

The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis

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Background There is conflicting literature on the effect of maternal asthma on congenital malformations and neonatal outcomes.

Objectives This review and meta-analysis sought to determine if maternal asthma is associated with an increased risk of adverse neonatal outcomes.

Search strategy We searched electronic databases for: (asthma or wheeze) and (pregnan* or perinat* or obstet*).

Selection criteria Cohort studies published between 1975 and March 2012 reporting at least one perinatal outcome of interest (congenital malformations, neonatal complications, perinatal mortality).

Data collection and analysis In all, 21 studies met inclusion criteria in pregnant women with and without asthma. Further analysis was conducted on 16 studies where asthmatic women were stratified by exacerbation history, corticosteroid use, bronchodilator use or asthma severity.

Main results Maternal asthma was associated with a significantly increased risk of congenital malformations (relative risk [RR] 1.11,

95% confidence interval [95% CI] 1.02–1.21, $I^2 = 59.5\%$), cleft lip with or without cleft palate (RR 1.30, 95% CI 1.01–1.68, $I^2 = 65.6\%$), neonatal death (RR 1.49, 95% CI 1.11–2.00, $I^2 = 0\%$), and neonatal hospitalisation (RR 1.50, 95% CI 1.03–2.20, $I^2 = 64.5\%$). There was no significant effect of asthma on major malformations (RR 1.31, 95% CI 0.57–3.02, $I^2 = 70.9\%$) or stillbirth (RR 1.06, 95% CI 0.9–1.25, $I^2 = 35\%$). Exacerbations and use of bronchodilators and inhaled corticosteroids were not associated with congenital malformation risk.

Authors' conclusions Despite limitations related to the observational nature of the primary studies, this review demonstrates a small increased risk of neonatal complications among pregnant women with asthma. Further investigations into mechanisms and potential preventive interventions to improve infant outcomes are required.

Keywords Asthma, congenital anomaly, malformation, neonatal death, neonatal intensive care unit, perinatal mortality, pregnancy, stillbirth.

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Introduction

Asthma is a commonly reported medical condition affecting pregnant women, and the course of the disease can change during pregnancy. There has been conflicting literature as to the effects of maternal asthma on pregnancy and

neonatal outcomes. In 2011, we published the first systematic review and meta-analysis of literature in this area examining the risk of adverse perinatal outcomes in women with asthma, focusing on preterm delivery, low birthweight and pre-eclampsia, some of the more commonly reported outcomes.¹ We found a moderately increased risk of each

of these outcomes in pregnant women with asthma compared with pregnant women without asthma.¹ Numerous other important adverse outcomes, particularly those affecting the neonate, have been reported in the literature, but with no previous attempt to summarise the data via meta-analysis. Studies on the effect of asthma on congenital malformations vary in terms of sample size, study design (cohort versus case-control), exposures tested (asthma or asthma medication use), adjustment for confounders and multiple testing, and examination of specific malformations, while studies of perinatal mortality have generally been underpowered. There are also few studies that examine the potential mechanisms contributing to these outcomes, such as disease severity, exacerbations or asthma medication use. This updated systematic review and meta-analysis attempts to overcome some of these limitations in the existing literature, by examining the relative risks of adverse neonatal outcomes among women with asthma compared with women without asthma, and to examine the possible roles of medication use, asthma exacerbations during pregnancy and asthma severity on these outcomes.

Methods

Search strategy and study selection

A review protocol was established by the investigators before commencement. The study protocol has been described in detail elsewhere¹ and further details are given in the online supporting information (see Supplementary material, Appendix S1). We recently completed an update to our original systematic review. The initial search identified English-language studies published between 1975 (when inhaled corticosteroids were introduced) and March 2009 from Medline ($n = 1642$), Embase ($n = 1755$), CINAHL ($n = 417$) and the Cochrane Central Register of Controlled Trials ($n = 75$), using the search terms ([asthma or wheeze] and [pregnan* or perinat* or obstet*]). Identified abstracts were independently assessed by two reviewers. The full text version of each potential article was obtained for assessment by two independent reviewers to establish whether it met the inclusion criteria. In the update, we used the same search terms to identify English language studies published between January 2009 and 11 March 2012 from Medline ($n = 681$), Embase ($n = 624$), CINAHL ($n = 84$) and the Cochrane Central Register of Controlled Trials ($n = 14$).

Inclusion criteria for analysis of the effect of maternal asthma on neonatal outcomes (Analysis A)

Included articles contained data from a group of pregnant women with asthma and a control group of pregnant women without asthma. Further inclusion criteria were (1) reporting at least one perinatal outcome of interest

(congenital malformation, major congenital malformation, perinatal mortality, stillbirth, neonatal death, neonatal hospitalisation, transient tachypnoea of the newborn, respiratory distress syndrome or neonatal sepsis) and (2) cohort study design (prospective or retrospective). Maternal asthma could be defined as physician-diagnosed (whether confirmed or subject self-report), database-coded asthma diagnosis, or asthma fulfilling American Thoracic Society criteria.

In all, 139 articles were identified for possible inclusion in the review (Analysis A); 73 of these were excluded for the following reasons: no control group ($n = 38$), no clear asthma group ($n = 3$), women with asthma selected based on exacerbation ($n = 3$), cross-sectional survey ($n = 3$), case-control study ($n = 3$), perinatal outcomes not suitably reported ($n = 10$), women studied before 1975 ($n = 2$), paper retracted ($n = 1$), abstract only ($n = 2$), not the primary paper/first report of results ($n = 2$), review ($n = 6$). Of the remaining 66 publications, 21 studies (eight prospective, 13 retrospective) were identified for inclusion in the analysis of the effect of maternal asthma on neonatal outcomes (see Supplementary material, Table S1).

Inclusion criteria for analysis of the effect of maternal asthma subtypes on neonatal outcomes (Analysis B)

Included articles contained data from pregnant women with asthma which had been subdivided based on asthma medication use (e.g. inhaled corticosteroid use, no inhaled corticosteroid use), asthma exacerbations requiring medical intervention during pregnancy, or asthma severity (mild, moderate/severe; see Supplementary material, Table S2). Cohort studies or randomised controlled trials were included if they reported at least one outcome of interest.

Of the studies identified for Analysis A, and the 38 studies that were excluded from Analysis A because they contained no control group, there were 16 studies (seven prospective, eight retrospective, one randomised controlled trial) identified for inclusion in the analysis of the effect of maternal asthma subtypes on neonatal outcomes (Analysis B).

Data extraction

Data extraction was completed on a standardised form by one reviewer and checked by a second reviewer. Investigators discussed any discrepancies to reach consensus. Studies were considered to have provided active asthma management when the study investigators were involved in the management and treatment of women with asthma and this was described (Table S1).

