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Review article

Pre-eclampsia and the risk of autism-spectrum disorder in offspring: meta-analysis

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Background

Evidence about the effect of intrauterine exposure to pre-eclampsia on offspring autism-spectrum disorder (ASD) is not well established.

Aims

To examine the association between pre-eclampsia and ASD.

Method

PubMed, Embase and PsycINFO databases were searched. Pooled relative risks (RR) with 95% confidence intervals were calculated. Subgroup and sensitivity analyses were performed. Heterogeneity was assessed using Cochran's *Q*- and the I^2–test. The presence of publication bias was evaluated by Egger's test and visual inspection of the symmetry in funnel plots.

Results

Ten studies meet the inclusion criteria. The risk of ASD was 32% higher in offspring who had intrauterine exposure to pre-eclampsia compared with those not exposed (RR = 1.32, 95% CI 1.20–1.45). Sensitivity analysis revealed consistent pooled estimates ranging from RR = 1.30 (95% CI 1.17–1.44) to RR = 1.37 (95% CI 1.26–1.48). We found no significant heterogeneity and evidence of publication bias.

Conclusion

Pre-eclampsia increased the risk of ASD in offspring. The finding suggests a need for early screening for ASD in offspring of women with pre-eclampsia.

Declaration of interest

None.

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Autism-spectrum disorder (ASD) is a developmental disability, classified as a neurodevelopmental disorder in DSM-5, characterised by deficits in social communication and social interaction and, restricted, repetitive patterns of behaviour, interests or activities.[1] Estimates from the US Centers for Disease Control and Prevention Autism and Developmental Disabilities Monitoring Network suggest that about 1 in 68 children are affected by ASD.[2]

Although the underlying causes of ASD are not fully understood, ASD is regarded as a multifactorial disorder with no single aetiological agent, but rather a range of genetic and environmental contributors.[3–5] In support of this view, some findings suggest that exposure to specific perinatal risk factors increases the risk of ASD in offspring.[5,6] One of these is pre-eclampsia, a perinatal condition that affects 3–5% of pregnancies.[7] Pre-eclampsia is a multiorgan diseases process characterised by raised blood pressure (systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg) and proteinuria.[8]

Evidence about the effect of intrauterine exposure to pre-eclampsia on offspring ASD is not well established. Some studies have suggested that pre-eclampsia is associated with higher risk of ASD in offspring,[9,10] whereas others have found no significant associations.[11,12] Therefore, the purpose of this study is to provide a systematic review and meta-analysis of the epidemiological literature on the relationship between pre-eclampsia and ASD.

Method

This systematic review and meta-analysis was conducted in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[13] The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPER, registration number: CRD42017060037, http://www.crd.york.ac.uk/PROSPERO).

Data sources and search strategies

PubMed, Embase and PsycINFO databases were searched using the keywords with no publication year restriction until 15 March 2017. The selected search terms included 'autism spectrum disorders', 'autism', 'child development disorders', 'asperger syndrome', 'autistic disorder', 'pervasive developmental disorder', in combination with 'gestational hypertension', 'preeclampsia', 'pre-eclampsia', 'eclampsia', 'hypertension during pregnancy', 'pregnancy induced hypertension', 'hypertensive diseases of pregnancy', 'hypertensive disorders of pregnancy', 'obstetric complications' and 'perinatal factors'. Details of the search terms were available as a supplementary Appendix 1, available at http://dx.doi.org/10.1192/bjp.2017.27). The reference lists of included studies were hand searched to identify additional articles. No authors were contacted for additional studies or data.

Study selection and eligibility criteria

An article was included if it met the following criteria: (i) was based on humans, (ii) was a cohort or case–control study, (iii) was published in English language, (iv) examined the association between pre-eclampsia and ASD, (v) defined ASD, (vi) provided exposure information, and (vii) reported the risk estimates (odds ratio or relative risk) with 95% confidence interval or provided sufficient information to calculate these. Conference abstracts, letters to editors, review and commentary articles were excluded. The eligibility of each study was assessed independently by two investigators (B.A.D. and J.C.M.) and disagreements were resolved by discussion. After duplicates removal, a total of 1736 records were identified, and 10 articles were found to be eligible for meta-analysis (Fig. 1).

