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Review

Maternal autoimmune diseases and the risk of autism spectrum disorders in offspring: A systematic review and meta-analysis

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HIGHLIGHTS

- A systematic review and meta-analysis based on nine case-control studies and one cohort study.
- Association between maternal autoimmune diseases and the risk of autism spectrum disorders in offspring.
- Maternal autoimmune diseases increasing the risk of autism spectrum disorders in offspring.

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ABSTRACT

Although inherited and immune disorder factors are known to be involved in autism spectrum disorders (ASD), controversy still exists as to whether maternal autoimmune disease is an independent risk of ASD in offspring. We aimed to quantitatively summarize the risk of ASD in offspring in relation to maternal autoimmune diseases. A literature search in Pubmed, Web of science, Embase, and China national knowledge internet was conducted to identify relevant studies. Pooled odd ratio (OR) and its 95% confidence interval (CI) were computed by STATA version 12.0. Nine case-control studies and one cohort studies comprising 9775 cases and 952,211 controls were included in this study. A positive association between maternal autoimmune diseases and the risk of ASD in offspring was identified assuming a fixed effect model (pooled OR, 1.34; 95% CI, 1.23–1.46; I^2, 27.9%). There were statistically significant associations between maternal autoimmune diseases developed during pregnancy or maternal thyroid disease and the risk of ASD in offspring (pooled OR, 1.30, 1.29, respectively). Maternal autoimmune disease is likely to be an independent risk factor of ASD in offspring.

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1. Introduction

Autism spectrum disorders (ASD) are a set of pervasive neurodevelopmental disabilities which are characterized by impaired social and motor skills, restricted communication capability and unusual repetitive behavior [1]. The uncommon conditions initiate in early childhood and would persist for the rest of their life with a prevalence ranging from 0.7% to 2.64% in general population [2], which adds health-care costs and the financial burden to family and society. To develop and implement effective preventions and interventions for ASD, it is necessary to identify possible causes and risk factors for the uncommon conditions.

Presently, although the etiology of ASD remains unclear, a lot of clues indicate that there is a possible association between abnormal immune responses and ASD [2]. Impact of maternal autoimmune diseases on ASD in offspring attracts much more attention. The altered immune system in mothers with autoimmune diseases is thought to stimulate much more autoantibodies and immune cytokines than in those mothers without autoimmune diseases [3]. Antibodies against certain proteins in fetal brain were detected in mothers who had children with ASD with a positive rates from 10% to 12%, but these antibodies were absent among those mothers who had children without ASD [1]. Animal studies demonstrated that autism-like manifestations were observed in offspring after injecting pregnant mice or rhesus monkey with IgG from the human case-mothers [4,5]. These hostile factors from mothers with autoimmune diseases may induce inflammation in fetal brain after crossing placental barrier and immature brain blood barrier, which could damage brain tissue and exert adverse influence on cerebral development [2]. Abnormal alterations in early cerebral development are important for genesis and development of ASD [6].

According to several observational studies [7–11], maternal autoimmune diseases acting during pregnancy, particularly rheumatic arthritis, psoriasis, systemic lupus erythematosus (SLE) and autoimmune thyroid disease are associated with an increased risk of ASD in offspring. These exposures could increase the risk of ASD accounting for 15–78% [7–11]. Recently, a systematic review and meta-analysis demonstrated that maternal diabetes including type I diabetes mellitus, an autoimmune disease, was associated with an increased risk of ASD in offspring [12]. However, some other studies showed that the association was not statistically significant [6,13,14]. The effect of maternal autoimmune diseases on ASD in offspring remains to be verified. Thus, we conducted a systematic review and meta-analysis to quantitatively assess the risk of ASD in offspring in relation to maternal autoimmune diseases.

