

## RESEARCH ARTICLE

# Medicines prescribed for asthma, discontinuation and perinatal outcomes, including breastfeeding: A population cohort analysis

Gareth Davies<sup>1</sup>, Sue Jordan<sup>1\*</sup>, Daniel Thayer<sup>1</sup>, David Tucker<sup>2</sup>, Ioan Humphreys<sup>1</sup>

**1** Faculty of Health and Life Science, Swansea University, Swansea, United Kingdom, **2** Public Health Wales, Cardiff, United Kingdom

\* [s.e.jordan@swansea.ac.uk](mailto:s.e.jordan@swansea.ac.uk)



## OPEN ACCESS

**Citation:** Davies G, Jordan S, Thayer D, Tucker D, Humphreys I (2020) Medicines prescribed for asthma, discontinuation and perinatal outcomes, including breastfeeding: A population cohort analysis. PLoS ONE 15(12): e0242489. <https://doi.org/10.1371/journal.pone.0242489>

**Editor:** Calistus Wilunda, African Population and Health Research Center, KENYA

**Received:** February 14, 2020

**Accepted:** November 3, 2020

**Published:** December 9, 2020

**Peer Review History:** PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0242489>

**Copyright:** © 2020 Davies et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** All relevant data are within the manuscript and its [Supporting Information](#) files. Additional data are available in the EUROMedicAT report and its appendices

## Abstract

### Objectives

To explore associations between exposures to medicines prescribed for asthma and their discontinuation in pregnancy and preterm birth [ $<37$  or  $<32$  weeks], SGA [ $<10$ th and  $<3$ rd centiles], and breastfeeding at 6–8 weeks.

### Methods

**Design.** A population-based cohort study.

**Setting.** The Secure Anonymised Information Linkage [SAIL] databank in Wales, linking maternal primary care data with infant outcomes.

**Population.** 107,573, 105,331, and 38,725 infants born 2000–2010 with information on premature birth, SGA and breastfeeding respectively, after exclusions.

**Exposures.** maternal prescriptions for asthma medicines or their discontinuation in pregnancy.

**Methods.** Odds ratios for adverse pregnancy outcomes were calculated for the exposed *versus* the unexposed population, adjusted for smoking, parity, age and socio-economic status.

### Results

Prescriptions for asthma, whether continued or discontinued during pregnancy, were associated with birth at  $<32$  weeks' gestation, SGA  $<10$ th centile, and no breastfeeding (aOR 1.33 [1.10–1.61], 1.10 [1.03–1.18], 0.93 [0.87–1.01]). Discontinuation of asthma medicines in pregnancy was associated with birth at  $<37$  weeks' and  $<32$  weeks' gestation (aOR 1.22 [1.06–1.41], 1.53 [1.11–2.10]). All medicines examined, except ICS and SABA prescribed alone, were associated with SGA  $<10$ th centile.

### Conclusions

Prescription of asthma medicines before or during pregnancy was associated with higher prevalence of adverse perinatal outcomes, particularly if prescriptions were discontinued

(reference 27 - publicly available). The datasets generated and analysed during the current study are not publicly available, because the anonymized data, held by SAIL, can only be accessed within the SAIL secure remote access environment within the context of an approved project, following governance review. No patient level data are available under the terms of ethical and governance reviews. No participant consent is obtained for population level studies. Individual records for all databases were anonymised, and individual patient data cannot be publicly deposited or fully shared upon request. They are only available directly from the database providers. All interested parties are able to apply to obtain the data in the same way as the current investigators. Data used in the study can be accessed within the SAIL secure environment subject to approval by the SAIL Information Governance Review Panel. The URL for the SAIL databank is: <https://saildatabank.com/>, and the non-author contacts are Cynthia McNerney, Information Governance Manager, The SAIL Team, Swansea University: [c.i.mcnerney@swansea.ac.uk](mailto:c.i.mcnerney@swansea.ac.uk) and Charlotte Arkley, Administrator, SAIL Databank [c.r.arkley@swansea.ac.uk](mailto:c.r.arkley@swansea.ac.uk). Dataset information (names of datasets and provenance) is provided under 'Methods, subsection Setting'. As indicated in the text, further details are in reference 27. The corresponding author will endeavour to meet requests for further data and information. We confirm that data that are not publicly available are not part of the minimal data set.

**Funding:** Funding This paper was developed from the EUROmedicat project, and uses the cohort identified in that project. The analyses presented here were completed outside the funded period. Financial support for the EUROmedicat study was provided by the European Union under the 7th Framework Program [grant agreement HEALTH-F5-2011-260598]. Start date: 1 March 2011. Duration: 48 months. Coordinator: Prof. Helen Dolk, University of Ulster. Further information can be found at [www.euromedicat.eu](http://www.euromedicat.eu). The paper is based on data in the all-Wales SAIL databank, which is supported by UK Research and Innovation funding to Swansea University through an Administrative Data Research Centre grant (2018-2021), project reference: ES/S007393/1, Principal Investigator: Professor David Ford. The funder played no part in the study or production of the paper.

**Competing interests:** The authors have declared that no competing interests exist.

during pregnancy. Women discontinuing medicines during pregnancy could be identified from prescription records. The impact of targeting close monitoring and breastfeeding support warrants exploration.

## Introduction

The prevalence of asthma in pregnancy has increased worldwide [1–3]. Approximately 9% of pregnant women in the UK are prescribed medicines for asthma, more than elsewhere in Europe [4]. However, there is no consensus on the effect of asthma or prescription of asthma medicines on perinatal outcomes. While older [5] and smaller [6, 7] studies were reassuring, asthma [3, 8] accompanied by symptoms [5, 9] or suboptimal spirometry recordings [10] has been associated with growth restriction [small for gestational age [SGA]]. Premature birth is associated with asthma diagnosis in some studies [11, 12], but not others [8]. Active management of asthma may reduce premature birth [13], and uncontrolled asthma increases the risk of adverse perinatal outcomes [3], but there is less information on medicines prescribed for asthma. Few RCTs have examined the impact of asthma medicines in pregnancy on perinatal outcomes, and no differences were seen in any of the small trials located [14]. Short-Acting Beta Agonists [SABA] have not been associated with growth restriction or premature birth, although studies have relatively low numbers [15], and there is no consensus on the impact of Long-Acting Beta Agonists [LABA] [15–17]. There are few differences between medicines within each class [18]. Up to 50% pregnant women discontinue asthma medicines, often without professional advice, frequently worsening asthma and outcomes [1, 9, 14].

Medicines prescribed for asthma cross the placenta and enter breastmilk [6, 13]. Prescription of asthma medicines in early pregnancy is associated with increased prevalence of congenital anomalies [aOR 1.20, 1.08–1.34], but the effects of asthma could not be separated from those of its treatment [19]. Premature birth, SGA, and suboptimum breastfeeding threaten survival, developmental potential and ill-health from non-communicable disease in developed and developing countries [20], and the effects of medicines and their discontinuation on the range of pregnancy outcomes, including lactation, need to be considered together.

UK guidelines recommend that women prescribed asthma medicines breastfeed, and offer reassurance on oral corticosteroids [5]. Few studies reporting medicines' use and breastfeeding were located, all relatively small, and suggesting that breastfeeding rates were lower if medicines were prescribed. None considered medicines for asthma [21]. Despite the known health and economic benefits of breastfeeding [22, 23], we were unable to locate reports of the impact of prescription medicines on the prevalence of breastfeeding amongst women with asthma.

To identify women likely to benefit from additional care, and target support, we aimed to explore any associations between prescriptions for asthma medicines during pregnancy, or their discontinuation, and the range of perinatal outcomes that matter to women [prematurity, SGA, and, for the first time, breastfeeding at 6–8 weeks, full or partial].

## Methods

A population-based cohort was built from prospectively collected routine NHS data and analysed retrospectively [24]. We explored association, rather than causality, as there was no randomisation.

## Ethics

The Secure Anonymised Information Linkage [SAIL] Databank Information Governance Review Panel [IGRP] approved the study on behalf of the National Research Ethics Service, Wales on 24th March 2011. Data were irrevocably anonymised and obtained with permission of the relevant Caldicott Guardian and Data Protection Officer.

## Setting

Data were extracted from existing routinely collected data in SAIL, housed in Swansea University <https://saildatabank.com/faq/> [25–27]. By 2014, ~40% of general practices had agreed to share data with SAIL, without payment. Women in the included population were slightly less deprived and older than the rest of Wales [27]. Using unique personal identifiers, which remained undisclosed to researchers to ensure anonymity, we linked primary care records, including prescriptions, to: the Office of National Statistics (ONS) births and deaths register, the National Community Child Health Database [NCCHD] [<http://www.publichealthwalesobservatory.wales.nhs.uk/ncchd>], the Patient Episode Database for Wales [<http://www.wales.nhs.uk/document/176173>], and CARIS [Congenital Anomaly Register and Information Service for Wales] [<http://www.caris.wales.nhs.uk/home>]. Databases were linked by a trusted third party [NHS Wales Informatics Service [NWIS]] [<http://www.wales.nhs.uk/sitesplus/956/home>].

## Population

The study population included all births in Wales after 24 gestational weeks between 1st January 2000 and 31st December 2010, with linked maternal prescription data. Infants were included where the associated maternal ID could be linked with the primary care dataset (dependent on the general practice) and the record was complete [27]. We included all infants where the woman was present in the linked database with primary care prescription information 91 days before LMP to birth. Information on start of pregnancy was obtained from ultrasound scan data recorded in the NCCHD for Wales [27]. Infants with congenital anomalies were excluded, as associations with asthma prescriptions are reported elsewhere [19]. The impact of antidepressants on breastfeeding, premature birth and SGA in this cohort has been reported [28].

## Exposure

Prescriptions reflect physicians' assessment of asthma severity [5, 29], since prescribers adhere to guidelines [5] that direct monitoring and prescribing. Exposure to "any asthma medicines" was defined as the woman having been prescribed at least one asthma medicine [ATC code R03] in the 3 trimesters of pregnancy, defined as 1st day of LMP to birth [15]. Exposure was grouped, based on 5-digit ATC codes [30] into 10 categories, listed in Table 1. Exposure to oral corticosteroids was restricted to those co-prescribed other asthma medicines.