We used the Newcastle–Ottawa Scale to assess study quality.² The Newcastle–Ottawa Scale is a validated tool for assessing the quality of non-randomised studies including cohort and case-control studies and has a maximum score

of 9. Quality was assessed and scored by two reviewers and all studies were considered to be of adequate quality for inclusion in the meta-analysis (minimum score 5, mean of all scores 7.8, Table S1).

Meta-analysis

The meta-analyses conformed to standard methodological guidelines for meta-analysis of observational studies.³ The relative risk of the perinatal outcome was examined in women with asthma compared with women without asthma (analysis A) or in subgroups of women with asthma stratified by severity (mild versus moderate-severe), exacerbations during pregnancy (expressed as a yes/no variable) and exposure to oral corticosteroids during pregnancy (expressed as a yes/no variable, analysis B) using REVIEW MANAGER software (REVIEW MANAGER (REVMAN) [computer program] Version 4.3.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, available online <http://ims.cochrane.org/revman/download/revman-4>). Sensitivity analyses were also performed in Analysis A by study design (prospective versus retrospective cohort) and asthma management (active versus no active management). For dichotomous outcomes the relative risk with 95% confidence interval was calculated using a random effects model, unless three or fewer studies were combined, in which case the fixed effects model was used. The difference between relative risks for the active management and no active management subgroups was determined using the method of Altman and Bland⁴ and expressed as a relative risk ratio (RRR) with 95% confidence intervals. Data from studies that provided adjusted odds ratios were pooled using the generic inverse variance method. Heterogeneity was examined using the chi-square test ($P < 0.1$ considered significant heterogeneity), the I^2 -square percentage ($I^2 \geq 60\%$ considered significant heterogeneity) and subgroup analyses.

Other analyses

When outcomes were reported in at least ten studies, Funnel plots and the Egger test were used to investigate publication bias (STATA 7, Stata Corporation, College Station, TX, USA, www.stata.com). Power calculations were conducted using the PS POWER AND SAMPLE SIZE program (version 2.1.30).⁵ In reporting results of the meta-analysis we followed recommendations from the PRISMA consensus statement.⁶

Further information is available in Appendix S1.

Results

Congenital malformations

Data on congenital malformations (all/any) were included in 16 publications,^{7–22} which represented 14 overall studies.

Data from Minerbi-Codish et al.¹⁴ were incomplete and therefore not included in the meta-analysis. Schatz et al.¹⁸ reported major and minor congenital malformations separately, which were added together to give total malformations. Clark et al.⁸ reported malformations as those which were the reason for neonatal hospital admissions, so these data were excluded because they did not capture all malformations.⁸ Data sources and definitions/confirmation of congenital malformations and major congenital malformations varied (see Supplementary material, Table S3).

There were four prospective cohort studies (all had active asthma management) included in the meta-analysis and eight retrospective cohort studies (none had active management).^{7,9,10,12,13,20–22} There was a significantly increased risk of congenital malformations in women with asthma compared with control women without asthma (Figure 1A; relative risk [RR] 1.11, 95% confidence interval [95% CI] 1.02–1.21, $I^2 = 59.5\%$, $P < 0.1$). Sensitivity analysis showed the effect was only significant in the subcategory of retrospective cohort studies (without active management, RR 1.12, 95% CI 1.03–1.22), whereas in the prospective cohort studies (with active asthma management) there was no significant effect (RR 1.40, 95% CI 0.54–3.59). However, the prospective cohort studies only had 10% power to detect an RR of 1.11, as observed in the retrospective studies. There was no significant publication bias (Egger test, $P = 0.977$).

A meta-analysis of the adjusted odds ratio from four studies (retrospective, no active management)^{9,12,13,22} found an increased odds of congenital malformations among women with asthma (Figure 1B; odds ratio 1.18, 95% CI 1.03–1.35).

The relative risk of congenital malformations among subgroups of women with asthma (Table 2) indicated no increased risk of malformations with bronchodilator use,^{23–25} inhaled corticosteroid use^{9,26,27} or exacerbations^{16,17,25} (Table 1).

Four prospective studies reported major congenital malformations.^{18,28–30} The meta-analysis indicated no significant risk of maternal asthma (Table 1; RR 1.31, 95% CI 0.57–3.02); however, there was significant heterogeneity between studies ($I^2 = 70.9\%$, $P < 0.1$). The study from Bakhireva et al.²⁸ reported an unusually low prevalence of major malformations in the control group, which contributed to the vastly different result from this study.

There was no significantly increased risk of major malformations with bronchodilator use when data from two studies^{31,32} were combined (Table 1; RR 1.00, 95% CI 0.80–1.26). Data on major congenital malformations among women with and without asthma exacerbations were extracted from four publications.^{25,32–34} However, there was significant similarity in the cohorts from the Canadian studies^{25,32,34} and data were included in

