Abstract

Objective: Maternal asthma during pregnancy is associated with a higher risk of negative perinatal outcomes. However, little is known about the direct effects of maternal asthma on infant cognitive development. We examined the evidence for an impact of maternal asthma during pregnancy on cognitive and behavioural development of the child.

Data sources: We conducted a MEDLINE, PSYCHInfo, and manual search of the databases for all available studies until January 9th, 2018.

Study Selections: Studies were deemed relevant if they included child cognitive and behavioural development as the outcome, with maternal asthma as the determinant of interest.

Results: Ten articles matched selection criteria. Some studies report that maternal asthma is associated with increased risk for autism and intellectual disability in children. However, these effects are small and are often eliminated when controlling for confounding variables. Other studies have found no association. The only prospective study found that well-managed asthma during pregnancy was not associated with negative developmental outcomes in children.

Conclusions: The evidence suggests that the relationship between maternal asthma during pregnancy and poor developmental and behavioural outcomes of children is weak. Children of mothers with well-managed asthma during pregnancy have similar developmental trajectories to those born to healthy mothers. Prospective, longitudinal studies are needed to confirm these conclusions. Optimal asthma management is important in pregnancy as it may have longer term benefits for the health of the offspring. As the rate of asthma increases in the population, the implications of maternal asthma on child development will be of greater importance.

1. Introduction

Asthma is one of the most common chronic diseases to affect women of childbearing age. It is estimated that up to 12% of pregnant Australian women suffer from asthma [1], and worldwide, the prevalence of asthma during pregnancy is increasing [2]. Asthma during pregnancy has been linked to poor physiological outcomes for both mother and child. For the pregnant mother, asthma can lead to a higher risk of gestational diabetes, pre-eclampsia, caesarean delivery, placenta previa, increased length of hospital stay, and pregnancy complications including haemorrhage and placental abruption (see Table 1) [3-5]. Further, up to half of women with asthma are estimated to experience an asthma exacerbation during pregnancy [6, 7].

Asthma and asthma exacerbations during pregnancy are associated with prenatal biological mechanisms that increase the risk of perinatal infant complications. More specifically, asthma is associated with respiratory alkalosis and hypoxia, which can reduce placental blood flow and impact oxygen supply to the developing fetus [8]. These events may have a more significant hypoxic impact on the foetus than the mother [9]. For instance, low birth weight is associated with reduced 11β-HSD 2 activity in the placentae of mothers with asthma [10, 11]. Several studies have reported adverse infant outcomes such as pre-term infant birth, congenital malformations, longer hospital length of stay, poor lung function, higher risk of asthma, and infant mortality (Table 1). Although the findings are not consistent and may be influenced by other factors, such as the biological sex of the child [8, 12], these potential physical health outcomes constitute risk factors for poor infant developmental outcomes.

Despite the evidence that maternal asthma during pregnancy is associated with a higher risk of negative perinatal outcomes [3, 13-15] that are known to impact infant cognitive development, little is known about the direct effects of maternal asthma on infant cognitive development. This systematic review addresses the question of whether maternal asthma during pregnancy is associated with atypical cognitive and behavioural development in offspring.

2. Methods

2.1 Search strategy

A systematic review of the literature for papers published for the full time period available up to January 9, 2018 was conducted using the statement on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as a guide [16]. Medline (531 items) and PsychInfo (29 items; see Figure 1) were searched for all papers published using the search strategy shown in Table 2. A manual search (date last searched 9 January, 2018) involving hand-searching of Google Scholar identified 71 items. An additional 37 studies were identified by hand-searching the reference list of included articles and related review articles.

2.1.1 Inclusion criteria

After excluding duplicates (n=56), 612 studies were screened for inclusion criteria by two independent investigators (OW, MKB) and assessed for eligibility. Discrepancies were resolved by a third independent investigator (LC). Studies were deemed eligible if they included mothers with a diagnosis of asthma, and if they reported child cognitive and developmental outcomes. The majority of studies investigated the physiological consequences of maternal asthma on the mother and infant (i.e. low birthweight, risk of childhood asthma) and thus are not relevant to this review. Studies that addressed genetic conditions, maternal smoking, child asthma, or allergies and autoimmune disorders, without the presence of maternal asthma were excluded. Reviews, conference publications and grey literature were excluded.

2.2 Study selection and summary measures

Five hundred and nineteen papers were excluded during title and abstract screening. The full text of remaining 93 papers was assessed for relevance. Of these, 83 papers were excluded for the following reasons: wrong patient population (n=20), wrong outcomes (n=40), or wrong study design (including review articles; n=23). After these exclusions, ten studies were identified for inclusion in this review.

Where studies presented risk estimates for child cognitive and behavioural outcomes as a result of maternal asthma, we extracted odds ratios (ORs) and relative risk with 95% confidence intervals (CI). For all studies, we also extracted study design, number and age of mothers and children, asthma diagnosis covariates used to adjust risk estimates, age of asthma diagnosis, and nature of cognitive/behavioural outcome.