Data extraction

Data from identified studies were extracted by using a standardised data extraction form. For each included study we extracted the following information: first author's last name, year of publication, study location, study design, sample size, ascertainment of exposure,

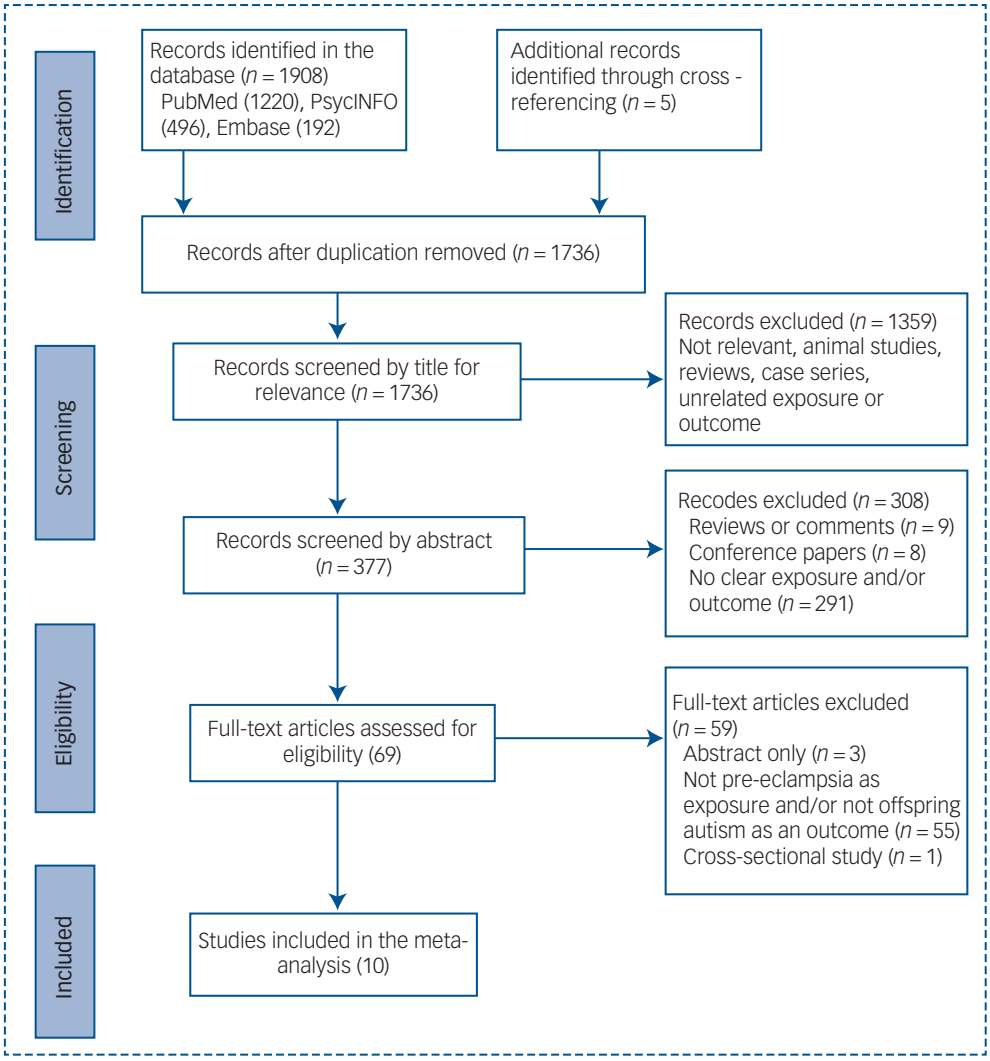

Fig. 1 Flow diagram of studies included in meta-analysis.

outcome diagnostic criteria, offspring age at diagnosis, confounding variables adjusted/matched and effect estimates (relative risk or odds ratio) with 95% confidence interval.

Quality assessment

The quality of the studies was assessed using the Newcastle–Ottawa quality assessment tool for cohort and case–control studies.[14] This tool consists of three domains: selection of study groups (four stars), ascertainment of exposure in a case–control or outcome in a cohort study (two stars) and the comparability groups (two stars). A maximum of nine stars were given to each study and results were summarised in three categories (good, fair and poor quality). For quantitative analysis, quality scores were assigned by dividing each score by the score of highest scoring study in the group. Quality assessment of each study was carried out by two of the authors independently (B.A.D. and J.C.M.) and any disagreements were resolved through discussion.

Data synthesis

Reported odds ratio were converted to relative risk using the Ersatz package.[15] Except for one study (3.96%),[12] the baseline risk of the remaining five case–control studies[10,11,16–18] was greater than 10% (ranging from 16.5 to 26.2%).