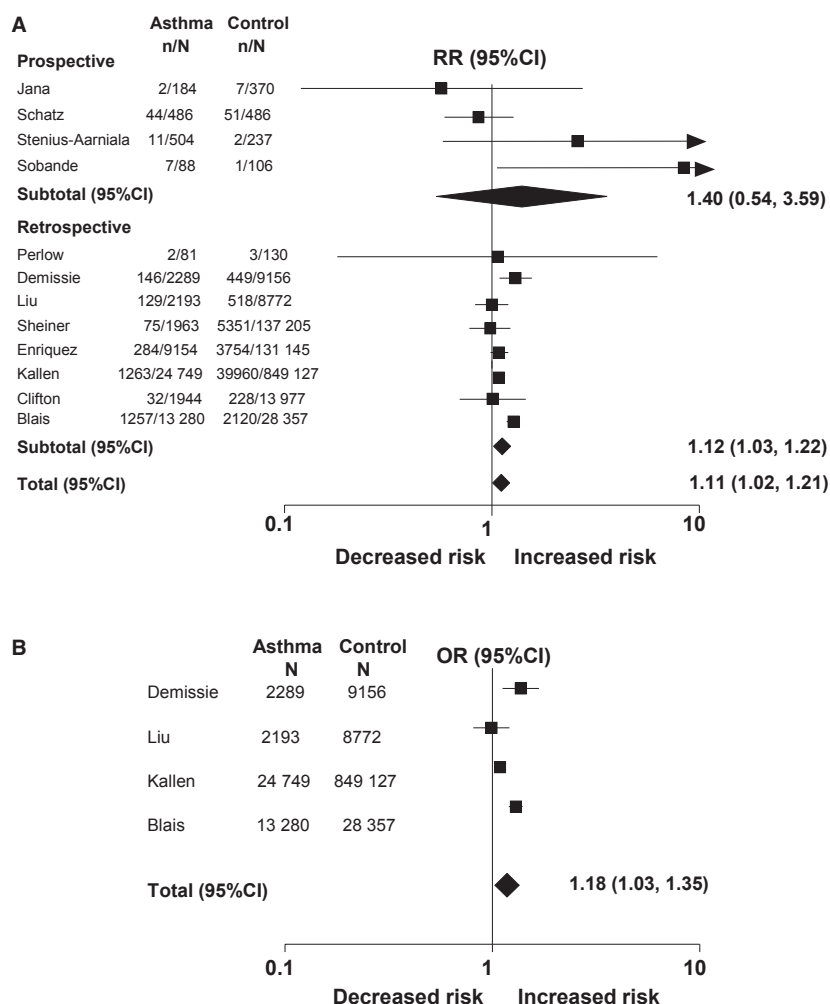


Figure 1. (A) Meta-analysis of cohort studies for congenital malformations. 'Increased risk' indicates that the outcome was more likely for women with asthma. (B) Meta-analysis of cohort studies that adjusted for confounders and presented data as odds ratios (OR) for congenital malformations. 'Increased odds' indicates that the outcome was more likely to women with asthma.

the meta-analysis from Eltonsy et al.²⁵ only, as this covered the longest time period (1990–2002) and the largest number of pregnancies in women with asthma (13 117 compared with 4344 and 4561 in Blais et al. 2008³⁴ and 2007,³² respectively). There was no significantly increased risk of major malformations among women with asthma exacerbations during pregnancy compared with women with no exacerbations during pregnancy (Table 1; RR 1.26, 95% CI 0.95–1.67), with no heterogeneity between studies ($I^2 = 0\%$, $P = 0.71$).

Specific congenital malformations were described in detail by Kallen et al.⁹ and Blais et al.²² Kallen et al.⁹ found a significant increase in cardiac defects and anal atresia among infants of women with asthma compared with population estimates. Blais et al.²² found that women with asthma were at increased risk of having infants with nervous system, respiratory system and digestive system

defects. We combined data on cleft lip and/or cleft palate, which was described in both papers, demonstrating that infants from women with asthma had a significantly increased risk of this malformation compared with infants from women without asthma (Table 1; RR 1.30, 95% CI 1.01–1.68, $I^2 = 65.6\%$).

Stillbirth

Data on stillbirth (fetal death *in utero* either >20 weeks, or >500 g or >28 weeks³⁵) were included in eight studies.^{13,15,18,21,24,35–37} Two publications from Stenius-Aarniala et al.^{15,16} contained the same population of women, but had inconsistencies in the description of perinatal deaths. The first publication contained a detailed description of all perinatal deaths (including separate data on stillbirths and neonatal deaths); therefore data from the original paper were included in this analysis.¹⁵ Overall, there was no sig-

Table 1. Congenital malformations and related outcomes in pregnant women with asthma

Outcome	Comparison	RR [95% CI]	Number of studies	Number of women (Group 1)	Number of women (Group 2)	Heterogeneity
Congenital malformations	Bronchodilator use versus No bronchodilator use	RR 1.04 [0.94–1.16]	3	7518 (Bronchodilator)	6316 (No bronchodilator)	$I^2 = 0\%$ ($P = 0.82$)
	ICS use versus No ICS use	RR 0.96 [0.89–1.04]	3	17 220 (ICS)	21 122 (no ICS)	$I^2 = 0\%$ ($P = 0.58$)
	Exacerbation versus No exacerbation	RR 1.18 [0.94–1.47]	3	717 (Exacerbation)	13 093 (No exacerbation)	$I^2 = 0\%$ ($P = 0.79$)
Major malformations	Asthma versus Control	RR 1.31 [0.57–3.02]	4	3239 (Asthma)	1850 (Control)	$I^2 = 70.9\%$ ($P = 0.02$)
	Bronchodilator use versus No bronchodilator use	RR 1.00 [0.80–1.26]	2	4809 (Bronchodilator)	1875 (No Bronchodilator)	$I^2 = 0\%$ ($P = 0.93$)
	Exacerbation versus No exacerbation	RR 1.26 [0.95–1.67]	2	681 (Exacerbation)	12 517 (No exacerbation)	$I^2 = 0$ ($P = 0.71$)
Cleft lip with or without cleft palate	Asthma versus Control	RR 1.30 [1.01–1.68]	2	38 029 (Asthma)	902 233 (Control)	$I^2 = 65.6\%$ ($P = 0.09$)

ICS, inhaled corticosteroids; I^2 , the percentage of the variability in effect estimates that is due to heterogeneity.

Table 2. Neonatal outcomes in pregnant women with asthma

Outcome	Comparison	Odds ratio or RR [95% CI]	Number of studies	Number of women (Group 1)	Number of women (Group 2)	Heterogeneity
Stillbirth	Asthma versus Control (adjusted ORs)	OR 1.07 [0.92–1.26]	2	46257 (Asthma)	278122 (Control)	$I^2 = 0\%$ ($P = 0.51$)
	Exacerbations versus No exacerbations	RR 2.98 [0.48–18.46]	2	75 (Exacerbations)	146 (No Exacerbations)	$I^2 = 22.7\%$ ($P = 0.26$)
	ICS use versus No ICS use	RR 0.77 [0.50–1.18]	2	8455 (ICS)	15 443 (No ICS)	$I^2 = 0\%$ ($P = 0.88$)
Perinatal mortality	Exacerbations versus No exacerbations	RR 3.22 [0.79–13.18]	3	88 (Exacerbations)	686 (No Exacerbations)	$I^2 = 31.7\%$ ($P = 0.23$)
	Moderate/Severe Asthma versus Mild Asthma	RR 1.32 [0.97–1.78]	3	11396 (Moderate/Severe Asthma)	14 909 (Mild Asthma)	$I^2 = 0\%$ ($P = 1.00$)
Transient tachypnoea of the newborn	Asthma versus Control	RR 1.24 [0.85–1.80]	2	2033 (Asthma)	1175 (Control)	$I^2 = 80.9\%$ ($P = 0.02$)
Respiratory distress syndrome	Asthma versus Control	RR 1.57 [0.88–2.81]	2	2225 (Asthma)	1367 (Control)	$I^2 = 0\%$ ($P = 0.77$)
Neonatal sepsis	Asthma versus Control	RR 2.27 [1.12–4.58]	2	2457 (Asthma)	1598 (Control)	$I^2 = 0\%$ ($P = 0.64$)

ICS, inhaled corticosteroids; I^2 , the percentage of the variability in effect estimates that is due to heterogeneity.

nificantly increased risk of stillbirth in infants of asthmatic mothers compared with control mothers (Figure 2A; RR 1.06, 95% CI 0.90–1.25), and there was no heterogeneity in the studies ($I^2 = 35\%$, $P > 0.1$). There was also no increased risk in the subanalyses by study design

(Figure 2A), asthma management (data not shown), or adjusted odds ratio (Table 2).