2.3 Risk of bias assessment and synthesis of results

The Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist 4: Case-control Studies (version 2 dated 28.05.12) [17] was used by a single reviewer (OW) to assess risk of bias in individual studies. The SIGN involves an assessment of both internal validity and an overall quality assessment. As the selected studies differed in design, approach and results, a meta-analysis was neither possible nor suitable for this review. Instead, we examine trends descriptively taking into consideration study design, age range and outcomes.

3. Results

3.1 Notes on risk of bias issues

3.1.1 Gordon et al. [18]

While the method of selection of cases and controls was acceptable, this study rated poorly in the SIGN quality assurance assessment. It was unclear whether controls were matched to cases. Paediatric outcomes were based on valid and reliable measures (e.g. mortality rates, APGAR scores), but the measures used to derive psychological and neurological outcomes were poorly defined and justified (i.e., no information on validity or reliability, no justification for their selection, no citation). There was no evidence that important confounding factors were controlled (e.g. socioeconomic status and comorbid allergies in mothers with asthma). Results do not always include p-values and/or

confidence intervals or standard deviations. This study was rated as unacceptable according to the SIGN assessment and conclusions should be treated with caution.

3.1.2 Flannery et al. [19]

This is a large case control, epidemiological study (n=17,283) where only 4% of cases had an immune disorder (n=743). Immune disorders were recorded as part of the Collaborative Perinatal Project (CPP) database and included ulcerative colitis, a history of asthma, Type 1 diabetes, hypothyroidism and hyperthyroidism. Medical history (recent and past) was recorded by trained staff during the mother's first perinatal visit. Controls were only screened for the above five immune disorders and therefore may have suffered from other immune disorders. The timing of the asthma diagnosis is not specified and the diagnosis itself was not independently confirmed. In the CPP, paediatric-neurological examinations occurred at 4 months, 12 months and 7 years, and psychological examinations occurred at 8 months, 4 years and 7 years. It is not clear when the Bayley Scales of Infant and Toddler Development and the assessments of fine and gross motor skills were completed. The diagnostic criteria used for assessment of neurodevelopmental disorders at 7 years (e.g. attention deficit disorder) are not explicitly specified.

3.1.3 Schatz et al. [20]

This study compared developmental outcomes of 15 month old infants born to mothers with and without asthma. It had a large sample size (>350/group), used valid and reliable measures of asthma (physical examination, spirometry, history and diagnosis of asthma) and infant development (Bayley Scales), and implemented appropriate analyses and adjustment of confounding variables. The mothers' asthma was managed by physicians during the study, in order to avoid exacerbations during pregnancy. Therefore the conclusions cannot be extended to infants born to mothers whose asthma is not well managed during pregnancy.

3.1.4 Micali et al. [21]

This epidemiological study examined 97 children who had been diagnosed with a pervasive developmental disorder (e.g. autism, Asperger's disorder and Pervasive Developmental Disorder-Not Otherwise Specified PDD-NOS). Diagnoses were not confirmed for the study. The control group included children diagnosed with learning difficulties, developmental delays, behavioural problems or

medical disorders (e.g. genetic conditions), but not typically developing children. Diagnosis of maternal asthma was obtained using a self-report sociodemographic questionnaire and in 51% of cases, the diagnoses of autoimmune conditions was confirmed by the participant's general practitioner (GP). Agreement between GP and self-report diagnosis was high. The response rate was lower for control parents than for case parents. The control parents who did respond, as compared to those who did not respond, reported higher rates of developmental abnormalities and psychiatric illnesses, which may have biased findings toward the null hypothesis. The authors concluded that there was no evidence of an increased incidence of maternal asthma or autoimmune disorders among offspring with pervasive developmental disorders.

3.1.5 Croen et al. [22]

This large case-matched control study used physician-documented, prospectively collected diagnoses of asthma in mothers, and examined diagnoses which occurred at different times during pregnancy. However, they did not use gold standard measures for case confirmation, and do not specify whether the asthma diagnosis occurred at peak symptom profile. As a result, it is possible that women who were asymptomatic during the study period did not receive a diagnosis and that acute respiratory infections may have been misdiagnosed as asthma.

3.1.6 Leonard et al. [23]

This large population-based study examined the incidence of asthma and other health conditions during pregnancy in mothers of children with intellectual disabilities. Maternal health conditions may have been underreported, as the study relied on accuracy of midwife reports, asthma diagnosis was not confirmed with gold-standard diagnostic procedures, and information on maternal medication use was not available, although level of asthma management was reported (i.e. well-controlled, uncontrolled, treatment as usual). These issues may have led to a bias in ORs toward the null hypothesis.