Combined LABA and ICS preparations [R03AK] were added to the separate exposure categories, and not analysed as one group as this would preclude discussion of the disparate biological effects. We did not analyse exposure to systemic beta2 agonists, cromolyns, theophylline or anti-cholinergic medicines separately, due to very low prescription rates in this population (<40 pregnant women exposed to any of these 2004–10) [4].

## Outcomes

**Prematurity** was defined as <37 completed weeks' gestation, and 'very premature' as <32 completed weeks [32].

Table 1. Exposure classification.

Description	Medicine	ATC	BTS step
Asthma before or during pregnancy	Any asthma medicine 1 year before pregnancy or during pregnancy pre4 to t3	R03	Any
Medicated asthma	Any asthma medicines t1-t3	R03	Any
Un-medicated asthma /Prescription discontinuation	Any asthma medicine 1 year before pregnancy [pre4 to pre1], but none in pregnancy	R03	Un-medicated asthma
SABA only	Inhaled Short-acting beta-2-agonists [SABA], as the only asthma medicine in pregnancy [t1-t3]	R03AC02 to R03AC04	1 [least severe]
SABA any	Inhaled Short-acting beta-2-agonists [SABA], any prescription in pregnancy [t1-t3]	R03AC02 to R03AC04	1 or higher
ICS only	Inhaled corticosteroids [ICS] as the only asthma medicine in pregnancy [t1-t3]	R03BA	2 and well controlled
ICS any	Inhaled corticosteroids [ICS] any prescription in pregnancy [t1-t3]	R03BA	2 or higher
LABA any	Inhaled long-acting beta-2-agonists [LABA] t1-t3	R03AC12, R03AC13	3 or higher
LKA any	Leukotriene receptor antagonists [LKA] t1-t3	R03DC	3 or higher
OCS asthma	Oral corticosteroids [OCS] in combination with any asthma medicine [R03] t1-t3	H02AB + [R03]	5 [most severe]

In the UK, asthma is initially managed with short acting beta2 agonist [SABA] bronchodilators for symptom relief [step 1]. However, if these are needed >twice per week or >once a week at night or if exacerbations have occurred in the last 2 years, inhaled corticosteroids [ICS] are recommended [step 2]. If these fail to control symptoms, *additional therapy is prescribed*, usually long acting beta2 agonists [LABA] or leukotriene antagonists [LKA], but occasionally oral beta2 agonists or theophylline [step 3]. Oral corticosteroids are prescribed if combinations of these medicines plus high dose ICS fail to control symptoms [step 5] or to manage acute exacerbations [5, 29]. British Thoracic Society [BTS] step 4 is characterised by high dose ICS plus step 3 medicines. We were unable to extract information on doses, so did not identify doses of oral medicines or step 4 [high dose ICS]: other inhalers are only available in standard doses. The only indications for these medicines is 'conditions associated with reversible airways obstruction' [29].

t represents trimester, t1-3 represents the time between 1st day of last menstrual period [LMP] and birth

Pre1-4 represents the 4 quarters preceding pregnancy

Pre1 represents the quarter immediately preceding pregnancy

Medicines were defined by ATC codes, and then matched to version 2 Read codes in the GP database, using reference data provided by NHS Digital Technology

Reference Data Update Distribution [<https://isd.digital.nhs.uk/trud3/user/guest/group/0/home>] [31].

There were 0 exposures to ATCs R03AC05-7.

<https://doi.org/10.1371/journal.pone.0242489.t001>

**Growth centiles** were calculated from WHO standards for the UK, and infants below the 10th and 3rd centiles were identified; the latter is defined as 2 standard deviations below the median or 50th centile [33].

**Breastfeeding** in this database is defined as 'any breastfeeding' (exclusive or combined, predominantly or partially, with other feeds, including formula milk) as routinely recorded by health visitors at birth and 6–8 weeks and entered into NCCHD [34]. Data collection is more complete in some Health Board regions than others [35]. Breastfeeding data were available from 2004. Breastfeeding at birth may represent intention to breastfeed, rather than actuality: a high proportion of dyads breastfeeding at birth have discontinued a week later. Therefore, this measure is downgraded as evidence of successful breastfeeding [36].

## Confounding

To minimise **confounding by co-exposure**, we restricted the dataset by excluding pregnancies known to be at risk of adverse outcomes [37]. We achieved a relatively homogeneous population by excluding from the main analysis infants: 1) with major congenital anomalies; [38] 2) from multiple pregnancies; 3) stillborn; 4) exposed in the quarter preceding pregnancy or trimester 1 to medicines more closely associated with adverse outcomes than asthma medicines:

anti-epileptic drugs [AEDs] [NO3] [39]; coumarins [B01AA], mainly warfarin [40]; insulins [A10A]58; [41] and 5) whose mothers had any record of: heavy alcohol use and/or substance misuse [42], (many of these substances are powerful vasoconstrictors). Prevalences were checked before exclusion (tabulated in Jordan et al 2019, S3 Table).

We did not exclude moderate alcohol use as this is not known to affect perinatal outcomes [42], and may be inconsistently recorded. To minimize **confounding by indication**, we investigated both medicated and unmedicated asthma, as discontinuation of medication in pregnancy. We adjusted for socioeconomic status [SES], as Townsend fifths (S1 Table), parity, smoking [as 'yes' or 'no'], year of birth, and maternal age, grouped [43].

## Statistical analysis

We explored associations between prematurity, SGA and breastfeeding and prescription of asthma medicines 1 year before or during pregnancy, prescription discontinuation during pregnancy, and individual asthma medicines [Table 1]. For medicines with sufficient numbers of exposures, and where feasible, data were explored by logistic regression, backwards likelihood ratio [44], with covariates, SES [45], parity, smoking, age, and year of birth [S1 Table], using SPSS version 25 for windows [46]. For each analysis we compared the exposed with the unexposed population. We compared outcomes for women with medicated and un-medicated asthma (S3 Table). Odds ratios, unadjusted and adjusted are reported together with 95% confidence / compatibility intervals. We explored demographic differences between women with and without breastfeeding data at 6–8 weeks.

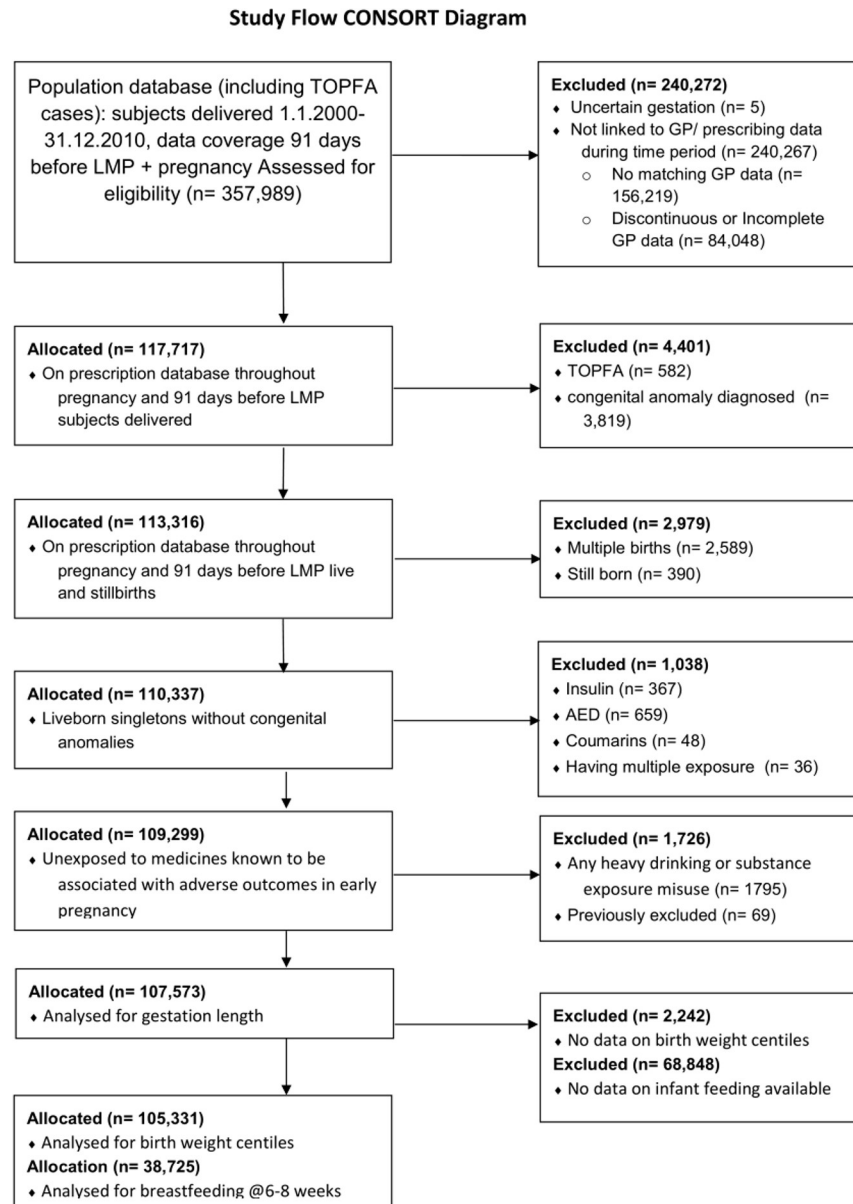
## Results

We identified 117,717 pregnancies with complete primary care prescription data. We excluded 4401 infants with congenital anomalies [including 582 termination of pregnancy for foetal anomalies] and 2589 multiples, leaving 110,727 singletons, of whom 390 were stillborn [41 stillborn multiples].

When those exposed to insulin, AEDs or coumarins were excluded, numbers fell to 109,299, reducing to 107,573 available for analysis when those exposed to heavy drinking or substance misuse were excluded; 105,311 and 38,725 had data on centiles and breastfeeding at 6–8 weeks [Fig 1].