There were no significant associations between exacerbations^{33,38} or inhaled corticosteroid use^{39,40} and the risk of stillbirth among women with asthma (Table 2).

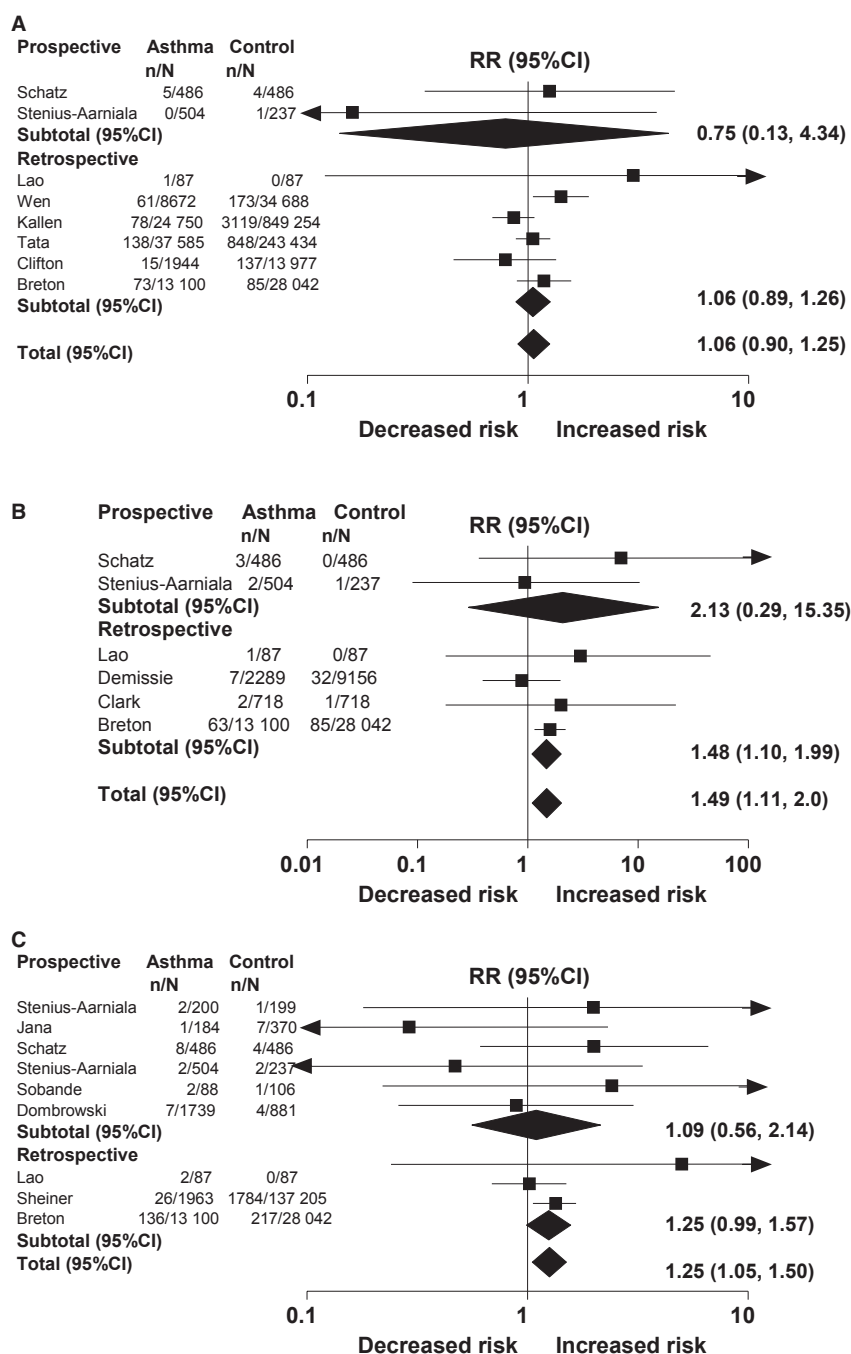


Figure 2. (A) Meta-analysis of cohort studies for stillbirth. (B) Meta-analysis of cohort studies for neonatal death. (C) Meta-analysis of cohort studies for perinatal mortality. 'Increased risk' indicates that the outcome was more likely in women with asthma.

Neonatal death

Data on neonatal death (death up to 1 month of age) were included in six studies, two prospective cohort studies^{15,18} and four retrospective cohort studies.^{8,24,37,41} Overall, there was a significantly increased risk of neonatal death in infants of asthmatic mothers compared with control mothers (Figure 2B; RR 1.49, 95% CI 1.11–2.00, no heterogeneity,

$I^2 = 0\%$, $P = 0.67$). Individually, only the retrospective cohort subcategory showed a statistically increased risk which was of similar magnitude to the overall effect size (RR 1.48, 95% CI 1.10–1.99).

In three studies, women had active management of their asthma by the study investigators or local hospital,^{15,18,24} whereas in three studies no active management of women

was given.^{8,37,41} In the subcategory with active management, there was no significant effect of maternal asthma on neonatal death, but the confidence interval was very wide (RR 2.28, 95% CI 0.46–11.40). These studies were underpowered (6%) to detect the difference observed in the retrospective cohort studies. In the subcategory of studies with no active management of women, there was a significant effect of maternal asthma on neonatal death (RR 1.47, 95% CI 1.09–1.98). The difference between the relative risks of the no active management and active management subgroups was not significant (RRR 1.55, 95% CI 0.30–7.94, $P = 0.598$).

Perinatal mortality

Data on perinatal mortality (a combination of stillbirths and neonatal deaths) were included in nine studies from ten publications. There were overlapping data presented in two publications from Schatz et al.^{18,19} Only the more recent paper with larger numbers and more definitively matched women was included in the analysis.¹⁸

There were six prospective cohort studies^{11,15,17,18,29,42} and three retrospective cohort studies.^{10,24,37} Overall, there was a significantly increased risk of perinatal mortality in infants of asthmatic mothers compared with control mothers (Figure 2C, RR 1.25, 95% CI 1.05–1.50, $I^2 = 0\%$), with the overall effect size being intermediate between that observed for stillbirth and neonatal death. Individually, neither the prospective or retrospective cohort subcategories showed a statistically increased risk of perinatal mortality (Figure 2C). The prospective cohort studies were underpowered to detect an RR of 1.25 (11%).