3.1.7 Mouridsen et al. [24]

This retrospective longitudinal case-control study investigated the incidence of autoimmune disease in parents of 330 control children and 111 cases with diagnosed infantile autism. The data were derived from a large population register and maternal autoimmune disease diagnoses were based on medical records (the Danish National Hospital Register; DNHR). The observation period of 27 years captured the cumulative incidence of autoimmune diseases through adult life. While the reliability of medical data is unknown, the validity of DHNR diagnoses ranged from 75-90% [25]. Cases who were originally given a diagnosis of 'childhood psychosis' or 'borderline condition', the terms used in the International Classification of Diseases, 8th edition (ICD-8) [26], had their psychiatric records assessed and were re-diagnosed in 1985 in accordance with the ICD-9 [27].

3.1.8 Lyall et al. [28]

This large, population-based, case control study identified cases from the California Department of Developmental Services and available state birth files. Case confirmation was ascertained through rigorous, well-described, validated methods, including medical records. Medical records however were only available for 65% of participants, and agreement between records and self-reported was over 60% for asthma, 55% for allergies and 30% for autoimmune conditions. Autoimmune conditions may not have been recorded in obstetric records if symptoms were not present during that time. Therefore, the authors were unable to exclude the chance of exposure misclassification, which may have biased results toward the null hypothesis. Individual analysis for specific autoimmune diseases was not possible due to low numbers.

3.1.9 Langridge et al. [29]

This population-based study was similar to Leonard et al. [23] in its design and approach. It used population-based data of children born between 1984 and 1999 who were diagnosed with either intellectual disability (ID) or autism spectrum disorder (ASD), with or without ID and examined the relationship with maternal conditions and perinatal factors. While a strength of this study is the ability to differentiate between effects on ASD and ID, the diagnoses were not confirmed and diagnostic criteria may have changed over those 15 years. Some children with an ASD with ID diagnosis did not complete all cognitive testing, and therefore the presence ID could not be confirmed, possibly

resulting in underestimation of ASD alone and ASD with ID differences. Only a few cases were diagnosed with severe ID which may have resulted in underestimation of ID effects.

3.1.10 Patel et al. [30]

This retrospective-cohort study compared the severity of autism spectrum disorder (ASD) symptoms in 220 children of mothers with a history of immune activation, a history of autoimmune conditions and those without. Mothers reported diagnoses of immune conditions occurring both pre-pregnancy (N=46) and post-pregnancy (N=3), but were not confirmed by the authors. The study selected cases with a DSM-IV clinical diagnosis of ASD, Asperger's Syndrome, or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS). ASD was confirmed by administering the Autism Diagnostic Observation Schedule-Generic (ADOS-G). However, the social interaction, language and repetitive/restrictive behaviours of the children were only assessed via caregiver report using the Social Responsiveness Scale (SRS). Allergies and asthma were the only conditions of women in the immune category, and were grouped in all analyses. Thus, any findings are not specific to asthma. Statistical analyses did not correct for multiple comparisons. There was a small but significant effect of immune status on the total score and the cognition and mannerisms subscales of the SRS (which were both completed by the mother) but not on the researcher-administered ADOS-G. There were no significant effects of maternal immune status on the motivation, communication or awareness subscales of the SRS. The authors concluded that a history of maternal immune activation is associated with caregiver-reported ASD severity symptoms but could not determine if these effects were specific to asthma.

3.2 Inconclusive evidence for an association between maternal asthma and atypical cognitive or behavioural development of infants

Table 3 provides an overview of the characteristics of the ten studies included in this review. Five studies provided inconclusive evidence for an association between maternal asthma and atypical cognitive or behavioural outcomes for the infants, whereas the remaining five studies provide evidence for no association.

3.2.1 Gordon et al. [18]

In 1970, 364 pregnant women with bronchial asthma were identified from 30,861 women enrolled in the Collaborative Research Project, which assessed cerebral palsy, intellectual disability and other neurological and sensory disorders that may occur in the perinatal period [31]. Of these, 47 women were excluded because they were classified as having acute bronchitis with bronchospasm but without asthmatic history, and 40 were excluded because they had a history of asthma but experienced no symptoms and had not sought treatment during their pregnancy. The final sample included 277 women who were receiving active management for their asthma, with 16 classified as having severe asthma.

Compared to infants of mothers without asthma who participated in the Collaborative Research Project, infants born to mothers with asthma had almost double the rate of perinatal mortality (3.2 vs. 5.9%, respectively) and a higher percentage of abnormal neurological findings by 12 months of age (1.7 vs 2.7%, respectively). Neurological findings were not clearly specified. Although the authors assessed psychological functioning at the 8 month psychological examination, they did not report any statistical differences in these results.