Stillbirth was more prevalent amongst women prescribed asthma medicines than the unexposed population [75/13,516, 0.55% vs.431/113,316, 0.38%, OR 1.56, 1.21–2.00], particularly if medicines had been discontinued throughout pregnancy [27/3850, 0.70%, OR1.91, 1.29–2.82]. Prevalence of deprivation, smoking, substance or alcohol misuse, prescription of insulin and AEDs was higher amongst women prescribed asthma medicines, with the exception of those prescribed ICS or ICS only. The prevalence of obesity [BMI>30] was higher amongst women with asthma, particularly those prescribed corticosteroids. Women discontinuing asthma medicines were younger, but not more deprived, than those continuing [S1 Table].

Asthma medicines were prescribed to 12,690/107,573 [11.8%] of the cohort before or during pregnancy; 3589/12690 [28.3%] received their last prescription before pregnancy, and were deemed to have 'discontinued' [S2 Table]. Most [8413, 92.4%] of the 9101 women prescribed asthma medicines in pregnancy received SABA, and 3820 [45.4%] of these 8413 received only SABA. Only 3875/ 9109 (42.6%) women received ICS, and 374 received ICS only. LABA were prescribed to 465 women and LKA to 89. OCS were prescribed to 519 women co-prescribed medicines for asthma. Women with breastfeeding data were older than those without [mean ages 28.48 [6.09] vs. 28.04 [6.04] years, mean difference 0.44 [0.36–0.51],  $t$  11.36,  $df$  79659,  $p < 0.001$ ], more deprived [mean Townsend score 0.40 [3.24] vs. 0.21 [3.12], mean difference



**Fig 1. Study flow diagram.**

<https://doi.org/10.1371/journal.pone.0242489.g001>

0.20 [0.16–0.24],  $t$  9.65,  $df$  77578,  $p < 0.001$ ], and less likely to be primiparous [16095/38725, 41.6% vs. 29388/68848, 42.7% OR 0.96 [0.93–0.98].

### Premature birth

Premature birth at  $<37$  or  $<32$  weeks was more prevalent if asthma prescriptions had been discontinued before pregnancy, when compared with the whole population [aOR 1.22, 1.06–1.41, and aOR 1.53, 1.11–2.10,]. Any asthma medicine prescription before or during pregnancy was not associated with birth at  $<37$  weeks, but was associated with extreme prematurity [aOR 1.33, 1.09–1.61]. Birth at  $<32$  weeks was associated with OCS prescriptions [aOR 2.16, 1.07–4.37]. Birth at  $<37$  and  $<32$  weeks' gestation was more prevalent if only SABA had

**Table 2. Premature birth <37 weeks (n = 107,573).**

Exposure	Exposed n [%]	Unexposed n [%]	Unadjusted OR [95% CI]	Adjusted* OR [95% CI]
Asthma	783/12,690 [6.17]	5374/94,883 [5.66]	1.10 [1.01 to 1.18]	1.08 [0.99 to 1.18]
Medicated asthma	538/9,101 [5.91]	5619/98,472 [5.71]	1.04 [0.95 to 1.14]	1.02 [0.92 to 1.12]
Un-medicated asthma	245/3,589 [6.83]	5912/103,984 [5.69]	1.22 [1.07 to 1.39]	1.22 [1.06 to 1.41]
SABA only	251/3,820 [6.57]	5906/103,753 [5.69]	1.17 [1.02 to 1.33]	1.13 [0.98 to 1.30]
SABA any	506/8,413 [6.01]	5651/99,160 [5.70]	1.06 [0.96 to 1.16]	1.04 [0.94 to 1.15]
ICS only	12/374 [3.21]	6145/107,199 [5.73]	0.55 [0.31 to 0.97]	0.64 [0.36 to 1.15]
ICS any	199/3,875 [5.14]	5958/103,698 [5.75]	0.89 [0.79 to 1.03]	0.87 [0.74 to 1.02]
LABA any	18/465 [3.87]	6139/107,108 [5.73]	0.66 [0.41 to 1.06]	0.60 [0.35 to 1.03]
LKA any	<5 /89	6155/107,484 [5.73]	OR >1Not significant	OR >1Not significant
OCS asthma	30/519 [5.78]	6127/107,054 [5.72]	1.01 [0.70 to 1.46]	0.93 [0.62 to 1.40]

Exclusions from analysis: all anomalies, terminations of pregnancy for foetal anomalies [TOPFA], stillbirths, multiple births [twins, triplets and quadruplets [no higher multiples in the dataset]], exposure to insulin, anti-epileptic drugs [AEDs] or coumarins in the quarter preceding pregnancy and trimester 1, heavy drinking/substance misuse [any record]. For each analysis we compared the exposed with the unexposed population.

\*adjusted for parity, smoking, year of birth, socio-economic status [SES] as Townsend fifth [quintile], and maternal age as: <20, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, >54.

Deprivation [Townsend] scores, ranks and fifths are based on geographical area of residence, using Lower Super Output Areas [LSOAs] defined by residential postcodes. This measure of material deprivation is calculated from rates of unemployment, vehicle ownership, home ownership, and overcrowding [Townsend et al 1988 [45].

Exposures were not mutually exclusive. All those exposed to OCS, LABA and LKA were exposed to other asthma medicine<sup>5</sup>.

Abbreviations and definitions are listed in Table 1.

OR odds ratio, CI confidence intervals.

The prevalence of premature birth reported here is congruent with WHO data<sup>31</sup>

<https://doi.org/10.1371/journal.pone.0242489.t002>

been prescribed, but interval estimates included no difference [aOR 1.13, 0.98–1.30 and 1.37, 0.99–1.89]. ICS (any or only) was associated with reduced prevalence of birth at <37 weeks', but interval estimates were compatible with no difference [aOR 0.87[0.74–1.02] and 0.64 (0.36–1.15)] [Tables 2 and 3].

## SGA

Birth weight <10th centile was associated with any asthma medication before or during pregnancy, SABA, ICS, LABA, LKA, and OCS. If prescriptions were discontinued or only ICS

**Table 3. Premature birth <32 weeks (n = 107,573).**

Exposure	Exposed n [%]	Unexposed n [%]	unadjusted OR [95% CI]	adjusted* OR [95% CI]
Asthma	131/ 12,690 [1.03]	802/ 94,883 [0.85]	1.22 [1.02 to 1.47]	1.33 [1.09 to 1.61]
Medicated asthma	88/9,101 [0.97]	845/98,472 [0.86]	1.13 [0.91 to 1.41]	1.21 [0.96 to 1.53]
Un-medicated asthma	43/3,589 [1.20]	890/103,984 [0.86]	1.40 [1.03 to 1.91]	1.53 [1.11 to 2.10]
SABA only	43/3,820 [1.13]	890/103,753 [0.86]	1.32 [0.97 to 1.79]	1.37 [0.99 to 1.89]
SABA any	84/8,413 [1.00]	849/99,160 [0.86]	1.17 [0.93 to 1.46]	1.26 [0.99 to 1.59]
ICS only	<5/374	929-932/107,199	OR <1Not significant	OR<1 Not significant
ICS any	30/3,875 [0.77]	903/103,698 [0.87]	0.89 [0.62 to 1.28]	0.92 [0.63 to 1.35]
LABA any	<5 /465	929/107,108	OR <1Not significant	OR >1Not significant
LKA any	<5 /89	932/107,484	OR >1Not significant	OR >1Not significant
OCS and asthma	9/519 [1.73]	924/107,054 [0.86]	2.03 [1.05 to 3.93]	2.16 [1.07 to 4.37]

Exclusions, definitions, adjustments and abbreviations as in Table 2.

<https://doi.org/10.1371/journal.pone.0242489.t003>

**Table 4. Small for Gestational Age [SGA] <10th centile (n = 105,331).**

Exposure	Exposed n [%]	Unexposed n [%]	unadjusted OR [95% CI]	adjusted* OR [95% CI]
Asthma	1192/12,413 [9.60]	7965/92,918 [8.58]	1.13 [1.06 to 1.21]	1.10 [1.03 to 1.18]
Medicated asthma	845/8,904 [9.50]	8312/96,427 [8.62]	1.11 [1.03 to 1.20]	1.09 [1.01 to 1.19]
Un-medicated asthma	347/3,509 [9.89]	8810/101,822 [8.65]	1.16 [1.04 to 1.30]	1.10 [0.98 to 1.25]
SABA only	343/3,739 [9.17]	8814/101,592 [8.68]	1.06 [0.95 to 1.19]	1.02 [0.90 to 1.15]
SABA any	785/8,225 [9.54]	8372/97,106 [8.62]	1.12 [1.04 to 1.21]	1.09 [1.01 to 1.19]
ICS only	35/370 [9.36]	9122/104,961 [8.69]	1.10 [0.78 to 1.56]	1.16 [0.80 to 1.69]
ICS any	380/3,786 [10.04]	8777/101,545 [8.64]	1.18 [1.06 to 1.31]	1.16 [1.03 to 1.30]
LABA any	57/457 [12.47]	9100/104,874 [8.68]	1.50 [1.14 to 1.98]	1.75 [1.31 to 2.34]
LKA any	12/87 [13.48]	9145/105,244 [8.69]	1.68 [0.91 to 3.10]	1.93 [1.01 to 3.69]
OCS and asthma	58/510 [11.37]	9099/104,821 [8.68]	1.35 [1.03 to 1.78]	1.41 [1.05 to 1.90]

Exclusions, definitions, adjustments and abbreviations as in [Table 2](#)

%s reported are of those with data.

–Unadjusted OR not significant

<https://doi.org/10.1371/journal.pone.0242489.t004>

prescribed, odds ratios were similar, but interval estimates included no difference. Lower odds ratios were seen where SABA was prescribed alone. LABA and LKA were associated with birth weight <3rd centile, but numbers were low [Tables 4, 5].

## Breastfeeding

Prevalence of breastfeeding at 6–8 weeks was some 3% lower following prescriptions before or during pregnancy or prescription discontinuation, but interval estimates in adjusted analyses included no difference. Association with any SABA or any ICS in unadjusted analyses diminished when smoking, maternal age and SES were accounted [Table 6].

In all analyses, smoking and SES were significant in the final models. Maternal age predicted breastfeeding, but not preterm delivery or SGA.

