%)	19333 (25)	9639 (30)	3140 (40)	226 (42)	740 (32)	4466 (34)
25-29 years (%)	21717 (28)	8889 (28)	1909 (24)	116 (21)	621 (27)	3518 (27)
30-34 (%)	22292 (29)	7890 (25)	1470 (19)	104 (19)	585 (26)	3023 (23)
35+ (%)	11764 (15)	4257 (13)	884 (11)	60 (11)	263 (12)	1696 (13)
Breastfeeding[d]						
No (%)	29516 (38)	13853 (44)	3925 (50)	283 (52)	997 (44)	6356 (48)
Yes (%)	32344 (42)	12391 (39)	2727 (34)	161 (30)	867 (38)	4285 (32)
NA (%)	15233 (20)	5476 (17)	1264 (16)	99 (18)	422 (19)	2639 (20)
Maternal smoking in first trimester						
No (%)	18384 (24)	6785 (21)	1381 (17)	86 (16)	474 (21)	2612 (20)
Yes (%)	5535 (7)	2821 (9)	985 (12)	60 (11)	202 (9)	1436 (11)
NA (%)	53174 (69)	22114 (70)	5550 (70)	397 (73)	1610 (70)	9232 (70)

[a] in Key Stage 1 assessment year as a proxy for level of deprivation beyond birth; [b] 6% missing data with a similar proportion in potential child adversity and emergency admission groups; [c] major or minor; [d] at birth or 6-8 weeks.

Table 7.2: Prevalence of potential child adversity by child's age

	Exposure measured up to age 1 year	Exposure measured up to age 5 years
N	77093	77093
A victimisation hospital admission=yes(%)	279 (0)	543 (1)
A household member with an alcohol problem in GP data or alcohol-related hospital admission=yes(%)	4378 (6)	7916 (10)
A household member with a common mental disorder in GP data=yes(%)	18910 (25)	31720 (41)
A household member with a serious mental illness in GP data=yes(%)	368 (1)	650 (1)
Household member died between child's age 1 year and KS1=yes(%)	NA	1283 (2)
Ever lived in a single adult household (≥16 years old) =yes(%)	17489 (23)	24535 (32)

Table 7.3: Number and rate of emergency hospital admission by child age

	Incidence of first asthma admission	Rate of multiple asthma admissions	Incidence of first all-cause admission	Rate of multiple all-cause admissions
Age 0–<1 year				
Total children in age group N	77093	77093	77093	77093
Number of emergency admissions (%=first admission)	107 (0.1)	119	20297 (26.3)	29015
Total person-years in age group	77065	77093	63913	77093
Rate (per 1000 person-years at risk)	1.4 (1.1-1.7)	1.5 (1.2-1.8)	317.6 (313.2-321.9)	376.3 (372.0-380.7)
Age 1–<5 years				
Total children in age group N	76986	77093	56796	77093
Number of emergency admissions (%=first admission)	1662 (2.2)	2860	17292 (30.4)	43777
Total person-years in age group	304395	308372	181603	308372
Rate (per 1000 person-years at risk)	5.5 (5.2-5.7)	9.2 (8.9-9.6)	95.2 (93.8-96.6)	141.9 (140.6-143.2)
Age 5 years–<KS1				
Total children in age group N	75324	77093	39504	77093
Number of emergency admissions (%=first admission)	517 (0.7)	1018	2885 (7.3)	10001
Total person-years in age group	160709	165782	81302	165782
Rate (per 1000 person-years at risk)	3.2 (3.0-3.5)	6.1 (5.7-6.5)	35.4 (34.2-36.8)	60.3 (59.1-61.5)

7.9.2 Statistical modelling results

Several ACEs were associated with an increased hazard for first asthma inpatient emergency admission (a measure of asthma incidence and possible asthma onset) and multiple admissions (a measure of the course of asthma from recurrent acute asthma exacerbations) in children. The highest risk for children was associated with experience of victimisation (measured as hospital admission due to victimisation). The risk decreased but was still sizeable for a household member with common mental disorder and eligibility for

free school meals (as a measure of poverty), Table 7.4. Both a child's first emergency admission and recurrent emergency admissions for asthma had surprisingly similar results even though the rate of multiple admission was higher than first admission after the age of 1 year. These results suggest there may be no change or modification to ACEs or asthma management after a child's first admission to hospital for asthma. Living with a household member with an alcohol problem was associated with increased risk for first asthma emergency admission in children but was no longer statistically significant for multiple admissions ($p<0.05$). A similar effect was found for living in a single parent household with slightly weaker hazards for children in adjusted models. Young mothers (< 18 years) were found to have a higher risk associated with asthma emergency admission in offspring. The size of this effect was comparable to a common mental disorder in the household for children's recurrent asthma emergency admission. These models showed male children and those born prematurely had higher risk for emergency asthma admissions.

For children's all-cause recurrent emergency hospital admissions, ACEs had similar patterns of increased risk associated with admissions for all-causes to those for asthma emergency admissions but the increased risks were smaller (Table 7.4). For recurrent all-cause admissions in children, an increased risk was found from exposure to a victimisation admission and had a stronger effect than the other ACEs. This result replicated the pattern in the asthma admissions model.

Table 7.4: Cox regression for time to first emergency inpatient hospital admission and Andersen Gill model for multiple emergency admissions

	First hospital admission for asthma		Multiple admissions for asthma		First all-cause hospital admission		Multiple admissions for all-cause	
	Unadjusted HR (95% CI)	Multivariable[b] HR (95 CI)	Unadjusted HR (95% CI)	Multivariable[b] HR (95 CI)	Unadjusted HR (95% CI)	Multivariable[b] HR (95 CI)	Unadjusted HR (95% CI)	Multivariable[b] HR (95 CI)
A victimisation hospital admission=yes	2.78 (1.88-4.09)	2.05 (1.39-3.02)	2.54 (1.73-3.74)	1.82 (1.23-2.69)	NA[c]	NA[c]	1.69 (1.41-2.02)	1.32 (1.10-1.58)
Household member with an alcohol problem in GP data or alcohol-related hospital admission=yes	1.46 (1.27-1.68)	1.16 (1.00-1.34)	1.41 (1.20-1.67)	1.08 (0.91-1.28)	1.22 (1.17-1.27)	1.05 (1.01-1.10)	1.25 (1.20-1.32)	1.06 (1.01-1.11)
Household with common mental disorder in GP data=yes	1.47 (1.35-1.60)	1.34 (1.22-1.46)	1.51 (1.35-1.68)	1.35 (1.20-1.51)	1.22 (1.19-1.25)	1.16 (1.13-1.19)	1.28 (1.25-1.31)	1.20 (1.17-1.23)
Household with a serious mental illness in GP data=yes	0.62 (0.31-1.25)	0.47 (0.23-0.94)	0.79 (0.32-1.97)	0.59 (0.24-1.48)	1.23 (1.07-1.41)	1.05 (0.91-1.20)	1.19 (1.03-1.36)	0.99 (0.86-1.14)
Household member died between child's age 1 year - KS1=yes	1.17 (0.62-2.18)	1.06 (0.57-1.98)	1.13 (0.64-1.97)	1.03 (0.59-1.81)	1.14 (0.87-1.50)	1.09 (0.83-1.42)	1.04 (0.88-1.24)	0.98 (0.82-1.16)
Ever lived in a single adult household (≥16 years old) =yes	1.22 (1.11-1.33)	1.11 (1.01-1.22)	1.23 (1.09-1.39)	1.10 (0.97-1.24)	1.08 (1.05-1.10)	1.02 (1.00-1.05)	1.07 (1.05-1.10)	1.01 (0.99-1.04)
Free school meals eligible[a]=yes	1.54 (1.40-1.69)	1.16 (1.04-1.30)	1.65 (1.44-1.88)	1.19 (1.02-1.39)	1.27 (1.24-1.31)	1.11 (1.08-1.14)	1.33 (1.29-1.37)	1.14 (1.10-1.17)
Townsend deprivation quintile at birth (ref=1 – least deprived)								
2	1.28 (1.10-1.49)	1.22 (1.04-1.42)	1.33 (1.10-1.61)	1.25 (1.03-1.51)	1.06 (1.03-1.10)	1.04 (1.01-1.08)	1.05 (1.01-1.10)	1.03 (0.99-1.07)
3	1.41 (1.22-1.64)	1.26 (1.08-1.46)	1.44 (1.21-1.73)	1.26 (1.05-1.51)	1.15 (1.11-1.19)	1.09 (1.05-1.12)	1.16 (1.11-1.20)	1.08 (1.04-1.12)
4	1.65 (1.43-1.90)	1.41 (1.21-1.63)	1.79 (1.50-2.13)	1.48 (1.23-1.77)	1.19 (1.15-1.23)	1.09 (1.05-1.12)	1.20 (1.15-1.24)	1.08 (1.04-1.12)
5 – most	1.79 (1.56-2.06)	1.39 (1.20-1.61)	1.99 (1.66-2.38)	1.47 (1.21-1.79)	1.29 (1.25-1.33)	1.13 (1.09-1.17)	1.34 (1.29-1.40)	1.14 (1.10-1.19)
Sex=male	1.86 (1.71-2.03)	1.84 (1.69-2.01)	1.89 (1.68-2.13)	1.86 (1.66-2.10)	1.24 (1.22-1.26)	1.23 (1.21-1.25)	1.25 (1.22-1.28)	1.22 (1.20-1.25)
Gestation at birth (ref=37+ weeks)								
24-32	2.63 (2.12-3.26)	2.42 (1.93-3.03)	2.47 (1.89-3.22)	2.15 (1.62-2.86)	2.11 (1.98-2.26)	2.00 (1.86-2.14)	2.32 (2.14-2.51)	2.12 (1.96-2.28)
33-36	1.19 (1.01-1.41)	1.16 (0.98-1.37)	1.33 (1.07-1.64)	1.26 (1.00-1.58)	1.35 (1.30-1.40)	1.34 (1.28-1.39)	1.40 (1.33-1.48)	1.36 (1.29-1.44)
Congenital anomaly=major/minor	1.57 (1.34-1.84)	1.44 (1.23-1.69)	1.63 (1.33-2.00)	1.49 (1.21-1.83)	1,83 (1.76-1.91)	1.76 (1.69-1.83)	2.16 (2.05-2.28)	2.04 (1.93-2.15)
Maternal age at childbirth (ref=25-29 years)								
<18	1.37 (1.08-1.73)	1.22 (0.95-1.57)	1.61 (1.18-2.20)	1.39 (1.01-1.92)	1.36 (1.28-1.44)	1.20 (1.13-1.27)	1.37 (1.28-1.46)	1.17 (1.09-1.25)
18-24	1.34 (1.21-1.50)	1.22 (1.10-1.37)	1.35 (1.17-1.56)	1.21 (1.04-1.39)	1.18 (1.15-1.21)	1.11 (1.08-1.14)	1.19 (1.15-1.23)	1.10 (1.07-1.14)
30-34	0.92 (0.82-1.02)	0.96 (0.86-1.08)	0.86 (0.75-1.00)	0.92 (0.79-1.06)	0.90 (0.87-0.92)	0.93 (0.90-0.95)	0.88 (0.86-0.91)	0.92 (0.89-0.95)
35+	0.78 (0.67-0.90)	0.81 (0.70-0.94)	0.75 (0.62-0.92)	0.80 (0.65-0.98)	0.87 (0.84-0.90)	0.90 (0.87-0.93)	0.87 (0.83-0.90)	0.89 (0.86-0.93)

[a] in Key Stage 1 assessment year to measure deprivation beyond birth; [b] adjusted for all variables in the table and small for gestational age at birth (<10th centile), parity, multiple births e.g. twins, breastfeeding at birth or 6-8 weeks, maternal smoking in first trimester; [c] not applicable as the exposure is a first admission for victimisation.

Table 7.5 shows several combinations of ACEs, sociodemographic characteristics and family structure for risk of recurrent emergency admissions for asthma and all-causes. The table highlights that poverty measured using eligibility for free school meals at KS1, when combined with ACEs, increases risk for emergency admissions even in the least deprived quintile of deprivation. The calculations show that a child in poverty with combinations of alcohol problems, common mental disorder in the household, and young maternal age (< 18 years) at childbirth has equivalent risk for recurrent emergency admissions as those who have experienced a victimisation hospital admission. The table highlights that ACEs increase the risk for emergency admissions in childhood even when there is no deprivation (either in individual or area measures) but that living in the most deprived quintile increases the risk associated with recurrent hospital admissions.

Table 7.5: Risk of recurrent emergency admissions associated with combinations of exposures and sociodemographic characteristics

	Recurrent emergency asthma admissions	Recurrent emergency all-cause admissions
Least deprived quintile of deprivation at birth or in first 4 months		
FSM + CMD	1.61 (1.34-1.92)	1.37 (1.31-1.42)
FSM + CMD + ALC	1.73 (1.39-2.16)	1.45 (1.36-1.54)
FSM + CMD + ALC + Young mother	2.40 (1.64-3.53)	1.69 (1.55-1.84)
FSM + Vict	2.17 (1.43-3.28)	1.50 (1.25-1.81)
CMD + ALC	1.45 (1.19-1.77)	1.27 (1.21-1.34)
CMD + ALC + Vict	2.64 (1.72-4.05)	1.68 (1.40-2.02)
CMD + ALC + Vict + Young mother	3.67 (2.16-6.23)	1.96 (1.62-2.39)
Most deprived quintile of deprivation at birth or in first 4 months		
FSM + CMD	2.37 (1.85-3.03)	1.56 (1.47-1.65)
FSM + CMD + ALC	2.55 (1.94-3.34)	1.65 (1.54-1.77)
FSM + CMD + ALC + Young mother	3.54 (2.36-5.30)	1.93 (1.76-2.11)
FSM + Vict	3.19 (2.06-4.94)	1.71 (1.42-2.07)
CMD + ALC	2.14 (1.63-2.80)	1.45 (1.36-1.55)
CMD + ALC + Vict	3.89 (2.46-6.15)	1.92 (1.59-2.32)
CMD + ALC + Vict + Young mother	5.40 (3.12-9.34)	2.24 (1.84-2.73)

FSM=eligible for free school meals at KS1; CMD=household member with a common mental disorder; ALC=household member with an alcohol problem; Vict=victimisation hospital admission; Young mother=maternal age at childbirth < 18 years.

In mediation analysis, when either first asthma or all-cause emergency inpatient admission was added to the model as a binary explanatory variable there was no change in the risk from ACEs for educational attainment at KS1. These findings were similar for a history of ACEs and ACEs beyond birth measured to age 1 year and any first emergency admission measured between age 1 year and KS1 (Table 7.6). The same results were obtained when analyses were repeated for ACEs measured to age 5 years and any first emergency admission measured between age 5 years and KS1 (data not shown). However, any first all-cause admission between age 5 years and KS1 was not significant ($p<0.05$) in univariate tests for not attaining the expected level at KS1, similar to findings seen in Section 4.8.2, Table 4.4. These analyses show that asthma or all-cause emergency inpatient admissions are not important mediators between ACEs and educational attainment at age 7 years (Table 7.6). That is, the variation ACEs and educational attainment at age 7 years have in common with asthma or all-cause admission (the indirect effect) is not sufficiently large to make a statistically significant difference to the risk of ACEs on not attaining KS1.

Table 7.6: Logistic regression for early child adversity and not attaining the expected level at KS1 adjusted for potential mediators: first emergency asthma admission between 1 year and KS1, first all-cause emergency inpatient admission between 1 year and KS1

	Total / Not attained KS1 (%)	Logistic regression KS1 not attained		LR KS1 not attained adjusted for 1st asthma admission 1 year - < KS1	LR KS1 not attained adjusted for 1st all-cause admission 1 year - < KS1
		Unadjusted OR (95% CI)	Multivariable[c] OR (95% CI)	Multivariable[cn] OR (95% CI)	Multivariable[c] OR (95% CI)
	77093 / 13280 (17)				
Ever a potential child adversity up to age 1 years:					
A victimisation hospital admission=yes(%)	279 / 96 (34)	2.28 (1.76-2.96)	1.55 (1.18-2.05)	1.54 (1.17-2.03)	1.59 (1.21-2.09)
A household member with an alcohol problem in GP data or alcohol-related hospital admission=yes(%)	4378 / 1143 (26)	1.59 (1.47-1.70)	1.17 (1.09-1.27)	1.17 (1.09-1.27)	1.18 (1.09-1.27)
A household member with a common mental disorder in GP data=yes(%)	18910 / 4051 (21)	1.39 (1.33-1.46)	1.21 (1.16-1.27)	1.21 (1.16-1.27)	1.21 (1.16-1.27)
A household member with a serious mental illness in GP data=yes(%)	368 / 93 (25)	1.47 (1.15-1.89)	1.09 (0.85-1.41)	1.10 (0.85-1.42)	1.09 (0.84-1.41)
Ever lived in a single adult household (≥16 years old) =yes(%)	17489 / 3460 (20)	1.17 (1.12-1.22)	1.03 (0.99-1.08)	1.03 (0.99-1.08)	1.03 (0.99-1.08)
Free school meals eligible[a]=yes(%)	12793 / 4323 (34)	2.74 (2.61-2.87)	2.11 (2.00-2.22)	2.11 (2.00-2.22)	2.11 (2.00-2.22)
First asthma emergency admission from age 1 year to KS1=yes(%)	2181 / 539 (25)	1.54 (1.39-1.71)	NA	1.23 (1.11-1.37)	NA
First all-cause emergency admission from age 1 year to KS1=yes(%)	20325 / 3777 (19)	1.13 (1.08-1.18)	NA	NA	1.13 (1.08-1.18)
Townsend deprivation quintile at birth					
1 - least (%)	14017 / 1370 (10)	1.00	1.00	1.00	1.00
2 (%)	14628 / 1958 (13)	1.28 (1.18-1.39)	1.19 (1.10-1.29)	1.19 (1.10-1.29)	1.19 (1.10-1.29)
3 (%)	15430 / 2620 (17)	1.59 (1.47-1.72)	1.35 (1.25-1.47)	1.35 (1.25-1.46)	1.35 (1.25-1.47)
4 (%)	15880 / 3073 (19)	1.88 (1.74-2.03)	1.48 (1.37-1.61)	1.48 (1.37-1.61)	1.48 (1.37-1.61)
5 - most (%)	16910 / 4221 (25)	2.38 (2.21-2.57)	1.61 (1.49-1.75)	1.61 (1.49-1.74)	1.61 (1.49-1.75)
Sex=male(%)	39726 / 8479 (21)	1.89 (1.81-1.96)	1.94 (1.86-2.02)	1.93 (1.85-2.01)	1.93 (1.86-2.01)
Gestation at birth[b]					
24-32 (%)	1173 / 374 (32)	2.26 (1.98-2.58)	2.09 (1.81-2.41)	2.08 (1.80-2.39)	2.11 (1.83-2.44)
33-36 (%)	4189 / 870 (21)	1.26 (1.17-1.36)	1.21 (1.12-1.32)	1.21 (1.12-1.32)	1.22 (1.12-1.32)
37+ weeks (%)	67317 / 11211 (17)	1.00	1.00	1.00	1.00
Maternal age at childbirth					
<18 (%)	1951 / 568 (29)	1.84 (1.65-2.05)	1.67 (1.48-1.87)	1.66 (1.48-1.87)	1.67 (1.49-1.88)
18-24 (%)	19333 / 4466 (23)	1.43 (1.36-1.51)	1.31 (1.24-1.38)	1.31 (1.24-1.38)	1.31 (1.24-1.38)
25-30 years (%)	21717 / 3518 (16)	1.00	1.00	1.00	1.00
30-34 (%)	22292 / 3023 (14)	0.86 (0.81-0.91)	0.90 (0.85-0.95)	0.90 (0.85-0.95)	0.90 (0.85-0.96)
35+ (%)	11764 / 1696 (14)	0.93 (0.87-1.00)	0.96 (0.90-1.03)	0.96 (0.90-1.03)	0.96 (0.90-1.03)

[a] in KS1 assessment year as a level of deprivation beyond birth; [b] 6% missing data; [c] adjusted for all variables in the table & small for gestational age at birth (<10th centile), parity, multiple births e.g. twins, congenital anomalies, breastfeeding, maternal smoking in first trimester, year take KS1 assessment (ref=2010); LR=logistic regression.

7.10 Discussion

This study shows children exposed to ACEs before the age of 7 years had increased risk for recurrent asthma emergency inpatient hospital admissions compared to those who were not exposed in a total population cohort. To my knowledge this is the largest study to relate six individually measured ACEs to this outcome. ACEs had a surprisingly similar risk for first and recurrent emergency asthma admissions in children in models adjusted for socio-demographics, perinatal health indicators, household composition, other ACEs and past admissions. These results may indicate that there is no modification to behaviour after a child's first emergency hospital admission for asthma for either exposures to ACEs or in asthma management to try to prevent a further admission. A similar pattern of weaker risks from ACEs were found in children for recurrent all-cause emergency admissions (and were comparable to previous reports for first all-cause admission).(10) No previous reports of analyses of ACEs and recurrent hospital admissions in children were found in the published literature.

In adjusted models, several ACEs but not all those measured were associated with an increased risk for asthma or all-cause recurrent inpatient admissions in children. This result illustrates the differing magnitude of effects from ACEs and may also be due in part to the interplay between ACEs on these outcomes. All-cause unplanned hospital admissions are common in children (e.g. respiratory infections, gastroenteritis, injury).(44) ACEs such as parental mental illness or alcohol abuse may disrupt children's routines in the household, leading to inconsistent and unpredictable care.(45,46) These maladaptive coping mechanisms in caregivers may mean children with chronic conditions such as asthma have less support to prevent their underlying condition escalating into poor control of symptoms and for asthma into acute exacerbations. These findings provide evidence to support the need for interventions to reduce ACE exposure or to mitigate their effects to reduce hospital admissions in children.

This study found children were up to twice as likely to have asthma hospitalisations (first or recurrent) if they had previously experienced a victimisation admission to hospital in adjusted models. This finding was similar to previous research but only for first asthma hospitalisation (asthma onset) in adolescence from a low-income cohort in the USA (21) in models adjusted for ACEs of poverty and living with someone with mental health issues. The analyses in this chapter found for all-cause recurrent hospital admissions children had a 32% increased risk of admission if they had experienced a previous inpatient admission

for victimisation. To my knowledge this is a new finding and is not reported elsewhere in the published literature.

Confirming previous research in smaller studies, this chapter found living with a caregiver who had a common mental disorder had increased risk for childhood asthma onset (first emergency admission) and course of asthma (35% increased risk from recurrent events) even after adjustment for other ACEs including poverty.(7,8,9,24) For all-cause emergency admissions this study found living with someone with a common mental disorder had similar risk for recurrent admissions (20% increased risk) in childhood to those previously reported for first admission.(10) These findings provide evidence that the effects of ACEs on the ongoing course of asthma and for recurrent all-cause emergency admissions in children do not diminish after a child's first admission to hospital, where modifications to prevent further admissions could be implemented. There is an opportunity to identify these children who have ACEs at their first emergency admission and intervene in the child's life to try to reduce the risk for further hospital admissions.

In this chapter, living with someone with an alcohol problem (recorded in GP data or alcohol-related inpatient admission) was found to have a strong association with emergency hospital admissions in childhood in univariate analyses. However, in adjusted models this exposure was only associated with a child's first admission for asthma (16% increased risk) and not for recurrent asthma admissions, and weakly associated with all-cause emergency admissions (both first and recurrent). This aligns with previous research for asthma that was limited to children who already had an asthma diagnosis, where no evidence between experiencing parent / guardian alcohol problems and asthma hospitalisation was discerned.(17) For children's all-cause admissions, this chapter used a broader definition for alcohol problems in the household that additionally included GP data records for heavy drinking and this may explain differences to a previous report.(10) A previous study found no evidence of an association between living with someone with an alcohol-related hospital admission and time to children's first all-cause emergency admission ($p>0.05$).(10)

Children's eligibility for free school meals at KS1 was used to measure the level of poverty beyond birth in this chapter. The results show child poverty increased the risk for emergency hospitalisations in children in adjusted models agreeing with the published literature,(8,21,25,26,35) but this effect was not as strong as exposure to a common mental disorder in the household. In this chapter young maternal age and living in a single

parent household before age 12 years were associated with increased risk for emergency hospital admissions in children but no evidence was found for bereavement or living with someone with a serious mental illness. Other studies found strong relationships for serious mental illness in caregivers and emergency hospitalisations in children for asthma or all-cause emergency admissions. In this chapter and the related previous study (10) the proportion of parents with serious mental illness in the population was much lower (1%) compared to (5-17%) in studies based in Sweden and Denmark.(11,34) In addition, in Wales, UK, approximately 70% of children who lived in a household with someone with a serious mental illness also lived with someone who had a common mental disorder diagnosis; these diagnoses may relate to the same person in the household.(10)

A further finding of this chapter was that for children to age 7 years, emergency hospital admission for either asthma or all-causes were not important mediators on the pathway between ACEs and educational attainment. The shared variation that ACEs and educational attainment have in common with asthma or all-cause admission (the potential mediator) was not sufficiently large enough to alter the association between ACEs and educational attainment outcome. The results of this chapter suggest both childhood health and social factors contribute to poorer educational attainment in childhood. Therefore, interventions may be required to address both adversity and specific health related issues for children to achieve their potential in education during childhood. Previous research shows no evidence relating to this research question. It is notable that Table 7.1 shows in comparison to children in the total cohort, children with an asthma emergency admission tended to be premature or small for gestational age. This contrasts to children with ACEs or those who did not attain KS1 who tended to have lower socio-economic status compared to the total cohort. The differences in patterning of these bi-variate relationships provides some evidence of the potential reasons for the mediation analysis results.