2. Methods

2.1. Search strategy

A broad literature search in Pubmed, Web of science, Embase, and China national knowledge internet (CNKI) was carried out to identify relevant publications on the topic of association between maternal autoimmune diseases and the risk of ASD in offspring. The electronic search was indexed from their inception to July 2015 without application of language or region restriction. Following key words were used: “autoimmune disease”; “rheumatoid arthritis”; “systemic lupus erythematosus”; “autoimmune thyroid disease”; “multiple sclerosis”; “psoriasis”; “myasthenia gravis”; “rheumatic fever”; “celiac disease”; “ulcerative colitis”; “crohn disease”; “inflammatory bowel disease”; “idiopathic thrombocytopenic purpura”; “systemic vasculitis”; “maternal”; “mother”; “parent”; “gestational”; “pregnancy”; “prenatal”; “perinatal”; “pervasive development disorders”; “asperger syndrome”; “autistic disorder”; “autism”. These autoimmune diseases were chosen as they have a known or suspected autoimmune cause [7]. However, type I diabetes mellitus was not included because a previous systematic review and meta-analysis has proved that maternal diabetes was associated with an increased risk of ASD in offspring [12]. The major plausible biological mechanism involves exposure to hyperglycemia in utero. Inclusion of type I diabetes mellitus may overrate the pooled effect between maternal autoimmune diseases and the risk of ASD in offspring. Moreover; we screened reference lists of retrieved articles to find additionally relevant studies.

2.2. Study selection criteria

Studies were included for review, if they had met criteria as follows: (1) on the topic of association between maternal autoimmune diseases and the risk of ASD in offspring; (2) case-control or cohort study; (3) reporting or providing data for calculation of the effect size (e.g., OR [ratio odd], RR [relative risk]). If the same research has duplicated reports, only the more comprehensive one was included in the meta-analysis.

2.3. Data extraction

Two investigators independently (X.S. Zhong, X.Y. Zheng) evaluated all publications from databases and reference lists of retrieved articles for eligibility by screening their titles, abstracts, or full texts. For eligible articles, main information (first author’s name, publication year, location, study design, maternal and children’s information, sample size, ORs or RRs and their 95% CIs, and adjusted or matched varieties) was extracted by two investigators (X.S. Zhong, L.N. Jiang) on their own. Disagreements about inclusion/exclusion of a study or calculation for effect sizes were resolved by discussion. Without achievement of consensus, a third investigator (S.W. Chen) was consulted to make a final decision.

2.4. Quality assessment

We assessed methodological quality of all eligible studies according to Newcastle-Ottawa Scale (NOS) which is a validated measure of methodological quality assessment for nonrandomized studies such as cohort and case-control studies [15,16]. The assessment was carried out by semi quantitatively allocating stars. There are mainly three segments of quality assessment as follows, participants selection (0–4 stars), comparability between the groups (0–2 stars), ascertainment of outcome (for cohort study) or exposure (for case-control study) of participants (0–3 stars). Each eligible study was allocated with a total score ranging from 0 to 9. Study scored between 0 and 3 was deemed as poor quality, 4 and 6 was moderate quality, equal or greater than 7 was high quality.

2.5. Statistical analysis

Pooled OR as well as its 95% CI was computed. Heterogeneity across the eligible studies was assessed both by χ^2-based *Cochran Q* statistic test and I^2 inconsistency test. *Cochran Q* statistic is a standardized measure of deviation among eligible studies and I^2 represents the percentage of total variation attributed to hetero-

Table 1
Characteristics of articles included.

