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Maternal infection during pregnancy and risk of autism spectrum disorders: A systematic review and meta-analysis

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ABSTRACT

Conflicting evidence exists with regard to the relationship between maternal infection during pregnancy and the risk of autism spectrum disorder (ASD) in offspring. The aim of this meta-analysis was to systematically assess this relationship. To identify relevant studies, we conducted systematic searches in PubMed and Embase of scientific articles published through March 2016. Random-effects models were adopted to estimate overall relative risk. A total of 15 studies (2 cohort and 13 case-control studies) involving more than 40,000 ASD cases were included in our meta-analysis. Our results showed that maternal infection during pregnancy was associated with an increased risk of ASD in offspring (OR = 1.13, 95% confidence interval (CI): 1.03–1.23), particularly among those requiring hospitalization (OR = 1.30, 95% CI: 1.14–1.50). Subgroup analyses suggested that risk may be modulated by the type of infectious agent, time of infectious exposure, and site of infection. These findings indicate that maternal infection during pregnancy increases the risk of ASD in offspring. Possible mechanisms may include direct effects of pathogens and, more indirectly, the effects of inflammatory responses on the developing brain.

1. Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by deficits in socialization and communication and by repetitive or unusual behaviors (Murray et al., 2005). The estimated prevalence of ASD has dramatically increased over the past decade (Baxter et al., 2015; Sun et al., 2013). Although genetic factors clearly contribute to the risk of ASD (Tick et al., 2016), environmental factors are involved as well (Gardener et al., 2009); hence, recognition of risk factors and appropriate interventions may help to prevent some cases. One suspected environmental risk factor is maternal infection during pregnancy, given that the teratogenic effects of maternal infections such as rubella (Chess, 1977), cytomegalovirus (Sweeten et al., 2004) or *Toxoplasma gondii* (Abdoli and Dalimi, 2014) on the central nervous system are well established. Research using animal models has gradually documented the connection between prenatal infection and autism-like behaviors in offspring (Ohkawara et al., 2015); therefore, it is plausible to hypothesize that maternal infection during pregnancy may also augment the risk of ASD. Several epidemiological studies have investigated the contribution of maternal infection during pregnancy to the risk of ASD with varying results; some (Lee et al., 2015; Visser et al., 2013) found a positive association, whereas others (Abdallah et al., 2012; Atladottir et al., 2010; Buchmayer et al., 2009; Dodds et al., 2011; Duan et al., 2014; Glasson et al., 2004; Langridge et al., 2013; Maimburg and Vaeth, 2006; Zerbo et al., 2013, 2015) reported no association. Given that the various factors associated with maternal infections during pregnancy (i.e., severity of infection, type of infectious agent, exposure time, and site of infection) may differentially affect the risk of ASD, it is reasonable to analyze these factors separately. Previous epidemiological investigations (Atladottir et al., 2012, 2010; Fang et al., 2015; Mamidala et al., 2013; Zerbo

Abbreviations: ASD, autistic spectrum disorder; CI, confidence interval; HRs, hazard risks; MIA, maternal immune activation; NOS, Newcastle–Ottawa Scale; ORs, odds ratios; poly(I:C), polyinosinic-polycytidylic acid; RRs, relative risks.

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et al., 2015) of the various factors associated with maternal infections have yielded inconsistent results. The most recent systematic review and meta-analysis (Gardener et al., 2009) found a positive association in an analysis limited to studies that controlled for multiple covariates; however, it also found no association between infection during pregnancy and ASD in the studies that did not control for covariates. The data included in the previous systematic review were limited to studies conducted before 2009. Many studies have been published since then. This should enable a more detailed analysis of the association between maternal infection during pregnancy and ASD risk.

Given the high prevalence of infection during pregnancy worldwide, it is important to determine whether there is a relationship between maternal infection during pregnancy and the risk of ASD. Therefore, this study conducted a systematic review and meta-analysis of all observational studies to estimate the risk of ASD among those who are born after being exposed to maternal infection.

2. Methods and materials

This meta-analysis was conducted according to the guidelines developed by the meta-analysis of Observational Studies in Epidemiology group (Stroup et al., 2000) (Supplementary Table 1). All of the steps involved in the literature search, study identification, study selection, assessment of quality, and data extraction were performed independently by two investigators from different subspecialties (H.Y.J. and L.L.X.). Disagreements were resolved through discussion, and consensus was achieved in the selection of articles for analysis.