The evidence continues to increase for a prenatal link between maternal distress and asthma onset and course of asthma with several studies finding differences in IgE foetus' cord blood.(1) Interestingly, one large administrative data cohort found no evidence of an association with asthma onset in offspring in depressed pregnant women who took newer forms of antidepressant.(47) Other suggested mechanisms follow those of ACEs and other outcomes; maternal prenatal stress impairs placenta regulation of foetal cortisol exposure and disruption of bacterial communities of the maternal gut / vagina that help to regulate immunity.(29,33) For ACEs in childhood, previous research has found differences in

asthma-relevant inflammatory markers,(27) immune response markers for allergy (17) and serum cortisol.(7,28) These studies suggest parental stress potentially causes biological changes in the child through disturbance of the hypothalamic-pituitary-adrenal (HPA) axis. Other studies report interactions between traffic air pollution and ACEs (maternal stress, inter-partner violence) (8) or between ACEs and children with a predisposition to disease (atopy, family history of asthma) (7,9) and asthma onset. These studies provide insight to the complexity of factors that may influence the risk of disease in children and suggest a diathesis-stress explanation for ACEs and asthma.

Recent reviews show ACE screening by clinicians such as GPs is acceptable to patients.(48,49) A number of caregivers with many ACEs in the household became tearful in GP consultations during ACE screening but they wished to continue with discussions because of potential health benefits. For ACE informed clinicians it added little time to consultations and built rapport with patients but required ease of referral to other services (e.g. mental health, social services). However, research shows clinicians felt ill equipped to screen for ACEs in low income settings.(48) For those implementing interventions, the dosage of intervention remains unclear from the ACE screen (potential count of ACEs) but instead the intervention was tailored to the individual patient.(50) Concern from policy makers remains about national programmes for ACE screening that may contain a count of ACEs with a cut point for referral (51) and stigma towards parents who inform health services about ACEs in their household.(52) Public health practitioners ask whether screening should include protective and compensatory experiences.(53)

The key strength of the study in this chapter is it uses a large total population cohort of administrative healthcare and education data sets. Previous research between ACEs and asthma onset or course of asthma was limited to mainly self-reported data in relatively small cohorts (<2000 children). This study used a greater number of ACEs from administrative data than previous studies, where most considered one ACE exposure with up to three ACEs (including poverty) in their design. Analyses in this study adjusted for multiple risk factors and confounders; perinatal, socio-demographic and other ACEs.

As mentioned in previous chapters, a limitation of the study in this chapter is the reliance on administrative data and potential for misclassification bias, but it is thought unlikely to be in any particular direction. This study did not adjust models for known prenatal risk factors for asthma diagnosis such as family history of asthma or atopy, but this allows the results to be compared more easily to general populations.

In this study emergency admissions for asthma or all-causes were used for outcome measures and may capture only the more extreme healthcare issues for children who live with ACEs in potentially more chaotic households. For children with asthma, it may be that asthma management plans are not adhered to due to household dysfunction or that symptoms are worse because of poor housing.(54) Children may have multiple emergency admissions because their asthma is difficult to control e.g. brittle asthma but there is currently no evidence to suggest that children with or without ACEs are more likely to have this diagnosis.

7.11 Implications for this thesis

This study provides compelling evidence that ACEs are associated with children's recurrent emergency inpatient hospital admissions for asthma or all-causes with similar magnitude to those for first admission. There is potential to screen children for ACEs at their first admission to hospital and potentially intervene to prevent further hospital admissions, both beneficial to the child, their family, health care providers and educators. This study shows for those parents experiencing problems such as stress and distress interventions to support their health may be beneficial to both them and their dependants. With constrained resources, there may be potential to provide a greater proportion of resource for ACE screening questions and related interventions to children who are most disadvantaged. For example, living in deprived areas is found to be associated with higher levels of ACEs. ACEs are an additional measure to that of deprivation and this approach could maximise benefit for children but care would need to be taken not to exclude those who require help.

Children's first emergency admission (for asthma or all-causes) was not an important mediator between ACEs and educational attainment at age 7 years. The contribution of both health and social risk factors should be considered in interventions to improve educational outcomes in children.

This thesis finds evidence for threats to educational attainment in childhood from unplanned hospital admissions including those associated with the chronic condition asthma, ACEs and poverty. New knowledge is provided from the analyses of this thesis on the relationships between multiple individually measured ACEs and finds independent effects from each ACE on educational attainment. Further, evidence in this thesis extends the knowledge to more ACEs than seen elsewhere and the risk for first emergency hospital

admission for asthma and for recurrent admissions for asthma or all-causes. The advances in knowledge provide evidence as to when ACEs have their greatest impact and which ACEs give greater risk than others on average from total population cohorts. It provides new insight into risk from both health and social factors where large administrative data sets have allowed multiple risk factors to be modelled together so that the magnitude of risk from different factors can be ordered in terms of their effect on educational outcomes.

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Chapter 8 : Summary of main findings, implications and conclusions

8. Overview

In this thesis I investigated the complex interplay of potentially modifiable health and social factors on children's educational attainment. The main focus of my thesis was research into areas where there was paucity of evidence and where interventions do not already exist as described in Figure 1.1. Specifically, I determined whether childhood exposures of (i) unplanned hospital admissions, (ii) asthma severity (an exemplar of a common chronic disease) and (iii) adverse childhood experiences (ACEs) that included the potential ACE of poverty, impacted on childhood educational attainment. Nearly 20% of children do not attain the expected level the Department of Education agree all children should aim to reach in assessments at age 6-7 years.(1,2) Preventing a poor start in education for children can enhance the trajectory of their life course.(3) Even modest increases in children's academic attainment are associated with improved adult health, employment and reductions in intergenerational poverty.(4,5) It is well-known there is social patterning in child health, educational attainment and ACEs in children,(6,7,8) and that young people (age 0-19 years) are disproportionately disadvantaged in the UK (Section 1.5.1) compared to the overall population. It is therefore important to know whether or not health and social factors are risks to children's educational outcomes where there is little evidence in the current published literature.

In this chapter, I summarise the main findings of this thesis for the research questions I proposed, reflect on the strengths and limitations of this research, and discuss the implications for future research, policy, and practice. Detailed discussions for the research objectives of this thesis placing the results in context with the pre-existing literature are found alongside the results in their respective chapters (Sections 4.9, 5.9, 6.9, 7.10).

8.1 Main findings

In this thesis administrative data sets were used to create novel empirical birth cohorts from record-linked healthcare and education databases. These large cohorts contain individual level data for each child born between 1998 and 2012 in Wales and data on the people they live with. All cohorts analysed in this thesis contained between 40,000-100,000 children. This section of the thesis summarises the contributions this thesis makes to the field.

8.1.1 Association between unplanned hospital admissions and children's educational attainment outcome

This thesis found all-cause emergency inpatient admission to hospital in the first seven years of life with a prevalence of 48% increased the risk by 12% for not attaining the expected level in educational attainment at age seven years (Key Stage 1, Section 4.8). To my knowledge there is no evidence in the extant literature about all-cause unplanned admissions and educational attainment outcomes at age 7 years. However, studies support the results of this thesis for tests at the start of compulsory schooling at age 5 to 6 years. They showed emergency admission for common causes (9,10) or chronic disease (11) were associated with increased risk for poorer school readiness in children. This thesis shows some children who experience unplanned admissions in the first seven years of life are not able to catch up in learning during the first two years of schooling.

This thesis found emergency inpatient admissions in infancy with a prevalence of 24% increased the risk by 31% for poorer educational attainment at KS1 (Section 4.8), a notably larger effect from an admission at a younger age. In addition, these effects increased with more bed days spent in hospital during the pre-school period (12% increase in risk per 10 bed days). Previous research shows a well-established association between health status at birth (gestational age,(12,13) birth weight,(12) Apgar score(14)), socioeconomic or school-level factors and lower educational attainment. This thesis adds new knowledge to a limited evidence base about unplanned hospital admissions and a role on the causal pathway between preterm birth and lower educational outcome.

The most common cause of inpatient admissions are infections particularly in younger children and respiratory diseases are more common in premature infants.(15,16) This thesis shows an independent effect between emergency admissions (after adjustment for

gestational age) on educational attainment and these children may require early intervention and additional support to achieve their academic potential.

Moreover, this thesis determined admissions due to injuries and external causes (most prevalent in children over 5 years at 9%) had greater effects with an increased risk of 19% for not attaining the expected level in educational attainment (Section 4.8). Previous research focussed on specific types of injuries: orthopaedic injury, burns and head injury with large impacts on educational attainment across different ages.(17,18,19) These studies suggest length of stay in hospital could measure the severity of a condition rather than each diagnosis.(19) For example, for orthopaedic injury children had an average 40 days absent from school.(17) It is well-known that absence from school impacts on educational attainment in childhood. For this chapter's analysis no information was available on children's days of absence post-discharge, nor on school absence generally and it is likely this risk is underestimated. It is also likely the effects observed in the analyses for this research question are conservative estimates because children who required Special Educational Needs (SEN) provision who may have increased use of healthcare services (14,19) were excluded.

Poor health due to chronic conditions that may lead to unplanned admissions can effect a child's daily activities, social interactions, school attendance and their educational attainment, either due to the illness itself or treatment.(20,21,22,23,24,25) The biological insults from chronic conditions in childhood may influence the neural connections required for optimal development, affecting concentration, memory and general cognitive ability. For infections there may be confounding from socio-economic status for educational outcomes, nevertheless recognition is increasing about an impact on brain function via cytokines and/or inflammatory markers.(26)

Reassuringly the results in this thesis show the effects of unplanned hospital inpatient admissions on childhood educational attainment were less than for many perinatal factors, area level socio-economic deprivation, school and individual poverty (using eligibility for free school meals), moving school, born late in the school year, or differences between schools. However, these risks accumulated and children may need a review of their health and support networks, possible additional learning support in school to achieve their potential, and it strengthens the case for more effective injury prevention strategies.

8.1.2 Prevalence of asthma severity or wheeze and association with educational attainment outcome

This thesis found 13% of children had an asthma diagnosis between birth and KS1 (age 6-7 years) in General Practice (GP) or hospital admission administrative data sets that aligns to previous surveys in the UK, USA and Australia.(27,28,29) In this cohort 4% of children had an inpatient hospital admission for asthma (Section 5.8.1). For a wheeze or asthma diagnosis prevalence was 22% in this cohort, corroborated by a global survey,(30) but slightly lower than other UK surveys,(31,20) likely due to different cohort demographics. The second diagnosis definition that included wheeze allowed inclusion of potentially underreported asthma, particularly relevant to children under 5 years.(32)

In this thesis two algorithms were developed, the first for asthma severity that closely matched the five levels of clinical asthma management (based partly around yearly prescriptions) in the UK (33,34) and USA (35) using diagnoses and GP prescriptions (Section 5.5). The second algorithm was a broader definition that included wheeze diagnoses. The prevalence of current chronic asthma severity between birth and KS1 was categorised as 0.6% with diagnosis only, 2.7% with intermittent bronchodilator, 7.3% persistent mild, 1.6% persistent moderate, 0.3% persistent severe. Compared to the asthma algorithm, the asthma or wheeze algorithm had higher proportions of children in the lower severity categories and for hospital admissions (Section 5.8.1).

Importantly, this thesis found an asthma inpatient hospital admission rather than current asthma severity increased risk by 14% for children not attaining the expected level at KS1 (age 6-7 years) after controlling for current asthma severity, deprivation, birth characteristics, other respiratory illness and school characteristics (Section 5.8.1). Very similar results were obtained for children using a broader definition of asthma which included wheeze. This result adds new knowledge to the evidence base because it shows having only a wheeze diagnosis was associated with increased risk for children not attaining KS1. For multiple admissions to hospital for asthma a dose-response association was found for poorer educational attainment, whereas the association only increased after age 2 years for a diagnosis of either asthma or wheeze. This new knowledge helps to give greater understanding about previous inconclusive reports in the evidence base.

It is notable that previous population representative studies of children adjusted for deprivation, found a detrimental effect for some but not all subjects (mathematics,

reading) but without consistency within these studies for current asthma.(36,37) No evidence of an effect was reported from asthma on grade retention.(38) These studies used different definitions for asthma (e.g. limitations to children's activities) and educational attainment (e.g. ≥ 6 months behind expected level). This thesis gives new insight because it separated chronic asthma severity (via GP prescriptions) and acute asthma (via inpatient hospital admissions) in analyses adjusted for all other respiratory illness, school and birth characteristics. The smaller adjusted risks in this thesis demonstrate the importance of controlling for confounding.

To my knowledge this thesis is the first to report the effects of asthma and common respiratory ailments on educational attainment. Children's presentations to primary care for respiratory tract infections (RTI), particularly lower RTI were independently associated with children not attaining the expected level at KS1, even after adjustment for school absence. RTIs were more common in children with asthma and this rose with increasing asthma severity. Yet there was no evidence of interaction between asthma and lower RTI, or asthma and upper RTI for children's educational attainment outcome. These findings indicate long-term effects and accumulating risk from hospital admissions for asthma and recurring respiratory illness from birth to KS1 through children's educational attainment. At key developmental ages younger children may have greater risk of hospital admission for asthma or wheeze as they experience more RTIs at younger ages,(39) and may be less able to communicate symptoms or manage their condition.

This thesis demonstrates school absence in the year a child takes KS1 assessment was a potential mediator in the association between asthma hospital admission and children not attaining the expected level at KS1. This contrasts with previous studies that mostly reported that asthma was associated with children having only two more days of school absence in a year (36,40,41,42,43) compared to their peers and this is unlikely to have an effect on educational outcomes. Additionally, one study noted only asthma in younger children tended to lead to higher school absence.(20) However, other studies considered more severe asthma using reliever prescriptions or Emergency Department visits and found children had 7 or more days absence from school in a year.(42,43) This agrees with the findings of this thesis where children had a higher proportion of absence as asthma severity increased. This thesis provides evidence that some children may improve their educational outcomes through better control of asthma symptoms that may be achieved through closer adherence to asthma guidelines.(44)

8.1.3 Prevalence of ACEs and association with educational attainment outcome

This thesis found ACEs were common in children. It estimated that 38% of children had lived with an adult who had a common mental disorder (CMD) between birth and age 6-7 years (KS1), rising to 47% by age 10-11 years (Key Stage 2; KS2). For a child living with someone with an alcohol problem (in GP data or an alcohol-related hospital admission) the respective prevalence's were 11% and 17% of children. Further, approximately 1% of children had lived with an adult who had a serious mental illness and a similar proportion of children had experienced victimisation. It was estimated that 3% of children had experienced a household bereavement, 19% of children were living in poverty (eligible for free school meals in year take KS) and a quarter of children were receiving some SEN provision (Section 6.9.1).

This thesis determined that children exposed to ACEs during childhood were less likely, compared to non-exposed peers, to attain the expected level of education at age 6-7 years (KS1) and age 10-11 years (KS2) after controlling for socio-demographic characteristics, perinatal health indicators, household composition and school factors. The magnitude of this association varied according to the type and timing of exposure. For example, exposure of a child during the first year of life to an adult with a history of CMD had a lower magnitude of effect on KS attainment compared to exposure during the years leading up to taking the KS assessments. The results of this thesis agree with the conceptual framework in the ACEs Pyramid where ACEs are thought to be associated with cognitive impairment (Figure 1.3, Section 6.1). This relationship is complex and it should be noted that ACEs such as maternal depression may mean support for learning or homework is suboptimal in childhood.(45)

The observed effect sizes for exposure to mental disorder (13% increased risk) or alcohol problem (16% increased risk) in the household for not attaining a KS were in addition to those observed for living in areas with high levels of deprivation. The results suggest that reducing the prevalence of these household exposures, ensuring children who are exposed are identified early and supported appropriately could make a difference to their educational outcomes.

In this thesis childhood victimisation and low family income had the biggest effect sizes for not attaining the expected level at KS (increased risk of 88% and 92% respectively), possibly reflecting the severity of these exposures. This study used hospital admissions as a

measure of victimisation and is therefore likely to underestimate the true impact of victimisation on education outcomes. These findings highlight the importance of trauma-informed services for early detection and intervention to mitigate the effect of ACEs on children's educational outcomes. Children who experienced victimisation also had a 90% increased risk for receiving SEN provision, illustrating further complexities in these relationships. Death of a household member was associated with a 14% increased risk for children not attaining the expected level at KS assessments. Poverty was considered to be a potential ACE because food insecurity (46) and deep poverty can potentially cause household stress, but debt advice and financial support may be more appropriate interventions than trauma-informed approaches.

The analyses in this thesis contribute to the evidence base because only one previous study has investigated more than two individual ACEs and found children had a poorer reading outcome at age 8 years.(47) This thesis goes beyond the analysis of that study because it includes low family income, serious mental illness in the household and death of a parent, takes account of school factors, and examines the cumulative effects of child adversity on educational outcome. Two studies considered two ACEs including potential ACE of low family income and agreed with the findings of this thesis supporting the importance of including low family income in analyses.(48,49)

This thesis found the effects of ACE exposures were cumulative, children who had multiple exposures had even higher likelihood for not attaining the expected level at KS assessments. This result supports Felitti et al's ACEs theory of a cumulative risk from co-occurring ACEs for poorer adult outcomes,(50) and theories about ACE exposures and cognitive impairment outcomes in the ACEs Pyramid (Figure 1.3, Section 6.1). Previous research shows that some ACEs are socio-economically patterned occurring more often in those more deprived and rarely occurring in isolation.(8,51) The results of this thesis suggest that the impact of ACEs on educational outcomes are in addition to those related to social deprivation. It found living in poverty, exposure to someone in the household with a mental disorder and alcohol related problems had increased likelihood for children not attaining KS1 of over 350% when living in the most compared to least deprived area. These analyses illustrate that of those children who did not attain KS1, approximately 1 in 10 could attain this expected level in language and mathematics if ACEs including poverty were entirely prevented or mitigated (Section 6.9.2).

This thesis adds to the current body of evidence by considering the collective impact of a range of ACEs detectable through current healthcare and education services, in addition to socio-economic indicators on children's educational outcomes. It provides evidence to support the introduction of trauma-informed interventions in schools to build positive environments, develop social-emotional learning, coping and support systems through early intervention.(52,53)

8.1.4 Association between ACEs and educational attainment outcome and potential mediation through emergency hospital admission

This thesis determined that exposure to ACEs was associated with increased risk for recurrent asthma emergency inpatient hospital admission before the age of 7 years compared to those not exposed in a total population cohort. This thesis adds to the evidence base because it relates six individually measured ACEs to this outcome. A similar but slightly weaker risk was found for children's recurrent all-cause emergency admission. The analysis of this thesis established that ACEs for children's recurrent emergency hospital admissions have surprisingly comparable effect sizes to their first admission,(8) after controlling for socio-demographics, perinatal health indicators, household composition, other ACEs and past admissions. These results suggest there may be no change or modification to ACEs or asthma management after a child's first admission to hospital for asthma. ACEs such as parental mental illness or alcohol abuse may disrupt routines in the household, leading to inconsistent care.(54,55) No previous reports of analyses of ACEs and recurrent hospital admissions were found in the published literature. This evidence calls attention to a possible opportunity to identify children with ACEs at their first admission and potentially intervene in the child's life to reduce the risk for further admissions through ACE screening.(56)

Several ACEs but not all those measured were associated with an increased risk for asthma or all-cause inpatient admissions in children in adjusted models. These results illustrate the differing magnitude of effects from ACEs and may also be due in part to the interplay between ACEs.

This thesis found a previous childhood victimisation hospital admission was associated with up to twice the likelihood of a child having asthma hospitalisations (first or recurrent) in adjusted models. This finding was consistent with previous research for first asthma hospitalisation (asthma onset) in adolescents.(57) Further, a previous childhood

victimisation admission had a 32% increased risk for children's recurrent all-cause admissions; this is not reported elsewhere in the literature.

Confirming previous smaller studies, this thesis found common mental disorder in the household had an association with children's asthma onset and course of asthma (35% increased risk) even after adjustment for other ACEs including poverty.(58,59,60,61) This effect size was a 20% increased risk for recurrent all-cause emergency admissions in children, and akin to previous reports for first admission.(8) For alcohol problems in the household only children's first admission for asthma had increased risk (16%), with a weaker association for recurrent all-cause emergency admissions. This aligns with previous research in asthmatic children where no evidence of an association between household alcohol problems and asthma hospitalisation was discerned.(62)

For child poverty (using free school meals eligibility), this thesis agreed with previous research (57,59,63,64,65) that there was increased risk for children's emergency hospitalisations in adjusted models, but the effect was not as strong as exposure to living with someone with a common mental disorder. There was no evidence of increased risk for emergency admissions for children with a bereavement or serious mental illness in the household. This latter finding contradicts other published literature and is probably due to different diagnosis definitions between studies in different countries.(66,67)

It is of interest that previous research in children exposed to ACEs after birth demonstrate differences in allergy or asthma markers, or in cortisol levels compared to those not exposed.(62,68) Other studies reported interactions between ACEs and traffic air pollution or predisposition to disease (atopy, family history of asthma) in children's asthma onset.(58,69) These studies illustrate the complexity of factors that may influence the risk of disease in children and suggest a diathesis-stress explanation between ACEs and asthma.(58,59,60) For children with asthma, it may be that asthma management plans are not adhered to due to household dysfunction.

This thesis determined emergency hospital admission for either asthma or all-cause was not an important mediator on the pathway between ACEs and educational attainment. To my knowledge no previous studies have investigated this relationship. These results suggest an alternative explanation of a partially independent effect for these health and social factors on poorer educational attainment in childhood. This thesis provides compelling evidence that both health and social risk factors impact on children's

educational outcomes. The contribution of both health and social risk factors should be considered in interventions to improve educational outcomes in children.

8.2 Reflecting on the key findings: strengths and limitations

An important strength of the analyses in this thesis was that it used very large cohorts from multiple record-linked health and education administrative data sets. There are several advantages to the use of routine data. Firstly data is prospectively collected so there is no recall bias, however the analysis and variables are retrospectively designed.(70) Secondly, administrative data sets have little attrition compared to rates seen in longitudinal surveys. In addition, long term outcomes that are too costly, not practical or where it is not ethical to withhold treatment can be observed in routine data and advice can be provided today.(71) In this thesis' analyses 20 years of data was used to follow children for 12 years from birth. Only 40% of GP practices in Wales had signed up to SAIL at the time of data extraction but the data was thought to be representative of the Welsh population (Section 2.2.3). In this birth cohort only 5% of children moved out of Wales each year so results are likely generalisable to the UK and other countries with similar socio-demographic and healthcare systems. It is also advantageous that results from routine data can estimate the prevalence of risk factors, particularly important to Public Health Practitioners when tailoring interventions, and to observe the incidence of outcomes.(72)

The limitations of using routine data are the reliance on coding and potential for misspecification, data are pre-collected and not collected by researchers. Therefore it can be difficult for a researcher to check how data was generated.(71) This thesis drew on previous researcher knowledge in Cardiff and Swansea Universities about the quality of administrative databases. The WECC research team (that I was part of) investigated the data sources for rates of agreement between variables over the years and coding consistency. For example, for emergency inpatient hospital admissions the research group reviewed the codes by NHS coders for cause of admission and found little variation in the codes for similar causes of admission. It was concluded that for variables from the data sets used in this theses' analyses any misclassification of coding was unlikely to disproportionately affect one group over another and so unlikely to have created a bias in any particular direction. The large administrative data sets meant cleaning and harmonisation of routine data needed to be automated so rules needed to minimise any potential information bias. The advantage of this automation is that methods used can be repeated for data refreshes.(70)

The use of routine GP and hospital inpatient admissions data allowed clinical diagnoses, symptoms, procedures and prescriptions to be used rather than parent-reported recall of diagnosis. The use of GP prescriptions data meant diagnoses or symptoms that may not be fully recorded during GP consultations informed prescribing so any selection or ascertainment bias could be minimised (e.g. asthma severity in Chapter 5). However, it is acknowledged that hospital admissions measure clinical need but may also reflect supply side factors such as availability and ability to access primary care, admission policies and other socially patterned factors. In this thesis unplanned admissions still had increased risk for lower attainment at KS1 in children even after adjustment for all available measures of socio-economic status and social deprivation. For potential differences in hospital admission policies, Local Education Authorities (LEAs; the same geographical areas as health boards before 2009) were added as an additional level to hierarchical models and showed little correlation and minimal selection bias. Also, some families may be more likely to contact their GP more often than others for any ailment. For example one family who has a child with a RTI may contact the GP more often than another family who has a child with a similar RTI. However, any additional visits to the GP for childhood RTIs would bias the risk for not attaining the expected level at KS1 towards the null (that is more GP visits would be required to show a statistically significant association $p<0.05$).