Author, year	Location	Study design	Period	Case/sample size	Race, *N* (%)	Maternal age	Child's age	Autoimmune diseases case ascertainment	ASD case ascertainment	Adjustment or matched variates
Khaiman et al. 2015 [25]	Thailand	case-control	From 2011 to 2014	231/466	NR	Case: 32.4 ± 7.3 years; control: 28.9 ± 6.1 years	Case: 8.4 ± 3.37 years; control: 8.4 ± 3.4 years	NR	DSM-IV	NR
Brown et al. 2015 [8]	Finland	Case-control	From 1987 to 2007	960/1920	NR	Case: 30.15 ± 5.34 years; Control: 29.24 ± 5.28 years	Born between 1987 and 2005	TPO-Ab،TSH and FT4; During pregnancy	ICD-10	NR
Lyall et al. 2014 [13]	The USA	Case-control	Initiated in 2002.	560/951	Caucasian:584 (61.4%); Hispanic: 222(23.3%); Other 145(15.2%)	Case: 31.1 ± 5.6 years; Control:31.1 ± 5.7 years	45.4 ± 10.1 months old	Questionnaire; During pregnancy	ADOS and ADI-R	Breastfeeding, medication use for asthma and allergies, maternal smoking, maternal race, education level, insurance status at delivery
Lyall et al. 2012 [10]	The USA	Case-control	From 1989 to 2003	793/66445	NR	Case: 32.3 ± 4.4 years; Control: 34.6 ± 4.7 years	NR	Questionnaire; During pregnancy	Questionnaire	Race, marital status, income, spouse education, age, age at first birth, parity, twin births, pregnancy complication, induced abortion, miscarriages
Andersen et al. 2014 [9]	Demark	Cohort	From 1991 to 2004	5311/857014	NR	<25 years: 16.7%; 25–29 years: 38.3%; 30–34 years: 31.9%; ≥35 years: 13.1%	3 years old	ICD-8, ICD-10;Before or after pregnancy	ICD-10	Gender, year of birth (child); age, origin, residence, cohabitation, income, parity (maternal)
keil et al. 2010 [11]	Sweden	Case-control	From 1977 to 2003	1227/31920	NR	<25 years: 28.2%; 26–30 years: 37.9%; 31–35 years: 25.0%; ≥36 years: 10.9%	1–10 years old	ICD	ICD-10	Child's age, hospital of birth, sex, and parents' ages at delivery, country of birth
Mouridsen et al. 2007 [14]	Demark	Case-control	From 1960 to 1984	111/441	NR	At the end of the 27-year observation period, case: 65.6 ± 9.6 years; control: 65.6 ± 9.6 years	5.4 ± 2.5 years	ICD-8, ICD-10	ICD-8, ICD-9	NR
Croen et al. 2005 [6]	The USA	Case-control	From 1995 to 1999	420/2520	White non-Hispanics: 1155(46.2%); White Hispanics: 536(21.4%); Black: 222(8.9%); Asian: 260(10.4%); Other: 323(12.9%)	Case: 31.1 ± 5.4 years; Control: 29.8 ± 5.7 years	3 and 7 years old	ICD-9;Before, during or after pregnancy	ICD-9	Maternal age, maternal education, maternal race/ethnicity, plurality
Sweeten et al. 2003 [7]	India	Case-control	NR	101/202	NR	NR	case: 10.2 ± 4.2 years; control: 6.5 ± 4.0 years	Questionnaire	DSM-IV	NR
Comi et al. 1999 [24]	The USA	Case-control	NR	61/107	NR	NR	case: mean (range) 9.8 (3–28) years; control: 8.7 (1–22)	Questionnaire; During pregnancy	Cases recruited from East Tennessee Chapter of the Autism Society of America	NR

Abbreviations: NR, no reported; TPO-Ab, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; fT4, free T4; ICD, International Classification of Diseases; ASD, autism spectrum disorders; ADOS, Autism Diagnostic Observation Schedule; ADI-R, Autism Diagnostic Interview Revised; DSM-, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

geneity rather than chance within these studies [17]. When *P* value of *Cochran Q* test was >0.10, no indication of heterogeneity was identified. A fixed effects model was employed to compute pooled OR and its 95% CI when there was no significant heterogeneity, otherwise the random effects model was used [18]. The heterogeneity was divided into three levels according to value of I^2 statistic as follows: mild (I^2, 0–25%), moderate (I^2, 25–50%), high (I^2, 50–100%) [19]. In order to identify resources of potential heterogeneity in this systematic review and meta-analysis, several subgroups which were stratified by different study designs, locations and local development degrees were analyzed. Funnel plot [20], Egger's statistical test (linear regression method) [21] and Begg's statistical test (rank correlation method) [22] were employed to evaluated possible publication bias. When funnel plot was asymmetric or *P* value (from Egger's statistical test or Begg's statistical test) was less than 0.05, substantial publication bias was confirmed. To assess robustness of the pooled result, sensitivity analyses were carried out by repeatedly calculating the pooled estimates after exclusion of each eligible study per iteration [23].

