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Asthma in women:

Implications for pregnancy and perinatal outcomes

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Abstract

Background

Asthma now affects up to 10% of pregnant women in high income countries and international prevalence is rising. It is already one of the commonest chronic diseases that can complicate pregnancy and previous studies have raised concern that women with asthma have increased pregnancy risks. Precise estimates of the magnitude of these risks and the extent to which they may differ by asthma severity and asthma exacerbation rates, have not been determined.

Aim

The overall aim of this thesis was to investigate the impact of asthma and asthma therapies on pregnancy and perinatal outcomes in the general female population.

Methods

The Health Improvement Network primary care database from the United Kingdom was used to develop a dataset of women matched to their liveborn children and all data on these pregnancies and on pregnancies ending in stillbirth, miscarriage or therapeutic abortion, were extracted for analysis. Three separate studies were carried out using the developed dataset. First, a cohort design was used to compare fertility rates of women with and without asthma or other allergic disease. Secondly, a cross-sectional design was used to compare risks of adverse pregnancy outcomes and obstetric complications in women with and without asthma. Thirdly, a case-control design was used to compare the risk of congenital malformation in children born to women with and without asthma, and to assess whether asthma medications are teratogenic.

Results

A study population of 1,059,246 women was obtained and pregnancies ending in 268,601 matched live births, 986 stillbirths, 35,272 miscarriages and 37,118 therapeutic abortions were identified. Women with asthma or other allergic disease had similar fertility rates (live births per 1,000 person-years) to women in the general population. Women with asthma also had a similar risk of pregnancy ending in stillbirth (Odds Ratio (OR)=1.04, 95% confidence interval (CI) 0.86-1.24)) or therapeutic abortion (OR=0.95, 95%CI 0.92-0.99), but had a small relative increase in risk of pregnancy ending in miscarriage (OR=1.10, 95%CI 1.06-1.13), compared with women without asthma. Risks of most obstetric complications were similar in women with and without asthma, regardless of asthma severity or acute exacerbations, with the exception of increased risks of antepartum haemorrhage (OR=1.20, 95%CI 1.08-1.34), postpartum haemorrhage (OR=1.38, 95%CI 1.21-1.57), depression in pregnancy (OR=1.52, 95%CI 1.36-1.69), caesarean section delivery (OR=1.11, 95%CI 1.07-1.16), preterm delivery (OR=1.15, 95%CI 1.06-1.24) and low birth weight (OR=1.18, 95%CI 1.05-1.32) in their offspring. Compared with children born to mothers without asthma, children born to mothers with asthma had a small increased risk of major congenital malformation (OR=1.10, 95%CI 1.01-1.20), however, this was not found for mothers with currently treated asthma (OR=1.06, 95%CI 0.94-1.20). Gestational exposure to asthma medications was safe apart from cromones which may increase the risk of musculoskeletal malformation.

Conclusions

Our findings indicate that women with asthma do not have substantially increased risks associated with pregnancy or with perinatal outcomes. Treatment with asthma medications before pregnancy and during gestation also appear to be safe for the mother and for the unborn child, providing support for the current practice of optimal pharmacological management of asthma in women of childbearing age.

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List of abbreviations

95% CI	95% Confidence Interval
BMI	Body Mass Index (measured as kilograms/meter squared)
CS	Corticosteroids
DBP	Diastolic Blood Pressure
EUROCAT	European Surveillance of Congenital Anomalies
FDA	Food and Drug Administration
FEV_1	Force Expiratory Volume in 1 second
GFR	General Fertility Rate
GP	General Practitioner
GPRD	General Practice Research Database
ICS	Inhaled Corticosteroid
InPS	In Practice Systems
IQR	Inter-quartile range
IRR	Incidence Rate Ratio
LABA	Long acting β-agonist
mmHg	Millimetres of mercury
OAI	Other anti-inflammatory
OBD	Other Bronchodilator
OCS	Oral Corticosteroid
ONS	Office for National Statitistics
OR	Odds Ratio
RCT	Randomised Controlled Trial
RR	Rate Ratio
SABA	Short acting β-agonist
SBP	Systolic Blood Pressure
THIN	The Health Improvement Network
UK	United Kingdom
US	United States

1 Introduction

While considerable research on the aetiology of asthma is ongoing, there has been much less exploration of the potential impacts of asthma on key life stages, such as women's child bearing years and pregnancies. The aim of this thesis is to estimate the true magnitude of a number of risks associated with pregnancy in women with asthma and determine if these are different to those of women in the general population. This introductory section provides an overview of what is currently known about the impact of asthma on women's reproductive experience and what gaps remain in the evidence. This is followed by a justification of the thesis work and detailed objectives of the thesis.

1.1 Background

1.1.1 The current burden of asthma

The incidence and prevalence of asthma has risen considerably over the past 40 years [1,2]. The World Health Organisation estimated that 300 million people had asthma in 2005[3]. Internationally, the highest prevalence of clinically defined asthma is currently in the United Kingdom (UK), where 15% to 18% of the population is affected, followed by New Zealand, Australia, Republic of Ireland, Canada and Peru[4,5]. There are fewer available data on the differences in incidence or prevalence by age and sex[6,7], but in general the incidence of asthma and related health service utilisation for asthma is higher in boys than in girls during childhood and then

reverses after puberty and for the rest of life, with a relative rate of new asthma in women compared with men ranging from 1.4 to 5.9[6,8]. The incidence of adult onset asthma is between 4% and 11%[7,9], however the high prevalence of adult disease is largely due to a recent decrease in the proportion of children whose asthma symptoms resolve in adulthood (i.e. children are now less likely to grow out of their asthma)[2,10]. In women of childbearing age, the United States (US) prevalence of diagnosed asthma has increased considerably from 8% before 1990 up to 14% in 2001[11]. The most recent estimates of currently treated asthma in women of childbearing age are 6% to 8% in the UK[12] and 5% to 10% in the US[11].

Advances in the treatment of asthma have been successful in reducing both morbidity and mortality from asthma[13], however, access to such treatment varies within and between countries. Each year in the UK, more than 1 in 4 people with asthma need acute services from hospital or medical practices while in the US, 1 in 10 need hospitalisation and 1 in 50 need emergency department treatment[2]. Such health care utilisation for asthma is associated with deprivation in these countries and internationally, largely because of under-treatment of asthma[14,15]. In 2005, over 255,000 people died of asthma, accounting for 1 in every 250 deaths worldwide, and 80% of these deaths were in low and middle-income countries with the most limited access to essential medication and emergency care[3,4]. The increasing prevalence of asthma will therefore have the most severe impact on countries that already have the highest asthma mortality and morbidity rates, which include China, Russia, Uzbekistan, Albania, South Africa, and Singapore[4].

In addition to building the body of research on the underlying physiological mechanisms of asthma[1] and the potential contributing factors to the international increase in asthma prevalence[1,16], there is pressing need to assess the current impact of asthma on other health outcomes, such as maternal morbidity.

1.1.2 The current burden of maternal and perinatal morbidity and mortality in high income countries

There has been a large reduction in maternal and perinatal mortality over the 20th century in high income countries. Maternal mortality is now extremely rare in the UK (11 per 100,000 pregnancies)[17] and in the US (9 per 100,000 pregnancies)[18]. The three leading causes of maternal mortality and severe morbidity in the UK are thrombosis or thromboembolism, hypertensive diseases in pregnancy, including pre-eclampsia, and haemorrhage, and these causes are similar in other high income countries [17,19-23]. Severe maternal morbidity may occur in only 4 per 1,000 pregnancies[20], however up to 30% of women may have pregnancy complications or pre-existing conditions that lead to complications during pregnancy, previous hypertension being the most common such condition[21].

Infant mortality is currently 4 per 1,000 births in the UK, while stillbirth rates are 6 per 1,000 births in the UK and in the US[24,25]. The leading cause of neonatal death in the UK is immaturity at birth, accounting for 48% of all deaths, followed by congenital malformation, accounting for 22% of deaths[24,26]. In contrast, congenital malformations are the leading cause of infant deaths in Canada and the US, followed by prematurity and low birth weight [18,27-29]. The cause of death is unexplained for most stillbirths, however, the known leading causes are congenital malformation and

antepartum haemorrhage, which account for 15% and 10% of all late foetal deaths, respectively. Pre-eclampsia, diabetes, infection during pregnancy and antepartum hypoxia also account for a large proportion of neonatal deaths and stillbirths[30,31].

The decline in total births in the UK may have recently reached a plateau; There were 706,000 births in 1990, 604,000 in 2000, and 646,000 in 2004[32,33]. Using these estimates, even rare obstetric complications with a prevalence of less than 1% currently affect up to 6,500 women and their babies annually.

1.1.3 Maternal asthma: Outline of potential risks to mother and child

Up to 12% of pregnant women have been diagnosed with asthma and up to 8% have actively treated asthma in pregnancy, according to recent national estimates from the US[11], making it one of the most common chronic medical conditions affecting pregnant women in high income countries[34-36]. Current evidence suggests that women with asthma may be at an increased risk of obstetric complications and adverse perinatal outcomes, however findings are inconsistent[34,37-45]. The earliest large study, conducted in 1972, compared over three hundred women with asthma with the general female population in Norway and found that these women were more than twice as likely to experience pre-eclampsia, and their babies were more likely to have a low birth weight, be born preterm, and have higher mortality[41]. The management of asthma since this time has improved considerably with the introduction of symptom-preventive asthma medications and more recent studies have shown less severe risks. However, some studies have again shown increased risks of pre-eclampsia, low birth weight babies and preterm babies, and additionally

risks of haemorrhage, placenta praevia, placental abruption, gestational diabetes and caesarean section in women with asthma compared to women without asthma[44,46-49]. Most recent studies have not found an increased risk of foetal mortality[49-52], however, some findings have indicated a potential increase in the risk of perinatal mortality and congenital malformations in babies born to women with asthma [44,53]. Most studies up to now have not been able to adjust for potential confounding factors and, because obstetric complications and adverse perinatal outcomes are rare in the populations studied, most analyses have not had adequate power to obtain accurate estimates of the true risk associated with asthma. The largest study included 13,000 women with asthma[44], but did not assess the risk of all potential obstetric complications and perinatal outcomes.

1.1.4 Potential explanations for obstetric risks in women with asthma

Pathophysiological effects of asthma in pregnancy

Definitive physiological explanations for pregnancy risks associated with asthma have not been established, however, changes in mechanical ventilation, immune responses and hormone levels have been implicated.

The clearest obstetric risk is foetal hypoxia which could affect growth and development or could cause foetal death. The most evident potential cause of foetal hypoxia is maternal hypoxia during acute asthma exacerbations. During pregnancy, women have a decreased lung capacity due to elevation of the diaphragm, a decrease in cell-mediated immunity which increases susceptibility to infections, and increased progesterone levels which can cause hyperventilation or triggering exacerbations[54,55].

While all of these changes may contribute directly to asthma exacerbations, they may also have more subtle worsening effects on asthma symptoms and inflammation. Other more prolonged causes of foetal hypoxia may be reduced utero-placental blood flow due to hypocapnia, alkalosis, or hypertension during pregnancy.

Women with asthma are more predisposed to infections during pregnancy, and these have been directly associated with poor pregnancy outcomes[56,57] including maternal anaemia, hypertension, premature delivery, low birth weight babies and perinatal death. Apart from infection, the raised immune function in asthma may also result in more severe immune reactions to the presence of a foreign foetus. Murphy *et al* recently proposed that inflammatory factors in pregnant women with asthma may directly affect foetal growth[58]. They found that, compared with women with asthma who were using corticosteroids during pregnancy, untreated women had impaired placental function and corresponding increases in inflammatory factors which were associated with reduced birth weight in their children.

There is also increasing evidence for a link between sex hormones and asthma, but the mechanisms are not known and their effect on asthma seems to be inconsistent in different women[59,60]. Laboratory and some clinical research has provided evidence that progesterone and other sex hormones which rise sharply in pregnancy may contribute to worsening or improving asthma, although most studies have not found a clear correlation between hormone levels, immune responses and active symptoms during pregnancy[61-63].

Asthma severity and acute exacerbations

One of the main difficulties in estimating risks associated with asthma during pregnancy is the varying severity of illness; it is not known whether risks are associated with asthma in general, or are isolated to women with severe asthma or poor asthma control. There have been case reports of status asthmatics (severe asthma with little response to treatment) that have only been alleviated after delivery of the child and some of have ended in maternal or foetal death[64-70], however, uncontrolled asthma usually responds well to acute treatment during pregnancy[69-71]. Although there is good evidence that the risk of asthma morbidity increases in people who are not using required medications[72,73], whether this affects pregnancy risks is less clear. There are limited data to support the proposal that maternal hypoxia experienced during asthma exacerbations has a direct detrimental effect on the foetus[74,75].

The largest study specifically investigating the incidence of asthma exacerbations in pregnancy was in a cohort of over a thousand women from the US[76]. In women with mild asthma who were not using symptom preventive medication, 13% had asthma exacerbations during pregnancy and 2% were prescribed oral corticosteroids for severe exacerbations. In women with more severe asthma, 26% and 9% had exacerbations and oral corticosteroids respectively. These results suggest that women with more severe asthma in general also have more severe asthma during pregnancy, but, more importantly, that even in women with mild asthma, exacerbations are an important problem during pregnancy. What needs further exploration, is whether these generally high risks of asthma exacerbations are because women tend to under-treat their asthma during pregnancy, perhaps because

of concerns about drugs harming their unborn child, and resultantly experience worsening asthma symptoms. There is evidence that some physicians under-prescribe asthma medication during pregnancy and that women reduce their medication use[77,78], however, this may alternatively be reflecting an improvement of asthma symptoms in pregnancy.

The safety of asthma medications

The specific effects of women's asthma medication use in pregnancy on the potential risks of congenital malformations and foetal development in their children, also need to be addressed. Although women are advised to avoid using medications during pregnancy in general, because of potential adverse effects on their unborn children, this is not the case for asthma medication[79,80] and they are resultantly one of the most common medications used in pregnancy[81]. A recent study in UK general practices showed that only prescriptions for folic acid, anti-bacterial/anti-infective medications, and antacids were more commonly used in pregnancy and asthma bronchodilators were the most commonly prescribed medication in drug class C of the US Food and Drug Administration, which stipulates a lack of sufficient data on safety in human pregnancy[82].

Pregnant women with asthma are currently advised to optimally manage their asthma by continuing to use prophylactic medications[83-85] and studies have generally shown this to be safe[42,43,86-94]. However, there are remarkably few such clinical studies of the safety of asthma therapies on human pregnancy. Most trials assessing the effects of treatment with asthma medication exclude pregnant women[95] and in those that have included pregnant women[96-99] assessment has mainly focussed on drug

tolerance and effectiveness in controlling asthma symptoms rather on potential obstetric risks. There has also not been research on what doses of asthma medication should be given during pregnancy and although there are changes in drug distribution levels during pregnancy, medications are usually given at similar doses in pregnant and non-pregnant periods[100].

In a 2000 systematic review, Jadad et al[42] identified only three studies assessing the teratogenic risks of asthma medication use during the first trimester of pregnancy, all of which were underpowered to the extent that they could not exclude a twofold increase in the risk of complications associated with a specific asthma therapy. This review concluded that there is a pressing need for much larger studies in this area. A more recent report re-emphasised the lack of adequate safety information on long acting β_2-agonists and newer asthma therapies such as leukotriene receptor antagonists in the current clinical guidelines[75,79,80,101,102].

Inhaled medications, which act more locally, should potentially by safer than oral medications, which have direct systemic effects. However, short acting β_2-agonists and inhaled corticosteroids both enter the systemic circulation and cross the placenta to enter the foetal circulation and body tissues[95,103,104]. Other asthma treatments which are given orally, such as oral corticosteroids, methylxanthines, and leukotriene receptor antagonists, are used less commonly, but also enter the systemic circulation and cross the placenta[75,105,106].

The results of animal experiments suggest that high doses of systemic corticosteroids cause reduced foetal growth, cleft palate or skeletal malformations in mice, rats and

rabbits, and that high doses of inhaled corticosteroids lead to decreased foetal survival in monkeys[75,107-111]. Short acting β_2-agonists are safe in many animal models when given by inhalation[112], but high doses may cause foetal death in rabbits[75]. Animal toxicology studies of theophylline have generally shown that the drug is safe, although adverse effects have been found in specific body tissues including the reproductive organs[113,114]. When given to pregnant mice and rats, theophylline has been associated with increased foetal death, low birth weight, cleft palate and digit defects in mice, but these effects do not appear in rats[75,115-118]. Leukotriene receptor antagonists may lead to increased foetal loss without evidence of teratogenicity in rabbits[75,106]. Most animal research studies have used much higher doses of drug than are used clinically and although many drugs with teratogenic effects in animals have proved to have no such effects in humans[119], these studies do raise concern that asthma therapies may adversely affect the development of the human foetus.

1.1.5 Weighing the benefit of asthma treatment with a potential for harm

The clear effectiveness of regular asthma medication use and acute therapy in reducing asthma morbidity and mortality indicates that pharmacological treatment of asthma is essential in most cases. The need for medications to control asthma during pregnancy, however, particularly for severe exacerbations which could pose serious harm to both the pregnant woman and the foetus, must be weighed against any drug-associated risks on pregnancy. It is difficult to separate the potential risks associated with symptom severity from the potential risks associated with asthma medications,

due to the reciprocal relationship of symptoms and treatment and few studies have attempted to investigate these effects separately[76].

In the recent British Thoracic Society Guidelines on Asthma Management[79,80], recommendations are graded depending on the strength of supporting research evidence, from A, representing the strongest evidence, to D, representing the weakest. For pregnancy, none of the recommendations are graded higher than C and many are graded D. It is unlikely that these gaps in the knowledge based will be filled by clinical trials, partly because the limited financial gains and possible associated risks mean that there is no commercial incentive for pharmaceutical companies to undertake such trials, but also because sample sizes of clinical trials are not large enough to identify risks of extremely rare events. Adverse event monitoring systems have various limitations such as bias in reporting, difficulties in finding appropriate comparison groups, and lack of availability of potential confounding factors[120,121]. Large observational studies are therefore required to detail the relationship and establish the true magnitude of pregnancy risks associated with asthma, asthma exacerbations and asthma medications.

1.2 Justification of thesis

Current evidence is limited, but indicates that women with asthma are at an increased risk of having obstetric complications and adverse perinatal outcomes. Reasons for this, however, are unclear because of the wide differences in severity and medication use among these women. Most drugs are contraindicated during pregnancy, however, women with asthma are advised to continue using their asthma medications

during pregnancy. Current clinical management guidelines on asthma medication use are not based on clinical trials and only a few human studies, which are underpowered, have investigated effects of antenatal exposures to these medications.

By determining the extent to which risks of obstetric complications and adverse perinatal outcomes are due to asthma per se, asthma exacerbations or to asthma medication, much needed evidence in support of, or possibly in contradiction to, the current management guidelines will be provided. If this research indicates that increased risks of obstetric complications and adverse perinatal outcomes are not due to asthma medications, but due to women under treating their asthma during pregnancy from concern to their unborn child and resultantly having more exacerbations, then women with asthma and the health professionals caring for them will be advised to more closely monitor asthma during pregnancy.

1.3 How this thesis will address current questions of obstetric risks in asthma

This thesis represents the largest cohort study of asthma in pregnant women ever undertaken. Using computerised general practice records from over 1 million women, over 250,000 pregnancies and over 200,000 live babies born to these women have been analysed. This has enabled the investigation of risks associated with asthma during pregnancy and delivery, affecting both the woman and the unborn child. The results of this thesis will provide a much needed addition to the evidence base on the management of asthma during pregnancy.

1.4 Thesis objectives

The overall aim of this thesis is to investigate the impact of asthma and asthma therapies on pregnancy and perinatal outcomes in the general female population, by completing the following objectives:

1. To determine whether women with diagnosed asthma have the same general fertility rate as women without asthma in the general population, and to additionally estimate the general fertility rate of women with eczema or hay fever to determine whether there are similarities between women with allergic disease.
2. To estimate the risk of the following specific adverse pregnancy outcomes in women with diagnosed asthma compared with women without asthma in the general population: Stillbirth, miscarriage and therapeutic abortion.
3. To estimate the risk of the following specific obstetric complications and delivery outcomes in women with diagnosed asthma compared with women without asthma in the general population: Antepartum haemorrhage, postpartum haemorrhage, pre-eclampsia or eclampsia, placental insufficiency, placental abruption, placenta praevia, pregnancy-related hypertension, pregnancy-related diabetes, pregnancy-related anaemia, pregnancy-related thyroid disorder, pregnancy-related depression, caesarean section delivery, assisted delivery, malpresentation and breech presentation in utero, breech delivery, premature delivery, and low birth weight of offspring.
4. To investigate the extent to which asthma severity and asthma control change during pregnancy and determine whether the above adverse pregnancy

outcomes, obstetric complications and delivery outcomes are associated with asthma severity and control before and during pregnancy.

5. To estimate the risk of congenital malformation in children born to women with diagnosed asthma compared with those born to women in the general population without asthma, and to determine if the occurrence of congenital malformations is associated with gestational exposure to specific asthma medications.

1.5 Outline of thesis sections

The subsequent sections of this thesis discuss the building of the thesis dataset and three separate studies that address the objectives of this thesis. The outline below briefly describes the content of each section.

Section 2: Description of The Health Improvement Network (THIN) general practice database and an overview of the thesis ethics, funding, database management and analysis tools.

Section 3: Description of building the thesis dataset of matched mothers and live born children; definitions and extraction of other obstetric outcomes, exposures and potential confounding variables; and a summary of the final thesis dataset structure and how it will be used for the three main studies.

Section 4: In the first study, the general fertility rate for women in THIN is estimated using live births from the thesis dataset. Comparisons are made between

the general fertility rate of women with diagnosed asthma, eczema or hay fever and that of women in the general population without these diagnoses.

Section 5: In the second study, pregnancies from the thesis dataset are used to compare risks of adverse pregnancy outcomes, obstetric complications and delivery outcomes in women with asthma with those in women without asthma in the general population. The impact of differing levels of asthma severity and asthma control on these risks is assessed.

Section 6: In the third study, live births from the thesis dataset are used to compare the risk of congenital malformations in children born to women with asthma with that in children born to women without asthma in the general population. The risk of congenital malformation associated with gestational exposure to specific asthma medications is assessed.

As three separate studies, sections 4, 5, and 6 each contain their own introduction, description of methods, results, discussion and conclusions.

Section 7: Summary of the main findings in the thesis and suggested directions for future research.

2 Description of the data and analysis tools

This section first describes The Health Improvement Network Database, a database of computerised general practice records used for all analyses in this thesis. I briefly discuss the study ethics, the funding for the thesis work, the data management and statistical software used.

2.1 The Health Improvement Network Database

The Health Improvement Network[122] (THIN) is a computerised primary care database of anonymised patient records. In April 2005, when the data for this thesis were collected, the database contained information from 255 general practices across England, Scotland, Wales and Northern Ireland, comprising 3.9 million patient records. The database was set up in 2002 through the collaboration of the Medical Database Research Company, known as EPIC, the company that managed the General Practice Research Database until 1999, and Cegedim, a European healthcare software and research company. Upon joining THIN, all contributing general practices must use the latest version of Vision Software, a practice management software programme from In Practice Systems[123] (InPS), for their prospective recording. Retrospective medical data are also available in each patient's record and although general practices will have previously used a number of different software systems to record their data, most were previously using the Value Added Medical Products (VAMP) system[124] to enter patient data, which was used in the well established General Practice Research Database[125,126] (GPRD). Standard use of

computers to record all data held on patients in general practice, including medical diagnoses and prescriptions, started in the 1980s. Medical history, however, is contained in the computerised record, since the patient's medical notes move with the patient to each new general practice registration in the UK. This means that the computer record should provide a complete history of past major medical events and diagnoses.

A main advantage of THIN for epidemiological researchers is the provision of routinely collected patient data in raw format from which researchers can extract relevant information. Information for each patient is contained in 4 separate tables, which are linked by a unique identification number (Table 2.1). Read medical codes are used to enter data into the Medical and the Additional Health Data (AHD) tables. Read codes comprise a comprehensive list of medical terms for signs, symptoms, diagnoses, procedures and investigations, compiled from the International Classification of Diseases Ninth Revision (ICD-9) and the Classification of Surgical Operations & Procedures Fourth Revision (OPCS-4). Multilex drug codes, linked to British National Formulary[127] chapters, are used to enter prescriptions into the Therapy table.

Table 2.1 Structure of The Health Improvement Network database

THIN Data Table	Information contained
Patient	Basic demographic information (e.g. registration date, transfer-out date, date of birth/death, sex, family number)
Medical	Medical symptoms, disease diagnoses, hospital admissions, medical procedures and investigations
Therapy	Drug prescriptions (including frequency, quantity, dose, and formulation of medication)
Additional Health Data	Additional information such as lifestyle and preventative health care (e.g. smoking habit, weight, height, blood pressure, vision, hearing, perinatal monitoring, birth details, physical/mental child development, immunisations, biological test results) N.B. Read medical codes will also be attached to some additional health data tables

Of the 3.9 million patients in the database, 1.9 million were actively registered patients when the data were collected. The remaining patients in the database, who had either left the practice or died before data collection, have records containing historical data from 1985 onwards. Fifty six percent (142 out of 255) of the contributing practices also contribute data to the GPRD, which has been used extensively and independent studies have found high validity of prescriptions and medical diagnoses including live births, adverse pregnancy outcomes, congenital malformations and respiratory diseases[128-139]. Consultation rates for asthma have specifically shown good agreement with national morbidity statistics collected by the Office for National Statistics[12,131] (ONS). An initial data quality study conducted by the directors of THIN showed a high level completeness of clinical information, including the prevalence of pregnancies and of prescriptions, when compared with national data[122]. A more recent independent publication of several validation studies in THIN demonstrated that data from non-GPRD practices have the same high standard of validity as data collected for GPRD practices[140]. This publication included validation of numerous medical outcomes and health measures, including hypertension, diabetes, obesity and smoking and specific drug prescriptions. As in

other general practice databases, prescribing information in THIN will be largely complete since doctors use the computer to issue prescriptions that are printed for the patient.

2.2 Data anonymity and ethical approval

Ethical approval for this study was obtained from the Medical Research Ethics Committee in 2004. All patient records in THIN are anonymised to ensure that researchers cannot identify individuals. Each record in THIN has a unique identification number for the individual as well as unique identification numbers for the individual's family (or household) and the general practice that the individual attends. The broad geographic location of a THIN general practice is available as one of 12 regions across England, Scotland, Wales and Northern Ireland. The location of a patient's household, however, is not provided to researchers as to protect the identity of the individual.

2.3 Funding

The work for this thesis was funded by a grant from Asthma UK, the national charity working for the wellbeing of the 5.2 million people in the UK who are affected by asthma (www.asthma.org.uk).

2.4 Data management, analysis and statistical software

In April 2005, the September 30th, 2004 update of the database was supplied by THIN in the form of flat ASCII (American Standard Code for Information Interchange) files. Data management and cleaning of the entire THIN database was initially conducted by Chris Smith in the Division of Epidemiology & Public Health at the University of Nottingham. Chris Smith and Laila Tata worked together to devise methods to extract populations of women and children from THIN and link their records together. This linking process was conducted by Chris Smith using Microsoft Office Access database software and SQL (Structured Query Language) software for Windows XP. Laila Tata subsequently conducted the data management of the initial linked records to obtain mother-child pairs that were valid matches. Using the population of matched women and children, Laila Tata subsequently extracted all information on pregnancy and perinatal outcomes, asthma exposures and covariate data, using Stata software (releases 8.0 and 9.0; Stata Corp., College Station, TX). All statistical analyses were conducted by Laila Tata using Stata software releases 8.0 and 9.0.

3 Building the thesis dataset

This section describes how the study populations were defined for this thesis and the process of building a dataset of matched mothers and live born children. Obstetric outcomes, asthma exposures and potential confounding variables are defined and a brief summary of the final thesis dataset structure is given with a description of how it is used for the three main studies.

3.1 Definition of the study populations

To investigate risks of obstetric complications in women as well as risks to their children, two initial study populations needed to be built. The first was a population of women of childbearing age for whom prospective data was available and information on pregnancies and deliveries could thus be extracted. The second was a population of children that may have been born to these women. The thesis study period was defined as April 1st, 1987 to September 30th, 2004 and all patient records over this time were extracted from THIN data as follows:

1. A population of women contributing prospective in-practice data at some time point between 15 and 50 years of age, which was defined as their potential childbearing years of prospective data collection (Figure 3.1). These data had to start on or after April 1st, 1987.
2. A population of children born on or after January 1st, 1988 who had at least one woman of childbearing age from population 1 registered in the same household.

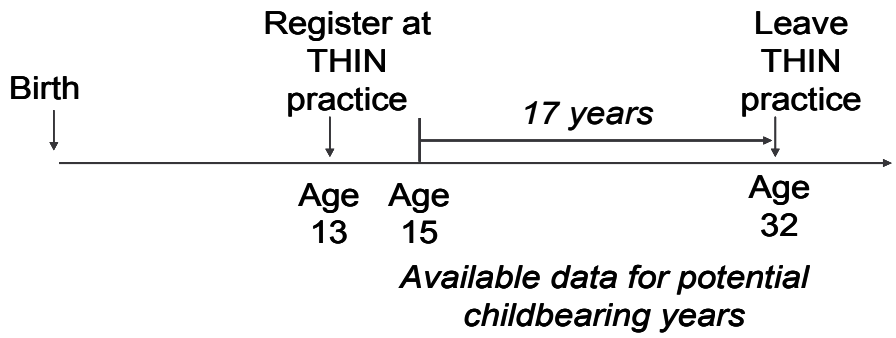

Figure 3.1 Data extraction for women in population 1 from THIN

3.2 Approximation of birth date

To extract these populations each patient's date of birth was initially approximated, since, as part of ensuring anonymity in THIN, a patient's precise date of birth (day, month, year) is not available in their record. The month and year of birth are recorded until the patient reaches his or her 15th birthday, after which only the year of birth is recorded. The database automatically updates the record at the date of a patient's 15th birthday, regardless of whether the patient has died or left the practice before this date.

For the 15% of patients in THIN with both month and year of birth recorded at the time of our data collection, date of birth was approximated as the 15th of the month and was updated to their registration date if they were registered in the same month they were born but before the 15th of the month. For the rest of the population who had only year of birth recorded, date of birth was approximated as June 30th of that year and was updated to their registration date if they were registered in the same year but before this date.

3.3 Definitions of pregnancy and delivery

In the population of women of childbearing age (population 1), all medical codes and additional health data codes indicating a pregnancy or delivery of a baby in a woman's record were extracted (code list in Appendix C). Any pregnancy codes occurring on or after April 1st, 1987 and any delivery codes occurring on or after January 1st, 1988, including both prospectively collected data and retrospective data, were retained. Some code descriptions that were not specific to successful pregnancies or live births (e.g. "Delivery", "Emergency caesarean section") were included, however, codes that were specific to adverse pregnancy outcomes, such as miscarriage or stillbirth, were excluded at this stage, because only codes that could potentially be matched to a live birth were required. Codes relating to the antenatal period, labour, and postnatal period were included (e.g. "Antenatal care: gravida NOS", "Failure to progress in second stage of labour", "Breast feeding problem"). A woman may have had only one code or several codes relating to a specific pregnancy or delivery event. A woman may have had codes relating to more than one pregnancy or delivery event. Any woman with at least one delivery or pregnancy code was considered to be a potential mother to one or more children in population 2.

3.4 Matching general practice records of mothers and children

The objective was then to link the general practice record of a woman with pregnancy and/or delivery codes (in population 1) to the general practice record of a child (in population 2) born at the same time these codes were entered into the

woman's record. To create a dataset of children matched to their mothers, a unique family identification number was used to link their records. When a new patient is registered at a general practice, the computer requests if this patient should be added to an existing family or if a new family should be created. In general, individuals residing at the same address will be given the same family number, which means that individuals in institutions such as residential homes or in apartment buildings may have the same family number. In order to maximise specificity of the matching, women and children who were in very large households, set as a cut-off of more than 20 people, were excluded.

Three basic methods were used in a hierarchical order to match mothers and children who had the same family identification number:

1. Firstly, a match was made if a delivery event in the woman's record occurred in the 45 days before or 45 days after a child's date of birth. This period of 45 days was based on one month and an additional 15 days to allow for the approximation of birth date.
2. Secondly, a match was made if a pregnancy event in the woman's record occurred in the 243 days before or 45 days after a child's date of birth or a birth event in the child's record.
3. Thirdly, for children who had reached their 15th birthday at data collection and only had their year of birth recorded, we allowed for our less precise approximation of birth date by additionally making a match if a birth event in the woman's record occurred in the 105 days before the child's registration. For this method, children had to be registered in the same year they were born. Since most children in the database are registered within the first three months of life,

the period of 105 days was based on 3 months and an additional 15 days to allow for the approximation of birth date.

After matching, all pregnancy and delivery codes relating to a matched mother-child pair were retained. In addition to using information on pregnancy and delivery in the women's records, records from the population of children were used to extract further information on birth events. Details about the child's birth, such as mode of delivery or gestation of the pregnancy may be in the child's record instead of the mother's record. To ensure that the birth event in the child's record was relating to that child's birth, only events occurring in the month before or after their date of birth were considered.

When 2 or more children were born on the same day and matched to the same woman they were considered as part of a multiple birth set (e.g. twins, triplets or quadruplets) and thus one set of pregnancy and delivery codes related to these children. To obtain the best approximation of birth date, a child's date of birth was updated to the date of the earliest delivery code if this code was before the child's registration date.

After completing the matching process, a number of validity criteria were applied to the matched pairs and both women and children were dropped if they did not meet these criteria:

- Any mother-child pairs where a child was matched to more than one woman were dropped from the dataset.

- An inter-pregnancy period was defined as a minimum of 9 months. When 2 or more children were matched to a woman and any of these children were born within 9 months of a previous child, all children and the matched woman were dropped from the dataset. The exception to this was multiple birth sets of children born on the same day.
- Children in multiple birth sets had to be registered within 9 months of one another and the household could not have more than 2 people in addition to the number of children (e.g. If a woman was matched to 3 children who were triplets, these children had to be registered within 9 months of one another and the household size had to be no larger than 5 people). If they did not meet this criteria, the matched set was dropped from the dataset.
- The mother and child populations had to be mutually exclusive. The thesis study period (1988 to 2004) was over 15 years which meant that individuals born in 1988 or 1989 had reached age 15 before the end of the study period. Therefore, because some women in the population of women of childbearing age (population 1) were only 15 years of age at data collection, they were also in the child population (population 2), and could potentially be matched as children to other women in population 1. When this occurred, these individuals were kept as matched children and removed from the population of women (population 1).

3.5 Definitions of outcomes

3.5.1 Gestation

Where available, the weeks of gestation at birth were extracted from the additional health data records of matched children. Any medical codes from the child's and the matched mother's record labelling the delivery as preterm, term or post term were also obtained (code list in Appendix C). Where exact length of gestation was not available, it was defined as 36 weeks if there was a code for preterm delivery, 43 weeks if there was a code for post term delivery and 40 weeks if there was a code for delivery at term. Most children with no information on weeks of gestation or term of delivery were likely delivered at term, however, they were recorded as having missing information for gestation. For all matched children with information on gestation, the exact or estimated weeks of gestation were used to interpolate the date of conception. A gestation of 40 weeks was used to interpolate the date of conception for children with no information on gestation.

3.5.2 Birth weight

The birth weight of a matched child was extracted from the mother's or child's additional health data record. Medical codes relating to the child's birth weight (e.g. "intrauterine growth retardation," "large-for-dates baby," or "low birth weight") were also obtained (code list in Appendix C). Children were categorised as having low, normal or high birth weight, defined as <2500g, 2500-4000g, >4000g respectively. If there was no information on birth weight in the mother's or child's record, they

were recorded as having missing information on birth weight, even though most children with no information on birth weight likely had normal birth weights.

3.5.3 Foetal position in utero and mode of delivery

For each matched child, codes relating to breech position or other malpresentation (e.g. "O/E - transverse lie," "O/E – oblique lie," or "fetal malposition and malpresentation NOS") of the foetus in utero were extracted from the mother's and child's record. Children without such codes were considered to have normal position in utero. Codes from the mother's or child's record indicating that the matched child was delivered by caesarean section, had an assisted birth (including forceps or vacuum delivery), or was delivered in breech position were also obtained. Pregnancies were categorised as having a normal vaginal delivery if they had a code indicating such a delivery (e.g. "normal delivery" or "vaginal delivery") or if they had no codes specifying mode of delivery. Code lists for foetal position in utero and mode of delivery are in Appendix C.

3.5.4 Congenital malformation

All codes for congenital malformation were extracted from each matched child's medical and additional health data records. These were classified according to the European Surveillance of Congenital Malformations (EUROCAT)[141] guidelines which are based on the International Classification of Diseases 10, Chapter XVII, Q00 to Q99. Each individual congenital malformation diagnosis is classified as one of eleven system-specific congenital malformation groups. Examples of individual

congenital malformation diagnoses in each system-specific group are shown in Table 3.1 and the full code lists for each malformation group are in Appendix C. The EUROCAT classification also labels each malformation as either major or minor, both of which were identified in our population, however, only major congenital malformations were retained for assessment.

Table 3.1 EUROCAT classification of congenital malformations

System	Selected congenital anomaly diagnosis
Nervous system	Neural tube defects, hydrocephalus, microcephalus
Eye, ear, face, neck	Anophthalmos, microphthalmos, anotia
Circulatory system	Defect of cardiac chambers, septae and valves
Respiratory system	Choanal atresia, bronchomalacia, cystic lung disease
Cleft lip and palate	Cleft lip with or without cleft palate, cleft lip nasal deformity
Digestive system	Tracheo-oesophageal fistula, atresia and stenosis of bowel
Genital organs	Absence of ovary, bicornuate uterus, hypospadia, congenital chordee
Urinary system	Epispadia , renal agenesis, congenital cystic kidney disease
Musculoskeletal system	Dislocation of hip, polydactyly, syndactyly, limb reduction
Other	Ichthyosis, epidermolysis bullosa, Prader-Willi syndrome
Chromosomal abnormalities, NEC	Trisomy 21, trisomy 13, trisomy 18, chromosome deletions

3.5.5 Obstetric complications

Information on the following obstetric complications was extracted from the women's records for pregnancies that were matched to a live child: Antepartum haemorrhage, postpartum haemorrhage, placental insufficiency, placental abruption, placenta praevia, pre-eclampsia and eclampsia, hypertension in pregnancy, diabetes in pregnancy, anaemia in pregnancy, thyroid disorder in pregnancy and depression in pregnancy.

Hypertension, diabetes, anaemia, thyroid disorder and depression in pregnancy were defined using either a general diagnosis that was recorded during pregnancy or as a pregnancy-specific code for the diagnosis (e.g. "pregnancy-induced hypertension," "gestational diabetes," "iron deficiency anaemia of pregnancy"). Since women with a diagnosis of these conditions during pregnancy may have had the same condition prior to pregnancy, I extracted general diagnoses that were coded before each pregnancy as well as codes specific to medical history (e.g. "H/O depression," "H/O diabetes mellitus").

To obtain additional information relating to hypertension in pregnancy, all measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were extracted from the women's additional health data. Each reading was classified as either hypertensive (SBP≥140mmHg and DBP≥90mmHg), hypotensive (SBP<90mmHg and DBP<60mmHg), or otherwise normal. The first reading in pregnancy, the last reading in pregnancy, and the change in mean arterial pressure (MAP) between the first and the last readings, where MAP = DBP + 1/3(SBP-DBP), were obtained for assessment. Code lists for obstetric complications, general diagnoses included in this section and blood pressure measurements are in Appendix C.

3.5.6 Stillbirth

Subsequent to the process of matching mothers to their children, codes for stillbirth or late foetal death (e.g. "foetal death due to prelabour anoxia") were extracted from

the records of all women in population 1. If a stillbirth occurred on the same day as the birth date of a live matched child, it was considered to be a stillborn sibling. With the exception of stillborn siblings, a woman had to have at least 9 months prior to the date of the stillbirth with no other pregnancy outcomes, for the stillbirth to be retained. For all stillbirths, we estimated the length of gestation as 32 weeks. The code list for stillbirth is in Appendix C.

3.5.7 Miscarriage

Miscarriage was defined as a spontaneous abortion or an early pregnancy loss coded as an ectopic pregnancy, blighted ovum or molar pregnancy. After matching mothers to their children, codes for miscarriage were extracted from the medical records of all women in population 1. A woman had to have at least 6 months prior to the date of the miscarriage with no other pregnancy outcomes, for the miscarriage to be retained. A miscarriage in the UK is considered as a pregnancy loss before 20 weeks of gestation, however, most miscarriages occur much earlier than this and I estimated the length of gestation as 10 weeks for all miscarriages. The code list for miscarriage is in Appendix C.

3.5.8 Therapeutic abortion

A therapeutic abortion was defined as an active termination of pregnancy using either chemical or instrumental means in utero. It is not standard for the general practitioner to include information on the reason for termination in the patient record. Therapeutic abortions, therefore, included all non-spontaneous abortions for medical

reasons relating to the safety of the pregnant woman or the development of the foetus, or for other reasons for which the woman chose to have an abortion, but did not include the use of an emergency contraceptive pill. In addition to codes clearly identifying an active termination of pregnancy (e.g. "suction termination of pregnancy") we used non-specific abortion codes (e.g. "unspecified abortion NOS" or "other abortion") unless there were other related codes indicating that it was a spontaneous abortion (miscarriage). After matching mothers to their children, therapeutic abortions were extracted from all records of women in population 1. A woman had to have at least 6 months prior to the date of the termination with no other pregnancy outcomes. Although the legal limit for conducting a therapeutic abortion in the UK is 24 weeks gestation, many clinics have much earlier limits of 12-18 weeks. We estimated the length of gestation for all therapeutic abortions as 16 weeks. The code list for therapeutic abortion is in Appendix C.

For estimating the gestational length of all pregnancies, whether ending in live or non-live outcomes, it is important to note that the first pregnancy code relating to a given pregnancy could not be used as an estimate of conception from which to measure gestation. For many miscarriages and therapeutic abortions, the codes for these adverse pregnancy outcomes were often the first markers of pregnancy, so no information was available on gestational age. Furthermore, the first pregnancy code was often a non-specific code (e.g. "Pregnant") and this may have represented when the woman first recognised she was pregnant and consulted for the pregnancy, rather than the date of conception. Use of this code may have resulted in systematic misclassification of gestational age, since women who identify their pregnancy

earlier differ in their risk of adverse pregnancy outcomes compared with women who identify later[142].

3.6 Definitions of exposures

3.6.1 Asthma

The main exposure for this thesis was a doctor diagnosis of asthma at any time in a woman's general practice record and all such diagnoses were extracted for women in population 1. A doctor diagnosis was defined as a non-specific asthma code (e.g. "bronchial asthma"), a specific diagnosis code (e.g. "exercise induced asthma" or "allergic asthma") or a code for an asthma exacerbation (e.g. "emergency admission, asthma"). The list of codes used to extract this diagnosis is in Appendix C. For each of the three main studies in this thesis (sections 4, 5, and 6), the definition of asthma in women is slightly different in accordance with the objective and design of the study. Since the onset of asthma can occur at any age, recent asthma exacerbations and asthma medication prescriptions were used to define currently active asthma, in addition to the overall definition of an asthma diagnosis at any time in the woman's record. Sections 3.6.2 and 3.6.3 will explain how asthma medications and exacerbations of asthma were used to further characterise asthma in women.

3.6.2 Asthma severity

Asthma severity is defined in a variety of different ways. It may be defined using the frequency of an individual's asthma symptoms, their amount of airflow obstruction

(measured using spirometry or peak expiratory flow), their requirement for asthma medications to remain as asymptomatic as possible, or any combination of these measures. A patient's asthma severity is often described as "mild," "moderate," or "severe." Since detailed information on daily symptoms and airflow obstruction measurements are not available in general practice data, asthma maintenance medications were used to define asthma severity in this thesis.

As a brief overview of asthma severity, asthma medications are generally classified as anti-inflammatory medications or bronchodilators, more commonly known as 'preventers' or 'reactors'. Bronchodilators include short acting and long acting β-agonists and more rarely used medications such as theophylline and cromones. Anti-inflammatory medications include inhaled and oral corticosteroids and more rarely used medications such as leukotriene receptor antagonists.