The very large cohorts allowed multiple risk factors and a wide range of perinatal, socio-demographic, school factors and school level data to be modelled together to investigate complex relationships between exposures and outcome. With a view to strengthening causal inference, Directed Acyclic Graphs (DAGs) were used to visualise relationships and aid choice of potential confounders (Section 3.1.2). In this thesis information on individual level poverty (eligibility for free school meals) was available for children, seldom seen in epidemiological analyses, in addition to small area-level deprivation and the proportion of children living in poverty at school level. Despite these advantages, there are limitations to administrative data as only those variables available can be used in analyses. This may mean there is a lack of information on all confounders and results of administrative data analyses must always caution for the potential of unmeasured residual confounding.(71) Not adjusting analyses for all confounders may lead to unimportant differences becoming statistically significant with narrow confidence intervals in large data sets.(72) It is therefore important to consider results in terms of clinical or public health significance rather than rely on univariate odds ratios. For example, the clinical significance that asthma may prevent a child attaining the expected level at KS1, may lead to reduced life chances in

later education and employment, with little comparative cost to update pre-existing guidance on asthma for clinicians and educators.

In the analyses of this thesis it was not possible to include data about parental education or child's IQ (as a proxy for variation in school engagement) that may influence educational attainment in children.(73) Parental education data is collected by the UK Census and may become available in the SAIL databank in the future. Education data sets were restricted to children in schools maintained by the LEA but in Wales fewer than 2% of primary school children attend independent schools so any resulting selection bias is unlikely to be large. In this thesis it was not possible to explore the appropriateness or access to SEN provision for children.(74) In addition, children requiring support for social, emotional or behavioural difficulties were only included in a broader category of need in SEN provision in this thesis and no specific measure such as from a Strengths and Difficulties Questionnaire was available on entry to school or at KS1.(75) Previous research shows children have higher prevalence of social, emotional or behavioural difficulties at school entry when they live in more deprived areas compared to those living in less deprived areas and this disparity widens in the first three years of school.(76) Children's social, emotional or behavioural difficulties may be part of the complex interplay between deprivation and educational attainment and more research is warranted.

For ACEs and education outcome analyses no information was available on contact with social care (77), quality of home environment(78) or neurodivergence in parents or children that might impact on children's educational outcomes.(79) In asthma and education outcome analyses there was no information available about children's compliance to asthma management plans.(80) In addition, Accident and Emergency (A & E) data was not available in sufficient detail for use in this thesis because only the speciality of the attending physician is recorded rather than diagnoses. Administrative data collection methods have recently changed in A & E and higher quality data should be available in the future. Further, there is increasing recognition that linkage of routine data to large surveys or registries can help to enhance the scope of variables within analyses.

In this thesis missing data was imputed using multiple chained equations.(81) Most missing data was under 6% of the cohorts of this thesis, except for breastfeeding at birth or 6 to 8 weeks and smoking in the first trimester of pregnancy where rates of missing data were higher. This missing data in these variables could be reasonably assumed to be missing at random (82) and the data subset available for each of these variables was large enough to

fit an imputation model for these covariates with sufficient precision (Section 4.9). In addition, little variation was seen in the estimates of associations between KS attainment and hospital admissions between imputations when these variables were added to the model. It was chosen to impute these variables because they are key factors that are socially patterned and known determinants of child health status. Multiple imputation by chained equations was used in all analyses including before Bayesian modelling with a pragmatic approach that excluded the multilevel structure of the data (e.g. schools, LEA) because this option was not available in Stata. In addition, interactions between covariates that improved model fit but were not between the exposure and main confounders were excluded from the imputation models and substantive findings. It is likely the estimates in the imputation models could be improved with the additional information from these variables. However, previous research suggests estimates may be adequate for the multilevel models using this imputed data, any interactions are likely to be underestimated (80) and these differences would be reflected in post estimations such as the Population Attributable Fraction (PAF).

It is acknowledged that multiple statistical tests in this thesis have used the same data source and therefore some of the results may have occurred by chance. For this reason, these results should be treated with some caution but many of the findings from each analysis of this thesis corroborate previous research in the field and give some external validity to these results.

8.3 Further work

The analysis of this thesis provides new evidence and insight into the complex relationship between health and social factors on educational attainment in childhood using administrative data. In this broad subject area several questions arose from the work in this thesis.

1. In Chapter 4, children's hospital bed-days were used as an approximation for days absent from school for an emergency admission but could not take account of days of absence post-discharge. Limited previous research showed days of school absence were very high for childhood injury such as burns and orthopaedic injury partly because of problems accessing school classrooms.(17,18) Further studies to investigate barriers to returning to school after children's discharge from hospital, particularly for injury warrant investigation.

2. In this thesis absence from school in the KS assessment year was found to be a potential mediator between asthma hospital admissions and educational attainment outcome. The evidence base shows there is little knowledge about the pattern of absence within a school year that may disrupt a child's learning to a greater extent. One study reported teachers preferred children's absence to be in blocks of time (for example two weeks) rather than one day a week for several weeks.(83) In the Netherlands, school absence for health reasons in primary school children was common, somewhat expected, relatively frequent and much higher than for truancy.(84) Schools in the UK may collect more detailed information about patterns and health reasons for school absence but this information is not currently available through anonymised record-linkage within the SAIL databank. Children may also be affected by health conditions whilst attending school (85) for reasons such as loss of concentration due to illness and to my knowledge no studies quantify this in terms of equivalence to days absent from school. A survey could provide more information about children's health during the school year. The patterns of school absence in children may also be a warning signal for progressing health conditions or mental health issues related to family dysfunction.(86)

3. The analyses for asthma in this thesis highlighted asthma or wheeze hospital admissions impacted on children's educational attainment rather than the severity of this condition. A more detailed analysis of the reasons why children have hospital admissions for asthma or wheeze is needed. Further research should include checks on children's adherence to asthma management plans, proper use of inhalers and ability to access health services reported to be poorer in Wales than England in a survey by Asthma UK.(80) A study that incorporated routine data could investigate these complex pathways of care for asthma.

4. The relationship of ACEs on SEN provision in children raised further questions about this provision in terms of unmet need, access, appropriateness of provision and the association between SEN provision and conditions recorded in GP and hospital records.(74)

5. Chapter 6 illustrated there is paucity of evidence about a death in the household (an ACE) for effects on educational attainment outcome in childhood.(87,88,89) Further exploration of the effects of this experience concerning the relationship of the child to the person who died, age of the child at occurrence and circumstances of the death is needed to refine the findings of this thesis.

6. In the ACEs and educational attainment analyses there was no information in the available data on Social Care Services. Children who have Social Service interventions often have multiple ACEs.(77) Investigation of the relationship between ACEs, Social Services and educational attainment outcome could help to determine whether there are opportunities to support children prior to escalation to possible maltreatment allegations and formal intervention by Social Care Services.

7. In all analyses of this thesis child IQ and maternal / parental education may provide further insight into children's educational attainment outcome. These measures may provide information about child and parental school engagement. A survey to collect data on direct measures of school engagement such as children attending after school clubs or parental school involvement would provide a better understanding of potential protective effects against ACEs for educational attainment outcomes.(90)

8. There is potential to evaluate ACE related screening or interventions using administrative data. For example, the suggested ACE screening of children at the time of first emergency inpatient hospital admission in childhood or evaluation of interventions such as trauma-informed services in schools.

9. In this thesis asthma was used as an exemplar of a chronic disease on educational attainment in childhood. Future analyses could look at other important health conditions in children that may impact on their educational attainment e.g. gastro-intestinal conditions, insomnia and more serious but less common diseases like cystic fibrosis.

10. This thesis has used a deficit model approach to understand the relationships between childhood health and ACEs on children's educational attainment outcomes. The next steps are to work out how to mitigate these effects on children's education. Further research to investigate these questions from an asset's perspective in children whose educational trajectories are positive despite harmful exposures could help to inform how to mitigate these effects.

8.4 Implications for Public Health, healthcare workers and educators

The aim of this thesis was to investigate gaps identified in the evidence base about the complex interrelationships health and social factors have on educational attainment outcomes in childhood. The evidence provided by this thesis should help Public Health, health and education services understand why some children may not attain the expected

level of education at Key Stages in childhood. From the work in this thesis, this thesis is able to make the following recommendations.

This thesis provides evidence that children admitted to hospital before starting school, even after consideration of socio-economic indicators and birth characteristics such as gestational age at birth, may need additional support to ensure they reach their academic potential. These admissions may be an early indicator for children who require additional checks on preventive primary care (e.g. development checks and vaccinations), their ability to access the GP (91) or who may need educational support in nursery settings.(92) In addition, this thesis draws attention to the higher impact of injuries and external causes on educational attainment in childhood that are common in pre-school and school-aged children. Children and parents need to know about effective injury prevention strategies such as the Safe Tea Campaign (93) or the WHO child injury prevention leaflet,(94) to reduce the incidence of these types of admissions and their consequences. It is recommended that rehabilitation programmes for these children should also address their educational needs including children's ability to access school classrooms.

This thesis also found hospital inpatient admissions from asthma, an exemplar of a chronic disease, was disruptive to a child's life and learning. Clinicians and educators need to be aware that children who have admissions for asthma or wheeze, or repeated visits to the GP for lower RTI, may need additional educational support for their educational outcomes. Moreover, children with asthma tended to have more GP visits for lower RTI than those without asthma, indicating accumulating risk. It is recommended that healthcare services should check children's adherence to asthma management plans (with yearly updates), inhaler technique and a GP consultation within 2 days of a hospital inpatient admission. In addition, healthcare services should check children and parents have access to timely primary care.(80)

This thesis provides compelling evidence that living with adults who have mental disorders or alcohol problems, experience of childhood victimisation or a death in the family increased risk for children not achieving their educational potential. A stronger effect was seen when ACEs were more proximal to the child's KS assessment. For these children, it is important that appropriate conversations are initiated with a coordinated approach when they come into contact with health, education and social care services. If properly resourced within schools, ACE interventions for children such as trauma-informed education services for post traumatic responses,(52,53) onsite counsellors or social

workers can help to reduce the risk of lower educational outcomes in children. Moreover, evidence-based interventions could mitigate the effects of ACEs in children through improving behaviour problems (95,96) or self-regulation.(89) Children living in poverty (free school meals eligible) were also more likely to fail academically compared to their peers. Extreme financial hardship can potentially cause stress in children from food insecurity (46) and this potential ACE may require different interventions such as pre-school enrichment programmes to improve school readiness,(97,98) financial advice and debt management strategies. This thesis recommends political investment into these interventions to ensure the current generation of children achieve their academic potential, and subsequent economic and social participation.

The analyses in this thesis provide persuasive evidence that ACEs are associated with children's recurrent emergency inpatient hospital admissions for asthma or all-causes with similar magnitude to those for first admission. This thesis recommends an investigation of the potential to screen children for ACEs at their first emergency admission to try to prevent further hospital admissions and provide help to caregivers and children through interventions tailored to their needs. ACEs are known to have higher prevalence in children living in areas of higher deprivation. With constrained resources, an approach such as proportionate universalism may be appropriate where a greater proportion of resources are allocated towards the most disadvantaged children.(99)

Recent reviews show ACE screening by clinicians such as GPs is acceptable to patients.(56,100) and to clinicians outside of low income settings.(56) Questions remain about whether the dosage of an intervention (type of intervention, individual or group intervention and duration of sessions such as for several weeks) from an ACE screen count can be determined.(101) Policy makers are concerned about the appropriateness of a cut point for referral for national programmes (102) and creating stigma towards parents who inform health services about ACEs in their household.(103) In addition, Public health practitioners have questions about the role of protective and compensatory experiences for children with ACEs.(104) This thesis recommends further research into ACE screening and referral to relevant interventions using trials in community settings.

The analyses in this thesis found a first emergency admission (for asthma or all-causes) was not an important mediator between ACEs and children's educational attainment outcome. This thesis provides evidence that both health and social factors contribute independently

to children's educational outcomes and interventions should consider both facets when attempting to improve educational outcomes in childhood.

8.5 Conclusion

This thesis finds evidence for threats to educational attainment in childhood from unplanned hospital admissions including those associated with the chronic condition asthma, from ACEs and poverty. With the use of large administrative data sets it provides new knowledge about the relationships between these risk factors because it was possible to model an extensive list of risk factors together. These analyses contribute insight to the hierarchical order of the magnitude of risk from different factors and the timing when risks are greatest on educational attainment in childhood. The findings of this thesis suggest health and social factors have partially independent causal effects on educational attainment outcomes.

Crucially, there is evidence that a poor start in education is strongly linked to poorer educational outcomes across all school years, poorer employment prospects and economic outlook across the life course.(3,51,105,106) The research in this thesis and related peer-reviewed journal articles inform Public Health and policy makers about where interventions could be implemented to reduce the effects of health inequalities and the attainment gap in children's education. These interventions in childhood could improve a child's life course through better educational outcomes and potentially unlock families from deprivation and ill health across generations.

8.6 References

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Appendices

Appendix A2 – Chapter 2: Hospital admission diagnosis code exclusions and Welsh population socio-demographics

Table A2.1: WHO ICD-10 diagnosis code exclusions in emergency hospital admission categories (temporary codes as listed below) for children in WECC analyses.

Table A2.2: Socio-demographic data for Wales

Appendix A4 – Chapter 4: Multilevel model results continued for confounders for models of Table 4.4

Table A4.1: Birth and individual covariates from multilevel logistic regression for not attaining Key Stage 1 at age 6-7 years and emergency inpatient hospital admissions (continued for confounders for Table 4.4), N=64,934.

Table A4.2: Area-level deprivation and school-level covariates from multilevel logistic regression for not attaining Key Stage 1 at age 6-7 years and emergency inpatient hospital admissions (continued for confounders for Table 4.4), N=64,934.

Appendix A5 – Chapter 5: Asthma or wheeze analyses in children

Appendix A5 part 1 - General Practice diagnosis and prescription codes for asthma or wheeze severity and respiratory diagnoses

Table A5.1: General Practice diagnosis codes for asthma and wheeze

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories

Table A5.3: General Practice prescription codes for endocrine corticosteroids

Table A5.4: General Practice respiratory diagnoses

Table A5.5: List of websites used to classify different types of asthma medications

Figure A5.1: Changes in asthma prescriptions during the cohort by year take KS1 assessment.

Figure A5.2: Changes in asthma or wheeze severity for discrete years of the child from birth.

Appendix A5 part 2 – Results of sensitivity analyses

Table A5.6: Multilevel multivariable models of asthma severity algorithm and multiple asthma inpatient hospital admissions for different ages of a child and not attaining the expected level at Key Stage 1 (at 6-7 years) – repeated for wheeze severity algorithm and wheeze inpatient hospital admissions

Table A5.7: Sub-sample multilevel multivariable models of asthma severity, acute asthma, respiratory illness and not attaining the expected level at Key Stage 1 (at 6-7 years) adjusted for absence from school (Week of birth 1 September 2000 to 31 August 2004), N=46,673

A5.8 Small correction

Appendix A2 – Chapter 2: Hospital admission diagnosis code exclusions and Welsh population socio-demographics

Table A2.1: WHO ICD-10 diagnosis code exclusions in emergency hospital admission categories (temporary codes as listed below) for children in WECC analyses.

We exclude all those whose ONLY admission codes are U or Z except where at least one U or Z is in the following set[a]:	
U50.1	Special care
U50.2	Level 2 intensive care (high dependency intensive care)
U50.3	Level 1 intensive care (maximal intensive care)
Z00-13	**Persons encountering health services for examination and investigation**
Z20-29	**Persons with potential health hazards related to communicable diseases**
Z40-54	**Persons encountering health services for specific procedures and health care**
Z58	**Problems related to physical environment**
Z59.4	**Lack of adequate food**
Z71.1, Z71.2, Z71.3	**Person with feared complaint in whom no diagnosis is made; person consulting for explanation of investigation findings; dietary counselling and surveillance**
Z72.3, Z72.4	**Lack of physical exercise; Inappropriate diet and eating habits**
Z74	**Problems related to care-provider dependency**
Z85-99	Persons with potential health hazards related to personal history and certain conditions influencing health status

[a]Codes used from 1 April 1995

Table A2.2: Socio-demographic data for Wales

	Total	
	n	**(%)**
Townsend Deprivation quintile: from 2003, child's age 0 – 14 years old[a]		
1 - least deprived	-	(19.3)
2	-	(19.3)
3	-	(19.3)
4	-	(20.5)
5 - most deprived	-	(21.7)
Sex: from 2001, child's age 0 – 14 years old[b]		
Male	281767	(51.3)
Female	267437	(48.7)
Breastfeeding at birth: Welsh residents 2011[c]		
No	14469	(40.5)
Yes	18062	(50.6)
no answer	3151	(8.8)
Maternal age at childbirth: Welsh residents 2011 [c]		
<16	57	(0.2)
16-19	2409	(6.8)
19-24	8115	(22.7)
25-29 years	10268	(28.8)
30-34	9107	(25.5)
35+	5722	(16.0)
no answer	4	(0.01)
Gestational age at birth: Welsh residents 2011 [c]		
20-<32 weeks	443	(1.2)
32-<37 weeks	2094	(5.9)
37-43 weeks	32985	(92.4)
no answer	160	(0.4)
Birthweight: Welsh residents 2011 [c]		
Low: < 2500g	2403	(6.7)
Normal: ≥ 2500 - < 4000g	28991	(81.2)
High: ≥ 4000g	4249	(11.9)
no answer	39	(0.1)

[a] Deprivation and health – report for the National Public Health Service for Wales 2004; [b] Welsh data from the UK Census 2001 at *https://statswales.gov.wales/*; [c] Births in Wales 2001 - 2011: Data from the National Community Child Health Database 2012.

Appendix A4 – Chapter 4: Multilevel model results continued for confounders for models of Table 4.4

Table A4.1: Birth and individual covariates from multilevel logistic regression for not attaining Key Stage 1 at age 6-7 years and emergency inpatient hospital admissions (continued for confounders for Table 4.4), N=64,934.

Characteristic		Unadjusted OR (95% CrI)	Model 3 with fully adjusted OR** (95% CrI)
Gender	Female	1.00	1.00
	Male	1.49 (1.40, 1.59)	1.57 (1.47, 1.68)
Gestational age	≤32	1.46 (1.10,1.93)	1.54 (1.13, 2.10)
	33-36	1.20 (1.04, 1.38)	1.19 (1.02,1.39)
	37-39	1.09 (1.02, 1.17)	1.07 (1.00, 1.5)
	40-42	1.00	1.00
Maternal age	≤19	1.78 (1.60, 1.99)	1.61 (1.43, 1.82)
	20-24	1.46 (1.33, 1.60)	1.34 (1.22, 1.47)
	25-29	1.00	1.00
	30-34	0.88 (0.80,0.97)	0.91 (0.82, 1.00)
	35-39	0.97 (0.85, 1.10)	0.98 (0.86, 1.12)
	≥40	1.10 (0.85, 1.43)	1.07 (0.82, 1.40)
Parity	0	1.00	1.00
	≥1	1.32 (1.23, 1.41)	1.53 (1.41, 1.65)
Multiple births at childbirth	No	1.00	1.00
	Yes	0.87 (0.69, 1.08)	0.73 (0.58, 0.92)
Congenital anomaly	No	1.00	1.00
	Minor	1.04 (0.86,1.25)	0.96 (0.79, 1.16)
	Major	1.31 (1.11, 1.55)	1.28 (1.08,1.52)
Perinatal/neonatal inpatient admission‡	No	1.00	1.00
	Yes	1.12 (0.99,1.27)	1.01 (0.89,1.16)
Caesarean section	No	1.00	1.00
	Yes	0.93 (0.86, 1.01)	0.99 (0.91, 1.08)
Small for gestational age (<10th centile)	No	1.00	1.00
	Yes	1.51 (1.37, 1.66)	1.48 (1.34, 1.64)
Breastfeeding	No	1.32 (1.23, 1.44)	1.11 (1.02,1.22)
	Yes	1.00	1.00
Maternal smoking in first trimester	No	1.00	1.00
	Yes	1.45 (1.32,1.60)	1.11 (1.01,1.23)
Academic season of birth	Sept-Dec	1.00	1.00
	Jan-Apr	1.54 (1.41, 1.69)	1.61 (1.47, 1.77)
	May-Aug	2.10 (1.92, 2.30)	2.27 (2.08,2.48)
Free School meal eligible	No	1.00	1.00
	Yes	2.55 (2.36, 2.76)	1.93 (1.77, 2.09)

Emergency hospital inpatient admission variables found in Table 4.4 are entered individually into adjusted models. ** Fully adjusted ORs are adjusted for all the variables in the partially adjusted model (found in this table) and area-level and school-level variables (Townsend deprivation quintile at birth, deprivation status change between birth and KS1, living environment at birth, number of school moves, average school size, average percentage of children eligible for free school meal at school; Table A4.2). OR=Odds ratio; CrI=Credible interval. ‡ emergency or elective.

Table A4.2: Area-level deprivation and school-level covariates from multilevel logistic regression for not attaining Key Stage 1 at age 6-7 years and emergency inpatient hospital admissions (continued for confounders for Table 4.4), N=64,934.

Characteristic		Unadjusted OR (95% CrI)	Model 3 with fully adjusted OR ** (95% CrI)
Townsend deprivation quintile at birth / first 4 months	1 least deprived	1.00	1.00
	2	1.32 (1.15, 1.53)	1.21 (1.05,1.40)
	3	1.56 (1.36, 1.78)	1.27 (1.08, 1.49)
	4	1.78 (1.56, 2.04)	1.24 (1.00,1.54)
	5 most deprived	2.56 (2.25, 2.92)	1.56 (1.26, 1.93)
Deprivation status change, using the Townsend score at birth / first 4 months and at taking KS1	Stayed low and least deprived (below median)	1.00	1.00
	Low to high (below to above median)	1.69 (1.47, 1.95)	1.34 (1.16, 1.55)
	High to low (above to below median)	1.56 (1.37, 1.77)	1.10 (0.91, 1.33)
	Stayed high and most deprived (above median)	2.00 (1.83, 2.19)	1.35 (1.14, 1.60)
Living environment in birth / first 4 months	Urban (>10K pop)	1.00	1.00
	Town & Fringe	0.85 (0.75, 0.96)	0.94 (0.83, 1.06)
	Village, hamlet & isolated dwellings	0.88 (0.77, 1.01)	1.21 (1.04, 1.40)
Number of school moves	0	1.00	1.00
	1	2.65 (2.40, 2.93)	2.27 (1.27, 4.05)
	2+	5.93 (4.47, 7.85)	4.48 (3.36, 5.97)
Average school size between 2006 and 2008	≤100	1.25 (0.97, 1.60)	1.29 (1.02, 1.65)
	101-200	1.09 (0.88, 1.34)	1.01 (0.83, 1.23)
	201-300	0.91 (0.73, 1.14)	0.90 (0.73, 1.10)
	>300	1.00	1.00
Average percentage of children eligible for free school meals in school during 2006-8	≤10	1.00	1.00
	10-20	1.41 (1.20, 1.67)	1.10 (0.92, 1.30)
	20-30	1.79 (1.45, 2.20)	1.07 (0.86, 1.32)
	30-40	2.54 (1.97, 3.26)	1.22 (0.94, 1.58)
	>40	5.30 (3.97, 7.06)	2.10 (1.55, 2.85)

Emergency hospital inpatient admission variables found in Table 4.4 are entered individually into adjusted models. ** Fully adjusted ORs are adjusted for gender, gestational age, maternal age, parity, multiple births at childbirth, congenital anomaly, perinatal/neonatal inpatient admission, caesarean section, small for gestational age (<10th centile), breastfeeding, maternal smoking in first trimester, academic season of birth, free school meal eligible (all variables found in Table A4.1) and area-level deprivation and school-level variables (all variables found in this table). OR=Odds ratio; CrI=Credible interval.