There were seven studies where women had active management of their asthma^{11,15,17,18,24,29,42} and two studies where no active management was given.^{10,37} There was no

significant heterogeneity between studies, and in neither subcategory was the risk of perinatal mortality significantly increased in women with asthma compared with control women, although the effect sizes were similar to the overall result (active management: RR 1.17, 95% CI 0.61–2.27; no active management: RR 1.23, 95% CI 0.95–1.58). The active management studies were underpowered to detect an RR of 1.23 (11%).

Women with exacerbations were not at significantly increased risk of perinatal mortality compared with women without exacerbations^{16,17,33} (Table 2). Women with moderate/severe asthma were not at significantly increased risk of perinatal mortality compared with women with mild asthma^{29,35,42} (Table 2).

Neonatal hospitalisation

Data on neonatal hospitalisation (treatment in or admission to the neonatal intensive care unit, or neonatal medical/surgical unit) were included in six publications. There were four prospective cohort studies^{16,29,42,43} and two retrospective cohort studies.^{8,20} Overall, there was a significantly increased risk of neonatal hospitalisation among infants of asthmatic mothers (Figure 3; RR 1.50, 95% CI 1.03–2.20) compared with infants of mothers without asthma. There was significant heterogeneity between studies ($I^2 = 64.5\%$, $P = 0.02$), and the risk was significant in the retrospective cohort subcategory only (RR 2.36, 95% CI 1.10–5.04). Three studies had active management,^{15,29,42} whereas three did not.^{8,20,43} There was a significant risk of neonatal hospitalisation among studies with no active management (RR 1.97, 95% CI 1.07–3.65), but not among studies with active management (RR 1.13, 95% CI 0.95–1.36). The difference between the relative risks of the no active management and active management subgroups

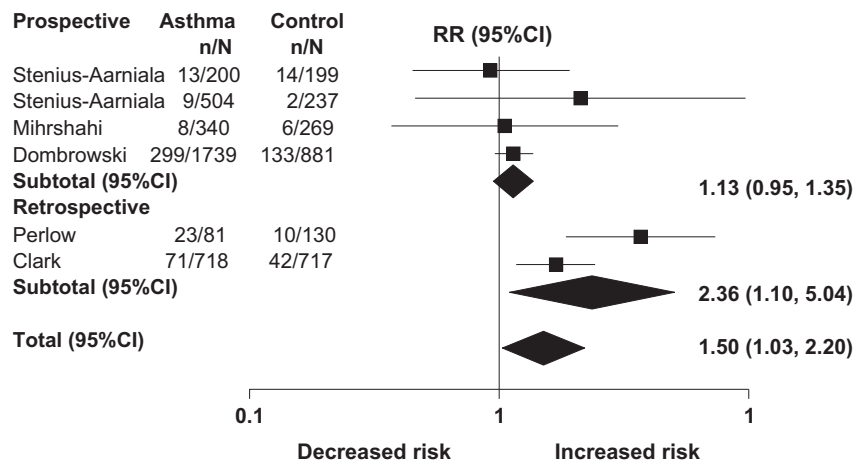


Figure 3. Meta-analysis of cohort studies for neonatal hospitalisation. 'Increased risk' indicates that the outcome was more likely in women with asthma.

was not significant (RRR 0.57, 95% CI 0.30–1.09, $P = 0.088$).

Two of the studies excluded both asthmatic and control women with earlier deliveries (one excluded women who were <36 weeks of gestation at recruitment,⁴³ while another excluded all preterm deliveries⁸), which may result in fewer neonatal complications than other studies. When sensitivity analysis was conducted without these two studies, the risk of neonatal hospitalisation among women with asthma was of a similar effect size (RR 1.58, 95% CI 0.84–2.99), but was not significant.

Transient tachypnoea of the newborn

Transient tachypnoea of the newborn (TTN) was evaluated in three studies.^{8,29,44} The TTN data were reported twice in publications from Schatz et al.,^{19,44} and the data from the publication specifically on TTN were used.⁴⁴ Two prospective cohort studies (both with active management) were included in the meta-analysis and there was a significantly increased risk of TTN among infants of asthmatic mothers (Table 2; RR 1.54, 95% CI 1.09–2.18) compared with infants of mothers without asthma and significant heterogeneity between studies ($I^2 = 84.3\%$, $P = 0.002$). The retrospective study from Clark et al.⁸ included more severe TTN requiring hospitalisation, and was the only study to individually report a significantly increased risk of TTN in neonates of mothers with asthma compared with mothers without asthma (RR 6.32, 95% CI 1.88–21.28). We included this study in the meta-analysis because it was not clear whether the TTN diagnosis required hospitalisation in the other studies, and because the criteria for the diagnosis of TTN in asthma and control women would be the same in each study, we expected the relative relationships between pregnancies in asthmatic versus control women to hold across studies.

Respiratory distress syndrome

Data on infant respiratory distress syndrome (also called hyaline membrane disease) were included in two studies, which were both prospective cohort studies with active asthma management.^{18,29} The meta-analysis did not identify an increased risk of respiratory distress syndrome among infants of asthmatic mothers (Table 2; RR 1.57, 95% CI 0.88–2.81).

Neonatal sepsis

Neonatal sepsis was defined as a discharge diagnosis of neonatal sepsis,²⁹ or sepsis resulting in admission to the neonatal medical or surgical unit,⁸ and there was a significantly increased risk of sepsis among infants of asthmatic mothers (Table 2; RR 2.27, 95% CI 1.12–4.58) compared with infants of mothers without asthma.

Discussion

Main findings

This meta-analysis indicates that infants of pregnant women with asthma are 11% more likely to manifest congenital malformations compared with infants of non-asthmatic women. Significance was reached in the retrospective studies, and among four studies that controlled for important confounders and reported adjusted odds ratio data. It is likely that some studies reported major malformations only (those that were recognised at birth); however, a separate analysis of studies reporting major malformations showed no increased risk with maternal asthma. One possibility is that the risk of malformations is driven by minor malformations, which would be reassuring, because these are less clinically significant. However, the analysis of major malformations may be inadequately powered, as there were fewer studies and women reporting this outcome. More data are needed to clarify these risks.

Pregnant women with asthma were at 30% increased risk of cleft lip and/or palate compared with pregnant women without asthma. Previous case-control studies demonstrated an association between first-trimester oral corticosteroid exposure and the risk of oral clefts.^{45,46} Our finding is consistent with the possibility that only those women with asthma who used oral steroids in the critical window for lip and palate closure are at risk for these specific defects.

Several cohort studies have specifically examined the effects of corticosteroid treatment on malformations. Two studies, exclusively in women using budesonide, found no increased risk of malformations.^{26,47} Kallen et al.⁹ evaluated the risk of malformations in women using oral or inhaled corticosteroids in early pregnancy, but found no significant associations. Another large study found a significantly reduced risk of malformations among first-trimester users of moderate-dose inhaled corticosteroids compared with nonusers.³² There was no increased risk with the use of high-dose inhaled corticosteroids; however, women who experienced exacerbations requiring medical intervention in the first trimester were at significantly increased risk of congenital malformations compared with women without exacerbations.³⁴ Our meta-analysis combined these data³⁴ with those from two other studies and no increased risk with exacerbation was observed.