A basic treatment regimen for mild asthma is use of a short acting β-agonist (SABA) when needed for symptomatic relief of bronchospasm. When this treatment is needed more than once a day, preventer drugs are introduced, starting with twice-daily use of an inhaled corticosteroid (ICS). If needed, a long acting β-agonist (LABA) will be added to or combined with the inhaled corticosteroid. In more severe asthma, a higher-dose inhaled corticosteroid may be used, followed by a leukotriene receptor antagonist or an oral β-agonist. For acute asthma exacerbations, a short course of oral corticosteroids (OCS), most often prednisolone in the UK, will be prescribed. This acute asthma treatment is usually only given for a few weeks, and only 1% of people with asthma take regular oral corticosteroid treatment.

To estimate asthma severity, all prescriptions for asthma medications were extracted from the therapy records of women in population 1. Asthma medications were classified into drug families according to the British National Formulary[127] (Table 3.2). Lists of Multilex drug codes for each drug family are in Appendix C. In addition to examining individual drug exposures, prescriptions were used to categorise women into different levels of asthma severity using the British Thoracic Society[80] asthma step definitions as a guide. The three main asthma severity steps were defined as: 1) an asthma diagnosis with no medications prescribed, 2) an asthma diagnosis with short acting β-agonists prescribed, and 3) an asthma diagnosis with inhaled corticosteroids with or without long acting β-agonists prescribed. Combination medications were included in the categorisation based on their drug components (e.g. A woman who was prescribed a combination inhaler of fluticasone & salmeterol was in the highest category of asthma severity). Drugs categorised as other bronchodilators or other anti-inflammatory medications were not included as a separate category of asthma severity since women prescribed these drugs almost always had prescriptions for a SABA, an ICS or a LABA also. Oral corticosteroid prescriptions were not used for categorisation of asthma severity because these drugs are not regular asthma maintenance medications and they are often used to treat other chronic diseases or acute symptoms. Asthma severity was categorised separately based on time periods before and during pregnancy, which is described in more detail in each of the study sections because the categorisation was in accordance with the objective and design of each study.

Table 3.2 Asthma medications by drug family

Drug family	Drug name
Short acting β-agonist	Fenoterol Salbutamol Terbutaline Bambuterol
Long acting β-agonist	Formoterol Salmeterol
Inhaled corticosteroid	Beclometasone Budesonide Fluticasone Mometasone
Oral corticosteroid	Betamethasone Cortisone acetate Deflazacort Dexamethasone Hydrocortisone Prednisolone Triamcinolone
Other Bronchodilator	Aminophylline *(methylxanthine)* Theophylline *(methylxanthine)* Ephedrine Orciprenaline Tiotropium *(long-acting anticholinergic/antimuscarinic)* Ipratropium *(short-acting anticholinergic/antimuscarinic)*
Other anti-inflammatory	cromoglicate *(cromone)* nedocromil *(cromone)* montelukast *(leukotriene receptor antagonist)* zafirlukast *(leukotriene receptor antagonist)*
Combination medications	combination formula from any two drug families above

3.6.3 Asthma control

Asthma control usually refers to how well an individual's asthma symptoms are kept under control, such as maintenance of good peak flow levels and prevention of acute exacerbations of asthma. For this thesis, asthma control for women in population 1 was characterised using asthma exacerbations in their general practice record. Exacerbations were defined as acute exacerbations reported to the general practitioner, including asthma-related emergency hospital admissions, which were extracted from the records. Prescriptions for oral corticosteroids were also used as

markers of an asthma exacerbation since these are prescribed following severe acute asthma attacks. In both pre-pregnancy and pregnancy time periods, women were defined as having "poor asthma control" if they had one or more exacerbations, or having "good asthma control" if they had no exacerbations. The term "poor asthma control" can imply patients' poor adherence to medications. Asthma exacerbations, however, may also result from sub-optimal treatment prescribed by the physician, lack of symptom relief from medications in asthma that regularly does not respond well to treatment (i.e. difficult-to-treat asthma or brittle asthma), or exposure to environmental triggers. All of these possible reasons for exacerbations were, therefore, included in the definition. The code list for asthma exacerbation is included in the general code list for asthma, which is in Appendix C.

3.6.4 Eczema and hay fever

All doctor diagnoses of eczema and hay fever at any time point in the general practice record for all women in population 1 were also extracted for the purpose of examining fertility rates in women with other allergic diseases (study 1 in section 4). Code lists for these diagnoses are in Appendix C.

3.7 Definitions of covariates

3.7.1 Smoking status

There are differences in the prevalence of smoking in people with asthma compared with people without asthma[143-145] and evidence indicates that smoking affects foetal

development[25,146-149]. All additional health data relating to smoking (e.g. "number of cigarettes smoked/day") and medical codes for smoking status (e.g. "non-smoker") were extracted from records of all women in population 1.

Women were categorised as non-smokers, ex-smokers or current smokers firstly over the entire childbearing period and secondly before each pregnancy outcome, for women with pregnancies only. Over the entire childbearing period, for the entire female population, if women had more than one record for smoking status, the following method of categorisation was used: 1) Women were categorised as non-smokers only if they never had codes for ex-smoking or current smoking; 2) Women were categorised as ex-smokers if they had codes for non-smoking and ex-smoking but no codes for current smoking; 3) Women were categorised as current smokers if they had a code for current smoking at any point in their record. For women with pregnancies, smoking status was categorised for each pregnancy using the most recent smoking-related code before the pregnancy outcome, however, if this was a non-smoking code and a woman had previous codes for current smoking or ex-smoking, she was categorised as an ex-smoker for the relevant pregnancy.

Although this categorisation will result in some misclassification, this method of summarising smoking status in general practice data has replicated the known associations of specific health outcomes with smoking in previous studies[136,150] and current smoking records in general practice have shown reasonable accuracy[151]. A code list for smoking status is in Appendix C.

3.7.2 Body mass index

Both low body mass index (BMI) and high BMI are associated with increases in numerous different pregnancy complications[147,152-154] and BMI is also associated with asthma and asthma severity in women[155,156].

All data on weight and height from the additional health data records and all medical codes relating to BMI (e.g. "Body Mass Index 25-29 – overweight"), were extracted. Body mass index was categorised using the World Health Organisation groups: Underweight (<18.5 Kg/m^2), normal (18.5-24.9 Kg/m^2), overweight (25.0-29.9 Kg/m^2) and obese (≥30.0 Kg/m^2). Most women had exact BMI measurements and for those with more than one measurement, the mean BMI over the entire childbearing period was used. For women with pregnancies, the BMI before each pregnancy was also categorised using the most recent BMI recorded before conception. A code list for BMI is in Appendix C.

3.7.3 Socioeconomic status

Differences in socioeconomic status have been shown to be associated with the frequency of asthma symptoms requiring medical attention and the use of asthma medication[14,157,158] as well as the risk of obstetric complications and successful pregnancy outcomes[24,146,159-162].

The socioeconomic status of women in population 1 was measured using the Townsend deprivation index, which is provided with THIN data and is a measure of

area-level deprivation which has been well-validated in health services research to explain the variation observed in a range of health outcomes[163,164]. The Townsend deprivation index is calculated as the sum of 4 z-scores calculated from the following area-level proportions:

- percentage of potentially economically active residents over 16 years of age who are unemployed
- percentage of households with ≥1 person per room
- percentage of households without car ownership
- percentage of households in which the occupier is not the owner

In THIN data, the Townsend deprivation index is based on patients' home postcodes, however, to maintain patient anonymity, postcodes are not available to researchers. Townsend deprivation indices were derived from information on each output area (a group of approximately 150 households) in the 2001 UK national census and these individual indices were converted into quintiles. Using conversion software provided by In Practice Systems, a Townsend deprivation index quintile was matched to each patient's postcode at the level of the general practice. The Townsend index quintile was then uploaded from the practice with the routine THIN data collection.

At the time of data collection for this thesis, Townsend deprivation index quintile was available for only 176 out of 255 (69%) general practices, since the process of integrating this variable into the database for research purposes was in development. In addition to maintaining patient anonymity, the categorisation of the Townsend

deprivation index into quintiles from the national census, ensures that values are representative of deprivation relative to the whole of the UK population.

3.7.4 Other covariates

Since recording can vary between general practice[165] and region in the UK, information on registered general practice was retained for all women and children to ensure findings were consistent across practices. Over the period of this study (1988 to 2004), important changes in asthma treatment as well as the prevalence of asthma, obstetric complications and adverse pregnancy outcomes have occurred[24,166,167]. Data on year of birth for all children or year of pregnancy outcome for stillbirths, miscarriages, and therapeutic abortions was, therefore, extracted to ensure findings were consistent over time. Where appropriate, the effects of maternal age, multiple pregnancy (twin, triplet or quadruplet) and the sex of the child were also assessed, since these have shown to be associated with different risk of obstetric complications and may also modify asthma severity during pregnancy[146,149,168-174].

3.8 Overview of the thesis dataset structure

After the process of matching mothers to their children and extracting information on other adverse perinatal outcomes (stillbirth, miscarriage, therapeutic abortion and congenital malformations) and exposures, the aim was to have a dataset with the general structure shown in Figure 3.2. From this thesis dataset, the appropriate study populations for each of the three main studies in this thesis were extracted. For the first study (Section 4. Fertility rates in women with asthma, eczema and hay fever) all liveborn children matched to women in the dataset were used. For the second study (Section 5. Adverse pregnancy outcomes and obstetric complications in women with asthma) all pregnancies, whether they ended in live births or other adverse pregnancy outcomes, were used. For the third study (Section 6. Congenital malformations in children born to women with asthma) a selection of liveborn children were used to create a case-control dataset.

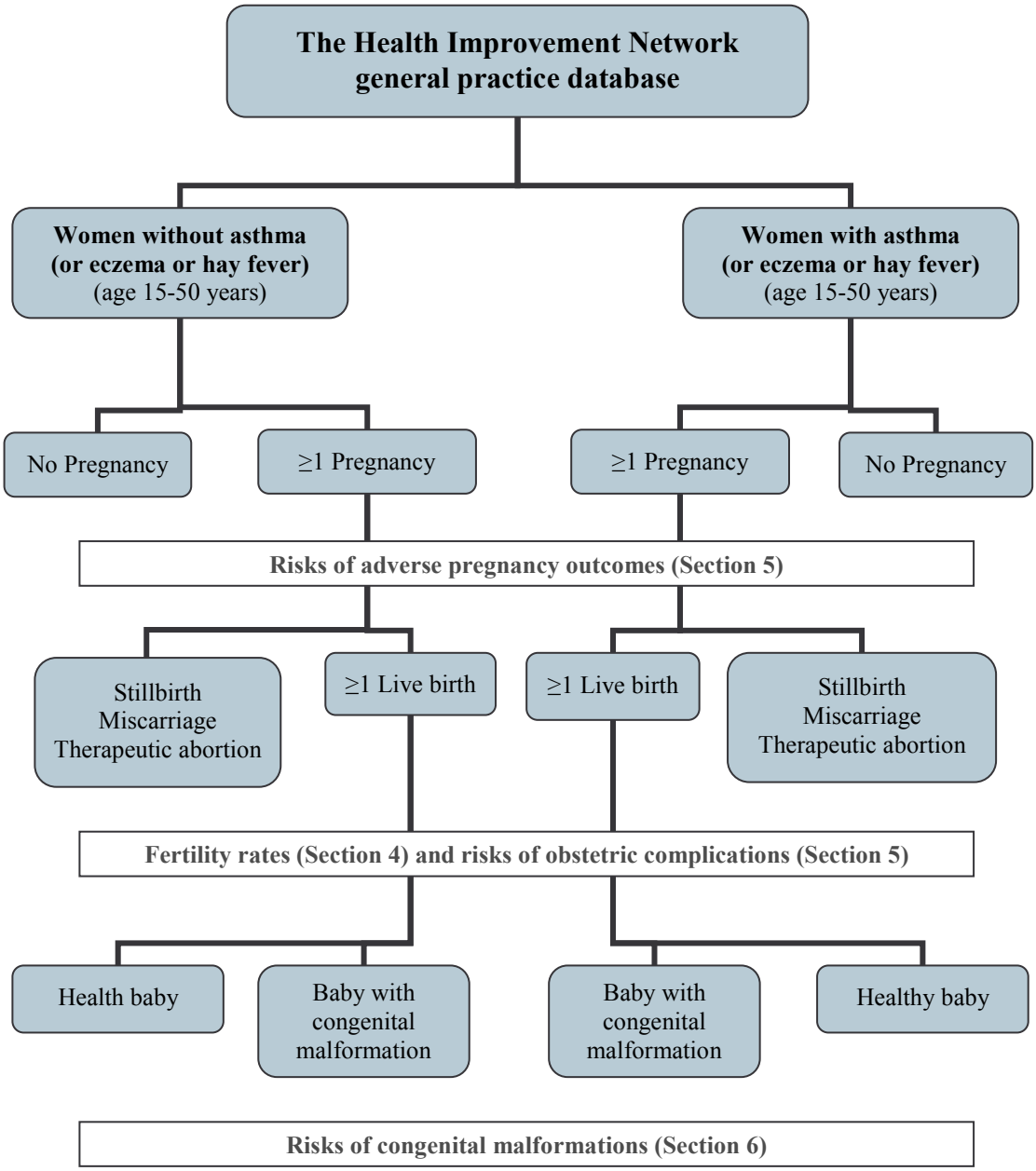

Figure 3.2 Overview of the thesis dataset structure

3.9 Results of building the thesis dataset

3.9.1 Summary of building and linking the study populations

The Health Improvement Network database contained the general practice records of 3,489,131 people with valid records at the time of data collection (Figure 3.3). Through initial data cleaning and restriction to the study population definitions, 1,064,451 women contributing general practice data between 15 and 50 years of age (population 1) and 509,444 children contributing general practice data who were born after 1987 (population 2) were obtained. These populations were used to match children to their mothers. From these populations, mothers and children that did not meet the criteria for validating matches (Section 3.4) were excluded and children for whom no matched mother was available were also excluded. This resulted in a final study population of 1,059,246 women with data between age 15 and 50 years of age. Of these women, 875,467 had no matched children and 183,779 were successfully matched to 268,601 children.

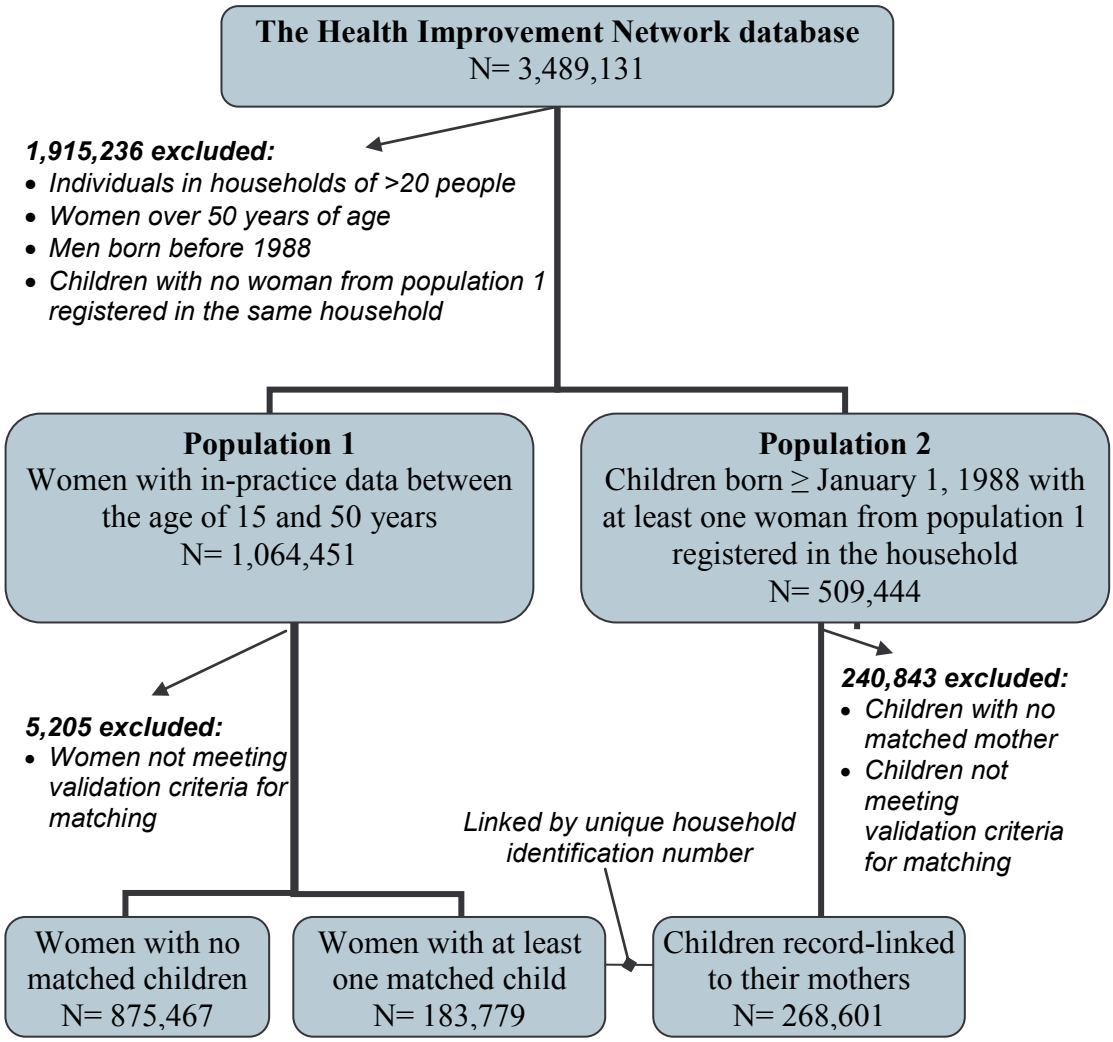

Figure 3.3 Summary of building and linking the study populations

3.9.2 Details of matching pregnancy and delivery codes to children

To dissect how mothers and children were matched in more detail, the following will describe the proportion of children who were matched using delivery and pregnancy codes, and explain why it was not possible to match some children to their mothers.

From the study population of 1,064,451 women (population 1), 192,555 women with one or more medical or additional health data codes for delivery were identified, representing 281,669 deliveries in these women occurring on or after January 1, 1988. An additional 73,061 women who had only codes for pregnancy occurring on or after April 1, 1987 were also identified.

Using the delivery codes, it was possible to match the 281,669 deliveries in women to 239,609 children, which represents an 85% success rate in matching children to deliveries in the maternal records (i.e. 239,609 matches out of 281,669 recorded deliveries in mothers). Using the pregnancy codes, it was possible to match an additional 28,992 children to their mothers. From the perspective of the final study population of 268,601 matched children, this means that 89% (239,609) were matched using delivery codes and 11% (28,992) were matched using pregnancy codes.

Figure 3.4 shows how the final study population of 268,601 matched children was obtained from the initially defined population of 509,444 children (population 2) and why it was not possible to match some children to their mothers. Of the 268,601 children who were successfully matched, 81% were registered during the 3 months after they were born and were, therefore, likely have general practice records available from birth. In contrast, of the 240,043 children who could not be matched to a mother, only 26% were registered during the first 3 months of life. The success rate of matching children who were registered within 3 months of their birth to their mothers' records was, therefore, 78% (i.e. 216,417 matches out of 278,333 children

who were registered within 3 months after birth). Figure 3.4 also shows that many unmatched children (29% of all unmatched children) had more than one population 1 woman registered in the same household.

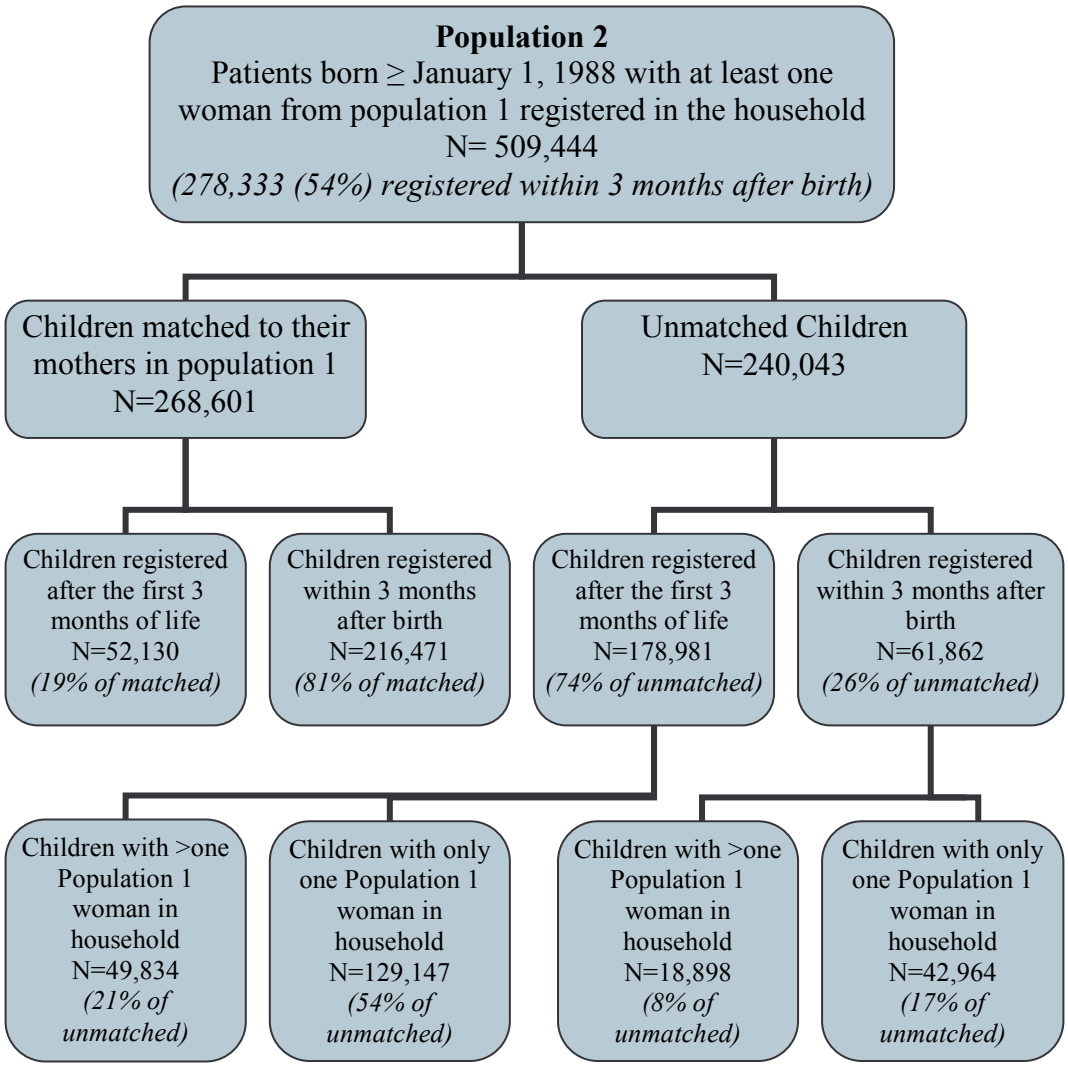

Figure 3.4 Breakdown of population 2 into matched and unmatched children

3.9.3 Brief description of liveborn matched children and adverse pregnancy outcomes

After the matching process, a final population of 1,059,246 women, of whom 183,779 were matched to 268,601 children was obtained. Because both prospective and retrospective general practice data were used for the matching process, some matched children were born before the mother's current general practice registration. For use in the thesis studies, the matches were restricted to those that occurred when the mother was registered in the current general practice, resulting in 151,711 women matched to 210,797 children (77% of the initial matches). Figure 3.5 shows the distribution of birth dates in the 210,797 matched children. Over 96% of these children were registered at the general practice within three months of their date of birth and children born in later years were slightly more likely to be registered soon after birth.

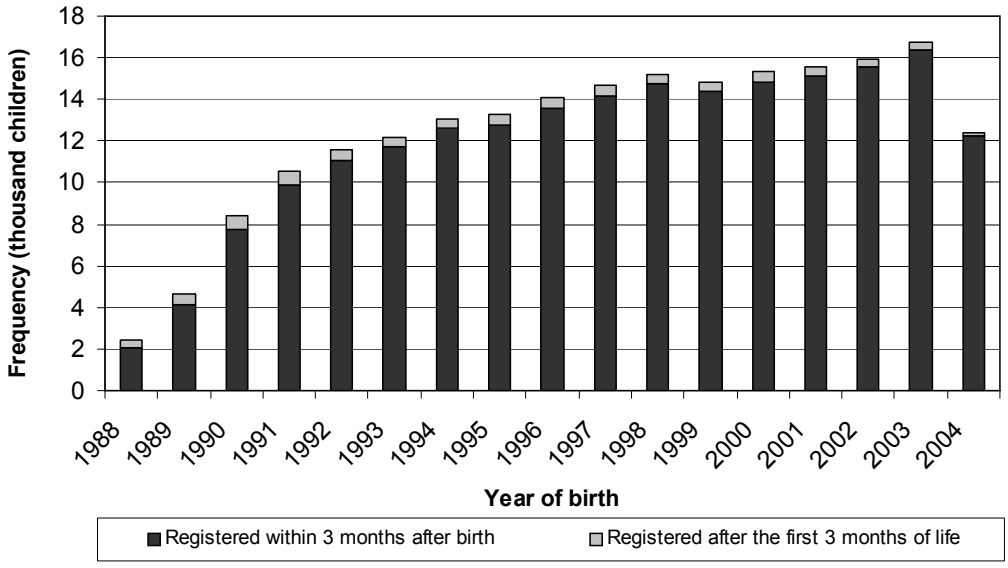

Figure 3.5 Calendar distribution of birth dates for matched children

Identification of adverse pregnancy outcomes that occurred during general practice registration in the 1,059,246 women, resulted in 986 stillbirths, 35,272 miscarriages, and 37,118 therapeutic abortions. Two brief validity checks of adverse pregnancy outcomes in the thesis dataset were conducted. Firstly, the proportions of pregnancies ending in miscarriage or therapeutic abortion and the stillbirth rate (stillbirths per 1,000 live and stillbirths) were plotted according to maternal age at the outcome of pregnancy.

Figure 3.6 shows that the proportion of pregnancies ending in miscarriage increases with advancing maternal age, whereas the proportion of pregnancies ending in therapeutic abortion is highest in young women and generally decreases with maternal age. Figure 3.7 shows that stillbirth rates are high in women who are in both the youngest and oldest age groups and lowest in women who are in the middle of their childbearing years. These patterns of pregnancy outcome across maternal age are consistent with national UK data and findings in other high income countries[24,149,170,174-176].

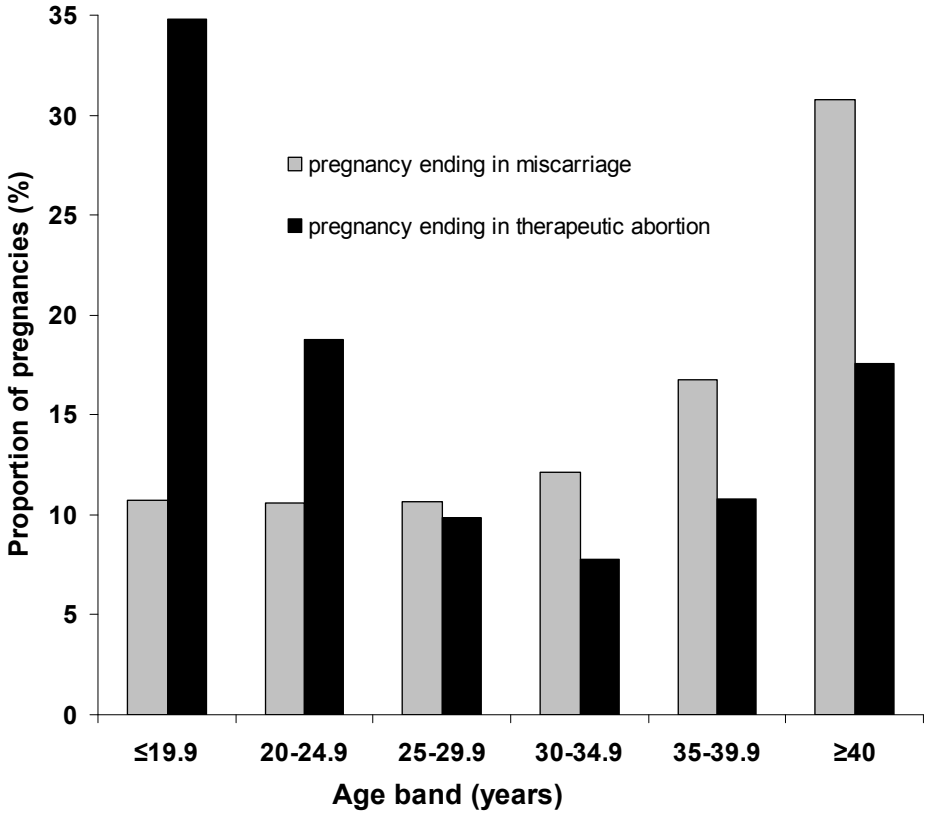

Figure 3.6 Proportion of pregnancies ending in miscarriage or therapeutic abortion by maternal age at the pregnancy outcome

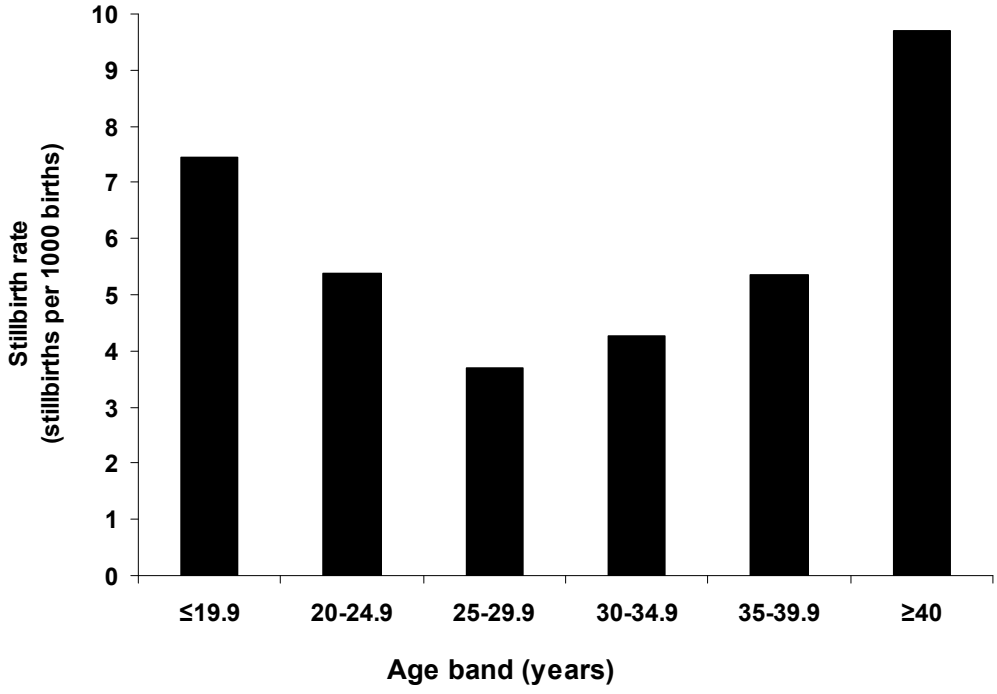

Figure 3.7 Stillbirth rate by maternal age at the pregnancy outcome

Secondly, a test was carried out of the well established associations of an increase in stillbirth rate for women who are current smokers and an increase stillbirth rate for women in living in areas of higher material deprivation which are seen in national UK data and data from other high income countries[24,26,146]. Figure 3.8 shows that there is an increase in stillbirth rate across quintiles of Townsend deprivation index, regardless of whether women were recorded as being non-smokers or smokers before the stillbirth event. Overall, however, women who are smokers have higher rates of stillbirth, regardless of their level of material deprivation.

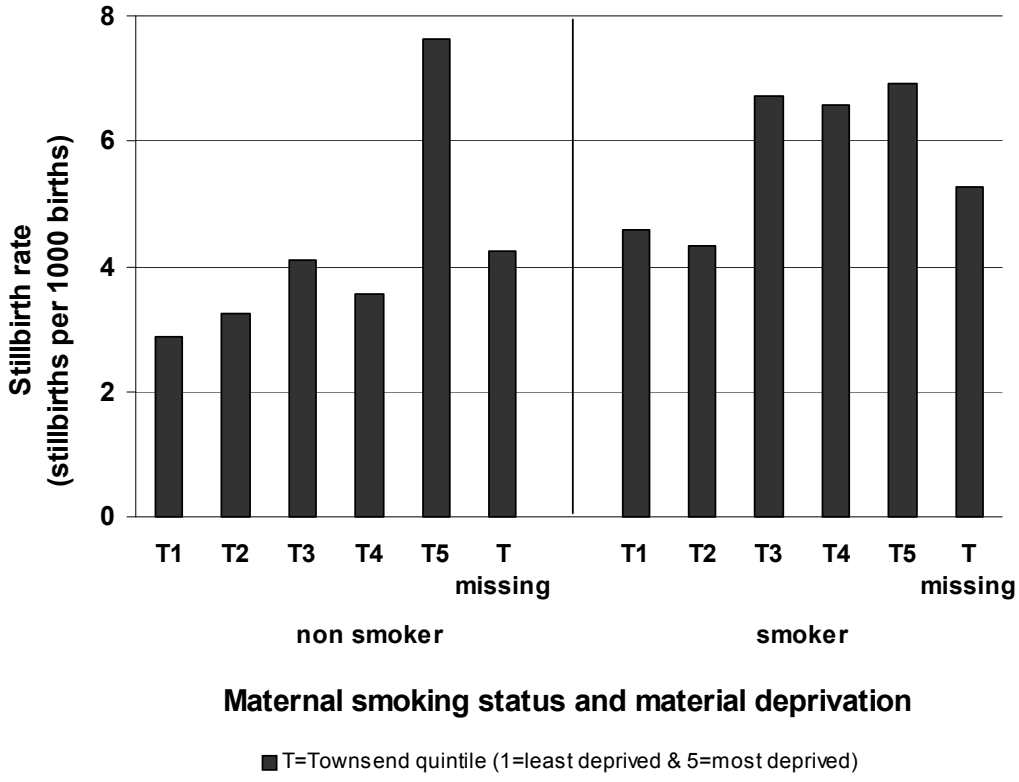

Figure 3.8 Stillbirth rate by maternal smoking status and material deprivation level

3.10 Validity and generalisability of the dataset

It is important to consider whether data from general practice have both internal and external validity and generalisablility for use in perinatal epidemiology studies. As previously discussed, data from THIN are obtained from general practices throughout the UK and previous studies have shown that the prevalence of major medical outcomes is generalisable to the national population. Major perinatal events should also be well recorded in THIN since it is rare that women attending antenatal care are not registered with a general practitioner in the UK, however, this thesis contains the first studies of perinatal epidemiology in THIN. In the previous section (3.9.3) some initial tests of data quality have been demonstrated, which indicate that our method for extracting live births and adverse pregnancy outcomes has ascertained a dataset that is representative of the national UK population. In each of the three following studies (sections 4 to 6), more detailed assessments of the validity, completeness and generalisability of the specific exposure, outcome and covariate variables are made.

A main advantage of the dataset used for this thesis is its size. This provides the opportunity to obtain precise estimates of prevalence and compare risks of obstetric complications and adverse pregnancy outcomes which are relatively rare on a population level. Contemporary data from 2004 spanning back to 1988 are used in this thesis, so the studies are relevant to the current population's reproductive experience.

The potential for random error and bias in data recording also requires consideration. The primary purpose of data collection by general practitioners is for use in managing the health of their patients. It is expected that there will be a certain degree of misclassification, whether due to coding errors or to possible misdiagnosis. Since the data are prospectively collected from routine medical visits or notifications from hospital, recall bias is avoided. However, the nature of this routine data collection can also introduce ascertainment biases which may relate to important factors of interest (e.g. disease status or age). Some patients may also have incomplete information for certain variables that were not recorded by the general practitioner (e.g. no record of body mass index). Since the general practitioner will first and foremost record data that are relevant to his or her patient care, there may also be biases in the amount of missing data according to factors of interest (e.g. more complete recording of smoking status in women with asthma compared with women without asthma). These potential limitations are carefully considered for the analysis and interpretation of each study.

3.11 Design of studies and statistical methods

Different study designs were used for each of the three main studies that address the aim of this thesis. In brief, a cohort design was used to assess fertility rates (section 4), a cross-sectional design was used to assess adverse pregnancy outcomes and obstetric complications (section 5), and a case-control design was used to assess congenital malformations (section 6). Full details of the study design, selection of the study population, and the statistical methods for analysis are described separately for each study.

4 Fertility rates in women with asthma, eczema and hay fever

This section describes a cohort study conducted to compare the general fertility rate of women with allergic disease (asthma, eczema and hay fever) with that of women in the general population without allergic disease. Current information on their fertility is described in the introduction, followed by the study methods which include the statistical analysis, the study results, a discussion of the findings in context of previous research, and a conclusion which addresses the clinical importance of the findings.

4.1 Introduction

Evidence from clinical and laboratory studies have provided support for the possibility of reduced biological fertility in women with allergic disease. Women with asthma or allergy have been found to have later onset of menarche[177,178], irregular menstruation[179] and endometriosis[180]. Perimenstrual asthma, experienced by up to 40% of women with asthma, has been linked to abnormal cyclical patterns of sex hormones[181-183], which may in part affect regulation of smooth muscle function[184]. Studies have also suggested that women with asthma have different concentrations of sex hormones[185] and different level of antibodies to progesterone and oestrogen[186], compared with women without asthma. Conversely, the physiology of atopic status towards T-helper 2 (Th2) cell cytokine production may actually promote conception and maintenance of pregnancy[187-189]. No study has yet

investigated fertility rates, however, in terms of the number of live births, in women with allergic disease.

Epidemiological data on the childhood prevalence of allergic disease indicate that there is a relationship between the risk of allergic disease and family size. There is strong evidence for a reduced risk of allergic disease in children of higher birth order (i.e. with more older siblings), and this phenomenon has yet to be explained by environmental factors[190-198]. Given the heritability of allergic disease[199], one possible explanation is that women with allergic disease have smaller families, either by choice or because of reduced biological fertility. It has in fact been suggested that the protective impact of higher birth order on the risk of developing allergic disease is mediated by decreased fertility in women with allergic disease. Findings in one study demonstrated that the birth order effect of allergic disease was independent of numerous factors, but could not be separated from household size[200]. Some studies of women with atopy and hay fever have indicated that they do tend to have fewer children[201-204]. While this has not been found specifically for women with asthma[203,204], selected data indicate that these women may have more pregnancies ending in adverse perinatal outcomes[40,44].

To assess whether women with allergic disease have fewer children than women with out allergic disease, this study provides estimates of population-based fertility rates in women with asthma, eczema and hay fever compared with those in women from the general female population without allergic disease. Prospective data from women in the thesis dataset were analysed.

4.2 Methods

4.2.1 Calculation and validation of fertility rates in THIN

The initial aim of this study was to create a comparable measure to the General Fertility Rate (GFR), the number of live births per 1,000 women between age 15 and 44 years, which is calculated yearly as a standard demographic measure of fertility in national populations[205]. The demographic approach was used to calculate fertility rates for two main reasons: Firstly, as a validation exercise to ensure fertility rates in the THIN dataset were comparable with national figures; Secondly, since birth control in the UK, including oral contraceptives and IUDs, can be obtained in family planning clinics and these data are not routinely recorded in general practice notes, it was not possible to accurately exclude time periods where women were not at risk of pregnancy.

From the thesis population of 1,059,246 women who were between 15 and 50 years of age, we excluded women who only contributed data between age 45 and 50 years. We retained all women contributing general practice data between 15 and 44 years of age, which was defined as the potentially fertile period. During this period all liveborn matched children were identified. In this whole potentially fertile THIN cohort, Poisson regression was then used to estimate fertility rates as the number of live births per 1,000 person-years women contributed to the potentially fertile period, which is analogous to the official GFR. This method of calculation differed slightly from the standard GFR because person-years were used as the denominator when women in the study were observed for part of one or more calendar years, rather than

the mid-year population number of women used in national statistics. To account for variation by age, fertility rates were calculated in each 5-year age band using a Lexis expansion[206] to construct an age-cohort model. This allows women to contribute person time to successive 5-year age bands as they get older through the study. Each woman in the study may have contributed person-time and birth events to one or more 5-year age bands and separate rates were calculated using the person-time contributed and births occurring during each specific 5-year age band. These age-specific fertility rates were therefore directly comparable with the standard presentation of GFRs in national data.

An initial validity test of the data was then carried out by comparing overall and age-specific fertility rates to the mean yearly overall and age-specific GFRs between 1995 and 2005 from the Office for National Statistics[205], which is a reliable source for an external comparison. This revealed that fertility rates in the THIN population were lower than expected. Subsequently, information provided by EPIC indicated that when general practices began using Vision software, some records of historic medical events were not fully transferred from the previous software system. There was no evidence that this was specific to any general practices, nor specific to individual disease status. The population was, therefore, restricted to women with potentially fertile data during Vision software use (Figure 4.1). In the Vision software potentially fertile THIN cohort, overall and age-specific fertility rates were re-calculated and compared with the yearly overall and age-specific GFR between 1995 and 2005 from the Office for National Statistics[205], and these were more similar. The comparison between fertility rates in the whole potentially fertile THIN cohort, the Vision software potentially fertile THIN cohort and the national GFR is

presented in the results section. In the Vision software potentially fertile THIN cohort the distribution of fertility rates is additionally presented across quintiles of the Townsend deprivation index, which was conducted to test whether this population was representative of the UK, where women who are in higher socioeconomic groups and attain higher educational qualifications have children at a later age[207,208].

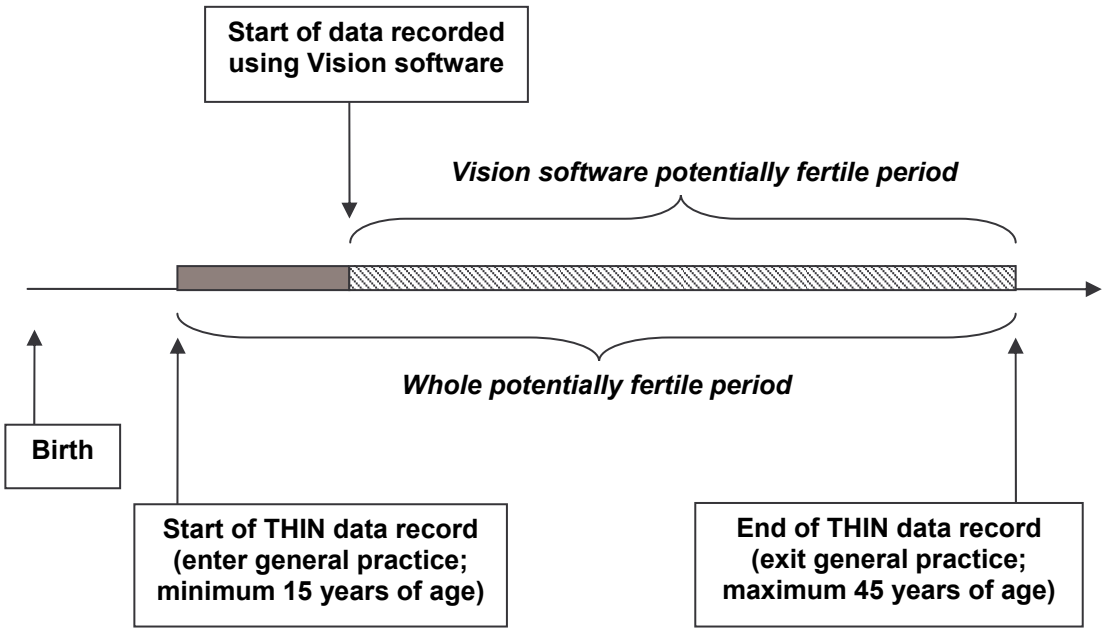

Figure 4.1 Collection of prospective data and live births occurring after the start of Vision software use in general practice.

4.2.2 Study population and extraction of potential confounders

The cohort of women with validated fertility rates (Vision software potentially fertile THIN cohort) was used as the study population for the fertility rate analysis. All diagnoses of asthma, eczema and hay fever were identified at any time point in the women's general practice records, which included time prior to the implementation

of Vision software use. Women with one or more diagnoses of asthma, eczema or hay fever were defined as being in the asthma cohort, eczema cohort or hay fever cohort respectively. For each woman, data on maternal smoking and body mass index over the fertile period, as well as socioeconomic status (quintile of Townsend deprivation index) were additionally extracted.