Appendix A5 – Chapter 5: Asthma or wheeze analyses in children

Appendix A5 part 1 - General Practice diagnosis and prescription codes for asthma or wheeze severity and respiratory diagnoses

Table A5.1: General Practice diagnosis codes for asthma or wheeze

General Practice Read codes version 2 for asthma diagnosis or wheeze symptoms (includes any diagnosis, symptom or procedure codes, extracted 2017)			
Asthma diagnosis			
Code	**Description**	**Code**	**Description**
H3120	Chronic asthmatic bronchitis	663P2	Asthma limits activit most day
H33..	Asthma	663Q.	Asthma not limiting activities
H330.	Extrinsic (atopic) asthma	663q.	Asthma daytime symptoms
H3300	Extrinsic asthma - no status	663r.	Asthma night symp 1-2 per mth
H3301	Extrinsic asthma + status	663s.	Asthma never causes day symps
H330z	Extrinsic asthma NOS	663t.	Asthma day symp 1-2 per mth
H331.	Intrinsic asthma	663U.	Asthma management plan given
H3310	Intrinsic asthma - no status	663u.	Asthma day symp 1-2 per week
H3311	Intrinsic asthma + status	663V.	Asthma severity
H331z	Intrinsic asthma NOS	663v.	Asthma daytime symps most days
H332.	Mixed asthma	663V0	Occasional asthma
H333.	Acute exacerbation of asthma	663V1	Mild asthma
H334.	Brittle asthma	663V2	Moderate asthma
H335.	Chron asthm w fix airflw obstr	663V3	Severe asthma
H33z.	Asthma unspecified	663W.	Asthma prophylaxis used
H33z0	Status asthmaticus NOS	663x.	Asthma limits walking on flat
H33z1	Asthma attack	66Y5.	Change in asthma managemt plan
H33z2	Late-onset asthma	66Y9.	Step up chnge asthm managmt pl
H33zz	Asthma NOS	66YA.	Step down chnge asthm managmt pl
H35y6	Sequoiosis (red-cedar asthma)	66YC.	Absent work/schl due to asthma
H35y7	Wood asthma	66YE.	Asthma monitoring due
H3B..	Asthma-COPD overlap syndrome	66YJ.	Asthma annual review
H47y0	Detergent asthma	66YK.	Asthma follow-up
663e0	Asthma sometime restr exercise	66YP.	Asthma night-time symptoms
1780	Aspirin induced asthma	66Yp.	Asthma review RCP 3 questions
1781	Asthma trigger - pollen	66YQ.	Asthma monitoring by nurse
1782	Asthma trigger - tobacco smoke	66Yq.	Asthma night symptom 1 to 2 wk
1783	Asthma trigger - warm air	66YR.	Asthma monitoring by doctor
1784	Asthma trigger - emotion	66Yr.	Asthma cause sympt most nights
1785	Asthma trigger - damp	66Ys.	Asthma never caus night symptm
1786	Asthma trigger - animals	66Yu.	Num dy abs sch asthma pst 6 mn
1787	Asthma trigger - seasonal	66YZ.	Does not have asthma man plan
1788	Asthma trigger - cold air	66Yz0	Asthma managemt plan declined
1789	Asthma trigger respiratory inf	66Yz5	Telehealth asthma monitoring
8791	Further asthma - drug prevent.	679J.	Health education - asthma
8793	Asthma control step 0	679J0	Heath educ - asthm self manag
8794	Asthma control step 1	679J1	Heal educ - struct asthma disc
8795	Asthma control step 2	8B3j.	Asthma medication review
8796	Asthma control step 3	8CE2.	Asthma leaflet given
8797	Asthma control step 4	8CMA0	Pat writt asthma pers act plan
8798	Asthma control step 5	8CR0.	Asthma clin management plan
21262	Asthma resolved	8H2P.	Emergency admission, asthma
14B4.	H/O: asthma	8HTT.	Referral to asthma clinic
14Ok0	At risk sevre asthma exacrbatn	9hA..	Except report: asthma qual ind
173A.	Exercise induced asthma	9hA1.	Except asthma qual ind: Pt uns
173c.	Occupational asthma	9hA2.	Excep asthma qual ind: Inf dis
173d.	Work aggravated asthma	9N1d.	Seen in asthma clinic
178..	Asthma trigger	9N1d0	Seen in school asthma clinic
178A.	Asthma trigger - airborne dust	9N4Q.	Did not attend asthma clinic
178B.	Asthma trigger - exercise	9NI8.	Asthma outreach clinic
1O2..	Asthma confirmed	9NNX.	Under care asthma spclst nurse

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Table A5.1: General Practice diagnosis codes for asthma or wheeze (cont)

General Practice Read codes version 2 for asthma diagnosis or wheeze symptoms (includes any diagnosis, symptom or procedure codes, extracted 2017)			
Asthma diagnosis			
Code	**Description**	**Code**	**Description**
212G.	Asthma resolved	9OJ..	Asthma monitoring admin.
388t.	RCP asthma assessment	9OJ1.	Attends asthma monitoring
38B8.	Sevr asthma exacer risk assess	9OJ2.	Refuses asthma monitoring
38DL.	Asthma control test	9OJ3.	Asthma monitor offer default
38DT.	Asthma control questionnaire	9OJ4.	Asthma monitor 1st letter
38DV.	Mini asthma QOL questionnaire	9OJ5.	Asthma monitor 2nd letter
38QM.	Childhood Asthma Control Test	9OJ6.	Asthma monitor 3rd letter
633y.	Num asthm exacer in past year	9OJ7.	Asthma monitor verbal invite
661M1	Asthma self-manage plan agreed	9OJ8.	Asthma monitor phone invite
661N1	Asthma self-manage plan review	9OJ9.	Asthma monitoring deleted
663e.	Asthma restricts exercise	9OJA.	Asthma monitoring check done
663e1	Asthma severely restr exercise	9OJB.	Asthma monitr invt SMS txt msg
663f.	Asthma never restrcts exercise	9OJB0	Asthma monitrng SMS 1st invit
663j.	Asthma - currently active	9OJB1	Asthma monitrng SMS 2nd invit
663N.	Asthma disturbing sleep	9OJB2	Asthma monitrng SMS 3rd invit
663N0	Asthma causing night waking	9OJC.	Asthma monitrng invitatn email
663N1	Asthma disturbs sleep weekly	9OJZ.	Asthma monitoring admin.NOS
663N2	Asthma disturbs sleep freqntly	9Q21.	Patient in asthma study
663O.	Asthma not disturbing sleep	TJF7.	AR - antiasthmatics
663O0	Asthma never disturbs sleep	TJF73	AR - theophylline (asthma)
663P.	Asthma limiting activities	TJF7z	AR - antiasthmatic NOS
663P0	Asthma limit act 1-2 time mth		
Wheeze diagnosis			
Code	**Description**		
1737.	Wheezing		
17370	Constant wheezing		
17371	Wheezing in absence of colds		
173B.	Nocturnal cough / wheeze		
173e.	Viral wheeze		
2326.	O/E - expiratory wheeze		
232H.	O/E inspiratory wheeze		
6635.	Increasing exercise wheeze		
R0609	Wheezing		
R060E	Mild wheeze		
R060F	Moderate wheeze		
R060G	Severe wheeze		
R060H	Very severe wheeze		

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).

Mild asthma: bronchodilators

Drug Category	Description
1	Short-acting beta$_2$ agonist and short-acting muscarinic antagonist
8	Xanthine bronchodilator assumed to be short-acting (not specified as injectable or with modified release^).
9	Bronchodilator + decongestant
15	Short-acting xanthine bronchodilator + Epinephrine, or Adrenaline inhaler
16	Theophylline, Ephedrine & Phenobarbital combination (relievers)
17	Nebuliser of reliever medication (code 1 in other forms)*

Severe Asthma: Injections and immunosuppressants or similar

Drug Category	Description
5	Injection prescription (patient probably hospitalised for treatment with injection)
21	Omalizumab and brand names, immunosuppressant IgE: mainly for allergic-asthma but can be for spontaneous hives (not in Cost of Asthma study coding).

*young children may need medication to be administered with a nebuliser as inhalers may be difficult to use e.g. for an asthma attack; older children and adults would usually only receive nebuliser treatment in hospital.
^ medication with modified release has a delayed release.

Moderate asthma medications: Inhaled corticosteroids, long-acting beta$_2$ agonists, leukotrienes or alternatives (excluding Asthma-related antihistamines coded as 12)

Drug Category	Description
2	Inhaled corticosteroid (ICS)
3	Long acting beta$_2$ agonist
4	Leukotriene receptor antagonist
6	Long-acting beta$_2$ agonist + corticosteroid
7	Long-acting antimuscarinic (also known as anticholinergic)
10	Short-acting beta$_2$ agonist + corticosteroid
11	Short-acting beta$_2$ agonist + non-steroid alternative
13	Non-steroid alternative
14	Other long-acting bronchodilator
18	Nebuliser of preventer medication (code 3 in other forms)*
19	Nebuliser ICS (code 2 other forms)*
20	Nebuliser non-steroid alternative (code as 13 in other forms)*
26	Long-acting xanthine bronchodilator (modified release^)

Read Code v2	Description	Drug category
c1	SELECTIVE BETA-ADRENOCEPTOR STIMULANT	1
c11	SALBUTAMOL [ORAL PREPARATIONS]	1
c111	*ASMAVEN 2mg tablets	1
c112	*ASMAVEN 4mg tablets	1
c113	*COBUTOLIN 2mg tablets	1
c114	*COBUTOLIN 4mg tablets	1
c115	*SALBULIN 2mg tablets	1
c116	*SALBULIN 4mg tablets	1
c117	*SALBULIN 2mg/2mL liquid	1
c118	*VENTOLIN 2mg tablets	1
c119	*VENTOLIN 4mg tablets	1

Read Code v2	Description	Drug category
c43a	SLO-PHYLLIN 250mg m/r capsules	26
c43A	THEOPHYLLINE 200mg/10mL injection	5
c43b	*THEO-DUR 200mg m/r tablets	26
c43B	THEOPHYLLINE 10mg/5mL sugar free solution	8
c43c	*THEO-DUR 300mg m/r tablets	26
c43d	*THEOGRAD 350mg m/r tablets	26
c43e	UNIPHYLLIN CONTINUS 400mg m/r tablets	26
c43f	UNIPHYLLIN CONTINUS 200mg m/r tablets	26
c43g	LABOPHYLLINE 200mg/10mL injection	5
c43h	UNIPHYLLIN CONTINUS 300mg m/r tablets	26
c43i	*BIOPHYLLINE 350mg m/r tablets	26

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c11a	*VENTOLIN 8mg m/r tablets	1	c43j	*BIOPHYLLINE 500mg m/r tablets	26
c11A	*VENTOLIN CR 4mg m/r tablets	1	c43k	THEOPHYLLINE 500mg m/r tablets	26
c11B	*SALBUTAMOL 4mg m/r tablets	1	c43m	*THEOPHYLLINE 125mg/5mL syrup	8
c11b	VENTOLIN 2mg/5mL syrup	1	c43n	*THEOPHYLLINE 125mg tablets	8
c11C	*VENTOLIN CR 8mg m/r tablets	1	c43o	*THEOPHYLLINE 60mg/5mL liquid	8
c11c	VOLMAX 4mg m/r tablets	1	c43p	THEOPHYLLINE 175mg m/r tablets	26
c11D	SALAPIN 2mg/5mL sugar free syrup	1	c43q	THEOPHYLLINE 250mg m/r tablets	26
c11d	VOLMAX 8mg m/r tablets	1	c43r	THEOPHYLLINE 300mg m/r capsules	26
c11e	*SALBUVENT 2mg tablets	1	c43s	THEOPHYLLINE 60mg m/r capsules	26
c11f	*SALBUVENT 4mg tablets	1	c43t	THEOPHYLLINE 125mg m/r capsules	26
c11g	*SALBUVENT 2mg/5mL syrup	1	c43u	THEOPHYLLINE 250mg m/r capsules	26
c11h	SALBUVENT 2mg/5mL syrup 2litre	1	c43v	THEOPHYLLINE 200mg m/r tablets	26
c11i	*VENTOLIN CR 4mg m/r tablets	1	c43w	THEOPHYLLINE 300mg m/r tablets	26
c11j	SALBUTAMOL 4mg m/r tablets	1	c43x	THEOPHYLLINE 350mg m/r tablets	26
c11k	*VENTOLIN CR 8mg m/r tablets	1	c43y	THEOPHYLLINE 400mg m/r tablets	26
c11m	LIBETIST 2mg/5mL sugar free syrup	1	c43z	*THEOPHYLLINE 200mg tablets	8
c11n	SALBUTAMOL 4mg m/r capsules	1	c44	CAFFEINE	8
c11o	SALBUTAMOL 8mg m/r capsules	1	c441	CAFFEINE solution	8
c11p	VENTMAX SR 4mg m/r capsules	1	c442	CAFFEINE CITRATE solution	8
c11q	VENTMAX SR 8mg m/r capsules	1	c5	COMPOUND BRONCHODILATORS	1
c11v	SALBUTAMOL 4mg tablets	1	c51	COMPOUND BRONCHODILATORS A-Z	1
c11w	*SALBUTAMOL 2mg/2mL liquid	1	c511	ADRENALINE+ATROPINE COMPOUND spray	17
c11x	SALBUTAMOL 2mg tablets	1	c512	ALUPENT EXPECTORANT 20mg tablets	1
c11y	SALBUTAMOL 8mg m/r tablets	1	c513	*ALUPENT EXPECTORANT mixture	1
c11z	SALBUTAMOL 2mg/5mL sugar free syrup	1	c514	*ASMA-VYDRIN spray	15
c12	SALBUTAMOL [PARENTERAL PREPARATIONS]	1	c515	*ASMA-VYDRIN spray 120mL	15
c121	VENTOLIN 250micrograms/5mL injection	5	c516	*BRICANYL COMPOUND tablets	1
c122	VENTOLIN 500microgram/1mL injection	5	c517	*BRICANYL EXPECTORANT elixir	1
c123	VENTOLIN 5mg/5mL intravenous infusion	5	c518	*BRONCHILATOR inhaler	1
c124	SALBUVENT 250microgram/5mL injection	5	c519	*BROVON spray 20mL	15
c125	SALBUVENT 500micrograms/1mL injection	5	c51a	*BROVON spray 50mL	15
c126	SALBUVENT 5mg/5mL intravenous infusion	5	c51A	FENOTEROL+IPRATROPIUM 100micrograms/40micrograms inhaler	1
c12w	*SALBUTAMOL 5mg/50mL injection	5	c51b	*BROVON MIDGET inhaler	15
c12x	SALBUTAMOL 250micrograms/5mL injection	5	c51B	FENOTEROL+IPRATROPIUM 100mcg/40mcg breath-act aerosol inhaler	1

Table A5.2: General Practice prescription codes for asthma severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c12y	SALBUTAMOL 500microgram/1mL injection	5	c51c	BROVON RESERVOIR+CLOSURE	15
c12z	SALBUTAMOL 5mg/5mL intravenous infusion	5	c51C	SALBUTAMOL+IPRATROPIUM 100micrograms/20micrograms inhaler	1
c13	SALBUTAMOL [INHALATION PREPRATIONS]	1	c51d	BROVON RUBBER BULB	15
c131	*ASMAVEN 100micrograms inhaler	1	c51D	COMBIVENT inhaler	1
c132	COBUTOLIN 100microgram inhaler	1	c51e	*BROVON pressurised inhaler	15
c133	SALBULIN 100micrograms inhaler	1	c51E	COMBIVENT Unit Dose Vials	1
c134	VENTOLIN 100micrograms inhaler	1	c51f	*CAM mixture	1
c135	VENTOLIN 2.5mg/2.5mL Nebules	17	c51F	SALBUTAMOL+IPRATROPIUM 2.5mg/500mcg nebulisation units	17
c136	VENTOLIN 200micrograms rotacaps	1	c51g	*DUO-AUTOHALER inhaler	9
c137	VENTOLIN 400micrograms rotacaps	1	c51h	DUO-AUTOHALER refill cannister	9
c138	ROTAHALER DEVICE	1	c51H	IPRATROPIUM BROMIDE+SALBUTAMOL 500mcg/2.5mg nebuliser soln	17
c139	VENTOLIN 100mg/20mL respirator solution	17	c51i	*DUOVENT inhaler	1
c13a	AEROLIN-400 100microgram inhaler	1	c51j	ISO-BROVON pressurised inhaler	15
c13A	STERI-NEB SALAMOL 2.5mg nebulisation units	17	c51k	ISO-BROVON PLUS pressurised inhaler	15
c13b	*ROTAHALER DEVICE	1	c51l	*MEDIHALER DUO inhaler	9
c13B	STERI-NEB SALAMOL 5mg nebulisation units	17	c51m	*NETHAPRIN DOSPAN m/r tablets	14
c13c	AEROLIN AUTO 100microgram inhaler	1	c51n	RYBARVIN INHALANT solution 30mL	15
c13C	SALBUTAMOL 200micrograms disks+disk inhaler	1	c51o	*RYBAR NO-1 inhaler	12
c13D	SALBUTAMOL 400micrograms disks+disk inhaler	1	c51p	*RYBAR NO-2 inhaler	12
c13d	VENTODISKS 200micrograms diskhaler 14x8	1	c51q	*TAUMASTHMAN tablets	16
c13E	SALBUTAMOL 200micrograms disk refill	1	c51r	*TEDRAL tablets	16
c13e	VENTODISKS 400micrograms diskhaler 14x8	1	c51s	*TEDRAL elixir	16
c13F	SALBUTAMOL 400micrograms disk refill	1	c51t	*FRANOL NEW 11mg/120mg tablets	15
c13f	VENTODISKS 200micrograms disk refill 14x8	1	c51u	FRANOL PLUS NEW 15mg/120mg tablets	15
c13G	SALBUTAMOL 100micrograms breath-act aerosol inhaler	1	c51v	DUOVENT UDV nebuliser solution 4mL	17
c13g	VENTODISKS 400micrograms disk refill 14x8	1	c51w	IPRATROPIUM BR+FENOTEROL HBR 500mcg/1.25mg neb solution 4mL	17
c13H	*SALAMOL 100micrograms inhaler	1	c51x	*DUOVENT Autohaler	1
c13h	SALBUVENT 100micrograms inhaler	1	c52	*BRONCHODILATORS + SEDATIVE	1
c13I	AIROMIR 100micrograms CFC-free inhaler	1	c521	*FRANOL OLD tablets	15
c13i	SALBUVENT RONDO 100microgram inhaler	1	c522	*FRANOL PLUS OLD tablets	15
c13J	SALBUTAMOL 100micrograms CFC-free inhaler	1	c523	*FRANOL EXPECTORANT elixir	15
c13j	SALBUVENT 5mg/mL respirator solution	17	c53	COMPOUND BRONCHODILATORS [1]	2
c13k	*SALBUVENT RONDO spacer x1	1	c531	IPRAMOL STERI-NEB 2.5mg/500micrograms nebuliser soln 2.5mL	17
c13K	SALAMOL EASI-BREATHE 100mcg breath-actuated aerosol inhaler	1	c6	CORTICOSTEROIDS [RESPIRATORY USE]	2

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c13l	AEROLIN 100micrograms Autohaler 200d	1	c61	BECLOMETASONE DIPROPIONATE [RESPIRATORY USE]	2
c13L	SALBUTAMOL 200micrograms breath-actuated dry powder inhaler	1	c611	BECLOFORTE 250microgram inhaler	2
c13M	VENTOLIN 200micrograms Accuhaler	1	c612	BECOTIDE-50 50microgram inhaler	2
c13m	VENTOLIN 5mg/2.5mL Nebules	17	c613	BECOTIDE 100micrograms rotacaps	2
c13n	AEROLIN 100micrograms Autohaler 100d	1	c614	BECOTIDE 200micrograms rotacaps	2
c13N	SALBUTAMOL 100micrograms vortex metered dose inhaler	1	c615	*BECOTIDE rotahaler device	2
c13o	SALBUTAMOL 5mg/2.5mL nebulisation units	17	c616	BECOTIDE 50micrograms/mL nebuliser solution	19
c13O	VENTOLIN EASI-BREATHE 100microgram inhaler	1	c617	BECOTIDE-100 100microgram inhaler	2
c13p	MAXIVENT 100microgram inhaler	1	c618	*VOLUMATIC spacer device	1
c13P	SALBUTAMOL 100micrograms Spacehaler	1	c619	BECODISK 100micrograms diskhaler 14x8	2
c13Q	ASMASAL 95micrograms Clickhaler	1	c61A	BECLOMETASONE DIPROPIONATE 400micrograms disks+disk inhaler	2
c13q	SALBUTAMOL 200 Cyclocaps	1	c61a	BECODISK 200micrograms diskhaler 14x8	2
c13R	SALBUTAMOL 100micrograms breath-act dry powder inhaler	1	c61B	BECLOMETASONE DIPROPIONATE 400micrograms disk refill	2
c13r	SALBUTAMOL 400 Cyclocaps	1	c61b	BECOTIDE 400micrograms rotacaps	2
c13s	*VENTOLIN rotahaler device	1	c61C	BECLOMETHASONE DIPROPIONATE 250mcg inhaler+spacer device	2
c13S	SALBUTAMOL 95micrograms breath-actuated dry powder inhaler	1	c61c	BECODISK 100micrograms disk refill 14x8	2
c13T	VENTOLIN 100micrograms Evohaler	1	c61D	BECLOMETASONE DIPROP 50mcg breath-actuated aerosol inhaler	2
c13U	SALBUTAMOL 100mcg CFC-free breath-actuated aerosol inhaler	1	c61d	BECODISK 200micrograms disk refill 14x8	2
c13V	AIROMIR 100micrograms CFC-free Autohaler	1	c61E	BECLOMETASONE DIPROP 250mcg breath-actuated aerosol inhaler	2
c13v	SALBUTAMOL 100microgram inhaler	1	c61e	BECODISK 400micrograms diskhaler 7x8	2
c13W	MAXIVENT 2.5mg/2.5mL Steripoules	17	c61F	BECLOMETASONE DIPROP 100mcg breath-actuated aerosol inhaler	2
c13w	SALBUTAMOL 2.5mg/2.5mL nebulisation units	17	c61f	BECODISK 400micrograms disk refill 7x8	2
c13X	MAXIVENT 5mg/2.5mL Steripoules	17	c61g	BECLOFORTE VM 250micrograms inhaler+volumatic	2
c13x	SALBUTAMOL 200micrograms inhalation capsules	1	c61G	FILAIR 50micrograms inhaler	2
c13Y	SALBULIN 100micrograms CFC-free inhaler	1	c61h	BECLOMETASONE DIPROPIONATE 400micrograms inhalation capsules	2
c13y	SALBUTAMOL 400micrograms inhalation capsules	1	c61H	FILAIR 100micrograms inhaler	2
c13Z	SALAMOL 100micrograms CFC-free inhaler	1	c61i	BECOTIDE-200 200microgram inhaler	2
c13z	SALBUTAMOL 100mg/20mL respirator solution	17	c61j	AEROBEC 50microgram Autohaler	2
c14	TERBUTALINE SULPHATE [RESPIRATORY USE]	1	c61J	FILAIR FORTE 250micrograms inhaler	2
c141	BRICANYL 5mg tablets	1	c61k	AEROBEC FORTE 250microgram Autohaler	2
c142	BRICANYL 1.5mg/5mL syrup	1	c61K	BECLAZONE 50micrograms inhaler	2
c143	BRICANYL 500micrograms/1mL injection	5	c61l	AEROBEC 100microgram Autohaler	2
c144	BRICANYL 250micrograms inhaler	1	c61L	BECLAZONE 100micrograms inhaler	2
c145	BRICANYL 250micrograms refill cannister	1	c61M	BECLAZONE 250micrograms inhaler	2