## Discussion

Prescription of asthma medicines during pregnancy or in the preceding year was associated with birth before 32 weeks' gestation and at <10th centile, and exclusive formula feeding at

**Table 5. Small for Gestational Age [SGA] <3rd centile (n = 105,331).**

Exposure	Exposed n [%]	Unexposed n [%]	unadjusted OR [95% CI]	adjusted* OR [95% CI]
Asthma	260/12,413 [2.09]	1707/92,918 [1.84]	1.14 [1.00 to 1.30]	1.07 [0.92 to 1.23]
Medicated asthma	179/8,904 [2.01]	1788/96,427 [1.85]	1.09 [0.93 to 1.26]	1.03 [0.87 to 1.22]
Un-medicated asthma	81/3,509 [2.31]	1886/101,822 [1.85]	1.25 [1.00 to 1.57]	1.14 [0.89 to 1.46]
SABA only	78/3,739 [2.09]	1889/101,592 [1.86]	1.13 [0.89 to 1.41]	1.02 [0.80 to 1.31]
SABA any	164/8,225 [1.99]	1803/97,106 [1.86]	1.08 [0.92 to 1.26]	1.02 [0.86 to 1.21]
ICS only	5-9/(370–373) [<5]**	1958-1962/104,961 [1.87]	1.16 [0.58 to 2.34]	1.22 [0.57 to 2.59]
ICS any	78/3,786 [2.06]	1889/101,545 [1.86]	1.11 [0.88 to 1.40]	1.09 [0.85 to 1.39]
LABA any	13/457 [2.84]	1954/104,874 [1.86]	1.54 [0.89 to 2.68]	1.84 [1.05 to 3.22]
LKA any	5-9/(85–88) [<10]**	1962/105,244 [1.86]	3.21 [1.30 to 7.94]	3.21 [1.16 to 8.93]
OCS asthma	9/510 [1.76]	1958/104,821 [1.87]	0.94 [0.49 to 1.83]	0.96 [0.48 to 1.29]

Exclusions, definitions, adjustments and abbreviations as in [Table 2](#)

\*\*These exact numbers cannot be disclosed, because these exposures are associated with <5 cases where the birth centile is unknown for this exposure.

%s reported are of those with data.

<https://doi.org/10.1371/journal.pone.0242489.t005>



**Table 6. Breastfeeding at 6–8 weeks (n = 38,725).**

Exposure	Exposed n [%]	Unexposed n [%]	unadjusted OR [95% CI]	adjusted* OR [95% CI]
Asthma	1499/4,915 [30.50]	11,294/33,810 [33.40]	0.88 [0.82–0.93]	0.93 [0.87 to 1.01]
Medicated asthma	1086/3,519 [30.86]	11,707/35,206 [33.25]	0.90 [0.83–0.97]	0.94 [0.87 to 1.03]
Un-medicated asthma	413/1,396 [29.58]	12,380/37,329 [33.16]	0.85 [0.75–0.95]	0.92 [0.81 to 1.05]
SABA only	453/1,449 [31.26]	12,340/37,276 [33.10]	0.92 [0.82–1.03]	1.00 [0.88 to 1.14]
SABA any	1006/3,275 [30.72]	11,787/35,450 [33.25]	0.89 [0.82–0.96]	0.95 [0.87 to 1.04]
ICS only	35/113 [30.97]	12,758/38,612 [33.04]	0.91 [0.61–1.36]	0.81 [0.52 to 1.28]
ICS any	423/1,403 [30.15]	12,370/37,322 [33.14]	0.87 [0.78–0.98]	0.91 [0.80 to 1.04]
LABA any	52/163 [31.90]	12,741/38,562 [33.04]	0.95 [0.68–1.32]	0.92 [0.62 to 1.36]
LKA any	19/45 [42.22]	12,774/38,680 [33.02]	1.48 [0.82–2.68]	1.73 [0.91 to 3.30]
OCS asthma	71/234 [30.34]	12,722/38,491 [33.05]	0.88 [0.67–1.17]	0.96 [0.70 to 1.31]

Exclusions, definitions, adjustments and abbreviations as in [Table 2](#)

%s reported are of those with data.

<https://doi.org/10.1371/journal.pone.0242489.t006>

6–8 weeks. However, discontinuation of medicines was associated with premature birth [ $<37$  and  $<32$  weeks]; whilst exclusive formula feeding and SGA were more prevalent, interval estimates were compatible with no effect in adjusted models.

Adverse outcomes were more common amongst women treated with OCS, the most severely asthmatic, but the highest prevalence of premature birth and exclusive formula feeding was amongst those discontinuing prescriptions. ICS prescription appeared to offer some protection against prematurity. Although SABA-only indicates the least severe asthma [BTS5 stage 1], women prescribed ICS for more persistent symptoms [BTS stage 2] had better outcomes [12].

### Premature birth

The association with premature birth reflects findings of a meta-analysis indicating increased risks for women diagnosed with asthma [3] or using OCS [47], contradicting earlier studies [6–8]. We did not confirm that increased risks are confined to those with more severe asthma [10, 11]. Rather, risks appeared to be increased by prescription discontinuation, which may worsen symptoms [48, 49]. Preterm birth appeared more likely where only SABA were prescribed, although interval estimates included no difference, supporting recent guidelines no longer recommending ‘SABA only’ regimens for any asthma [50].

### SGA

Intrauterine growth restriction is associated with asthma [8, 9, 51, 52], particularly if severe [53–55], or symptomatic [7] or accompanied by reduced spirometry parameters [10], congruent with our findings that all asthma medicines, except ICS-only or SABA-only, were associated with increased prevalence of SGA ( $<10^{\text{th}}$  centile). Prescription discontinuation increased the prevalence of SGA, but interval estimates included no difference [55]. SGA is often secondary to placental insufficiency, subsequent to vasoconstriction of any aetiology, including pre-eclampsia, hypoxia [56, 57], smoking, cocaine [58], or, possibly, other sympathomimetics, such as beta2 agonists. Associations between LABA and birth weight  $<10^{\text{th}}$  or  $<3^{\text{rd}}$  centile and SABA with  $<10^{\text{th}}$  centile may reflect vasoconstrictor properties [Tables 4, 5]. Associations with OCS, as elsewhere [7, 47], may reflect hypoxic asthma exacerbations or severity or the pharmacodynamics of corticosteroids. The associations between LABA and LKA and SGA  $<3^{\text{rd}}$  centile may be confounded by asthma severity. These data might support a dose-

response vasoconstriction hypothesis, only partly dependent on hypoxia: infants exposed to more than one medicine, likely associated with more severe asthma, were rather more vulnerable to SGA.

### Un-medicated asthma

Many women (28.3%) discontinued their asthma medicines during pregnancy, unlike in Scandinavian cohorts [59, 60]. Un-medicated asthma was associated with premature birth, but the interval estimates for associations with SGA and exclusive formula feeding included no difference.

To meet the physiological demands of pregnancy, tidal volume and resting alveolar ventilation increase and expiratory reserve declines [61, 62]. In some women, pulmonary reserve may be insufficient to meet the increased demands for oxygen, accounting for increases in prescribing of SABA and ICS in trimester 2 [4]. In women with severe asthma, symptoms of asthma, and attendant risks of hypoxia, may intensify late in trimester 2 or *post-partum* [62]. In contrast, some women become symptom-free during pregnancy [16]. However, even if asthma becomes asymptomatic, persistent airway remodelling [basement membrane thickening] and immunological changes, predictive of subclinical bronchial hyper-responsiveness, remain [63]. Some women voluntarily suspend medication during pregnancy, opting to tolerate symptoms rather than risk harming their unborn children [64]. Any uncontrolled asthma may cause chronic or intermittent hypoxia and inflammation, which adversely affect both mother and foetus [62, 63], and may impair foetal development, causing intrauterine growth restriction, foetal distress, pre-term birth and, occasionally, death: stillbirths were more prevalent amongst women discontinuing asthma prescriptions [0.70%] when compared with UK rates 2000–2010 [0.51–0.58%] [65], and women never prescribed asthma medicines [0.38%] [S1 Table].

Non-adherence to asthma therapies exacerbates symptoms [5, 66]. Absence of prescriptions for 9 months indicates withdrawal of therapy, as it is unlikely that stockpiled inhalers would be sufficient over this length of time. We do not know why women discontinued prescriptions or whether they experienced respiratory symptoms or they or their healthcare professionals attributed dyspnea to pregnancy [67] or they remained well themselves, while their foetuses suffered episodes of hypoxia. Hypoxia stimulates release of placental corticotrophin-releasing hormone [CRH] and inflammatory cytokines. Placental CRH increases maternal and foetal cortisol production, which augments placental CRH release *via* positive feedback mechanisms, amplifying signals that may culminate in premature birth in ~5% infants [54, 68]. The strongest predictors of premature birth were medicines discontinuation and OCS, supporting the hypoxic trigger hypothesis. The apparent protection against prematurity afforded by ICS suggests that ICS may have been controlling inflammation and asthma, thereby preventing hypoxia, and consequent CRH release, despite the potential to mimic endogenous corticosteroids. Only 374 women were using ICS alone, and, since they did not need SABA, their asthma was probably well controlled, suggesting little risk from hypoxia. Beta2 agonists were formerly prescribed as tocolytics, but here they did not protect against premature birth, indicating that other factors were over-riding their actions on myometrial receptors.

### Breastfeeding

Breastfeeding rates were reduced if asthma medicines had been prescribed before or during pregnancy, and if prescriptions had been discontinued, but adjusted interval estimates included no difference [Table 6]. Assurances [5, 28] on the safety of SABA, ICS, most LABA, and OCS at <40mg per day may have contributed to the absence of a negative effect of

prescriptions on breastfeeding. Manufacturers advise against breastfeeding while using LKA; [28, 69] however, it would appear these warnings were discounted.

Beta2 agonists are generally considered safe during lactation [28, 69], although high doses and oral administration can cause tachycardia and restlessness in the infant [70]. Only small quantities of inhaled medicines reach the infant, and further work is needed to explore whether sympathomimetic effects cause sufficient restlessness [70] to impede latching, making early breastfeeding more difficult and painful or whether the sympathomimetic properties of beta2 agonists might hinder lactogenesis: [71] either might account for a reduced prevalence of breastfeeding, which was not seen here when SES, maternal age and smoking were accounted. Breastfeeding was not adversely affected by LKA and OCS, which are prescribed for severe asthma. Transfer of ICS to the infant is low [69], but too few women were prescribed only ICS to assess the impact on breastfeeding.