Pooled relative risk estimates with 95% confidence interval were calculated using random-effects and quality-effects models. Forest plots were constructed to show the study-specific relative-risk estimates and pooled relative-risk estimates. The size of the box represents the relative weight of an individual study in calculating the pooled relative-risk estimates. Heterogeneity was assessed using Cochran's *Q*-statistic ($P<0.10$ used to determine statistical significance of heterogeneity) and the I^{2-}test (I^2 values of 25, 50 and 75% were considered as low, medium and high heterogeneity, respectively). The presence of publication bias was evaluated by Egger's test ($P<0.05$) and visual inspection of the symmetry in funnel plots.

Subgroup analysis were performed by study design and study quality as possible sources of heterogeneity between studies. Sensitivity analysis were performed by excluding each study one by one and calculating a pooled estimate for the remaining studies. All statistical analyses were carried out using MetaXL version 5.3 and the Stata14*metan* package.

Results

Study characteristics

A total of ten studies were included in the meta-analysis. Three studies were conducted in the USA[9,10,19] and the remaining

studies were conducted in Canada,[20,21] Australia,[11,17] Denmark,[12] Finland[16] and Sweden.[18] The sample size of the included studies ranged from 847 to 377 708. Age at the diagnosis of ASD varied between 1 year and 24 years. Of the included studies, six were case–control studies,[10–12,16–18] whereas the other four were cohort studies.[9,19–21] One study[9] used ICD in the ascertainment of pre-eclampsia and the remaining studies used medical records, registries or databases.[10–12,16–21] Seven of the studies used ICD as a diagnostic criterion for ASD[9,12,16,18–21] (Table 1). Five studies were good in quality,[9,10,16,18,20] two were fair[12,17] and three were poor[11,19,21] (supplementary Table 1).

Confounding variables

Among the ten studies included in the analysis, seven studies[8–10,12,16–18,20] adjusted for child gender and half of the studies controlled for maternal age and substance use during pregnancy. However, some other confounding factors such as maternal body mass index (BMI), infection during pregnancy, gestational diabetes, parity, birth weight and gestational age were commonly unaccounted for (supplementary Table 2).

Pre-eclampsia and the risk of ASD

Of the included studies, seven reported positive associations between pre-eclampsia and ASD,[9,10,16,18–21] whereas the other three reported null associations.[11,12,17] Studies reporting null associations were case–control studies in design. Among studies reporting positive associations, a good-quality, retrospective cohort study found that intrauterine exposure to pre-eclampsia increased the risk of ASD by 69% (OR = 1.69, 95% CI 1.26–2.28).[9] However, this study relied upon administrative data and the author's acknowledged the possible misclassification errors in the ascertainment of both ASD and pre-eclampsia. Another good-quality, large, cohort study in Alberta, Canada, found an association between pre-eclampsia and offspring ASD at ages 4–10 years.[20] In this study, offspring with intrauterine exposure to pre-eclampsia had a 49% higher risk of ASD compared with non-exposed offspring. On the other hand, a more recent case–control study by Langridge *et al*[17] found no associations between pre-eclampsia and ASD in children with intellectual disability, whereas exposure to pre-eclampsia was found to be protective in children with ASD and no intellectual disability. Estimates were adjusted for sociodemographic characteristics, pregnancy complications, labour and delivery factors, and neonatal outcomes.

The pooled effect of studies included in the meta-analysis showed that pre-eclampsia was associated with increased risk of ASD (RR = 1.32, 95% CI 1.20–1.45) (Fig. 2). The quality-effects model provided a consistent finding (RR = 1.34, 95% CI 1.22–1.47).

Assessment of bias and variability between studies

We found no evidence of heterogeneity ($Q = 12.37$, $P = 0.19$ and $I^2 = 27\%$) and no evidence of publication bias (Egger's test, $P = 0.53$) and funnel plots (Fig. 3). Sensitivity analysis yielded similar pooled estimates ranging from RR = 1.30 (95% CI 1.17–1.44) to RR = 1.37 (95% CI 1.26–1.48) (supplementary Table 3). Subgroup analysis demonstrated stronger effect estimates among cohort studies (RR = 1.41, 95% CI 1.26–1.58) than case–control studies (RR = 1.25, 95% CI 1.10–1.42). No between-study heterogeneity was noted for both cohort ($Q = 309$, $P = 0.38$ and $I^2 = 3\%$) and case–control studies ($Q = 6.93$, $P = 0.23$ and $I^2 = 28\%$). We further conducted subgroup analyses by study quality and found stronger estimates among good-quality studies (RR = 1.41, 95% CI 1.26–1.57) compared with poor-quality studies (RR = 1.32, 95% CI 1.20–1.45).