Statistical analyses were done using STATA version 12.0 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Literature search

A total of 399 potentially relevant records were identified from the electronic databases and screening reference lists of potentially eligible articles. After screening titles or abstracts of these articles, 357 records were excluded because they were regarding duplicated records, irrelevant topics, reviews, letters/meetings or animals/genetic/in-vitro studies. Full texts of the remaining 42 studies were assessed for eligibility. Eventually, we included 10 studies in this systematic review and meta-analysis. Details are exhibited in the flow diagram (Fig. 1).

3.2. Characteristics of included studies

Nine case-control studies and one cohort study comprising 9775 cases and 952,211 controls were included in this study (Table 1). All eligible studies were written in English. Six studies [8–11,14,24] reported that there was a positive association between maternal autoimmune diseases and ASD in offspring, while the remaining four [6,7,13,25] did not revealed a substantially significant association. Among these studies, four [8,9,11,14] were from Europe, four [6,10,13,24] from North America and two [7,25] from Asia. Fiver studies [6,9,10,13,25] adjusted or matched with a broad range of potential confounding factors as follow: child's age, child's gender, maternal age, maternal age at delivery, maternal education, family income and etc., while other five [7,8,11,14,24] were failed to provide these information.

For definition of maternal autoimmune diseases in eligible studies, four studies [6,9,11,14] collected cases of maternal autoimmune diseases according to International Classification of Diseases (ICD), four studies [7,10,13,24] according to questionnaire, one [8] according to thyroid peroxidase antibody, thyroid stimulating hormone and free T4 and one [25] was not specified. Information about maternal autoimmune diseases diagnosed during pregnancy period was reported in six studies [6,8–10,13,24], whereas only five studies [6,8,10,13,24] could provide valid data to analyze. In addition, studies by Andersen et al. [9] and Croen et al. [6] also evaluated the association between maternal autoimmune diseases before or after pregnancy period and ASD in offspring.

There were several diagnostic criteria for ascertainment of ASD cases in eligible studies. The diagnosis of ASD was made according to ICD in five studies [6,8,9,11,14], manual of mental disorders, fourth edition (DSM-IV) in two studies [7,25], both the autism diagnostic interview-revised (ADI-R) and the autism diagnostic observation schedule (ADOS) in one study [13], questionnaire in one study [10] and the remaining one study [24] recruited ASD cases from East Tennessee Chapter of the Autism Society of America.

Table 2
Summary of Newcastle-Ottawa Scale (NOS) core of eligible studies.

Study	Selection of study population	Comparability between groups	Exposure/ outcome assessment	Score
Khaiman et al. 2015 [25]	3	1	1	5
Brown et al. 2015 [8]	4	1	2	7
Lyall et al. 2014 [13]	3	1	1	5
Lyall et al. 2012 [10]	2	2	2	6
Andersen et al. 2014 [9]	4	2	2	8
keil et al. 2010 [11]	2	2	2	6
Mouridsen et al. 2007 [14]	4	1	2	7
Croen et al. 2005 [6]	3	2	3	8
Sweeten et al. 2003 [7]	4	1	1	6
Comi et al. 1999 [24]	2	1	1	4

3.3. Quality assessment

The NOS scores of included studies ranged from 4 to 8 and median score was 6, suggesting methodological qualities of eligible studies were moderate to high (Table 2). The cohort [9] study and two case-control studies [6,8] were considered as high quality, while the other seven case-control studies [7,10,11,13,14,24,25] were considered as moderate quality.