The breastfeeding rates at 6–8 weeks reported here reflect Wales's current data (2131/6366, 33.47%) [72]. Contemporary recruited cohorts elsewhere report higher breastfeeding rates amongst women with asthma, for example, 536/605, 88% at birth, 230/605 38% at 6 months [73]. Increasing breastfeeding rates in the UK by 0.1% would offer considerable benefit: the associated small increase in infants' average IQ gains >£27.8 million in economic productivity across each annual birth cohort [74], suggesting that the ~3% improvement identified here would be worthwhile. Breastfeeding support should not end at birth. Mild or moderate asthma may worsen *post-partum*: how this, and the associated loss of sleep, affects breastfeeding is unknown.

### Supporting women with asthma

Premature birth, SGA and suboptimal breastfeeding are public health concerns [75]. Extreme prematurity carries a 6.2% risk of cerebral palsy and a 40% risk of broncho-pulmonary dysplasia, whilst birth before 37 weeks carries a 1% risk of cerebral palsy and 40% risk of cognitive impairment [76]. Birth weight below the 10th centile is linked to a range of conditions from neonatal asphyxia to mental health conditions in adulthood [58], changes in brain morphology [77] and beta cell function [78].

The associations between un-medicated asthma and premature birth support the consensus that uncontrolled asthma increases the risk of adverse perinatal outcomes subsequent to premature birth [3], but risks were not confined to severe asthma [5, 79]. Rather, we highlight the importance of identifying the 28% of women with asthma who completely discontinue medicines, often ICS [80], as being at increased risk of premature birth and exclusive formula feeding; these women were apparently without symptoms sufficiently severe to warrant prescriptions.

We confirmed associations with SES and smoking [58, 81], but asthma medicines before or during pregnancy or their discontinuation independently predicted adverse outcomes. Lower family income and education intensify the impact on families of behavioural and neurodevelopmental sequelae of premature birth [cerebral palsy, cognitive impairment, impaired hearing or vision] [82], and the concentration of adverse outcomes and asthma prescriptions amongst the most economically deprived in Wales [83] [S1 and S2 Tables] accentuates the importance of using these findings to target support.

Prescription patterns, regardless of diagnoses, particularly discontinuation in pregnancy, offer primary care practitioners a convenient marker to identify pregnancies at increased risk, analogous to 'intention to treat' analyses: pragmatic but of unproven biological certainty. Alternative markers, such as smoking or socioeconomic deprivation, would not identify women discontinuing prescriptions [S1 and S2 Tables]. Women with severe illness are usually

actively managed in specialist clinics in secondary or tertiary care, minimizing risks reported here: [3] our findings on prescription discontinuation, SABA and 'SABA-only' support this. Although current UK guidelines do not recommend additional surveillance before or during pregnancy [5] or initiatives to target support to optimize prescription regimens and infant feeding, 'at risk' women [those discontinuing or using SABA or OCS] need extra help. Additional monitoring by specialist respiratory nurses, in parallel with midwifery care, can improve asthma control [84], but large studies are needed to assess impact on perinatal outcomes.

### Strengths and limitations

Retrospective cohorts, such as ours, have minimal volunteer selection and attrition bias [83] and no recall bias [24].

### Generalisation

The prevalence of asthma prescribing in our cohort reflects that across the UK and USA, but there is less confidence in **generalisation** to populations with lower prescription [3, 4], or higher breastfeeding rates. Coverage was limited to 40% of the population, due to suboptimal GP participation [27]. Restrictions of our cohort were due to incomplete GP participation and data, due to practices' technical failures or women moving to practices not covered by SAIL [27]. The breastfeeding outcome was further restricted by variations in recording practices across the seven Health Boards, but there was no self-selection by participants. Had a volunteer bias been operating, we should have expected to see older, less deprived women over-represented [83]; this was not the case.

Restricting the dataset by excluding pregnancies exposed to AEDs, insulin, coumarins, heavy drinking or substance misuse and multiple pregnancies increased internal validity without introducing bias, at the cost of generalisation to these groups [37, 85]. The higher prevalence of these exposures amongst women prescribed asthma medicines (S1 Table) would have caused overestimation of harm attributed to asthma medicines. Rarer co-morbidities were not excluded. Co-morbid rheumatoid arthritis and inflammatory bowel disease were more likely amongst women prescribed oral corticosteroids, who would have received specialist care [5].

### Detail in the database

We have **no information** as to whether premature births were spontaneous or induced: asthma is associated with conditions necessitating preterm induction of labour, such as pre-eclampsia [54, 86]. Neither population databases nor fieldwork fully capture symptoms, histories, spirometry, oxygen saturation, or psychosocial stressors. Maternal stress, short and long-term, increases the risk of pre-term birth [68, 81]. Substance misuse is notoriously difficult to capture, and may be under-reported; however, it is often persistent. We excluded the most vulnerable women [39–42]. The proportion of missing data [35.5% overall, 29.3% in women with asthma], precluded inclusion of BMI in regression analyses [S1 Table]. Any increased prevalence of these predictors of adverse outcomes amongst exposed women would lead to overestimation of associations [87]. Paternity and paternal sibships are not recorded, as in many databases [88], but impact on perinatal outcomes are believed to be modest [89]. We considered each pregnancy separately, as exposures and covariates (e.g. smoking, deprivation) often vary between pregnancies. We acknowledge the genetic determinants of perinatal outcomes [90], but, without information on their association with asthma, are unable to predict how accounting for this would have affected this study. The database's timeframe did not allow us to distinguish women receiving their first ever prescription during pregnancy.

No data were available on miscarriage and induced terminations. Confining analyses to otherwise healthy live-born infants introduces a survival / survivorship bias, leaving some harms unreported, and under-estimating overall harm [87]. This was confirmed by the slightly higher rates of stillbirth (S1 Table). Congenital anomalies and stillbirths are associated with SGA and preterm birth [88], and the higher prevalence of congenital anomalies amongst women exposed to asthma medicines in this cohort is known [19]; therefore, affected infants were excluded.

We have no data on dispensing or hospital or private prescribing or internet purchasing. It is unlikely that anyone hospitalized with asthma or consulting privately would not be receiving prescriptions from primary care practitioners. Abolition of prescription charges in Wales in 2007 reduces the likelihood of private prescriptions and purchasing. Our data predate primary care prescription of monoclonal antibodies for severe eosinophilic asthma persisting despite oral corticosteroid therapy. Manufacturers advise avoiding these medicines in pregnancy [28]; therefore, population databases may be unable to describe their safety in pregnancy for some time. Too few women were prescribed LABA (465) or LKA (89) or ICS only (362) to draw conclusions relating to extreme prematurity or SGA, but findings are congruent with other studies [86].

We do not know whether any women had been over- or mis-diagnosed with asthma [91], or if any withdrawal symptoms arose [92–95] and remained un-medicated. Without data on medicines purchased without prescription, we could not explore the hypothesis that ‘asthma with hay fever’ is a stronger predictor of premature birth than non-atopic asthma [86]. Similarly, paucity of testing for exhaled nitric oxide, known not to improve outcomes [14], made it impossible to ascribe eosinophilic or allergic aetiology to the diagnosis.

**Adherence to prescribed regimens** cannot be ascertained from prescription or dispensing data. 30–50% of patients prescribed long-term treatment do not take medicines as recommended [92], and we also have no information on inhaler techniques or any stockpiling or sharing of inhalers. (Excluding substance misusers reduces the latter possibility.) Non-adherence dilutes the impact of medicines on outcomes; however, since discontinuation was associated with harm, unreported discontinuation in those receiving prescriptions might lead to an over-estimation of harms attributed to prescriptions.

### Multiple testing

We acknowledge the hazards of **multiple testing**, without correction. Our independent (predictor) variables are highly correlated. This makes standard adjustments, such as the Bonferroni method, unduly conservative, risking false negatives [96]. Observation studies are limited by unmeasured confounding, and the impossibility of including all contextual variables [97, 98]. Our findings are consistent with biological plausibility and the literature.

### Confounding and effect mediation

For most adverse outcomes, retrospective analysis yields lower odds or risk ratios than prospective studies [93]. However, this is not true of cohorts examining asthma in pregnancy. This might be interpreted as prospective cohort studies offering enhanced opportunities to control asthma, particularly to optimize prophylaxis with ICS [3], supported here by suggestions of improved outcomes with ICS prescriptions.

In evaluating the impact of medicines using population databases, it is rarely possible to avoid residual **confounding by indication** and severity of indication without randomisation [99, 100]. Prescriptions are sometimes taken as proxies for diagnoses [101], as diagnoses are not always recorded in healthcare databases, and these medicines have no other indications in

the UK [28]. Since the risks of poorly controlled asthma outweigh the risks of harm to the foetus, only the mildest maternal asthma is un-medicated on medical advice [5, 50], but we do not know whether continuing prescriptions indicated recurrent symptoms or a propensity to compliance. We acknowledge the difficulties of disentangling the effects of asthma from its management. Nevertheless, these findings should alert practitioners to the need for targeted care preconception, and during pregnancy and lactation.

### **Implications: Support before, during and after pregnancy**

The clinical consequences of premature birth, including cerebral palsy and cognitive impairment [76], increase the importance of the modest [ORs <2] associations identified. Women discontinuing prescriptions were probably relatively unaffected by symptoms, whilst an additional ~1% of their infants were born preterm: discontinuation may have increased the risk of hypoxia [and hence premature birth]. Taken with lower breastfeeding rates, these findings identify unmet needs amongst women discontinuing prescriptions, and militate against medication reduction in pregnancy [102]. Reduced risks with ICS suggest that increased monitoring, targeted support and active asthma management [3, 50] are needed before, during and after pregnancy. Programming primary care electronic records to alert professionals to contact women who leave >4 months between prescriptions for asthma medicines might make this feasible.