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c146	BRICANYL 250micrograms spacer inhaler	1	c61m	BECLOFORTE DISKHALER 400micrograms 14x8	2
c147	BRICANYL RESPULES 5mg/2mL nebuliser solution	17	c61N	BECLAZONE 50 EASI-BREATHE inhaler	2
c148	BRICANYL 100mg/10mL respirator solution	17	c61n	BECLOFORTE DISKS 400micrograms disk refill 14x8	2
c149	*BRICANYL SA 7.5mg m/r tablets	1	c61O	BECLAZONE 100 EASI-BREATHE inhaler	2
c14a	*MONOVENT 5mg tablets	1	c61P	BECLAZONE 250 EASI-BREATHE inhaler	2
c14b	*MONOVENT 1.5mg/5mL syrup	1	c61p	BECLOMETASONE DIPROPIONATE 100micrograms disks+disk inhaler	2
c14c	*MONOVENT SA 7.5mg m/r tablets	1	c61Q	BECLOFORTE INTEGRA 250micrograms inhaler+compact spacer	2
c14d	*NEBUHALER spacer device	1	c61q	BECLOMETASONE DIPROPIONATE 200micrograms disks+disk inhaler	2
c14e	BRICANYL 2.5mg/5mL injection	5	c61R	BECLOFORTE INTEGRA 250micrograms refill	2
c14f	BRICANYL 500micrograms Turbohaler	1	c61r	BECLOMETASONE DIPROPIONATE 100micrograms disk refill	2
c14g	TERBUTALINE 500micrograms inhaler	1	c61s	BECLOMETASONE DIPROPIONATE 200micrograms disk refill	2
c14h	TERBUTALINE 2.5mg/5mL injection	5	c61S	BECLOMETHASONE DIPROPIONATE 250mcg inhaler+compact spacer	2
c14i	TERBUTALINE SULPHATE 200mg/20mL nebuliser solution	17	c61t	BECLOMETASONE DIPROPIONATE 250micrograms inhaler	2
c14j	TERBUTALINE 500micrograms breath-actuated dry powder inhaler	1	c61T	BECLOMETHASONE DIPROPIONATE 250mcg compact spacer refill	2
c14k	BRICANYL 200mg/20mL respirator solution	17	c61u	BECLOMETASONE DIPROPIONATE 200micrograms inhaler	2
c14r	TERBUTALINE 5mg tablets	1	c61U	BECLOMETHASONE rotahaler device	2
c14s	TERBUTALINE 500microgram/1mL injection	5	c61v	BECLOMETASONE DIPROPIONATE 50micrograms inhaler	2
c14t	TERBUTALINE 250micrograms inhaler	1	c61V	BECLOMETHASONE DIPROPIONATE 50mcg vortex metered dose inh	2
c14u	TERBUTALINE 250micrograms refill cannister	17	c61W	*BDP 50micrograms Spacehaler	2
c14v	TERBUTALINE 250micrograms spacer	1	c61w	BECLOMETASONE DIPROPIONATE 100micrograms inhalation capsules	2
c14w	TERBUTALINE 5mg/2mL nebuliser solution	17	c61x	BECLOMETASONE DIPROPIONATE 200micrograms inhalation capsules	2
c14x	TERBUTALINE 100mg/10mL respirator solution	17	c61X	BECLOMETHASONE DIPROPIONATE 100mcg vortex metered dose inh	2
c14y	*TERBUTALINE 7.5mg m/r tablets	1	c61Y	*BDP 100micrograms Spacehaler	2
c14z	TERBUTALINE 1.5mg/5mL syrup	1	c61y	BECLOMETHASONE DIPROPIONATE 50mcg/mL nebuliser solution	19
c15	FENOTEROL HYDROBROMIDE	1	c61z	BECLOMETASONE DIPROPIONATE 100micrograms inhaler	2
c151	*BEROTEC 200micrograms inhaler	1	c61Z	BECLOMETHASONE DIPROPIONATE 250mcg vortex metered dose inh	2
c152	BEROTEC 100mg/20mL respirator solution	17	c62	BECLOMETASONE COMPOUNDS	2
c153	*BEROTEC 100micrograms inhaler	1	c621	*VENTIDE inhaler	10
c154	FENOTEROL 100micrograms inhaler	1	c622	*VENTIDE Rotacaps	10
c15y	FENOTEROL 200micrograms inhaler	1	c623	*VENTIDE paediatric Rotacaps	10
c15z	FENOTEROL 100mg/20mL respirator solution	17	c624	*VENTIDE Rotahaler device	10
c16	PIRBUTEROL	1	c63	*BETAMETHASONE VALERATE	2
c161	*EXIREL 10mg capsules	1	c631	*BEXTASOL 100microgram inhaler	2
c162	*EXIREL 15mg capsules	1	c63z	BETAMETHASONE 100micrograms inhaler	2

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c163	*EXIREL 7.5mg/5mL syrup	1	c64	BUDESONIDE [RESPIRATORY USE]	2
c164	*EXIREL 200micrograms inhaler	1	c641	PULMICORT 200microgram inhaler 200dose	2
c16w	*PIRBUTEROL 10mg capsules	1	c642	PULMICORT 200micrograms refill 100dose	2
c16x	*PIRBUTEROL 15mg capsules	1	c643	PULMICORT 200micrograms refill 200dose	2
c16y	*PIRBUTEROL 7.5mg/5mL syrup	1	c644	PULMICORT LS 50microgram inhaler	2
c16z	PIRBUTEROL 200micrograms inhaler	1	c645	PULMICORT LS 50micrograms refill	2
c17	REPROTEROL HYDROCHLORIDE	3	c646	*NEBUHALER spacer device	1
c171	*BRONCHODIL 20mg tablets	3	c647	PULMICORT 200microgram inhaler 100dose	2
c172	*BRONCHODIL 10mg/5mL elixir	3	c648	PULMICORT 200microgram Turbohaler 100dose	2
c173	BRONCHODIL 500micrograms inhaler	3	c649	PULMICORT 400microgram Turbohaler 50dose	2
c174	BRONCHODIL 10mg/mL respirator solution	3	c64A	BUDESONIDE 200micrograms refill cannister	2
c17w	*REPROTEROL 20mg tablets	3	c64a	PULMICORT 500micrograms Respules 2mL unit	2
c17x	*REPROTEROL 10mg/5mL elixir	3	c64B	BUDESONIDE 50micrograms spacer inhaler	2
c17y	REPROTEROL 500micrograms inhaler	3	c64b	PULMICORT 1mg Respules 2mL unit	2
c17z	REPROTEROL 10mg/mL respirator solution	18	c64c	PULMICORT 100microgram Turbohaler 200dose	2
c18	RIMITEROL HYDROBROMIDE	1	c64C	PULMICORT 200micrograms spacer inhaler	2
c181	PULMADIL 200micrograms inhaler	1	c64d	BUDESONIDE 100micrograms breath-actuated dry powder inhaler	2
c182	PULMADIL 200micrograms autohaler	1	c64D	PULMICORT LS 50micrograms spacer inhaler	2
c183	PULMADIL 200micrograms auto refill cannister	1	c64e	BUDESONIDE 50micrograms refill cannister	2
c184	RIMITEROL 200micrograms breath-actuated aerosol inhaler	1	c64E	PULMICORT 200micrograms inhaler with NebuChamber	2
c18y	RIMITEROL 200micrograms inhaler	1	c64F	BUDESONIDE 200micrograms/dose dry powder cartridge refill	2
c18z	RIMITEROL 200micrograms auto refill cannister	1	c64g	BUDESONIDE 200micrograms breath-actuated dry powder inhaler	2
c19	SALMETEROL XINAFOATE	3	c64G	NOVOLIZER BUDESONIDE 200micrograms/dose cartridge refill	2
c191	SALMETEROL 25microgram inhaler	3	c64h	BUDESONIDE 400micrograms breath-actuated dry powder inhaler	2
c192	*SEREVENT 25microgram inhaler	3	c64H	EASYHALER BUDESONIDE 100mcg breath-actuated dry powder inh	2
c193	SEREVENT 50microgram diskhaler	3	c64i	BUDESONIDE 500micrograms/2mL nebuliser solution	19
c194	SEREVENT 50micrograms disk refill	3	c64I	EASYHALER BUDESONIDE 200mcg breath-actuated dry powder inh	2
c195	SALMETEROL 50micrograms disks+disk inhaler	3	c64j	BUDESONIDE 1mg/2mL nebuliser solution	19
c196	SALMETEROL 50micrograms disk refill	3	c64J	EASYHALER BUDESONIDE 400mcg breath-actuated dry powder inh	2
c197	SALMETEROL 50micrograms breath-actuated dry powder inhaler	3	c64k	BUDESONIDE 200 Cyclocaps	2
c198	SEREVENT 50micrograms Accuhaler	3	c64K	PULMICORT 100micrograms CFC-free inhaler	2
c199	SEREVENT 25micrograms Evohaler	3	c64L	BUDESONIDE 100micrograms CFC-free inhaler	2
c19A	NEOVENT 25micrograms CFC-free inhaler	3	c64l	BUDESONIDE 400 Cyclocaps	2
c19B	VERTINE 25micrograms CFC-free inhaler	3	c64m	BUDESONIDE 200micrograms inhalation capsules	2

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c19z	SALMETEROL 25micrograms CFC-free inhaler	3	c64M	PULMICORT 200micrograms CFC-free inhaler	2
c1A	SALINE FOR NEBULISATION	1	c64N	BUDESONIDE 200micrograms CFC-free inhaler	2
c1a	TULOBUTEROL HYDROCHLORIDE	3	c64n	BUDESONIDE 400micrograms inhalation capsules	2
c1a1	*TULOBUTEROL 2mg tablets	3	c64o	BUDESONIDE 200micrograms inhaler with spacer device	2
c1A1	STERI-NEB SALINE 0.9% nebules	1	c64p	NOVOLIZER BUDESONIDE 200micrograms/dose cartridge+inhaler	2
c1a2	*BRELOMAX 2mg tablets	3	c64u	BUDESONIDE 200micrograms/dose dry powder cartridge+inhaler	2
c1A2	SODIUM CHLORIDE 0.9% nebules	1	c64v	BUDESONIDE 200microgram inhaler	2
c1a3	*RESPACAL 2mg tablets	3	c64w	*BUDESONIDE refill 100dose	2
c1A3	SODIUM CHLORIDE 6% solution for inhalation	1	c64x	*BUDESONIDE refill 200dose	2
c1a4	TULOBUTEROL 1mg/5mL sugar free liquid	3	c64y	BUDESONIDE 50microgram inhaler	2
c1a5	RESPACAL 1mg/5mL sugar free liquid	3	c64z	BUDESONIDE 200micrograms spacer inhaler	2
c1A5	SODIUM CHLORIDE 0.9% Steripoules	1	c65	FLUTICASONE PROPIONATE [RESPIRATORY USE]	2
c1A6	SALINE 0.9% Steripoules 2.5ml	1	c651	FLIXOTIDE 50micrograms diskhaler	2
c1A7	SODIUM CHLORIDE 7% nebuliser solution	1	c652	FLIXOTIDE 100micrograms diskhaler	2
c1A8	NEBUSAL 7% hypertonic sodium chloride nebuliser solution	1	c653	FLIXOTIDE 250micrograms diskhaler	2
c1AA	SODIUM CHLORIDE 3% solution for inhalation	1	c654	FLUTICASONE PROPIONATE 50micrograms disks+disk inhaler	2
c1B	BAMBUTEROL HYDROCHLORIDE	3	c655	FLUTICASONE PROPIONATE 100micrograms disks+disk inhaler	2
c1B1	BAMBEC 10mg tablets	3	c656	FLUTICASONE PROPIONATE 250micrograms disks+disk inhaler	2
c1B2	BAMBEC 20mg tablets	3	c657	FLIXOTIDE 50micrograms disk refill	2
c1B3	BAMBUTEROL HYDROCHLORIDE 10mg tablets	3	c658	FLIXOTIDE 100micrograms disk refill	2
c1B4	BAMBUTEROL HYDROCHLORIDE 20mg tablets	3	c659	FLIXOTIDE 250micrograms disk refill	2
c1c	FLUTICASONE PROPIONATE+FORMOTEROL FUMARATE	6	c65a	FLIXOTIDE 2mg/2mL Nebules	19
c1C	FORMOTEROL	3	c65A	FLUTICASONE PROPIONATE 50micrograms disk refill	2
c1c1	FLUTIFORM 50micrograms/5micrograms inhaler	2	c65B	FLUTICASONE PROPIONATE 100micrograms disk refill	2
c1C1	FORMOTEROL FUMARATE 12micrograms inhalation capsules+inhaler	3	c65b	FLUTICASONE PROPIONATE 125micrograms CFC-free inhaler	2
c1c2	FLUTIFORM 125micrograms/5micrograms inhaler	2	c65c	FLUTICASONE PROPIONATE 250micrograms CFC-free inhaler	2
c1C2	FORADIL 12micrograms inhalation capsules+inhaler	3	c65C	FLUTICASONE PROPIONATE 250micrograms disk refill	2
c1c3	FLUTIFORM 250micrograms/10micrograms inhaler	2	c65d	FLIXOTIDE 125micrograms Evohaler	2
c1C3	FORMOTEROL FUMARATE 6micrograms breath-act dry powder inh	3	c65D	FLIXOTIDE 25micrograms inhaler	2
c1C4	FORMOTEROL FUMARATE 12micrograms breath-act dry powder inh	3	c65e	FLIXOTIDE 250micrograms Evohaler	2
c1C5	OXIS 6micrograms Turbohaler	3	c65E	FLIXOTIDE 50micrograms inhaler	2
c1C6	OXIS 12micrograms Turbohaler	3	c65F	FLIXOTIDE 125micrograms inhaler	2
c1C7	ATIMOS MODULITE 12micrograms metered dose inhaler	3	c65f	FLUTICASONE PROPIONATE 50micrograms CFC-free inhaler	2
c1C8	FORMOTEROL EASYHALER 12micrograms breath-act dry powder inh	3	c65g	FLIXOTIDE 50micrograms Evohaler	2

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c1cx	FLUTICASONE PROPIONATE+FORMOTEROL FUMARATE 250mcg/10mcg inh	6	c65G	FLUTICASONE PROPIONATE 25micrograms inhaler	2
c1cy	FLUTICASONE PROPIONATE+FORMOTEROL FUMARATE 125mcg/5mcg inh	6	c65H	FLUTICASONE PROPIONATE 50micrograms inhaler	2
c1Cy	FORMOTEROL FUMARATE DIHYDRATE 12mcg breath-act dry pdr inh	3	c65I	FLUTICASONE PROPIONATE 125micrograms inhaler	2
c1cz	FLUTICASONE PROPIONATE+FORMOTEROL FUMARATE 50mcg/5mcg inh	6	c65J	FLUTICASONE PROPIONATE 250micrograms inhaler	2
c1Cz	FORMOTEROL FUMARATE DIHYDRATE 12mcg metered dose inhaler	3	c65K	FLIXOTIDE 250micrograms inhaler	2
c1D	SALMETEROL+FLUTICASONE PROPIONATE	6	c65L	FLIXOTIDE 500micrograms diskhaler	2
c1D1	SERETIDE 100 Accuhaler	6	c65M	FLIXOTIDE 500micrograms disk refill	2
c1D2	SERETIDE 250 Accuhaler	6	c65N	FLUTICASONE PROPIONATE 500micrograms disks+disk inhaler	2
c1D3	SERETIDE 500 Accuhaler	6	c65O	FLUTICASONE PROPIONATE 500micrograms disk refill	2
c1D4	SERETIDE 50 Evohaler	6	c65P	FLUTICASONE PROPIONATE 50mcg breath-actuated dry powder inh	2
c1D5	SERETIDE 125 Evohaler	6	c65Q	FLUTICASONE PROPIONATE 100mcg breath-actuated dry powder inh	2
c1D6	SERETIDE 250 Evohaler	6	c65R	FLUTICASONE PROPIONATE 250mcg breath-actuated dry powder inh	2
c1D7	SIRDUPLA 25micrograms/125micrograms inhaler	6	c65S	FLUTICASONE PROPIONATE 500mcg breath-actuated dry powder inh	2
c1D8	SIRDUPLA 25micrograms/250micrograms inhaler	6	c65T	FLIXOTIDE 50micrograms Accuhaler	2
c1Du	SALMETEROL+FLUTICASONE PROPIONATE 25mcg/50mcg CFC-free inh	6	c65U	FLIXOTIDE 100micrograms Accuhaler	2
c1Dv	SALMETEROL+FLUTICASONE PROPIONATE 25mcg/125mcg CFC-free inh	6	c65V	FLIXOTIDE 250micrograms Accuhaler	2
c1Dw	SALMETEROL+FLUTICASONE PROPIONATE 25mcg/250mcg CFC-free inh	6	c65W	FLIXOTIDE 500micrograms Accuhaler	2
c1Dx	SALMETEROL+FLUTICASONE PROPIONATE 50mcg/100mcg b-act pdr inh	6	c65X	FLUTICASONE PROPIONATE 0.5mg/2mL nebulisation units	19
c1Dy	SALMETEROL+FLUTICASONE PROPIONATE 50mcg/250mcg b-act pdr inh	6	c65Y	FLUTICASONE PROPIONATE 2mg/2mL nebulisation units	19
c1Dz	SALMETEROL+FLUTICASONE PROPIONATE 50mcg/500mcg b-act pdr inh	6	c65Z	FLIXOTIDE 0.5mg/2mL Nebules	19
c1E	SALBUTAMOL [INHALATION PREPRATIONS 2]	1	c66	BECLOMETASONE DIPROPIONATE [RESPIRATORY USE 2]	2
c1E1	SALAMOL EASI-BREATHE 100mcg CFC-free breath-act aerosol inh	1	c661	*BDP 250micrograms Spacehaler	2
c1E2	PULVINAL SALBUTAMOL 200mcg breath-act dry powder inhaler	1	c662	BECOTIDE 50 EASI-BREATHE inhaler	2
c1E3	VENTODISKS 200micrograms diskhaler 15x8	1	c663	BECOTIDE 100 EASI-BREATHE inhaler	2
c1E4	VENTODISKS 400micrograms diskhaler 15x8	1	c664	BECLOFORTE EASI-BREATHE 250micrograms inhaler	2
c1E5	VENTODISKS 200micrograms disk refill 15x8	1	c665	QVAR 50 inhaler	2
c1E6	VENTODISKS 400micrograms disk refill 15x8	1	c666	QVAR 100 inhaler	2
c1E7	EASYHALER SALBUTAMOL 100mcg breath-actuated dry powder inh	1	c667	QVAR 50 Autohaler	2
c1E8	EASYHALER SALBUTAMOL 200mcg breath-actuated dry powder inh	1	c668	QVAR 100 Autohaler	2
c1E9	SALBULIN NOVOLIZER 100micrograms cartridge and inhaler	1	c669	BECLAZONE 200 inhaler	2
c1EA	SALBUTAMOL 100micrograms dry powder cartridge and inhaler	1	c66A	BECLOMETASONE DIPROP 50mcg breath-act dry powder inhaler	2
c1EB	SALBULIN NOVOLIZER 100micrograms dry powder cartridge refill	1	c66a	QVAR EASI-BREATHE 100mcg CFC-free breath-act dry pdr inhaler	2
c1EC	SALBUTAMOL 100micrograms dry powder cartridge refill	1	c66B	BECLOMETASONE DIPROP 100mcg breath-act dry powder inhaler	2
c1ED	VENTOLIN 50mg/10mL respirator solution	1	c66b	EASYHALER BECLOMETASONE 200mcg breath-act dry powder inhaler	2

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c1EE	SALBUTAMOL 50mg/10mL respirator solution	17	c66C	BECLOMETASONE DIPROP 250mcg breath-act dry powder inhaler	2
c2	OTHER ADRENOCEPTOR STIMULANTS	1	c66c	CLENIL MODULITE 50micrograms CFC-free inhaler	2
c21	ADRENALINE [RESP]	5	c66D	ASMABEC 50micrograms Clickhaler	2
c211	ADRENALINE 500microgram/0.5mL injection	5	c66d	CLENIL MODULITE 100micrograms CFC-free inhaler	2
c212	*ADRENALINE 1mg/1mL injection	5	c66E	ASMABEC 100micrograms Clickhaler	2
c213	MEDIHALER-EPI 280micrograms inhaler	5	c66e	CLENIL MODULITE 200micrograms CFC-free inhaler	2
c214	MIN-I-JET ADREN 500microgram/0.5mL injection	5	c66F	ASMABEC 250micrograms Clickhaler	2
c215	MIN-I-JET ADREN 1mg/1mL injection	5	c66f	CLENIL MODULITE 250micrograms CFC-free inhaler	2
c216	ADRENALINE 280micrograms inhaler	5	c66G	BECLOMETASONE DIPROP 400mcg breath-act dry powder inhaler	2
c22	EPHEDRINE HYDROCHLORIDE [RESPIRATORY USE]	1	c66g	BECLOMETASONE DIPROPIONATE 200micrograms CFC-free inhaler	2
c221	EPHEDRINE HYDROCHLORIDE 15mg tablets	1	c66H	BECLOMETASONE DIPROP 200mcg breath-act dry powder inhaler	2
c222	EPHEDRINE HYDROCHLORIDE 30mg tablets	1	c66h	BECLOMETASONE DIPROPIONATE 250micrograms CFC-free inhaler	2
c223	EPHEDRINE HYDROCHLORIDE 60mg tablets	1	c66I	PULVINAL BECLOMETHASONE DIPROP 100mcg breath-act dry pdr inh	2
c224	EPHEDRINE HYDROCHLORIDE 15mg/5mL elixir	1	c66J	PULVINAL BECLOMETHASONE DIPROP 200mcg breath-act dry pdr inh	2
c225	*CAM SF 15mg/5mL mixture	1	c66K	PULVINAL BECLOMETHASONE DIPROP 400mcg breath-act dry pdr inh	2
c226	CAM 4mg/5mL sugar free mixture	1	c66L	BECLOMETASONE 100 Cyclocaps	2
c227	EPHEDRINE HYDROCHLORIDE 4mg/5mL sugar free mixture	1	c66M	BECLOMETASONE 200 Cyclocaps	2
c23	*ISOETHARINE HYDROCHLORIDE	1	c66N	BECLOMETASONE 400 Cyclocaps	2
c231	*NUMOTAC 10mg m/r tablets	1	c66P	BECODISK 100micrograms diskhaler 15x8	2
c23z	ISOETHARINE HCL 10mg m/r tablets	1	c66Q	BECODISK 200micrograms diskhaler 15x8	2
c24	ISOPRENALINE SULPHATE	1	c66R	BECODISK 400micrograms diskhaler 15x8	2
c241	*ALEUDRIN 20mg tablets	1	c66S	BECODISK 100micrograms disk refill 15x8	2
c242	ALEUDRIN 1% spray for nebuliser	17	c66T	BECODISK 200micrograms disk refill 15x8	2
c243	ISO-AUTOHALER 80microgram inhaler	1	c66U	BECODISK 400micrograms disk refill 15x8	2
c244	ISO-AUTOHALER 80microgram inhaler	1	c66V	BECLOMETASONE DIPROPIONATE 50micrograms CFC-free inhaler	2
c245	MEDIHALER-ISO 80micrograms inhaler	1	c66W	BECLOMETASONE DIPROPIONATE 100micrograms CFC-free inhaler	2
c246	MEDIHALER-ISO FORTE 400micrograms inhaler	1	c66X	BECLOMETASONE DIPROPIONATE 50mcg CFC-free br-act inhaler	2
c24v	ISOPRENALINE SULPHATE 20mg tablets	1	c66Y	BECLOMETASONE DIPROPIONATE 100mcg CFC-free br-act inhaler	2
c24w	ISOPRENALINE SULPHATE 1% spray for nebuliser	17	c66Z	QVAR EASI-BREATHE 50mcg CFC-free breath-act dry pdr inhaler	2
c24x	ISOPRENALINE SULPHATE 80micrograms inhaler	1	c67	BUDESONIDE+FORMOTEROL	6
c24y	ISOPRENALINE SULPHATE 80micrograms inhaler refill	1	c671	SYMBICORT 100/6 Turbohaler	6
c24z	ISOPRENALINE SULPHATE 400micrograms inhaler	1	c672	SYMBICORT 200/6 Turbohaler	6
c25	ORCIPRENALINE SULPHATE [RESPIRATORY USE]	1	c673	SYMBICORT 400/12 Turbohaler	6
c251	*ALUPENT 20mg tablets	1	c674	DUORESP SPIROMAX 160mcg/4.5mcg breath-act dry powder inhaler	6