3.4. Maternal autoimmune diseases and the risk of ASD in offspring

A positive association between maternal autoimmune diseases and the risk of ASD in offspring was identified either assuming a fixed effect model (pooled OR, 1.34; 95% CI, 1.23–1.46) (Fig. 2) or assuming a random effect model (pooled OR, 1.37; 95% CI, 1.19–1.55). Two studies (Lyall et al. and Andersen et al) [9,10] made up a large portion in overall analyses, weighting 31.71%, 41.31%, respectively. After omitting these two studies [9,10], the positive association between comparison groups also existed (pooled OR, 1.46; 95% CI, 1.24–1.71; I^2, 37.4%). Moderate heterogeneity was noted between data resources in overall analyses (I^2, 27.9%; *P*, 0.188). In order to identify resource of the heterogeneity, several subgroups were analyzed. Our findings suggested that subgroup stratified by local development degrees could account for a portion of heterogeneity (64.9%) identified in overall analyses (Table 3). The funnel plot (Fig. 5) was visually symmetrical and *P* values of Egger's test (*P* value, 0.073) and Begg's test (*P* value, 0.152) were large than 0.05, which indicated there was no evidence of publication bias in this systematic review and meta-analysis.

We further evaluated the association between maternal autoimmune diseases developed during pregnancy and the risk of ASD in offspring. Compared with the control groups, children exposed to mothers with autoimmune diseases developed during pregnancy

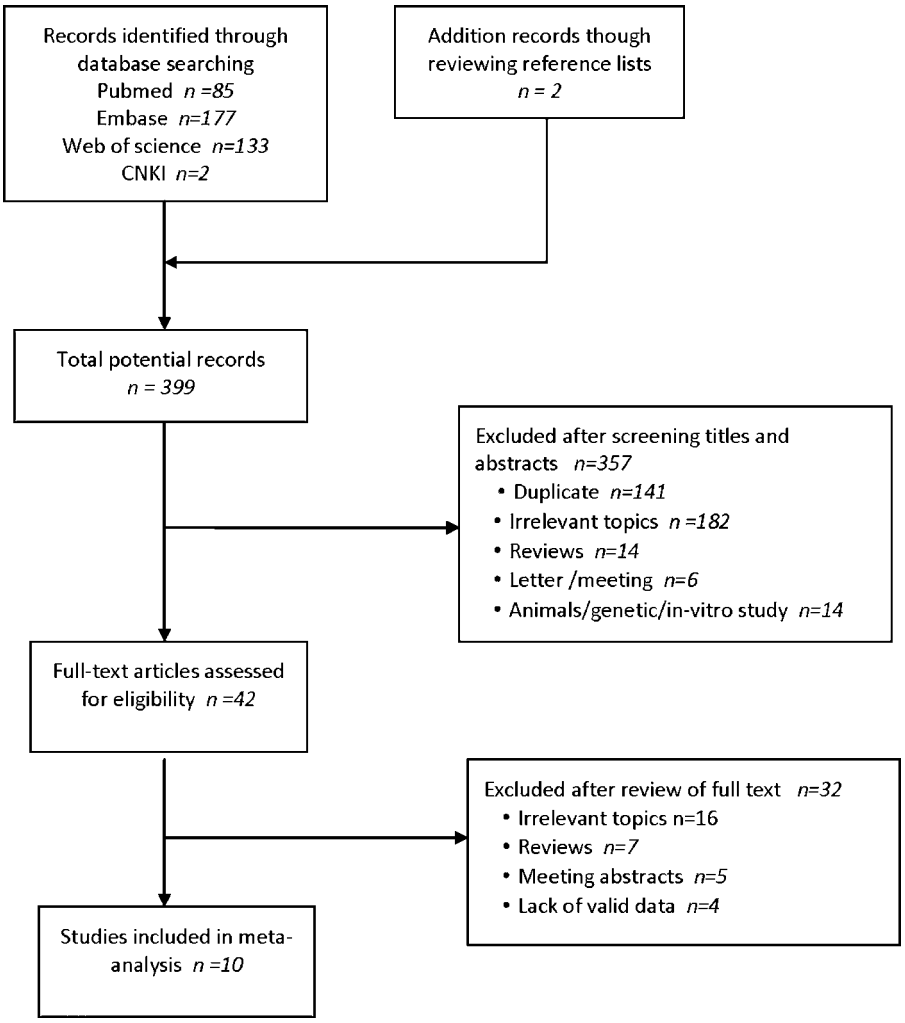

Fig. 1. Flow diagram of the selection of the studies.