### **Supporting information**

#### **S1 Checklist.**

(DOC)

#### **S1 Table. Demographic details of population, excluding congenital anomalies [n = 113316].**

(DOCX)

#### **S2 Table. Demographic details of subjects included in the analysis [n = 107573].**

(DOCX)

#### **S3 Table. Medicated and unmedicated asthma: Descriptive data n = 107573.**

(DOCX)

### **Acknowledgments**

This study uses anonymised data held in the Secure Anonymised Information Linkage [SAIL] system, which is part of the national e-health records research infrastructure for Wales. We should like to acknowledge all the data providers who make anonymised data available for research. Data held in SAIL databases are anonymised and aggregated and have been obtained with permission of relevant Data Protection Officers, as approved by the National Research Ethics Service, Wales. Permissions are conditional on non-disclosure of numbers <5 in any cell. The project was approved by the SAIL Information Governance Review Panel [IGFRP] on 24th March 2011. Since the project uses only anonymised data, ethical review was deemed unnecessary.

**We should like to thank:** Hildrum Sundseth from the European Institute of Women's Health for advice as service user representative on EUROmediCAT, and Professor Helen Dolk for her role as lead of EUROmediCAT and continuing support.

## Author Contributions

**Conceptualization:** Gareth Davies, Sue Jordan, David Tucker.

**Data curation:** Gareth Davies, Sue Jordan, David Tucker.

**Formal analysis:** Gareth Davies, Sue Jordan.

**Funding acquisition:** Sue Jordan, David Tucker.

**Investigation:** Gareth Davies, Sue Jordan, David Tucker.

**Methodology:** Gareth Davies, Sue Jordan.

**Project administration:** Gareth Davies, Sue Jordan.

**Resources:** Sue Jordan.

**Visualization:** Gareth Davies, Sue Jordan, Daniel Thayer, David Tucker, Ioan Humphreys.

**Writing – original draft:** Sue Jordan.

**Writing – review & editing:** Gareth Davies, Sue Jordan, Daniel Thayer, David Tucker, Ioan Humphreys.

## References

1. Kwon HL, Triche EW, Belanger K, Bracken MB. The epidemiology of asthma during pregnancy: prevalence, diagnosis, and symptoms. *Immunol Allergy Clin North Am*. 2006 Feb; 26[1]:29–62. Review. <https://doi.org/10.1016/j.iac.2005.11.002> PMID: 16443142.
2. Burr ML, Wat D, Evans C, Dunstan FD, Doull IJ; British Thoracic Society Research Committee. Asthma prevalence in 1973, 1988 and 2003. *Thorax*. 2006; 61[4]:296–9 <https://doi.org/10.1136/thx.2005.045682> PMID: 16396947
3. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG*. 2011 Oct; 118[11]:1314–23. <https://doi.org/10.1111/j.1471-0528.2011.03055.x> PMID: 21749633
4. Charlton RA, Pierini A, Klungsøyr K, Neville AJ, Jordan S, de Jong-van den Berg LT, et al. Asthma medication prescribing before, during and after pregnancy: a study in seven European regions. *BMJ Open*. 2016 Jan 19; 6[1]:e009237. <https://doi.org/10.1136/bmjopen-2015-009237> PMID: 26787250
5. BTS 2019. SIGN 158 British Guideline on the Management of Asthma: A national clinical guideline. First published 2003, revised 2019. Scottish Intercollegiate Guidelines Network [SIGN]/ British Thoracic Society [BTS], Edinburgh, London available, accessed 1.12.19: <https://www.sign.ac.uk/assets/sign158.pdf>
6. Dombrowski MP, Schatz M, Wise R, Momirova V, Landon M, Mabie W, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network and the National Heart, Lung, and Blood Institute. Asthma during pregnancy. *Obstet Gynecol*. 2004 Jan; 103[1]:5–12. <https://doi.org/10.1097/01.AOG.0000103994.75162.16> PMID: 14704237.
7. 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 Oct; 102[4]:739–52. [https://doi.org/10.1016/s0029-7844\(03\)00621-5](https://doi.org/10.1016/s0029-7844(03)00621-5) PMID: 14551004.
8. Clifton VL, Engel P, Smith R, Gibson P, Brinsmead M, Giles WB. Maternal and neonatal outcomes of pregnancies complicated by asthma in an Australian population. *Aust N Z J Obstet Gynaecol*. 2009 Dec; 49[6]:619–26. <https://doi.org/10.1111/j.1479-828X.2009.01077.x> PMID: 20070710
9. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax*. 2006 Feb; 61[2]:169–76. Review. <https://doi.org/10.1136/thx.2005.049718> PMID: 16443708; PubMed Central PMCID: PMC2104591.
10. Schatz M, Dombrowski MP, Wise R, Momirova V, Landon M, Mabie W, et al. Spirometry is related to perinatal outcomes in pregnant women with asthma. *Am J Obstet Gynecol*. 2006 Jan; 194[1]:120–6. <https://doi.org/10.1016/j.ajog.2005.06.028> PMID: 16389020.
11. Källén B, Rydhstroem H, Aberg A. Asthma during pregnancy—a population based study. *Eur J Epidemiol*. 2000 Feb; 16[2]:167–71. <https://doi.org/10.1023/a:1007678404911> PMID: 10845267.

12. Gage S, Kan P, Lee HC, Gould JB, Stevenson DK, Shaw GM, et al. Maternal Asthma, Preterm Birth, and Risk of Bronchopulmonary Dysplasia. *J Pediatr*. 2015 Oct; 167[4]:875–880.e1. <https://doi.org/10.1016/j.jpeds.2015.06.048> PMID: 26254835
13. Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalization among pregnant women with asthma: a systematic review and meta-analysis. *BJOG* 2014; 121:812–22
14. Bain E, Pierides KL, Clifton VL, Hodyl NA, Stark MJ, Crowther CA, et al. Interventions for managing asthma in pregnancy. *Cochrane Database of Systematic Reviews* 2014, Issue 10. Art. No.: CD010660. <https://doi.org/10.1002/14651858.CD010660.pub2> PMID: 25331331
15. Eltonsy S, Kettani FZ, Blais L. Beta2-agonists use during pregnancy and perinatal outcomes: a systematic review. *Respir Med*. 2014 Jan; 108[1]:9–33. Epub 2013 Dec 17. Review. <https://doi.org/10.1016/j.rmed.2013.07.009> PMID: 24360293.
16. Gluck JC, Gluck PA. The effect of pregnancy on the course of asthma. *Immunol Allergy Clin North Am*. 2006 Feb; 26[1]:63–80. <https://doi.org/10.1016/j.iac.2005.10.008> PMID: 16443143
17. Cossette B, Forget A, Beauchesne MF, Rey É, Lemièrre C, Larivée P, et al. Impact of maternal use of asthma-controller therapy on perinatal outcomes. *Thorax*. 2013 Aug; 68[8]:724–30. Epub 2013 Apr 13. <https://doi.org/10.1136/thoraxjnl-2012-203122> PMID: 23585516.
18. Cossette B, Beauchesne MF, Forget A, Lemièrre C, Larivée P, Rey E, et al. Relative perinatal safety of salmeterol vs formoterol and fluticasone vs budesonide use during pregnancy. *Ann Allergy Asthma Immunol*. 2014 May; 112[5]:459–64. <https://doi.org/10.1016/j.ana.2014.02.010> PMID: 24656659
19. Garne E, Vinkel Hansen A, Morris J, Jordan S, Klungsøyr K, Engeland A, et al. Risk of congenital anomalies after exposure to asthma medication in the first trimester of pregnancy—a cohort linkage study. *BJOG*. 2016 Sep; 123[10]:1609–18. <https://doi.org/10.1111/1471-0528.14026> PMID: 27172856
20. Lawn JE, Rohde J, Rifkin S, Were M, Paul VK, Chopra M. Alma-Ata 30 years on: revolutionary, relevant, and time to revitalise. *Lancet*. 2008 Sep 13; 372[9642]:917–27. [https://doi.org/10.1016/S0140-6736\(08\)61402-6](https://doi.org/10.1016/S0140-6736(08)61402-6) PMID: 18790315.
21. Saha MR, Ryan K, Amir LH. Postpartum women's use of medicines and breastfeeding practices: a systematic review. *Int Breastfeed J*. 2015 Oct 28; 10:28. <https://doi.org/10.1186/s13006-015-0053-6> PMID: 26516340
22. Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, et al.; Lancet Breastfeeding Series Group. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet*. 2016 Jan 30; 387[10017]:475–90. [https://doi.org/10.1016/S0140-6736\(15\)01024-7](https://doi.org/10.1016/S0140-6736(15)01024-7) PMID: 26869575
23. Rollins NC, Bhandari N, Hajeebhoy N, Horton S, Lutter CK, Martines JC, et al; Lancet Breastfeeding Series Group. Why invest, and what it will take to improve breastfeeding practices? *Lancet*. 2016 Jan 30; 387[10017]:491–504. [https://doi.org/10.1016/S0140-6736\(15\)01044-2](https://doi.org/10.1016/S0140-6736(15)01044-2) PMID: 26869576
24. Thygesen L.C. & Ersbøll A.K. When the entire population is the sample: strengths and limitations in register-based epidemiology *Eur J Epidemiol* (2014) 29: 551. <https://doi.org/10.1007/s10654-013-9873-0> PMID: 24407880
25. Ford DV, Jones KH, Verplancke JP, Lyons RA, John G, Brown G, et al. The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Services Research*. 2009 9:157. <https://doi.org/10.1186/1472-6963-9-157> PMID: 19732426
26. Jones KH., Ford DV, Thompson S, Lyons RAD. A Profile of the SAIL Databank on the UK Secure Research Platform. *International Journal of Population Data Science*. Vol 4 No 2 (2019): IJPDS Special issue: Data Centre Profiles DOI <https://doi.org/10.23889/ijpds.v4i2.1134>
27. EUROMediCAT. [EMC] Selective Serotonin Reuptake Inhibitor [SSRI] antidepressants in Pregnancy and Congenital Anomalies: population cohort study using linked electronic data in 3 countries V2. Deliverable number 21. 2015 –ISBN 978–0956746252 <http://www.EUROMediCAT.eu/publicationsandpresentations/publications>
28. BNF [2019] British National Formulary no.78, British Medical Association and the Royal Pharmaceutical Society of Great Britain, London.
29. Jordan S, Davies GI, Thayer DS, Tucker D, Humphreys I (2019) Antidepressant prescriptions, discontinuation, depression and perinatal outcomes, including breastfeeding: A population cohort analysis. *PLOS ONE* 14(11): e0225133. <https://doi.org/10.1371/journal.pone.0225133> PMID: 31738813
30. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2015. Oslo, 2015 available [http://www.whocc.no/filearchive/publications/2016\\_guidelines\\_web.pdf](http://www.whocc.no/filearchive/publications/2016_guidelines_web.pdf) 14.5.16