4.2.3 Statistical analysis

Using Poisson regression, three separate analyses were carried out to estimate fertility rates in women with diagnoses of asthma, eczema or hay fever and each of these were compared with fertility rates in women without the respective diagnosis. Overall Fertility Rate Ratios (FRR) were calculated, comparing each cohort of women with diagnoses of asthma, eczema or hay fever, with the respective comparison cohort. Using a Lexis expansion[206], an age-cohort model was developed, which allowed women to contribute person time to successive 5-year age bands as they got older through the study. Using this expansion, age-specific FRRs were calculated for all 5-year age bands, comparing each cohort of women with diagnoses of asthma, eczema or hay fever, with the respective comparison cohort. Since some women had overlap of allergic disease diagnoses, analyses were repeated with cohorts of exposed women with two allergic disease diagnoses (asthma and eczema, asthma and hay fever, eczema and hay fever). To address this as an issue of specificity of diagnosis, the analyses were also repeated after excluding women with more than one diagnosed allergic disease.

In multivariate Poisson regression analyses, potential confounding by maternal smoking status, body mass index and socioeconomic status was explored. Since women in this analysis may have had more than one child during the potentially fertile period, clustering by woman[209] was accounted for using the robust standard error option. We also assessed the potential effect of clustering by general practice. Missing values for covariates were fitted as a separate category and all models were re-fitted using women with complete data. To best approximate total family size, the analyses were restricted to women with complete records from the beginning of the potentially fertile period (age 15 years) and the FRR for each allergic disease cohort was re-calculated in relation to its comparison cohort.

4.3 Results

4.3.1 Calculation and validation of fertility rates in THIN

From the population of 1,059,246 women, 949,260 women contributed potentially fertile general practice data between 15 and 44 years of age. In this whole potentially fertile THIN cohort, the 949,260 women had 210,481 live births over 5,295,546 person-years, resulting in an overall fertility rate of 39.7 live births per 1,000 person years from 1988 to 2004. This was markedly lower than the mean GFR over the period of 1995 to 2005 from the Office of National Statistics, which was 57.8 live births per 1,000 person years. When the cohort was restricted to 491,516 women with potentially fertile data after the implementation of Vision software use in practice, an overall fertility rate of 52.4 live births per 1,000 person-years was derived from 91,147 live children born over a total of 1,740,266 fertile person-years

from 1994 to 2004. A comparison of overall and age-specific fertility rates from national data, the whole potentially fertile THIN cohort and the Vision software potentially fertile THIN cohort is shown in Figure 4.2. The overall fertility rate for the Vision software cohort was still lower than the national GFR, however, it was more comparable than that of the whole THIN cohort, and was similar to that found in a previous population-based study using the GPRD[129].

Although age-specific fertility rates in the whole THIN cohort were also substantially lower than the age-specific GFR values from national data, they showed the same age pattern as national data, indicating that the whole THIN cohort was a representative sample of the general female population of the same age. Age-specific fertility rates from the Vision software THIN cohort were again higher than those for the whole cohort and closer to the national age-specific GFR values, however, they showed a shift towards older age groups, indicating that we had captured a cohort of women having children at a slightly later age compared with women in the general population. Figure 4.3 shows the distribution of age-specific fertility rates across levels of area level deprivation. Compared with women in areas of higher deprivation, women in areas of lower deprivation have lower fertility rates at younger ages and higher fertility rates at older ages, which is consistent with the age shift in fertility found in women with socioeconomic or educational advantage in national data sources.

Since the fertility rates in the Vision software THIN cohort were more representative of national data than those in the whole THIN cohort, the study population for analyses of fertility in women with allergic disease was restricted to the Vision software cohort of 491,516 women.

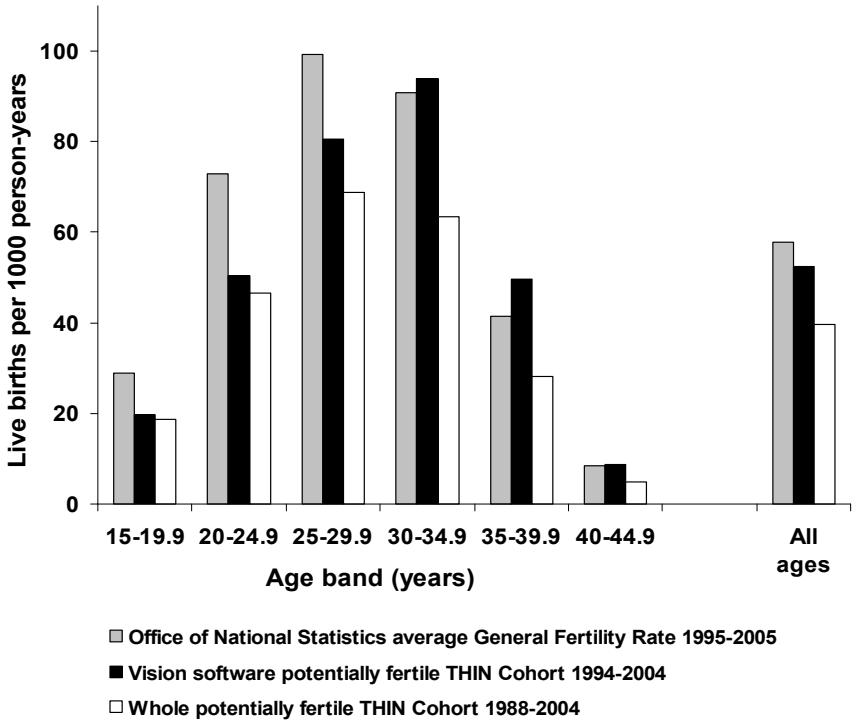

Figure 4.2 Comparison of fertility rates in THIN with the national General Fertility Rate

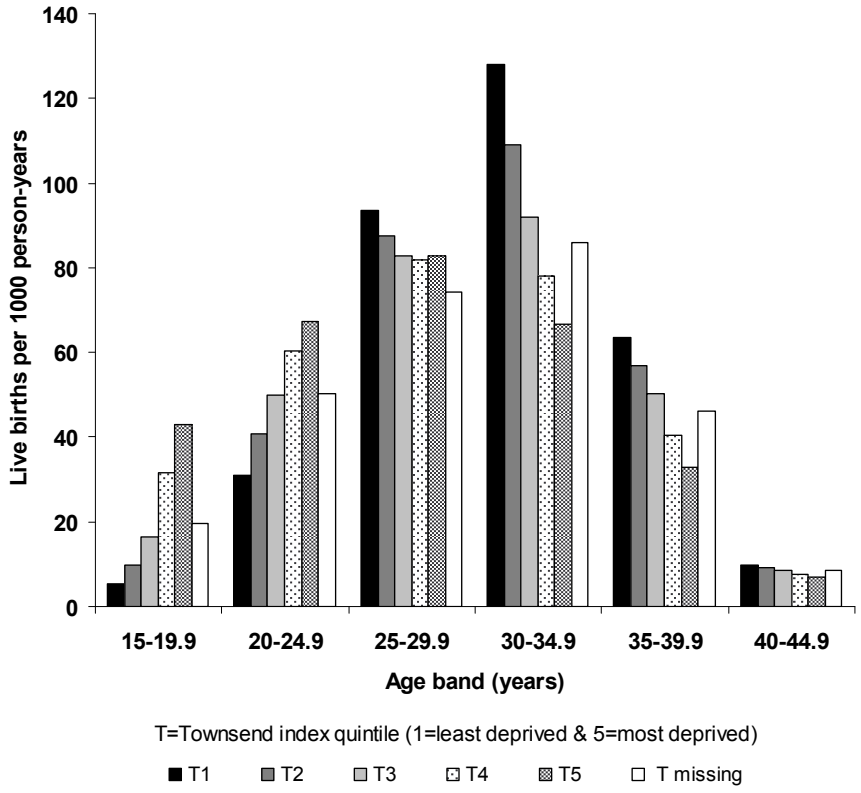

Figure 4.3 Fertility rates in the Vision software potentially fertile THIN cohort by material deprivation level

4.3.2 Study population

In the cohort of 491,516 women with potentially fertile data after Vision software was used in practice, 61,528 (13%) had diagnosed asthma, 68,764 (14%) had diagnosed eczema and 56,914 (12%) had diagnosed hay fever. Some women (6%) had two of these diagnoses and only a small proportion (1%) had all three diagnoses (Figure 4.4).

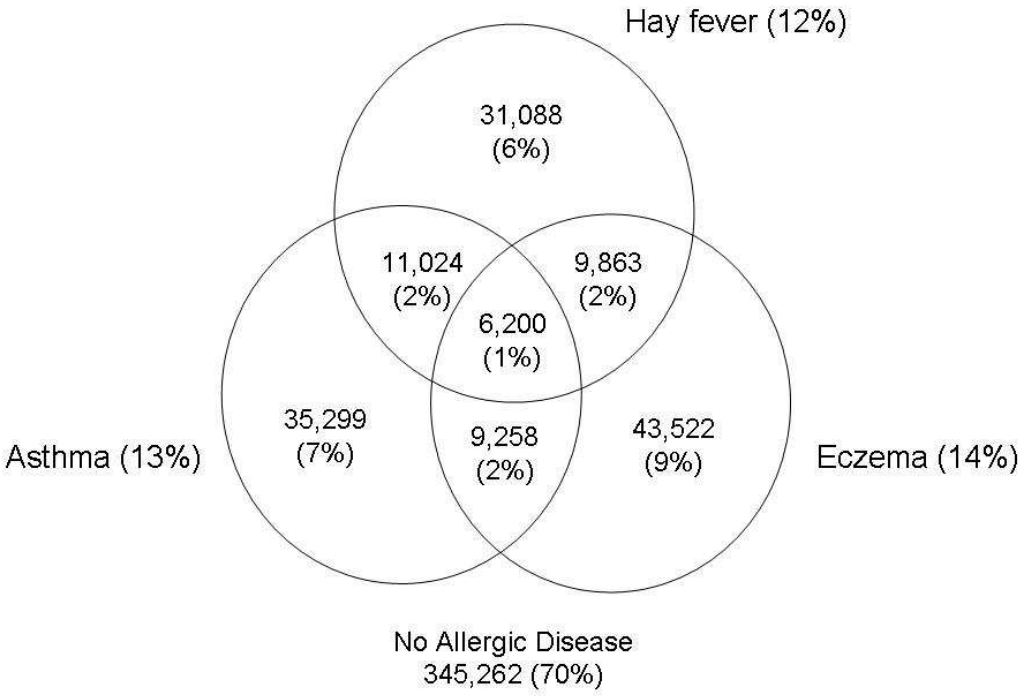

Figure 4.4 Venn diagram of women with asthma, eczema and hay fever diagnoses in the general population cohort, 1994-2004; Proportions are of total potentially fertile population (N=491,516)

The distribution of women in the whole cohort across categories of smoking status, BMI, and quintiles of the Townsend deprivation index are shown in Table 4.1. Thirty percent of women were current smokers and 26% were either overweight or obese. The distribution of Townsend index quintile (available for 54% of the population) was skewed towards the least deprived quintile. The covariates presented in Table 4.1 for the whole cohort showed almost identical distributions to those in the three comparison cohorts of 429, 735 women with no asthma (Table 4.2), 422,673 women with no eczema (Table 4.5) and 433,341 women with no hay fever (Table 4.8), indicating that the comparison population for each of the three allergic disease analyses was representative of the whole population. Study follow-

up time of potentially fertile years for women in the whole population was 3.1 years Inter Quartile Range (IQR) 1.8-4.9, which was slightly shorter than that of women with asthma (3.3 years IQR 2.1-5.1), eczema (3.8 years IQR 2.3-5.8) or hay fever (3.7 years IQR 2.3-5.6).

Table 4.1 Characteristics of whole potentially fertile cohort

Covariate	Whole cohort (n=491,516)	
	n	*(%)*
Smoking status		
non-smoker	203,273	*(41.4)*
ex-smoker	20,878	*(4.2)*
current smoker	149,675	*(30.5)*
missing	117,690	*(23.9)*
Body mass index (kg/m^2)		
underweight(<18.5)	16,576	*(3.4)*
normal(18.5-24.9)	216,750	*(44.1)*
overweight(25-29.9)	80,187	*(16.3)*
obese(≥30)	47,254	*(9.6)*
missing	130,749	*(26.6)*
Townsend index quintle		
1 (least deprivation)	67,936	*(13.8)*
2	53,901	*(11.0)*
3	56,172	*(11.4)*
4	50,127	*(10.2)*
5 (most deprivation)	39,721	*(8.1)*
missing	223,659	*(45.5)*

4.3.3 Fertility rates in women with asthma

When compared with women without diagnosed asthma, women with diagnosed asthma were more likely to be current smokers and to have a higher body mass index

(Table 4.2). However, it is important to note that women without asthma were less likely to have their smoking status and body mass index recorded. The distribution across Townsend index quintiles was similar in women with and without asthma.

Table 4.2 Characteristics of women with and without asthma

Covariate	Asthma cohort (n=61,781)		Comparison cohort (n=429,735)	
	n	*(%)*	n	*(%)*
Smoking status				
non-smoker	27,542	*(44.6)*	175,731	*(40.9)*
ex-smoker	3,110	*(5.0)*	17,768	*(4.1)*
current smoker	21,879	*(35.4)*	127,796	*(29.7)*
missing	9,250	*(15.0)*	108,440	*(25.2)*
Body mass index (kg/m^2)				
underweight(<18.5)	1,972	*(3.2)*	14,604	*(3.4)*
normal(18.5-24.9)	25,723	*(41.6)*	191,027	*(44.5)*
overweight(25-29.9)	11,210	*(18.1)*	68,977	*(16.1)*
obese(≥30)	8,360	*(13.5)*	38,894	*(9.1)*
missing	14,516	*(23.5)*	116,233	*(27.0)*
Townsend index quintle				
1 (least deprivation)	8,616	*(13.9)*	59,320	*(13.8)*
2	6,906	*(11.2)*	46,995	*(10.9)*
3	7,342	*(11.9)*	48,830	*(11.4)*
4	6,735	*(10.9)*	43,392	*(10.1)*
5 (most deprivation)	5,206	*(8.4)*	34,515	*(8.0)*
missing	26,976	*(43.7)*	196,683	*(45.8)*

Women with asthma had 12,344 live births over a total of 232,768 fertile person-years, whereas women without asthma had 78,803 live births over a total of 1,507,497 person-years. This equated to fertility rates of 53.0 and 52.3 live births per 1,000 person-years in women with and without asthma, respectively. The crude fertility rate ratio (FRR) for women with asthma compared to women without asthma was 1.01, 95% Confidence Interval (CI) 1.00-1.04 (Table 4.3, Figure 4.5).

Crude age-specific fertility rate ratios showed that differences in fertility rates between the two cohorts varied with women's age (Table 4.3, Figure 4.5) such that women with asthma tended to have slightly higher fertility rates when younger (e.g. The FRR for age band 15-19.9 years was 1.08, 95%CI 1.01-1.16) and lower fertility rates when older (e.g. The FRR for age band 40-44.9 years was 0.86, 95%CI 0.75-0.99), compared with women without asthma. These differences were not seen when comparing fertility rates in women with asthma who were between 30 and 40 years of age with women of the same age without asthma (e.g. The FRR for age band 30-34.9 years was 1.02, 95%CI 0.99-1.06).

Table 4.3 Overall and age-specific fertility rates and unadjusted fertility rate ratios in women with asthma compared with women without asthma

	Asthma Cohort (n=61,781)			Comparison Cohort (n=429,735)			
Fertile age band (years)	Number of live births	Fertile person-time (1000 p-y*)	Fertility Rate$^{\alpha}$ (95% CI**)	Number of live births	Fertile person-time (1000 p-y*)	Fertility Rate$^{\alpha}$ (95% CI**)	Unadjusted Fertility Rate Ratio (95%CI)
15-19.9	1,066	50	21.1 (19.9-22.4)	4,060	208	19.5 (18.9-20.1)	1.08 (1.01-1.16)
20-24.9	2,471	43	57.8 (55.6-60.1)	11,514	234	49.1 (48.2-50.0)	1.18 (1.13-1.23)
25-29.9	3,483	39	89.3 (86.4-92.3)	21,480	271	79.4 (78.3-80.5)	1.12 (1.09-1.17)
30-34.9	3,479	36	95.8 (92.7-99.1)	26,582	284	93.7 (92.6-94.9)	1.02 (0.99-1.06)
35-39.9	1,608	33	49.0 (46.7-51.5)	12,996	262	49.6 (48.8-50.5)	0.99 (0.94-1.04)
40-44.9	237	31	7.5 (6.6-8.6)	2,171	249	8.7 (8.4-9.1)	0.86 (0.75-0.99)
All ages	12,344	233	53.0 (52.1-54.0)	78,803	1,507	52.3 (51.9-52.6)	1.01 (1.00-1.04)

**person-years, **confidence interval, $^{\alpha}$ per 1000 person-years*

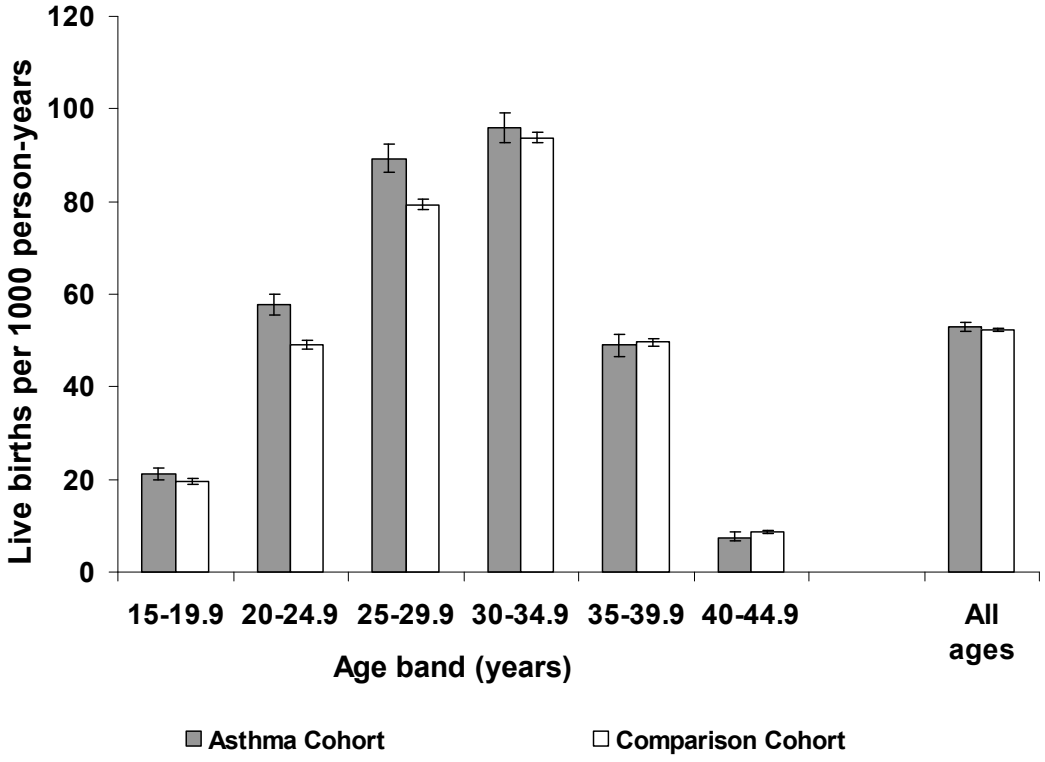

Figure 4.5 Overall and age-specific fertility rates (95% confidence intervals) in women with and without asthma

After adjusting the fertility rate ratios for smoking status, body mass index and Townsend index quintile (Table 4.4), the age-specific fertility rate ratios showed much less variation and were all similar to the adjusted FRR for all ages, indicating that there was no substantial age variation in relative fertility between the two groups. Fertility rate ratios for each age band were close to 1.00 and 95% confidence intervals indicated that differences in most age-specific fertility rates between women with and without asthma were not statistically significant at the 5% level. Women with asthma between 20 to 29.9 years of age, however, had a small statistically significant increase in fertility rates of approximately 6% compared to women without asthma. Overall, the FRR was 1.02, 95%CI 1.00-1.04 after adjusting

for age, smoking status, body mass index and Townsend index quintile. This was only marginally higher than the crude FRR.

Table 4.4 Overall and age-specific adjusted fertility rate ratios comparing women with asthma with women without asthma

Fertile age band (years)	Adjusted Fertility Rate Ratio*** (95%CI)
15-19.9	0.96 (0.89-1.03)
20-24.9	1.07 (1.02-1.12)
25-29.9	1.06 (1.02-1.09)
30-34.9	1.01 (0.97-1.04)
35-39.9	0.99 (0.94-1.05)
40-44.9	0.90 (0.78-1.03)
All ages	1.02 (1.00-1.04)

****Adjusted for body mass index, smoking status, Townsend index quintile. FRR for all ages additionally adjusted for age band*

4.3.4 Fertility rates in women with eczema

Women with diagnosed eczema were more likely to be current smokers compared with women without eczema and were also slightly more likely to be overweight, however, they had a similar distribution across Townsend index quintiles (Table 4.5). As in the asthma analysis, it is important to note that women without eczema were less likely to have their smoking status and body mass index recorded.

Table 4.5 Characteristics of women with and without eczema

Covariate	Eczema cohort (n=68,843)		Comparison cohort (n=422,673)	
	n	*(%)*	n	*(%)*
Smoking status				
non-smoker	31,329	*(45.5)*	171,944	*(40.7)*
ex-smoker	2,963	*(4.3)*	17,915	*(4.2)*
current smoker	23,385	*(34.0)*	126,290	*(29.9)*
missing	11,166	*(16.2)*	106,524	*(25.2)*
Body mass index (kg/m^2)				
underweight(<18.5)	2,278	*(3.3)*	14,298	*(3.4)*
normal(18.5-24.9)	30,973	*(45.0)*	185,777	*(44.0)*
overweight(25-29.9)	12,198	*(17.7)*	67,989	*(16.1)*
obese(≥30)	7,412	*(10.8)*	39,842	*(9.4)*
missing	15,982	*(23.2)*	114,767	*(27.2)*
Townsend index quintle				
1 (least deprivation)	10,039	*(14.6)*	57,897	*(13.7)*
2	7,820	*(11.4)*	46,081	*(10.9)*
3	7,997	*(11.6)*	48,175	*(11.4)*
4	7,140	*(10.4)*	42,987	*(10.2)*
5 (most deprivation)	5,178	*(7.5)*	34,543	*(8.2)*
missing	30,669	*(44.5)*	192,990	*(45.7)*

Women with eczema had 16,973 live births over a total of 285,566 person-years, whereas women without eczema had 74,174 live births over a total of 1,454,699 person-years. The overall fertility rate in women with eczema was considerably higher than that in women without eczema (59.4 and 51.0 live births per 1,000 person-years in women with and without eczema, respectively). This resulted in a crude fertility rate ratio (FRR) for women with eczema compared to women without eczema of 1.17, 95%CI 1.15-1.19 (Table 4.6, Figure 4.6).

Crude age-specific fertility rates were higher for women with eczema than for women without eczema for all age bands, with the exception of women in the youngest age band (FRR for age band 15-19.9 years was 1.00, 95%CI 0.94-1.08).

Although women between 25 and 29.9 years of age with eczema had the highest relative fertility (27% higher) compared with women without eczema, FRR 95% confidence intervals overlapped for all age bands from 20 years and above (Table 4.6).

Table 4.6 Overall and age-specific fertility rates and unadjusted fertility rate ratios in women with eczema compared with women without eczema

Fertile age band (years)	Eczema Cohort (n=68,843)			Comparison Cohort (n=422,673)			Unadjusted Fertility Rate Ratio (95%CI)
	Number of live births	Fertile person-time (1000 p-y*)	Fertility Rate$^{\alpha}$ (95% CI**)	Number of live births	Fertile person-time (1000 p-y*)	Fertility Rate$^{\alpha}$ (95% CI**)	
15-19.9	1,059	53	19.9 (18.7-21.1)	4,067	205	19.8 (19.2-20.4)	1.00 (0.94-1.08)
20-24.9	2,827	48	59.2 (57.1-61.5)	11,158	230	48.6 (47.7-49.5)	1.22 (1.17-1.27)
25-29.9	4,887	50	98.3 (95.6-101.1)	20,076	260	77.3 (76.2-78.3)	1.27 (1.24-1.31)
30-34.9	5,351	49	109.2 (106.3-112.2)	24,710	271	91.2 (90.1-92.3)	1.20 (1.17-1.23)
35-39.9	2,441	44	56.0 (53.8-58.3)	12,163	251	48.4 (47.6-49.3)	1.16 (1.11-1.21)
40-44.9	408	42	9.6 (8.8-10.6)	2,000	238	8.4 (8.1-8.8)	1.15 (1.03-1.28)
All ages	16,973	286	59.4 (58.5-60.3)	74,174	1,455	51.0 (50.6-51.4)	1.17 (1.15-1.19)

**person-years, **confidence interval, $^{\alpha}$ per 1000 person-years*

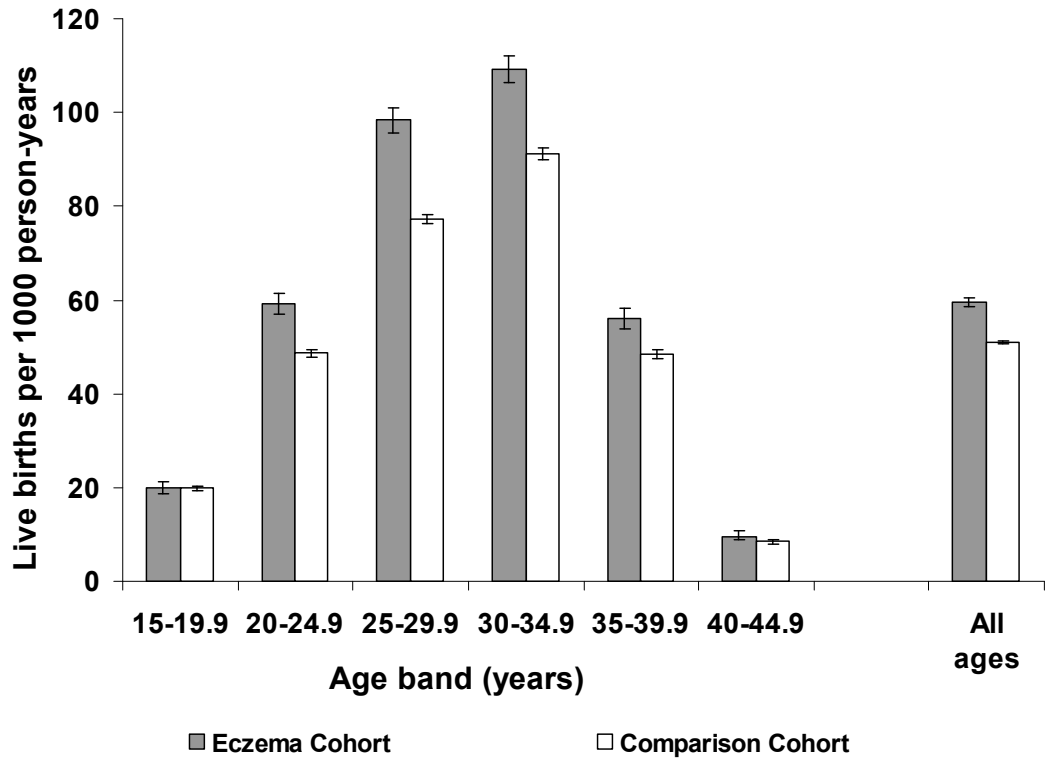

Figure 4.6 Overall and age-specific fertility rates (95% confidence intervals) in women with and without eczema

After adjusting our fertility rate ratios for smoking status, body mass index and Townsend index quintile (Table 4.7), there was only a modest reduction in all FRRs, however, they still indicated higher fertility rates of 15-22% in women with eczema compared with women without eczema, and the relative increase in fertility rate was similar across all but the lowest age band. The overall FRR adjusted for age, smoking status, body mass index and Townsend index quintile (1.15, 95%CI 1.13-1.17), was almost identical to the crude overall FRR.

Table 4.7 Overall and age-specific adjusted fertility rate ratios comparing women with eczema with women without eczema

Fertile age band (years)	Adjusted Fertility Rate Ratio*** (95%CI)
15-19.9	0.96 (0.90-1.03)
20-24.9	1.15 (1.10-1.20)
25-29.9	1.22 (1.18-1.25)
30-34.9	1.17 (1.14-1.20)
35-39.9	1.15 (1.10-1.20)
40-44.9	1.16 (1.04-1.29)
All ages	1.15 (1.13-1.17)

****Adjusted for body mass index, smoking, socioeconomic status (Townsend index). FRR for all ages additionally adjusted for age band*

4.3.5 Fertility rates in women with hay fever

The proportion of current smokers was similar in women with and without diagnosed hay fever as were the proportions in different categories of body mass index and Townsend index quintile (Table 4.8). Women with hay fever had a similar amount of missing data for smoking status and body mass index compared to women with

asthma and eczema, which was lower than the amount of missing data on these covariates for women without hay fever diagnosed.

Table 4.8 Characteristics of women with and without hay fever

Covariate	Hayfever cohort (n=58,175)		Comparison cohort (n=433,341)	
	n	*(%)*	n	*(%)*
Smoking status				
non-smoker	29,331	*(50.4)*	173,942	*(40.1)*
ex-smoker	2,679	*(4.6)*	18,199	*(4.2)*
current smoker	16,732	*(28.8)*	132,943	*(30.7)*
missing	9,433	*(16.2)*	108,257	*(25.0)*
Body mass index (kg/m^2)				
underweight(<18.5)	1,911	*(3.3)*	14,665	*(3.4)*
normal(18.5-24.9)	26,599	*(45.7)*	190,151	*(43.9)*
overweight(25-29.9)	10,439	*(17.9)*	69,748	*(16.1)*
obese(≥30)	6,383	*(11.0)*	40,871	*(9.4)*
missing	12,843	*(22.1)*	117,906	*(27.2)*
Townsend index quintle				
1 (least deprivation)	8,922	*(15.3)*	59,014	*(13.6)*
2	6,711	*(11.5)*	47,190	*(10.9)*
3	6,733	*(11.6)*	49,439	*(11.4)*
4	5,626	*(9.7)*	44,501	*(10.3)*
5 (most deprivation)	4,266	*(7.3)*	35,455	*(8.2)*
missing	25,917	*(44.6)*	197,742	*(45.6)*

Women with hay fever had 13,685 live births over a total of 237,248 person-years, whereas women without hay fever had 77,462 live births over a total of 1,503,018 person-years. This equated to fertility rates of 57.7 and 51.5 live births per 1,000 person-years in women with and without hay fever, respectively. The crude fertility rate was 12% higher in women with hay fever compared to women without hay fever (FRR 1.12, 95%CI 1.10-1.14) (Table 4.9, Figure 4.7).

Crude age-specific FRRs for most age bands also showed a relatively higher fertility rate in women with hay fever compared to women without hay fever, at a 5% statistically significant level (Table 4.9, Figure 4.7). The pattern of age-specific fertility rate ratios in women with hay fever was similar to that in the eczema analysis, showing a comparable relative increase in each age band compared to women without hay fever, with the exception of the youngest women in the 15-19.9 year age band who had a similar fertility rate to women of the same age without hay fever.

Table 4.9 Overall and age-specific fertility rates and unadjusted fertility rate ratios in women with hay fever compared with women without hay fever

	Hay fever Cohort (n=58,175)			Comparison Cohort (n=433,341)			
Fertile age band (years)	Number of live births	Fertile person-time (1000 p-y*)	Fertility Rate$^{\alpha}$ (95% CI**)	Number of live births	Fertile person-time (1000 p-y*)	Fertility Rate$^{\alpha}$ (95% CI**)	Unadjusted Fertility Rate Ratio*** (95%CI)
15-19.9	843	44	19.3 (18.1-20.7)	4,283	215	19.9 (19.3-20.5)	0.97 (0.90-1.05)
20-24.9	2,320	42	55.3 (53.1-57.6)	11,665	235	49.6 (48.7-50.5)	1.12 (1.07-1.17)
25-29.9	3,969	43	91.9 (89.1-94.8)	20,994	266	78.8 (77.8-79.9)	1.17 (1.13-1.21)
30-34.9	4,269	41	105.0 (101.9-108.2)	25,792	279	92.4 (91.2-93.5)	1.14 (1.10-1.17)
35-39.9	1,963	35	56.2 (53.7-58.7)	12,641	260	48.6 (47.8-49.5)	1.16 (1.10-1.21)
40-44.9	321	33	9.7 (8.7-10.9)	2,087	247	8.4 (8.1-8.8)	1.16 (1.03-1.31)
All ages	13,685	237	57.7 (56.7-58.7)	77,462	1,503	51.5 (51.2-51.9)	1.12 (1.10-1.14)

**person-years, **confidence interval, $^{\alpha}$ per 1000 person-years*

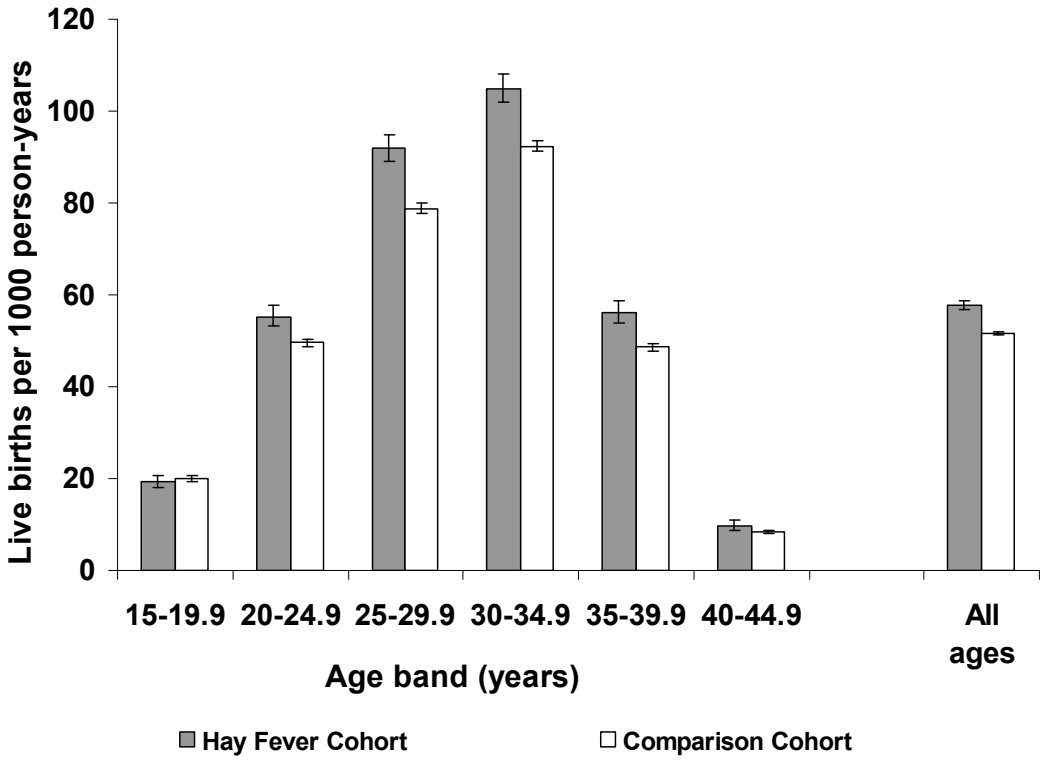

Figure 4.7 Overall and age-specific fertility rates (95% confidence intervals) in women with and without hay fever

Adjusted fertility rate ratios for smoking status, body mass index and Townsend index quintile (Table 4.10), were reduced in all age groups compared with the crude estimates, however they still indicated higher fertility rates of 8-12% in women with hay fever over 20 years of age compared to women without hay fever. The adjusted FRR for women under 20 years of age indicated that these women with hay fever had a similar fertility rate to women without hay fever. The overall FRR adjusted for age, smoking status, body mass index and Townsend index quintile was 1.08, 95%CI 1.06-1.10.

Table 4.10 Overall and age-specific adjusted fertility rate ratios for women with hay fever compared with women without hay fever

Fertile age band (years)	Adjusted Fertility Rate Ratio*** (95%CI)
15-19.9	0.95 (0.88-1.02)
20-24.9	1.09 (1.04-1.14)
25-29.9	1.11 (1.07-1.15)
30-34.9	1.08 (1.05-1.12)
35-39.9	1.11 (1.06-1.17)
40-44.9	1.12 (1.00-1.27)
All ages	1.08 (1.06-1.10)

****Adjusted for body mass index, smoking, socioeconomic status (Townsend index). FRR for all ages additionally adjusted for age band*

4.3.6 Fertility rates in women with more than one or only one allergic disease diagnosis

When the analysis was repeated using a cohort of women with all three allergic disease diagnoses (6,200 women), there was a 7% increase in fertility rate (FRR=1.07, 95%CI 1.01-1.12), compared with that for women with no allergic disease diagnoses (345,262 women). This small increase in fertility rate compared with women with no diagnoses, was also similar for women with any two allergic disease diagnoses (FRR=1.12, 95%CI, 1.09-1.16 for women with asthma and eczema; FRR=1.05, 95%CI, 1.02-1.09 for women with asthma and hay fever; FRR=1.12, 95%CI, 1.09-1.16 for women with eczema and hay fever). In specificity analyses, after excluding women with more than one allergic disease diagnosis, which represented 7% of the whole population, the adjusted FRRs were similar to

those in the main analyses for women with asthma only (0.98, 95%CI 0.96-1.01), eczema only (1.17, 95%CI 1.14-1.19), and hay fever only (1.09, 95%CI 1.07-1.12).

4.3.7 Full covariate data and age-restricted analyses

The main fertility rate ratio models for each allergic disease were repeated using only 170,528 women who had full covariate data for smoking status, body mass index and Townsend index quintile. Estimates of adjusted FRRs for each allergic disease group were similar to the analyses of the full dataset (FRR=1.02, 95%CI 0.99-1.05 for women with asthma; FRR=1.12, 95%CI 1.09-1.14 for women with eczema; FRR=1.05, 95%CI 1.03-1.08 for women with hay fever).

Models were also restricted to the 100,528 women with data available from the beginning of the fertile period (age 15 years) onwards. The adjusted overall fertility rate ratio for women with asthma observed from the age of 15 years onwards was similar to that in the overall analysis for women with asthma (1.03, 95%CI 0.99-1.07). For women with eczema and hay fever, the FRRs among women observed from the age of 15 years onwards were modestly lower than the FRRs for all women (1.09, 95%CI 1.04-1.13 and 1.02, 95%CI 0.98-1.06 respectively).

4.4 Discussion and Interpretation

4.4.1 Summary of findings

The results of this study provide no evidence to suggest that the fertility rates of women with asthma, eczema or hay fever are lower than that of women in the general population. Indeed there is some evidence that fertility rates in women with eczema and hay fever may be slightly higher than those expected in the general population over the study period. This was generally true across all but the youngest age bands. In this study, individual fertility or clinical infertility was not directly measured in women, and the results, therefore, do not provide etiological information on the biological fecundity or fertility of women with and without allergic disease. The findings of similar fertility rates in women with and without allergic disease do, however, indicate that reduced fertility in women with allergic disease does not explain the increase in allergy in children of low birth order that has been observed on a population level. The study shows that women with allergic disease do not have fewer children than women without allergic disease in the UK population.

4.4.2 Strengths and limitations

Statistical power

Deriving fertility rates from a large general population-based cohort representative of the UK female population and our stratification of these fertility rates by age, has enabled the provision of the first precise estimates of fertility in women with allergic disease that are comparable to national estimates of the General Fertility Rate. The

overall fertility rate of 54.2 live births per 1,000 person-years in the THIN cohort was similar to the average national general fertility rate of 57.8 over the same calendar period as the study (1995 to 2005) and the age-specific rates were also similar to those from national statistics[210]. Compared to national age-specific fertility rates, however, women in this study population tended to have babies slightly later, when they were over 30 years of age. This age shift in fertility rates is found across increasing socioeconomic and educational gradients[207,208] and the distribution of the population across quintiles of Townsend index did indicate that this population had a higher representation of women in less deprived areas. Nevertheless, the comparability of these data to an external source suggests the method developed for extracting births and linking children to their mothers captured nearly all births and is thus a valid method of determining incidence rates of live births in this population. Although the overall fertility rates and FRRs contain a small over-representation of older women compared with national data, age-specific estimates have also been presented, which were generally similar to the overall age-adjusted FRRs.

Validity of exposure and outcome data

The current national prevalence of allergic disease is not available specifically for women of childbearing age, however, the population prevalence figures in the THIN data were similar to national estimates for men and women between age 16 and 44 years (14% diagnosed asthma, 19% diagnosed hay fever, 16% diagnosed eczema, 8% with 2 of these diagnoses and 2% with all three diagnoses)[211], indicating the completeness of THIN records for these conditions. Although, THIN is a relatively new general practice database, validation studies in the GPRD, from which over half

of THIN general practices originate, have indicated that recording of births and major diagnoses, including respiratory conditions, are accurate and complete[133,137,138], and I do not anticipate any reason for significant differential recording of births between women with and without allergic disease. Due to the nature of general practice registration, however, only a relatively short follow-up time was captured in each woman's entire reproductive period, and data were not available on total family size or attained parity. This was addressed with a restricted analysis, using women with data from the start of their fertile period, which showed similar fertility rate ratios to the overall analysis. This indicates that the measure of fertility rates on a population level for women throughout the entire fertile period is a good proxy for family size. The short follow-up period, relative to a woman's entire fertile period, also limited the ability to determine the actual age of onset of a woman's allergic disease; one cannot be sure that the date of diagnosis is close to the first onset of disease or a re-appearance after an inactive disease period. The incidence of new allergic disease[6,212] in women of childbearing age, however, is low relative to childhood onset and loss of allergy is also rare, so most of the women in our study will have prevalent allergy when the diagnosis occurs. Furthermore, the cohort definition of ever having been diagnosed with an allergic disease was best for addressing the question of the birth order effect of allergic disease on a population level, as the objective was not to determine on an individual level whether active allergic disease affects having a child.

Accounting for missing covariate data

A potential limitation of this study is that comprehensive data on ethnicity is not available in THIN because ethnicity is not routinely recorded for patients in general

practice in the UK. Ethnicity is associated with family size, the main difference being that families of white ethnicity are considerably smaller than families of other ethnic groups[213,214]. However, it is unlikely that confounding by ethnicity would have an important effect on these findings as studies of the association of ethnicity with the prevalence of allergic disease diagnosis in the UK have shown inconsistent results[215-219], indicating that there is little evidence for a strong direct association between ethnicity and allergic disease diagnosis in the UK.

It is also recognised that missing data for smoking, BMI and socioeconomic status is a disadvantage of using general practice records, however, this is comparable with the proportion of missing data from non-response in epidemiological cross-sectional surveys and follow-up studies. In this study, these variables did not have important confounding effects, as their distributions were similar between women with and without allergic disease. Furthermore, the generous study power enabled restriction analyses of women with full data, which showed almost identical effect sizes to the overall analysis.

4.4.3 Interpretation in context of other studies

Association of allergy and atopy with family size

Although this is the first study to calculate fertility rates in women with allergic disease, an inverse relationship between atopy and number of offspring has been demonstrated both through raised maternal serum IgE[220], skin prick test sensitivity[203,221] and reported allergic disease[187,202,204]. Studies have not found

associations between the number of previous pregnancies or live births and wheeze or asthma[203,204,221].

Most research has only assessed the cross-sectional relationship between the number of previously born children or pregnancies and women's current atopic or allergic disease status[187,202-204,220]. The largest cross-sectional study, a Danish telephone survey of over 30,000 pregnant women, showed a lower self-reported prevalence of hay fever in women who had previously been pregnant or had a live birth, however, the prevalence of hay fever was very similar between women with 1, 2 or more previous live births[187]. Similar results were found in a general population-based study of women in Italy, where Forastiere reported an inverse trend between number of live births and maternal hay fever, however, individual odds ratios for hay fever in women with 2, 3, 4 or more children, compared to only one child, were not statistically significant and no associations were found between hay fever and number of previous pregnancies[204]. Only one study found that women with any allergic disease were more likely to have more than one child when compared with women with no allergic disease history[222].

Prospective studies have shown mixed results[221,223]. Sunyer found that although women with atopy initially had fewer children there was no difference in the number of children after 8 years of follow-up, indicating that these women may tend to delay having their first child[223], which is partially in keeping with our finding of only young women with allergic disease having a slightly lower relative fertility compared with young women without allergic disease. Harris showed a loss of maternal atopy or hay fever, but not asthma, with each intervening pregnancy over a seven year

period[221]. This study, however, was only in women who had initially had live births, and although the effect was still present after adjusting for maternal age, it did not reach statistical significance at the 5% level. Nevertheless, this proposed successive loss of allergy through each pregnancy[221,224,225], possibly from gestational exchange of cells between mother and foetus[225], rather than a decrease in number of live births in women with allergic disease, is in keeping with the birth order effect.