3.2.2 Croen et al. [22]

This case control study investigated the association between diagnoses of maternal autoimmune diseases, asthma and allergies in mothers and autism spectrum disorder (ASD) diagnoses in their offspring. The case control study was nested in a cohort of 88,163 infants born between January 1995 and June 1999 at the Kaiser Permanente Medical Care Program facility in northern California. Of this cohort, 420 children aged 3 - 7 years were identified as having an ASD diagnosis. Five controls without an ASD diagnosis per case were randomly selected from the cohort of births (n=2100) and were frequency matched to cases on the basis of sex, year of birth and hospital of birth. After controlling for maternal age, maternal education, maternal ethnicity and plurality, odds ratios higher than 2.0 were observed for asthma diagnoses that were recorded during trimesters one (OR, 2.8; 95% CI, 1.3-6.1) and two (OR, 2.2; 95% CI, 1.1-4.2) of pregnancy. When controlling for

maternal medication use, odds ratios were only slightly reduced for maternal asthma reported in the second trimester of pregnancy (OR, 1.9; 95% CI, 1.0-3.7).

3.2.3 Leonard et al. [23]

This study investigated the relationship between a range of maternal health conditions and intellectual disability in offspring in a Western Australian (WA) sample. They used birth records of children born in WA between 1983 and 1992 who were identified as having an intellectual disability (ID) either through the Disability Services Commission or educational sources and who had midwife-completed records of pre-existing maternal health conditions. Mild to moderate ID was defined as an IQ between 35-40 and 69 depending on the assessment used. Severe and profound ID was defined as an IQ less than 35-40, which is consistent with the Diagnostic and Statistical Manual of Mental Disorders (IV edition) [32]. There were 3387 cases of diagnosed intellectual disability in Western Australia during that timeframe, of which 522 cases had a biomedical cause (i.e. chromosomal anomalies, injuries) and were excluded. The remaining 2865 children were categorised as mild-moderate ID (n=2462), severe or profound ID (n=212), or autistic spectrum disorder (ASD) with ID (n=191). A comparison group consisted of 236,964 children without ID that were part of the same birth cohort. Asthma was found to be the most common condition to affect mothers of children with mild-moderate ID (4.8%). This is in comparison to 3.2% in mothers of children without ID (OR, 1.52; 95% CI, 1.26-1.83). In a stepwise logistic regression analysis that looked at mild-moderate ID as the outcome variable and contained all maternal conditions (e.g. asthma, diabetes mellitus, hypertension, anaemia), sociodemographic variables and birth year, maternal asthma was a significant predictor (OR, 1.25; 95% CI, 1.02-1.54), along with stronger predictors of maternal epilepsy (OR, 3.01; CI, 2.10–4.33), and maternal renal and urinary conditions (OR, 1.65; CI, 1.06–2.56). Maternal asthma was not significant when severe ID was included as the primary outcome variable in these stepwise regression analyses.

3.2.4 Langridge et al. [26]

This study used birth records data for 383,153 live births in Western Australia between 1984 and 1999 to examine the effect of a range of maternal health conditions, socioeconomic status, labour

and delivery issues, and neonatal outcomes on risk of ASD with/without ID, and ID without a known cause in children. In total, 1179 cases of ASD (727 cases of ASD with ID, 452 cases of ASD without ID), 4576 cases of ID without ASD (4339 mild cases and 237 severe cases) and 376,539 control children (without and ASD or ID diagnosis) were included. Univariate analyses revealed that maternal asthma was associated with an increased risk of mild – moderate ID (OR, 1.46; CI, 1.30 - 1.63), and ASD without ID (OR, 1.78; CI, 1.29 - 2.46). After adjusting for maternal conditions and pregnancy complications, sociodemographic variables and birth year, multivariate analyses revealed that asthma was associated with an increased risk of mild-moderate ID (OR, 1.28; CI 1.12 - 1.47), and ASD without ID (OR, 1.41; CI 0.98 - 2.04). In a fully adjusted model (i.e., maternal conditions, pregnancy complications, labour and delivery factors, and neonatal and sociodemographic characteristics were taken into account), asthma was associated with 25% increased risk of mild-moderate ID. No positive associations were found for ASD alone or severe ID.

3.2.5 Patel et al. [30]

This recent study examined the relationship between maternal immune and autoimmune conditions and severity of symptoms in autism spectrum disorder (ASD) for their children. Two hundred and twenty children with a diagnosis of ASD, Asperger's syndrome or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) were selected from a cohort of participants in the Western Australian Autism Biological Registry. The Autism Diagnostic Observation Schedule-Generic (ADOS-G) was used by the researchers to confirm a diagnosis of autism in the children. Caregivers reported on the mother's medical history, and completed the Social Responsiveness Scale (SRS) which measures a child's level of social interaction, language skills and repetitive or restrictive behaviours. Children were then categorised based on the immune and autoimmune history of the mother. The immune category consisted of mothers with asthma and/or allergy. There was a significant main effect of immune status on the children's total and some subscale scores on the SRS. This indicates that children whose mothers reported suffering from an immune condition (asthma or allergy) were rated as having more severe SRS total scores, as well as more severe symptoms on the cognition (ability to understand social situations) and mannerisms

(presence of restricted behaviours and/or unusual interests) subscales. These associations remained significant after removing from the analyses mothers who were diagnosed with an immune disorder post-pregnancy. No associations were found between immune profile and the remaining three subscales of the SRS, nor between immune profile and results of the ADOS-G. Asthma-specific information was not available.