31. Price T., Humphreys C., Williams N., Heaven M., Holloway M., Davies G., et al. Asthma in Swansea, Public Health Service for Wales. 2009 Available: <http://www.saildatabank.com/data-dictionary/publications/81.aspx>
32. WHO Per-term Birth Fact Sheet. 2013 Available: <http://www.who.int/en/news-room/fact-sheets/detail/preterm-birth> accessed 10.9.18
33. Royal College of Paediatrics and Child Health. Early years—UK-WHO growth charts and resources. 2015 Available: <https://www.rcpch.ac.uk/resources/uk-who-growth-charts-0-4-years> accessed 10.9.18
34. NHS Wales Data Dictionary 2017 <http://www.datadictionary.wales.nhs.uk/#!WordDocuments/infant-feedingdatarequirements.htm>
35. Wales Statistics. Birth Statistics from the National Community Child Health Database [NCCHD] Quality Report. 2013. available: <http://gov.wales/docs/statistics/2013/130730-births-in-wales-quality-report-en.pdf> accessed 13.4.16
36. IFF Research. (2013). Infant Feeding Survey, 2010. [data collection]. 2nd Edition. UK Data Service. SN: 7281, <http://doi.org/10.5255/UKDA-SN-7281-2>
37. Schulz KF and Grimes DA 2006 The Lancet Handbook of Essential concepts in Clinical Research. Elsevier, Edinburgh.
38. EUROCAT. EUROCAT European surveillance of congenital anomalies. Guide 1.4. EUROCAT Central Registry, University of Ulster, Newtownabbey, Co Antrim, UK. 2013 Available: <http://www.eurocatnetwork.eu/content/EUROCAT-Guide-1.4-Full-Guide.pdf> [accessed 26.2.15]
39. Morrow J, Russell A, Guthrie E, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006; 77 [2]:193–8. <https://doi.org/10.1136/jnnp.2005.074203> PMID: 16157661
40. Sillesen M, Hjortdal V, Vejlstrup N, Sørensen K. Pregnancy with prosthetic heart valves—30 years' nationwide experience in Denmark. *Eur J Cardiothorac Surg*. 2011 Aug; 40[2]:448–54. <https://doi.org/10.1016/j.ejcts.2010.12.011> PMID: 21277217
41. Casson IF, Clarke CA, Howard CV, et al. Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. *BMJ* 1997; 315[7103]:275–8. <https://doi.org/10.1136/bmj.315.7103.275> PMID: 9274545
42. Cooper DL, Petherick ES, Wright J. The association between binge drinking and birth outcomes: results from the Born in Bradford cohort study. *J Epidemiol Community Health*. 2013 Oct; 67[10]:821–8. Epub 2013 May 31. <https://doi.org/10.1136/jech-2012-202303> PMID: 23729326.
43. Jordan S., RA Charlton K Tingay, DS Thayer, GI Davies, M Morgan, et al. SSRI use in pregnancy: a study in 6 European databases. *The Marce Society. Arch Womens Ment Health* [2015] 18:269–408 P.368 <https://doi.org/10.1007/S00737-014-0488-6>
44. Royston P, Moons KG, Altman DG, Vergouwe Y Prognosis and prognostic research. Developing a prognostic model. *BMJ* 2009 338: b604. <https://doi.org/10.1136/bmj.b604> PMID: 19336487
45. Townsend P, Phillimore P, Beattie A: Health and Deprivation: Inequality and the North. London: Routledge; 1988.
46. Corp IBM. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.
47. Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C, Schatz M. Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *Eur Respir J*. 2013 May; 41[5]:1082–90. <https://doi.org/10.1183/09031936.00195111> PMID: 22903964
48. Bakhireva LN, Schatz M, Jones KL, Chambers CD; Organization of Teratology Information Specialists Collaborative Research Group. Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth. *Ann Allergy Asthma Immunol*. 2008 Aug; 101[2]:137–43. [https://doi.org/10.1016/S1081-1206\(10\)60201-3](https://doi.org/10.1016/S1081-1206(10)60201-3) PMID: 18727468
49. Kempainen M, Lahesmaa-Korpinen AM, Kauppi P, et al. Maternal asthma is associated with increased risk of perinatal mortality. *PLoS One*. 2018; 13[5]:e0197593. Published 2018 May 18. <https://doi.org/10.1371/journal.pone.0197593> PMID: 29775476
50. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2020, Available: [https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report\\_-final-\\_wms.pdf](https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf)
51. Enriquez R, Griffin MR, Carroll KN, Wu P, Cooper WO, Gebretsadik T, et al. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol*. 2007 Sep; 120 [3]:625–30. <https://doi.org/10.1016/j.jaci.2007.05.044> PMID: 17658591
52. Rejnö G, Lundholm C, Larsson K, Larsson H, Lichtenstein P, D'Onofrio BM, et al. Adverse Pregnancy Outcomes in Asthmatic Women: A Population-Based Family Design Study. *J Allergy Clin Immunol Pract*. 2018 May -Jun; 6(3):916–922.e6. Epub 2017 Oct 4. <https://doi.org/10.1016/j.jaip.2017.07.036> PMID: 28988783.

53. Wadhwa PD, Entringer S, Buss C, Lu MC. The contribution of maternal stress to preterm birth: issues and considerations. *Clin Perinatol*. 2011 Sep; 38[3]:351–84. <https://doi.org/10.1016/j.clp.2011.06.007> PMID: 21890014
54. Rejnö G, Lundholm C, Gong T, Larsson K, Saltvedt S, Almqvist C. Asthma during pregnancy in a population-based study—pregnancy complications and adverse perinatal outcomes. *PLoS One*. 2014 Aug 20; 9(8):e104755. eCollection 2014. <https://doi.org/10.1371/journal.pone.0104755> PMID: 25141021; PubMed Central PMCID: PMC4139314.
55. Herrera Emilio A., Krause Bernardo, Ebensperger German, Reyes Roberto V., Casanello Paola, Mauro Parra-Cordero, et al., The placental pursuit for an adequate oxidant balance between the mother and the fetus, *Frontiers in Pharmacology*, 10.3389/fphar.2014.00149, 5, (2014). <https://doi.org/10.3389/fphar.2014.00149> PMID: 25009498
56. Wareing M. Oxygen sensitivity, potassium channels, and regulation of placental vascular tone. *Microcirculation*. 2014; 21(1):58–66. <https://doi.org/10.1111/micc.12069> PMID: 23710683
57. Ali Z, Nilas L, Ulrik CS. Low risk of adverse obstetrical and perinatal outcome in pregnancies complicated by asthma: A case control study. *Respir Med*. 2016 Nov; 120:124–130. Epub 2016 Oct 11. <https://doi.org/10.1016/j.rmed.2016.10.004> PMID: 27817809.
58. Sharma D, Shastri S, Sharma P. Intrauterine Growth Restriction: Antenatal and Postnatal Aspects. *Clinical Medicine Insights. Pediatrics*. 2016; 10:67–83. <https://doi.org/10.4137/CMPed.S40070> PMID: 27441006
59. Malm H., Martikainen J., Klaukka T. et al. Prescription drugs during pregnancy and lactation—a Finnish register-based study. *Eur J Clin Pharmacol* 59, 127–133 (2003). <https://doi.org/10.1007/s00228-003-0584-4> PMID: 12700878
60. Olesen C, Sørensen HT, de Jong-van den Berg L, Olsen J, Steffensen FH, The Euromap Group. Prescribing during pregnancy and lactation with reference to the Swedish classification system. A population-based study among Danish women. *Acta Obstet Gynecol Scand*. 1999; 78(8):686–692. <https://doi.org/10.1034/j.1600-0412.1999.780805.x> PMID: 10468060
61. Mehta N, Chen K, Hardy E, Powrie R. Respiratory disease in pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2015 Jul; 29[5]:598–611. <https://doi.org/10.1016/j.bpobgyn.2015.04.005> PMID: 25997564
62. Rey E, Boulet LP. Asthma in pregnancy. *BMJ*; 2007 334[7593]:582–5. <https://doi.org/10.1136/bmj.39112.717674.BE> PMID: 17363831
63. Broekema M, Timens W, Vonk JM, Volbeda F, Lodewijk ME, Hylkema MN, et al. Persisting remodeling and less airway wall eosinophil activation in complete remission of asthma. *Am J Respir Crit Care Med*. 2011 Feb 1; 183[3]:310–6. <https://doi.org/10.1164/rccm.201003-0494OC> PMID: 20813885
64. Zetstra-van der Woude AP., van Gelder MM., Wang H., Vroegop JH., de Jong-van den Berg LTW. A Study investigating the perceptions of women about the use of their asthma medication during pregnancy and the safety for their baby. Chapter 4.3 pp. 145–169 in: Zetstra-van der Woude AP Data Collection on Risk Factors in Pregnancy. Doctoral thesis, University of Groningen, Netherlands. 2016 ISBN: 978-90-367-8524-2
65. ONS 2018 <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/childmortalitystatisticschildhoodinfantandperinatalchildhoodinfantandperinatalmortalityinenglandandwales>
66. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. *Respir Med*. 2013 Oct; 107[10]:1481–90. <https://doi.org/10.1016/j.rmed.2013.04.005> PMID: 23643487
67. Chamberlain C, Williamson GR, Knight B, Daly M, Halpin DM. Investigating Women’s Experiences of Asthma Care in Pregnancy: A Qualitative Study. *Open Nurs J*. 2014; 8:56–63. Published 2014 Dec 11. <https://doi.org/10.2174/1874434601408010056> PMID: 25538796
68. Wadhwa PD, Garite TJ, Porto M, Glynn L, Chicz-DeMet A, Dunkel-Schetter C, et al. Placental corticotropin-releasing hormone [CRH], spontaneous preterm birth, and fetal growth restriction: a prospective investigation. *Am J Obstet Gynecol*. 2004 Oct; 191[4]:1063–9. <https://doi.org/10.1016/j.ajog.2004.06.070> PMID: 15507922
69. Hale T Medications and Mothers’ Milk: a manual of lactation pharmacology. 14th edition. Hale Publishing, Amarillo, Texas 2010
70. Merlob P. & Weber-Schondorfer C. Antiallergics, antiasthmatics and antitussives. In: Schaefer C., Peters P., Miller R. [eds] *Drugs During Pregnancy and Lactation* 2015 pp.671–6 3rd edition
71. Aljazaf K, Hale TW, Ilett KF, et al. Pseudoephedrine: effects on milk production in women and estimation of infant exposure via breastmilk. *British Journal of Clinical Pharmacology*. 2003; 56[1]:18–24. <https://doi.org/10.1046/j.1365-2125.2003.01822.x> PMID: 12848771