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c252	ALUPENT 10mg/5mL syrup	1	c675	DUORESP SPIROMAX 320mcg/9mcg breath-act dry powder inhaler	6
c253	ALUPENT 500microgram/1mL injection	5	c67x	BUDESONIDE+FORMOTEROL FUMARATE 400/12mcg b-act dry pdr inh	6
c254	*ALUPENT 750micrograms inhaler	1	c67y	BUDESONIDE+FORMOTEROL FUMARATE 200/6mcg bth-act dry pdr inh	6
c255	ALUPENT 750micrograms inhaler refill	1	c67z	BUDESONIDE+FORMOTEROL FUMARATE 100/6mcg bth-act dry pdr inh	6
c25v	*ORCIPRENALINE 20mg tablets	1	c68	MOMETASONE [RESPIRATORY USE]	2
c25w	ORCIPRENALINE 10mg/5mL syrup	1	c681	MOMETASONE FUROATE 200mcg breath-act dry powder inhaler	2
c25x	ORCIPRENALINE 500microgram/1mL injection	5	c682	MOMETASONE FUROATE 400mcg breath-act dry powder inhaler	2
c25y	ORCIPRENALINE 750micrograms inhaler	1	c683	ASMANEX TWISTHALER 200mcg breath-act dry powder inhaler	2
c25z	ORCIPRENALINE 750micrograms inhaler refill	1	c684	ASMANEX TWISTHALER 400mcg breath-act dry powder inhaler	2
c3	ANTICHOLINERGIC BRONCHODILATORS	1	c69	CICLESONIDE	2
c31	IPRATROPIUM BROMIDE [1]	1	c691	ALVESCO 160micrograms inhaler	2
c311	*ATROVENT 20micrograms inhaler	1	c692	ALVESCO 80micrograms inhaler	2
c312	ATROVENT 500microgram/2mL nebuliser solution	17	c69y	CICLESONIDE 80micrograms inhaler	2
c313	ATROVENT FORTE 40microgram inhaler	1	c69z	CICLESONIDE 160micrograms inhaler	2
c314	ATROVENT 250microgram/1mL nebuliser solution	17	c6A	BECLOMETASONE+FORMOTEROL	6
c315	ATROVENT 20micrograms Autohaler	1	c6A1	FOSTAIR 100micrograms/6micrograms inhaler	6
c316	STERI-NEB IPRATROPIUM 250micrograms/1mL nebulisation units	17	c6A2	FOSTAIR NEXTHALER 100micrograms/6micrograms powder inhaler	6
c317	STERI-NEB IPRATROPIUM 500micrograms/2mL nebulisation units	17	c6Ay	BECLOMET DIPROP+FORMOTERL FUMARATE DIHYD 100mcg/6mcg pdr	6
c318	ATROVENT 40micrograms Aerocaps refill pack	1	c6Az	BECLOMETASONE+FORMOTEROL 100micrograms/6micrograms inhaler	6
c319	ATROVENT 40micrograms Aerocaps+Aerohaler device	1	c6B	FLUTICASONE+VILANTEROL	6
c31A	IPRATROPIUM BROMIDE 40mcg inhalation capsules	1	c6B1	RELVAR ELLIPTA 184micrograms/22micrograms inhaler	6
c31B	IPRATROPIUM BROMIDE 40mcg inhalation capsules+inhaler device	1	c6B2	FLUTICASONE FUROATE+VILANTEROL 184mcg/22mcg dry pdr inhaler	6
c31C	RESPONTIN 250micrograms/1mL Nebules	17	c6B3	RELVAR ELLIPTA 92micrograms/22micrograms inhaler	6
c31D	RESPONTIN 500micrograms/2mL Nebules	17	c6B4	FLUTICASONE FUROATE+VILANTEROL 92mcg/22mcg dry pdr inhaler	6
c31E	TROPIOVENT 250micrograms/1mL Steripoules	17	c7	ASTHMA PROPHYLAXIS	1
c31F	TROPIOVENT 500micrograms/2mL Steripoules	17	c71	SODIUM CROMOGLICATE [ASTHMA]	13
c31G	ATROVENT 20micrograms CFC-free inhaler	1	c711	*INTAL 1mg inhaler	13
c31t	IPRATROPIUM BROMIDE 20micrograms CFC-free inhaler	1	c712	*INTAL HALERMATIC insufflator	13
c31u	IPRATROPIUM 20micrograms breath-actuated aerosol inhaler	1	c713	INTAL 20mg spincaps	13
c31v	IPRATROPIUM 250micrograms/1mL nebuliser solution	17	c714	INTAL SPINHALER insufflator	13
c31w	IPRATROPIUM 500micrograms/2mL nebuliser solution	17	c715	INTAL 20mg/2mL nebuliser solution	20
c31x	IPRATROPIUM 20micrograms inhaler	1	c716	*INTAL 5mg inhaler	13
c31y	IPRATROPIUM 250micrograms/mL nebuliser solution	17	c717	SODIUM CROMOGLICATE 20mg inhalation capsules	20
c31z	IPRATROPIUM 40microgram inhaler	1	c718	SODIUM CROMOGLICATE 20mg/2mL nebuliser solution	20

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c32	OXITROPIUM BROMIDE	1	c719	SODIUM CROMOGLICATE 5mg inhaler	13
c321	OXITROPIUM 100micrograms/dose inhaler 200dose	1	c71a	*INTAL 5mg Autohaler	13
c322	OXIVENT 100micrograms/dose inhaler 200dose	1	c71b	STERI-NEB CROMOGEN 20mg nebulisation units	20
c323	OXIVENT 100micrograms Autohaler	1	c71c	CROMOGEN 5mg inhaler	13
c324	OXITROPIUM 100micrograms breath-actuated aerosol inhaler	1	c71d	INTAL FISONAIR 5mg inhaler + spacer device	13
c33	TIOTROPIUM	7	c71e	SODIUM CROMOGLICATE 5mg inhaler + spacer device	13
c331	TIOTROPIUM 18micrograms inhalation capsules	7	c71f	SODIUM CROMOGLYCATE 5mg auto inhaler	13
c332	TIOTROPIUM 18micrograms capsules with inhaler device	7	c71g	INTAL SYNCRONER 5mg inhaler + spacer device 2x112dose	13
c333	TIOTROPIUM 2.5micrograms inhalation carts+inhaler device	7	c71h	SODIUM CROMOGLICATE 5mg breath-actuated aerosol inhaler	13
c33x	SPIRIVA RESPIMAT 2.5mcg cartridges+Respimat inhaler device	7	c71i	INTAL 5mg CFC-free inhaler	13
c33y	SPIRIVA COMBOPACK 18mcg caps+HandiHaler inhaler device	7	c71j	CROMOGEN EASI-BREATHE 5mg breath-actuated aerosol inhaler	13
c33z	SPIRIVA 18micrograms inhalation capsules	7	c71k	SODIUM CROMOGLICATE 5mg CFC-free inhaler	13
c4	XANTHINE BRONCHODILATORS	8	c72	SODIUM CROMOGLICATE COMPOUNDS	13
c41	AMINOPHYLLINE	8	c721	*INTAL COMPOUND spincaps	13
c411	AMINOPHYLLINE 100mg tablets	8	c722	*AEROCROM inhaler	11
c412	AMINOPHYLLINE 250mg/10mL injection	5	c723	AEROCROM SYNCRONER inhaler + spacer device	11
c413	AMINOPHYLLINE 500mg/2mL injection	5	c72y	SODIUM CROMOGLICATE+SALBUTAMOL 1mg/100mcg inhaler + spacer	11
c414	AMINOPHYLLINE 50mg suppositories	8	c72z	SODIUM CROMOGLICATE+SALBUTAMOL 1mg/100micrograms inhaler	11
c415	AMINOPHYLLINE 100mg suppositories	8	c73	KETOTIFEN [ASTHMA PROPHYLAXIS]	12
c416	AMINOPHYLLINE 150mg suppositories	8	c731	*ZADITEN 1mg capsules	12
c417	AMINOPHYLLINE 180mg suppositories	8	c732	ZADITEN 1mg tablets	12
c418	AMINOPHYLLINE 360mg suppositories	8	c733	ZADITEN 1mg/5mL elixir	12
c419	*THEODROX tablets	8	c734	*KETOTIFEN 1mg capsules	12
c41A	*NORPHYLLIN 100mg tablets	8	c735	KETOTIFEN 1mg tablets	12
c41a	PHYLLOCONTIN CONTINUS 225mg m/r tablets	26	c736	KETOTIFEN 1mg/5mL elixir	12
c41B	NORPHYLLIN SR 225mg m/r tablets	26	c73x	*KETOTIFEN 1mg capsules	12
c41b	PHYLLOCONTIN FORTE 350mg m/r tablets	26	c73y	*KETOTIFEN 1mg tablets	12
c41C	NORPHYLLIN SR 350mg m/r tablets	26	c73z	*KETOTIFEN 1mg/5mL elixir	12
c41c	PHYLLOCONTIN PAEDIATRIC 100mg m/r tablets	26	c74	NEDOCROMIL SODIUM [ASTHMA]	13
c41d	AMINOPHYLLINE 225mg m/r tablets	26	c741	*TILADE MINT 2mg inhaler	13
c41e	*PECRAM 225mg m/r tablets	26	c742	*NEDOCROMIL SODIUM 2mg inhaler	13
c41f	AMINOPHYLLINE 350mg m/r tablets	26	c743	*TILADE MINT 2mg inhaler	13
c41g	AMINOPHYLLINE 100mg m/r tablets	26	c744	TILADE MINT SYNCRONER 2mg inhaler	13
c41h	*AMNIVENT 225mg m/r tablets	26	c745	NEDOCROMIL SODIUM 2mg inhaler + spacer	13

Table A5.2: General Practice prescription codes for asthma or wheeze severity categories (cont)

General Practice Read Code version 2 asthma prescriptions that have been categorised into diagnosis only, intermittent bronchodilator, persistent mild, persistent moderate and persistent severe prescription types (update extracted 2017).					
Read Code v2	**Description**	**Drug category**	**Read Code v2**	**Description**	**Drug category**
c41i	*AMNIVENT 350mg m/r tablets	26	c746	NEDOCROMIL SODIUM 2mg CFC-free inhaler	13
c41j	MIN-I-JET AMINOPHYLLINE 250mg/10mL injection	5	c747	TILADE 2mg CFC-free inhaler	13
c41k	AMINOPHYLLINE 250mg/10mL prefilled syringe	5	cA	LEUKOTRIENE RECEPTOR ANTAGONIST	4
c41m	AMINOPHYLLINE HYDRATE 225mg m/r tablets	26	cA1	MONTELUKAST	4
c42	CHOLINE THEOPHYLLINATE	8	cA11	MONTELUKAST 10mg tablets	4
c421	*CHOLEDYL 100mg tablets	8	cA12	MONTELUKAST 5mg chewable tablets	4
c422	*CHOLEDYL 200mg tablets	8	cA13	SINGULAIR 10mg tablets	4
c423	*CHOLEDYL 62.5mg/5mL syrup	8	cA14	SINGULAIR PAEDIATRIC 5mg chewable tablets	4
c424	SABIDAL SR-270 424mg m/r tablets	26	cA15	SINGULAIR PAEDIATRIC 4mg chewable tablets	4
c42w	CHOLINE THEOPHYLLINATE 100mg tablets	8	cA16	SINGULAIR PAEDIATRIC 4mg/sachet granules	4
c42x	CHOLINE THEOPHYLLINATE 200mg tablets	8	cA1y	MONTELUKAST 4mg/sachet granules	4
c42y	CHOLINE THEOPHYLLINATE 62.5mg/5mL syrup	8	cA1z	MONTELUKAST 4mg chewable tablets	4
c42z	CHOLINE THEOPHYLLINATE 424mg m/r tablets	26	cA2	ZAFIRLUKAST	4
c43	THEOPHYLLINE	8	cA21	ZAFIRLUKAST 20mg tablets	4
c431	*BIOPHYLLINE 125mg/5mL syrup	8	cA22	ACCOLATE 20mg tablets	4
c432	*NUELIN 125mg tablets	8	ck1	OMALIZUMAB	21
c433	*NUELIN 60mg/5mL liquid	8	ck11	OMALIZUMAB 150mg injection(pdr for recon)+solvent	21
c434	*LASMA 300mg m/r tablets	4	ck12	XOLAIR 150mg injection(pdr for recon)+solvent	21
c435	NUELIN SA 175mg m/r tablets	26	ck13	OMALIZUMAB 75mg/0.5mL soln for injection prefilled syringe	21
c436	NUELIN SA-250 250mg m/r tablets	26	ck14	XOLAIR 75mg/0.5mL solution for injection prefilled syringe	21
c437	*PRO-VENT 300mg m/r capsules	26	ck15	OMALIZUMAB 150mg/1mL soln for injection prefilled syringe	21
c438	SLO-PHYLLIN 60mg m/r capsules	26	ck16	XOLAIR 150mg/1mL solution for injection prefilled syringe	21
c439	SLO-PHYLLIN 125mg m/r capsules	26			

Table A5.3: General Practice prescription codes for endocrine corticosteroids

General Practice Read Code version 2 corticosteroids used in the endocrine system (extracted 2017)	
Endocrine corticosteroids tablets or oral solution	
Code	**Description**
fe1z.	BETAMETHASONE 4mg/1mL injection
fe3A.	DEXSOL 2mg/5mL oral solution
fe3B.	DEXAMETHASONE 10mg/5mL oral solution
fe3C.	MARTAPAN 2mg/5mL oral solution
fe3r.	DEXAMETHASONE 500micrograms/5mL solution
fe3s.	DEXAMETHASONE 2mg/5mL sugar free solution
fe3u.	DEXAMETHASONE 2mg/5mL liquid
fe41.	HYDROCORTISONE 10mg tablets
fe42.	HYDROCORTISONE 20mg tablets
fe43.	*HYDROCORTISTAB 20mg tablets
fe44.	*HYDROCORTONE 10mg tablets
fe45.	*HYDROCORTONE 20mg tablets
fe51.	MEDRONE 2mg tablets
fe52.	MEDRONE 4mg tablets
fe53.	MEDRONE 16mg tablets
fe5f.	MEDRONE 100mg tablets
fe5m.	METHYLPREDNISOLONE 100mg tablets
fe5n.	METHYLPREDNISOLONE 2mg tablets
fe5o.	METHYLPREDNISOLONE 4mg tablets
fe5p.	METHYLPREDNISOLONE 16mg tablets
fe61.	PREDNISOLONE 1mg tablets
fe62.	PREDNISOLONE 5mg tablets
fe64.	*DELTA-PHORICOL 5mg tablets
fe65.	DELTACORTRIL ENTERIC 2.5mg tablets
fe66.	DELTACORTRIL ENTERIC 5mg tablets
fe67.	*DELTALONE 1mg tablets
fe68.	*DELTALONE 5mg tablets
fe69.	*DELTASTAB 1mg tablets
fe6a.	*DELTASTAB 5mg tablets
fe6c.	*PRECORTISYL 1mg tablets
fe6d.	*PRECORTISYL 5mg tablets
fe6e.	PRECORTISYL FORTE 25mg tablets
fe6f.	*PREDNESOL 5mg tablets
fe6g.	*SINTISONE 5mg tablets
fe6h.	PREDNISOLONE 2.5mg e/c tablets
fe6i.	PREDNISOLONE 5mg e/c tablets
fe6j.	PREDNISOLONE 5mg soluble tablets
fe6k.	PREDNISOLONE 50mg tablets
fe6l.	DILACORT 5mg gastro-resistant tablets
fe6m.	DILACORT 2.5mg gastro-resistant tablets
fe6n.	PEVANTI 2.5mg tablets
fe6o.	PEVANTI 25mg tablets
fe6p.	PEVANTI 5mg tablets
fe6q.	PEVANTI 10mg tablets
fe6r.	PEVANTI 20mg tablets
fe6s.	PREDNISOLONE 20mg tablets
fe6t.	PREDNISOLONE 10mg tablets
fe6v.	PREDNISOLONE 2.5mg tablets
fe6w.	*PREDNISOLONE 2.5mg tablets
fe71.	*PREDNISONE 1mg tablets
fe72.	*PREDNISONE 5mg tablets
fe73.	*DECORTISYL 5mg tablets
fe74.	*ECONOSONE 1mg tablets
fe75.	*ECONOSONE 5mg tablets
fe81.	*TRIAMCINOLONE 2mg tablets
fe82.	*TRIAMCINOLONE 4mg tablets
fe86.	*LEDERCORT 2mg tablets
fe87.	*LEDERCORT 4mg tablets
fe91.	DEFLAZACORT 6mg tablets
fe92.	CALCORT 6mg tablets
fe93.	*DEFLAZACORT 30mg tablets

Table A5.3: General Practice prescription codes for endocrine corticosteroids (cont)

General Practice Read Code version 2 corticosteroids used in the endocrine system (extracted 2017)	
Endocrine Corticosteroids generic terms (assumed as tablets or liquid)	
Code	**Description**
fe94.	*CALCORT 30mg tablets
fe95.	*DEFLAZACORT 1mg tablets
fe96.	*CALCORT 1mg tablets
fe3..	DEXAMETHASONE [ENDOCRINE]
fe4..	HYDROCORTISONE
fe5..	METHYLPREDNISOLONE [ENDOCRINE]
fe6..	PREDNISOLONE [ENDOCRINE]
fe7..	PREDNISONE
fe8..	TRIAMCINOLONE [ENDOCRINE]
fe9..	DEFLAZACORT
Endocrine corticosteroid injections	
Code	**Description**
fe34.	*DECADRON 8mg/2mL injection
fe35.	DECADRON SHOCK-PAK 100mg/5mL injection
fe38.	*ORADEXON 5mg/1mL injection
fe39.	*ORADEXON 10mg/2mL injection
fe3D.	DEXAMETHASONE 3.8mg/1mL solution for injection
fe3p.	DEXAMETHASONE 6.6mg/2mL solution for injection
fe3q.	DEXAMETHASONE 3.3mg/1mL solution for injection
fe3w.	DEXAMETHASONE 8mg/2mL injection
fe3x.	DEXAMETHASONE 100mg/5mL injection
fe3z.	DEXAMETHASONE 4mg/1mL injection
fe46.	HYDROCORTISONE 100mg injection
fe47.	HYDROCORTISONE 500mg injection
fe48.	EFCORTELAN SOLUBLE 100mg injection
fe49.	EFCORTESOL 100mg/1mL injection
fe4a.	EFCORTESOL 500mg/5mL injection
fe4b.	SOLU-CORTEF+WATER 100mg injection
fe4c.	SOLU-CORTEF 100mg injection
fe4d.	HYDROCORTISONE 100mg/1mL injection
fe54.	MIN-I-MIX METHYLPREDNIS. 500mg injection
fe55.	MIN-I-MIX METHYLPREDNISOLONE 1g injection
fe56.	SOLU-MEDRONE 40mg injection powder+diluent
fe57.	SOLU-MEDRONE 125mg injection powder+diluent
fe58.	SOLU-MEDRONE 500mg injection powder+diluent
fe59.	SOLU-MEDRONE 1g injection powder+diluent
fe5a.	SOLU-MEDRONE 2g injection
fe5b.	DEPO-MEDRONE 40mg/1mL injection
fe5c.	DEPO-MEDRONE 80mg/2mL injection
fe5d.	*DEPO-MEDRONE 80mg syringe
fe5e.	DEPO-MEDRONE 120mg/3mL injection
fe5g.	METHYLPREDNISOLONE 500mg injection (pdr for recon)
fe5h.	METHYLPREDNISOLONE 1g injection (pdr for recon)
fe5q.	METHYLPREDNISOLONE 500mg injection
fe5r.	METHYLPREDNISOLONE 1g injection
fe5s.	METHYLPREDNISOLONE 40mg injection powder+diluent
fe5t.	METHYLPREDNISOLONE 125mg injection powder+diluent
fe5u.	METHYLPREDNISOLONE 500mg injection powder+diluent
fe5v.	METHYLPREDNISOLONE 1g injection powder+diluent
fe5w.	METHYLPREDNISOLONE 2g injection powder+diluent
fe5x.	METHYLPREDNISOLONE 40mg/1mL injection
fe5y.	METHYLPREDNISOLONE 80mg/2mL injection
fe5z.	METHYLPREDNISOLONE 200mg/5mL injection
fe63.	*CODELSOL 32mg/2mL injection
fe6b.	DELTASTAB 25mg/1mL injection
fe6u.	PREDNISOLONE 32mg/2mL injection
fe6y.	PREDNISOLONE 125mg/5mL injection
fe6z.	PREDNISOLONE 25mg tablets
fe83.	KENALOG 40mg/mL injection

Table A5.3: General Practice prescription codes for endocrine corticosteroids (cont)

General Practice Read Code version 2 corticosteroids used in the endocrine system (extracted 2017)	
Endocrine corticosteroid injections	
Code	**Description**
fe84.	*KENALOG 40mg/1mL syringe
fe85.	*KENALOG 80mg/2mL injection
fe88.	KENALOG 80mg/2mL i-m prefilled syringe
fe8u.	TRIAMCINOLONE ACETONIDE 40mg/1mL intramuscular injection
fe8v.	TRIAMCINOLONE ACETONIDE 80mg/2mL i-m prefilled syringe
fe8w.	TRIAMCINOLONE ACETONIDE 40mg/1mL i-m prefilled syringe
fe8x.	TRIAMCINOLONE 40mg/1mL injection
fe8y.	TRIAMCINOLONE 80mg/2mL injection

Table A5.4: General Practice respiratory diagnoses

General Practice Read code version 2 respiratory diagnosis categories (extracted 2017)	
Upper respiratory tract infection	
Code	**Description**
H0...	Acute respiratory infections
H00..	Acute nasopharyngitis
H01..	Acute sinusitis
H010.	Acute maxillary sinusitis
H011.	Acute frontal sinusitis
H012.	Acute ethmoidal sinusitis
H01y.	Other acute sinusitis
H01z.	Acute sinusitis NOS
H02..	Acute pharyngitis
H021.	Acute phlegmonous pharyngitis
H022.	Acute ulcerative pharyngitis
H023.	Acute bacterial pharyngitis
H023z	Acute bacterial pharyngitis NOS
H024.	Acute viral pharyngitis
H02z.	Acute pharyngitis NOS
H03..	Acute tonsillitis
H030.	Acute erythematous tonsillitis
H031.	Acute follicular tonsillitis
H032.	Acute ulcerative tonsillitis
H033.	Acute catarrhal tonsillitis
H035.	Acute bacterial tonsillitis
H0351	Acute staphylococcal tonsillitis
H035z	Acute bacterial tonsillitis NOS
H036.	Acute viral tonsillitis
H037.	Recurrent acute tonsillitis
H03z.	Acute tonsillitis NOS
H04..	Acute laryngitis and tracheitis
H040.	Acute laryngitis
H0402	Acute catarrhal laryngitis
H040w	Acute viral laryngitis unspecified
H040z	Acute laryngitis NOS
H041.	Acute tracheitis
H0410	Acute tracheitis without obstruction
H041z	Acute tracheitis NOS
H042.	Acute laryngotracheitis
H0420	Acute laryngotracheitis without obstruction
H042z	Acute laryngotracheitis NOS
H043.	Acute epiglottitis (non strep)
H0432	Acute obstructive laryngitis
H043z	Acute epiglottitis NOS
H04z.	Acute laryngitis and tracheitis NOS
H05..	Other acute upper respiratory infections
H050.	Acute laryngopharyngitis
H051.	Acute upper respiratory tract infection
H052.	Pharyngotracheitis
H053.	Tracheopharyngitis
H054.	Recurrent upper respiratory tract infection
H055.	Pharyngolaryngitis
H05y.	Other upper respiratory infections of multiple sites
H05z.	Upper respiratory infection NOS
H15..	Peritonsillar abscess – quinsy
H271.	Influenza with other respiratory manifestation
H2710	Influenza with laryngitis
H2711	Influenza with pharyngitis
H271z	Influenza with respiratory manifestations NOS
Hyu0.	[X]Acute upper respiratory infections
Hyu02	[X]Acute tonsillitis due to other specified organisms

Table A5.4: General Practice respiratory diagnoses (cont)

General Practice Read code version 2 respiratory diagnosis categories (extracted 2017)	
Influenza and pneumonia	
Code	**Description**
H2...	Pneumonia and influenza
H20..	Viral pneumonia
H201.	Pneumonia due to respiratory syncytial virus
H202.	Pneumonia due to parainfluenza virus
H20y.	Viral pneumonia NEC
H20z.	Viral pneumonia NOS
H21..	Lobar (pneumococcal) pneumonia
H22..	Other bacterial pneumonia
H222.	Pneumonia due to haemophilus influenzae
H223.	Pneumonia due to streptococcus
H224.	Pneumonia due to staphylococcus
H22y.	Pneumonia due to other specified bacteria
H22yz	Pneumonia due to bacteria NOS
H22z.	Bacterial pneumonia NOS
H23..	Pneumonia due to other specified organisms
H231.	Pneumonia due to mycoplasma pneumoniae
H23z.	Pneumonia due to specified organism NOS
H24..	Pneumonia with infectious diseases EC
H243.	Pneumonia with whooping cough
H25..	Bronchopneumonia due to unspecified organism
H26..	Pneumonia due to unspecified organism
H260.	Lobar pneumonia due to unspecified organism
H2600	Lung consolidation
H261.	Basal pneumonia due to unspecified organism
H27..	Influenza
H270.	Influenza with pneumonia
H2700	Influenza with bronchopneumonia
H270z	Influenza with pneumonia NOS
H27y1	Influenza with gastrointestinal tract involvement
H27z.	Influenza NOS
H28..	Atypical pneumonia
H2y..	Other specified pneumonia or influenza
H2z..	Pneumonia or influenza NOS
Hyu08	[X]Other viral pneumonia
Hyu0H	[X]Other pneumonia, organism unspecified
Lower respiratory tract infection including bronchiolitis when coded with bronchitis	
Code	**Description**
H06..	Acute bronchitis and bronchiolitis
H060.	Acute bronchitis
H0603	Acute purulent bronchitis
H0604	Acute croupous bronchitis
H0605	Acute tracheobronchitis
H0606	Acute pneumococcal bronchitis
H0609	Acute neisseria catarrhalis bronchitis
H060A	Acute bronchitis due to mycoplasma pneumoniae
H060E	Acute bronchitis due to rhinovirus
H060w	Acute viral bronchitis unspecified
H060x	Acute bacterial bronchitis unspecified
H060z	Acute bronchitis NOS
H062.	Acute lower respiratory tract infection
H06z.	Acute bronchitis or bronchiolitis NOS
H06z0	Chest infection NOS
H06z1	Lower resp tract infection
H06z2	Recurrent chest infection
H07..	Chest cold
H0y..	Other specified acute respiratory infections
H0z..	Acute respiratory infection NOS
H3...	Chronic obstructive pulmonary disease
H30..	Bronchitis unspecified
H300.	Tracheobronchitis NOS