There was a 25% increased risk of perinatal mortality in women with asthma, which was probably driven by the increase in neonatal deaths. However, this risk was small compared with risks for *in vitro* fertilisation pregnancies (odds ratio 2.2, 95% CI 1.6–3.0)⁴⁸ or pregnancies in women with diabetes (RR 3.01, 95% CI 1.55–5.84).⁴⁹ The increase in neonatal mortality may be a result of the

increased risk of preterm deliveries,¹ because the increased risk of perinatal mortality reported by one study was eliminated when adjusted for prematurity.³⁷

Subgroup analyses did not confirm a relationship between asthma management or severity and adverse neonatal outcomes. However, the primary studies were limited in their ability to define asthma control and successful management in individual women. A recent RCT demonstrated that neonatal outcomes could be modified when asthma therapy was adjusted according to the degree of airway inflammation, rather than symptoms and lung function.⁵⁰ This management strategy halved the rate of exacerbations requiring medical intervention during pregnancy, suggesting the potential to improve maternal and neonatal health through active management. Large prospective studies with comprehensive assessment of individual patient control and treatment variables as well as relevant confounders may further support the hypothesis that optimal asthma control during pregnancy mitigates the increased perinatal risks demonstrated in the pregnancies of women with asthma.

Strengths and weaknesses

In this systematic review and meta-analysis, we have identified numerous risks, which, although small in size, are consistent and significant. The major strength of this approach is the large number of pregnancies studied and the large number of rare events reported. There are limitations arising from the observational nature of the included studies, such as risk of bias (including reporting bias), the influence of confounders and the presence of significant heterogeneity in some analyses. For congenital malformations, we were able to combine data that adjusted for confounders and found a similar result to that obtained when combining unadjusted data, suggesting a minimal effect of confounders. Significant heterogeneity was present in several of the analyses. However, analyses for stillbirth, neonatal death and perinatal mortality and asthma subgroup analyses for congenital malformations were not affected by heterogeneity. It is possible that the very large sample sizes in some of the retrospective studies result in heterogeneity that is overstated compared with traditional meta-analyses.

Interpretation

It is plausible that maternal asthma may contribute to adverse neonatal outcomes because women with asthma are at increased risk of low birthweight infants,¹ preterm delivery,¹ gestational diabetes and placental problems,⁵¹ which all increase the risk of neonatal complications and death. Using data from different populations and settings, with various study designs, results indicate that neonates of women with asthma are at a small risk of serious complica-

tions including intensive care hospitalisation. Although we did not observe associations between asthma severity or exacerbations and neonatal outcomes, the number of available studies was low. There was a small but inconsistent effect of asthma on congenital malformations and further research is needed to clarify the risk of this outcome, and whether the risks found here could be driven by minor malformations.

Conclusions

Asthma is a common chronic disease among pregnant women, and the risks of adverse outcomes for both mother and baby during the perinatal period make this a significant health issue. Pregnant women with asthma are at increased risk of any congenital malformation and specifically of cleft lip and/or cleft palate. The currently available evidence does not indicate any relationship between malformations and bronchodilator use, inhaled corticosteroid use or exacerbations. Neonates were also at increased risk of intensive care hospitalisation and death, although further studies are needed to elucidate the mechanisms involved. Results should be interpreted with caution because of the small absolute risks for women with this prevalent condition. Pending additional data, early pregnancy care to achieve good asthma control and avoid exacerbations seems warranted, which should improve maternal and neonatal health.

Disclosure of interests

VM, WG and HP have no conflicts of interest to report. JN has links with Genentech. PG has links with Glaxo Smith Kline and Boehringer Ingelheim; CC has links with Amgen, Abbott, Apotex, Sandoz, Barr, Heritage, Kali, Bristol Myers Squibb, Sanofi Aventis and Sanofi Pasteur; and MS has links with Aerocrine, Glaxo Smith Kline, Genentech, Merck and Amgen.

Contribution to authorship

VM contributed to the conception of the study and to study search and identification, inclusion/exclusion, data extraction, quality assessment, interpretation and writing. WG contributed to study search and identification, inclusion/exclusion, data extraction, quality assessment and manuscript editing. JN contributed to study search and identification, inclusion/exclusion, data extraction, quality assessment, interpretation and manuscript editing. HP contributed to study search and identification, inclusion/exclusion, data extraction, quality assessment, analysis and manuscript editing. PG contributed to study design and conception, interpretation, writing and manuscript editing. CC contributed to interpretation and manuscript editing and MS contributed to study design and conception, interpretation, writing and manuscript editing.

Details of ethics approval

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary methods.

Table S1. Details of included studies.

Table S2. Exposure definitions for analysis of asthma subgroups.

Table S3. Definitions and data source for congenital malformations and major congenital malformations. ■

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Appendix S1. Supplementary Methods

Overlapping Studies: Overlapping data was published in 1988¹ and 1995² by Schatz et al. Therefore, we included only data from the latest publication which covered the longest time period (1978-1989)². There were two papers published by Stenius-Aarniala et al in 1995³ and 1996⁴ which had the same total number of subjects. Therefore, we included outcome data from the original publication only³. There was significant similarity in the cohorts studies from Quebec⁵⁻⁸. Where data was available from more than one of these studies in a single meta-analysis, only the most recent data were used, as this covered the longest time period and largest number of pregnancies in asthmatic women.

Data extraction:

Data were extracted for: study design, study characteristics (including year, country of study), subject characteristics (including gestational age at recruitment, subject exclusions, maternal age, body mass index, age, smoking, socioeconomic status, prenatal care, race/ethnicity, co-morbidities), asthma diagnosis, severity, management, and perinatal outcome data for asthma and control groups (mostly as n [%], mean [SD] or adjusted odds ratios). Table S1 gives details of the included studies.

For sub-group analyses of asthmatic women by exacerbation or asthma severity, there were variations in the definitions used for exacerbation, mild and moderate/severe asthma in the primary studies (Table S2). Definitions and data sources for congenital malformations and major congenital malformations are given in Table S3.