3.3 Evidence for no association between maternal asthma and atypical cognitive or behavioural development of infants

3.3.1 Flannery et al. [19]

An epidemiological sample of 743 cases and 16 540 controls was derived from the Collaborative Perinatal Project (CPP), a prospective study of pregnancy outcomes of 48 000 women enrolled at one of 12 university hospital clinics in the USA between 1959 and 1965. Children were assessed for neurological, physical and psychological development through to 8 years of age via medical examinations at various time points. Neurodevelopmental disorders were recorded at the 7 year follow up, and included cerebral palsy, intellectual disability, seizures, articulation disorder, reading or arithmetic disability, verbal or performance aptitude deficits, and attention deficit disorder. Cases included mothers with ulcerative colitis and asthma. Controls were mothers without ulcerative colitis, asthma, Type 1 diabetes, hypothyroidism or hyperthyroidism. Neither ulcerative colitis nor asthma were associated with increased risk of any neurodevelopmental disorder in the offspring.

3.3.2 Schatz et al. [20]

This study examined cognitive (e.g. perceptual abilities, memory, object permanence, problem solving and abstract thinking), language and psychomotor development of 15 month old infants born to 379 mothers with well-managed asthma compared to 376 non-asthmatic mothers, matched for age, smoking status, parity and date of delivery. Asthma diagnosis was confirmed using spirometry, asthma history, and physical examination. Asthma was actively medically managed during pregnancy, in order to avoid acute episodes, night waking and interference with normal daily activities. There was no significant difference in developmental indices of the Bayley Scales between

infants of mothers with asthma and control mothers. Additionally, there was no relationship between asthma severity (as indexed by emergency room visits, corticosteroid use) and developmental scores on the Bayley Scales. Regardless of maternal asthma status, lower psychomotor development was associated with low birthweight (<2500g) and low mental development was associated with lower socioeconomic status. .

3.3.3 Micali et al. [21]

This epidemiological study compared 79 cases with pervasive developmental disorders (PDD) and 61 controls who had diagnoses of learning difficulties, developmental delay, behavioural problems and medical disorders. Maternal asthma was one of a range of maternal autoimmune disorders (including arthritis, psoriasis, eczema, inflammatory bowel disease, type 1 diabetes among others). The two groups did not differ in the percentage of mothers suffering from asthma (11.4% in PDD, 13.5% in controls) or any autoimmune disorder.

3.3.4 Lyall et al. [25]

This study investigated whether maternal autoimmune disease, asthma and/or allergy were associated with autism spectrum disorder (ASD) or developmental delay without autism (DD) in offspring, in 560 cases with ASD (mean age 45.4±10.1 months), 168 cases with DD (42.4±9.4 months), and 391 control (46.2±9.0 months) children. Autism diagnosis was confirmed using the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised [33, 34] delivered by trained clinicians, but children's age at time of assessment is not reported. Autism-like symptoms and behaviours were screened in DD cases and controls using the Social Communication Questionnaire (SCQ) [35]. Inclusion criteria for controls included a score above 70 on the Mullen Scales of Early Learning (MSEL) [36] and on the Vineland Adaptive Behaviour Scales (VABS) [37], and 14 or less on the SCQ. Inclusion criterial for DD was a score of 69 or less on the MSEL and VABS, and 14 or less on the SCQ. Maternal exposure status was assessed when the children were aged between 2-5 years. Maternal autoimmune disease, asthma and allergy diagnoses were confirmed via self-report on the Environmental Exposures Questionnaire (EEQ), and Autoimmune Survey (AIS), family medical history and medical records. These questionnaires assessed diagnosis, index period

(3mths prior to pregnancy through to breastfeeding), lifetime history, and age of onset (asthma). Medical records provided information on medication use, diagnosis, time period (before and/or during pregnancy) and age of onset. Overall, presence of maternal autoimmune disease was associated with elevated odds of DD (OR = 1.58, 95 % CI 0.96 - 2.60), and ASD (OR = 1.43, 95 % CI 0.96 - 2.14). Combined risk for ASD+DD reached statistical significance (OR = 1.46, 95% CI 1.01 - 2.09). No significant associations were present for specific autoimmune disorders. In mediation analyses, asthma medication use accounted for <1% of the association between maternal asthma and ASD in the offspring. Maternal index period asthma and allergies, or incident onset of asthma were not significantly associated with increased risk of ASD or DD.