2.1. Search strategy

We conducted a comprehensive search of the PubMed and Embase databases for peer-reviewed studies published in English through to March 2016. We selected synonymous terms and used these to develop the search strategy (Supplementary Table 2). The reference lists of retrieved articles were hand searched for additional relevant articles. When the available information was incomplete, attempts were made to contact the study investigators for additional information.

2.2. Study selection

We included case-control studies and cohort studies that examined the association between maternal infection during pregnancy and the risk of ASD by using odds ratios (ORs), relative risks (RRs) or hazard risks (HRs). Only articles written in English were reviewed. We excluded studies involving fewer than 100 ASD cases. The titles and abstracts of papers identified in the initial search were evaluated by one author (H.Y.J.) for appropriateness with respect to the study question, and all potentially relevant papers were retrieved. Any discrepancies were resolved through discussion with another author (L.L.X. or L.S.).

2.3. Data extraction and quality assessment

Data were extracted independently by two authors (R.M.X. and Z.H.Y.), and disagreements were resolved through discussion with a third author (Z.X.L., M.D., or F.Y.). From each paper, we extracted information pertaining to study design, study time period/year of publication, country of origin of the population under study, total number of subjects in each group, information regarding infection exposure, diagnostic criteria, outcome measures, and statistical adjustments. Study-specific ORs, RRs, or HRs with their 95% CIs are presented in Supplementary Table S3. Two authors independently (L.L.X. and L.S.) assessed the risk of bias using the Newcastle–Ottawa Scale (NOS) developed to assess the quality of non-randomized studies (Higgins, 2014). This scale scores observational studies on three dimensions relevant to research quality: selection (four questions) and comparability (two questions) of the study group, as well as ascertainment of the outcome of interest (three questions), with all questions having a value of one. Studies with scores $\geqslant 7$ were considered to be of high quality.

2.4. Outcomes assessed

The analysis focused on assessing the risk of ASD among individuals exposed to maternal infection in comparison with those who had not been exposed. To investigate potential sources of heterogeneity, the subgroup analyses were stratified using the following parameters: type of infectious agent, timing of infection, organ-specific infections, whether hospitalization was required, and whether effect estimates were adjusted (Table 2). We also performed a *post hoc* sensitivity analysis by including only one study from the same database. We analyzed the type of infection data in the following four broad categories: (1) any infection, including bacterial, viral, parasitic, fungal, and unknown infections; (2) bacterial infection; (3) viral infection; and (4) other infection, i.e., parasitic, fungal, and unknown organism infections.

2.5. Statistical analysis

The data were pooled using a random-effects model. The risks of ASD were expressed as the OR with 95% confidence interval (CI) for case-control studies and HR with the 95% CI for cohort studies. ORs were considered approximations of RRs or HRs because the outcome under study is rare in all populations and subgroups under review (Baxter et al., 2015; Greenland, 1987). Heterogeneity among studies was assessed using the χ^2 test and I^2 statistic, where an I^2 value of >50% or a P value of <0.05 for the Q-statistic was considered to indicate significant heterogeneity (Higgins and Thompson, 2002). We assessed publication bias using Egger's test (Egger et al., 1997) rather than Begg's test because the latter will not yield a robust result unless a minimum of 15–20 studies are included in the meta-analysis (Begg and Mazumdar, 1994). The statistical analysis was performed using Stata 12.0 (Stata Corp., College Station, TX, USA).

3. Results

3.1. Study selection

Our keywords identified 3577 potentially eligible articles in the two databases we searched. Of these, 81 citations were identified and retrieved for full-text screening. After full-text review, 13 case-control (Abdallah et al., 2012; Buchmayer et al., 2009; Dodds et al., 2011; Duan et al., 2014; Fang et al., 2015; Glasson et al., 2004; Langridge et al., 2013; Lee et al., 2015; Maimburg and Vaeth, 2006; Mamidala et al., 2013; Visser et al., 2013; Zerbo et al., 2013, 2015) studies and two cohort studies (Atladottir et al., 2012, 2010) were included. Fig. 1 presents the number of articles excluded at each stage of the eligibility assessment, along with the reasons for exclusion.

3.2. Characteristics and quality of studies

The main characteristics of the studies included are presented in Table 1. The earliest (Glasson et al., 2004) and most recent studies (Lee et al., 2015) were published in 2004 and 2015, respectively.