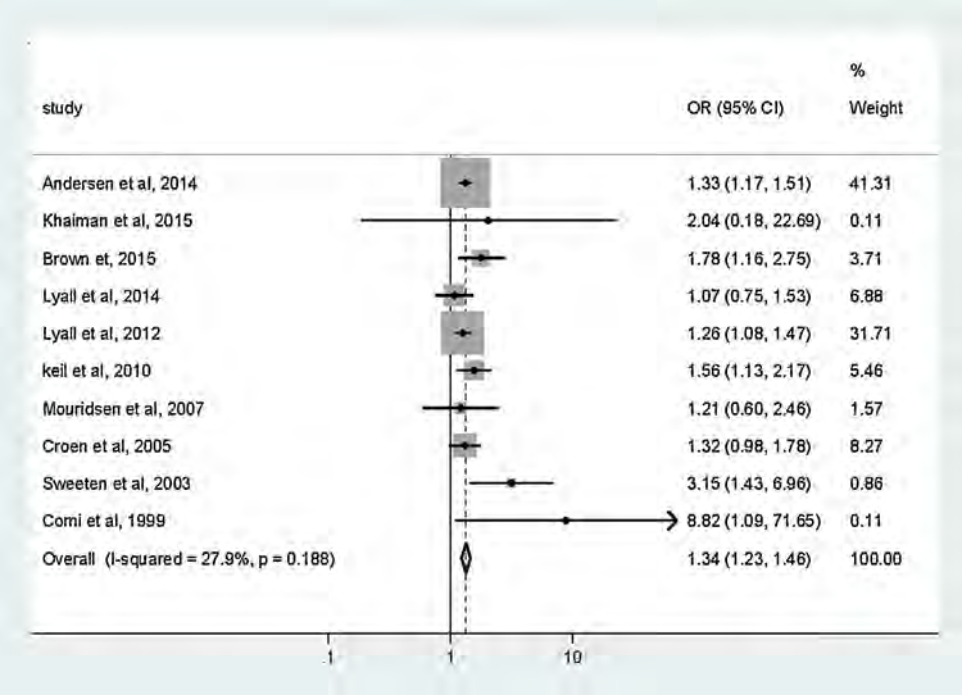

Fig. 2. Forest plot of overall autism spectrum disorders risk in offspring with maternal autoimmune diseases exposure.

Table 3
Summary of subgroup analysis showing the associations between maternal autoimmune diseases and autism spectrum disorders in offspring.

Study	NO. studies	OR	95% CI	Test for heterogeneity		
				Model	*P* Value	I^2 (%)
Overall analysis	10	1.34	(1.23,1.46)	Fixed	0.188	27.9
Study design						
Cohort	1	1.33	(1.17,1.51)	–	–	–
Case-control	9	1.35	(1.21,1.51)	Fixed	0.132	35.8
Location						
Europe	4	1.38	(1.23,1.55)	Fixed	0.496	0.0
North America	4	1.26	(1.11,1.43)	Fixed	0.238	29.1
Asia	2	3.02	(1.43,6.41)	Fixed	0.737	0.0
Local development degree						
Developing	2	3.02	(1.43,6.41)	Fixed	0.737	0.0
Developed	8	1.33	(1.22,1.44)	Fixed	0.354	9.8
Adjusted risk factors	5	1.30	(1.19,1.43)	Fixed	0.551	0.0
Specific autoimmune diseases						
Psoriasis	4	1.34	(0.68,2.65)	Fixed	0.785	0.0
IBD	4	1.70	(0.77,3.77)	Random	0.077	56.2
ITP	2	6.07	(0.46,80.96)	Random	0.022	80.9
SLE	2	2.79	(0.78,10.06)	Fixed	0.995	0.0
Rheumatoid arthritis	2	0.71	(0.30,1.69)	Fixed	0.695	0.0

Abbreviations: OR; odd ratio; 95% CI, 95% confidence interval; SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease; ITP, idiopathic thrombocytopenic purpura.