Different fertility rate in asthma compared with eczema and hay fever?

Reasons for the finding of a possibly increased fertility rate in women with eczema or hay fever but not in women with asthma are unclear. While it is possible that it is a true effect, it may also be due to differential ascertainment of diagnoses via antenatal care. Women attending for antenatal care at their general practitioner will likely have more chance of being diagnosed with a medical condition, particularly milder cases of eczema or hay fever, compared to women not attending for antenatal care who visit the general practitioner less often. There is most probably not such a significant increase in ascertainment of asthma diagnoses through antenatal care compared to regular attendance, since symptoms of asthma are generally more severe and require prescription medication.

An alternative explanation may be a physiological promotion of conception in these women related to a balance towards Th2 cells in allergic disease[188,189]. This theory is supported by evidence that shows monthly cycling of female sex hormones to be closely associated with shifts between Th1 and Th2 cytokine production[226] and fluctuating IgE levels[182], which show sharp premenstrual decreases that may aid implantation. Hormonal changes may also contribute to increased asthma

exacerbations when oestrogen levels are low, although there is limited evidence to support this as an important link[227-229]. A potential beneficial effect on fertility by the Th2 cell phenotype, however, does not aid in explaining why we did not find the same increased fertility rates in women with asthma, although it may be possible that a proportion of women with asthma diagnoses in this study population do not have allergy-related disease. Allergy testing for people diagnosed with asthma is not routinely carried out in general practice, so it was not possible to separate women with and without atopy in the analysis. This division is also not necessarily relevant for this study since the birth order effect of asthma has been found both in studies of atopic disease and all clinically diagnosed disease (which includes both atopic and non-atopic people with asthma). Specifically, the birth order effect of all diagnosed asthma has been found in previous studies using general practice data from the GPRD[135]. Our results will, therefore, be applicable to both groups with atopic and non-atopic asthma.

Fertility rate in young women under 20 years of age

A final important observation in this study was the marginally reduced relative fertility rate in women with eczema or hay fever under 20 years of age in contrast to the relative increase after this age. This may reflect a slightly higher socioeconomic level in this group, as similar fertility rate patterns have been seen across socioeconomic gradients[207,208]. Socioeconomic status has an important effect on fertility rates[207] and although it has been suggested there are socioeconomic differentials in allergic disease, being higher in eczema and hay fever but lower in asthma[15,194,230] compared with people without these conditions, there were not marked differences in Townsend index quintile for women with and without allergic

disease in this study. In fact, while there is evidence to suggest that deprivation is associated with poorer lung function[164], bronchospasm[231], and severe exacerbation of asthma[14,232], there is a lack of consistent evidence that lower socioeconomic status is related to asthma, eczema, hay fever or atopic sensitisation and many studies have found no association, particularly in adults[9,15,193,197,198,231,233,234].

4.4.4 Conclusions

This study provides reassuring evidence to suggest that fertility rates of women with asthma, eczema or hay fever are not lower than those of women in the general population. The estimates of similar or possibly increased fertility rates in the cohorts with allergic disease do not support the proposal that a protective effect of higher birth order on allergic disease development is mediated through women with allergic disease having fewer children.

5 Adverse pregnancy outcomes and obstetric complications in women with asthma

This section describes a cross-sectional study conducted to compare the risks of adverse pregnancy outcomes and obstetric complications in women with asthma with those of women in the general population without asthma. The impact of asthma severity and asthma control on these risks is also assessed. An overview of the current reported risks is given in the introduction, followed by the study methods which include the statistical analysis, the study results, a discussion of the findings in context of previous research, and a conclusion which addresses the clinical importance of the findings.

5.1 Introduction

Since Bahna's 1972 report[41] showing increased risks of obstetric complications in women with asthma, the management of asthma through new treatment medications and optimisation of drug doses has improved considerably. More recent studies of pregnancy have shown mixed results[44,47-49,51,86,88,97,235-245], but have still indicated that risks of pre-eclampsia[44,47-49,241-243], haemorrage[49,240], gestational diabetes[44,47,49,241], perinatal mortality[44,241], and other obstetric complications[47-49,51,240] may be increased in women with asthma, which is alarming since the prevalence estimates of current asthma in women of childbearing age have increased from 3% to 8% over the past thirty years[11]. Thus far, very few studies investigating obstetric complications in women with asthma have adjusted for potential confounding factors or have had the

ability to assess whether risks differ by the degree of both asthma severity and control[88,236,242], and none have had adequate study population size to estimate individual risks of miscarriage, stillbirth, and therapeutic abortion.

Using data on pregnancies from the thesis dataset, this study is a comprehensive analysis of the reproductive experience of women with asthma which aims to estimate the precise magnitude of their risks of obstetric complications and adverse pregnancy outcomes compared with women without asthma. Since asthma symptoms and pharmacological management can change during pregnancy, these effects were examined both before and during pregnancy.

5.2 Methods

5.2.1 Study population and outcome variables

From the initial population of 1,059,246 women, all women with one or more pregnancies with outcomes occurring after the woman's registration in general practice were identified. I examined whether these pregnancies ended in live birth, stillbirth, miscarriage or therapeutic abortion. For pregnancies ending in live births only, haemorrhage (antepartum and postpartum), placental insufficiency, placental abruption, placenta praevia, pre-eclampsia or eclampsia, hypertension, change in blood pressure, diabetes, anaemia, thyroid disorders and depression in pregnancy were examined. I assessed whether women delivered live births by caesarean section or assisted delivery as well as the gestation of the pregnancy. For each child, I

assessed their birth weight, whether they had any malpresentation or specific breech presentation in utero and whether they were delivered breech.

5.2.2 Definition of exposure variables and covariates

Pregnant women were defined as having asthma if they had a medical code for asthma at any time in their general practice record. For women with asthma, all prescriptions for asthma medications and all medical codes for asthma exacerbations during the year before each pregnancy and during the pregnancy were extracted. If a woman had less than a year between the end of one pregnancy and the start of another, only prescriptions and exacerbation codes occurring after the birth of the first child and up to the start of the second pregnancy were used.

Using the prescriptions, women were categorised into different levels of asthma severity in accordance with the British Thoracic Society asthma guidelines[79,80] in both pre-pregnancy and during pregnancy time periods. The three categories of asthma severity were defined as 1) un-medicated asthma (no asthma prescriptions), 2) medicated asthma with at least one prescription of a short acting β-agonist (SABA), and 3) medicated asthma with at least one prescription for an inhaled corticosteroid (ICS) with or without a long acting β-agonist (LABA). An asthma exacerbation was defined as either a code for an exacerbation or a prescription for an oral corticosteroid. Using this definition women were categorised as having good asthma control (no exacerbations) or having poor asthma control (at least one asthma exacerbation) both in pre-pregnancy and during pregnancy time periods. The methods used to categorise women by asthma severity and asthma control, including

reasons for why these definitions were used were previously detailed in section 3.6.2 and section 3.6.3.

For each pregnancy, data on the woman's age at the pregnancy outcome, most recent smoking status and BMI before the pregnancy, as well as socioeconomic status (quintile of Townsend deprivation index), year of birth, multiple pregnancy (twin, triplet, quadruplet), gestation of the pregnancy, and sex of the child, were extracted.

5.2.3 Statistical analysis

The unit of analysis was a pregnancy for the assessment of adverse pregnancy outcomes and for obstetric complications that were specific to the pregnancy or delivery. If a woman had more than one pregnancy in her general practice record during the study period, from January 1, 1988 to November 30, 2004, all of her pregnancies were included in the analysis. The prevalence of each pregnancy outcome was calculated as a proportion of all pregnancies. The prevalence of each obstetric complication was calculated as a proportion of all pregnancies ending in live births. For outcomes that were specific to the child (malpresentation, breech presentation, breech delivery and birth weight) the unit of analysis was a child and the prevalence of each outcome was calculated as a proportion of all liveborn children.

Using logistic regression, odds ratios were estimated for each outcome comparing either pregnancies or children born to women with asthma, with those in women without asthma. To investigate whether there were differences in risks related to

severity or control of asthma, separate odds ratios were also estimated for the pregnancies of women at each level of asthma severity (un-medicated, SABA, ICS/LABA) and asthma control (good=no exacerbations, poor=at least one exacerbation) compared with the pregnancies of women without asthma. These associations were assessed using asthma severity and control in the year before pregnancy. For pregnancies ending in live births, these associations were additionally assessed using asthma severity and control during pregnancy. It was not possible to carry out the same during-pregnancy assessment of stillbirth, miscarriage or therapeutic abortion, because of the much shorter duration of gestation for these outcomes (32 weeks for stillbirth, 10 weeks for miscarriage, 16 weeks for therapeutic abortion) compared with gestation for live births (average of 40 weeks). Furthermore, the interpolation of length of gestation for miscarriage and therapeutic abortions will generally be less precise.

The reference group for all analyses of asthma severity and control was women without asthma, since the objective was to estimate the relative difference in odds of each outcome in women with asthma compared with those in women in the general population. To specifically examine the impact of asthma exacerbations in pregnancy, the analyses were repeated using only women with asthma, comparing odds of outcomes in women with and without exacerbations in pregnancy.

In multivariate logistic regression analyses, all models were adjusted for maternal age, smoking habit and body mass index. I subsequently explored the effects of socioeconomic status (quintile of Townsend index), year of birth, multiple pregnancy (twin, triplet, quadruplet), gestation of the pregnancy, and sex of the child, where

appropriate, retaining in the models only those variables that changed the odds ratios more than 10%. Since more than one pregnancy per woman could be included in this analysis during the study period, the potential effect of clustering by woman[209] was accounted for by using robust standard errors. Missing values for covariates were fitted as a separate category and all models were re-fitted using women with complete data.

5.3 Results

5.3.1 Study population

During the study period, 187,502 women met the selection criteria and had a total of 281,019 pregnancies, with 121,092 women (64%) having one pregnancy, 46,447 women (25%) having two pregnancies and 19,963 women (11%) having 3 or more pregnancies. Of all pregnancies, 207,643 (74%) ended in one or more live births, 35,272 (13%) ended in miscarriage, 37,118 (13%) ended in therapeutic abortion, and 986 (<1%) ended in a stillbirth (Figure 5.1).

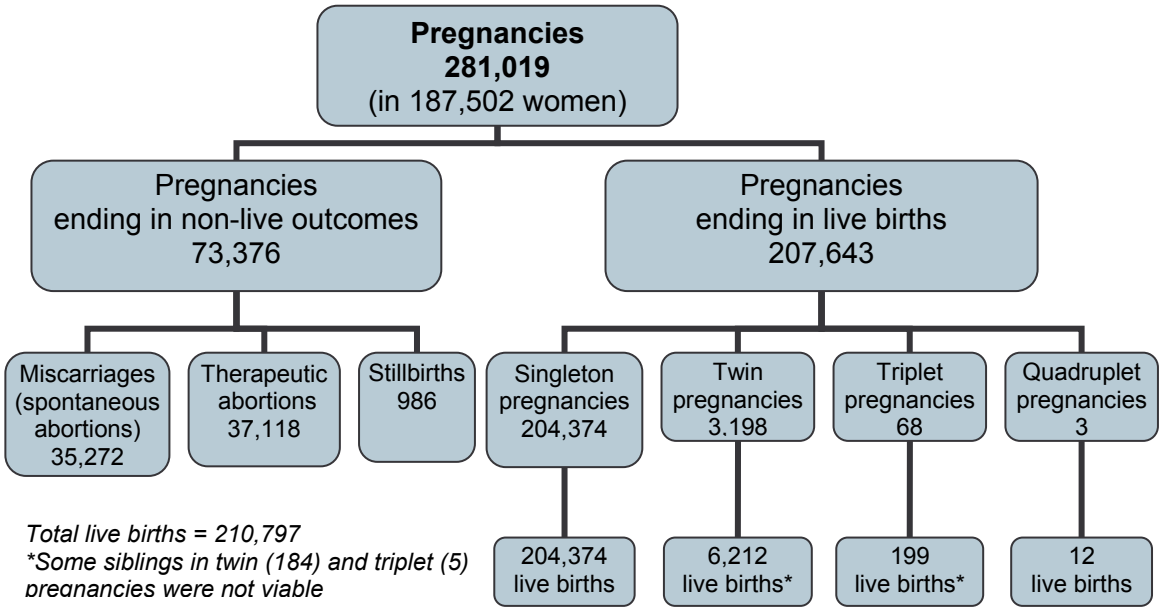

Figure 5.1 Pregnancies in the study population

5.3.2 Characteristics of pregnancies in women with and without asthma

Thirteen percent (37,585) of all pregnancies were to women with diagnosed asthma (Table 5.1). Maternal age was slightly lower in pregnancies of women with asthma compared with those of women without asthma. There was also a larger proportion of pregnancies in women with asthma in later calendar years compared with those in women without asthma. Current smoking, a BMI over 25 Kg/m^2 before pregnancy and higher material deprivation as measured by the Townsend index quintile, were all associated with maternal asthma. The pregnancies of asthmatic mothers, however, were considerably more likely to have data available on smoking status, BMI and Townsend index. Most pregnancies ending in live births were singleton

pregnancies and there were no differences between the proportions of twin, triplet or quadruplet pregnancies in mothers with and without asthma. Half of the liveborn children were female and there was no difference in the sex profile of children with asthmatic mothers and those without.

Table 5.1 Characteristics of pregnant women and their offspring

Covariate	Pregnancies in women with asthma (n=37,585)		Pregnancies in women without asthma (n=243,434)	
	n	*(%)*	n	*(%)*
Maternal age at pregnancy outcome				
Median *(Inter-quartile range)*	28.2 *(23.4-32.5)*		29.3 *(24.9-33.3)*	
Year of pregnancy outcome				
1988-1989	1,027	*(2.7)*	8,512	*(3.5)*
1990-1994	9,071	*(24.1)*	64,103	*(26.3)*
1995-1999	13,268	*(35.3)*	82,757	*(34.0)*
2000-2004	14,219	*(37.8)*	88,062	*(36.2)*
Smoking status before pregnancy				
non-smoker	17,374	*(46.2)*	112,553	*(46.2)*
ex-smoker	2,266	*(6.0)*	11,862	*(4.9)*
current smoker	10,238	*(27.2)*	55,876	*(23.0)*
missing	7,707	*(20.5)*	63,143	*(25.9)*
Body Mass Index (Kg/m^2) before pregnancy				
underweight(<18.5)	1,028	*(2.7)*	6,259	*(2.6)*
normal(18.5-24.9)	13,235	*(35.2)*	84,081	*(34.5)*
overweight(25-29.9)	5,291	*(14.1)*	27,862	*(11.4)*
obese(≥30)	3,155	*(8.4)*	13,257	*(5.4)*
missing	14,876	*(39.6)*	111,975	*(46.0)*
Townsend index quintile				
1 (least deprivation)	5,332	*(14.2)*	36,642	*(15.1)*
2	4,053	*(10.8)*	27,411	*(11.3)*
3	4,395	*(11.7)*	27,339	*(11.2)*
4	4,270	*(11.4)*	23,957	*(9.8)*
5 (most deprivation)	3,548	*(9.4)*	18,674	*(7.7)*
missing	15,987	*(42.5)*	109,411	*(44.9)*
Sex of child*				
female	13,599	*(49.1)*	89,194	*(48.7)*
male	14,123	*(50.9)*	93,881	*(51.3)*
Singleton and multiple pregnancies**				
singleton	26,922	*(98.6)*	177,636	*(98.5)*
twin	388	*(1.4)*	2,631	*(1.5)*
triplet	8	*(<0.1)*	55	*(<0.1)*
quadruplet	0	*(0.0)*	3	*(<0.1)*

**Proportions based on live births (n=210,797)*

***Proportions based only on pregnancies ending in live births (n=207,643)*

5.3.3 Asthma severity and control before and during pregnancy

For the pregnancies of women with diagnosed asthma (37,585), the categorisation of disease severity (based on medication use) in the year before the pregnancy showed that most pregnancies (64%) were to women with un-medicated asthma, 13% were to women on SABA therapy only, and 24% were to women on ICS with or without LABA therapy (Table 5.2). In the same pregnancies, the categorisation of asthma control (based on exacerbations) showed that 7% of pregnancies were to women with poor asthma control (at least one recorded exacerbation) in the year before the pregnancy. The distribution of pregnancies across levels of asthma severity during pregnancy was very similar to that before pregnancy, whereas only 4% of pregnancies were to women with poor asthma control during pregnancy (Table 5.2).

Table 5.2 Asthma severity and control before pregnancy and during pregnancy

Asthma variable	Pregnancies in women with asthma (n=37,585)	
	n	%
Before pregnancy		
Asthma severity		
Unmedicated asthma	23,898	*(63.6)*
SABA medicated asthma**	4,838	*(12.9)*
ICS/LABA medicated asthma**	8,849	*(23.5)*
Asthma control		
No exacerbations	34,990	*(93.1)*
≥1 exacerbation	2,595	*(6.9)*
During pregnancy		
Asthma severity		
Unmedicated asthma	23,730	*(63.1)*
SABA medicated asthma**	5,084	*(13.5)*
ICS/LABA medicated asthma**	8,771	*(23.3)*
Asthma control		
No exacerbations	35,966	*(95.7)*
≥1 exacerbation	1,619	*(4.3)*

***SABA=short acting β-agonist therapy; ICS/LABA=inhaled corticosteroid with or without long acting β-agonist therapy*

It is important to note, however, that asthma severity and control for individual pregnancies changed from before to during pregnancy (Table 5.3 and Table 5.4). Overall, women's asthma severity did not change (i.e. stayed at the same step of asthma severity) for 70%, became worse (i.e. changed to a higher step of asthma severity) for 15% and became better (i.e. changed to a lower step of asthma severity) for 15% of pregnancies (Table 5.3). Of pregnancies in women with no asthma exacerbations before pregnancy, only 3% had exacerbations during pregnancy, while in those with exacerbations before pregnancy, 20% also had exacerbations during pregnancy (Table 5.4).

Table 5.3 Change in asthma severity from before to during pregnancy

Change in asthma severity from before to during pregnancy*	Asthma severity before pregnancy							
	unmedicated (n=23,898)		*SABA* (n=4,838)		*ICS/LABA* (n=8,849)		*All asthma* (n=37,585)	
	n	%	n	%	n	%	n	%
no change	19,233	*(80.5)*	1,762	*(36.4)*	5,605	*(63.3)*	26,600	*(70.8)*
"better"	----------		2,211	*(45.7)*	3,244	*(36.7)*	5,455	*(14.5)*
"worse"	4,665	*(19.5)*	865	*(17.9)*	----------		5,530	*(14.7)*

**no change=same asthma severity category before pregnancy and during pregnancy;*
"better"=moving to a lower asthma severity step during pregnancy compared with before pregnancy;
"worse"=moving to a higher asthma severity step during pregnancy compared with before pregnancy

Table 5.4 Change in asthma control from before to during pregnancy

Change in asthma control from before to during pregnancy*	Asthma control before pregnancy					
	no exacerbations (n=34,990)		*≥1 exacerbations* (n=2,595)		*All asthma* (n=37,585)	
	n	%	n	%	n	%
no change	33,899	*(96.9)*	528	*(20.3)*	34,427	*(91.6)*
"better"	----------		2,067	*(79.7)*	2,067	*(5.5)*
"worse"	1,091	*(3.1)*	----------		1,091	*(2.9)*

**no change=same asthma control category before pregnancy and during pregnancy;*
"better"=moving from ≥1 exacerbations before pregnancy to no exacerbations during pregnancy;
"worse"=moving from no exacerbations before pregnancy to ≥1 exacerbations during pregnancy

Table 5.5 shows the proportion of pregnancies where women had exacerbations in pregnancy, according to whether their asthma severity was "better" or "worse" during pregnancy, compared with before pregnancy. Women who moved to a higher asthma severity step during pregnancy were more likely to have exacerbations in pregnancy, compared with women who stayed at the same severity level or moved to a lower step.

Table 5.5 Exacerbations in pregnancy by changes in asthma severity

Change in asthma severity from before to during pregnancy*		Asthma control during pregnancy					
		no exacerbations (n=35,966)		*≥1 exacerbations* (n=1,619)		*All asthma* (n=37,585)	
		n		n		n	%
no change	*(%)*	25,694	*(96.6)*	906	*(3.4)*	26,600	*(100.0)*
"better"	*(%)*	5,341	*(97.9)*	114	*(2.1)*	5,455	*(100.0)*
"worse"	*(%)*	4,931	*(89.2)*	599	*(10.8)*	5,530	*(100.0)*

**no change=same asthma severity category before pregnancy and during pregnancy;*
"better"=moving to a lower asthma severity step during pregnancy compared with before pregnancy;
"worse"=moving to a higher asthma severity step during pregnancy compared with before pregnancy

In the following sections I examine the associations of asthma in women with live births and adverse pregnancy outcomes (5.3.4), obstetric complications (5.3.5) and child-specific outcomes (5.3.6). As described in the study methods (5.2), the specific asthma exposures are a diagnosis of asthma in the woman's record at any time, asthma severity and control before pregnancy, and asthma severity and control during pregnancy. All results presented are adjusted for maternal age, smoking status, and BMI, since other potential confounders (socioeconomic status, year of pregnancy outcome, multiple pregnancy, gestation of pregnancy, and sex of the child) had no substantial effects on the odds ratios.

5.3.4 Live births and adverse pregnancy outcomes

The proportions of pregnancies ending in any foetal death were similar in pregnancies of women with and without asthma (27% and 26% respectively). However, after adjusting for maternal age, smoking status and BMI, a small increase in odds of miscarriage, and a marginal decrease in odds of therapeutic abortion was found in the pregnancies of women with asthma compared with those without asthma (Table 5.6).

Table 5.6 Pregnancy outcomes in women with and without asthma

Pregnancy outcome	Pregnancies in women with asthma (n=37,585)		Pregnancies in women without asthma (n=243,434)		Adjusted Odds Ratio** (95% CI)
	n	*(%)*	n	*(%)*	
Live birth	27,318	*(72.7)*	180,325	*(74.1)*	0.98 (0.95 - 1.00)
Still birth	138	*(0.4)*	848	*(0.3)*	1.04 (0.86 - 1.24)
Miscarriage*	4,967	*(13.2)*	30,305	*(12.4)*	**1.10 (1.06 - 1.13)**
Therapeutic abortion	5,162	*(13.7)*	31,956	*(13.1)*	**0.95 (0.92 - 0.99)**

**Or other early pregnancy loss (ectopic pregnancy, blighted ovum, molar pregnancy)*
***Comparing pregnancies in women with asthma to pregnancies in women without asthma; adjusted for maternal age, smoking habit and body mass index*
p<0.05 for odds ratios in bold

When pregnancy outcomes were compared across categories of asthma severity and control before pregnancy (Table 5.7), the overall increased odds of miscarriage associated with maternal asthma was restricted to medicated asthma only and the odds ratio were highest for poorly controlled maternal asthma. The overall marginal decreased odds of therapeutic abortion was limited to un-medicated and well controlled maternal asthma, and there was a slight increased odds of pregnancies ending in therapeutic abortion if the mother had been on SABA therapy or if she had exacerbations before the pregnancy. As a result of the increased odds of miscarriage and abortion, there was a small decreased odds of pregnancies ending in live births for women with medicated or less well controlled asthma. When each analysis was restricted firstly to pregnancies in women with full data for covariates and secondly to women with at least one year of in-practice data before conception of the pregnancy, similar effect sizes to the overall analyses were obtained (data not shown).

Table 5.7 Associations of pregnancy outcomes with asthma severity and control before pregnancy

Pregnancy outcome	Pregnancies by asthma severity			Pregnancies by asthma control	
	Unmedicated asthma (n=23,898)	SABA** medicated asthma (n=4,838)	ICS/LABA** medicated asthma (n=8,849)	No exacerbations (n=34,990)	≥1 exacerbation (n=2,595)
	Adjusted Odds Ratios* (95% CI) for pregnancy outcomes				
Live birth	1.03 (1.00-1.06)	**0.87 (0.81-0.93)**	**0.90 (0.86-0.95)**	0.99 (0.97-1.02)	**0.78 (0.72-0.85)**
Still birth	0.98 (0.78-1.23)	1.17 (0.75-1.82)	1.10 (0.79-1.55)	1.02 (0.84-1.23)	1.28 (0.72-2.28)
Miscarriage	1.03 (0.99-1.08)	**1.14 (1.05-1.24)**	**1.24 (1.17-1.32)**	**1.08 (1.05-1.12)**	**1.28 (1.15-1.43)**
Therapeutic abortion	**0.93 (0.89-0.96)**	**1.10 (1.02-1.20)**	0.95 (0.89-1.01)	**0.94 (0.91-0.97)**	**1.16 (1.04-1.30)**

**Reference group is pregnancies in women with no asthma (n=243,434). OR's adjusted for maternal age, smoking habit and body mass index*

***SABA=short acting β-agonist therapy; ICS/LABA=inhaled corticosteroid with or without long acting β-agonist therapy*

p<0.05 for odds ratios in bold

5.3.5 Obstetric complications

For pregnancies ending in live births, the adjusted odds ratio estimates showed little difference in the risks of placental abruption, placenta praevia, pre-eclampsia or eclampsia, hypertension, diabetes, thyroid disorders, and assisted delivery in the pregnancies of women with and without asthma (Table 5.8). The pregnancies of women with asthma had a 20% increased odds of antepartum haemorrhage, a 38% increased odds of postpartum haemorrhage, a 6% increased odds of anaemia, a 52% increased odds of depression, and an 11% increased odds of being delivered by caesarean section, compared with the pregnancies of women without asthma. Most associations found for hypertension, diabetes, anaemia, thyroid disorder and depression in pregnancy were similar when women with a history of these conditions before the pregnancy were excluded (hypertension: Odds Ratio (OR)=1.01, 95%CI 0.88-1.17; diabetes OR=1.11, 95%CI 0.91-1.34; anaemia OR=1.06, 95%CI 1.00-1.12; thyroid disorder OR=0.96, 95%CI 0.70-1.32; depression OR=1.52, 95%CI 1.31-1.78). Placental insufficiency was recorded in only 2 pregnancies of women

without asthma and none occurred in pregnancies to women with asthma. Pregnancies in women with asthma were also more likely to be delivered preterm, but had a similar chance of being delivered post-term. It is important to note that gestation was not available for 80% of pregnancies ending in live births, however, this proportion was similar for women with and without asthma, indicating no disease-related bias in recording of gestational age.

Table 5.8 Obstetric complications in women with and without asthma

Obstetric complication	Pregnancies in women with asthma (n=27,318)		Pregnancies in women without asthma (n=180,325)		Adjusted Odds Ratio** (95% CI)
	n	*(%)*	n	*(%)*	
Antepartum haemorrhage	407	*(1.5)*	2,177	*(1.2)*	**1.20 (1.08 - 1.34)**
Postpartum haemorrhage	287	*(1.1)*	1,367	*(0.8)*	**1.38 (1.21 - 1.57)**
Placental abruption	27	*(0.1)*	163	*(0.1)*	1.08 (0.72 - 1.62)
Placenta praevia	33	*(0.1)*	207	*(0.1)*	1.08 (0.74 - 1.57)
Pre-eclampsia or eclampsia	140	*(0.5)*	804	*(0.4)*	1.12 (0.93 - 1.34)
Hypertension during pregnancy	269	*(1.0)*	1,707	*(0.9)*	1.01 (0.88 - 1.15)
Diabetes during pregnancy	174	*(0.6)*	1,084	*(0.6)*	1.01 (0.85 - 1.21)
Anaemia during pregnancy	1,890	*(6.9)*	11,486	*(6.4)*	**1.06 (1.01 - 1.12)**
Thyroid disorder during pregnancy	105	*(0.4)*	558	*(0.3)*	1.23 (0.99 - 1.53)
Depression during pregnancy	468	*(1.7)*	1,854	*(1.0)*	**1.52 (1.36 - 1.69)**
Caesarean section delivery	4,169	*(15.3)*	25,048	*(13.9)*	**1.11 (1.07 - 1.16)**
Assisted delivery	1,843	*(6.7)*	11,788	*(6.5)*	1.05 (1.00 - 1.11)
Term of gestation at delivery					
term	4,718	*(17.3)*	29,448	*(16.3)*	reference
preterm	939	*(3.4)*	5,200	*(2.9)*	**1.15 (1.06 - 1.24)**
postterm	46	*(0.2)*	242	*(0.1)*	1.19 (0.86 - 1.65)
missing	21,615	*(79.1)*	145,435	*(80.7)*	0.98 (0.95 - 1.02)

***Comparing pregnancies in women with asthma with pregnancies in women without asthma; adjusted for maternal age, smoking habit and body mass index*
p<0.05 for odds ratios in bold

Gestational blood pressure measurements were available for 13,914 pregnancies in women with asthma (51%) and for 88,441 pregnancies in women with out asthma (50%). Blood pressure was only recorded once in about half of these 102,355 pregnancies, while 55,806 pregnancies had 2 or more readings. Table 5.9 shows that the prevalence of hypertensive and hypotensive blood pressure readings in pregnancy as well as changes in mean arterial pressure in pregnancy were similar for women with and without asthma.

Table 5.9 Gestational blood pressure in women with and without asthma

	Pregnancies in women with asthma (n=13,914)		Pregnancies in women without asthma (n=88,441)		Adjusted measure of association (95%CI)
	n	*(%)*	n	*(%)*	
≥1 Hypertensive BP recording in pregnancy*	360	*(2.6)*	2195	*(2.5)*	1.01 (0.89 - 1.14)[α]
≥1 Hypotensive BP recording in pregnancy*	88	*(0.6)*	601	*(0.7)*	0.93 (0.73 - 1.17)[α]
Change in MAP (mmHg) from 1st to 3rd trimester** (median, IQR)	3 (-5 to 10)		2 (-5 to 9)		0.03 (-0.2 to 0.3)[β]

*A hypertensive BP recording is defined as SBP>=140mmHg and DBP>=90mmHg; A hypotensive BP recording is defined as SBP<90mmHg and DBP<60mmHg.

**Mean Artierial Pressure (MAP) = DBP + 1/3(SBP-DBP). Change in MAP based only on pregnancies with a first BP record in the 1st trimester of pregnancy and a last BP record in the 3rd trimester of pregancy (n=25,322)

[α]Odds ratio comparing pregnancies in women with asthma with pregnancies in women without asthma; adjusted for maternal age, smoking habit and body mass index

[β]Linear regression coefficient comparing pregnancies in women with asthma with pregnancies in women without asthma; adjusted for maternal age, smoking habit and body mass index

For live births in women with asthma (27,318) the distribution of pregnancies across categories of maternal asthma severity and control before pregnancy was the same as that for all pregnancies in women with asthma (37,585). The increased odds of antepartum haemorrhage found in the overall analysis, was slightly higher in women taking ICS with or without LABA therapy (Table 5.10). The increased odds of postpartum haemorrhage found in the overall analysis, was restricted to pregnancies of mothers who had less severe and well controlled asthma. The overall increased

odds of anaemia in pregnancy was only statistically significant at the 5% level in pregnancies to women with good asthma control before pregnancy. The odds of depression in pregnancy for women with asthma increased with higher severity and poorer control of asthma, compared with pregnancies in women without asthma.

Although there was no overall increased odds of placenta praevia in pregnancies for women with asthma compared with those without asthma, pregnancies in women with previous exacerbation conferred an increased odds compared with pregnancies in women without asthma. An increased odds of thyroid disorders in pregnancies to women on ICS with or without LABA therapy was also found. The increased caesarean section odds for deliveries in asthmatic mothers was predominantly in deliveries to women with more severe and less well controlled asthma.

The increased risk of preterm delivery for pregnancies in women with asthma was highest in women on SABA therapy and in women with previous asthma exacerbations, however there was no clear trend of increased odds of preterm delivery with increasing asthma severity since women taking ICS with or without LABA therapy did not have an increased odds. It is important to note, however, that pregnancies in women with more severe and less well controlled asthma were more likely to have gestation recorded compared with women without asthma and women with currently untreated asthma were less likely to have gestation recorded.

Table 5.10 Associations of obstetric complications with asthma severity and control before pregnancy

Obstetric complication	Pregnancies by asthma severity			Pregnancies by asthma control	
	Unmedicated asthma (n=17,604)	SABA** medicated asthma (n=3,409)	ICS/LABA** medicated asthma (n=6,305)	No exacerbations (n=25,541)	≥1 exacerbation (n=1,777)
	Adjusted Odds Ratios* (95% CI) for pregnancy complications				
Antepartum haemorrhage	**1.17 (1.02-1.33)**	1.22 (0.93-1.60)	**1.27 (1.04-1.55)**	**1.19 (1.06-1.33)**	1.33 (0.93-1.91)
Postpartum haemorrhage	**1.47 (1.27-1.71)**	**1.56 (1.13-2.16)**	1.01 (0.75-1.35)	**1.42 (1.24-1.62)**	0.83 (0.46-1.52)
Placental abruption	1.00 (0.60-1.67)	1.26 (0.47-3.41)	1.21 (0.56-2.60)	0.99 (0.64-1.52)	2.44 (0.89-6.66)
Placenta praevia	0.85 (0.49-1.45)	2.02 (1.00-4.10)	1.18 (0.61-2.28)	0.92 (0.60-1.39)	**3.24 (1.53-6.88)**
Pre-eclampsia or eclampsia	1.19 (0.96-1.48)	0.96 (0.58-1.60)	1.00 (0.69-1.45)	1.15 (0.96-1.39)	0.58 (0.24-1.41)
Hypertension during pregnancy	1.04 (0.88-1.22)	0.96 (0.68-1.37)	0.95 (0.73-1.23)	1.00 (0.88-1.15)	1.04 (0.66-1.62)
Diabetes during pregnancy	1.08 (0.87-1.33)	0.63 (0.36-1.11)	1.05 (0.79-1.41)	1.00 (0.84-1.18)	1.22 (0.74-2.01)
Anaemia during pregnancy	1.07 (1.00-1.14)	1.04 (0.91-1.19)	1.08 (0.97-1.19)	**1.07 (1.01-1.12)**	1.04 (0.86-1.25)
Thyroid disorder during pregnancy	0.92 (0.69-1.24)	1.19 (0.68-2.07)	**2.03 (1.46-2.81)**	1.19 (0.95-1.48)	1.79 (0.98-3.27)
Depression during pregnancy	**1.47 (1.29-1.68)**	**1.49 (1.15-1.94)**	**1.64 (1.36-1.97)**	**1.47 (1.32-1.64)**	**2.06 (1.53-2.78)**
Caesarean section delivery	**1.09 (1.03-1.14)**	1.03 (0.93-1.14)	**1.24 (1.15-1.33)**	**1.10 (1.06-1.14)**	**1.37 (1.22-1.55)**
Assisted delivery	1.03 (0.97-1.10)	1.14 (1.00-1.31)	1.06 (0.96-1.18)	1.05 (0.99-1.10)	1.13 (0.94-1.36)
Term of gestation at delivery					
preterm	**1.18 (1.07-1.31)**	**1.23 (1.01-1.49)**	1.02 (0.88-1.19)	**1.13 (1.04-1.23)**	**1.30 (1.02-1.66)**
postterm	1.28 (0.86-1.89)	1.35 (0.63-2.89)	0.94 (0.49-1.79)	1.15 (0.82-1.62)	1.69 (0.68-4.15)
missing	**1.08 (1.03-1.13)**	0.94 (0.86-1.03)	**0.82 (0.77-0.88)**	1.00 (0.96-1.04)	**0.84 (0.75-0.95)**

**Reference group is pregnancies in women with no asthma (n=180,325). OR's adjusted for maternal age, smoking habit and body mass index*

***SABA=short acting β-agonist therapy; ICS/LABA =inhaled corticosteroid with or without long acting β-agonist therapy*

p<0.05 for odds ratios in bold

The associations of obstetric complications with different levels of asthma severity and asthma control during pregnancy were very similar to those before pregnancy (Table 5.11). In contrast, there was no increase in odds of placenta praevia in pregnancies of women who experienced asthma exacerbations during pregnancy.

Although there was no increase in odds of pre-eclampsia associated with asthma severity before pregnancy, women on SABA therapy during pregnancy had and increased odds (OR=1.49, 95%CI 1.02-2.18). In women with exacerbations during pregnancy, there was also an increased odds of diabetes in pregnancy (OR=1.79, 95%CI 1.11-2.90) and a higher odds of thyroid disorder in pregnancy (OR=2.00, 95%CI 1.03-3.86).

Table 5.11 Association of obstetric complications with asthma severity and control during pregnancy

Obstetric complication	Pregnancies by asthma severity			Pregnancies by asthma control	
	Unmedicated asthma (n=15,940)	SABA** medicated asthma (n=4,099)	ICS/LABA** medicated asthma (n=7,279)	No exacerbations (n=25,991)	≥1 exacerbation (n=1,327)
	Adjusted Odds Ratios* (95% CI) for pregnancy complications				
Antepartum haemorrhage	1.14 (0.99-1.31)	**1.32 (1.03-1.69)**	**1.26 (1.04-1.52)**	**1.20 (1.07-1.34)**	1.19 (0.77-1.86)
Postpartum haemorrhage	**1.49 (1.27-1.74)**	1.21 (0.88-1.67)	1.23 (0.96-1.58)	**1.41 (1.23-1.60)**	0.90 (0.47-1.74)
Placental abruption	1.17 (0.71-1.94)	1.32 (0.54-3.20)	0.74 (0.31-1.81)	1.09 (0.72-1.66)	0.80 (0.11-5.77)
Placenta praevia	1.22 (0.77-1.94)	0.64 (0.20-2.02)	1.04 (0.53-2.01)	1.04 (0.71-1.51)	1.89 (0.60-5.95)
Pre-eclampsia or eclampsia	1.01 (0.79-1.30)	**1.49 (1.02-2.18)**	1.13 (0.81-1.56)	1.13 (0.93-1.36)	0.95 (0.42-2.13)
Hypertension during pregnancy	0.99 (0.84-1.18)	1.22 (0.92-1.63)	0.91 (0.71-1.17)	1.02 (0.89-1.17)	0.72 (0.38-1.34)
Diabetes during pregnancy	1.02 (0.81-1.28)	0.69 (0.43-1.10)	1.17 (0.89-1.52)	0.97 (0.80-1.16)	**1.79 (1.11-2.90)**
Anaemia during pregnancy	**1.09 (1.02-1.17)**	1.03 (0.91-1.17)	1.02 (0.93-1.13)	**1.07 (1.01-1.13)**	1.03 (0.83-1.27)
Thyroid disorder during pregnancy	1.07 (0.79-1.43)	1.31 (0.81-2.13)	**1.51 (1.07-2.12)**	1.19 (0.94-1.49)	**2.00 (1.03-3.86)**
Depression during pregnancy	**1.39 (1.21-1.60)**	**1.45 (1.13-1.85)**	**1.81 (1.53-2.15)**	**1.49 (1.33-1.66)**	**2.06 (1.46-2.92)**
Caesarean section delivery	1.05 (1.00-1.11)	**1.17 (1.07-1.28)**	**1.22 (1.14-1.31)**	**1.11 (1.06-1.15)**	**1.27 (1.10-1.47)**
Assisted delivery	1.04 (0.97-1.11)	1.12 (0.99-1.27)	1.04 (0.94-1.14)	1.05 (1.00-1.11)	0.98 (0.78-1.23)
Term of gestation at delivery					
preterm	**1.33 (1.21-1.48)**	1.11 (0.92-1.34)	0.87 (0.76-1.01)	**1.13 (1.04-1.23)**	**1.33 (1.01-1.74)**
postterm	1.38 (0.92-2.07)	0.82 (0.34-2.00)	1.09 (0.63-1.89)	1.25 (0.90-1.73)	0.41 (0.06-2.91)
missing	**1.13 (1.08-1.19)**	0.95 (0.87-1.03)	**0.78 (0.73-0.83)**	1.00 (0.96-1.04)	**0.73 (0.64-0.84)**

**Reference group is pregnancies in women with no asthma (n=180,325). OR's adjusted for maternal age, smoking habit and body mass index*

***SABA=short acting β-agonist therapy; ICS/LABA =inhaled corticosteroid with or without long acting β-agonist therapy*

p<0.05 for odds ratios in bold

In the last assessment of obstetric complications, which was restricted to 27,318 pregnancies in women with asthma that ended in live births, there was an increase in odds of diabetes in pregnancy for women with exacerbations compared with women with no exacerbations in pregnancy (Table 5.12).

Table 5.12 Associations of obstetric complications with asthma exacerbations during pregnancy in women with asthma only

Obstetric complication	≥1 exacerbation during pregnancy (n=1,327)
	Adjusted Odds Ratio* (95%CI)
Antepartum haemorrhage	1.00 (0.64-1.58)
Postpartum haemorrhage	0.65 (0.33-1.26)
Placental abruption	0.72 (0.10-5.40)
Placenta praevia	1.68 (0.52-5.42)
Pre-eclampsia or eclampsia	0.86 (0.38-1.95)
Hypertension during pregnancy	0.71 (0.37-1.33)
Diabetes during pregnancy	**1.81 (1.10-2.99)**
Anaemia during pregnancy	0.97 (0.78-1.21)
Thyroid disorder during pregnancy	1.66 (0.83-3.32)
Depression during pregnancy	1.40 (0.98-2.00)
Caesarean section delivery	1.14 (0.98-1.33)
Assisted delivery	0.93 (0.74-1.17)
Term of gestation at delivery	
preterm	1.17 (0.89-1.55)
postterm	0.30 (0.04-2.23)
missing	**0.73 (0.64-0.84)**

**Reference group is pregnancies in women with asthma who have no exacerbations in pregnancy (n=25,991). OR's adjusted for maternal age, smoking habit and body mass index*
p<0.05 for odds ratios in bold

When each obstetric outcome analysis (for asthma, asthma severity and control in pregnancy, asthma severity and control during pregnancy) was restricted firstly to pregnancies in women with full data for covariates and secondly to pregnancies in women with at least one year of in-practice data before conception of the pregnancy, similar effect sizes to the overall analyses were obtained (data not shown).

5.3.6 Outcomes specific to the child

During gestation, 5% of children had inter-uterine malpresentation, however, the risks of overall malpresentation, breech presentation, and subsequent breech delivery were similar for children born to women with asthma compared with those born to women without asthma (Table 5.13). Although birth weight information was only available for 25% of all children, the proportion of children with no information on birth weight was only slightly lower for those born to women with asthma compared with those born to women without asthma. For children with information, there was an 18% increased odds of having a low birth weight if they were born to women with asthma compared with children born to women without asthma.

Table 5.13 Child-specific outcomes in children born to women with and without asthma

Child-specific outcome	Children born to women with asthma (n=27,722)		Children born to women without asthma (n=183,075)		Adjusted Odds Ratio** (95% CI)
	n	*(%)*	n	*(%)*	
malpresentation in utero*	1,395	*(5.1)*	8,982	*(5.0)*	0.99 (0.94 - 1.06)
breech presentation in utero	1,022	*(3.7)*	6,398	*(3.5)*	1.03 (0.96 - 1.10)
breech delivery	268	*(1.0)*	1,635	*(0.9)*	1.09 (0.94 - 1.25)
Birth weight group					
normal	3,748	*(13.7)*	22,555	*(12.5)*	reference
low (<2500g)	446	*(1.6)*	2,302	*(1.3)*	**1.18 (1.05 - 1.32)**
high (>4000g)	495	*(1.8)*	3,299	*(1.8)*	0.91 (0.81 - 1.01)
missing	23,033	*(84.3)*	154,919	*(85.9)*	**0.95 (0.91 - 0.99)**

**Including breech presentation*

***Comparing children born to women with asthma to children born to women without asthma; adjusted for maternal age, smoking habit and body mass index*

p<0.05 for odds ratios in bold

In contrast to the finding of no overall increased risks of malpresentation in utero, breech presentation, or breech delivery for children born to women with asthma, there was an increased odds in children born to women who had been taking ICS with or without LABA in the year before pregnancy, and smaller increased odds in children born to women who had taken SABA therapy, compared with children born to women without asthma (Table 5.14). The increase in odds of low birth weight for children born to women with asthma was highest in those born to women who had taken ICS with or without LABA in the year before pregnancy and there was a reciprocal decrease in odds of high birth weight for children of these women. It is important to note, however, that birth weight was more likely to be recorded for pregnancies in women with severe or poorly controlled asthma in the year before pregnancy compared with pregnancies in women without asthma.