Table A5.4: General Practice respiratory diagnoses (cont)

General Practice Read code version 2 respiratory diagnosis categories (extracted 2017)	
Lower respiratory tract infection including bronchiolitis when coded with bronchitis (cont)	
Code	**Description**
H301.	Laryngotracheobronchitis
H302.	Wheezy bronchitis
H30z.	Bronchitis NOS
H3101	Smokers' cough
H3122	Acute exacerbation of chronic obstructive airways disease
Hyu10	[X]Acute bronchitis due to other specified organisms
Bronchiolitis	
Code	**Description**
H061.	Acute bronchiolitis
H0612	Acute bronchiolitis with bronchospasm
H0613	Acute exudative bronchiolitis
H0615	Acute bronchiolitis due to respiratory syncytial virus
H061z	Acute bronchiolitis NOS
Hyu20	[X]Other seasonal allergic rhinitis
Hz...	Respiratory system diseases NOS
Chronic upper respiratory disease	
Code	**Description**
H025.	Allergic pharyngitis
H1...	Other upper respiratory tract diseases
H10..	Deviated nasal septum – acquired
H11..	Nasal polyps
H110.	Polyp of nasal cavity
H110z	Polyp of nasal cavity NOS
H11z.	Nasal polyp NOS
H12..	Chronic pharyngitis and nasopharyngitis
H120.	Chronic rhinitis
H1200	Chronic simple rhinitis
H1201	Chronic catarrhal rhinitis
H1202	Chronic hypertrophic rhinitis
H120z	Chronic rhinitis NOS
H121.	Chronic pharyngitis
H1210	Simple chronic pharyngitis
H1211	Atrophic pharyngitis
H1212	Granular pharyngitis
H122.	Chronic nasopharyngitis
H13..	Chronic sinusitis
H130.	Chronic maxillary sinusitis
H131.	Chronic frontal sinusitis
H135.	Recurrent sinusitis
H13z.	Chronic sinusitis NOS
H14..	Chronic tonsil and adenoid disease
H140.	Chronic tonsillitis
H141.	Tonsil and/or adenoid hypertrophy
H1410	Hypertrophy of tonsils and adenoids
H1411	Hypertrophy of tonsils alone
H1412	Hypertrophy of adenoids alone
H141z	Hypertrophy of tonsils and adenoids NOS
H143.	Chronic adenotonsillitis
H14y4	Tonsil ulcer
H14y7	Cyst of tonsil
H14z0	Chronic tonsil disease NOS
H160.	Chronic laryngitis
H1601	Chronic catarrhal laryngitis
H161.	Chronic laryngotracheitis
H17..	Allergic rhinitis
H170.	Allergic rhinitis due to pollens
H171.	Allergic rhinitis due to other allergens
H1710	Allergy to animal
H1711	Dog allergy
H172.	Allergic rhinitis due to unspecified allergen
H17z.	Allergic rhinitis NOS

Table A5.4: General Practice respiratory diagnoses (cont)

General Practice Read code version 2 respiratory diagnosis categories (extracted 2017)	
Chronic upper respiratory disease (cont)	
Code	**Description**
H18..	Vasomotor rhinitis
H1y..	Other specified diseases of upper respiratory tract
H1y0.	Nasal turbinate hypertrophy
H1y1.	Other nasal cavity and sinus disease
H1y10	Nasal septum abscess
H1y12	Nasal septum ulcer
H1y16	Nasal obstruction
H1y1z	Nasal cavity and sinus disease NOS
H1y2.	Other pharyngeal disease NEC
H1y22	Parapharyngeal abscess
H1y23	Retropharyngeal abscess
H1y2z	Other pharyngeal disease NOS
H1y3.	Paralysis of vocal cords or larynx
H1y56	Vocal cord nodule
H1y73	Stenosis of larynx
H1y74	Laryngeal spasm
H1y77	Obstruction of larynx NOS
H1y7B	Laryngomalacia
H1yz.	Other upper respiratory tract diseases NOS
H1z..	Upper respiratory tract disease NOS
H3123	Bronchiolitis obliterans
H31y0	Chronic tracheitis
H5B..	Sleep apnoea
H5B0.	Obstructive sleep apnoea
H5C..	Choking due to airways obstruction
H5y04	Tracheo-oesophageal fistula following tracheostomy
Hy...	Other specified diseases of respiratory system
Chronic lower respiratory disease	
Code	**Description**
H263.	Pneumonitis, unspecified
H34..	Bronchiectasis
H34z.	Bronchiectasis NOS
H35..	Extrinsic allergic alveolitis
H357.	Ventilation pneumonitis
H4...	Lung disease due to external agents
H462.	Upper respiratory inflammation due to chemical fumes
H47..	Pneumonitis due to inhalation of solids or liquids
H470.	Pneumonitis due to inhalation of food or vomitus
H5...	Other respiratory system diseases
H50..	Empyema
H51..	Pleurisy
H51z.	Pleural effusion NOS
H51zz	Pleural effusion NOS
H52..	Pneumothorax
H520.	Spontaneous tension pneumothorax
H52y.	Other spontaneous pneumothorax
H52yz	Other spontaneous pneumothorax NOS
H52z.	Pneumothorax NOS
H541.	Pulmonary congestion
H541z	Pulmonary oedema NOS
H58..	Other diseases of lung
H580.	Pulmonary collapse with atelectasis
H581.	Interstitial emphysema
H58y0	Broncholithiasis
H58z.	Lung disease NOS
H59..	Respiratory failure
H590.	Acute respiratory failure
H5yy.	Other diseases of respiratory system NEC
H5yz.	Other diseases of respiratory system NOS
H5z..	Respiratory system diseases NOS

Table A5.4: General Practice respiratory diagnoses (cont)

General Practice Read code version 2 respiratory diagnosis categories (extracted 2017)	
Unspecified respiratory illness	
Code	**Description**
H....	Respiratory system diseases
Croup	
Code	**Description**
H044.	Croup

Table A5.5: List of websites used to classify different types of asthma medications

Asthma medications – websites
https://www.evidence.nhs.uk/formulary/bnf/current/
https://www.drugs.com/cons/
https://www.medicines.org.uk/emc/
https://medlineplus.gov/druginfo/meds/
https://www.drugs.com/
https://www.epharmapedia.com/medicine/profile/190978/Slepia.html?lang=en&tab=druginfo
http://www.ndrugs.com/?s=mandalyn%20paediatric
https://pubchem.ncbi.nlm.nih.gov
https://www.drugbank.ca/drugs
https://edudrugs.com
https://www.lgcstandards.com/GB/en
http://www.ebi.ac.uk/chebi/
http://home.intekom.com/pharm/
http://www.druginfosys.com/
https://www.gov.uk/guidance/find-product-information-about-medicines
http://www.cochrane.org
https://pharmacybook.net/
http://www.mims.com/malaysia/drug/info/
https://www.ncbi.nlm.nih.gov/pubmed
https://www.aaaai.org/global/latest-research-summaries/Current-JACI-Research/
https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
https://www.mydr.com.au/search-medicines
https://www.healthdirect.gov.au/medicines
http://www.mims.com/india/drug/info/
https://www.catalog.md/
http://www.medicines.ie/medicine/
https://books.google.co.uk/ Turner P, Volans GN (1985). *The Drugs Handbook 1985-86*. London: Macmillan Press.
https://www.epharmapedia.com/medicine/profile/193547?lang=en&tab=druginfo
http://www.encepp.eu/
https://www.who.int/selection_medicines/country_lists/en/
http://www.gmedication.com/
http://www.medicatione.com
http://www.sickle-thal.nwlh.nhs.uk/ForHealthcareProfessionals/
http://www.inchem.org/#/search
https://www.ncbi.nlm.nih.gov/pmc/articles/
http://www.medindia.net/drug-price/

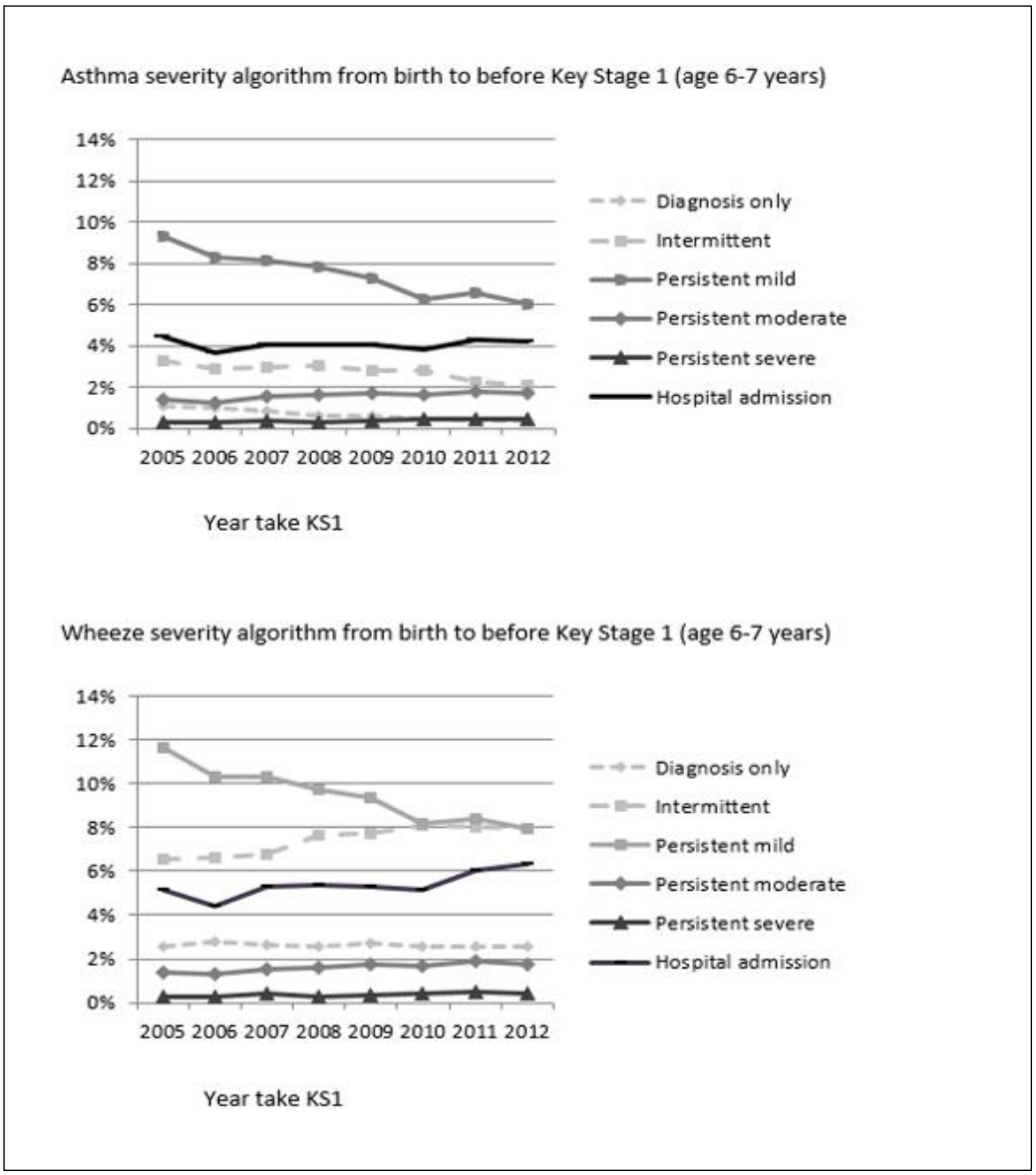

Figure A5.1: Changes in asthma prescriptions during the cohort by year take KS1 assessment.

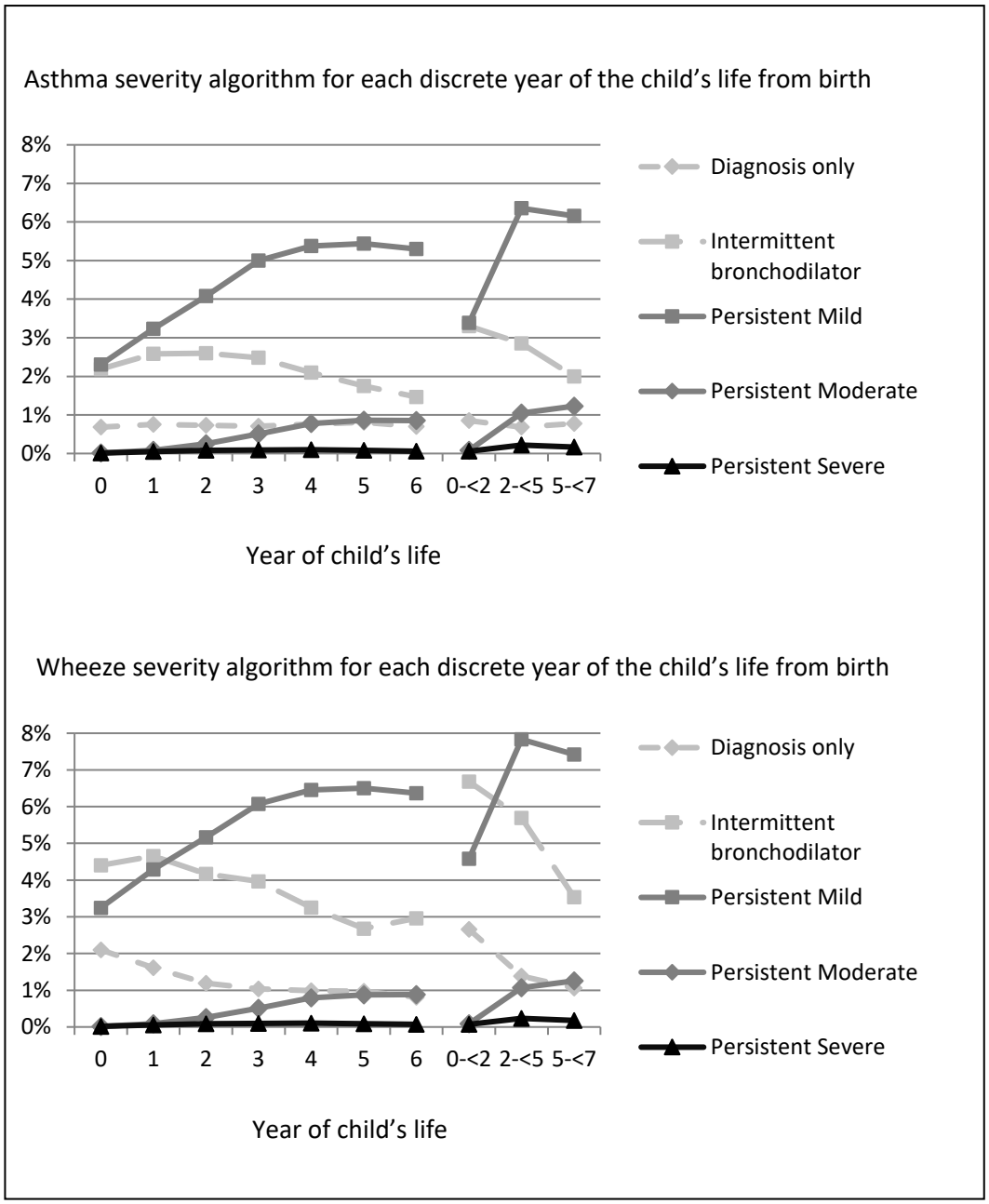

Figure A5.2: Changes in asthma or wheeze severity for discrete years of the child from birth.

Appendix A5 part 2 – Results of sensitivity analyses

Table A5.6: Multilevel multivariable models of asthma severity algorithm and multiple asthma inpatient hospital admissions for different ages of a child and not attaining the expected level at Key Stage 1 (at 6-7 years) – repeated for wheeze severity algorithm and wheeze inpatient hospital admissions.

	Child age 0 - < 2 years			Child age 2 - < 5 years			Child age 5 - < 7 years		
	Not attained / Total (%)	Unadjusted OR (95% CI)	Multivariable[a] OR (95% CI)	Not attained / Total (%)	Unadjusted OR (95% CI)	Multivariable[a] OR (95% CI)	Not attained / Total (%)	Unadjusted OR (95% CI)	Multivariable[a] OR (95% CI)
N	14935 / 85906 (17)								
Asthma severity algorithm									
No asthma (ref)	13459 / 79301 (17)	1.0	1.0	12980 / 76324 (17)	1.0	1.0	13120 / 77041 (17)	1.0	1.0
Diagnosis only	178/ 732 (24)	1.5 (1.2-1.8)	1.1 (0.9-1.3)	133 / 590 (23)	1.4 (1.1-1.7)	1.0 (0.8-1.3)	122 / 664 (18)	1.0 (0.9-1.3)	0.8 (0.7-1.0)
Intermittent bronchodilator	606 / 2837 (21)	1.3 (1.2-1.4)	1.0 (0.9-1.1)	460 / 2448 (19)	1.1 (1.0-1.2)	0.9 (0.8-1.0)	330 / 1715 (19)	1.1 (1.0-1.3)	0.9 (0.8-1.1)
Persistent Mild	663 / 2910 (21)	1.4 (1.3-1.6)	1.1 (1.0-1.2)	1110 / 5459 (20)	1.2 (1.2-1.3)	1.0 (0.9-1.1)	1100 / 5290 (21)	1.3 (1.2-1.4)	1.0 (0.9-1.1)
Persistent moderate	17 / 73 (23)	1.6 (0.9-2.8)	1.1 (0.6-2.0)	213 / 897 (24)	1.5 (1.3-1.7)	1.1 (0.9-1.3)	229 / 1055 (22)	1.3 (1.2-1.6)	1.1 (0.9-1.3)
Persistent severe	12 / 53 (23)	1.7 (0.9-3.3)	1.3 (0.7-2.7)	39 / 188 (21)	1.3 (0.9-1.9)	0.9 (0.6-1.3)	34 / 141 (24)	1.6 (1.1-2.4)	1.1 (0.7-1.6)
Hospital inpatient admission (asthma severity algorithm)[b]									
1 (%) (ref=0)	139 / 518 (27)	1.7 (1.4-2.1)	1.1 (0.9-1.4)	293 /1208 (24)	1.5 (1.3-1.7)	1.1 (1.0-1.3)	240 / 924 (26)	1.6 (1.4-1.9)	1.3 (1.1-1.6)
2 (%)	33 / 103 (32)	2.0 (1.3-3.2)	1.2 (0.7-1.9)	91 / 331 (28)	1.8 (1.4-2.3)	1.4 (1.1-1.9)	40 / 142 (28)	1.6 (1.1-2.4)	1.3 (0.9-2.0)
3+ (%)	20 / 51 (39)	3.1 (1.7-5.5)	1.8 (1.0-3.4)	66 / 221 (30)	2.0 (1.5-2.7)	1.5 (1.0-2.0)	21 / 67 (31)	2.2 (1.3-3.8)	1.3 (0.7-2.4)
N	14935 / 85906 (17)								
Wheeze severity algorithm									
No asthma (ref)	12354 / 73804 (17)	1.0	1.0	12147 / 71977 (17)	1.0	1.0	12586 / 74350 (17)	1.0	1.0
Diagnosis only	475 / 2284 (21)	1.3 (1.1-1.4)	1.0 (0.9-1.2)	245 / 1188 (21)	1.2 (1.1-1.4)	1.0 (0.9-1.2)	175 / 915 (19)	1.1 (0.9-1.3)	0.9 (0.8-1.1)
Intermittent bronchodilator	1206 / 5738 (21)	1.3 (1.2-1.4)	1.0 (1.0-1.1)	946 / 4891 (19)	1.1 (1.1-1.2)	1.0 (0.9-1.1)	607 / 3039 (20)	1.2 (1.1-1.3)	1.0 (0.9-1.1)
Persistent Mild	866 / 3939 (22)	1.4 (1.3-1.5)	1.1 (1.0-1.2)	1337 / 6728 (20)	1.2 (1.1-1.3)	1.0 (0.9-1.1)	1296 / 6374 (20)	1.2 (1.2-1.3)	1.0 (0.9-1.1)
Persistent moderate	19 / 78 (24)	1.8 (1.0-3.0)	1.2 (0.7-2.2)	218 / 921 (24)	1.5 (1.3-1.8)	1.0 (0.9-1.3)	234 / 1078 (22)	1.4 (1.2-1.6)	1.0 (0.9-1.2)
Persistent severe	15 / 63 (24)	1.8 (1.0-3.3)	1.4 (0.7-2.6)	42 / 201 (21)	1.3 (0.9-1.9)	0.9 (0.6-1.4)	37 / 150 (25)	1.7 (1.1-2.4)	1.0 (0.7-1.7)
Hospital inpatient admission (wheeze severity algorithm)[b]									
1 (%) (ref=0)	376 / 1559 (24)	1.5 (1.3-1.7)	1.1 (0.9-1.2)	372 / 1655 (23)	1.4 (1.2-1.5)	1.1 (0.9-1.2)	272 /1054 (26)	1.6 (1.4-1.9)	1.3 (1.1-1.6)
2 (%)	115 / 391 (29)	1.9 (1.5-2.4)	1.2 (0.9-1.6)	113 / 501 (23)	1.3 (1.1-1.7)	1.1 (0.9-1.4)	49 / 166 (30)	1.8 (1.2-2.5)	1.4 (1.0-2.1)
3+ (%)	64 / 215 (30)	1.8 (1.4-2.5)	1.0 (0.7-1.4)	96 / 323 (30)	1.9 (1.5-2.5)	1.4 (1.1-1.4)	23 / 72 (32)	2.3 (1.4-3.9)	1.5 (0.8-2.6)

[a] adjusted for sex, gestation at birth, small for gestational age (<10th centile), parity, major or minor congenital anomalies, maternal age, breastfeeding, maternal smoking in first trimester, free school meals eligible in year preceding Key Stage 1 assessment proxy start date 1st May to approximate deprivation beyond birth, academic season of birth (autumn, spring, summer), school moves from start school to KS1 (1+), urban or rural dwelling at birth, year take Key Stage 1 (ref 2010), other respiratory illness (as described in Table 5.5), Townsend deprivation quintiles; for each age group, asthma severity and hospital admission variables in the table added as a pair to the model without other age group variable pairs due to multicollinearity; [b] excludes first admission if before first GP visit.

Table A5.7: Sub-sample multilevel multivariable models of asthma severity, acute asthma, respiratory illness and not attaining the expected level at Key Stage 1 (at 6-7 years) adjusted for absence from school (Week of birth 1st September 2000 to 31st August 2004), N=46,673.

	Asthma severity algorithm Multivariable[a] OR (95% CI)	Asthma severity algorithm model adjusted for school absence Multivariable[a] OR (95% CI)
N		
Asthma severity algorithm		
None (ref)	1.00	1.00
Diagnosis only	1.05 (0.74-1.48)	0.96 (0.67-1.37)
Intermittent bronchodilator	0.97 (0.83-1.15)	0.96 (0.81-1.13)
Persistent Mild	0.96 (0.85-1.08)	0.95 (0.84-1.07)
Persistent moderate	1.03 (0.83-1.27)	0.97 (0.78-1.20)
Persistent severe	1.17 (0.77-1.77)	1.06 (0.70-1.62)
Hospital inpatient admission (acute asthma)[b] =yes(%)	1.08 (0.93-1.27)	1.05 (0.90-1.24)
LRTI[c] GP contacts[d] (ref=None)		
1	0.98 (0.91-1.05)	0.97 (0.90-1.04)
2	1.05 (0.95-1.15)	1.03 (0.93-1.14)
3+	1.16 (1.05-1.29)	1.13 (1.02-1.26)
URTI[e] GP contacts (ref=None)		
1-4	0.99 (0.92-1.06)	0.96 (0.90-1.03)
5-6	0.97 (0.87-1.07)	0.92 (0.83-1.02)
7+	1.02 (0.93-1.13)	0.93 (0.84-1.03)
School absence percentage in year preceding KS1 (proxy start date May)		
<5%	NA	1.00
5 -<10%	NA	1.27 (1.18-1.36)
10-<15%	NA	1.80 (1.66-1.96)
15-<20%	NA	2.45 (2.18-2.76)
20+%	NA	3.40 (2.95-3.91)

OR=odds ratio; CI=confidence interval; [a] adjusted for all variables in the table, other respiratory illness significant at the 5% level in unadjusted analyses (GP contacts for bronchiolitis (1+), GP contacts for chronic lower respiratory disease (1+)), Townsend deprivation quintile at birth, sex, gestation at birth, small for gestational age (<10th centile), parity, major or minor congenital anomalies, maternal age (25-29 years, <18, 18-24, 30-34, 35+), breastfeeding at birth or 6-8 weeks, maternal smoking in first trimester, free school meals eligible in year preceding Key Stage 1 assessment proxy start date 1st May (to approximate deprivation beyond birth), academic season of birth (autumn, spring, summer), school moves from start school to KS1 (1+), urban or rural (inc. town) dwelling at birth, year take Key Stage 1 (ref 2010); [b] excludes first admission if before first GP visit; [c] Lower respiratory tract infection; [d] includes bronchiolitis if coded with bronchitis; [e] Upper respiratory tract infection.