Table 1 Characteristics of studies included in the meta-analysis ($n = 10$)

Author, year	Country	Study design	Sample size	Ascertainment of exposure	Outcome diagnostic criteria	Age range, years	Risk measure	Estimates (95% CI)
Walker *et al.* (2015)[10]	USA	Case–control	867 (517 cases, 350 controls)	Medical records and self-reported	ADI-R	2–5	Odds ratio	2.36 (1.18–4.68)
Xiang *et al.* (2015)[19]	USA	Cohort	332 323 (3388 cases)	Medical records	ICD-9	2.2–8.7 (median 5.5)	Hazard ratio	1.44 (1.72–1.7)
Polo-Kantola *et al.* (2014)[16]	Finland	Case–control	5168 (1036 cases and 4132 controls)	Medical records	ICD-9/ICD-10	2–17	Odds ratio	1.49 (1.1–2.1)
Mann *et al.* (2010)[9]	USA	Cohort	87 677 (472 cases)	ICD-9	ICD-9	7–13	Odds ratio	1.69 (1.26–2.28)
Langridge *et al.* (2013)[17]	Australia	Case–control	377 708 (1179 cases and 376 529 controls)	Medical records	DSM-III R and DSM-IV	6–21	Odds ratio	1.03 (0.83–1.27)
Dodds *et al.* (2011)[21]	Canada	Cohort	128 809 (924 Cases)	Perinatal database	ICD-9/ICD-10	1–17	Relative risk	1.24 (1.02–1.52)
Burstyn *et al.* (2010)[20]	Canada	Cohort	215 217 (1138 cases)	Medical records	ICD-9	4–10	Relative risk	1.49 (1.00–2.23)
Buchmayer *et al.* (2009)[18]	Sweden	Case–control	7296 (1216 cases and 6080 controls)	Medical records	ICD-9/ICD-10	<10	Odds ratio	1.64 (1.08–2.49)
Larsson *et al.* (2005)[12]	Denmark	Case–control	9464 (364 cases and 9100 controls)	Medical birth register	ICD-8/ICD-10	1–24	Relative risk	1.54 (0.83–2.86)
Glasson *et al.* (2004)[11]	Australia	Case–control	1778 (465 cases and 1313 controls)	Research database	DSM-IV	4–19	Odds ratio	0.99 (0.66–1.50)

ADI-R, Autism Diagnostic Interview – revised.