Table 5.14 Association of asthma severity and control before pregnancy, with child-specific outcomes

Child-specific outcome	Pregnancies by asthma severity			Pregnancies by asthma control	
	Unmedicated asthma (n=17,849)	SABA** medicated asthma (n=3,456)	ICS/LABA** medicated asthma (n=6,417)	No exacerbations (n=25,908)	≥1 exacerbation (n=1,814)
	Adjusted Odds Ratios*** (95% CI) for child-specific outcomes				
malpresentation in utero*	**0.88 (0.81-0.95)**	1.15 (1.00-1.33)	**1.21 (1.09-1.34)**	0.98 (0.92-1.04)	1.17 (0.97-1.41)
breech presentation in utero	0.91 (0.83-1.00)	1.13 (0.95-1.35)	**1.25 (1.11-1.41)**	1.01 (0.94-1.09)	1.19 (0.95-1.48)
breech delivery	0.92 (0.77-1.10)	**1.53 (1.12-2.08)**	**1.33 (1.03-1.71)**	1.08 (0.93-1.24)	1.23 (0.78-1.96)
Birth weight group					
low (<2500g)	1.13 (0.97-1.32)	1.20 (0.90-1.60)	**1.25 (1.03-1.53)**	**1.16 (1.02-1.31)**	1.37 (0.98-1.93)
high (>4000g)	0.95 (0.83-1.09)	1.12 (0.88-1.43)	**0.74 (0.61-0.89)**	0.92 (0.82-1.02)	0.81 (0.58-1.13)
missing	1.04 (0.98-1.09)	0.98 (0.88-1.08)	**0.76 (0.71-0.82)**	0.96 (0.92-1.01)	**0.77 (0.67-0.87)**

**Including breech presentation*

***SABA=short acting β-agonist therapy; ICS/LABA =inhaled corticosteroid with or without long acting β-agonist therapy*
****Reference group is children born to women with no asthma (n=183,075). OR's adjusted for maternal age, smoking habit and body mass index*
p<0.05 for odds ratios in bold

The associations of child-specific outcomes with different levels of asthma severity and asthma control during pregnancy were very similar to those before pregnancy (Table 5.15). There was an additional increase in odds of malpresentation in utero and breech delivery in children born to women with asthma exacerbations in pregnancy compared with those born to women without asthma. The increase in odds of low birth weight was higher for children born to women with unmedicated asthma rather than to those whose mothers were taking ICS with or without LABA therapy in pregnancy. There was, however, a large increase in odds of low birth weight (and decrease in odds of high birth weight) in children born to women with exacerbations in pregnancy compared with those born to women without asthma. There was still a bias in data availability for birth weight, with more recording in pregnancies in women with severe or poorly controlled asthma during pregnancy compared to pregnancies in women without asthma.

Table 5.15 Association of asthma severity and control during pregnancy, with child-specific outcomes

Child-specific outcome	Pregnancies by asthma severity			Pregnancies by asthma control	
	Unmedicated asthma (n=16,165)	SABA** medicated asthma (n=4,156)	ICS/LABA** medicated asthma (n=7,401)	No exacerbations (n=26,369)	≥1 exacerbation (n=1,353)
	Adjusted Odds Ratios*** (95% CI) for child-specific outcomes				
malpresentation in utero*	**0.88 (0.82-0.96)**	1.02 (0.88-1.17)	**1.21 (1.09-1.33)**	0.98 (0.92-1.04)	**1.32 (1.06-1.64)**
breech presentation in utero	0.93 (0.85-1.03)	0.96 (0.81-1.15)	**1.25 (1.11-1.40)**	1.01 (0.94-1.09)	1.28 (0.99-1.66)
breech delivery	1.01 (0.84-1.22)	1.08 (0.77-1.51)	1.25 (0.99-1.59)	1.06 (0.92-1.22)	**1.65 (1.06-2.58)**
Birth weight group					
low (<2500g)	**1.25 (1.07-1.46)**	1.04 (0.79-1.38)	1.13 (0.93-1.36)	**1.14 (1.01-1.29)**	**1.64 (1.12-2.39)**
high (>4000g)	1.02 (0.89-1.17)	0.99 (0.77-1.27)	**0.71 (0.59-0.86)**	0.93 (0.84-1.04)	**0.52 (0.32-0.83)**
missing	**1.09 (1.03-1.15)**	0.93 (0.85-1.03)	**0.74 (0.69-0.79)**	0.97 (0.93-1.01)	**0.70 (0.60-0.81)**

**Including breech presentation*

***SABA=short acting β-agonist therapy; ICS/LABA =inhaled corticosteroid with or without long acting β-agonist therapy*
****Reference group is children born to women with no asthma (n=183,075). OR's adjusted for maternal age, smoking habit and body mass index*
p<0.05 for odds ratios in bold

In the last assessment of child-specific outcomes, which was restricted to 27,722 children born to women with asthma, an increase in odds of malpresentation in utero was found for children whose mothers had had exacerbations in pregnancy compared with mothers with none (Table 5.16). Children were also less likely to have a high birth weight, however, children whose mothers had exacerbations in pregnancy were more likely to have birth weight recorded compared with children whose mothers did not have exacerbations in pregnancy.

Table 5.16 Association of asthma exacerbations in pregnancy with child-specific outcomes in women with asthma only

Child-specific outcome	≥1 exacerbation during pregnancy (n=1,353)
	Adjusted Odds Ratio* (95%CI)
Malpresentation in utero**	**1.34 (1.07-1.67)**
Breech presentation in utero	1.25 (0.96-1.63)
Breech delivery	1.55 (0.97-2.46)
Birth weight group	
low (<2500g)	1.42 (0.96-2.10)
high (>4000g)	**0.56 (0.35-0.91)**
missing	**0.72 (0.62-0.84)**

***including breech presentation*

**Reference group is pregnancies in women with asthma who have no exacerbations in pregnancy (n=26,369). OR's adjusted for maternal age, smoking habit and body mass index*

p<0.05 for odds ratios in bold

When each child-specific outcome analysis (for asthma, asthma severity and control in pregnancy, asthma severity and control during pregnancy) was restricted firstly to children born to women with full data for covariates and secondly to children born to women with at least one year of in-practice data before conception of the pregnancy, similar effect sizes to the overall analyses were obtained (data not shown).

5.4 Discussion and Interpretation

5.4.1 Summary of findings

The findings of this study indicate that women with asthma in general have similar risks of reproductive outcomes compared with women without asthma for most of the outcomes studied. Of concern, was a small increased risk of miscarriage, which was higher in women with more severe asthma and exacerbations prior to pregnancy. However, these data provide no evidence for an increased risk of stillbirth in women with asthma, regardless of asthma severity or exacerbations. Other findings include modest increased risks of haemorrhage, depression, caesarean section delivery, preterm birth and low birth weight, and a marginal increased risk of anaemia.

When pregnancies in women with asthma were examined separately it was found that asthma severity, characterised by use of asthma medications, and asthma control, characterised by asthma exacerbations, changed from before pregnancy to during pregnancy. Although asthma severity did not change for most pregnancies, the proportion of pregnancies where asthma severity increased was similar to the proportion where asthma severity decreased. This pattern was similar for changes in exacerbations from before to during pregnancy. Exacerbations during gestation were more likely to occur in pregnancies where women's asthma severity became worse rather than in those who had become better or had no change in severity. I did not assess whether women were prescribed additional asthma medications as a result of exacerbations, because this would require more complex analysis methods in general practice data. It was not possible to determine whether women were reducing their

asthma medication use and resultantly had asthma exacerbations, however, these data do not support this possibility.

The analyses of asthma severity and control before pregnancy showed similar risks of obstetric complications and child-specific outcomes to analyses using asthma severity and control during pregnancy. The increased risk of postpartum haemorrhage, low birth weight and preterm birth were not clearly associated with asthma severity or control, while risks of antepartum haemorrhage, depression and caesarean section delivery increased in women with higher severity and exacerbations, whether before or during pregnancy. Although there was no relative increase of malpresentation and breech presentation of the baby in pregnancies to women with asthma overall, there appeared to be an increased risk in women with more severe asthma and exacerbations before or during pregnancy.

Other isolated increased risks included pre-eclampsia for women on SABA therapy during pregnancy, diabetes in women with asthma exacerbations during pregnancy, placenta praevia for women with exacerbations before pregnancy, and thyroid disorder for women taking ICS with or without LABA therapy before pregnancy, however, in consideration of the large number of outcomes studied, the possibility that some findings may be due to chance cannot be excluded.

5.4.2 Strengths and limitations

Statistical power

This is the largest general population-based study characterising the reproductive experience of women with asthma and the first analysis to quantify the individual risks of stillbirth, miscarriage and therapeutic abortion in one study population. Most previous studies of reproductive risks have excluded multiple pregnancies and pregnancies ending in non-live birth outcomes. In these data, it was additionally possible to investigate the associations with differing asthma severity and acute exacerbations in these women. Although poor asthma control was defined by the occurrence of asthma exacerbations, it is acknowledged that asthma exacerbations may also reflect asthma severity or may result from poor adherence to medication, sub-optimal prescribed treatment, lack of relief from asthma medications or exposure to external triggers. Since asthma severity and exacerbations change during pregnancy, associations of obstetric complications and child-specific outcomes with these measures both before and during pregnancy were investigated. It was not possible to investigate during pregnancy exposures for stillbirth, miscarriage or therapeutic abortion because of the much shorter duration of gestation for these outcomes, compared with gestation for live births.

Validity of exposure and outcome data

The population-based prevalence of currently treated asthma in this study (5%) was similar to both UK[12] and US[11] national figures. Although current figures for all diagnosed asthma in women of child-bearing age are not available in the United

Kingdom, the prevalence of all diagnosed asthma in this study (13%) was similar to US estimates[11].

Previous studies of live births and stillbirths in the General Practice Research Database, from which over half of THIN practices originate, have shown similar prevalence figures to national data[129,133,134]. The proportion of singleton and multiple pregnancies, the sex ratio of liveborn children and the mean maternal age at delivery in this study population are the same as those in national data over the time period of the study[32,33]. The overall stillbirth rate in this study was 4.7 stillbirths per 1,000 births(live births and stillbirths), which is similar to the rate reported by national perinatal mortality surveillance in the UK (5.7 per 1,000 births)[24] and national data from the US (6.4 per 1,000 births)[25].

With regards to therapeutic abortion, the figures in this study are lower than those reported in US (22% of pregnancies)[246] and UK (20% to 23% of pregnancies) [17,208] national data. It is possible that ascertainment of therapeutic abortions is incomplete in this study, although recording should be fairly complete in the general practice setting as therapeutic abortion is a medical procedure.

Miscarriage ascertainment in primary care will also be lower than the true population prevalence, as early miscarriages may not be clinically reported, however our proportion is comparable to US national data (15% of pregnancies)[246] and is the same as that found in the 2001 National Women's Health Study which collected detailed reproductive histories on about 30,000 pregnancies in women in the UK[247]. I do not anticipate any reason for differential recording of live and stillbirths between women

with and without asthma, however I acknowledge the possibility that women with asthma are more likely to have miscarriages or therapeutic abortions recorded, as people with a chronic condition visit the general practitioner more often than those without. Therefore, the odds ratio estimates for miscarriage and therapeutic abortion in this study may be slight overestimates, but not underestimates, of the true risk.

There has not been validation of obstetric complications in THIN. All important medical events should be recorded in the general practice notes since information on hospital admissions is routinely sent to the general practice, however, minor complications that are well controlled through maternity care and routinely recorded information in a woman's maternity record in hospital, may not be transferred to the general practice record. There are few national UK data or international data estimating the prevalence of various obstetric complications and considerable regional and national variations exist. Where available, I have compared the prevalence figures in this study with other data sources.

For bleeding complications during pregnancy, available estimates of postpartum haemorrhage range from 2% to 8% of pregnancies, whereas severe postpartum haemorrhage requiring transfusion occurs in less than 0.1%[20,21,54]. The prevalence of postpartum haemorrhage in the study population (1% of pregnancies), was therefore likely limited to more severe haemorrhage. Placental abruption occurs in 0.4% to 1% of pregnancies and placenta praevia in less than 0.5% of pregnancies[54,248] which are slightly higher than our prevalence of 0.1% for each. The prevalence of antepartum haemorrhage (1.2% of all pregnancies) in the study population was similar to that of 1.6% reported in US data from the same period[21].

Sources from various countries, including the US where prevalence is highest, indicate that hypertension occurs in 1% to 5% of pregnancies while pregnancy-induced hypertension in late gestation may occur in 5 to 10% of pregnancies[21,249,250]. Hypertension is defined as a high blood pressure measurement (SPB≥140 mmHg and DBP≥90), and although almost 3% of our pregnancies had a hypertensive blood pressure recording, a medical diagnosis of hypertension was recorded in only 1% of pregnancies, so it is likely that the latter represent the severe clinically important cases. Pre-eclampsia occurs in 2% to 5% of pregnancies[22,23,54,249,251] while severe pre-eclampsia affects 0.6%[21], and eclampsia affects only 0.03% to 0.2% of pregnancies[20-22,54,251,252]. The prevalence of 0.5% pre-eclampsia or eclampsia is this study indicates that recorded diagnoses again captured the more severe cases of these complications. A large US study of 152,000 pregnancies estimated that the prevalence of hypertension, pre-eclampsia, and eclampsia combined, was 3% of all pregnancies[21], and in comparison with this estimate, it is likely that I had good ascertainment of clinically important cases.

The prevalence of diabetes in pregnancy in this study (0.6%) was similar to national estimates from the UK (0.3% to 0.4%)[253] and slightly higher than Canadian estimates of diabetes causing severe pregnancy complication (0.1%)[20]. I was not able to find current prevalence estimates of diagnosed anaemia in pregnancy. In the study population, anaemia was the most common condition complicating pregnancy (6%). This recording was likely complete since laboratory results of iron status are routinely sent to a woman's general practice and ensuring adequate iron status in pregnancy is a clinical priority because of the adverse effects of low folate on the

foetus. Folic acid supplements are resultantly the most frequently prescribed drugs in pregnancy[82]. Although I was not able to compare the prevalence of diagnosed depression in pregnancy (<2%) with other general practice data, this figure was lower than estimates from studies that have specifically surveyed depression in women during pregnancy[254-258]. These studies report prevalence figures for antenatal depression of 10% or higher and also indicate that clinical monitoring of potential depression in women needs more recognition during pregnancy. Current estimates of thyroid disorder in pregnancy were not available, however, the prevalence of 0.3% in this study was similar to current estimates of hypothyroidism in pregnancy (0.1% to 2% of pregnancies)[259]. Older studies have estimated the prevalence of hyperthyroidism as 0.02% to 3.7% of pregnancies, with an average of 0.2%[260,261].

Delivery by caesarean section has increased considerably over the past 20 years and ranges from 13% to 25% in high income countries including the UK, US, Sweden, France and Denmark[17,21,262,263]. In the UK, estimates of caesarean section as a proportion of all deliveries were 13% in 1989, 16% in 1995 and 19% in 1999 [17,262]. The caesarean section prevalence of 15% in this study over the period of 1988 to 2004 indicates that there was complete recording of this procedure. The prevalence of breech presentation in utero declines with gestational age reaching 3% to 4% at full term[251], which is the same as the prevalence of 3.5% in this study. Very few babies are now delivered in breech position, however, due to the increasing use of caesarean section delivery when breech position persists into labour[264], which is why the prevalence of breech delivery was less than 1% in this study. In the UK, the prevalence of assisted delivery has been estimated to be between 5% and 10%[265], which is similar to the prevalence in this study (6% to 7%).

The proportion of births delivered preterm is between 5% and 7% in high income countries [266-268] and the proportion of babies born with a low birth weight is 7% to 8%[18,269]. Gestational age at delivery and birth weight were only recorded for 20% and 15% of babies in this study, respectively, so I was not able to estimate the population-based prevalence for preterm delivery and low birth weight. For children with these data recorded, the prevalence of preterm delivery was 15% and the prevalence of low birth weight was 8%.

In summary, my comparison with external prevalence figures has shown that recording of mild obstetric complications that are likely well managed in antenatal care, such as mild hypertension, and routinely recorded pregnancy data, such as gestation, may not always be recorded in a woman's general practice notes. Major or more severe complications and medical procedures of delivery, however, are likely well recorded in the general practice notes.

Accounting for missing covariate data

I recognise that there were quite high levels of missing data for smoking, BMI and socioeconomic status and there were differences of approximately 5% in the amount of missing data between pregnancies in women with and without asthma, which is common in studies using general practice data. However, this amount of missing data must be seen in the context of a 100% participation rate achieved through using totally anonymised data, so that I had complete data on 55-75% of women. This level of response and follow-up rate in a primary epidemiological questionnaire study of pregnancy would be seen as high. In the analyses, I ensured that missing

data for covariates were included as a separate category in all analyses. Because of the generous study power, I was also able to restrict analyses to women with full data. While this restricted sample may not have been representative of the general population, similar effect sizes to the overall analyses were found.

It was not possible to adjust for ethnicity since it is not routinely recorded in THIN, however, it is unlikely that this would have an impact on the study findings. Studies in the US have shown that the prevalence of major pregnancy complications, including pre-eclampsia, placental abruption, placenta praevia and haemorrhage, is similar in women of black ethnicity compared with women of white ethnicity[270]. Furthermore, although racial differences between these groups have been found in markers of asthma morbidity during pregnancy, the contribution of socioeconomic differences as an explanation of these differences has not been determined[15,271]. Some studies have found that socioeconomic status in fact does explain most of the racial disparity of asthma during pregnancy[271,272].

5.4.3 Interpretation in context of other studies

Changes in asthma during pregnancy

With few exceptions[235,239], most previous studies have also found that for some women asthma improves during pregnancy and for others it worsens[55,62,76,78,243,273-278], although most findings are more related to subjective reporting of symptoms rather than changes in lung function or immune reactions to bronchial challenge during pregnancy[276,277]. Some studies have found that pregnant women with asthma may decrease their basic medication use during pregnancy[78,279] but it is still not clear

whether this results in increased exacerbations and the findings of this study do not support this.

Potential physiological explanations for a worsening of disease presentation during pregnancy include a decrease in thoracic capacity because of elevation of the diaphragm, a decrease in cell-mediated immunity which increases susceptibility to viral infections, the occurrence of immune reactions to the presence of a foreign foetus, or increased progesterone levels mediating hyperventilation or triggering exacerbations[54,55,280]. Some of these factors, however, may also potentially improve asthma symptoms. Increased progesterone, oestrogen or circulating cortisol during pregnancy may act to decrease smooth muscle cell contraction. Although raised sex steroid hormones have been found to have a direct effects on reducing the contractility of uterine [281] and intestinal[282,283] smooth muscle during pregnancy, a clear relationship with airway smooth muscle has not been found[62,63], which indicates that these act by different mechanisms. The typical increased immune response in asthma may also be depressed through higher levels of cyclic-AMP in pregnancy, which reduce mast cell release of histamine when exposed to antigens, and decreased cell-mediated immunity in pregnancy[55].

Overall obstetric risks in asthma

Proposed mechanisms for increased obstetric risks in women with asthma are maternal hypoxia during asthma exacerbations, abnormal smooth muscle activity of the uterus and the use of asthma medications, all of which may have direct adverse effects on the woman during pregnancy or on the immediate viability of the foetus in utero. Studies estimating obstetric risks in asthma, however, have been

inconsistent[34,75,79,80,102,284,285]. These discrepancies are likely because most reported findings have been limited by either no multivariate analyses, a lack of adequate study power, or both.

Table 5.17[41,44,47-50,52,235,239,243,278,286-290] and Table 5.18[39,40,45,46,51,86,88,96,97,99,236-238,240-242,244,274,275,291-310] include 52 published studies that have reported to assess associations of adverse pregnancy outcomes and obstetric complications with asthma, asthma severity characterised by medication use and symptoms, asthma exacerbations or asthma drug use. About half of these studies (24 studies) were adjusted for potential confounding factors. Only six studies, however, have included more than 1,000 women with asthma and a similar or larger number of comparison women without asthma[44,47-49,238,288]. For outcomes with a prevalence of less than 1% of all pregnancies, such as stillbirth or placental abruption, over 7,000 women with asthma are needed to detect an odds ratio of 1.5 with 85% power if there are twice as many women without asthma included, and 6,000 are needed if there are 4 times as many women without asthma included. For more common outcomes, such as anaemia, with a prevalence of 6% all pregnancies, over 1,000 women with asthma are needed to detect an odds ratio of 1.5 with 85% power if there are twice as many women without asthma included, and over 800 are needed if there are 4 times as many women without asthma included.

Asthma and adverse pregnancy outcomes

The results of this study showing similar risks for adverse pregnancy outcomes in women with and without asthma, are consistent with most previous findings. With the exception of two analyses[44,241], most studies have found that risks of stillbirth[41,49]

or perinatal mortality[41,51,52,88,238,242-244,275,291] were not increased in women with asthma compared with women without asthma, however most of these studies were either not adequately powered for such assessments, with fewer than 20 perinatal deaths in women with asthma, or were not controlled for potential confounders. In the two largest studies of perinatal mortality, Wen *et al*[49] found no increased risk for women with asthma after controlling for maternal age in an analysis of 233 foetal deaths, whereas Kallen *et al*[44] found a small increased risk for women with asthma after controlling extensively for confounding variables, in an analysis of 312 infant deaths, which included 103 stillbirths. No studies have conducted specific analyses of miscarriage or therapeutic abortion risks in women with asthma compared with women without asthma in the general population. In a study of only 186 women, Sobande *et al*[241] reported no increase in therapeutic abortions or perinatal deaths, however, they did not report the number of such outcomes.

Asthma and obstetric complications

Studies of obstetric complications in women with asthma compared with women without asthma have reported increased risks of placenta praevia[47,49], placental abruption[48,49,288], diabetes in pregnancy[44,49,52,241,292], and hypertension in pregnancy[47-49,51,52,97,278], and up to two-fold increased risks of pre-eclampsia[44,47-49,86,241-243], which are in contrast to our findings. However, most were in small selected populations and only seven of these studies were controlled for potential confounders using multivariate analysis[44,47-49,52,86,88]. Two of the largest studies, of over 11,000 and 43,000 women respectively[47,49], both found increased risks of hypertension and pre-eclampsia, however, their populations were derived from hospital register data with reported asthma prevalences of 0.5% and 0.43% respectively, indicating that there

was considerable under-recording of true asthma prevalence in their populations[11]. In a large US study investigating respiratory risk factors for placental abruption, the overall risk for women with asthma was not increased (RR=1.1, 95%CI 1.0–1.2), however, when stratified by race there was an increased risk for women of black race (RR=1.5, 95%CI 1.4-1.6) but not of white race[288].

In keeping with our findings, some studies have also found no overall increase of placenta praevia[48,286], placental abruption[47,243,244,286,288], diabetes in pregnancy[51,240,242-244,278,286,297], hypertension in pregnancy[88,240,243,286,297], or pre-eclampsia[51,236,238,244,278,286]. Only one previous study of investigated anaemia in 757 women with asthma showing no difference in risk of anaemia in women with asthma compared to women without asthma[286]. Although I found a large increase in odds of placenta praevia restricted to women with exacerbations, and of thyroid disorder restricted to women with severe asthma, these did not show general trends with asthma severity and exacerbations, and it is possible that they were chance finding considering the large numbers of outcomes studied. No previous studies have examined the risk of thyroid disorder diagnoses in women with asthma.

The general finding of an increased risk of haemorrhage was in agreement with three studies that reported similar or higher increased risks[41,49,240] but in contrast with others[47,48,97,238,242,244,286]. Compared with women without asthma, Alexander *et al*[240] found that all women with asthma had an increased risk of postpartum haemorrhage regardless of different levels of asthma medication use, whereas only women with severe asthma, had an increased risk of antepartum haemorrhage. I found a 38% relative increase of postpartum haemorrhage which was mainly in women with un-

medicated asthma and a smaller 20% relative increase of antepartum haemorrhage which was mainly in women with medicated asthma, although there was not a clear trend with asthma severity.

While it has been suggested that variations in previous studies may be related to differing asthma severity and management, I found no clear trends of associations by varying asthma severity levels or exacerbations for most obstetric complications. This can be particularly seen for the risks of antepartum and postpartum haemorrhage, which raises the possibility that women with asthma in general, whether or not their disease is currently active, may have persisting immunological, hormonal or other yet unknown physiological differences compared with women without asthma. Particular concern has been raised in asthma reviews over an increasing risk of pre-eclampsia with more severe or less well controlled asthma however study results are inconsistent and do not indicate a clear trend[51,86,236,242,244].

The most striking finding in our study, was a large increased risk of depression in pregnancy in women with asthma which was independent of previous diagnoses of depression and was larger in women with more severe asthma. To our knowledge, this has not been previously investigated on a population level, and while the association of depression with pregnancy is well known[254-258,311] and people with asthma in general have reported poorer mental health[312], the finding that this may be more common in pregnant women with asthma warrants further investigation. One possible explanation is that having a chronic disease such as asthma during pregnancy may present added stress in a time when women are already at an increased risk of depression, and it is possible that being on higher levels of

medications or having worse symptoms increases this stress further. An alternative explanation is potential ascertainment bias since women with asthma visit their doctor more often and so have a greater opportunity to have depression recognised.

Asthma and mode of delivery

Most other studies with few exceptions[41,238,240,278,291,297], found an increased risk of caesarean section delivery, but studies have not found increased risks of assisted delivery or breech delivery. The increased risk of caesarean but not of assisted delivery or breech delivery for women with asthma in this study may be explained by physician and patient concern over the safety of normal delivery rather than a result of an asthma-related emergency. This could also be supported by the findings of higher increased risks of caesarean section in women with severe asthma and asthma exacerbations.

When using general practice data, it is important to consider that some of the associations found may reflect an increased tendency of doctors to ascertain some outcomes or to take specific precautions when treating women with asthma because they see them more often. This will result in the risk estimates being inflated for women with asthma and may also differentially inflate these estimates for levels of asthma severity. This inflation from the true risk may be an explanation for the choice of delivering by caesarean section for women with asthma in general and the increased risk of in utero malpresentation or breech presentation in women at the highest level of asthma severity. The increased risk of breech delivery in women with medicated asthma and asthma exacerbations during pregnancy, however, may represent a true risk and warrants further investigation. A potential explanation may

be that having a baby with malpresentation in utero poses more physical stress on the mother, resulting in asthma exacerbations or worsening of symptoms requiring increased medication use. It is also possible that the increased risk of breech delivery is related to an increased risk of low birth weight babies in women with asthma, since small fetal size is an important risk factor for breech birth at term[313].

Asthma, preterm delivery and low birth weight

Although there were considerable amounts of missing data for gestation and birth weight in this study, children born to women with asthma were slightly more likely to be born preterm and have a low birth weight, which is in keeping with some previous studies[41,45,47,48,52,241,275,290,292]. Most previous studies, however, show no differences in birth weight or term of delivery between women with and without asthma and it is possible that the findings in this study are due to a small increase in recording of this information in the records of women with asthma compared with those of women without asthma. There is some evidence that preterm delivery and low birth weight is associated with asthma severity or exacerbations in pregnancy[74,238,291,302,310]. The analyses of gestation and birth weight by asthma severity and control were limited by differential recording between these groups. In general, women with more severe and less well controlled asthma were more likely to have the gestation of their pregnancy or birth weight of their child recorded, which demonstrates the tendency of doctors to more readily ascertain these outcomes from women with asthma who they see most often.

Table 5.17 Studies of adverse pregnancy outcome and obstetric complication risks associated with maternal asthma

First author, publication year	Bahna, 1972	Schatz, 1975	Sims, 1976	Stenius-Aarniala, 1988	Doucette, 1993	Demissie, 1998	Demissie, 1998	Kallen, 2000	Liu, 2001
Study population (pregnancies in women with / without asthma)	381 / 112,530	55 / 0	27 / 11	198 / 198	32 / 3,859	2,289 / 9,156	2,289 / 9,156	13,344 / 23,641	2,193 / 8,772
Country	Norway	USA	UK	Finland	USA	USA	USA	Sweden	Canada
Statistic	χ^2 test & t-test	none; compared prevalence to general population	t-test	χ^2 test & ANOVA	RR	none; percentages compared	OR	OR	OR
Multivariate adjusted analysis	no	no	no	no	yes	-------	yes	yes	yes
Miscarriage									
Termination									
Stillbirth	≈								
Foetal death		≈							
Perinatal mortality	≈			≈				↑	
Neonatal mortality	↑	≈				≈			
Haemorrhage	↑	≈			≈				
Antepartum haemorrhage				≈					
Postpartum haemorrhage						≈	≈		≈
Placental abruption				≈		≈	≈		↑
Placenta praevia						↑	↑		≈
Pre-eclampsia or eclampsia				↑		↑	↑	↑	↑
Hypertension in pregnancy				≈		↑	↑		↑
Diabetes in pregnancy				≈		↑		↑	
Anaemia in pregnancy									
Caesarean section delivery	≈			↑		↑	↑		↑
Assisted delivery	≈			≈		↓	≈		
Breech delivery				≈					
Difference in gestation	≈			≈					
Preterm delivery	↑	↑			≈	↑	↑		↑
Postterm delivery						≈	≈		≈
Difference in birth weight	↓		≈	≈					
Low birth weight	↑				≈	↑	↑		≈

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Table 5.17 continued from previous page

First author, publication year	Wen, 2001	Mihrshahi, 2003	Sorensen, 2003	Acs, 2005	Sheiner, 2005	Getahun, 2006
Study population (pregnancies in women with / without asthma)	8,672 / 34,688	340 / 271	34 / 702	757 / 37,394	963 / 135,205	332,357 / 36,902,066
Country	Canada	Australia	Sweden	Hungary	Israel	USA
Statistic	OR	OR	OR	t-test & OR	OR	OR
Multivariate adjusted analysis	yes	yes	yes	no	yes	yes
Miscarriage						
Termination						
Stillbirth						
Foetal death	≈					
Perinatal mortality					≈	
Neonatal mortality						
Haemorrhage						
Antepartum haemorrhage				≈		
Postpartum haemorrhage	↑					
Placental abruption	↑			≈		↑
Placenta praevia	↑			≈		
Pre-eclampsia	↑	≈		≈		
Hypertension in pregnancy	↑	↑		≈	↑	
Diabetes in pregnancy	↑	≈		≈	↑	
Anaemia in pregnancy				≈		
Caesarean section delivery	↑	≈			↑	
Assisted delivery		≈				
Breech delivery		≈				
Gestation		≈				
Preterm delivery			↑	≈		
Postterm delivery				≈		
Birth weight		≈		≈		
Low birth weight		≈		≈	↑	

Table 5.18 Studies of adverse pregnancy outcome and obstetric complication risks associated with maternal asthma, asthma severity, asthma control and specific asthma medication use

First author, publication year	Fitzsimons, 1986	Greenberger, 1988	Schatz, 1988	Lao, 1990	Neff, 1990	Schatz, 1990	Perlow, 1992	Jana, 1995	Kramer, 1995	Schatz, 1995
Study population (pregnancies in women with / without asthma)	56 / 0	80 / 0	360 / 295	87 / 87	709 / 51,112	325 / 0	183 / 183	182 / 364	64 / 491	486 / 486
Country	USA	USA	USA	Hong Kong	USA	USA	USA	India	Canada	USA
Maternal exposures	asthma emergency therapy	asthma emergency therapy	asthma, asthma drugs	asthma, asthma drugs	asthma drug (theophylline)	lung function (% predicted FEV_1)	asthma, asthma severity	asthma, asthma severity	asthma, asthma symptoms	asthma, asthma emergency therapy
Statistic	χ^2 test & t-test	chi2-test	OR	χ^2 test & t-test	RR	OR	χ^2 test	χ^2 test & t-test	OR	t-test
Multivariate adjusted analysis	no	no	yes	no	no	yes	no	no	yes	no
Miscarriage										
Termination										
Stillbirth		≈			≈					
Foetal death		≈								≈
Perinatal mortality			≈	≈				≈		≈
Neonatal mortality			≈							
Haemorrhage										
Antepartum haemorrhage										
Postpartum haemorrhage			≈	≈						
Placental abruption										
Placenta praevia										
Pre-eclampsia or eclampsia										≈
Hypertension in pregnancy	≈	≈	≈							↑
Diabetes in pregnancy	≈	≈					↑			≈
Anaemia in pregnancy										
Caesarean section delivery				↑			↑	≈		
Assisted delivery				≈				≈		
Breech delivery								≈		
Difference in gestation								≈		
Preterm delivery		≈	≈	≈		≈	↑	≈	↑	≈
Postterm delivery				≈						
Difference in birth weight			≈			↑				
Low birth weight		≈	≈	↑		≈	↑	≈, ↑		≈

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Table 5.18 continued from previous page

First author, publication year	Stenius-Aarniala, 1995	Dombrowski, 1996	Stenius-Aarniala, 1996	Wendel, 1996	Schatz, 1997	Alexander, 1998	Minerbi-Codish, 1998
Study population (pregnancies in women with / without asthma)	504 / 237	54 / 0	504 / 237	84 / 0	824 / 678	817 / 13,709	101 / 77
Country	Finland	USA	Finland	USA	USA	Canada	Israel
Maternal exposures	asthma, asthma drugs (theophylline)	asthma drugs	asthma, asthma exacerbation	asthma exacerbation (RCT for acute therapy)	asthma drugs	asthma, asthma drugs	asthma, asthma severity
Statistic	ANOVA & t-test	χ^2 test & t-test	χ^2 test & t-test	none; compared prevalence to general population	OR	OR	χ^2 test
Multivariate adjusted analysis	no	no	no	---	yes	yes	no
Miscarriage				≈			
Termination							
Stillbirth							
Foetal death							
Perinatal mortality	≈		≈				
Neonatal mortality							
Haemorrhage				≈			
Antepartum haemorrhage	≈, ↓					≈, ↑	
Postpartum haemorrhage			↓, ≈			↑, ≈	
Placental abruption							
Placenta praevia							
Pre-eclampsia or eclampsia	≈, ↑		↑, ≈		↑		
Hypertension in pregnancy				↑		≈	≈
Diabetes in pregnancy	≈		≈	≈		≈	≈
Anaemia in pregnancy							
Caesarean section delivery	↑		↑	↑		≈	≈
Assisted delivery							≈
Breech delivery							
Gestation	≈		≈	≈			
Preterm delivery	≈	≈	≈	≈	≈	≈	≈
Postterm delivery							
Birth weight	≈	≈	≈	≈			
Low birth weight					≈	≈	≈

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Table 5.18 continued from previous page

First author, publication year	Dombrowski, 1999	Olesen, 2001	Kircher, 2002	Sobande, 2002	Bracken, 2003	Murphy, 2003	Norjavaara, 2003	Dombrowski, 2004
Study population (pregnancies in women with / without asthma)	54 / 0	303 / 8,717	568 / 0	88 / 106	873 / 1,333	138 / 44	293,948 (asthma breakdown not reported)	385 / 0
Country	USA	Denmark	USA	Saudi Arabia	USA	Australia	Sweden	USA
Maternal exposures	asthma drugs	asthma drugs	self-reported asthma improvement / worsening, no change in pregnancy	asthma, asthma emergency admission	asthma, asthma symptoms, asthma drugs(severity step)	asthma, asthma severity, asthma drugs	asthma drugs	asthma drug (beclomethasone vs. thephylline RCT)
Statistic	χ^2 test & t-test	linear regression	χ^2 test	%s presented; χ^2 test & t-test for some outcomes	OR	Generalised linear model	t-test	RR
Multivariate adjusted analysis	no	yes	no	no	yes	yes	no	no
Miscarriage								
Termination				↑				
Stillbirth							≈	
Foetal death								
Perinatal mortality			↑	↑				
Neonatal mortality								
Haemorrhage								≈
Antepartum haemorrhage								
Postpartum haemorrhage								
Placental abruption								
Placenta praevia								
Pre-eclampsia or eclampsia			≈	↑				≈
Hypertension in pregnancy								
Diabetes in pregnancy				↑				
Anaemia in pregnancy								
Caesarean section delivery				↑			↑	≈
Assisted delivery								
Breech delivery								
Gestation	≈	≈	≈	≈	≈, ↓		≈	≈
Preterm delivery	≈		≈	≈	≈, ↑			≈
Postterm delivery				≈				
Birth weight	≈	≈	≈	↓		↓, ≈	≈	≈
Low birth weight			≈	↑				

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Table 5.18 continued from previous page

First author, publication year	Dombrowski, 2004	Namazy, 2004	Schatz, 2004	Triche, 2004	Bakhireva, 2005	Martel, 2005	Murphy, 2005	Otsuka, 2005
Study population (pregnancies in women with / without asthma)	1,739 / 881	474 / 0	2,123 / 0	656 / 1,052	654 / 303	4,593 / 0	146 / 0	592 / 0
Country	USA	USA	USA	USA	USA	Canada	Australia	Japan
Maternal exposures	asthma, asthma severity	asthma drugs	asthma drugs	asthma, asthma symptoms, asthma drugs(severity step)	asthma drugs	asthma drugs (inhaled and oral corticosteroids)	asthma exacerbation	asthma drug treatment
Statistic	OR	none; compared prevalence to general population	OR	OR	ANOVA & OR	ANOVA & t-test	ANOVA & t-test	χ^2 test
Multivariate adjusted analysis	yes	-------	yes	yes	yes	no	no	no
Miscarriage								
Termination								
Stillbirth							≈	
Foetal death								≈
Perinatal mortality	≈							
Neonatal mortality								
Haemorrhage								
Antepartum haemorrhage								
Postpartum haemorrhage	≈							≈
Placental abruption								
Placenta praevia								
Pre-eclampsia or eclampsia	≈			≈, ↑		≈	≈	
Hypertension in pregnancy			≈			≈, ↑	≈	
Diabetes in pregnancy	≈, ↑							
Anaemia in pregnancy								
Caesarean section delivery	≈						≈	≈
Assisted delivery								
Breech delivery								
Gestation							≈	
Preterm delivery	≈	≈	↑, ≈				≈	≈
Postterm delivery								
Birth weight					↓, ≈		≈	
Low birth weight	≈	≈	↑, ≈				≈	

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Table 5.18 continued from previous page

First author, publication year	Silverman, 2005	Rudra, 2006	Schatz, 2006	Martel, 2007
Study population (pregnancies in women with / without asthma)	7,241 / 0	286 & 470 pre-eclampsia cases and controls	2,123 / 0	4,593 / 0
Country	UK	Sweden	USA	Canada
Maternal exposures	asthma drugs (budesonide vs. placebo RCT)	asthma, asthma severity	<80% of predicted FEV_1	asthma drugs (short acting β-agonists)
Statistic	none	OR	OR	OR
Multivariate adjusted analysis	--------	yes	yes	yes
Miscarriage	≈			
Termination	≈			
Stillbirth				
Foetal death				
Perinatal mortality				
Neonatal mortality				
Haemorrhage				
Antepartum haemorrhage				
Postpartum haemorrhage				
Placental abruption				
Placenta praevia				
Pre-eclampsia or eclampsia		≈, ↑		≈
Hypertension in pregnancy			↑	↓
Diabetes in pregnancy				
Anaemia in pregnancy				
Caesarean section delivery				
Assisted delivery				
Breech delivery				
Gestation				
Preterm delivery			↑	
Postterm delivery				
Birth weight				
Low birth weight			≈	

5.4.4 Conclusions

The results of this study provide reassuring evidence that the risks of most adverse pregnancy outcomes and obstetric complications are similar in women with and without asthma, however, some new questions have been raised that warrant further study. The risk of pregnancy ending in miscarriage may be higher in women with asthma and with more severe asthma. The high relative increase of depression in pregnancy for women with asthma and with more severe asthma is also of concern. For other obstetric complications where an increased risk was found, most represent very small differences in absolute risk. Higher severity of asthma and the occurrence of acute exacerbations in women with asthma was only associated with modest increased risks of some obstetric complications. With the possible exception of increased vigilance in monitoring certain complications in pregnant women with asthma, these findings do not indicate a necessity to alter current practice of optimal monitoring and pharmacological management of asthma in women of childbearing age in the general population.

6 Congenital malformations in children born to women with asthma

This section describes a case-control study conducted to compare the risk of congenital malformation in children born to women with asthma with that in children born to women in the general population without asthma, and to assess whether gestational exposure to asthma medication increases the risk of congenital malformation in offspring. The introduction provides an overview of the current data on the potential teratogenicity of asthma treatment, followed by the study methods which include the statistical analysis, the study results, a discussion of the findings in context of previous research, and a conclusion which addresses the clinical importance of the findings.

6.1 Introduction

Although clinical advice to pregnant women with asthma is to maintain optimal therapeutic management, the potential adverse effects of their condition and indicated treatments on foetal development remain uncertain. Asthma medications are in the second most commonly used therapeutic drug class in pregnancy[314] which means they could have a potentially large impact on congenital malformations even if they pose moderate teratogenic risk[315].

Studies have shown reductions in drug clearance during pregnancy[316] and we know that asthma drugs distribute throughout the body tissues, likely crossing the placenta

with potential effects on fetal growth[105]. Animal studies have shown toxic and teratogenic effects of budesonide[109], triamcinolone[317], leukotriene receptor antagonists[106] and methylxanthines [113,115]. Observational human studies using relatively lower therapeutic drug doses are of course required to assess the true risks in the population. As shown by Jadad *et al*[42], such studies require extremely large numbers beyond the reach of the pharmaceutical industry and selected hospital-based studies. Meta-analyses of human studies have shown no risk of overall congenital malformations associated with maternal exposure to inhaled corticosteroids[93] or oral corticosteroids[318], however women in these studies had varying medical conditions.

Considering that congenital malformations continue to be the leading cause of infant mortality in the US[27] and the second leading cause in the UK[26], it is surprising that the current asthma management guidelines of the US National Institutes of Health[102] and British Thoracic Society[80] contain only five epidemiological studies assessing the teratogenic effects of asthma treatments against unexposed comparison groups[43,86,88,240,244]. None of these studies reported increased risks of congenital malformation, however, Jadad *et al*[42] demonstrated that the only three studies to assess early gestational exposures[43,86,88] were severely underpowered to assess these associations such that they could not exclude a 50% increased risk of malformations associated with the use of specific asthma therapies. The combined populations of the other two studies[240,244], included only 40 children with congenital malformations who were exposed to asthma therapies. More recently, a large Hungarian study[53] of data up to 1996, found that mothers of children with malformations were 20% more likely to have asthma compared with mothers of children without malformations. Although antenatal medical records were available, a substantial proportion of

maternal asthma in this study[53] was self-reported by postal questionnaire and was ascertained after the outcome of the child was known. It is likely that asthma medication exposures were also self-reported, since the antenatal records used, in the form of a log book kept by the mother, included prescriptions from obstetricians but not from other physicians such as general practitioners[319]. The study by Tamasi *et al*[53] was also limited by only a small proportion of women taking recommended asthma medications, possibly due to incomplete ascertainment, and there was evidence of differential response rates between cases and controls[320,321].

There is clear need for further data on asthma medication use in pregnancy. A recent report particularly emphasised the lack of adequate safety information on long acting β-agonists and newer asthma therapies, such as leukotriene receptor antagonists, in the current guidelines[101]. While some high-risk teratogens have previously been identified after a small number of reported exposures, many more exposures are needed to identify moderate-risk teratogens even when used widely in the population. To put this in context, over 10,000 children were born with severe malformations to women who had taken thalidomide during pregnancy before the drug was recognised to be teratogenic and its use was stopped in pregnancy. The American Food and Drug Administration only decided to include women in all phases of clinical drug trials in 1993, to assess possible sex differences in drug safety, and this lead to the formation of the FDA's Office for Women's Health in 1994[322]. Pregnant women are still, however, very unlikely to ever be included in randomised trials of asthma therapies in sufficient numbers to allow an assessment of the teratogenicity of such therapies and comprehensive surveillance is not

available[315,323]. This calls for large population-based studies in currently available data.

Using data from liveborn children in the thesis dataset, a case-control study was conducted to assess the risk of maternal asthma and current asthma therapies on all major congenital malformations and system-specific malformations in offspring.

6.2 Methods

6.2.1 Dataset structure and validation of study population

Using the EUROCAT classification[141] (which is described in detail in section 3.5.4), all major congenital malformations were identified in the 268,601 live children who were matched to mothers from the initial population of 1,059,246 women. To test the validity of congenital malformation diagnoses in THIN, I compared the prevalence of any congenital malformation and system-specific malformations in this dataset to that of the EUROCAT registries. For this study, I then restricted the population to mother-child pairs where the mother was registered before the beginning of the pregnancy and ensured that prevalence of any malformation and system-specific malformations was similar to the overall dataset.

To create the case-control dataset from the restricted population, cases were defined as liveborn children with one or more major malformation and for each case I identified up to six liveborn control children matched by year of birth, general practice and singleton or twin delivery. To test the validity of the case-control

dataset, the distribution of maternal age in Trisomy 21 cases was compared with that in their controls, to confirm the expected higher maternal age distribution in cases.