3.3.5 Mouridsen et al. [24]

Overall, this study found no association between any maternal autoimmune diseases and childhood diagnosis of infantile autism. Out of a possible 35 autoimmune disorders and asthma that were studied, only maternal ulcerative colitis and paternal type 1 diabetes occurred more frequently in parents of cases with infantile autism. For cases with intellectual disabilities, mothers with an autoimmune disease were significantly more likely to have children with an IQ<50 than those without any autoimmune disease (9/48 vs 3/62, p=0.03, OR=4.5, 95% CI=1.2–17.8).

4 Discussion

This is the first systematic review to examine the influence of maternal asthma on child cognitive and behavioural development. Only ten studies met our inclusion criteria and their findings were mixed. Some studies report a slightly increased incidence of asthma in mothers of children with autistic spectrum disorder [22, 29], and one study showed that, grouped together, the presence of asthma and/or allergy in the mother is associated with more severe social symptoms of ASD on some measures, but not others [30]. Additionally, Lyall et al. [28] found that overall, the presence of maternal autoimmune disease was associated with elevated odds of developmental delay, ASD, and combined ASD+DD. However, they did not find any significant effect of any specific autoimmune

disorder. Other studies have found no association between maternal asthma and autism [24], neurodevelopmental disorder [19] or pervasive developmental disorders [21].

Compared to a range of maternal health conditions, maternal asthma was associated with an increased risk for mild-moderate intellectual disability in offspring [23, 29]. However, maternal diabetes, renal and urinary conditions and epilepsy were even stronger predictors of risk of ID in offspring. Schatz et al. [20] concluded that the risk of negative infant developmental outcomes did not differ between mothers with well-managed asthma during pregnancy and non-asthmatic mothers.

Where maternal asthma was found to be significantly associated with ASD, this association disappeared once sociodemographic and other variables were taken into account [29]. Asthma has also been reported significantly more often in mothers of children with autism as compared to controls [22], especially families who had more than one child affected by autism, possibly suggestive of a common gene link between the etiology of autism and atopic diseases. The association between maternal asthma and child autism was stronger when asthma was diagnosed during the second trimester, but was eliminated after controlling for confounding factors. Additionally Lyall et al. [28] found that maternal index period asthma and allergies, or incident onset of asthma were not significantly associated with increased risk of ASD or DD in offspring, suggesting no adverse effect of maternal asthma onset on child behavioural development.

A number of other studies [19, 21, 24] found no effect of maternal asthma on diagnosis or risks for autism, pervasive developmental disorder or neurodevelopmental disorders. Discrepancies may be due to differences in source of diagnostic information (e.g., medical records vs. self-report), study power and sample size, severity and treatment of asthma, inclusion of range of immune and autoimmune diseases, differences in the time periods examined, and/or inconsistencies in classification and diagnosis of allergies, ASD and related disorders and other illnesses.

Gordon et al. [18] reported that infants born to mothers with asthma showed greater incidence of vaguely defined “neurological abnormalities” compared to control infants. This contrasts with the finding of Schatz et al. [20] who reported no negative neurodevelopmental in offspring of mothers with well-controlled asthma. Gordon’s study was published prior to the introduction of inhaled

corticosteroids for preventative treatment of asthma. A previous meta-analysis of adverse perinatal outcomes in pregnant women with asthma found that studies which reported active management of asthma during pregnancy demonstrated no increased risk of outcomes including preterm delivery and neonatal hospitalisation, while studies which did not report active management showed a statistically increased risk [3, 4]. This suggests that the adverse effects of maternal asthma on perinatal outcomes may be modifiable by improved asthma management, and this may extend to better outcomes in childhood. These findings are encouraging as they show clear evidence that, when asthma is actively and aggressively medically managed throughout pregnancy, there are no negative outcomes for infants. However, none of the existing studies assessed whether asthma medication or treatment impacts cognitive and behavioural outcomes of the child. Further work is needed to confirm that there are no negative outcomes for the children of pregnant women receiving treatment as usual for their asthma.

5 Conclusion

While some studies report a link between atypical development and maternal asthma during pregnancy, these findings are weak and rely mostly on retrospective or epidemiological studies. It is difficult to directly compare many of the studies included in this review because they differ in when and where they were conducted, and this leads to large variation in the asthma medications used, the access to medical facilities, the level of pollution and the exposure to infection. None of the studies examined the effects of different asthma medications or treatment as usual during pregnancy on the cognitive or behavioural development of the child. The only prospective, well-controlled study shows that, when well-managed medically, maternal asthma during pregnancy does not impact the infant's cognitive and behavioural development at 15 months [20]. This is consistent with evidence that well managed asthma during pregnancy is not associated with increased perinatal mortality or morbidity [e.g. 38, 39]. However, these conclusions need to be considered with caution, given the paucity of prospective, well-controlled, longitudinal studies examining cognitive and behavioural developmental in children born to mothers with asthma during pregnancy. Given the state of the evidence, the current

recommendation is that asthma during pregnancy needs to be actively and aggressively managed so as to minimise any risk of atypical cognitive or behavioural development in the offspring. We recommend that future studies include more consistent measures to assess and monitor the severity and control of asthma in the mother during pregnancy. Likewise, there is a need for studies that use well-established, valid and reliable measures of cognitive, language and motor development of the child, and well-established criteria for diagnosing intellectual disability, developmental delay, ASD and ASD-related disorders in the child.