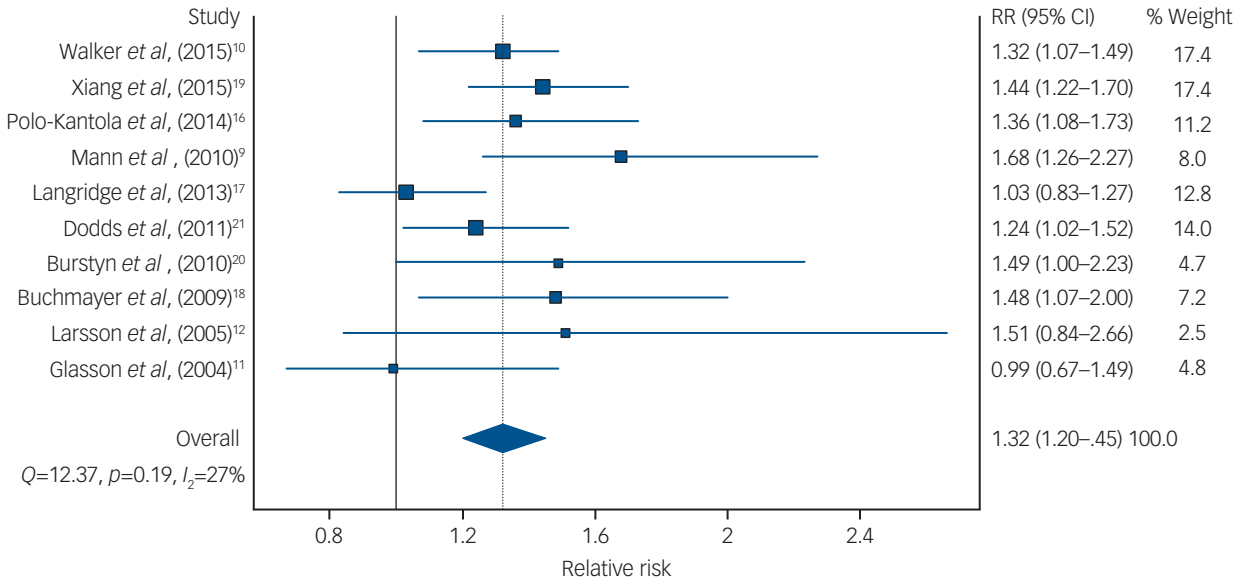

Fig. 2 Forest plot of studies assessing pre-eclampsia and offspring autism-spectrum disorder using a random-effect model (pooled relative risk (RR), with 95% confidence interval).

Discussion

Main findings

To our knowledge, this is the first meta-analysis that has assessed the association between intrauterine exposure to pre-eclampsia and ASD in offspring. Our findings show that offspring who had intrauterine exposure to pre-eclampsia had a 32% higher risk of ASD compared with non-exposed offspring. Evidence suggests that pre-eclampsia has also been liked to schizophrenia[22] and other mental disorders.[23]

Possible biological mechanisms

Although the mechanisms underlying the association between pre-eclampsia and autism are not clearly identified, there are several plausible biological mechanisms by which pre-eclampsia may increase the risk of ASD. In pre-eclampsia there is inadequate invasion of the maternal uterine spiral arteries into the placental trophoblast.[24] This results in poor placental perfusion and leads to placental and fetal hypoxia.[25] Depleted oxygen supply to the fetus may impair neurodevelopment and thus contribute to greater risk of ASD.[26]

Limited nutrients and oxygen can also cause oxidative stress, which encourages the release of proteins into the maternal bloodstream in an attempt to improve circulation.[10] The brain is highly vulnerable to oxidative stress because of its limited antioxidant capacity[27] and there is evidence suggesting that oxidative stress may increase the risk of ASD.[27]

In addition, micronutrient deficiency[28] and metabolic dysfunction[29] are other potential biological mechanisms that may explain the link between pre-eclampsia and the increased risk of ASD we found in offspring. Moreover, adverse birth outcomes such as preterm birth, low birth weight and small-for-gestational-age are more common in women with pre-eclampsia[30] and are also

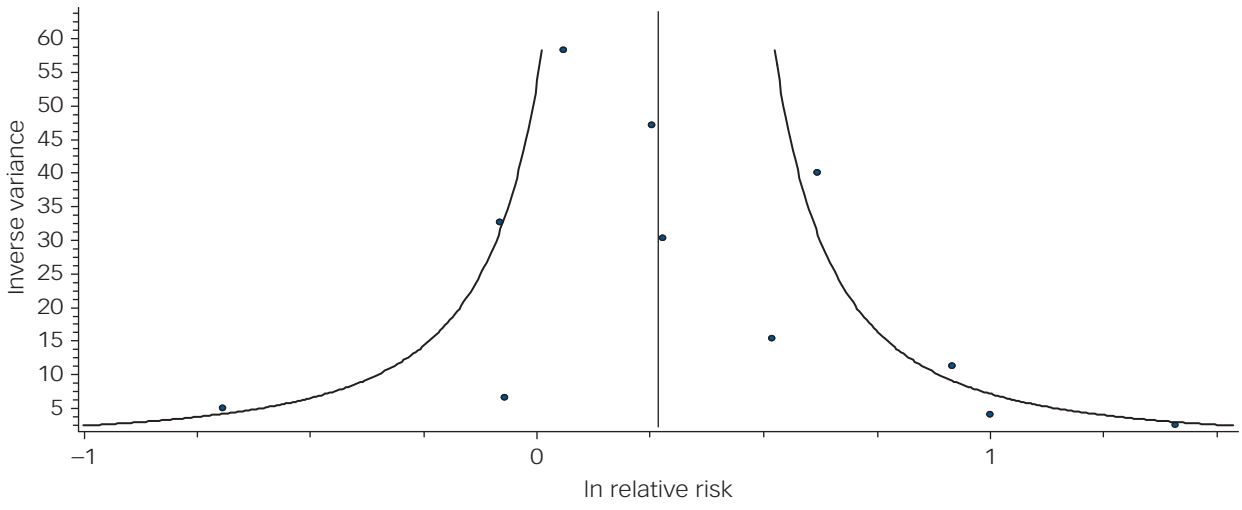

Fig. 3 Funnel plot of studies assessing intrauterine exposure to pre-eclampsia and offspring autism-spectrum disorder.