6.2.2 Statistical analyses

The unit of analysis was the child. Conditional logistic regression was used to assess the association of any major congenital malformation or any system-specific major congenital malformation with maternal asthma and maternal asthma drug treatments. Maternal asthma was defined on the basis of recorded diagnoses at any time before the delivery of the child or the use of asthma medication during pregnancy or in the year before pregnancy. Since some of the mothers had an asthma diagnosis but no asthma medication use, and other mothers used asthma medications but had no diagnosis, I assessed the separate risk of congenital malformations in four groups: 1) children born to mothers with an all-inclusive definition of maternal asthma which was either diagnosed asthma or exposure to asthma maintenance medication, 2) children born to mothers with diagnosed asthma but no exposure to asthma maintenance medication, 3) children born to mothers with exposure to asthma maintenance medication but no asthma diagnosis, and 4) children born to mothers with both a diagnosis of asthma and exposure to asthma maintenance medication. Asthma maintenance medications were classified as short acting β-agonists, inhaled corticosteroids, long acting β-agonists, other bronchodilators, or other anti-inflammatory medications. Details of the specific drugs included in each of these drug groups are in Table 3.2 in section 3.6.2. In all children with a record of maternal asthma, I additionally assessed the association of congenital malformation with clinically reported maternal asthma exacerbations during pregnancy.

To test the teratogenicity of specific asthma drug groups the risk of congenital malformation associated with gestational exposures to the asthma maintenance medications classified above as well as oral corticosteroids, was examined. Since oral corticosteroids are used to treat chronic conditions other than asthma, I additionally assessed the effect of gestational oral corticosteroid exposure after excluding exposed mothers with no diagnosis of asthma at any point in their record (including postnatal diagnoses).

All models were adjusted for exact maternal age as a continuous variable and the effects of other potential confounding factors were assessed (maternal smoking and body mass index before pregnancy, socioeconomic status (Townsend index quintile), sex of the child, and delivery before, at, or after term). Missing values for covariates were fitted as a separate category and all models were re-fitted using cases and controls with complete data.

6.2.3 Statistical power and multiple testing

The study population size provided over 95% power to detect an odds ratio of 1.2 or greater for any major malformation and over 90% power to detect an odds ratio of 2.0 or greater for most system-specific major malformations.

For the drug safety analyses, a large number of multiple comparison tests were carried out in the gestational exposure assessment of 6 different drug families with malformations overall and with 11 system-specific malformations (72 odds ratios).

Some odds ratios will therefore be statistically significant at the 5% level by chance alone, while only odds ratios with highly significant p-values ($p<0.01$) should be considered as those most likely not to be due to chance. I present 95% confidence intervals for odds ratios, however, in light of these multiple comparisons, I have also provided exact p-values to allow appropriate interpretation of the findings.

6.3 Results

6.3.1 Validation of the study population

Of the 286,601 children in the initial dataset, 7,671 had at least one major congenital malformation, corresponding to a prevalence of 286 per 10,000 live births which was similar to the overall prevalence for EUROCAT registries in the UK[324] (238 per 10,000 births, which includes live births, stillbirths, foetal deaths and pregnancy terminations). Prevalence figures for any system-specific malformations by maternal age at delivery were only available for all European member registries of EUROCAT as a proportion of all births (including live births, stillbirths, foetal deaths and pregnancy terminations) in women age 20 years and older for 2002. These prevalence figures were also in slightly different groupings of malformation to my data, however, comparisons are made in Table 6.1.

Table 6.1 Comparison of system-specific major congenital malformation prevalence in EUROCAT data (gray) and THIN data (white)

Classification	Prevalence of congenital malformation (per 10,000 births* *or* per 10,000 live births**)
Nervous system*	*24.2*
Nervous system**	13.8
Neural tube defects	*10.3*
Nerural tube defect	2.1
Eye, ear, face, neck	15.9
Eye	*4.4*
Eye	9.8
Ear	*4.1*
Ear	5.6
Circulatory system	69.5
Congenital heart disease	*52.0*
Heart anomaly	52.6
Respiratory system	2.6
Cleft lip and palate	13.7
Cleft lip with or without palate	*8.5*
Cleft lip with or without palate	6.5
Cleft palate	*5.3*
Cleft palate	7.2
Digestive system	*15.0*
Digestive system	9.5
Genital organs	50.9
Urinary system	17.2
Internal urogenital system	*35.9*
Internal urogenital system	67.4
External genital system	*14.8*
External genital system	50.7
Musculoskeletal and connective tissue	*22.6*
Limb	*37.2*
Musculoskeletal system	79.5
Other anomalies	23.2
Chromosomal	*40.9*
Chromosome abnormality	14.3

*EUROCAT 2002 categorisation for all European registries and prevalence per 10,000 births, including live births, stillbirths, miscarriages, foetal deaths and pregnancy terminations.

**Categorisation and prevalence per 10,000 live births in THIN dataset for children born to women age ≥20 years (N=250,660)

The overall prevalence figures for most system-specific congenital malformations in the THIN population were similar to those from EUROCAT. Prevalence of nervous system and chromosomal malformations were much lower, which is likely because most children with these malformations die at or before birth and are therefore identified in the EUROCAT data, but not in the THIN population. Prevalence of some malformations in THIN data, such as urogenital system malformations, were considerably higher than EUROCAT figures. This may be related to small differences in categorisation or differences in prevalence between the UK and the rest of Europe, but a more likely explanation is that these malformations are mainly restricted to live born children and are diagnosed at a later date after birth, so the THIN data captured more of these diagnoses than the EUROCAT data.

In Table 6.2, the available EUROCAT prevalence figures are compared with the equivalent prevalence figures from the THIN dataset, across groups of maternal age. It shows that there is not a large variation in prevalence of malformation across maternal age groups. This is evident in both THIN data and EUROCAT data. Both, however, show the marked increase in prevalence of chromosomal malformations with increasing maternal age.

Table 6.2 Comparison of maternal age-specific prevalence of system-specific major congenital malformation in EUROCAT data (gray) and THIN data (white)

Classification	Prevalence of congenital malformation (per 10,000 births* or per 10,000 live births**)				
	Maternal age at delivery (years)				
	<20	20-24.9	25-29.9	30-34.9	≥35
Nervous system*	*31.5*	*22.8*	*22.3*	*22.6*
Nervous system**	13.9	15.9	12.7	13.7	13.6
Neural tube defects	*12.2*	*10.7*	*8.9*	*9.3*
Nerural tube defect	1.7	2.7	2.4	1.6	1.6
Eye, ear, face, neck	12.8	18.8	16.6	13.8	14.7
Eye	*6.5*	*3.5*	*4.2*	*4.1*
Eye	7.2	11.6	10.0	8.3	10.1
Ear	*4.4*	*3.2*	*3.9*	*4.8*
Ear	5.6	7.0	5.8	5.4	3.5
Circulatory system	76.4	66.3	69.7	66.4	79.8
Congenital heart disease	*53.7*	*48.9*	*51.7*	*54.8*
Heart anomaly	56.9	49.2	52.7	50.5	61.1
Respiratory system	1.1	3.3	1.9	3.2	1.9
Cleft lip and palate	14.5	14.1	14.0	14.7	10.4
Cleft lip with or without palate	*8.0*	*8.1*	*9.3*	*8.4*
Cleft lip with or without palate	8.4	7.6	7.1	6.3	3.7
Cleft palate	*7.3*	*5.4*	*3.7*	*5.4*
Cleft palate	6.1	6.4	6.9	8.3	6.7
Digestive system	*16.4*	*14.5*	*15.1*	*14.7*
Digestive system	10.0	10.1	8.7	9.0	11.2
Genital organs	44.6	57.6	53.4	47.6	43.2
Urinary system	16.7	17.1	17.3	16.7	18.4
Internal urogenital system	*32.7*	*35.7*	*37.3*	*35.7*
Internal urogenital system	60.8	73.7	69.8	63.7	60.8
External genital system	*18.3*	*14.2*	*13.4*	*13.9*
External genital system	44.6	57.6	53.2	47.4	42.7
Musculoskeletal and connective tissue	*26.9*	*20.7*	*20.2*	*21.6*
Limb	*45.3*	*34.2*	*36.4*	*33.9*
Musculoskeletal system	77.5	70.5	82.1	82.9	79.0
Other anomalies	20.1	23.8	23.7	22.2	23.2
Chromosomal	*18.2*	*21.1*	*29.9*	*111.2*
Chromosome abnormality	11.7	9.9	11.0	12.5	31.2

*EUROCAT 2002 categorisation for all European registries and prevalence per 10,000 births, including live births, stillbirths, miscarriages, foetal deaths and pregnancy terminations.

**Categorisation and prevalence per 10,000 live births in THIN dataset for children born to women age ≥20 years (N=250,660)

Of children in the initial dataset, 180,064 (67%) were born to women who were registered at the general practice before the pregnancy and 5,200 of these children had at least one major congenital malformation. This resulted in a similar prevalence of congenital malformation (289 per 10,000 live births) to the overall prevalence in the thesis dataset. Table 6.3 shows that the prevalence of each system-specific malformation was also similar between the overall dataset and the restricted study population which was used to obtain the case-control dataset for this study.

Table 6.3 Congenital malformation prevalence in all children and in children born to women registered at the general practice before the pregnancy

	All children in thesis population (N=268,601)		Children born to women registered at the general practice before pregnancy (N=180,064)*	
	Number	Prevalence (per 10,000 live births)	Number	Prevalence (per 10,000 live births)
Any congenital malformation[θ]	7,671	286	5,200	289
Any system-specific malformation[δ]:				
Nervous system	371	14	244	14
Eye, ear, face, neck	422	16	298	17
Circulatory system	1,879	70	1,282	71
Respiratory system	67	2	50	3
Cleft lip and palate	370	14	258	14
Digestive system	255	9	170	9
Genital organs	1,357	51	928	52
Urinary system	462	17	317	18
Musculoskeletal system	2,132	79	1,444	80
'Other'	618	23	414	23
Chromosomal abnormality	379	14	263	15

** Study population used to obtain the case-control dataset of congenital malformations*

[θ] Children with more than one malformation are counted only once in 'any congenital malformation' total.

[δ] Children with more than one malformation in the same system-specific group are counted only once in each system-specific malformation total.

Using the 5,200 children with one or more major congenital malformation and the remaining 174,864 children with no major congenital malformations in the population of 180,064 children, 5,124 cases were successfully matched to 30,053 control children. Among the cases were 153 children with Trisomy 21, and these data confirmed the marked increasing trend in risk of having a child with Trisomy 21, with older maternal age (OR=2.01, 95% CI 1.36-2.95 for women age 30-39 compared to women under 20 years of age; OR=10.84, 95%CI 5.38-21.85 for women over age 40 compared to women under 20 years of age).

6.3.2 Description of the case-control dataset

Basic characteristics of the cases and controls are shown in
Table 6.4. Maternal age for the 5,124 cases with any major congenital malformation was similar to that for the 30,053 matched controls. There was no trend in maternal body mass index with case status, however, mothers of cases were more likely to have measurements at the extremes of the scale, being either obese (OR=1.16, 95%CI 1.03-1.31) or underweight (OR=1.19, 95%CI 1.00-1.42) before the pregnancy, compared with mothers of controls. Cases and controls had a similar proportion of mothers who were current smokers before the pregnancy (OR=1.00, 95%CI 0.92-1.08) and had the same distribution across levels of socioeconomic status. More cases than controls were delivered before term (OR=2.62, 95%CI 2.21-3.11) and cases were more likely to be male (OR=1.32, 1.25-1.40).

Table 6.4 Characteristics of congenital malformation cases and controls

Covariate	cases (n=5,124) n	*(%)* [α]	controls (n=30,053) n	*(%)* [α]	Unadjusted Odds Ratio (95%CI)
Maternal age at delivery (years)					
Median *(Inter-quartile range)*	29.6 *(25.5-33.2)*		29.4 *(25.5-33.1)*		1.01 (1.00-1.01)
Maternal smoking status					
non-smoker	2,590	*(50.5)*	15,046	*(50.1)*	reference
ex-smoker	269	*(5.2)*	1,473	*(4.9)*	1.06 (0.92-1.22)
current smoker	1,136	*(22.2)*	6,637	*(22.1)*	1.00 (0.92-1.08)
missing	1,129	*(22.0)*	6,897	*(23.0)*	0.92 (0.84-1.01)
Maternal body mass index (Kg/m^2)					
underweight(<18.5)	163	*(3.2)*	827	*(2.8)*	1.19 (1.00-1.42)
normal(18.5-24.9)	2,031	*(39.6)*	12,280	*(40.9)*	reference
overweight(25-29.9)	709	*(13.8)*	4,131	*(13.7)*	1.04 (0.95-1.14)
obese(≥30)	385	*(7.5)*	1,997	*(6.6)*	1.16 (1.03-1.31)
missing	1,836	*(35.8)*	10,818	*(36.0)*	1.01 (0.93-1.10)
Townsend index quintile					
1 (least deprivation)	826	*(16.1)*	4,976	*(16.6)*	reference
2	592	*(11.6)*	3,499	*(11.6)*	1.02 (0.90-1.15)
3	586	*(11.4)*	3,387	*(11.3)*	1.05 (0.93-1.19)
4	506	*(9.9)*	2,833	*(9.4)*	1.08 (0.95-1.24)
5 (most deprivation)	400	*(7.8)*	2,337	*(7.8)*	1.04 (0.90-1.21)
missing	2,214	*(43.2)*	13,021	*(43.3)*	0.87 (0.67-1.12)
Term of the pregnancy					
preterm	366	*(7.1)*	858	*(2.9)*	2.62 (2.21-3.11)
term	705	*(13.8)*	4,503	*(15.0)*	reference
postterm	8	*(<0.5)*	39	*(<0.5)*	1.29 (0.54-3.05)
missing	4,045	*(78.9)*	24,653	*(82.1)*	1.01 (0.88-1.16)
Sex of child					
female	2,172	*(42.4)*	14,829	*(49.4)*	reference
male	2,952	*(57.6)*	15,224	*(50.7)*	1.32 (1.25-1.40)
Singleton or multiple delivery					
singleton	4,996	*(97.5)*	29,655	*(98.7)*	*matching variable*
twin	128	*(2.5)*	398	*(1.3)*	
Year of birth					
1988 to 1989	196	*(3.8)*	1,104	*(3.7)*	
1990 to 1994	1,567	*(30.6)*	9,192	*(30.6)*	*matching variable*
1995 to 1999	1,768	*(34.5)*	10,389	*(34.6)*	
2000 to 2004	1,593	*(31.1)*	9,368	*(31.2)*	

[α] *Proportion of cases or controls*

6.3.3 Associations of any major malformation with maternal asthma

The proportion of mothers with either a diagnosis of asthma, exposure to asthma maintenance medication before the delivery of the child, or both was 14% for cases with congenital malformation and 13% for matched control children (Table 6.5). Cases were marginally more likely than controls to have mothers with asthma in each of the defined groups, ranging from a 6% to 17% relative increase, however, it was only in the most inclusive definition of maternal asthma, with the largest number of exposed cases, where a statistically significant association at the 5% level was found. The highest relative increase of congenital malformation was in children born to mothers with diagnosed asthma but no asthma medication use, whereas the smallest was in children born to mothers with diagnosed asthma who were using asthma medications. Cases were no more likely than controls to have a mother with clinically reported asthma exacerbations in pregnancy (OR=1.09, 95%CI 0.65-1.82; p=0.754).

Table 6.5 Risk of any major congenital malformation in children born to women with asthma

	Cases (n=5,124)		Controls (n=30,053)		Adjusted Odds Ratio[β] (95% CI)	p-value
	n	(%)[α]	n	(%)[α]		
Maternal asthma status:						
no asthma diagnosis or medications before delivery	4,420	*(86.3)*	26,235	*(87.3)*	reference	
asthma diagnosis or medication[γ] before delivery	704	*(13.7)*	3,818	*(12.7)*	1.10(1.01-1.20)	0.032
diagnosis with no medication before delivery	171	*(3.3)*	881	*(2.9)*	1.17(0.99-1.39)	0.071
asthma medication[γ] but no diagnosis before delivery	183	*(3.6)*	968	*(3.2)*	1.13(0.96-1.33)	0.132
diagnosis and asthma medication[γ] before delivery	350	*(6.8)*	1,969	*(6.6)*	1.06(0.94-1.20)	0.329
≥1 asthma exacerbation during pregnancy	18	*(<0.5)*	94	*(<0.5)*	1.09(0.65-1.82)	0.754
≥1 medication exposure during pregnancy*:						
Short acting β-agonist	375	*(7.3)*	2,085	*(6.9)*	1.06(0.94-1.19)	0.336
Inhaled corticosteroid	220	*(4.3)*	1,209	*(4.0)*	1.07(0.92-1.24)	0.407
Long acting β-agonist	25	*(<0.5)*	131	*(<0.5)*	1.12(0.72-1.75)	0.614
Oral corticosteroid	46	*(0.9)*	216	*(0.7)*	1.23(0.89-1.69)	0.201
Other bronchodilator medication**	13	*(<0.5)*	72	*(<0.5)*	1.05(0.59-1.87)	0.872
Other anti-inflammatory medication***	9	*(<0.5)*	27	*(<0.5)*	2.02(0.96-4.28)	0.065

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids during pregnancy or in the year before the pregnancy

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

In the assessment of asthma drug exposures during pregnancy, cases were as likely as controls to be exposed to each of the 6 asthma drug categories (Table 6.5). Most odds ratios for drug exposures were close to unity with the exception of exposure to other anti-inflammatory medications (OR=2.02, 95%CI 0.96-4.28; p=0.065). This odds ratio was based on only a small number of gestational exposures to these medications and all 9 exposed cases were to cromones, while in controls, 26 were exposed to cromones and only 1 was exposed to montelukast.

To assess the effect of oral corticosteroids used during gestation for women with asthma only, I excluded 17 cases and 69 controls whose mothers had prescriptions

for oral corticosteroids in pregnancy but had no diagnosis of asthma. Using this restriction, I found a lower odds ratio (OR=1.13, 95%CI, 0.76-1.69; p=0.552) compared with the use of oral corticosteroids for all women.

In multivariate analyses, none of the potential confounding factors that were available (maternal smoking and body mass index before pregnancy, socioeconomic status, sex of the child and gestational term at delivery) changed the risk estimates by more than 10% (Table 6.6), so final odds ratios for all analyses are only adjusted for maternal age. Since there were missing values for some covariates, I repeated each analysis using only those with full data for covariates and obtained similar effect sizes to the overall analyses (e.g. Fully adjusted OR=1.07, 95%CI 0.88-1.29 for maternal asthma diagnosis and medication before delivery in 1,730 cases and 10,138 controls with full covariate data).

Table 6.6 Comparison of maternal age-adjusted odds ratios with fully adjusted odds ratios for the risk of any major congenital malformation in children born to women with asthma

	Odds Ratio (95% CI) adjusted for maternal age	p-value	Odds Ratio (95% CI) adjusted for maternal age, smoking, BMI, socioeconomic status, sex of child, gestation of pregnancy	p-value
Maternal asthma status:				
no asthma diagnosis or medications before delivery	reference		reference	
asthma diagnosis or medication[γ] before delivery	1.10(1.01-1.20)	0.032	1.09(0.99-1.19)	0.071
diagnosis with no medication before delivery	1.17(0.99-1.39)	0.071	1.15(0.97-1.37)	0.111
asthma medication[γ] but no diagnosis before delivery	1.13(0.96-1.33)	0.132	1.11(0.94-1.31)	0.212
diagnosis and asthma medication[γ] before delivery	1.06(0.94-1.20)	0.329	1.05(0.93-1.19)	0.418
≥1 asthma exacerbation during pregnancy	1.09(0.65-1.82)	0.754	1.10(0.65-1.85)	0.732
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	1.06(0.94-1.19)	0.336	1.05(0.94-1.18)	0.400
Inhaled corticosteroid	1.07(0.92-1.24)	0.407	1.05(0.91-1.23)	0.484
Long acting β-agonist	1.12(0.72-1.75)	0.614	1.12(0.72-1.75)	0.623
Oral corticosteroid	1.23(0.89-1.69)	0.201	1.12(0.80-1.57)	0.492
Other bronchodilator medication**	1.05(0.59-1.87)	0.872	1.03(0.57-1.86)	0.927
Other anti-inflammatory medication***	2.02(0.96-4.28)	0.065	2.15(0.98-4.71)	0.057

[γ] Any asthma medication except oral corticosteroids during pregnancy or in the year before the pregnancy

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

6.3.4 Associations of system-specific malformation with maternal asthma

When analyses of maternal asthma (overall and grouped by diagnoses or medication use) and clinically reported exacerbations in pregnancy for the 11 major system-specific malformation categories were carried out (Table 6.7 to Table 6.18), the results were similar to those for any major congenital malformation (Table 6.5). All odds ratios were smaller than 2.00 and had p-values larger than 0.01. The only exceptions were an association of musculoskeletal system malformations with

maternal asthma overall (OR=1.25, 95%CI 1.06-1.47; p=0.009) and with previous asthma medication but no diagnosis before delivery (OR=1.46, 95%CI 1.11-1.93; p=0.007) (Table 6.16). The associations of system-specific malformations with actively treated diagnosed asthma (diagnosis and asthma medication before delivery) are summarised in Table 6.7 and show similar odds for cases and controls. All tables from Table 6.8 to Table 6.18 contain the full analysis of maternal asthma and gestational drug exposures.

Table 6.7 Risk of system-specific congenital malformation in children born to women with actively treated diagnosed asthma

Maternal asthma (diagnosis and medication before delivery)	cases		controls		Adjusted Odds Ratio[β] (95% CI)	p-value
	n	(%)[α]	n	(%)[α]		
Any congenital malformation[θ]	5,124	(6.8)	30,053	(6.6)	1.06(0.94-1.20)	0.329
Any system-specific malformation[δ]:						
Nervous system	237	(7.2)	1,377	(6.8)	1.08(0.63-1.86)	0.783
Eye, ear, face, neck	293	(5.8)	1,718	(5.8)	1.01(0.58-1.76)	0.972
Circulatory system	1,256	(7.6)	7,356	(6.6)	1.18(0.94-1.49)	0.163
Respiratory system	46	(10.9)	265	(7.2)	1.71(0.50-5.78)	0.390
Cleft lip and palate	255	(7.1)	1,513	(6.8)	1.05(0.62-1.77)	0.852
Digestive system	166	(7.2)	974	(7.0)	1.03(0.53-2.00)	0.932
Genital organs	913	(6.2)	5,345	(6.3)	0.98(0.73-1.31)	0.874
Urinary system	313	(6.7)	1,850	(6.6)	1.03(0.63-1.68)	0.921
Musculoskeletal system	1,431	(7.3)	8,372	(6.6)	1.14(0.91-1.43)	0.241
'Other'	407	(7.1)	2,400	(6.5)	1.15(0.75-1.77)	0.518
Chromosomal abnormality	260	(2.3)	1,519	(5.7)	0.43(0.18-1.02)	0.054

[α] Proportion of cases or controls whose mothers have an asthma diagnosis and medication before delivery

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[θ] Children with more than one malformation are counted only once in 'any congenital malformation' total.

[δ] Children with more than one malformation in the same system-specific group are counted only once in each system-specific malformation total.

For gestational exposure to asthma medications, there was no evidence of increased odds of most major system-specific malformations (p-values>0.01 and most odds ratios smaller than 2.00) apart from a large relative increase of musculoskeletal

system malformations in children born to mothers with gestational exposure to cromones (OR=9.38, 95% CI 2.31-38.10; p=0.002) compared with no exposure, however this was based on only 5 exposed cases (all anti-inflammatory drugs were cromones) (Table 6.16).

For some system-specific malformations there were no gestational exposures to certain drug groups, so it was not possible to assess the following associations: 1) long acting β-agonist exposure with respiratory system, oral cleft, digestive system, urinary system and chromosomal malformations; 2) oral corticosteroid exposure with respiratory system malformations; 3) other bronchodilator medication exposures with nervous system, respiratory system and digestive system malformations; 4) other anti-inflammatory medication exposures with nervous system, respiratory system, digestive system urinary system or 'other' classified malformations.

Table 6.8 Risk of nervous system malformation in children born to women with asthma

	cases (n=237) n (%)[α]	controls (n=1,377) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	204 *(86.1)*	1,205 *(87.5)*	reference	
asthma diagnosis or medication[γ] before delivery	33 *(13.9)*	172 *(12.5)*	1.14(0.78-1.69)	0.495
diagnosis with no medication before delivery	10 *(4.2)*	38 *(2.8)*	1.59(0.78-3.25)	0.205
asthma medication[γ] but no diagnosis before delivery	6 *(2.5)*	41 *(3.0)*	0.88(0.38-2.03)	0.765
diagnosis and asthma medication[γ] before delivery	17 *(7.2)*	93 *(6.8)*	1.08(0.63-1.86)	0.783
≥1 asthma exacerbation during pregnancy	0 *(<0.5)*	2 *(<0.5)*	n/a	0.627
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	16 *(6.8)*	94 *(6.8)*	0.98(0.58-1.65)	0.942
Inhaled corticosteroid	8 *(3.4)*	46 *(3.3)*	1.04(0.47-2.31)	0.915
Long acting β-agonist	2 *(0.8)*	5 *(<0.5)*	2.60(0.39-17.17)	0.322
Oral corticosteroid	3 *(1.3)*	6 *(<0.5)*	2.93(0.74-11.66)	0.126
Other bronchodilator medication**	0 *(<0.5)*	3 *(<0.5)*	n/a	
Other anti-inflammatory medication***	0 *(<0.5)*	2 *(<0.5)*	n/a	

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

Table 6.9 Risk of eye, ear, face or neck malformation in children born to women with asthma

	cases (n=293) n (%)[α]	controls (n=1,718) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	262 *(89.4)*	1,529 *(89.0)*	reference	
asthma diagnosis or medication[γ] before delivery	31 *(10.6)*	189 *(11.0)*	0.96(0.64-1.44)	0.844
diagnosis with no medication before delivery	7 *(2.4)*	31 *(1.8)*	1.30(0.55-3.04)	0.552
asthma medication[γ] but no diagnosis before delivery	7 *(2.4)*	58 *(3.4)*	0.70(0.32-1.50)	0.356
diagnosis and asthma medication[γ] before delivery	17 *(5.8)*	100 *(5.8)*	1.01(0.58-1.76)	0.972
≥1 asthma exacerbation during pregnancy	1 *(<0.5)*	7 *(<0.5)*	0.85(0.10-7.02)	0.880
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	15 *(5.1)*	109 *(6.3)*	0.80(0.46-1.40)	0.431
Inhaled corticosteroid	9 *(3.1)*	65 *(3.8)*	0.82(0.41-1.62)	0.565
Long acting β-agonist	1 *(<0.5)*	8 *(<0.5)*	0.75(0.09-6.04)	0.786
Oral corticosteroid	4 *(1.4)*	12 *(0.7)*	1.99(0.64-6.22)	0.238
Other bronchodilator medication**	1 *(<0.5)*	5 *(<0.5)*	1.19(0.14-10.13)	0.872
Other anti-inflammatory medication***	1 *(<0.5)*	5 *(<0.5)*	1.20(0.14-10.30)	0.868

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

Table 6.10 Risk of circulatory system malformation in children born to women with asthma

	cases (n=1,256) n (%)[α]	controls (n=7,356) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	1,073 *(85.4)*	6,429 *(87.4)*	reference	
asthma diagnosis or medication[γ] before delivery	183 *(14.6)*	927 *(12.6)*	1.20(1.01-1.43)	0.037
diagnosis with no medication before delivery	37 *(2.9)*	213 *(2.9)*	1.07(0.74-1.54)	0.714
asthma medication[γ] but no diagnosis before delivery	51 *(4.1)*	227 *(3.1)*	1.36(0.99-1.86)	0.055
diagnosis and asthma medication[γ] before delivery	95 *(7.6)*	487 *(6.6)*	1.18(0.94-1.49)	0.163
≥1 asthma exacerbation during pregnancy	6 *(<0.5)*	24 *(<0.5)*	1.44(0.51-4.05)	0.495
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	107 *(8.5)*	497 *(6.8)*	1.29(1.03-1.61)	0.024
Inhaled corticosteroid	68 *(5.4)*	293 *(4.0)*	1.38(1.04-1.82)	0.025
Long acting β-agonist	9 *(0.7)*	49 *(0.7)*	1.05(0.48-2.27)	0.910
Oral corticosteroid	15 *(1.2)*	48 *(0.7)*	1.85(1.03-3.33)	0.040
Other bronchodilator medication**	6 *(<0.5)*	20 *(<0.5)*	1.80(0.74-4.42)	0.198
Other anti-inflammatory medication***	1 *(<0.5)*	4 *(<0.5)*	1.47(0.16-13.65)	0.733

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

Table 6.11 Risk of respiratory system malformation in children born to women with asthma

	cases (n=46) n (%)[α]	controls (n=265) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	38 *(82.6)*	228 *(86.0)*	reference	
asthma diagnosis or medication[γ] before delivery	8 *(17.4)*	37 *(14.0)*	1.30(0.50-3.39)	0.596
diagnosis with no medication before delivery	1 *(2.2)*	7 *(2.6)*	0.70(0.07-6.93)	0.761
asthma medication[γ] but no diagnosis before delivery	2 *(4.3)*	11 *(4.2)*	1.14(0.25-5.20)	0.865
diagnosis and asthma medication[γ] before delivery	5 *(10.9)*	19 *(7.2)*	1.71(0.50-5.78)	0.390
≥1 asthma exacerbation during pregnancy	0 *(<0.5)*	0 *(<0.5)*	n/a	
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	6 *(13.0)*	20 *(7.5)*	2.04(0.68-6.13)	0.203
Inhaled corticosteroid	3 *(6.5)*	12 *(4.5)*	1.67(0.35-8.02)	0.519
Long acting β-agonist	0 *(<0.5)*	1 *(<0.5)*	n/a	
Oral corticosteroid	0 *(<0.5)*	1 *(<0.5)*	n/a	
Other bronchodilator medication**	0 *(<0.5)*	0 *(<0.5)*	n/a	
Other anti-inflammatory medication***	0 *(<0.5)*	0 *(<0.5)*	n/a	

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

Table 6.12 Risk of cleft lip and palate in children born to women with asthma

	cases (n=255) n (%)[α]	controls (n=1,513) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	214 *(83.9)*	1,296 *(85.7)*	reference	
asthma diagnosis or medication[γ] before delivery	41 *(16.1)*	217 *(14.3)*	1.15(0.79-1.67)	0.477
diagnosis with no medication before delivery	11 *(4.3)*	55 *(3.6)*	1.25(0.60-2.61)	0.559
asthma medication[γ] but no diagnosis before delivery	12 *(4.7)*	59 *(3.9)*	1.24(0.65-2.37)	0.506
diagnosis and asthma medication[γ] before delivery	18 *(7.1)*	103 *(6.8)*	1.05(0.62-1.77)	0.852
≥1 asthma exacerbation during pregnancy	0 *(<0.5)*	7 *(<0.5)*	n/a	
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	14 *(5.5)*	115 *(7.6)*	0.69(0.39-1.24)	0.216
Inhaled corticosteroid	5 *(2.0)*	64 *(4.2)*	0.45(0.18-1.11)	0.082
Long acting β-agonist	0 *(<0.5)*	7 *(<0.5)*	n/a	
Oral corticosteroid	1 *(<0.5)*	13 *(0.9)*	0.47(0.06-3.67)	0.471
Other bronchodilator medication**	1 *(<0.5)*	8 *(0.5)*	0.80(0.10-6.44)	0.832
Other anti-inflammatory medication***	1 *(<0.5)*	2 *(<0.5)*	3.21(0.29-35.08)	0.340

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

Table 6.13 Risk of digestive system malformation in children born to women with asthma

	cases (n=166) n (%)[α]	controls (n=974) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	139 *(83.7)*	825 *(84.7)*	reference	
asthma diagnosis or medication[γ] before delivery	27 *(16.3)*	149 *(15.3)*	1.10(0.71-1.70)	0.670
diagnosis with no medication before delivery	4 *(2.4)*	45 *(4.6)*	0.54(0.19-1.52)	0.243
asthma medication[γ] but no diagnosis before delivery	11 *(6.6)*	36 *(3.7)*	1.86(0.96-3.62)	0.066
diagnosis and asthma medication[γ] before delivery	12 *(7.2)*	68 *(7.0)*	1.03(0.53-2.00)	0.932
≥1 asthma exacerbation during pregnancy	0 *(<0.5)*	2 *(<0.5)*	n/a	
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	18 *(10.8)*	76 *(7.8)*	1.47(0.86-2.51)	0.156
Inhaled corticosteroid	8 *(4.8)*	41 *(4.2)*	1.17(0.50-2.69)	0.719
Long acting β-agonist	0 *(<0.5)*	2 *(<0.5)*	n/a	
Oral corticosteroid	2 *(1.2)*	8 *(0.8)*	1.38(0.32-5.97)	0.669
Other bronchodilator medication**	1 *(0.6)*	0 *(<0.5)*	n/a	
Other anti-inflammatory medication***	0 *(<0.5)*	0 *(<0.5)*	n/a	

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

Table 6.14 Risk of genital organ malformation in children born to women with asthma

	cases (n=913) n (%)[α]	controls (n=5,345) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	797 *(87.3)*	4,675 *(87.5)*	reference	
asthma diagnosis or medication[γ] before delivery	116 *(12.7)*	670 *(12.5)*	1.01(0.82-1.26)	0.904
diagnosis with no medication before delivery	30 *(3.3)*	138 *(2.6)*	1.31(0.87-1.97)	0.203
asthma medication[γ] but no diagnosis before delivery	29 *(3.2)*	194 *(3.6)*	0.89(0.59-1.33)	0.559
diagnosis and asthma medication[γ] before delivery	57 *(6.2)*	338 *(6.3)*	0.98(0.73-1.31)	0.874
≥1 asthma exacerbation during pregnancy	3 *(<0.5)*	21 *(<0.5)*	0.66(0.23-1.89)	0.439
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	64 *(7.0)*	375 *(7.0)*	0.98(0.74-1.30)	0.905
Inhaled corticosteroid	37 *(4.1)*	225 *(4.2)*	0.93(0.65-1.32)	0.681
Long acting β-agonist	3 *(<0.5)*	24 *(<0.5)*	0.72(0.22-2.35)	0.582
Oral corticosteroid	10 *(1.1)*	40 *(0.7)*	1.33(0.68-2.61)	0.407
Other bronchodilator medication**	3 *(<0.5)*	15 *(<0.5)*	1.11(0.34-3.63)	0.863
Other anti-inflammatory medication***	1 *(<0.5)*	9 *(<0.5)*	0.67(0.08-5.23)	0.699

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

Table 6.15 Risk of urinary system malformation in children born to women with asthma

	cases (n=313) n (%)[α]	controls (n=1,850) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	267 *(85.3)*	1,628 *(88.0)*	reference	
asthma diagnosis or medication[γ] before delivery	46 *(14.7)*	222 *(12.0)*	1.25(0.89-1.76)	0.193
diagnosis with no medication before delivery	14 *(4.5)*	54 *(2.9)*	1.59(0.87-2.90)	0.132
asthma medication[γ] but no diagnosis before delivery	11 *(3.5)*	45 *(2.4)*	1.50(0.77-2.90)	0.232
diagnosis and asthma medication[γ] before delivery	21 *(6.7)*	123 *(6.6)*	1.03(0.63-1.68)	0.921
≥1 asthma exacerbation during pregnancy	2 *(0.6)*	3 *(<0.5)*	4.32(0.74-25.21)	0.104
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	24 *(7.7)*	122 *(6.6)*	1.16(0.74-1.83)	0.518
Inhaled corticosteroid	11 *(3.5)*	75 *(4.1)*	0.83(0.42-1.63)	0.587
Long acting β-agonist	0 *(<0.5)*	12 *(0.6)*	n/a	
Oral corticosteroid	4 *(1.3)*	10 *(0.5)*	2.40(0.76-7.60)	0.138
Other bronchodilator medication**	1 *(<0.5)*	1 *(<0.5)*	6.39(0.40-102.91)	0.191
Other anti-inflammatory medication***	0 *(<0.5)*	0 *(<0.5)*	n/a	

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

Table 6.16 Risk of musculoskeletal system malformation in children born to women with asthma

	cases (n=1,431) n (%)[α]	controls (n=8,372) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	1,213 *(84.8)*	7,304 *(87.2)*	reference	
asthma diagnosis or medication[γ] before delivery	218 *(15.2)*	1,068 *(12.8)*	1.25(1.06-1.47)	0.009
diagnosis with no medication before delivery	50 *(3.5)*	246 *(2.9)*	1.23(0.89-1.70)	0.214
asthma medication[γ] but no diagnosis before delivery	64 *(4.5)*	266 *(3.2)*	1.46(1.11-1.93)	0.007
diagnosis and asthma medication[γ] before delivery	104 *(7.3)*	556 *(6.6)*	1.14(0.91-1.43)	0.241
≥1 asthma exacerbation during pregnancy	6 *(<0.5)*	22 *(<0.5)*	1.71(0.70-4.17)	0.241
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	118 *(8.2)*	598 *(7.1)*	1.17(0.95-1.45)	0.132
Inhaled corticosteroid	68 *(4.8)*	355 *(4.2)*	1.13(0.86-1.48)	0.383
Long acting β-agonist	10 *(0.7)*	29 *(<0.5)*	2.12(1.00-4.49)	0.050
Oral corticosteroid	8 *(0.6)*	65 *(0.8)*	0.71(0.33-1.52)	0.381
Other bronchodilator medication**	2 *(<0.5)*	14 *(<0.5)*	0.84(0.19-3.63)	0.814
Other anti-inflammatory medication***	5 *(<0.5)*	4 *(<0.5)*	9.38(2.31-38.10)	0.002

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

Table 6.17 Risk of other non-categorised malformation in children born to women with asthma

	cases (n=407) n (%)[α]	controls (n=2,400) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	356 *(87.5)*	2,102 *(87.6)*	reference	
asthma diagnosis or medication[γ] before delivery	51 *(12.5)*	298 *(12.4)*	1.04(0.76-1.44)	0.795
diagnosis with no medication before delivery	14 *(3.4)*	70 *(2.9)*	1.23(0.68-2.21)	0.499
asthma medication[γ] but no diagnosis before delivery	8 *(2.0)*	73 *(3.0)*	0.65(0.31-1.36)	0.258
diagnosis and asthma medication[γ] before delivery	29 *(7.1)*	155 *(6.5)*	1.15(0.75-1.77)	0.518
≥1 asthma exacerbation during pregnancy	2 *(<0.5)*	7 *(<0.5)*	1.94(0.40-9.37)	0.408
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	25 *(6.1)*	164 *(6.8)*	0.50(0.24-1.06)	0.070
Inhaled corticosteroid	19 *(4.7)*	92 *(3.8)*	1.27(0.76-2.13)	0.361
Long acting β-agonist	1 *(<0.5)*	8 *(<0.5)*	0.80(0.10-6.58)	0.837
Oral corticosteroid	3 *(0.7)*	21 *(0.9)*	0.81(0.24-2.78)	0.741
Other bronchodilator medication**	1 *(<0.5)*	6 *(<0.5)*	0.95(0.12-7.84)	0.963
Other anti-inflammatory medication***	0 *(<0.5)*	0 *(<0.5)*	n/a	

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

Table 6.18 Risk of chromosomal abnormalities not elsewhere classified in children born to women with asthma

	cases (n=260) n (%)[α]	controls (n=1,519) n (%)[α]	Adjusted Odds Ratio[β] (95% CI)	p-value
Maternal asthma:				
no asthma diagnosis or medications before delivery	238 *(91.5)*	1,320 *(86.9)*	reference	
asthma diagnosis or medication[γ] before delivery	22 *(8.5)*	199 *(13.1)*	0.62(0.37-1.03)	0.066
diagnosis with no medication before delivery	9 *(3.5)*	57 *(3.8)*	1.01(0.43-2.36)	0.984
asthma medication[γ] but no diagnosis before delivery	7 *(2.7)*	55 *(3.6)*	0.59(0.25-1.41)	0.236
diagnosis and asthma medication[γ] before delivery	6 *(2.3)*	87 *(5.7)*	0.43(0.18-1.02)	0.054
≥1 asthma exacerbation during pregnancy	0 *(<0.5)*	2 *(<0.5)*	n/a	
≥1 medication exposure during pregnancy*:				
Short acting β-agonist	9 *(3.5)*	99 *(6.5)*	0.50(0.24-1.06)	0.070
Inhaled corticosteroid	1 *(<0.5)*	52 *(3.4)*	0.11(0.01-0.80)	0.030
Long acting β-agonist	0 *(<0.5)*	1 *(<0.5)*	n/a	
Oral corticosteroid	1 *(<0.5)*	12 *(0.8)*	0.74(0.09-5.95)	0.774
Other bronchodilator medication**	1 *(<0.5)*	7 *(<0.5)*	0.87(0.10-7.71)	0.901
Other anti-inflammatory medication***	1 *(<0.5)*	2 *(<0.5)*	5.04(0.40-63.36)	0.211

[α] Proportion of cases or controls whose mothers have diagnosis or at least one selected drug prescription in pregnancy

[β] Odds Ratios (95% Confidence Intervals) adjusted for maternal age at birth of case or control child; Maternal smoking status, body mass index, socioeconomic status, sex of the child, gestation of pregnancy had no confounding effects.

[γ] Any asthma medication except oral corticosteroids

**Reference groups are mothers with no prescriptions for the selected drug group in pregnancy*

***Aminophylline, theophylline, ephedrine, orciprenaline, titropium, or ipratropium*

****Cromoglicate, nedocromil, montelukast or zafirlukast*

6.4 Discussion

6.4.1 Summary of findings

The results of this study show that the risk of major congenital malformation in children born to mothers with asthma is similar to that in children born to mothers without asthma. Cases were only marginally more likely than controls to have mothers with asthma in each of the defined groups of maternal asthma and there was only a statistically significant association at the 5% level when the number of maternal asthma-exposed cases was highest and hence statistical power was greatest. Since the effect seen here was small (10% increase) and was not present for cases whose mothers were treated for asthma, this pattern of results overall does not support an important increased risk of malformation in children born to women with asthma.

Gestational exposure to asthma therapies did not appear to increase the risk of any type of congenital malformation, or system-specific malformation, providing evidence of their general safety in pregnancy. The only exposure of possible concern was a marked increase in the risk of musculoskeletal malformations associated with cromone anti-inflammatory medications.

6.4.2 Strengths and limitations

Statistical power

This is the largest comprehensive multivariate analysis of the potential teratogenic effects of current asthma medications associated with overall and system-specific malformations. Since the data are from a large database of prospectively collected clinical records, the possibility of recall-bias in the exposures of maternal asthma and prescription medication use can be excluded.

Validity of exposure and outcome data

In assessing the external validity of our study, the population-based prevalence of current asthma in women of child-bearing age was similar to both UK[12] and US[11] national figures.

Since congenital malformations have not previously been investigated in THIN, I compared prevalence figures for any major malformation and system-specific malformations in the THIN study population to those from the European Surveillance of Congenital Malformations and found these to be similar[324]. The prevalence of any congenital malformation in this study population (286 per 10,000 live births) was slightly higher than the prevalence in UK-based EUROCAT registries (238 per 10,000 total births). Although the inclusion of only congenital malformation diagnoses from birth in this study will mean that my estimates are different from the true prevalence in the population[142,325], I do not expect that prenatal diagnosis and resultant termination of pregnancy would be differential between women with and without asthma.

It was only possible to compare prevalence figures of system-specific malformations in the study population with EUROCAT estimates based on all European registries, which may partially explain the differences found in the prevalence of some malformations, since there is considerable international and regional variation in the prevalence of congenital malformations[28,326,327]. The difference in baseline populations of live births in this study and all live and non-live pregnancy outcomes in the EUROCAT estimates, more likely explain most of the discrepancy in prevalence, especially for severe malformations with low survival rates[328]. I did not extract potential data on congenital malformation for pregnancies ending in stillbirth, miscarriage, or therapeutic abortion because it is likely that these details are often not known or not recorded for non-live birth outcomes which are recorded in the woman's record. Furthermore, data from national registries indicate low ascertainment of congenital malformations for all adverse pregnancy outcomes, particularly, because of a lack of information on prenatal congenital malformation diagnoses that result in pregnancy terminations via therapeutic abortion[325].