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Table 1.

Summary of studies that examined physiological outcomes of asthma during pregnancy.

	Outcome	Reference	Articles included (*n*)	Summary statistic
Mother	Preterm delivery	Jaakkola et al. (2006) [40]; Murphy et al. (2011) [3];	19, 10	OR 1.074 (95% CI, 1.072-1.075), RR 1.50^{+} (95% CI 1.28-1.75)
	Caesarean delivery	Wang et al. (2014) [5];	23	RR 1.31 (95% CI 1.22-1.39)
	Pre-eclampsia	Murphy et al. (2006); [41] ; Murphy et al. (2011) [3];	2, 14	RR 1.48* (95% CI 1.07-2.04), RR 1.54 (95% CI 1.32–1.81)
	Gestational diabetes	Wang et al. (2014) [5];	12	RR 1.45^{+} (95% CI 1.18-1.78)
	Antepartum/postpartum haemorrhage	Wang et al. (2014) [5];	11/7	RR 1.25 (95% CI 1.10-1.42)/ RR 1.29^{+} (95% CI 1.18-1.42)
	Placenta previa	Wang et al. (2014) [5];	8	RR 1.23 (95% CI 1.07-1.40)
	Placental abruption	Wang et al. (2014) [5];	11	RR 1.29 (95% CI 1.14-1.47)
	Premature rupture of membranes	Wang et al. (2014) [5];	9	RR 1.21 (95% CI 1.07–1.37)
Infant	Low birthweight	Murphy et al. (2006); (2011) [3];	3, 13	RR 2.54* (95% CI 1.52-4.25), RR 1.46 (95% CI 1.22-1.75)
	Small for gestational age	Murphy et al. (2011) [3];	8	RR 1.22 (95% CI 1.14-1.31)
	Congenital malformations	Murphy et al. (2013) [4]	8	RR 1.11^{+} (95% CI 1.02-1.21)
	Neonatal death	Murphy et al. (2013) [4];	6	RR 1.49 (95% CI 1.11-2.00)
	Asthma in offspring	Lim et al. (2010) [42];	18	OR 3.04 (95% CI 2.59-3.50)

*with exacerbation during pregnancy

**without exacerbation during pregnancy

+without active asthma management

Table 2. *Key words used in database searches*.

Pregnancy OR gestation	AND: Maternal health OR embryonic development OR fetal development OR prenatal exposure OR post natal OR preterm birth OR corticosteroid OR atopy OR maternal asthma OR fetus OR infant OR newborn OR gestational age OR premature birth OR respiratory OR risk assessment OR maternal health OR pregnancy outcomes OR risk factors OR birth weight OR maternal welfare OR perinatal OR prenatal OR growth OR infant welfare OR gestational age OR high risk	AND: Asthma	AND: 5 ADJ child* prefix to each term: cognition OR outcomes OR intellectual disability OR mental retardation OR executive function OR childhood morbidity OR health status OR hospitalisation OR developmental disabilities OR fetal development OR intelligence OR intellectual OR development OR disorders OR autistic disorders OR developmental delay OR psychomotor performance OR parent-child relations OR immune OR achievement OR behaviour OR temperament OR disability

Note: child* is a truncation which returns results for child, children, childhood etc.

5 ADJ child* is a proximity operator which returns articles with titles where child* appears within 5 words of each term listed.

Figure 1. Flow diagram detailing the information sources, screening procedure and number of papers included in this review.

Table 3. Methodological characteristics and findings of the ten studies included in this review.