associated with ASD.[11] It is also important to note that pre-eclampsia can be associated with seizures,[31] another known risk factor for autism.[32]

On the other hand, the association between pre-eclampsia and ASD may also be because of confounding effects as some studies have only reported unadjusted estimates[11,19,21] and others did not consistently adjust for confounding factors such as parity, pregnancy obesity, gestational diabetes and infection during pregnancy (supplementary Table 2). It is well established that factors such as BMI and gestational diabetes are associated with both the risk of pre-eclampsia[33,34] and neurodevelopmental disorders in offspring.[35,36] For example, a recent meta-analysis showed that children born to overweight and obese mothers have a 28 and 36% higher risk of ASD respectively compared with children whose mothers were of normal weight.[35] This study reported a linear dose–response relationship between maternal BMI and offspring ASD; the risk of ASD increased by 16% for each 5 kg/m^2 increment in maternal BMI compared with normal weight.

Similarly, a positive association between gestational diabetes and ASD in children has been reported.[19,36] A systematic review and meta-analysis of cohort and case–control studies found that maternal gestational diabetes was associated with increased risk of ASD with the pooled estimates of 1.48 (95% CI 1.25–1.75) for cohort studies and 1.73 (95% CI 1.24–2.41) for case–control studies.[36] Finally, the confounding role of socioeconomic position is often difficult to assess in epidemiological studies.[37]

Strength and limitations

The strength of this systematic review and meta-analysis are that we included all studies without study time restrictions and we used a standardised quality-assessment tool. We also conducted subgroup and sensitivity analysis to account for possible sources of heterogeneity across studies. We presented the summary results using relative risks, which gives us a true population risk estimates compared with odds ratios. Associations were still seen after adjustment for bias using a quality-effect model. This is a more robust model that allows us to avoid some problems with traditional random-effect models.[38] These methodological strengths add confidence to the validity of our findings.

This meta-analysis also has some limitations. Relevant studies published in a language other than English may have been missed. Three of the ten studies included in the meta-analysis only reported unadjusted risk estimates. However, when we excluded these from our analyses the results remained unchanged (RR = 1.34, 95% CI 1.18–1.52). We could not fully rule out bias from confounding, as six studies[9,11,12,19,21,39] did not consistently adjust for important confounding factors such as maternal obesity, parity, gestational diabetes and infection during pregnancy. It is also worth noting that no studies were able to account for genetic susceptibility and other environmental and socioeconomic exposures. There may also have been misclassification bias, as studies used different diagnostic criteria for ASD. However, this may not be a major concern because most ($n = 7$) studies used the ICD for the diagnosis of ASD and our estimates did not change substantively when the analysis was restricted to these studies (RR = 1.41, 95% CI 1.28–1.55). Because of the small number of studies ($n = 10$) included in the meta-analysis the statistical power to detect heterogeneity across studies was limited. However, we used $P < 0.1$ rather than the conventional level of 0.05 to determine statistical significance of heterogeneity[40] and Cochran's Q revealed no significant heterogeneity ($P = 0.19$).

Three studies[16,17,21] included gestational hypertension and/or pre-exiting hypertension when defining pre-eclampsia. When we excluded these studies, we found slightly stronger pooled estimates (RR = 1.40, 95% CI, 1.27–1.54). Three[11,19,21] of the ten studies included in the meta-analysis were poor in quality. However, when we excluded these in analyses the results remained the same (RR = 1.34, 95% CI 1.18–1.52). Also, most of the studies included in this meta-analysis were case–control studies ($n = 6$). When we stratified by study design to further assess this limitation, we found results did not change and estimates remained in the expected direction, with the strength of association becoming slightly stronger for cohort studies. Finally, since all studies we included were conducted in Western countries, the findings may not be generalisable to other populations.

Implications

Although the underlying causes of ASD are not fully understood, this meta-analysis showed that intrauterine exposure to pre-eclampsia increased the risk of ASD in offspring. Given the limited number of cohort studies, and the fact that some of the studies in this review and meta-analysis were not originally designed to assess the association between pre-eclampsia and ASD, our findings need to be replicated using well-designed, large, birth cohort studies. This study suggests that early screening for ASD in offspring of women with pre-eclampsia may be warranted and, future studies should assess the effect of early screening and treatment of pre-eclampsia on the prevention of ASD in offspring.

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Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2017.27.

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