The most marked discrepancy between my data and the EUROCAT figures were for neural tube defects which often end in miscarriage or elective termination of pregnancy[329]. The prevalence of neural tube defects in this study population (2.1 per 10,000 live births) was closer to figures from a UK-based prevalence study of neural tube defects at birth (5.6 per 10,000 live and stillbirths between 1984-1996)[330] and the UK Office for National Statistics (from 5.1 per 10,000 live and stillbirths to 1.2 per 10,000 live and stillbirths over the period of 1985 to 1999)[328].

The prevalence figures for system-specific malformations were similar to those from EUROCAT for each band of maternal age, indicating that ascertainment of cases did not differ by maternal age. The marked increase in risk of having a child with Trisomy 21 for women of older maternal age was also demonstrated in the study population.

Accounting for missing covariate data

I recognise the presence of some missing data for maternal smoking, body mass index and socioeconomic status. To assess the impact of missing covariate data, I ensured that they were included as a separate category in all analyses. The proportions of missing data for each covariate were the same between cases and controls, however, I repeated analyses using only those with full data for covariates and obtained similar effect sizes to the overall analyses.

Multiple testing

All studies using repeated statistical analysis to assess several drug exposures in one population are at risk of revealing spurious associations, because high numbers of multiple comparison tests result in statistically significant p-values by chance alone and it is important to consider whether these associations are causal. Studies of drug safety typically use a 5% level for statistical significance ($p<0.05$), however, in consideration of the multiple comparisons in this study odds ratios with highly significant p-values ($p<0.01$) should be considered as those most likely not due to chance. Only the association of musculoskeletal malformations with gestational cromone exposure had a p-value near this level ($p=0.002$), however cromone

exposure was still extremely rare and the possibility that this finding was due to chance cannot be excluded. Exposure to newer leukotriene receptor antagonists was also rare in this population which limited a current assessment of their teratogenic safety in pregnancy.

6.4.3 Interpretation in context of other studies

Association of maternal asthma with congenital malformation

Most previous studies have found no relative increase in congenital malformation in children born to women with asthma compared with those born to women without asthma[44,48,51,238,241-243], which is in keeping with the results of currently active asthma for women in this study, however, few of these previous studies had adequate statistical power and only two adjusted for potential confounding factors [44,48]. One study of approximately 600 malformations reported a relative increase of congenital malformation in children born to women with asthma[47] and although the largest study of over 20,000 malformations in Hungary found a marginal increased risk overall (1.2, 95%CI 1.0-1.3), the only system-specific malformation to reach statistical significance at the 5% level was club foot, which the authors attribute to more preterm births in women with asthma[53]. Table 6.19 summarises published studies that have assessed the risk of congenital malformation associated with maternal asthma only[44,47,48,51,241-243].

Table 6.19 Studies assessing the association of maternal asthma with congenital malformation in offspring

Author, publication year	Country	Source of study population	Study period	Asthma study population (pregnancies in women with / without asthma)	N=total pregnancies	Congential malformations (Number or percent children born to women with / without asthma)	N=total children with malformation	Statistic	Association of maternal asthma with congenital malformation	multivariate adjusted analysis
Liu et al, 2001	Canada	Acute care hospital admissions database, Quebec Med-Echo	1991-92 & 1995-96	2,193 / 8,772	10,965	5.9% / 5.9%	647*	OR	0.99 (0.81-1.21)	yes
Demissie et al, 1998	USA	Database of hospitals, New Jersey	1989-92	2,289 / 9,156	11,445	6.4% / 4.9%	595*	OR	1.37 (1.12-1.68)	yes
Schatz et al, 1995	USA	Health centre recruiting, San Diego Kaiser-Permanente Health Care Program	1978-89	486 / 486; matched	972	Major: 4.2% / 6.3% Minor: 5.0% / 4.2%	51* major; 36* minor	χ^2 test	p=0.149; p=0.537	no
Stenius-Aarniala et al, 1996 (Same population as Stenius-Aarniala et al, 1995)	Finland	Hospital recruitment, Helsinki Univeristy Central Hospital	1982-92	504 (including 47 with exacerbations) / 237; matched	741	4.3% in asthma with attack 2.5% in asthma no attack 0.8% in non-asthma	15*	none	Only percentages presented	no
Sobande et al, 2002	Saudi Arabia	Hospital recruitment, Emergency room of Abha Maternity Hospital	1997-2000	88 / 106; matched	194	7 (7.9%) / 1 (1.0%)	8	not reported		
Stenius-Aarniala et al, 1988	Finland	Hospital recruitment, Helsinki Univeristy Central Hospital	1978-82	198 (182 women) / 198; matched	396	not reported			Reported "no higher incidence" of malformations in asthma but no data presented.	
Kallen et al, 2000	Sweden	Birth register, Swedish Medical Birth Registry	1984-95	13,344 / 23,641	36,985	not reported		OR	1.05 (0.99-1.10)	yes

*Numbers estimated from published percentages (no numbers presented in paper)

Only one previous study has compared the prevalence of congenital malformations in women with and without asthma exacerbations in pregnancy[242] and although the prevalence was slightly higher in women with exacerbations, the study was too small to a conduct statistical comparison. Schatz *et al*[310] examined the association with lung function and found no difference in the prevalence of congenital malformation in children born to women with a mean FEV_1<80% predicted compared with that in children born to women with a mean FEV_1≥80% predicted.

Association of asthma drug treatment with congenital malformation

Regarding asthma treatment, Jadad *et al*[42] emphasised the need for large observational studies as the only current way to assess the safety of conventional and new asthma medications in 2000, however, recent reports have again raised the lack of sufficient data[101]. The US Food and Drug administration continue to classify all asthma medications as B or C[85,331], which stipulate that only animal studies have provided evidence against teratogenicity and there are no adequate human data to estimate true risks. The British Thoracic Society grades asthma medications as C or D[79,80] which provide the weakest evidence for safety in pregnancy.

Table 6.20 summarises studies that have reported statistical analyses of congenital malformations associated with specific gestational drug exposures in maternal asthma and have used unexposed comparison groups[46,53,86,88,240,244,332], and shows a comparison with the analysis in this THIN study. Three drug studies were controlled for potential confounding factors[88,240,332] and only one study had adequate statistical power to test the effects of varying asthma medication groups but was unable to control for potential confounders[53]. This latter Hungarian study[53] was the only to

find an increased risk of malformation associated with gestational asthma drug exposure and this was with fenoterol exposure (unadjusted OR=1.6, 95%CI 1.3-2.0) although they did not assess this exposure with system-specific malformation. Relative differences of the Hungarian study to this THIN study include self-reported maternal asthma drug exposures that were obtained via postal questionnaires after the birth of the child, differential ascertainment of information between mothers of case and control children, inclusion of some minor malformations such as club foot and undescended testis, and an earlier study period (1980 to 1996) resulting in less asthma medication use overall and rare use of newer asthma therapies such as long acting β-agonists[53,319-321].

Table 6.20 Studies reporting statistical analyses of congenital malformation associated with gestational exposure to asthma medication compared with no exposure

Author, publication year	Gestational exposure	Children with congenital malformation (Number born to women with / without asthma)	Multivariate analysis	Increased risk[α]
Schatz et al, 1988	Inhaled bronchodilators	<50 / <50 *	yes	no
Stenius-Aarniala et al, 1995	theophylline	10 / 2	no	no
Schatz et al, 1997	β-agonists, theophylline, cromolyn, CS, antihistamines, decongestants	<50 / <50 *	no	no
Alexandre et al, 1998	β-agonists, CS	88 / 981	yes	no
Schatz et al, 2004	β-agonist, ICS, OCS, theophylline, cromoglicates	42 / 0 *	no	no
Tamasi et all, 2006	SABA, ICS, LABA, OCS, xanthines, sodium cromoglicate	511 / 22,322 major malformation***	no	yes with fenoterol, no with other medication
Blais et al, 2006	ICS	418 / 0	yes	no
Current THIN study	SABA, ICS, LABA, OCS, other bronchodilators, other anti-inflammatories	704 / 4,420 major malformation	yes	no

[α] Statistically significant increase in malformation with gestational drug exposure (at 5% level)

* Numbers estimated from published percentages (no numbers presented in paper)

***Mostly major malformations but included some minor (clubfoot, pyloric stenosis, undescended testis)

SABA=short acting β-agonist; LABA=long acting β-agonist

CS=Corticosteroid (unspecified formula); ICS=Inhaled corticosteroid; OCS=oral corticosteroid
other bronchodilators=aminophylline, theophylline, ephedrine, orciprenaline, tiotropium, or ipratropium
other anti-inflammatories=cromoglicate, nedocromil, motelukast or zafirlukast

Table 6.21 and Table 6.22 include comprehensive lists of publications that have reported teratogenic assessments of asthma medications using study populations of women with asthma only[46,99,294,304,306,332] and with non-asthma comparison groups[53,86,88,238,240,244], respectively. Most studies have been considerably underpowered and multivariate analyses to adjust for potential confounding factors have not been conducted.

Table 6.21 Studies assessing the association of maternal asthma medication use in pregnancy with congenital malformations in offspring, using populations of women with maternal asthma only

Author, publication year	Country	Source of study population	Study period	Pregnancy drug exposures in gestation	N=total pregnancies	Congential malformations (Number or percent children in exposure group)	N=total children with malformation	Statistic	Association of congenital malformation with gestational drug exposure	multivariate adjusted analysis
Blais et al, 2006	Canada	linkage of 3 Quebec databases containing births(ISQ), medication dispensing (RAMQ) & hospitalisations (MED-ECHO)	1990-2000	1,821 pregnancies ICS-treated in 1st trimester (4,561 pregnancies in 3,505 women)	4,561	278 major / 140 minor	418	OR	*No analysis of asthma versus no asthma or drugs in asthma versus no asthma.* Any Malformation: [Compared with no ICS use in 1st trimester-Low dose 0.76 (0.56-1.05); Medium dose: 0.39 (0.19-0.82); High dose 0.92 (0.42-2.03)]; [ICS use before pregnancy 1.19 (0.89-1.60) ; LABA use before pregnancy 2.83 (1.34-5.97)] / Major malformation: [Compared with no ICS use in 1st trimester: Low dose 0.94 (0.63-1.39); Medium dose: 0.56 (0.22-1.43); High dose 1.92 (0.78-4.74)]	yes
Schatz et al, 2004 (Same study population as Schatz et al, 2006)	USA	Health units recruiting, asthma observational study or RCT of beclomethasone versus theophylline, 16 centres of Maternal-Fetal Medicine Units Network (MFMU) Network	1995-99	1,828 on β-agonist, 722 on ICS, 185 on OCS, 273 on theophylline, 60 on cromolyn-nedocromil	2, 123	2.0% of β-agonist-treated, 1.9% of ICS-treated, 2.2% of OCS-treated, 1.5% of theophylline-treated, 3.3% of cromolyn-nedocromil-treated / average of 2.0% in pregnancies unexposed to each drug.	42*	χ^2 test	Reported non-significant p-value but no statistical testing presented.	no
Silverman et al, 2005	UK	Selected from patients in RCT of low-dose budesonide versus placebo in 32 countries	1996-98	102 on budesonide / 117 on placebo	219	1 (1.0%) in budesonide / 4 (3.4%) in placebo	5	none		
Namazy et al, 2004	USA	Recruited patients of allergists, 35 states, American College & Academy of Allergy, Asthma and Immunology	1996-2002	396 all ICS-treated	396	4 (1.0%)	4	none	Reported that 'rate' was no higher than in the general population(All 1991 American single live births)	
Greenberger et al, 1988	USA	Recruited from consultation, Northwestern University Allergy Service	1981-87	80 in 73 women with severe asthma requiring ICS or OCS	80	2 (2.5%)	2	χ^2 test	1 malformation in group with and 1 in group without emergency asthma therapy	no
Otsuka et al, 2005	Japan	Hospital recruitment, Showa University Fujigaoka Hospital	1987-2003	592, divided into before/after 1994	592	1.5% in ICS exposed before 1994 (136 women), 0% in ICS exposed after 1994.	2*	none		

CS=Corticosteroid(unspecified formula); ICS= Inhaled corticosteroid; OCS=oral corticosteroid; FEV1=Forced expiratory volume in 1 second; RCT=Randomised controlled trial
*Numbers estimated from published percentages (no numbers presented in paper)

Table 6.22 Studies assessing the association of maternal asthma medication use in pregnancy with congenital malformations in offspring, using populations of women with maternal asthma and comparison women without asthma

Author, publication year	Country	Source of study population	Study period	Asthma study population (pregnancies in women with / without asthma)	N=total pregnancies	Congential malformations (Number or percent children born to women with / without asthma)	N=total children with malformation	Statistic	Association of maternal asthma with congenital malformation	multivariate adjusted analysis
Tamasi et al, 2006 (Same population as Czeizel et al, 1997 and 2003)	Hungary	National congenital malformation registry, Hungarian Case-Control Surveillance of Congenital Abnormalities	1980-96	1,268 (511 with maternal asthma in cases (2.2% of cases) & 757 with maternal asthma in controls (2.0% of controls)) / 59,726 [N.B. Study population was of malformation case-control]	60,994	511 / 22,322 [N.B. Study was case-control of malformation: 22,843 cases malformation & 38,151 controls]	22,843	OR	1.2 (1.0-1.3). Analyses of association between congenital malformation & asthma drugs were only in children of women with asthma (N=1,268): No evidence of associations found.	yes for maternal asthma; no for asthma drug exposures
Alexandre et al, 1998	Canada	Hospital delivery recruitment, Grace Maternity Hospital	1991-93	817 (375 no medication, 303 on β-agonists, 139 on CS) / 13,709	14,526	56 (24 (6.9%) no medication, 24 (8.5%) on β-agonists, 8 (6.2%) on CS) / 981 (7.7%)	1,037	OR	0.9 (0.6-1.4) no medication; 1.0 (0.6-1.6) on β-agonists; 0.8 (0.4-1.7) on CS	yes
Dombrowski et al, 2004	USA	Health units recruiting, 16 centres of Maternal-Fetal Medicine Units Network (MFMU)	1994-99	1,739 (divided into mild, moderate-severe divisions) / 881 [N.B. Severity classfication included symptoms, FEV1, medication use where mild=no daily medication, moderate-severe=daily maintenance medications or regular OCS]	2,620	69 (36(4.2%) moderate-severe, 33(3.9%) mild) / 34(3.9%)	103	OR	1.1 (0.7-1.7) moderate-severe asthma; 1.0 (0.6-1.6) mild asthma	no

Table continues on next page

CS=Corticosteroid(unspecified formula); ICS= Inhaled corticosteroid; OCS=oral corticosteroid

Table 6.22 continued from previous page

Author, publication year	Country	Source of study population	Study period	Asthma study population (pregnancies in women with / without asthma)	N=total pregnancies	Congential malformations (Number or percent children born to women with / without asthma)	N=total children with malformation	Statistic	Association of maternal asthma with congenital malformation	multivariate adjusted analysis
Schatz et al, 1988	USA	Health centre recruiting, Kaiser-Permante Prospective Study of Asthma During Pregnancy	1978-84	360 (259 on β-agonists & 101 not using β-agonists) / 295	655	Major: (3.9% on β-agonists, 6.0% no β-agonist) asthma / 6.4% no asthma; Minor: (4.7% on β-agonist, 5.0% no β-agonist) asthma / 7.5% no asthma. Similar proportions for 1st trimester drug exposure only	Not calculable (estimate: definitely <100)	χ^2 test, OR	p≥0.05 for β-agonist exposed or unexposed compared with no asthma (1st trimester or all gestation) and for dose-related trend. Reported no relationship found in multivariate analyses but no data presented.	reported yes, but not presented
Schatz et al, 1997	USA	Health centre recruiting, Kaiser-Permante Prospective Study of Asthma During Pregnancy	1978-89	824 / 678	1,502	No proportions presented by maternal asthma status. Proportions presented for exposed & unexposed to several medication groups (range=3.7-6.9%). Categorisation by CS: 7.0% on OCS, 5.4% on ICS (for asthma) or intranasal CS (for rhinitis) / average of 4.9% in unexposed	Not calculable (estimate: definitely <100)	χ^2 test	*No analysis of asthma versus no asthma or drugs in asthma versus no asthma.* p≥0.05 for all comparisons of exposed versus unexposed to β-agonist, theophylline, cromolyn, CS (including inhaled, intranasal), antihistamines, decongestants (1st trimester or all gestation) and for dose-related trend across corticosteroid categorisation.	no
Stenius-Aarniala et al, 1995 (Same population as Stenius-Aarniala et al, 1996)	Finland	Pulmonary medicine and maternity outpatient clinic recruitment	1982-1990	504 (212 on theophylline & 292 not using theophylline) / 237	741	8(3.8%) in exposed asthma/ 2(1%) in unexposed asthma / 2(0.8%) in no asthma	12	χ^2 test	Reported non-significant p-value (level not indicated) comparing exposed and unexposed asthma with no asthma	no

CS=Corticosteroid(unspecified formula); ICS= Inhaled corticosteroid; OCS=oral corticosteroid

Some studies that have reported to assess the potential teratogenic effects of medications used for asthma have been in general populations with no identification of the condition for which the medications were indicated and it is therefore likely that some women were prescribed these medications for reasons other than asthma. Table 6.23 summarises these studies, most of which assessed the effects of corticosteroids[43,318,333-336], one which assessed the effect of aminophylline[337] and one which assessed the effect of unspecified inhaled bronchodilators[335]. These studies show that drug exposures do not pose an overall risk of any congenital malformation. Studies of corticosteroid exposures have mostly assessed combinations of forms or unspecified forms that may or may not be used for asthma specifically[333-336], while some have made separate assessments of oral[318,334] and inhaled[43] corticosteroids. In the study assessing oral aminophylline[337], less than 3% of exposed women had a diagnosis of asthma.

Table 6.23 Studies assessing the association of congenital malformations in offspring with gestational use of medications used for asthma, but no asthma populations specified

Author, publication year	Country	Source of study population	Study period	Pregnancies exposed / unexposed in gestation	N=total births	Study population of congential malformations (& controls)	N=total children with malformation	Statistic	Association of congenital malformation with gestational drug exposure	multivariate adjusted analysis
Czeizel et al, 2003 (Same population as Czeizel et al, 1997 & Tamasi et al, 2006)	Hungary	National congenital malformation registry, Hungarian Case-Control Surveillance of Congenital Abnormalities	1980-96	6% of both cases and controls oral aminophylline exposed	60, 994	22,843 (& 38,151 controls)	22,843	OR	p≥0.05 for most OR associations system-specific malformations. 4.7(1.3-17.2) early pregnancy or 1.5(0.9-2.2) all gestation exposure & musculoskeletal malformation.	yes
Czeizel et al, 1997 (Same population as Czeizel et al, 2003 & Tamasi et al, 2006)	Hungary	National congenital malformation registry, Hungarian Case-Control Surveillance of Congenital Abnormalities	1980-1994	392(1.9%) cases CS exposed / 616 (1.7%) controls CS exposed (categorised as oral, ointment, spray)	56,557	20,830 (& 35,727 controls)	20,830	χ2 test, OR	*No multivarate analysis presented for CS exposure and any malformation.* p=0.17 for all CS exposed. p≥0.05 for all OR associations of oral/topical CS with any malformation and most system-specific malformations.	yes, but only for system-specific malformation
Carmichael et al, 1965	USA	Hospital/genetic counselling records, California Birth Defects Monitoring System	1987-89	13 CS exposed	2,033	662 orofacial clefts, 207 heart defects, 265 nerual tube defects, 165 limb reductions (& 734 controls)	1,299	OR	5.3(1.1-26.5) for cleft palate and 4.3(1.1-17.2) for cleft lip w/wo palate associated with CS use; p≥0.05 for all OR associations of other congenital malformations with CS use.	no
Queisser-Luft et al, 1996	Germany	Recruited from all births, Mainz birth defects monitoring system	1990-94	102 bronchodilator exposed, 57 CS exposed	11,154	1,472 (& 9,682 controls)	1,472	OR	0.3(0.2-0.7) continuous bronchodilator exposed, 1.0(0.2-4.2) continuous CS exposed for any malformation. 5.8(1.4-24.0) continuous & 5.3(1.3-22.0) acute bronchodilator exposed for heart defect.	no
Rodriguez-Pinilla et al, 1998	Spain	Hospital-based surveillance, Spanish Collaborative Study of congenital Malformations	1976-95	5 case & 1 controls CS exposed in early pregnancy (prednisolone, triamcinolone, or hydrocortisone)	2,356	1,184 oral clefts (& 1,172 controls)	1,184	OR	5.0 (0.6-12.6)	no
Kallen et al, 1999	Sweden	Birth register, Swedish Medical Birth Registry	1995-1997	2,014 women ICS(budesonide) exposed in early pregnancy / Comparison= rest of birth register	2,014	75 (3.7%), including 41 major [N.B. Study population was selection of women in pregnancy]	75	none	Reported similar period prevalence to that in all infants from birth register (3.5%)	no
Park-Willey et al, 2000	Canada	Recruited from telephone callers to the Motherisk Program (& Meta-analysis of 4 studies)	1985-95	111 women CS(prednisolone) exposed in 1st trimester / 172 women unexposed	283	4(3.6%) in exposed / 3(2.0%) in unexposed [N.B. Study population was selection of women in pregnancy]	7	χ^2 test	p=0.3 all malformations. Oral clefts but not all malformations associated with CS in meta-analysis	no

CS=Corticosteroid(unspecified formula); ICS= Inhaled corticosteroid; OCS=oral corticosteroid

6.4.4 Conclusions

The findings of this study indicate no increase in the risk of major congenital malformation in children born to mothers with currently treated asthma, however, there may be a small increase for children born to women with previous asthma diagnoses. Management of asthma with medications during gestation, in accordance with the current guidelines, appears to be safe overall. However, older cromones may carry a moderate teratogenic risk and their use in pregnancy should be cautioned.

7 Conclusions and recommendations for future research

7.1 Summary of main findings

The main findings of my thesis are as follows:

- Fertility rates are not lower in women with asthma compared with women in the general population without asthma, and women with eczema and hay fever have slightly higher fertility rates than women in the general population. The strong birth order effects in allergic disease are not explained by reduced fertility in women with allergic disease.
- Women with asthma have a similar risk of pregnancy ending in stillbirth or therapeutic abortion, but may have a small relative increase in risk of pregnancy ending in miscarriage, compared with women without asthma.
- Women with asthma have similar risks of pregnancy complications compared with women without asthma. They do, however, have an increased risk of antepartum haemorrhage, postpartum haemorrhage and depression in pregnancy.
- Children born to women with asthma are more likely to be delivered by caesarean section and may have a small increase in risk of preterm delivery and low birth weight.
- Asthma severity and acute exacerbations, whether before or during pregnancy, do not have a large impact on the risk of adverse pregnancy outcomes or obstetric complications, with the exception of miscarriage, depression in pregnancy and caesarean section delivery.

- The risk of major congenital malformation in children born to mothers with asthma is marginally higher than that in children born to mothers without asthma, however, this is not found in children whose mothers are currently treated for asthma. Gestational exposure to commonly used asthma medications does not increase the risk of major congenital malformation, but cromone use may increase the risk of musculoskeletal malformation in offspring.

7.2 Clinical implications

The studies in this thesis provide reassuring evidence that women with asthma have similar risks associated with pregnancy and with perinatal outcomes to women without asthma. Three principal implications can be drawn for women with asthma:

Firstly, this research provides the most compelling evidence thus far in support of the current clinical guidelines on the management of asthma during pregnancy. In view of the established effectiveness of asthma medications in reducing immediate and prolonged morbidity from asthma symptoms, it is advisable not to alter current practice of optimal monitoring and pharmacological management of asthma in women of childbearing age and pregnant women.

Secondly, with regard to the potential teratogenic effect of cromones, it is advisable that theses medications are avoided during pregnancy unless future studies provide evidence otherwise. The UK guidelines on asthma management currently contain no information on the use of cromones during pregnancy and the US guidelines include only two small human studies, so this information is an important addition.

Thirdly, the largest risk for women with asthma by far, was an increase in depression in pregnancy. This was independent of prior depression and increased with asthma severity. Increased vigilance in monitoring this complication should be considered in light of the established adverse effects of depression on pregnancy.

7.3 Suggestions for further research

- The finding of an increased risk of haemorrhage was unexpected and requires further investigation. Although this thesis captured rare, severe haemorrhage it is likely that less severe occurrences of haemorrhage were not included in the general practice data, and these also have clinical importance. One possible way to further study haemorrhage would be to use prospective data collection of from antenatal care starting in the first trimester. These data would provide the most comprehensive information on prevalence and severity of antepartum and postpartum haemorrhage. With information from numerous clinical centres, a case-control approach would be the most efficient way to assess the risk associated with maternal asthma and asthma severity.

- The increased risk of miscarriage was also unexpected and needs consideration. Miscarriage is difficult to study because women recognise their pregnancies at different stages of gestation and many miscarriages occur without the woman notifying any medical care services. A large case-control study of women with multiple miscarriages could provide initial information as to whether the risk found in this thesis is a true increase. To study the impact of current asthma

severity on miscarriage, however, a cohort study of women from the first identification of pregnancy would be required.

- The potential for higher depression rates in pregnant women with asthma compared with pregnant women without asthma is of great importance for monitoring and clinical management as it is perhaps the biggest threat to the obstetric health of these women. Depression has already been recognised as a significant problem during pregnancy and in the postnatal period. Higher rates of depression are also found in people with chronic conditions, including asthma, than in people without chronic medical conditions. Further clarification is needed to determine whether the increased risk of gestational depression found in this study is specifically associated with pregnancy or whether it represents the already higher prevalence of depression in all women with asthma. A cohort study of the incidence of depression and antidepressant use in pre-conception, gestational and postnatal periods has already been planned using the thesis data. This approach could also identify whether antenatal or postnatal depression is modified by changes in asthma severity and acute exacerbations in pregnancy.

- Although the teratogenic assessment of asthma medications in this population indicated that they were generally safe, larger studies are still required to assess newer drugs. Cromones are now in less use, however, population-based case-control studies of leukotriene receptor antagonists will be needed as these medications become more widely used.

- The studies in this thesis have also demonstrated the usefulness of primary care data as a research tool for perinatal epidemiology, a field which requires large study populations. This provides an exciting opportunity to assess the impact of other chronic illnesses and gestational drug exposures on pregnancy and perinatal outcomes.

Appendix A. Published papers from thesis work

LJ Tata, RB Hubbard, TM McKeever, CJP Smith, P Doyle, L Smeeth, J West and SA Lewis. Fertility Rates in Women with Asthma, Eczema and Hay Fever: A General Population-Based Cohort Study. ***American Journal of Epidemiology 2007; 165(9): 1023-30.***

LJ Tata, SA Lewis, TM McKeever, CJP Smith, P Doyle, L Smeeth, J West and RB Hubbard. A Comprehensive Analysis of Adverse Obstetric and Pediatric Complications in Women with Asthma. ***American Journal of Respiratory and Critical Care Medicine 2007; 175(10): 991-7.***

LJ Tata, SA Lewis, TM McKeever, CJP Smith, P Doyle, L Smeeth, JE Gibson and RB Hubbard. Congenital malformations in children born to women with asthma. ***Submitted and currently under review.***

Appendix B. Abstracts of thesis work presented at conferences

American Thoracic Society International Conference, May 2006

Oral presentation of original research:

Fertility in Women with Asthma, Eczema and Hay Fever: A Population-Based Cohort Study

L.J. Tata[1], C.JP. Smith[2], T.M. McKeever[1], P. Doyle[3], L. Smeeth[3], J. West[1], J. Britton[1], S.A. Lewis[2] and R.B. Hubbard[1]

[1]Epidemiology & Public Health, University of Nottingham, Nottingham, England; [2]Respiratory Medicine, University of Nottingham, Nottingham, England and [3]Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, London, England

Introduction It has been suggested that the protective impact of higher birth order on the risk of developing allergic disease is mediated by decreased fertility in women with allergic disease. Furthermore, current evidence indicates that women with asthma have later onset of menarche and irregular menstruation, thereby possibly reducing their fertility.

Methods We used computerised primary care data from the United Kingdom to conduct a cohort analysis of 491,538 women. We estimated the general fertility rate (number of live births per female population age 15 to 45 years) and age-specific fertility rates over the period of 1994 to 2004. We compared these rates in women with asthma, eczema or hay fever to women without these diagnoses, using Poisson regression.

Results Fertility rates were 53.0 and 52.3 live births per 1,000 person-years in women with and without asthma, respectively. The fertility rate ratio for women with asthma compared to women without asthma was 1.02, 95% confidence interval (CI) 1.00-1.04 after adjusting for age, smoking status and body mass index. The equivalent fertility rate ratios for women with eczema or hay fever were 1.15, 95%CI 1.13-1.17 and 1.09, 95%CI 1.07-1.11, respectively. Age-specific fertility rates were similar to the overall rates when we compared women in each allergic disease group to women in the general population.

Conclusion We found no evidence to suggest that the fertility of women with asthma, eczema or hay fever is lower than that of women in the general population. Indeed there is some evidence that their fertility rates are slightly higher than that expected over this period.

European Respiratory Society Annual Congress, October 2006

Oral presentation of original research:

Adverse pregnancy outcomes in women with asthma

L J Tata[1], C JP Smith[3], T M McKeever[1], P Doyle[2], L Smeeth[2], J West[1], J Britton[1], S A Lewis[3] and R B Hubbard[1]

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Introduction Previous studies have raised concern that women with asthma have increased risks of obstetric complication and have babies with reduced foetal growth and higher risk of neonatal death. No studies have quantified risks of stillbirth, miscarriage and therapeutic abortion in women with asthma compared to women in the general population.

Methods We extracted information on 371,210 pregnancies in 231,410 women from computerised primary care data in the United Kingdom. Using logistic regression, we compared the risk of stillbirth, miscarriage (spontaneous abortion) or therapeutic abortion in women with asthma to that in women without asthma. We calculated odds ratios (OR) with 95% confidence intervals (CI) unadjusted and adjusted for maternal age, smoking status and body mass index.

Results In 49,223 pregnancies in women with asthma, there was no evidence of an increased risk of stillbirth when compared to 321,987 pregnancies in women without asthma (Table). Women with asthma had a modest increase in risk of miscarriage however they were less likely to have a therapeutic abortion.

Conclusion We found reassuring evidence that women with asthma are not at a large increased risk of adverse pregnancy outcome compared to women without asthma. Although some evidence indicates that they are more likely to experience miscarriage, they have the same risk of stillbirth and have lower risk of therapeutic abortion compared to women in the general population.

Adverse pregnancy outcome	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Stillbirth	1.04 (0.90 to 1.20)	1.00 (0.87 to 1.16)
Miscarriage	1.10 (1.07 to 1.14)	1.13 (1.10 to 1.16)
Therapeutic abortion	1.03 (1.01 to 1.06)	0.93 (0.91 to 0.96)

The 23rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 2007

Submitted for oral or poster presentation of original research:

Congenital Malformations in Children born to Women with Asthma

L J Tata[1], S A Lewis[1], T M McKeever[1], C JP Smith[1], P Doyle[2], L Smeeth[2], J E Gibson[1] and R B Hubbard[1]

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Background: Clinical advice to pregnant women with asthma is to maintain optimal therapeutic management, however, the potential adverse effects of asthma treatments on foetal development remain uncertain. Considering that congenital malformations remain one of the leading causes of neonatal mortality in western countries and that asthma now affects 10% of pregnant women, there is pressing need for large studies to examine the potential teratogenic effects of asthma medications.
Objectives: To assess the association of maternal asthma and gestational exposure to asthma medication with the risk of congenital malformation
Methods: Using primary care data from The Health Improvement Network, we conducted a matched case-control study.
Results: 5,124 cases of children born with congenital malformations and 30,053 matched controls were included. Children born to women with asthma had a marginal increased risk of major congenital malformation (OR=1.10, 95%CI 1.01-1.20). However, no association was present in children born to women receiving asthma treatment in the year before or during pregnancy (OR=1.06, 95%CI 0.94-1.20). Gestational exposure to short acting-agonists, inhaled corticosteroids, long acting-agonists, oral corticosteroids, other bronchodilator medications or cromones was not associated with an increased risk of malformation overall. Maternal asthma was associated with circulatory system malformations in children (OR=1.20, 95%CI 1.01-1.43) and this increase in risk was primarily in children with gestational short acting-agonist and corticosteroid exposure. There was a similar risk of musculoskeletal system malformation associated with maternal asthma (OR=1.25, 95%CI 1.06-1.47) which was primarily in children with gestational cromones.
Conclusions: Women with currently treated asthma did not have an increased risk of having children with congenital malformation, although we found some evidence of an increased risk for women with previous asthma diagnoses. Gestational asthma drug exposures were safe overall, however, cromones may pose moderate risk and the potential risk of circulatory system malformation associated with some asthma medications is of concern.

Appendix C. Code lists of medical diagnoses, clinical measurements and prescriptions on attached CD

Medical 1. Pregnancy and delivery

Medical 2. Gestation (preterm, term, post-term delivery)

Medical 3. Birth weight (low, normal, high birth weight)

Medical 4. Fetal position in utero

Medical 5. Mode of delivery

Medical 6. Congenital malformation (11 system-specific malformation groups)

Medical 7. Haemorrhage (antepartum and postpartum)

Medical 8. Placental insufficiency

Medical 9. Placental abruption

Medical 10. Placenta praevia

Medical 11. pre-eclampsia and eclampsia

Medical 12. Hypertension (general and pregnancy-specific)

Medical 13. Diabetes (general and pregnancy-specific)

Medical 14. Anaemia (general and pregnancy-specific)

Medical 15. Thyroid disorder (general and pregnancy-specific)

Medical 16. Depression (general and pregnancy-specific)

Medical 17. Blood pressure

Medical 18. Stillbirth

Medical 19. Miscarriage

Medical 20. Therapeutic abortion

Medical 21. Asthma (asthma diagnoses and asthma exacerbations)

Medical 22. Eczema

Medical 23. Hay fever

Medical 24. Smoking status

Medical 25. Body mass index (weight and height)

Prescription 1. Short acting β-agonist

Prescription 2. Inhaled corticosteroid

Prescription 3. Long acting β-agonist

Prescription 4. Oral corticosteroid

Prescription 5. Other bronchodilator

Prescription 6. Other anti-inflammatory

Prescription 7. Combination therapy of respiratory medication

References

1. Lordan JL, Holgate ST. Recent developments in the pathogenesis and epidemiological trends of asthma. *J R Coll Physicians Lond* 1999;33(5):418-25.

2. Braman SS. The global burden of asthma. *Chest* 2006;130(1 Suppl):4S-12S.

3. WHO. Asthma - Factsheet No. 307: http://www.who.int/mediacentre/factsheets/fs307/en/. World Health Organisation. August 2006.

4. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59(5):469-78.

5. Jarvis D, Lai E, Luczynska C, Chinn S, Burney P. Prevalence of asthma and asthma-like symptoms in young adults living in three east Anglian towns. *Br J Gen Pract* 1994;44(388):493-7.

6. de Marco R, Locatelli F, Sunyer J, Burney P. Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med* 2000;162(1):68-74.

7. Eagan TM, Bakke PS, Eide GE, Gulsvik A. Incidence of asthma and respiratory symptoms by sex, age and smoking in a community study. *Eur Respir J* 2002;19(4):599-605.

8. Schatz M, Camargo CA, Jr. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Ann Allergy Asthma Immunol* 2003;91(6):553-8.

9. Bodner C, Ross S, Douglas G, et al. The prevalence of adult onset wheeze: longitudinal study. *Bmj* 1997;314(7083):792-3.

10. Oswald H, Phelan PD, Lanigan A, Hibbert M, Bowes G, Olinsky A. Outcome of childhood asthma in mid-adult life. *Bmj* 1994;309(6947):95-6.

11. Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. *Ann Epidemiol* 2003;13(5):317-24.

12. Hoare J, Bruce M, Majeed A. Prevalence of treated asthma and its management in general practice in England and Wales, 1994-1998. *Health Statistics Quarterly 17, Spring 2003*.

13. Higenbottam T, Hay I. Has the treatment of asthma improved? *Chest* 1990;98(3):706-12.

14. Watson JP, Cowen P, Lewis RA. The relationship between asthma admission rates, routes of admission, and socioeconomic deprivation. *Eur Respir J* 1996;9(10):2087-93.

15. Rona RJ. Asthma and poverty. *Thorax* 2000;55(3):239-44.

16. Rees J. ABC of asthma. Prevalence. *Bmj* 2005;331(7514):443-5.

17. CEMD. Why mothers die 1997-1999: The confidential enquiries into maternal deaths in the United Kingdom: Confidential Enquiry into Maternal Deaths. Published by the Royal College of Obstetricians and Gynaecologists. London; 2001.

18. Atrash HK, Johnson K, Adams MM, Cordero JF, Howse J. Preconception care for improving perinatal outcomes: the time to act. *Matern Child Health J* 2006;10(5 Suppl):3-11.

19. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. *Bmj* 2001;322(7294):1089-93; discussion 1093-4.

20. Wen SW, Huang L, Liston R, et al. Severe maternal morbidity in Canada, 1991-2001. *Cmaj* 2005;173(7):759-64.

21. Danel I, Berg C, Johnson CH, Atrash H. Magnitude of maternal morbidity during labor and delivery: United States, 1993-1997. *Am J Public Health* 2003;93(4):631-4.

22. Duley L, Meher S, Abalos E. Management of pre-eclampsia. *Bmj* 2006;332(7539):463-8.

23. Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. *Lancet* 2001;357(9249):53-6.

24. CEMACH. Perinatal Mortality Surveillance Report 2004: England, Wales and Northern Ireland: Confidential Enquiry into Maternal and Child Health. Manor Press, Maidenhead, Berks., 2006.

25. Fretts RC. Etiology and prevention of stillbirth. *Am J Obstet Gynecol* 2005;193(6):1923-35.

26. Cooper N. Chapter 7: Analysis of infant mortality risk factors and by cause of death in England and Wales in Geographic Variations in Health - Decennial Supplement DS16: Published with permission of the Controller of Her Majesty's Stationery Office (HMSO). Office for National Statistics, London, England, 2002.

27. Petrini J, Damus K, Russell R, Poschman K, Davidoff MJ, Mattison D. Contribution of birth defects to infant mortality in the United States. *Teratology* 2002;66 Suppl 1:S3-6.

28. Petrini J, Damus K, Johnston RB, Jr. An overview of infant mortality and birth defects in the United States. *Teratology* 1997;56(1-2):8-10.

29. Liu S, Joseph KS, Wen SW, et al. Secular trends in congenital anomaly-related fetal and infant mortality in Canada, 1985-1996. *Am J Med Genet* 2001;104(1):7-13.

30. Bell R, Glinianaia SV, Rankin J, Wright C, Pearce MS, Parker L. Changing patterns of perinatal death, 1982-2000: a retrospective cohort study. *Arch Dis Child Fetal Neonatal Ed* 2004;89(6):F531-6.

31. Bell R, Parker L, MacPhail S, Wright C. Trends in the cause of late fetal death, 1982-2000. *Bjog* 2004;111(12):1400-7.

32. ONS. Series FM1 no.34: Birth Statistics - Review of the registrar general on births and patterns of family building in England and Wales, 2005.

33. ONS. Series FM1 no.29: Birth Statistics - Review of the registrar general on births and patterns of family building in England and Wales, 2000.

34. Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: mechanisms and treatment implications. *Eur Respir J* 2005;25(4):731-50.

35. Schatz M. Interrelationships between asthma and pregnancy: a literature review. *J Allergy Clin Immunol* 1999;103(2 Pt 2):S330-6.

36. Sears MR. Descriptive epidemiology of asthma. *Lancet* 1997;350 Suppl 2:SII1-4.

37. Schatz M. Special considerations for the pregnant woman and senior citizen with airway disease. *J Allergy Clin Immunol* 1998;101(2 Pt 2):S373-8.

38. Schatz M. Asthma and pregnancy. *Lancet* 1999;353(9160):1202-4.

39. Murphy VE, Gibson PG, Giles WB, et al. Maternal asthma is associated with reduced female fetal growth. *Am J Respir Crit Care Med* 2003;168(11):1317-23.

40. Namazy JA, Schatz M. Treatment of asthma during pregnancy and perinatal outcomes. *Curr Opin Allergy Clin Immunol* 2005;5(3):229-33.

41. Bahna SL, Bjerkedal T. The course and outcome of pregnancy in women with bronchial asthma. *Acta Allergol* 1972;27(5):397-406.

42. Jadad AR, Sigouin C, Mohide PT, Levine M, Fuentes M. Risk of congenital malformations associated with treatment of asthma during early pregnancy. *Lancet* 2000;355(9198):119.

43. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. *Obstet Gynecol* 1999;93(3):392-5.

44. Kallen B, Rydhstroem H, Aberg A. Asthma during pregnancy--a population based study. *Eur J Epidemiol* 2000;16(2):167-71.

45. Kramer MS, Coates AL, Michoud MC, et al. Maternal asthma and idiopathic preterm labor. *Am J Epidemiol* 1995;142(10):1078-88.

46. Schatz M, Dombrowski MP, Wise R, et al. The relationship of asthma medication use to perinatal outcomes. *J Allergy Clin Immunol* 2004;113(6):1040-5.

47. Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. *Am J Respir Crit Care Med* 1998;158(4):1091-5.

48. Liu S, Wen SW, Demissie K, Marcoux S, Kramer MS. Maternal asthma and pregnancy outcomes: a retrospective cohort study. *Am J Obstet Gynecol* 2001;184(2):90-6.

49. Wen SW, Demissie K, Liu S. Adverse outcomes in pregnancies of asthmatic women: results from a Canadian population. *Ann Epidemiol* 2001;11(1):7-12.

50. Demissie K, Marcella SW, Breckenridge MB, Rhoads GG. Maternal asthma and transient tachypnea of the newborn. *Pediatrics* 1998;102(1 Pt 1):84-90.

51. Schatz M, Zeiger RS, Hoffman CP, et al. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. *Am J Respir Crit Care Med* 1995;151(4):1170-4.

52. Sheiner E, Mazor M, Levy A, Wiznitzer A, Bashiri A. Pregnancy outcome of asthmatic patients: a population-based study. *J Matern Fetal Neonatal Med* 2005;18(4):237-40.

53. Tamasi L, Somoskovi A, Muller V, et al. A population-based case-control study on the effect of bronchial asthma during pregnancy for congenital abnormalities of the offspring. *J Asthma* 2006;43(1):81-6.

54. Rizk NW, Kalassian KG, Gilligan T, Druzin MI, Daniel DL. Obstetric complications in pulmonary and critical care medicine. *Chest* 1996;110(3):791-809.

55. Gluck JC, Gluck P. The effects of pregnancy on asthma: a prospective study. *Ann Allergy* 1976;37(3):164-8.

56. Gravett MG, Holmes KK. Pregnancy outcome and maternal infection: the need for comprehensive studies. *Jama* 1983;250(13):1751-2.

57. Schieve LA, Handler A, Hershow R, Persky V, Davis F. Urinary tract infection during pregnancy: its association with maternal morbidity and perinatal outcome. *Am J Public Health* 1994;84(3):405-10.

58. Murphy VE, Zakar T, Smith R, Giles WB, Gibson PG, Clifton VL. Reduced 11beta-hydroxysteroid dehydrogenase type 2 activity is associated with decreased birth weight centile in pregnancies complicated by asthma. *J Clin Endocrinol Metab* 2002;87(4):1660-8.

59. Balzano G, Fuschillo S, Melillo G, Bonini S. Asthma and sex hormones. *Allergy* 2001;56(1):13-20.

60. Asthma, progesterone, and pregnancy. *Lancet* 1990;335(8683):204.

61. Saleem MA, Jha P, Buckshee K, Farooq A. Studies on the immunosuppressive role of steroid hormones during pregnancy. *Immunol Invest* 1992;21(1):1-10.

62. Juniper EF, Daniel EE, Roberts RS, Kline PA, Hargreave FE, Newhouse MT. Improvement in airway responsiveness and asthma severity during pregnancy. A prospective study. *Am Rev Respir Dis* 1989;140(4):924-31.

63. Juniper EF, Daniel EE, Roberts RS, Kline PA, Hargreave FE, Newhouse MT. Effect of pregnancy on airway responsiveness and asthma severity. Relationship to serum progesterone. *Am Rev Respir Dis* 1991;143(3 Pt 2):S78.

64. Hardy CC, Lorigan P, Ratcliffe A, Carroll KB. Asthma in pregnancy complicated by iatrogenic pulmonary oedema. *Postgrad Med J* 1989;65(764):407-9.

65. Holland SM, Thomson KD. Acute severe asthma presenting in late pregnancy. *Int J Obstet Anesth* 2006;15(1):75-8.

66. Gelber M, Sidi Y, Gassner S, et al. Uncontrollable life-threatening status asthmaticus--an indicator for termination of pregnancy by cesarean section. *Respiration* 1984;46(3):320-2.