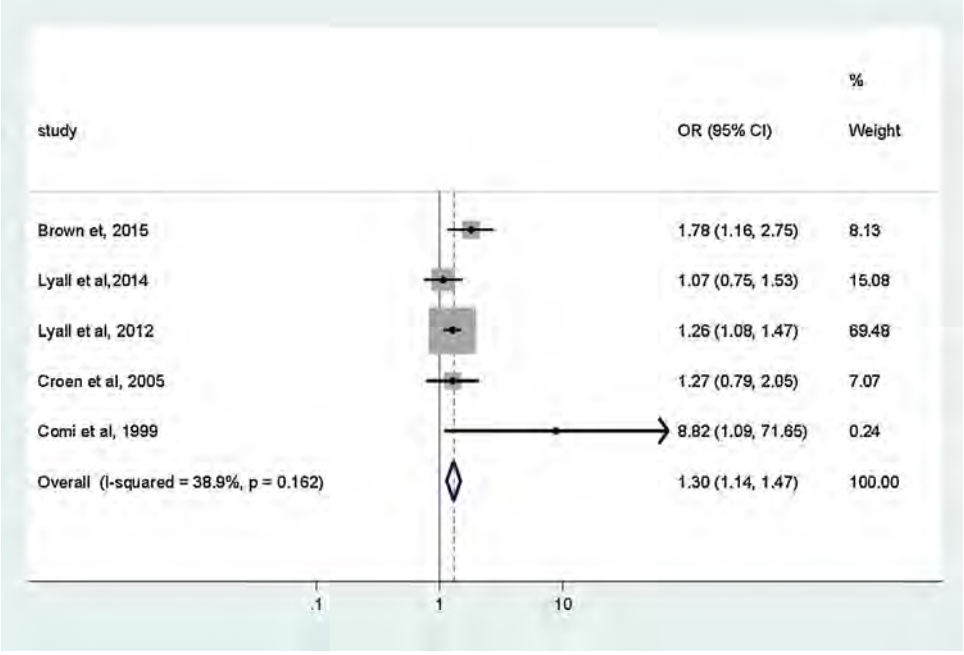

Fig. 3. Forest plot of autism spectrum disorders risk in offspring with maternal autoimmune diseases exposure developed during pregnancy.

had a 30% greater risk of ASD (pooled OR, 1.30; 95% CI, 1.14–1.47; I^2, 38.9%) (Fig. 3).

Data of several specific kinds of maternal autoimmune diseases was separated and analyzed. A positive association was identified between maternal autoimmune thyroid disease and ASD in offspring (pooled OR, 1.29; 95% CI, 1.14–1.45; I^2, 48.7%) (Fig. 4). However, for maternal SLE, inflammatory bowel disease (IBD), idiopathic thrombocytopenic purpura (ITP), psoriasis and rheumatoid arthritis, the associations were not statistically significant (Table 3).

In sensitivity analyses, there was no large fluctuation in pooled estimates via omitting study one by one (Fig. 6). The minimum and maximum of the 10 study-specific pooled ORs were 1.33 (95% CI, 1.22–1.44) and 1.38 (95% CI, 1.25–1.52) by omitting study of Brown et al. [8] and study of Lyall et al. [10], respectively.

4. Discussion

To our knowledge, this is the first meta-analysis to quantitatively evaluate the association between maternal autoimmune diseases and the risk of ASD in offspring. Findings from this systematic review and meta-analysis suggested that maternal autoimmune diseases were associated with a 34% increased risk of ASD in offspring compared with the control groups. The summary estimate was robust according to sensitivity analyses and no substantial publication bias was observed. Maternal autoimmune diseases not only have adverse impact on the mothers themselves, but are likely to be an independent risk for ASD in their children.