72. Stats Wales 2019 Breastfeeding, quarterly counts by age and LHB. accessed 18.5.19 <https://statswales.gov.wales/Catalogue/Health-and-Social-Care/NHS-Primary-and-Community-Activity/Breastfeeding/breastfeedingquarterlycounts-by-age-lhb>
73. Harvey SM, Murphy VE, Gibson PG, Collison A, Robinson P, Sly P, et al. Maternal asthma, breastfeeding, and respiratory outcomes in the first year of life. *Pediatric Pulmonology*. 2020; 1–7. <https://doi.org/10.1002/ppul.24756>
74. Renfrew MJ, Pokhrel S., Quigley M. McCormick F, Fox-Rushby J., Dodds R., et al. Preventing disease and saving resources: the potential contribution of increasing breastfeeding rates in the UK. Unicef UK, London. 2012 Available on: [http://www.unicef.org.uk/Documents/Baby\\_Friendly/Research/Preventing\\_disease\\_saving\\_resources.pdf?epslanguage=en](http://www.unicef.org.uk/Documents/Baby_Friendly/Research/Preventing_disease_saving_resources.pdf?epslanguage=en) accessed 3.11.12
75. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, et al. Every Newborn: progress, priorities, and potential beyond survival. *Lancet*. 2014 Jul 12; 384[9938]:189–205. Erratum in: *Lancet*. 2014 Jul 12;384[9938]:132. [https://doi.org/10.1016/S0140-6736\(14\)60496-7](https://doi.org/10.1016/S0140-6736(14)60496-7) PMID: 24853593.
76. Platt MJ. Outcomes in preterm infants. *Public Health*. 2014 May; 128[5]:399–403. Epub 2014 May 1. Review. <https://doi.org/10.1016/j.puhe.2014.03.010> PMID: 24794180.
77. Østgård HF, Løhaugen GC, Bjuland KJ, Rimol LM, Brubakk AM, Martinussen M, et al. Brain morphology and cognition in young adults born small for gestational age at term. *J Pediatr*. 2014 Nov; 165[5]:921–7.e1. <https://doi.org/10.1016/j.jpeds.2014.07.045> PMID: 25217202
78. Milovanovic I, Njuieyon F, Deghmoun S, Chevenne D, Levy-Marchal C, Beltrand J. SGA children with moderate catch-up growth are showing the impaired insulin secretion at the age of 4. *PLoS One*. 2014 Jun 30; 9[6]:e100337. eCollection 2014. Erratum in: *PLoS One*.2014;9[9]:e108008. <https://doi.org/10.1371/journal.pone.0100337> PMID: 24979613
79. Belanger K, Hellenbrand ME, Holford TR, Bracken M. Effect of pregnancy on maternal asthma symptoms and medication use. *Obstet Gynecol*. 2010; 115(3):559–567. <https://doi.org/10.1097/AOG.0b013e3181d06945> PMID: 20177287
80. Robijn AL, Jensen ME, McLaughlin K, Gibson PG, Murphy VE. Inhaled corticosteroid use during pregnancy among women with asthma: A systematic review and meta-analysis. *Clin Exp Allergy*. 2019; 49(11):1403–1417. <https://doi.org/10.1111/cea.13474> PMID: 31357230
81. Christiaens I, Hegadoren K, Olson DM. Adverse childhood experiences are associated with spontaneous preterm birth: a case-control study. *BMC Med*. 2015 Jun 11; 13:124. <https://doi.org/10.1186/s12916-015-0353-0> PMID: 26063042
82. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet*. 2008 Jan 19; 371[9608]:261–9. Review. [https://doi.org/10.1016/S0140-6736\(08\)60136-1](https://doi.org/10.1016/S0140-6736(08)60136-1) PMID: 18207020.
83. Jordan S, Watkins A, Storey M, Allen SJ, Brooks CJ, Garaiova I, et al. Volunteer Bias in Recruitment, Retention, and Blood Sample Donation in a Randomised Controlled Trial Involving Mothers and Their Children at Six Months and Two Years: A Longitudinal Analysis. *PLoS ONE* 2013 [7]: e67912. <https://doi.org/10.1371/journal.pone.0067912> PMID: 23874465
84. Grzeskowiak LE, Smith B, Roy A, Dekker GA, Clifton VL. An observational study of the impact of an antenatal asthma management service on asthma control during pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2016 Feb; 197:48–53. Epub 2015 Dec 2. <https://doi.org/10.1016/j.ejogrb.2015.11.038> PMID: 26706835.
85. Jonathan AC Sterne, Miguel A Hernán, Alexandra McAleenan, Barnaby C Reeves, Julian PT Higgins Chapter 25 In:Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*. Cochrane, 2019. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).
86. Gluck PA, Gluck JC. A review of pregnancy outcomes after exposure to orally inhaled or intranasal budesonide. *Curr Med Res Opin*. 2005 Jul; 21[7]:1075–84. <https://doi.org/10.1185/030079905X50570> PMID: 16004676
87. Schnitzer ME, Blais L. Methods for the assessment of selection bias in drug safety during pregnancy studies using electronic medical data. *Pharmacol Res Perspect*. 2018; 6(5):e00426. Published 2018 Sep 21. <https://doi.org/10.1002/prp2.426> PMID: 30258633
88. Miquel-Verges F, Mosley BS, Block AS, Hobbs CA. A spectrum project: preterm birth and small-for-gestational age among infants with birth defects. *J Perinatol*. 2015 Mar; 35[3]:198–203. Epub 2014 Oct 2. <https://doi.org/10.1038/jp.2014.180> PMID: 25275696.
89. Oldereid NB, Wennerholm UB, Pinborg A, et al. The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis. *Hum Reprod Update*. 2018; 24(3):320–389. <https://doi.org/10.1093/humupd/dmy005> PMID: 29471389

90. Liu X, Helenius D, Skotte L, et al. Variants in the fetal genome near pro-inflammatory cytokine genes on 2q13 associate with gestational duration. *Nat Commun*. 2019; 10(1):3927. Published 2019 Sep 2. <https://doi.org/10.1038/s41467-019-11881-8> PMID: 31477735
91. Heffler E, Pizzimenti S, Guida G, Bucca C, Rolla G. Prevalence of over-/misdiagnosis of asthma in patients referred to an allergy clinic. *J Asthma*. 2015; 52[9]:931–4. Epub 2015 Aug 18. <https://doi.org/10.3109/02770903.2015.1026442> PMID: 26291138.
92. Nunes V, Neilson J, O'Flynn N, Calvert N, Kuntze S, Smithson H, et al. [2009]. Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners.
93. Martins AC, Giordani F, Rozenfeld S. Adverse drug events among adult inpatients: A meta-analysis of observational studies. *J Clin Pharm Ther* 2014 Dec; 39[6]:609–20 <https://doi.org/10.1111/jcpt.12204> PMID: 25219403
94. Mori K, Fujisawa T, Inui N, Hashimoto D, Enomoto N, Nakamura Y, et al. Step-down treatment from medium-dosage of budesonide/formoterol in controlled asthma. *Respir Med*. 2016 Oct; 119:1–6. Epub 2016 Aug 15. <https://doi.org/10.1016/j.rmed.2016.08.007> PMID: 27692128.
95. Brozek JL, Kraft M, Krishnan JA, et al. Long-Acting  $\beta$ 2-Agonist Step-off in Patients With Controlled Asthma Systematic Review With Meta-analysis. *Arch Intern Med*. 2012; 172[18]:1365–1375. <https://doi.org/10.1001/archinternmed.2012.3250> PMID: 22928176
96. Rothman K. J. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990 1, 43–6. PMID: 2081237
97. Greenland S, Daniel R, Pearce N. Outcome modelling strategies in epidemiology: traditional methods and basic alternatives. *Int J Epidemiol*. 2016; 45(2):565–575. <https://doi.org/10.1093/ije/dyw040> PMID: 27097747
98. York R. Residualization is not the answer: Rethinking how to address multicollinearity. *Soc Sci Res*. 2012; 41(6):1379–1386. <https://doi.org/10.1016/j.ssresearch.2012.05.014> PMID: 23017962
99. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENCePP]. Guide on Methodological Standards in Pharmacoepidemiology [Revision 7]. EMA/95098/2010. [http://www.encepp.eu/standards\\_and\\_guidances/documents/ENCePPGuideonMethStandardsinPE\\_Rev7.pdf](http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideonMethStandardsinPE_Rev7.pdf) 22.3.19
100. Fewell Zoe, George Davey Smith Jonathan A. C. Sterne, The Impact of Residual and Unmeasured Confounding in Epidemiologic Studies: A Simulation Study, *American Journal of Epidemiology*, Volume 166, Issue 6, 15 September 2007, Pages 646–655, <https://doi.org/10.1093/aje/kwm165> PMID: 17615092
101. Turkeltaub PC, Cheon J, Friedmann E, Lockey RF. The Influence of Asthma and/or Hay Fever on Pregnancy: Data from the 1995 National Survey of Family Growth. *J Allergy Clin Immunol Pract*. 2017 Nov–Dec; 5[6]:1679–1690. <https://doi.org/10.1016/j.jaip.2017.03.036> PMID: 28550983.
102. McLaughlin K, Foureur M, Jensen ME, Murphy VE. Review and appraisal of guidelines for the management of asthma during pregnancy. *Women Birth*. 2018 Dec; 31[6]:e349–e357. Epub 2018 Feb 21. Review. <https://doi.org/10.1016/j.wombi.2018.01.008> PMID: 29475603.