67. Shanies HM, Venkataraman MT, Peter T. Reversal of intractable acute severe asthma by first-trimester termination of pregnancy. *J Asthma* 1997;34(2):169-72.

68. Baker ER, Flanagan MF. Fetal atrial flutter associated with maternal beta-sympathomimetic drug exposure. *Obstet Gynecol* 1997;89(5 Pt 2):861.

69. Patterson R, Greenberger PA, Frederiksen MC. Asthma and pregnancy: responsibility of physicians and patients. *Ann Allergy* 1990;65(6):469-72.

70. Apter AJ, Greenberger PA, Patterson R. Outcomes of pregnancy in adolescents with severe asthma. *Arch Intern Med* 1989;149(11):2571-5.

71. Greenberger PA, Patterson R. Beclomethasone diproprionate for severe asthma during pregnancy. *Ann Intern Med* 1983;98(4):478-80.

72. Walsh LJ, Wong CA, Cooper S, Guhan AR, Pringle M, Tattersfield AE. Morbidity from asthma in relation to regular treatment: a community based study. *Thorax* 1999;54(4):296-300.

73. Schatz M, Leibman C. Inhaled corticosteroid use and outcomes in pregnancy. *Ann Allergy Asthma Immunol* 2005;95(3):234-8.

74. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax* 2006;61(2):169-76.

75. NIH. NAEPP Report of the Working Group on Asthma and Pregnancy: Management of Asthma During Pregnancy. Available from URL: http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.txt. Bethesda, MD, U.S. Department of Health and Human Servies; National Institutes of Health; National Heart, Lung and Blood Institute, 1993.

76. Schatz M, Dombrowski MP, Wise R, et al. Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol* 2003;112(2):283-8.

77. Cydulka RK, Emerman CL, Schreiber D, Molander KH, Woodruff PG, Camargo CA, Jr. Acute asthma among pregnant women presenting to the emergency department. *Am J Respir Crit Care Med* 1999;160(3):887-92.

78. Enriquez R, Wu P, Griffin MR, et al. Cessation of asthma medication in early pregnancy. *Am J Obstet Gynecol* 2006;195(1):149-53.

79. BTS. The British guidelines on asthma management. British Thoracic Society. *Thorax* 2003;58 Suppl 1:i1-94.

80. BTS. The British Guideline on the Management of Asthma. British Thoracic Society. 2003;Revised edition April 2004.

81. Headley J, Northstone K, Simmons H, Golding J. Medication use during pregnancy: data from the Avon Longitudinal Study of Parents and Children. *Eur J Clin Pharmacol* 2004;60(5):355-61.

82. Hardy JR, Leaderer BP, Holford TR, Hall GC, Bracken MB. Safety of medications prescribed before and during early pregnancy in a cohort of 81,975 mothers from the UK General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2006;15(8):555-64.

83. Namazy JA, Schatz M. Update in the treatment of asthma during pregnancy. *Clin Rev Allergy Immunol* 2004;26(3):139-48.

84. Namazy JA, Schatz M. Pregnancy and asthma: recent developments. *Curr Opin Pulm Med* 2005;11(1):56-60.

85. Liccardi G, Cazzola M, Canonica GW, D'Amato M, D'Amato G, Passalacqua G. General strategy for the management of bronchial asthma in pregnancy. *Respir Med* 2003;97(7):778-89.

86. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol* 1997;100(3):301-6.

87. Gluck PA, Gluck JC. A review of pregnancy outcomes after exposure to orally inhaled or intranasal budesonide. *Curr Med Res Opin* 2005;21(7):1075-84.

88. Schatz M, Zeiger RS, Harden KM, et al. The safety of inhaled beta-agonist bronchodilators during pregnancy. *J Allergy Clin Immunol* 1988;82(4):686-95.

89. Kelsen SG. Asthma and pregnancy. *J Allergy Clin Immunol* 2003;112(2):268-70.

90. Rayburn WF, Atkinson BD, Gilbert K, Turnbull GL. Short-term effects of inhaled albuterol on maternal and fetal circulations. *Am J Obstet Gynecol* 1994;171(3):770-3.

91. Wilton LV, Shakir SA. A post-marketing surveillance study of formoterol (Foradil): its use in general practice in England. *Drug Saf* 2002;25(3):213-23.

92. Wilton LV, Pearce GL, Martin RM, Mackay FJ, Mann RD. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. *Br J Obstet Gynaecol* 1998;105(8):882-9.

93. Rahimi R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. *Hum Exp Toxicol* 2006;25(8):447-52.

94. Makino S, Fueki M, Fueki N. Efficacy and safety of methylxanthines in the treatment of asthma. *Allergology International* 2004;53:13-22.

95. Harrison TW, Wisniewski A, Honour J, Tattersfield AE. Comparison of the systemic effects of fluticasone propionate and budesonide given by dry powder inhaler in healthy and asthmatic subjects. *Thorax* 2001;56(3):186-91.

96. Dombrowski MP, Schatz M, Wise R, et al. Randomized trial of inhaled beclomethasone dipropionate versus theophylline for moderate asthma during pregnancy. *Am J Obstet Gynecol* 2004;190(3):737-44.

97. Wendel PJ, Ramin SM, Barnett-Hamm C, Rowe TF, Cunningham FG. Asthma treatment in pregnancy: a randomized controlled study. *Am J Obstet Gynecol* 1996;175(1):150-4.

98. Sheffer AL, Silverman M, Woolcock AJ, Diaz PV, Lindberg B, Lindmark B. Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study. *Ann Allergy Asthma Immunol* 2005;94(1):48-54.

99. Silverman M, Sheffer A, Diaz PV, et al. Outcome of pregnancy in a randomized controlled study of patients with asthma exposed to budesonide. *Ann Allergy Asthma Immunol* 2005;95(6):566-70.

100. Cragan JD, Friedman JM, Holmes LB, Uhl K, Green NS, Riley L. Ensuring the safe and effective use of medications during pregnancy: planning and prevention through preconception care. *Matern Child Health J* 2006;10(5 Suppl):129-35.

101. Demoly P, Daures JP. Managing asthma during pregnancy. *Lancet* 2005;365(9466):1212-3.

102. NIH. NAEPP Working Group Report on managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment. Update 2004. Bethesda, MD, U.S. Department of Health and Human Servies; National Institutes of Health; National Heart, Lung and Blood Institute, March 2005.

103. Bennett JA, Harrison TW, Tattersfield AE. The contribution of the swallowed fraction of an inhaled dose of salmeterol to it systemic effects. *Eur Respir J* 1999;13(2):445-8.

104. Gardey-Levassort C, Richard MO, Hauguel S, Thiroux G, Olive G. [3H]-Salbutamol placental transfer in pregnant rats on the 19th day of gestation. *Dev Pharmacol Ther* 1982;4(3-4):151-7.

105. Andersson P, Appelgren LE, Ryrfeldt A. Tissue distribution and fate of budesonide in the mouse. *Acta Pharmacol Toxicol (Copenh)* 1986;59(5):392-402.

106. Hagopian GS, Hoover DM, Markham JK. Teratology studies of compound LY171883 administered orally to rats and rabbits. *Fundam Appl Toxicol* 1988;10(4):672-81.

107. Zhou M, Walker BE. Potentiation of triamcinolone-induced cleft palate in mice by maternal high dietary fat. *Teratology* 1993;48(1):53-7.

108. Walker BE. Cleft Palate Produced in Mice by Human-Equivalent Dosage with Triamcinolone. *Science* 1965;149(3686):862-63.

109. Kihlstrom I, Lundberg C. Teratogenicity study of the new glucocorticosteroid budesonide in rabbits. *Arzneimittelforschung* 1987;37(1):43-6.

110. Fainstat T. Cortisone-induced congenital cleft palate in rabbits. *Endocrinology* 1954;55(4):502-8.

111. Reinisch JM, Simon NG, Karow WG, Gandelman R. Prenatal exposure to prednisone in humans and animals retards intrauterine growth. *Science* 1978;202(4366):436-8.

112. Alexander DJ, Mather A, Dines GD. A snout-only inhalation exposure system for use in rabbit teratology studies. *Inhalation Toxicology* 1997;9(5):477-90.

113. NTP Toxicology and Carcinogenesis Studies of Theophylline (CAS No. 58-55-9) in F344/N Rats and B6C3F1 Mice (Feed and Gavage Studies). *Natl Toxicol Program Tech Rep Ser* 1998;473:1-326.

114. Lindamood C, 3rd, Lamb JCt, Bristol DW, Collins JJ, Heath JE, Prejean JD. Studies on the short-term toxicity of theophylline in rats and mice. *Fundam Appl Toxicol* 1988;10(3):477-89.

115. Hart AD, Grimble RF. The effect of methylxanthines on milk volume and composition, and growth of rat pups. *Br J Nutr* 1990;64(2):339-50.

116. Hart AD, Grimble RF. Effect of methylxanthines on lactational performance of rats. *Ann Nutr Metab* 1990;34(5):297-302.

117. Lamb J. Reproductive toxicology. Theophylline. *Environ Health Perspect* 1997;105 Suppl 1:355-6.

118. Morrissey RE, Collins JJ, Lamb JCt, Manus AG, Gulati DK. Reproductive effects of theophylline in mice and rats. *Fundam Appl Toxicol* 1988;10(3):525-36.

119. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. *N Engl J Med* 1998;338(16):1128-37.

120. Shields KE, Wiholm BE, Hostelley LS, Striano LF, Arena SR, Sharrar RG. Monitoring outcomes of pregnancy following drug exposure: a company-based pregnancy registry program. *Drug Saf* 2004;27(6):353-67.

121. Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996;49(2):247-50.

122. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care* 2004;12(3):171-7.

123. InPS. In Practice Systems. www.inps3.co.uk.

124. Lis Y, Mann RD. The VAMP Research multi-purpose database in the U.K. *J Clin Epidemiol* 1995;48(3):431-43.

125. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997;350(9084):1097-9.

126. EPIC. The General Practice Research Database - A Guide for Researchers. 2001.

127. BMA. British National Formulary no. 49. www.bnf.org: British Medical Association & Royal Pharmaceutical Society of Great Britain, March 2005.

128. Garcia Rodriguez LA, Perez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol* 1998;45(5):419-25.

129. Tata LJ, Card TR, Logan RF, Hubbard RB, Smith CJ, West J. Fertility and pregnancy-related events in women with celiac disease: a population-based cohort study. *Gastroenterology* 2005;128(4):849-55.

130. Wood SL, Jick H, Sauve R. The risk of stillbirth in pregnancies before and after the onset of diabetes. *Diabet Med* 2003;20(9):703-7.

131. Hollowell J. The General Practice Research Database: quality of morbidity data. *Popul Trends* 1997(87):36-40.

132. Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. A UK general practice database study of prevalence and mortality of people with neural tube defects. *Clin Rehabil* 2000;14(6):627-30.

133. Howard LM, Kumar C, Leese M, Thornicroft G. The general fertility rate in women with psychotic disorders. *Am J Psychiatry* 2002;159(6):991-7.

134. Howard LM, Goss C, Leese M, Thornicroft G. Medical outcome of pregnancy in women with psychotic disorders and their infants in the first year after birth. *Br J Psychiatry* 2003;182:63-7.

135. McKeever TM, Lewis SA, Smith C, et al. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. *Thorax* 2001;56(10):758-62.

136. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am J Respir Crit Care Med* 2000;161(1):5-8.

137. Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999;54(5):413-9.

138. Soriano JB, Maier WC, Visick G, Pride NB. Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database. *Eur J Epidemiol* 2001;17(12):1075-80.

139. Jick SS, Terris BZ. Anticonvulsants and congenital malformations. *Pharmacotherapy* 1997;17(3):561-4.

140. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2006.

141. EUROCAT. European Surveillance of Congenital Anomalies. Malformation Coding Guides (http://www.eurocat.ulster.ac.uk/pubdata/Publications.html).

142. Savitz DA, Hertz-Picciotto I, Poole C, Olshan AF. Epidemiologic measures of the course and outcome of pregnancy. *Epidemiol Rev* 2002;24(2):91-101.

143. Zimlichman E, Mandel D, Mimouni FB, Shochat T, Grotto I, Kreiss Y. Smoking habits in adolescents with mild to moderate asthma. *Pediatr Pulmonol* 2004;38(3):193-7.

144. Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. *Eur Respir J* 2004;24(5):822-33.

145. Hamzacebi H, Unsal M, Kayhan S, Bilgin S, Ercan S. Prevalence of asthma and respiratory symptoms by age, gender and smoking behaviour in Samsun, North Anatolia Turkey. *Tuberk Toraks* 2006;54(4):322-9.

146. Dodds L, King WD, Fell DB, Armson BA, Allen A, Nimrod C. Stillbirth Risk Factors According to Timing of Exposure. *Ann Epidemiol* 2006.

147. Little RE, Weinberg CR. Risk factors for antepartum and intrapartum stillbirth. *Am J Epidemiol* 1993;137(11):1177-89.

148. Jaakkola JJ, Gissler M. Maternal Smoking in Pregnancy, Fetal Development, and Childhood Asthma. *Am J Public Health* 2004;94(1):136-140.

149. Risch HA, Weiss NS, Clarke EA, Miller AB. Risk factors for spontaneous abortion and its recurrence. *Am J Epidemiol* 1988;128(2):420-30.

150. Tata LJ, West J, Harrison T, Farrington P, Smith C, Hubbard R. Does influenza vaccination increase consultations, corticosteroid prescriptions, or exacerbations in subjects with asthma or chronic obstructive pulmonary disease? *Thorax* 2003;58(10):835-9.

151. Lewis JD, Brensinger C. Agreement between GPRD smoking data: a survey of general practitioners and a population-based survey. *Pharmacoepidemiol Drug Saf* 2004;13(7):437-41.

152. Ray JG, Wyatt PR, Vermeulen MJ, Meier C, Cole DE. Greater maternal weight and the ongoing risk of neural tube defects after folic acid flour fortification. *Obstet Gynecol* 2005;105(2):261-5.

153. Sebire NJ, Jolly M, Harris J, Regan L, Robinson S. Is maternal underweight really a risk factor for adverse pregnancy outcome? A population-based study in London. *Bjog* 2001;108(1):61-6.

154. Sebire NJ, Jolly M, Harris JP, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. *Int J Obes Relat Metab Disord* 2001;25(8):1175-82.

155. Hancox RJ, Milne BJ, Poulton R, et al. Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. *Am J Respir Crit Care Med* 2005;171(5):440-5.

156. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005;171(4):334-9.

157. Olesen C, Thrane N, Henriksen TB, Ehrenstein V, Olsen J. Associations between socio-economic factors and the use of prescription medication during pregnancy: A population-based study among 19,874 Danish women. *Eur J Clin Pharmacol* 2006;62(7):547-53.

158. Austin JB, Selvaraj S, Godden D, Russell G. Deprivation, smoking, and quality of life in asthma. *Arch Dis Child* 2005;90(3):253-7.

159. Clausen T, Oyen N, Henriksen T. Pregnancy complications by overweight and residential area. A prospective study of an urban Norwegian cohort. *Acta Obstet Gynecol Scand* 2006;85(5):526-33.

160. Smith LK, Draper ES, Manktelow BN, Dorling JS, Field DJ. Socioeconomic inequalities in very preterm birth rates. *Arch Dis Child Fetal Neonatal Ed* 2007;92(1):F11-4.

161. Kramer MS, Seguin L, Lydon J, Goulet L. Socio-economic disparities in pregnancy outcome: why do the poor fare so poorly? *Paediatr Perinat Epidemiol* 2000;14(3):194-210.

162. Kramer MS, Goulet L, Lydon J, et al. Socio-economic disparities in preterm birth: causal pathways and mechanisms. *Paediatr Perinat Epidemiol* 2001;15 Suppl 2:104-23.

163. Morris R, Carstairs V. Which deprivation? A comparison of selected deprivation indexes. *J Public Health Med* 1991;13(4):318-26.

164. Shohaimi S, Welch A, Bingham S, et al. Area deprivation predicts lung function independently of education and social class. *Eur Respir J* 2004;24(1):157-61.

165. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. *Pharmacotherapy* 2003;23(5):686-9.

166. Burr ML, Wat D, Evans C, Dunstan FD, Doull IJ. Asthma prevalence in 1973, 1988 and 2003. *Thorax* 2006;61(4):296-9.

167. Phillips K, Harrison TW, Tattersfield A. New drugs in asthma. *J R Coll Physicians Lond* 1999;33(5):425-30.

168. Dildy GA, Jackson GM, Fowers GK, Oshiro BT, Varner MW, Clark SL. Very advanced maternal age: pregnancy after age 45. *Am J Obstet Gynecol* 1996;175(3 Pt 1):668-74.

169. Jolly MC, Sebire N, Harris J, Robinson S, Regan L. Obstetric risks of pregnancy in women less than 18 years old. *Obstet Gynecol* 2000;96(6):962-6.

170. Jolly M, Sebire N, Harris J, Robinson S, Regan L. The risks associated with pregnancy in women aged 35 years or older. *Hum Reprod* 2000;15(11):2433-7.

171. Kwon HL, Belanger K, Holford TR, Bracken MB. Effect of fetal sex on airway lability in pregnant women with asthma. *Am J Epidemiol* 2006;163(3):217-21.

172. Beecroft N, Cochrane GM, Milburn HJ. Effect of sex of fetus on asthma during pregnancy: blind prospective study. *Bmj* 1998;317(7162):856-7.

173. Dodds L, Armson BA, Alexander S. Use of asthma drugs is less among women pregnant with boys rather than girls. *Bmj* 1999;318(7189):1011.

174. Maconochie N, Doyle P, Prior S, Simmons R. Risk factors for first trimester miscarriage--results from a UK-population-based case-control study. *Bjog* 2007;114(2):170-86.

175. Ruddock V, Lancucki L. The calculation of abortion rates for England and Wales. *Health Satistics Quarterly*;10(Summer 2001).

176. Cleary-Goldman J, Malone FD, Vidaver J, et al. Impact of maternal age on obstetric outcome. *Obstet Gynecol* 2005;105(5 Pt 1):983-90.

177. Doull IJ. The effect of asthma and its treatment on growth. *Arch Dis Child* 2004;89(1):60-3.

178. Moudiou T, Theophilatou D, Priftis K, Papadimitriou A. Growth of asthmatic children before long-term treatment with inhaled corticosteroids. *J Asthma* 2003;40(6):667-71.

179. Svanes C, Real FG, Gislason T, et al. Association of asthma and hay fever with irregular menstruation. *Thorax* 2005;60(6):445-50.

180. Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. *Hum Reprod* 2002;17(10):2715-24.

181. Tan KS. Premenstrual asthma: epidemiology, pathogenesis and treatment. *Drugs* 2001;61(14):2079-86.

182. Vellutini M, Viegi G, Parrini D, et al. Serum immunoglobulins E are related to menstrual cycle. *Eur J Epidemiol* 1997;13(8):931-5.

183. Vrieze A, Postma DS, Kerstjens HA. Perimenstrual asthma: a syndrome without known cause or cure. *J Allergy Clin Immunol* 2003;112(2):271-82.

184. Tan KS, McFarlane LC, Lipworth BJ. Paradoxical down-regulation and desensitization of beta2-adrenoceptors by exogenous progesterone in female asthmatics. *Chest* 1997;111(4):847-51.

185. Rubio Ravelo L, Gago Rodriguez B, Almirall Collazo JJ, Bell Heredia L, Fernandez Fernandez L. Comparative study of progesterone, estradiol and cortisol concentrations in asthmatic and non-asthmatic women. *Allergol Immunopathol (Madr)* 1988;16(4):263-6.

186. Roby RR, Richardson RH, Vojdani A. Hormone allergy. *Am J Reprod Immunol* 2006;55(4):307-13.

187. Westergaard T, Begtrup K, Rostgaard K, Krause TG, Benn CS, Melbye M. Reproductive history and allergic rhinitis among 31145 Danish women. *Clin Exp Allergy* 2003;33(3):301-5.

188. Makhseed M, Raghupathy R, Azizieh F, Omu A, Al-Shamali E, Ashkanani L. Th1 and Th2 cytokine profiles in recurrent aborters with successful pregnancy and with subsequent abortions. *Hum Reprod* 2001;16(10):2219-26.

189. Piccinni MP, Scaletti C, Maggi E, Romagnani S. Role of hormone-controlled Th1- and Th2-type cytokines in successful pregnancy. *J Neuroimmunol* 2000;109(1):30-3.

190. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Reitmeir P, Thiemann HH. Skin test reactivity and number of siblings. *Bmj* 1994;308(6930):692-5.

191. Bodner C, Anderson WJ, Reid TS, Godden DJ. Childhood exposure to infection and risk of adult onset wheeze and atopy. *Thorax* 2000;55(5):383-7.

192. Strachan DP. Hay fever, hygiene, and household size. *Bmj* 1989;299(6710):1259-60.

193. Strachan DP, Harkins LS, Johnston ID, Anderson HR. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997;99(1 Pt 1):6-12.

194. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax* 2000;55 Suppl 1:S2-10.

195. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. *J Epidemiol Community Health* 2002;56(3):209-17.

196. McKeever TM, Lewis SA, Smith C, et al. Early exposure to infections and antibiotics and the incidence of allergic disease: a birth cohort study with the West Midlands General Practice Research Database. *J Allergy Clin Immunol* 2002;109(1):43-50.

197. Gibbs S, Surridge H, Adamson R, Cohen B, Bentham G, Reading R. Atopic dermatitis and the hygiene hypothesis: a case-control study. *Int J Epidemiol* 2004;33(1):199-207.

198. Cullinan P, Harris JM, Newman Taylor AJ, et al. Can early infection explain the sibling effect in adult atopy? *Eur Respir J* 2003;22(6):956-61.

199. Rona RJ, Duran-Tauleria E, Chinn S. Family size, atopic disorders in parents, asthma in children, and ethnicity. *J Allergy Clin Immunol* 1997;99(4):454-60.

200. Ponsonby AL, Couper D, Dwyer T, Carmichael A. Cross sectional study of the relation between sibling number and asthma, hay fever, and eczema. *Arch Dis Child* 1998;79(4):328-33.

201. Grodstein F, Goldman MB, Ryan L, Cramer DW. Self-reported use of pharmaceuticals and primary ovulatory infertility. *Epidemiology* 1993;4(2):151-6.

202. Karmaus W, Eneli I. Maternal atopy and the number of offspring: is there an association? *Pediatr Allergy Immunol* 2003;14(6):470-4.

203. Sunyer J, Anto JM, Harris J, et al. Maternal atopy and parity. *Clin Exp Allergy* 2001;31(9):1352-5.

204. Forastiere F, Sunyer J, Farchi S, et al. Number of offspring and maternal allergy. *Allergy* 2005;60(4):510-4.

205. ONS. Population Trends: Summer 2003. No.112: Published with permission of the Controller of Her Majesty's Stationery Office (HMSO). Office for National Statistics, London, England, 2003.

206. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. Lyon: IARC Scientific Publications No. 82, 1987.

207. Armitage B. Variation in fertility between different types of local area. *Popul Trends* 1997(87):20-8.

208. ONS. Population Trends: Spring 2003. No.111: Published with permission of the Controller of Her Majesty's Stationery Office (HMSO). Office for National Statistics, London, England, 2003.

209. Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics* 2000;56(2):645-6.

210. ONS. UK National Statistics Website: www.statistics.gov.uk. Crown copywright material is reproduced with the permission of the Controller of Her Majesty's Stationery Office (HMSO).

211. Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy* 2004;34(4):520-6.

212. Eagan TM, Brogger JC, Eide GE, Bakke PS. The incidence of adult asthma: a review. *Int J Tuberc Lung Dis* 2005;9(6):603-12.

213. Murphy M. Chapter 8: Household and family structure among ethnic minority groups. In: Coleman D, Salt J, eds. Ethnicity in the 1991 Census: Wolume 1: HMSO: London, 1996.

214. ONS. Population Trends: Summer 2002. No.108: Published with permission of the Controller of Her Majesty's Stationery Office (HMSO). Office for National Statistics, London, England, 2002.

215. Basagana X, Sunyer J, Kogevinas M, et al. Socioeconomic status and asthma prevalence in young adults: the European Community Respiratory Health Survey. *Am J Epidemiol* 2004;160(2):178-88.

216. Netuveli G, Hurwitz B, Levy M, et al. Ethnic variations in UK asthma frequency, morbidity, and health-service use: a systematic review and meta-analysis. *Lancet* 2005;365(9456):312-7.

217. Netuveli G, Hurwitz B, Sheikh A. Ethnic variations in incidence of asthma episodes in England & Wales: national study of 502,482 patients in primary care. *Respir Res* 2005;6:120.

218. Neame RL, Berth-Jones J, Kurinczuk JJ, Graham-Brown RA. Prevalence of atopic dermatitis in Leicester: a study of methodology and examination of possible ethnic variation. *Br J Dermatol* 1995;132(5):772-7.

219. Sheikh A, Panesar SS, Lasserson T, Netuveli G. Recruitment of ethnic minorities to asthma studies. *Thorax* 2004;59(7):634.

220. Karmaus W, Arshad SH, Sadeghnejad A, Twiselton R. Does maternal immunoglobulin E decrease with increasing order of live offspring? Investigation into maternal immune tolerance. *Clin Exp Allergy* 2004;34(6):853-9.

221. Harris JM, White C, Moffat S, Mills P, Newman Taylor AJ, Cullinan P. New pregnancies and loss of allergy. *Clin Exp Allergy* 2004;34(3):369-72.

222. Nilsson L, Kjellman NI, Lofman O, Bjorksten B. Parity among atopic and non-atopic mothers. *Pediatr Allergy Immunol* 1997;8(3):134-6.

223. Sunyer J, Anto JM, Plana E, et al. Maternal atopy and changes in parity. *Clin Exp Allergy* 2005;35(8):1028-32.

224. Rangaraj S, Doull I. Hormones not hygeine? Birth order and atopy. *Clin Exp Allergy* 2003;33(3):277-8.

225. Doull IJ. Does pregnancy prevent atopy? *Clin Exp Allergy* 2001;31(9):1335-7.

226. Agarwal SK, Marshall GD, Jr. Perimenstrual alterations in type-1/type-2 cytokine balance of normal women. *Ann Allergy Asthma Immunol* 1999;83(3):222-8.

227. Skobeloff EM, Spivey WH, Silverman R, Eskin BA, Harchelroad F, Alessi TV. The effect of the menstrual cycle on asthma presentations in the emergency department. *Arch Intern Med* 1996;156(16):1837-40.

228. Brenner BE, Holmes TM, Mazal B, Camargo CA, Jr. Relation between phase of the menstrual cycle and asthma presentations in the emergency department. *Thorax* 2005;60(10):806-9.

229. Zimmerman JL, Woodruff PG, Clark S, Camargo CA. Relation between phase of menstrual cycle and emergency department visits for acute asthma. *Am J Respir Crit Care Med* 2000;162(2 Pt 1):512-5.

230. Forastiere F, Agabiti N, Corbo GM, et al. Socioeconomic status, number of siblings, and respiratory infections in early life as determinants of atopy in children. *Epidemiology* 1997;8(5):566-70.

231. Ernst P, Demissie K, Joseph L, Locher U, Becklake MR. Socioeconomic status and indicators of asthma in children. *Am J Respir Crit Care Med* 1995;152(2):570-5.

232. Higgins BG, Britton JR. Geographical and social class effects on asthma mortality in England and Wales. *Respir Med* 1995;89(5):341-6.

233. Butland BK, Strachan DP, Lewis S, Bynner J, Butler N, Britton J. Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts. *Bmj* 1997;315(7110):717-21.

234. Ross S, Godden D, McMurray D, et al. Social effects of wheeze in childhood: a 25 year follow up. *Bmj* 1992;305(6853):545-8.

235. Sims CD, Chamberlain GV, de Swiet M. Lung function tests in bronchial asthma during and after pregnancy. *Br J Obstet Gynaecol* 1976;83(6):434-7.

236. Triche EW, Saftlas AF, Belanger K, Leaderer BP, Bracken MB. Association of asthma diagnosis, severity, symptoms, and treatment with risk of preeclampsia. *Obstet Gynecol* 2004;104(3):585-93.

237. Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe asthma exacerbations during pregnancy. *Obstet Gynecol* 2005;106(5 Pt 1):1046-54.

238. Dombrowski MP, Schatz M, Wise R, et al. Asthma during pregnancy. *Obstet Gynecol* 2004;103(1):5-12.

239. Sims CD. Asthma in pregnancy. *Proc R Soc Med* 1977;70(2):97.

240. Alexander S, Dodds L, Armson BA. Perinatal outcomes in women with asthma during pregnancy. *Obstet Gynecol* 1998;92(3):435-40.

241. Sobande AA, Archibong EI, Akinola SE. Pregnancy outcome in asthmatic patients from high altitudes. *Int J Gynaecol Obstet* 2002;77(2):117-21.

242. Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. *Thorax* 1996;51(4):411-4.

243. Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. *Thorax* 1988;43(1):12-8.

244. Stenius-Aarniala B, Riikonen S, Teramo K. Slow-release theophylline in pregnant asthmatics. *Chest* 1995;107(3):642-7.

245. Beckmann CA. The effects of asthma on pregnancy and perinatal outcomes. *J Asthma* 2003;40(2):171-80.

246. Saraiya M, Berg CJ, Shulman H, Green CA, Atrash HK. Estimates of the annual number of clinically recognized pregnancies in the United States, 1981-1991. *Am J Epidemiol* 1999;149(11):1025-9.

247. Maconochie N, Doyle P, Prior S. The National Women's Health Study: assembly and description of a population-based reproductive cohort. *BMC Public Health* 2004;4(1):35.

248. Ananth CV, Berkowitz GS, Savitz DA, Lapinski RH. Placental abruption and adverse perinatal outcomes. *Jama* 1999;282(17):1646-51.

249. Ros HS, Cnattingius S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. *Am J Epidemiol* 1998;147(11):1062-70.

250. Magee LA, Ornstein MP, von Dadelszen P. Fortnightly review: management of hypertension in pregnancy. *Bmj* 1999;318(7194):1332-6.

251. Shennan AH. Recent developments in obstetrics. *Bmj* 2003;327(7415):604-8.

252. Douglas KA, Redman CW. Eclampsia in the United Kingdom. *Bmj* 1994;309(6966):1395-400.

253. CEMACH. Pregnancy in women with type1 and type 2 diabetes in 2002-2003, England, Wales and Northern Ireland. Confidenial Enquiry into Maternal and Child Health. London; 2005.

254. Ryan D, Milis L, Misri N. Depression during pregnancy. *Can Fam Physician* 2005;51:1087-93.

255. Evans J, Heron J, Francomb H, Oke S, Golding J. Cohort study of depressed mood during pregnancy and after childbirth. *Bmj* 2001;323(7307):257-60.

256. Heron J, O'Connor TG, Evans J, Golding J, Glover V. The course of anxiety and depression through pregnancy and the postpartum in a community sample. *J Affect Disord* 2004;80(1):65-73.

257. Rubertsson C, Wickberg B, Gustavsson P, Radestad I. Depressive symptoms in early pregnancy, two months and one year postpartum-prevalence and psychosocial risk factors in a national Swedish sample. *Arch Womens Ment Health* 2005;8(2):97-104.

258. Bowen A, Muhajarine N. Antenatal depression. *Can Nurse* 2006;102(9):26-30.

259. Montoro MN. Management of hypothyroidism during pregnancy. *Clin Obstet Gynecol* 1997;40(1):65-80.

260. Becker WF, Sudduth PG. Hyperthyroidism and pregnancy. *Ann Surg* 1959;149(6):867-72; discussion 872-4.

261. Drury MI. Hyperthyroidism in pregnancy. *J R Soc Med* 1986;79(6):317-8.

262. Dobson R. Caesarean section rate in England and Wales hits 21. *Bmj* 2001;323(7319):951.

263. Fleissig A. Prevalence of procedures in childbirth. *Bmj* 1993;306(6876):494-5.

264. Hofmeyr GJ, Hannah ME. Planned caesarean section for term breech delivery. *Cochrane Database Syst Rev* 2003(3):CD000166.

265. Chamberlain G, Steer P. ABC of labour care: operative delivery. *Bmj* 1999;318(7193):1260-4.

266. Joseph KS, Kramer MS, Marcoux S, et al. Determinants of preterm birth rates in Canada from 1981 through 1983 and from 1992 through 1994. *N Engl J Med* 1998;339(20):1434-9.

267. Steer P, Flint C. ABC of labour care: preterm labour and premature rupture of membranes. *Bmj* 1999;318(7190):1059-62.

268. Tucker J, McGuire W. Epidemiology of preterm birth. *Bmj* 2004;329(7467):675-8.

269. Chamberlain G. ABC of antenatal care. Small for gestational age. *Bmj* 1991;302(6792):1592-6.

270. Tucker MJ, Berg CJ, Callaghan WM, Hsia J. The Black-White disparity in pregnancy-related mortality from 5 conditions: differences in prevalence and case-fatality rates. *Am J Public Health* 2007;97(2):247-51.

271. Carroll KN, Griffin MR, Gebretsadik T, Shintani A, Mitchel E, Hartert TV. Racial differences in asthma morbidity during pregnancy. *Obstet Gynecol* 2005;106(1):66-72.

272. Chung KD, Demissie K, Rhoads GG. Asthma in pregnancy--its relationship with race, insurance, maternal education, and prenatal care utilization. *J Natl Med Assoc* 2004;96(11):1414-21.

273. Schatz M, Harden K, Forsythe A, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. *J Allergy Clin Immunol* 1988;81(3):509-17.

274. Kircher S, Schatz M, Long L. Variables affecting asthma course during pregnancy. *Ann Allergy Asthma Immunol* 2002;89(5):463-6.

275. Lao TT, Huengsburg M. Labour and delivery in mothers with asthma. *Eur J Obstet Gynecol Reprod Biol* 1990;35(2-3):183-90.

276. White RJ, Coutts, II, Gibbs CJ, MacIntyre C. A prospective study of asthma during pregnancy and the puerperium. *Respir Med* 1989;83(2):103-6.

277. Kwon HL, Belanger K, Bracken MB. Effect of pregnancy and stage of pregnancy on asthma severity: a systematic review. *Am J Obstet Gynecol* 2004;190(5):1201-10.

278. Mihrshahi S, Belousova E, Marks GB, Peat JK. Pregnancy and birth outcomes in families with asthma. *J Asthma* 2003;40(2):181-7.

279. Malm H, Martikainen J, Klaukka T, Neuvonen PJ. Prescription drugs during pregnancy and lactation--a Finnish register-based study. *Eur J Clin Pharmacol* 2003;59(2):127-33.

280. Schatz M, Hoffman C. Interrelationships between asthma and pregnancy: clinical and mechanistic considerations. *Clin Rev Allergy* 1987;5(4):301-15.

281. Garfield RE, Kannan MS, Daniel EE. Gap junction formation in myometrium: control by estrogens, progesterone, and prostaglandins. *Am J Physiol* 1980;238(3):C81-9.

282. Bielefeldt K, Waite L, Abboud FM, Conklin JL. Nongenomic effects of progesterone on human intestinal smooth muscle cells. *Am J Physiol* 1996;271(2 Pt 1):G370-6.

283. Everson GT. Gastrointestinal motility in pregnancy. *Gastroenterol Clin North Am* 1992;21(4):751-76.

284. Mabie WC. Asthma in pregnancy. *Clin Obstet Gynecol* 1996;39(1):56-69.

285. Mays M, Leiner S. Asthma. A comprehensive review. *J Nurse Midwifery* 1995;40(3):256-68.

286. Acs N, Puho E, Banhidy F, Czeizel AE. Association between bronchial asthma in pregnancy and shorter gestational age in a population-based study. *J Matern Fetal Neonatal Med* 2005;18(2):107-12.

287. Doucette JT, Bracken MB. Possible role of asthma in the risk of preterm labor and delivery. *Epidemiology* 1993;4(2):143-50.

288. Getahun D, Ananth CV, Peltier MR, Smulian JC, Vintzileos AM. Acute and chronic respiratory diseases in pregnancy: associations with placental abruption. *Am J Obstet Gynecol* 2006;195(4):1180-4.

289. Schatz M, Patterson R, Zeitz S, O'Rourke J, Melam H. Corticosteroid therapy for the pregnant asthmatic patient. *Jama* 1975;233(7):804-7.

290. Sorensen TK, Dempsey JC, Xiao R, Frederick IO, Luthy DA, Williams MA. Maternal asthma and risk of preterm delivery. *Ann Epidemiol* 2003;13(4):267-72.

291. Jana N, Vasishta K, Saha SC, Khunnu B. Effect of bronchial asthma on the course of pregnancy, labour and perinatal outcome. *J Obstet Gynaecol* 1995;21(3):227-32.

292. Perlow JH, Montgomery D, Morgan MA, Towers CV, Porto M. Severity of asthma and perinatal outcome. *Am J Obstet Gynecol* 1992;167(4 Pt 1):963-7.

293. Fitzsimons R, Greenberger PA, Patterson R. Outcome of pregnancy in women requiring corticosteroids for severe asthma. *J Allergy Clin Immunol* 1986;78(2):349-53.

294. Greenberger PA, Patterson R. The outcome of pregnancy complicated by severe asthma. *Allergy Proc* 1988;9(5):539-43.

295. Neff RK, Leviton A. Maternal theophylline consumption and the risk of stillbirth. *Chest* 1990;97(5):1266-7.

296. Schatz M, Zeiger RS, Hoffman CP. Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. Kaiser-Permanente Asthma and Pregnancy Study Group. *Chest* 1990;98(2):389-92.

297. Minerbi-Codish I, Fraser D, Avnun L, Glezerman M, Heimer D. Influence of asthma in pregnancy on labor and the newborn. *Respiration* 1998;65(2):130-5.

298. Dombrowski MP, Brown CL, Berry SM. Preliminary experience with triamcinolone acetonide during pregnancy. *J Matern Fetal Med* 1996;5(6):310-3.

299. Temmerman M, Chomba EN, Ndinya-Achola J, Plummer FA, Coppens M, Piot P. Maternal human immunodeficiency virus-1 infection and pregnancy outcome. *Obstet Gynecol* 1994;83(4):495-501.

300. Olesen C, Thrane N, Nielsen GL, Sorensen HT, Olsen J. A population-based prescription study of asthma drugs during pregnancy: changing the intensity of asthma therapy and perinatal outcomes. *Respiration* 2001;68(3):256-61.

301. Dombrowski M, Thom E, McNellis D. Maternal-Fetal Medicine Units (MFMU) studies of inhaled corticosteroids during pregnancy. *J Allergy Clin Immunol* 1999;103(2 Pt 2):S356-9.

302. Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. *Obstet Gynecol* 2003;102(4):739-52.

303. Norjavaara E, de Verdier MG. Normal pregnancy outcomes in a population-based study including 2,968 pregnant women exposed to budesonide. *J Allergy Clin Immunol* 2003;111(4):736-42.

304. Otsuka H, Narushima M, Suzuki H. Assessment of Inhaled Corticosteroid Therapy for Asthma Treatment during Pregnancy. *Allergology International* 2005;54:381-6.

305. Bakhireva LN, Jones KL, Schatz M, Johnson D, Chambers CD. Asthma medication use in pregnancy and fetal growth. *J Allergy Clin Immunol* 2005;116(3):503-9.

306. Namazy J, Schatz M, Long L, et al. Use of inhaled steroids by pregnant asthmatic women does not reduce intrauterine growth. *J Allergy Clin Immunol* 2004;113(3):427-32.

307. Martel MJ, Rey E, Beauchesne MF, et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. *Bmj* 2005.

308. Rudra CB, Williams MA, Frederick IO, Luthy DA. Maternal asthma and risk of preeclampsia: a case-control study. *J Reprod Med* 2006;51(2):94-100.

309. Martel MJ, Rey E, Beauchesne MF, et al. Use of short-acting beta(2)-agonists during pregnancy and the risk of pregnancy-induced hypertension. *J Allergy Clin Immunol* 2006.

310. Schatz M, Dombrowski MP, Wise R, et al. Spirometry is related to perinatal outcomes in pregnant women with asthma. *Am J Obstet Gynecol* 2006;194(1):120-6.

311. Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. Prevalence of depression during pregnancy: systematic review. *Obstet Gynecol* 2004;103(4):698-709.

312. Ford ES, Mannino DM, Homa DM, et al. Self-reported asthma and health-related quality of life: findings from the behavioral risk factor surveillance system. *Chest* 2003;123(1):119-27.

313. Roberts CL, Algert CS, Peat B, Henderson-Smart D. Small fetal size: a risk factor for breech birth at term. *Int J Gynaecol Obstet* 1999;67(1):1-8.

314. Andrade SE, Gurwitz JH, Davis RL, et al. Prescription drug use in pregnancy. *Am J Obstet Gynecol* 2004;191(2):398-407.

315. Mitchell AA. Systematic identification of drugs that cause birth defects--a new opportunity. *N Engl J Med* 2003;349(26):2556-9.

316. Gardner MJ, Schatz M, Cousins L, Zeiger R, Middleton E, Jusko WJ. Longitudinal effects of pregnancy on the pharmacokinetics of theophylline. *Eur J Clin Pharmacol* 1987;32(3):289-95.

317. Jerome CP, Hendrickx AG. Comparative teratogenicity of triamcinolone acetonide and dexamethasone in the rhesus monkey (Macaca mulatta). *J Med Primatol* 1988;17(4):195-203.

318. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000;62(6):385-92.

319. Rockenbauer M, Olsen J, Czeizel AE, Pedersen L, Sorensen HT. Recall bias in a case-control surveillance system on the use of medicine during pregnancy. *Epidemiology* 2001;12(4):461-6.

320. Czeizel AE, Petik D, Vargha P. Validation studies of drug exposures in pregnant women. *Pharmacoepidemiol Drug Saf* 2003;12(5):409-16.

321. Czeizel AE. The role of pharmacoepidemiology in pharmacovigilance: rational drug use in pregnancy. *Pharmacoepidemiol Drug Saf* 1999;8 Suppl 1:S55-61.

322. Wood SF. Women's health and the FDA. *N Engl J Med* 2005;353(16):1650-1.

323. Meijer WM, Cornel MC, Dolk H, de Walle HE, Armstrong NC, de Jong-van den Berg LT. The potential of the European network of congenital anomaly registers (EUROCAT) for drug safety surveillance: a descriptive study. *Pharmacoepidemiol Drug Saf* 2006;15(9):675-82.

324. EUROCAT. European Surveillance of Congenital Anomalies. Prevalence data 1988-2004 (http://www.bio-medical.co.uk/eurocatlive/results1.cgi accessed October 2006).

325. Boyd PA, Armstrong B, Dolk H, et al. Congenital anomaly surveillance in England--ascertainment deficiencies in the national system. *Bmj* 2005;330(7481):27.

326. Rankin J, Pattenden S, Abramsky L, et al. Prevalence of congenital anomalies in five British regions, 1991-99. *Arch Dis Child Fetal Neonatal Ed* 2005;90(5):F374-9.

327. Improved national prevalence estimates for 18 selected major birth defects--United States, 1999-2001. *MMWR Morb Mortal Wkly Rep* 2006;54(51):1301-5.

328. Botting B. Trends in neural tube defects: Health Statistics Quarterly 10. Published with permission of the Controller of Her Majesty's Stationery Office (HMSO). Office for National Statistics, London, England, Summer 2001.

329. Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural-tube defects. *N Engl J Med* 1999;341(20):1509-19.

330. Rankin J, Glinianaia S, Brown R, Renwick M. The changing prevalence of neural tube defects: a population-based study in the north of England, 1984-96. Northern Congenital Abnormality Survey Steering Group. *Paediatr Perinat Epidemiol* 2000;14(2):104-10.

331. Lipkowitz MA. The American College of Allergy, Asthma, and Immunology Registry for Allergic, Asthmatic Pregnant Patients (RAAPP). *J Allergy Clin Immunol* 1999;103(2 Pt 2):S364-72.

332. Blais L, Beauchesne MF, Rey E, Malo JL, Forget A. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among asthmatic women. *Thorax* 2006.

333. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. *Am J Med Genet* 1999;86(3):242-4.

334. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. *Teratology* 1997;56(5):335-40.

335. Queisser-Luft A, Eggers I, Stolz G, Kieninger-Baum D, Schlaefer K. Serial examination of 20,248 newborn fetuses and infants: correlations between drug exposure and major malformations. *Am J Med Genet* 1996;63(1):268-76.

336. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. *Teratology* 1998;58(1):2-5.

337. Czeizel AE, Puho E, Bartfai Z, Somoskovi A. A Possible Association between Oral Aminophylline Treatment during Pregnancy and Skeletal Congenital Abnormalities. *Clin Drug Invest* 2003;23(12):803-16.