Study	Sample size	Child Age	Predictor variables	Outcome variables	Finding
Gordon, M., Niswander, K.R., Berendes, H., Kantor, A. G. (1970). [18]	n=277 adult women with actively treated asthma during pregnancy (n=16 of these with severe asthma) and their offspring, n=30,497 controls	~0-12 months	• Presence of bronchial asthma during pregnancy • Maternal ethnicity	• Infant 8 month mental, motor and global scores from psychological examination, • Infant 12 month neurological examination • Perinatal and infant mortality • 1 and 5 minute infant APGAR scores • Infant birthweight • Maternal complications	Significantly higher perinatal mortality for infants born to mothers with asthma, as well as suggested increase in neurological abnormalities at 12mths
Flannery, K. A., Liederman, J. (1994). [19]	n=743 cases with ulcerative colitis and asthma, n=16 540 controls	~0-7 years	• Presence of ulcerative colitis or asthma in the mother	• Socioeconomic status • Medical history • Diagnosis of neurodevelopmental disorder (cerebral palsy, intellectual disability, seizures, articulation disorder, reading or arithmetic disability, performance or verbal aptitude deficits, and attention deficit disorder) • IQ and academic achievement • Hand preference	Maternal asthma was associated with increased risk of any neurodevelopmental disorder in the offspring
Schatz, M., Harden, K., Kagnoff, M., Zeiger, R. S., Chilingar, L. (2001). [20]	n=379 infants of asthmatic mothers, n=376 control infants	15 months	• Asthma severity during pregnancy • socioeconomic status • infant prematurity	• Psychomotor and mental scales of the Bayley Scales of Infant development	No differences in developmental indices between infants of asthmatic mothers and controls. No significant relationships were identified between developmental indices and maternal asthma severity
Micali, N. Chakrabarti, S. Fombonne, E. (2004). [21]	n=79 cases with pervasive developmental disorders, n=61 controls	5-5.5 years	• Presence of psychiatric or medical disorders (including asthma) in parents	• Pervasive developmental disorder diagnosis	11.4% of case mothers and 13.5% of control mothers were reported to suffer from asthma. This difference was not significant. Differences between case and control mothers with

	with non-autistic disorders				any autoimmune disorder were also not significant.
Croen, L. A., Grether, J. K., Yoshida, C. K., Odouli, R., Van de Water, J. (2005). [22]	n=407 children with ASD diagnosis, n=2095 matched-controls	3-7 years	• Presence of diagnosed maternal autoimmune diseases, allergies and asthma in the 2 years preceding pregnancy and 2 years post delivery	• Diagnosis of autism in offspring	Asthma was significantly more often reported for mothers of ASD affected children. Asthma diagnosed in first trimester: OR 2.8 (95% CI 1.3-6.1) Second trimester: 2.2(1.1-4.2)
Leonard, H., de Klerk, N., Bourke, J., Bower, C. (2006). [23]	n=2865 children with an intellectual disability (ID), n=236,964 controls without ID	0-16 years	• Presence of common maternal medical conditions during pregnancy including asthma	• Diagnosis of mild-moderate and severe ID, and ID with autism	Modest increased risk of mild-moderate ID in children of mothers with asthma. Mild to moderate ID: OR 1.52 (95% CI 1.26-1.83) Severe ID: 1.18(0.58-2.39) ID with autism: 1.32(0.65-2.67)
Mouridsen, S.E., Rich, B., Isager, T., Nedergaard, N.J. (2007). [24]	n=111 children with infantile autism, n=330 controls	5.4 years	• Presence of maternal autoimmune disease	• Diagnosis of infantile autism in offspring	Overall, no association was found between any maternal autoimmune diseases and childhood diagnosis of infantile autism. Maternal asthma was not associated with infantile autism in the offspring (p= 0.31).
Langridge, A. T., Glasson, E. J., Nassar, N., Jacoby, P., Pennell, C., Hagan, R., ... & Stanley, F. J. (2013). [29]	N=1179 cases with ASD, n=4576 cases of ID without ASD, n=376,539 controls without ASD or ID diagnosis	Diagnoses were recorded by at least 6 years of age	• Maternal health conditions, sociodemographic factors, labour and delivery characteristics, neonatal outcomes	• Diagnosis of ASD (with or without ID), or ID with an unknown cause in offspring	In a fully adjusted model, asthma was associated with an increased risk of 25% for mild-moderate ID. No positive associations were found for ASD alone or severe ID.
Lyall, K., Ashwood, P., Van de Water, J., Herz-Picciotto, I. (2014).	n=560 ASD cases, n=391 typically developing controls, n=168	~3.5 years	• Presence of maternal autoimmune disease, asthma and/or allergy	• Diagnosis of ASD or developmental delay without autism in offspring.	No significant associations were present for specific autoimmune disorders. Maternal index period asthma and allergies, or incident onset of asthma

[28]	cases with developmental delay				were not significantly associated with increased risk of ASD or DD.
Patel, S., Masi, A., Dale, R. C., Whitehouse, A. J. O., Pokorski, I., Alvares, G. A., ... & Guastella, A. J. (2017). [30]	N=220 children with ASD, Asperger's syndrome, or PDD-NOS	~7-10 years	• Presence of maternal immune (asthma or allergy) condition, autoimmune condition	• ASD symptom severity	Maternal immune condition (asthma or allergy) was associated with more severe social symptoms of ASD in the child

Abbreviation: APGAR – score on Appearance, Pulse, Grimace, Activity, and Respiration; ASD - Autism Spectrum Disorder; ID - Intellectual Disability; DD - Developmental delay; PDD-NOS – Pervasive Developmental Disorder-Not Otherwise Specified