A5.8 Small correction.

In the interests of transparency, I outline a data issue in the results due to coding error. The interpretation of the results of this chapter have not changed. I report the omission of 805 children from the cohort of 85,906 children (<1%) where 26 children had died and 779 children had moved out of Wales between the ages of 6 – 15 years. The death or move from Wales occurred after the outcome of interest: Key Stage 1 (KS1) at age 6-7 years. Of those children omitted who died, low numbers were classified with persistent moderate asthma or wheeze and none were classified with persistent severe asthma or wheeze. I have rerun the analyses and find only up to a 1% difference between the two population-based cohorts in cross-tabulations and no difference in percentages to one decimal place for the developed asthma or wheeze severity categories or hospital admissions (Table A5.9d). In modelling I found there was up to a 0.02 difference between the population-based cohorts in the odds ratios in adjusted and unadjusted variables reported except for Townsend deprivation at birth where the difference in odds ratios ranged from least deprived of 0.02 to most deprived 0.08. In the omitted children who died, 81% had no asthma in either inpatient hospital admissions or GP data, and 69% had no wheeze or lower respiratory tract infection (LRTI) in GP data (or inpatient hospital admissions for wheeze). Rates of no asthma, wheeze and LRTI were the same as the total population cohort for children omitted who had moved out of Wales. In the Table Appendix A5.7 (subgroup analysis split by age of child) I report differences of up to only 2% between the two total population cohorts and up to a 0.1 difference in adjusted odds ratios (reported to 1 decimal place) for asthma or wheeze severity or number of hospital admissions associated with not attaining KS1. The interpretation of the data has not changed.

Difference between cohorts = 805 children

Original cohort in the paper = 85906 children
New cohort including children who died after KS1 or moved out of Wales in cohort follow-up timeframe = 86711 children
Extra children in new cohort who died after KS1 in cohort follow-up timeframe = 26 children
Extra children in new cohort who moved out of Wales after KS1 in cohort follow-up timeframe =779 children

Table A5.8a: Difference between cohorts – Age at death

Age at death	Count
6 – 8	6
9 – 11	8
12 – 15	12
Total	26

Table A5.8b: Difference between cohorts – moved out of Wales

Age when moved out of Wales	Count
7	182
8	166
9	127
10	125
11	84
12	45
13	32
14	10
Total	779

Table A5.8c: Demographics of the study population (Bold numbers show differences in this table compared to the original published journal article)

	Asthma algorithm				
	No asthma	**Diagnosis only or intermittent bronchodilator**	**Persistent mild[a]**	**Persistent moderate or severe**	**Inpatient hospital admission[b]**
N	**75870**	**2872**	**6298**	**1671**	**3513**
Gestation at birth[c]					
≤32	**1001** (1)	73 (3)	**183** (3)	56 (3)	**154** (4)
33-36	**4010** (5)	**177** (6)	**393** (6)	131 (8)	**247** (7)
37+ weeks	**66473** (88)	**2457** (86)	**5379 (85)**	**1393 (83)**	**2933** (84)
Congenital anomaly[d]=Yes(%)	**3552** (5)	187 (7)	**376** (6)	115 (7)	**274** (8)
Townsend deprivation quintile at birth					
1 - least (%)	**13853** (18)	**426** (15)	**922** (15)	**220** (13)	**462** (13)
2 (%)	**14905** (20)	**477 (17)**	**1112** (18)	**307** (18)	**598** (17)
3 (%)	**15291** (20)	**566** (20)	**1257** (20)	**341** (20)	**683** (19)
4 (%)	**15564** (21)	**618** (22)	**1421** (23)	**393 (24)**	**829** (24)
5 - most (%)	**16035** (21)	**774** (27)	**1565** (25)	**404** (24)	**927** (26)
Free school meals eligible[e]=yes(%)	**12469** (16)	**652** (23)	**1285** (20)	**343 (21)**	**805** (23)
School absence percentage[ef]					
<5 (%)	**19986** (48)	**613** (41)	**1261** (39)	**298** (31)	**627** (33)
5-9 (%)	**12892** (31)	**478** (32)	**1171** (36)	**334** (35)	**684** (36)
10-14 (%)	**4515** (11)	**198** (13)	**467** (14)	**175** (18)	**304** (16)
15-19 (%)	**1558** (4)	**78** (5)	**143** (4)	**70** (7)	**120** (6)
20+ (%)	**927** (2)	60 (4)	111 (3)	**46** (5)	**93** (5)
NA (%)	**1528** (4)	**75** (5)	**118** (4)	38 (4)	**84** (4)

[a] Inhaled corticosteroid or alternative. [b] for asthma or wheeze; [c] 6% missing data evenly found across asthma groups; [d] major or minor; [e] in year preceding Key Stage 1 assessment proxy start date 1st May; [f] sub-sample due to availability of school absence data, births between Sept 2000-Aug 2004 N=47140.

Table A5.8d: Asthma severity algorithms (Bold numbers show differences in this table compared to the original published journal article)

	Asthma severity algorithm[a] n (%)	**Wheeze severity algorithm[b] n (%)**
N	**86711**	**86711**
No asthma	**75870** (87.5)	**68143** (78.6)
Diagnosis only	**539** (0.6)	**2263** (2.6)
Intermittent Bronchodilator	**2333** (2.7)	**6535** (7.5)
Persistent Mild	**6298** (7.3)	**8031** (9.3)
Persistent moderate	**1372** (1.6)	**1414** (1.6)
Persistent severe	299 (0.3)	325 (0.4)
Hospital inpatient admission[c]=yes(%)	**3513** (4.1)	**4715** (5.4)

[a] developed with an asthma diagnosis

[b] developed with either a wheeze or asthma diagnosis

[c] excludes first admission if before first GP visit

Table A5.8e: Respiratory illness between birth and before Key Stage 1 assessment by asthma severity (Bold numbers show differences in this table compared to the original published journal article)

	Asthma severity algorithm						
	No asthma	**Diagnosis only**	**Intermittent bronchodilator**	**Persistent mild[a]**	**Persistent moderate**	**Persistent severe**	**Inpatient hospital admission[b]**
N	**75870**	**539**	**2333**	**6298**	**1372**	299	**3513**
Hospital inpatient admission (Algorithm 1)[c]=yes (%)	0	173 (32)	480 (21)	1993 (32)	662 (48)	205 (69)	3513 (100)
LRTI GP contacts[d]							
0 (%)	**52711 (70)**	**353 (66)**	**1084 (47)**	**2540** (40)	**448** (33)	71 (24)	**1211 (35)**
1 (%)	**13473** (18)	**94 (17)**	**524** (23)	**1453** (23)	**292** (21)	50 (17)	**769** (22)
2 (%)	**5365** (7)	48 (9)	**325** (14)	**870** (14)	**209** (15)	30 (10)	**514** (15)
3+ (%)	**4321** (6)	44 (8)	**400** (17)	**1435** (23)	**423** (31)	148 (50)	**1019** (29)
URTI GP contacts							
0 (%)	**20781** (27)	**207** (38)	**430 (18)**	**1030** (16)	169 (12)	25 (8)	**602** (17)
1-4 (%)	**40135** (53)	**247** (46)	**1213** (52)	**3195** (51)	**619** (45)	126 (42)	**1679** (48)
5-6 (%)	**7238** (10)	39 (7)	**302** (13)	**865** (14)	**206** (15)	52 (17)	**475** (14)
7+ (%)	**7716** (10)	46 (9)	**388** (17)	**1208** (19)	**378** (28)	96 (32)	**757** (22)

[a]Inhaled corticosteroid or alternative. [b] for asthma or wheeze; [c] excludes first admission if before first GP visit; [d] includes bronchiolitis if coded with bronchitis.

Table A5.8f: Multilevel multivariable models of asthma severity algorithm, respiratory illness and not attaining Key Stage 1 (at 6-7 years) (Bold numbers show differences in this table compared to the original published journal article)

	Not attained / Total (%)	Univariable OR (95% CI)	Asthma severity algorithm 1 Multivariable[a] OR (95% CI)	Wheeze severity algorithm 2 Multivariable[a] OR (95% CI)
N	**15115 / 86711** (17)			
Asthma severity algorithm				
No asthma (ref)	**12892 / 75870** (17)	1.00	1.00	NA
Diagnosis only	**135 / 539** (25)	**1.57 (1.28-1.93)**	**1.22 (0.98-1.52)**	NA
Intermittent bronchodilator	**451 / 2333** (19)	1.11 (1.00-1.24)	**0.90 (0.80**-1.01)	NA
Persistent Mild	**1270 / 6298** (20)	1.21 (1.13-**1.29)**	0.96 (**0.89**-1.04)	NA
Persistent moderate	**301 / 1372** (22)	1.36 (**1.19**-1.55)	1.05 (0.90-**1.23**)	NA
Persistent severe	66 / 299 (22)	1.45 (1.09-**1.92**)	1.02 (0.75-1.40)	NA
Hospital inpatient admission (asthma severity algorithm)[b]=yes(%)	**846 / 3513** (24)	1.48 (1.36-1.61)	**1.15 (1.03-1.28)**	NA
Wheeze severity algorithm				
No asthma (ref)	**11388 / 68143** (17)	1.00	NA	1.00
Diagnosis only	**457 / 2263** (20)	1.24 (1.11-1.39)	NA	1.06 (0.94-1.19)
Intermittent bronchodilator	**1291 / 6535** (20)	1.20 (1.12-1.28)	NA	1.01 (0.94-**1.09**)
Persistent mild	**1597 / 8031** (20)	**1.21** (1.14-1.29)	NA	**0.97** (0.90-**1.04**)
Persistent moderate	**309 / 1414** (22)	**1.38** (1.20-1.57)	NA	**1.06** (0.91-**1.23**)
Persistent severe	73 / 325 (23)	**1.52** (1.16-2.00)	NA	1.08 (**0.81**-1.45)
Hospital inpatient admission (wheeze severity algorithm)[b]=yes(%)	**1129 / 4715** (24)	1.48 (**1.38**-1.59)	NA	1.14 (1.04-1.25)
LRTI[c] GP contacts[d] (ref=None)				
1	**2758 / 15886** (17)	1.05 (1.00-1.10)	1.01 (0.96-**1.07**)	1.01 (**0.96**-1.06)
2	**1270 / 6847 (19)**	1.14 (**1.06**-1.22)	1.05 (**0.98**-1.13)	**1.05 (0.98-1.13)**
3+	**1431 / 6771** (21)	1.33 (**1.24-1.42**)	**1.15 (1.07-1.24)**	**1.15 (1.06-1.23)**
URTI[e] GP contacts (ref=None)				
1-4	**7809 / 45535** (17)	0.98 (0.93-1.02)	1.00 (**0.96**-1.05)	1.00 (**0.96**-1.05)
5-6	**1496 / 8702** (17)	**0.99** (0.93-1.07)	**1.02 (0.95-1.10)**	1.01 (**0.95-1.10**)
7+	**1853 / 9832** (19)	**1.09 (1.02**-1.17)	**1.09** (1.01-**1.17**)	1.08 (1.00-1.16)
GP contacts				
Influenza and pneumonia 1+ (ref=None)	**441 / 2616** (17)	0.96 (0.86-1.07)	NA	NA
Bronchiolitis 1+ (ref=None)	**896 / 4258** (21)	1.26 **(1.17-1.37)**	**1.02 (0.94-1.11)**	**1.01 (0.93-1.10)**
Chronic lower respiratory disease 1+ (ref=None)	**158 / 635** (25)	**1.41 (1.16-1.70)**	**1.16 (0.95-1.42)**	**1.16 (0.95-1.42)**
Respiratory unknown 1+ (ref=None)	**70 / 477** (15)	**0.76 (0.58-1.00)**	NA	NA
Chronic upper respiratory disease GP				
1	**924 / 5417** (17)	0.98 (0.91-1.06)	NA	NA
2+	**310 / 1799** (17)	1.02 (0.90-1.16)	NA	NA
Croup GP contacts (ref=None)				
1	**890 / 5284** (17)	0.98 (0.91-1.06)	NA	NA
2+	**266 / 1439** (19)	1.14 (0.99-1.31)	NA	NA
Townsend deprivation quintile				
1 - least (ref)	**1533 / 15421** (10)	1.00	1.00	1.00
2	**2307 / 16801** (14)	**1.28** (1.18-**1.38)**	**1.18 (1.09-1.28)**	**1.18 (1.09-1.27)**
3	**2980 / 17455** (17)	**1.54 (1.43-1.66)**	**1.32 (1.22-1.43)**	**1.32 (1.22-1.43)**
4	**3523 / 17996** (20)	1.84 (1.71-1.98)	**1.47 (1.36-1.58)**	**1.47 (1.36-1.58)**
5 – most	**4730 / 18778** (25)	2.32 (2.16-2.49)	**1.63 (1.51-1.76)**	**1.63 (1.51-1.76)**

[a] adjusted for all variables in the table significant at the 5% level in univariable analyses, sex, gestation at birth, small for gestational age (<10th centile), parity, major or minor congenital anomalies, maternal age, breastfeeding, maternal smoking in first trimester, free school meals eligible in year preceding Key Stage 1 assessment proxy start date 1st May to approximate deprivation beyond birth, academic season of birth (autumn, spring, summer), school moves from start school to KS1 (1+), urban or rural (inc. town) dwelling at birth, year take Key Stage 1 (ref 2010); [b] excludes first admission if before first GP visit; [c] Lower respiratory tract infection; [d] includes bronchiolitis if coded with bronchitis; [e] Upper respiratory tract infection.

Table A5.8g: Attained expected level at Key Stage 1 (at 6-7 years) and the difference between two cohort definitions

		Difference between cohorts			
		Died between age 6 and 15 years n=26		Moved out of Wales between age 6 and 15 years n=779	
		Count	Column N %	Count	Column N %
Attained expected level at KS1	Yes	14	53.8%	611	78.4%
	Not attained	12	46.2%	168	21.6%
	Total	26	100.0%	779	100.0%

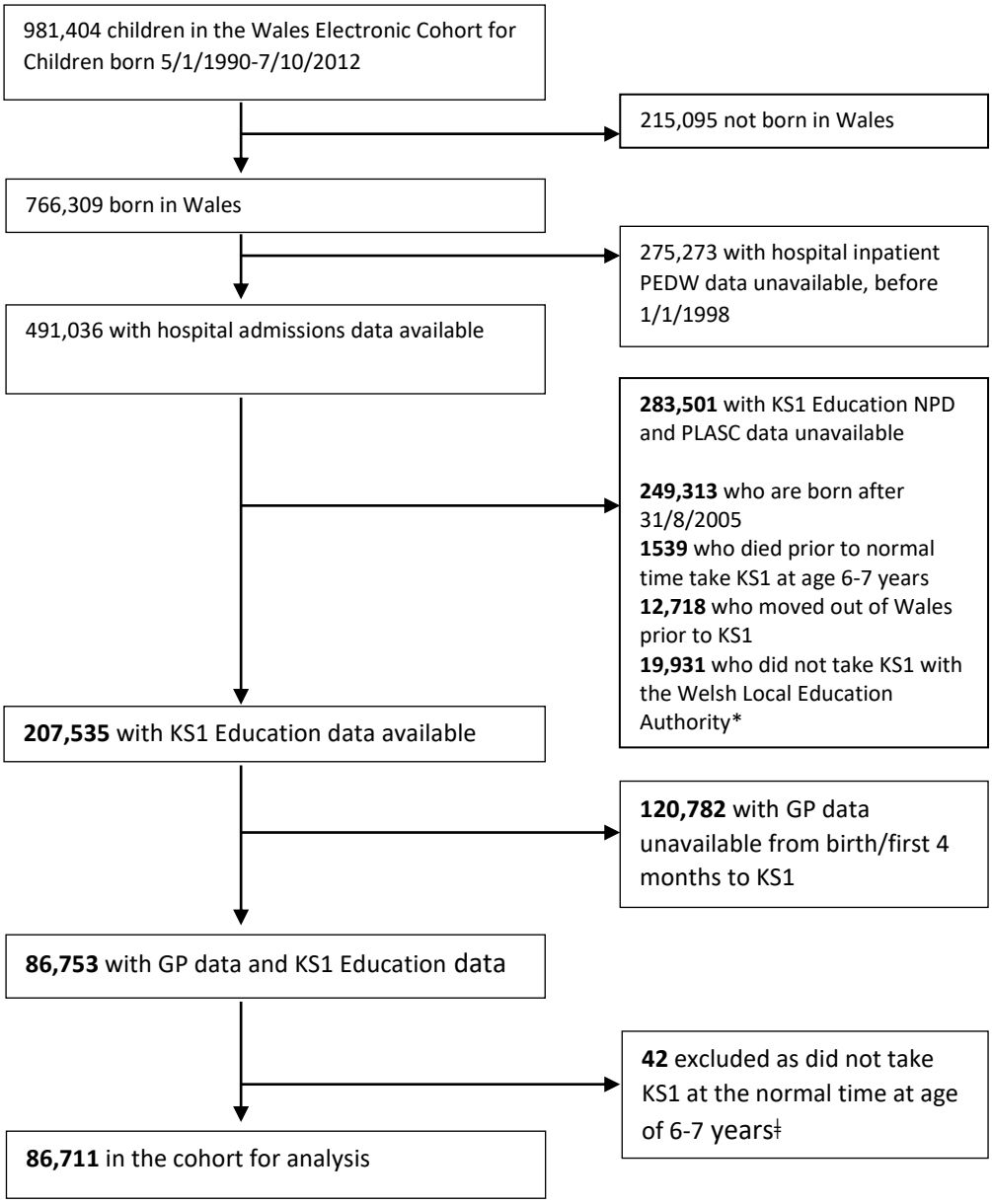

Figure A5.8: Anonymised participant selection (Bold numbers show differences in this table compared to the original published journal article).
PEDW=Patient Episode Database Wales, KS1=Key Stage 1, NPD=National Pupil Database, PLASC=Pupil Level Annual School Census.
*private schools, severely disabled children who are not catered for by Special Educational Needs provision in the LEA school system, those outside administrative systems e.g. travellers; ‡ to adhere to no overlap between exposure and outcome time windows.

Table A5.8h: Multilevel multivariable models of asthma severity algorithm and asthma inpatient hospital admissions for different ages of the child and not attaining the expected level at Key Stage 1 (at 6-7 years) – repeated for wheeze severity algorithm and wheeze inpatient hospital admissions.

Updated table with update to cohort to include extra 805 children (26 that died age 6-15 years and 779 that moved out of Wales age 6-15 years).

	Child age 0 - < 2 years			Child age 2 - < 5 years			Child age 5 - < 7 years		
	Not attained / Total (%)	Unadjusted OR (95% CI)	Multivariable[a] OR (95% CI)	Not attained / Total (%)	Unadjusted OR (95% CI)	Multivariable[a] OR (95% CI)	Not attained / Total (%)	Unadjusted OR (95% CI)	Multivariable[a] OR (95% CI)
N	15115 / 86711								
Asthma severity algorithm									
No asthma (ref)	13625 / 80055	1.00	1.00	13143 / 77050 (17)	1.00	1.00	13283 / 77778	1.00	1.00
Diagnosis only	181/ 739 (25)	1.5 (1.2-1.8)	1.1 (0.9-1.3)	135 / 601 (22)	1.4 (1.1-1.7)	1.0 (0.8-1.3)	124 / 672 (18)	1.0 (0.9-1.3)	0.8 (0.7-1.0)
Intermittent bronchodilator	612 / 2859 (21)	1.3 (1.2-1.4)	1.0 (0.9-1.1)	465 / 2471 (19)	1.1 (1.0-1.2)	0.9 (0.8-1.0)	332 / 1729 (19)	1.1 (1.0-1.2)	0.9 (0.8-1.1)
Persistent Mild	668 / 2932 (23)	1.4 (1.3-1.5)	1.1 (1.0-1.2)	1119 / 5501 (20)	1.2 (1.1-1.3)	1.0 (0.9-1.1)	1111 / 5332 (21)	1.3 (1.2-1.4)	1.0 (0.9-1.1)
Persistent moderate	17 / 73 (23)	1.6 (0.9-2.8)	1.1 (0.6-1.9)	214 / 900 (24)	1.5 (1.3-1.7)	1.1 (0.9-1.3)	231 / 1059 (22)	1.3 (1.2-1.6)	1.1 (0.9-1.3)
Persistent severe	12 / 53 (23)	1.7 (0.9-3.2)	1.3 (0.7-2.7)	39 / 188 (21)	1.3 (0.9-1.9)	0.9 (0.6-1.3)	34 / 141 (24)	1.6 (1.1-2.4)	1.1 (0.7-1.6)
Hospital inpatient admission (asthma severity algorithm)									
1 (%) (ref=0)	139 / 519 (27)	1.7 (1.4-2.1)	1.1 (0.9-1.4)	298 /1220 (24)	1.5 (1.3-1.7)	1.1 (1.0-1.3)	241 / 930 (26)	1.6 (1.4-1.9)	1.3 (1.1-1.6)
2 (%)	34 / 104 (33)	2.1 (1.3-3.2)	1.2 (0.8-1.9)	91 / 333 (27)	1.7 (1.4-2.2)	1.4 (1.1-1.9)	40 / 143 (28)	1.6 (1.1-2.4)	1.3 (0.8-1.9)
3+ (%)	20 / 51 (39)	3.1 (1.7-5.5)	1.8 (1.0-3.5)	67 / 225 (30)	2.0 (1.5-2.7)	1.4 (1.0-2.0)	21 / 68 (31)	2.1 (1.2-3.7)	1.3 (0.7-2.3)
N	15115 / 86711								
Wheeze severity algorithm									
No asthma (ref)	12503 / 74502	1.00	1.00	12300 / 75663 (17)	1.00	1.00	12742 / 75069	1.00	1.00
Diagnosis only	484 / 2309 (21)	1.3 (1.2-1.4)	1.0 (0.9-1.2)	250 / 1207 (21)	1.3 (1.1-1.5)	1.0 (0.9-1.2)	178 / 925 (19)	1.1 (0.9-1.3)	0.9 (0.8-1.1)
Intermittent bronchodilator	1220 / 5787 (21)	1.3 (1.2-1.4)	1.0 (1.0-1.1)	956 / 4939 (19)	1.1 (1.1-1.2)	1.0 (0.9-1.1)	613 / 3064 (20)	1.2 (1.1-1.3)	1.0 (0.9-1.1)
Persistent Mild	874 / 3972 (22)	1.4 (1.3-1.5)	1.1 (1.0-1.2)	1348 / 6777 (20)	1.2 (1.1-1.3)	1.0 (0.9-1.1)	1309 / 6421 (20)	1.2 (1.2-1.3)	1.0 (0.9-1.1)
Persistent moderate	19 / 78 (24)	1.8 (1.0-3.0)	1.2 (0.7-2.1)	219 / 924 (24)	1.5 (1.3-1.7)	1.1 (0.9-1.3)	236 / 1082 (22)	1.4 (1.2-1.6)	1.1 (0.9-1.2)
Persistent severe	15 / 63 (24)	1.8 (1.0-3.3)	1.4 (0.7-2.6)	42 / 201 (21)	1.3 (0.9-1.9)	0.9 (0.6-1.4)	37 / 150 (25)	1.7 (1.1-2.4)	1.1 (0.7-1.7)
Hospital inpatient admission (wheeze severity algorithm)									
1 (%) (ref=0)	384 / 1576 (24)	1.5 (1.3-1.7)	1.1 (0.9-1.2)	378 / 1673 (23)	1.4 (1.2-1.5)	1.1 (0.9-1.2)	273 /1061 (26)	1.6 (1.4-1.8)	1.3 (1.1-1.6)
2 (%)	116 / 393 (30)	1.9 (1.5-2.4)	1.2 (1.0-1.6)	113 / 503 (22)	1.3 (1.1-1.7)	1.1 (0.9-1.4)	49 / 167 (29)	1.8 (1.2-2.5)	1.4 (1.0-2.1)
3+ (%)	65 / 218 (30)	1.8 (1.4-2.5)	1.0 (0.7-1.4)	97 / 328 (30)	1.9 (1.5-2.4)	1.4 (1.1-1.9)	23 / 73 (32)	2.2 (1.3-3.8)	1.4 (0.8-2.5)

[a] adjusted for sex, gestation at birth, small for gestational age (<10th centile), parity, major or minor congenital anomalies, maternal age, breastfeeding, maternal smoking in first trimester, free school meals eligible in year preceding Key Stage 1 assessment proxy start date 1st May to approximate deprivation beyond birth, academic season of birth (autumn, spring, summer), school moves from start school to KS1 (1+), urban or rural dwelling at birth, year take Key Stage 1 (ref 2010), other respiratory illness (as described in Table 5.5), Townsend deprivation quintiles; for each age group, asthma severity and hospital admission variables in the table added as a pair to the model without other age group variable pairs due to multicollinearit