Table S1. Details of Included Studies

Study (First Author, Year)	Asthma Participants	Control Participants	Study Design	Data Source	Asthma Diagnosis	Study Year	Study Country	Adjusted Data (Confounders)	Outcomes	Analysis	Quality Score
Alexander 1998 ⁹	N=817	N=13709	R	Database	Database code	1991-1993	Canada	Smoking, parity, age, pre delivery weight	Congenital malformations	B	8
Bakhireva 2005 ¹⁰	N=654	N=303	P	Interview, medical records	Dr diagnosis	1998-2003	USA/ Canada		Major malformations	A	6
Blais 2009 ⁷	N=13280 (total) N=8734 (no 1 st Trimester ICS) N=4392 (1 st Trimester ICS use 0-1000ug) N=154 (1 st Trimester ICS >1000ug)	None	R	Database	Database code	1990-2002	Canada	Pre-pregnancy asthma severity, use of LABA, diabetes, multiple pregnancy	Congenital malformations	B	8
Blais 2010 ¹¹	N=13280	N=28357	R	Database	Database code	1990-2002	Canada	Maternal age, receipt of social assistance, education, area of residence, parity, hypertension, diabetes mellitus	Congenital malformations Cleft lip/palate	A	8
Breton 2009 ¹²	N=13100, 23% > 1 pregnancy)	N=28042, 33% random sample, 23% > 1pregnancy	R	Database	Database code	1990-2002	Canada	Pregnancy induced hypertension, gestational diabetes, placental abruption, infection amniotic cavity	Stillbirth Neonatal death Perinatal mortality	A	8
Breton	N=13004	None	R	Database	Database	1990-	Canada	Education,	Stillbirth	B	8

2010 ¹³	(total) N=4140 (0- 250 ug ICS) N=1140 (>250ug ICS) N=7724 (ICS non- users)				code	2002			placental abruption, infection of amniotic cavity, cord around neck, SABA use, intranasal corticosteroid use, other asthma therapy			
Clark 2007 ¹⁴	N=718	N=718	R	Database	Self report	2001- 2003	UK			Congenital malformations Neonatal death Neonatal hospitalisation TTN Neonatal Sepsis	A, B	9
Clifton 2009 ¹⁵	N=1944	N=13977	R	Database	Database code	1995- 1999	Australia			Congenital malformations Stillbirth	A	7
Demissie ¹⁶ , Demissie ¹⁷	N=2289	N=9156	R	Database -	Database code	1989- 1992	USA	Maternal age, education, marital status, parity, race, diabetes, preexisting hypertension, smoking, alcohol use		Congenital malformations Neonatal death	A	9
Dombrowski 2004 ¹⁸	N=1739, 50% mild, 50% mod/severe	N=881	P	Clinical, Medical records	Self report	1994- 1999	USA			Major malformations Perinatal mortality Neonatal hospitalisation TTN RDS Neonatal	A, B	9

Eltonsy 2011 ⁸	N=13117 (total) N=7182 SABA users, N=5935 SABA non-users	None	R	Database	Database code	1990-2002	Canada	Maternal age, receipt of social assistance, area of residence, education level, hypertension, diabetes, epilepsy, uterine complications during pregnancy	sepsis Congenital malformations Major malformations	B	8
Enriquez 2007 ¹⁹	N=9154, Asthma subjects more likely to smoke , more comorbidities than controls	N=131145	R	Database	Database code	1995-2003	USA		Congenital malformations	A	9
Greenberger 1988 ²⁰	N=73 (total) N=26 (Emergency therapy) N=52 (No emergency therapy)	None	P	Clinical, case notes	ATS criteria	1981-1987	USA		Major malformations Stillbirth Perinatal mortality	B	8
Jana 1995 ²¹	N=182, 182 pregnancies in 158 women, 2 x twins	N=364, Matched for age & parity, delivered within 48hrs of asthma cases, 6 x twins	P	Clinical, case notes	ATS criteria	1983-1992	Not stated		Congenital malformations Perinatal mortality	A,B	8
Kallen 2007 ^{22 23}	N=24369 N=24750 N=24749 Multiple	N=835848 N=849254 N=849127 Multiple	R	Database	Self report	1995-2004	Sweden	Year of birth, maternal age, parity, smoking, years of	Congenital malformations Cleft lip/palate Stillbirth	A,B	9

Lao 1990 ²⁴	pregnancies included N=87	pregnancies included N=87, matched for age & parity	R	Case Notes	Not stated	1984-1987	Hong Kong	unwanted childlessness	Perinatal mortality Congenital malformations Stillbirth Neonatal death Perinatal mortality	A,B	8
Liu 2001 ²⁵	N=2193, Likely to represent non severe asthma	N=8772	R	Database	Database code	1991-1992 & 1995-1996	Canada	Maternal age, diabetes, preexisting hypertension	Congenital malformations	A	8
Mihrshahi ²⁶	N=340	N=271, 21 without asthma were using medications	P	Clinical, medical records	Dr diagnosis		Australia		Neonatal hospitalisation		9
Murphy 2005 ²⁷	N=146 (total) N=52 (Exacerbation) N=92 (No Exacerbation)	None	P	Clinical, medical records	Dr diagnosis	1997-2003	Australia		Stillbirth	B	7
Norjavaara 2003 ²⁸	N=11186 (total) N=7719 (asthma drugs other than CS) N=3364 (ICS only) N=103 (OCS + ICS)	None	R	Database	Use of anti-asthmatic drugs	1995-1998	Sweden		Stillbirth	B	7
Perlow 1992 ²⁹	N=81	N=130, matched for	R	Database and	Dr diagnosis	1985-1990	USA		Congenital malformations	A	5

		time of delivery – next 2 deliveries after asthma cases		patient chart review				Neonatal hospitalisation		
Sarkar 2009 ³⁰	N=180	N=180	P	Maternal interview	Dr diagnosis	Unknown	Canada, Italy, Israel, USA	Major malformations	A	5
Schatz 1995 ² ,	N=486	N=486	P	Clinical, medical records	Dr diagnosis, objective lung function	1978- 1989	USA	Congenital malformations	A	9
Schatz 1988 ¹ ,	N=360	N=295				1978- 1984		Major malformations		
Schatz 1991 ³¹	N=294	N=294 matched for age, parity, smoking, delivery date				1978- 1984		Stillbirth Neonatal death Perinatal mortality RDS TTN		
Schatz 2004 ³²	N=2123 (total) N=1828 (Bronchodil ator use) N=295 (no Bronchodila tor use)	None	P	Clinical, case notes	Dr diagnosis	1994- 2000	USA	Major malformations	B	8
Sheiner 2005 ³³	N=1963	N=137205	R	Database	Database code	1998- 2002	Israel	Congenital malformations Perinatal mortality	A	9
Silverman 2005 ³⁴	N=313 (total) N=196 Budesonide N=117 Placebo	None	RCT	Pregnanc y specific form	Lung function	1996- 1998	32 countries	Congenital malformations	B	7
Sobande 2002 ³⁵	N=88, Acute asthma	N=106	P	Medical records	Dr diagnosis	1997- 2000	Saudi Arabia	Congenital malformations Perinatal	A	7

Stenius Aarniala 1988 ³⁶	N=181, 198 pregnancies	N=198, matched for age, parity & time of delivery	P-asthma R-control	Clinical, medical records	ATS criteria	1978-1982	Finland		mortality Perinatal mortality Neonatal hospitalisation	A,B	7
Stenius-Aarniala 1995 ³ , Stenius-Aarniala 1996 ⁴	N=504	N=237, matched for age & parity	P-asthma, R-control	Clinical, medical records	ATS criteria	1982-1992	Finland		Congenital malformations Stillbirth Neonatal death Perinatal mortality Neonatal hospitalisation	A,B	8
Tata 2007 ³⁷	N=37585, Includes multiple pregnancies – similar between groups	N=243434, Includes multiple pregnancies – similar between groups	R	Database	Database code	1998-2004	UK	Maternal age, smoking, BMI	Stillbirth	A	9
Wen 2001 ³⁸	N=8672	N=34688	R	Database	Database code	1989-1990 & 1995-1996	Canada	Maternal age, diabetes, preexisting hypertension, cesarean also adjusted for pregnancy complications	Stillbirth	A	7

R: Retrospective, P: Prospective, RCT: Randomised controlled trial, TTN: Transient Tachypnea of the Newborn, RDS: Respiratory Distress Syndrome, SABA: short acting beta agonist, LABA: long acting beta agonist, ICS: inhaled corticosteroid, OCS: oral corticosteroid.

Table S2. Exposure definitions for analysis of asthma subgroups

Study	Exacerbation Definition	Mild Asthma Definition	Moderate/Severe Asthma Definition
Greenberger 1988 ²⁰	Asthma requiring epinephrine and OCS in the outpatient service, emergency department or hospital		
Jana 1995 ²¹	Asthma requiring emergency services and/or hospitalisation		
Stenius-Aarniala 1996 ⁴	Asthma which was not controlled by the woman's usual rescue medication and was treated as an emergency		
Murphy 2005 ²⁷	Hospital admission, emergency department presentation, unscheduled doctor's visit or course of oral steroids		
Eltonsy 2011 ⁸	Emergency department presentation, hospital admission or a filled prescription of OCS for asthma		
Stenius-Aarniala 1988 ³⁶		Classified as very mild or mild based on no exacerbations and use of no treatment or inhaled bronchodilator or sodium cromoglycate or beclomethasone or oral bronchodilator.	Classified as moderately severe or severe based on having one or more exacerbations during pregnancy, and treatment with oral bronchodilator in addition to other treatments.
Dombrowski 2004 ¹⁸		Asthma symptoms in the prior 6 months, asthma symptoms fewer than 8 days in prior 4 weeks, FEV1 $\geq$ 80% predicted, not taking daily asthma medication	Asthma symptoms on 8 or more days during the prior 4 weeks not attributable to upper respiratory infection, FEV1 $<$ 60-79% predicted, use of one or more daily medications which may include oral corticosteroids in severe asthmatics.
Kallen 2007 ^{22 23}		1 asthma drug	2 or more asthma drugs

Table S3. Definitions and data source for congenital malformations and major congenital malformations

Study	Data Source	Congenital Malformations Definition/Confirmation	Major Congenital Malformations Definition/Confirmation
Bakhireva 2005 ¹⁰	Review of maternal and infant medical records		"Major structural anomalies"
Blais 2009 ⁷ , Blais 2010 ¹¹	Database recorded ICD-9 diagnosis codes	(ICD-9: 152, 155, 186, 188, 190-192, 197-198, 204-205, 237, 740-759, 778). List of congenital malformations was verified by a geneticist for exactness and completeness. At least one diagnosis of congenital malformations recorded at birth, or in the first year of life.	
Clifton 2009 ¹⁵	Recorded in hospital's Obstetric Database	"Birth defects"	
Demissie 1998 ¹⁶	Database that contains linked birth certificate, infant death certificate, maternal and newborn hospital discharge claims	"Defined 3 groups of congenital anomalies using ICD-9-CM diagnosis codes for deformations, non-deformation congenital anomalies and all congenital anomalies".	
Dombrowski 2004 ¹⁸ Eltonsy 2011 ⁸	Postpartum chart reviews Database recorded ICD-9 diagnosis codes	ICD revision codes: 740–759 and 778.6 List of congenital malformations was verified by a geneticist for exactness and completeness. At least one diagnosis of congenital malformations recorded at birth, or in the first year of life.	"Major congenital anomalies" Geneticist classified malformations as major or minor with major being those which were potentially life threatening, resulted in major cosmetic defects, or required at least one hospitalisation in the first year of life.
Enriquez 2007 ¹⁹	ICD-9 diagnosis codes	Birth certificate indicates any congenital anomaly or ICD code 740-759 in infant or maternal record after date of Birth	
Greenberger 1988 ²⁰	Examination by Paediatrician		"Major malformations". Initial examination conducted by Paediatrician, further information collected up to 3 years later from mothers.
Jana 1995 ²¹ Kallen 2007 ²²	Case notes Swedish Medical Birth Register plus linkage with Register of Congenital Malformations and the Hospital Discharge Register	"Congenital anomalies" "Any congenital malformation diagnosis (using all sources of information)"	
Lao 1990 ²⁴ Liu 2001 ²⁵	Review of case notes Database ICD-9-CM codes	"Congenital malformation" "Defined 3 groups of congenital anomalies according to ICD-9-	

Perlow 1992 ²⁹	Perinatal database and chart review	CM diagnosis codes—deformations, congenital anomalies other than deformations, and all congenital anomalies”	
Sarkar 2009 ³⁰	Standardised questionnaire		Information on “any congenital malformation” collected. “Major malformations” reported.
Schatz 1995 ² Schatz 1988 ¹	Standardised obstetric forms	Major congenital malformations plus minor congenital malformations (based on “standard textbook definitions” and referencing Marden et al., J Pediatr 1964 ³⁹).	Major congenital malformations ³⁹
Schatz 2004 ³²	Case notes		“Major malformations (including multiple malformation syndromes) defined at birth, as classified by an independent dysmorphology specialist on the basis of descriptions by the attending paediatricians-neonatologists”.
Sheiner 2005 ³³	Perinatal database – data recorded directly after delivery by Obstetrician, with assessment of medical prenatal care records and routine hospital documents before entry/coding in database	“Congenital malformations”	
Silverman 2005 ³⁴	Study specific pregnancy form	“Congenital abnormality”	
Sobande 2002 ³⁵	Hospital records	“the presence of congenital malformations”	
Stenius-Aarniala 1995 ³ 4	Hospital records	“malformations”	

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