The positive association between maternal autoimmune diseases and children's ASD is biologically plausible through the

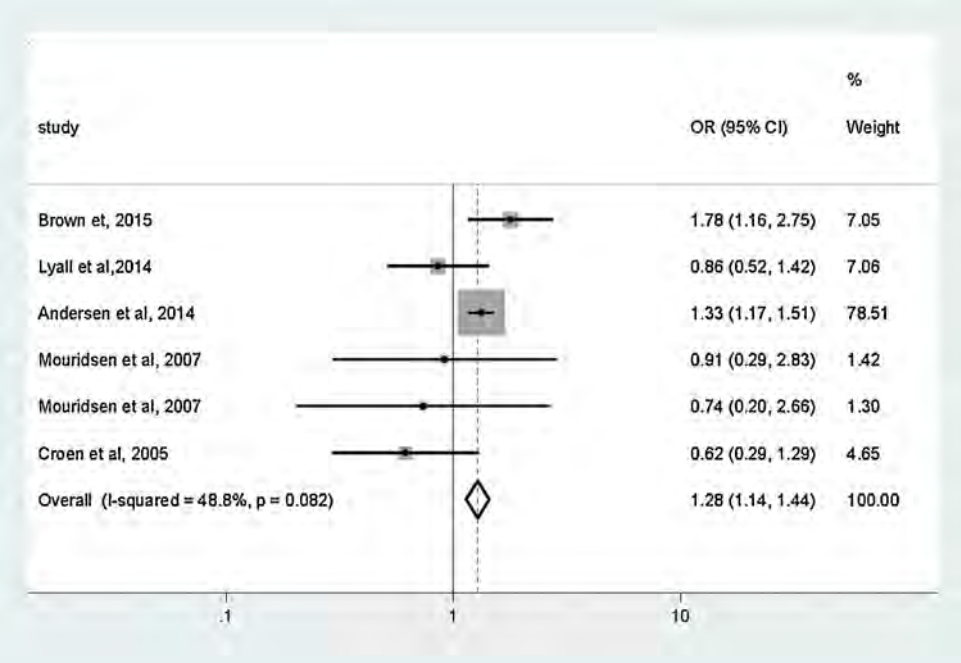

Fig. 4. Forest plot of autism spectrum disorders risk in offspring with maternal autoimmune thyroid disease exposure.

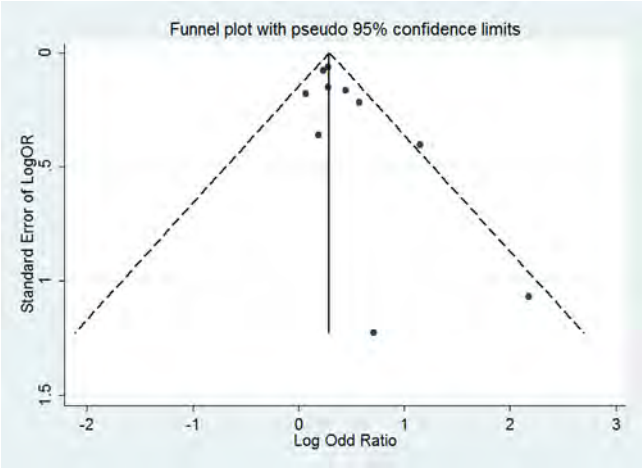

Fig. 5. Funnel plot of overall autism spectrum disorders risk in offspring with maternal autoimmune diseases exposure.

following mechanisms. Firstly, in the area of immunogenetics, children's immune modification at genetic level which may largely be affected by abnormal immune system of mothers during pregnancy has been proved to be involved in occurrence of ASD [26,27]. A serine and threonine kinase C gene namely PRKCB1 which plays an important role in the process of B cell activation has been demonstrated to be concerned in autistic disorder [28]. More specifically, an increasing number of studies have focused on the association between human leukocyte antigen (HLA) genes and the risk of ASD. For example, HLA-DR4, a major susceptibility allele for rheumatoid arthritis, was considered to be associated with an increased risk of ASD in children acting in mothers during pregnancy [29,30]. Secondly, maternal abnormal autoimmunity has adverse impact on fetal brain development through immune mediators including cytokines, T cells and autoantibodies [2,3,26,31]. Microglia, the macrophages of the central nervous system, exerts a role on antigen presence, cytokines production and etc. [2]. Immune mediators form mothers activate microglia in fetal brain after passing through blood-placental barrier and immature blood brain barrier, which in turns activate neuroinflammatory pathways in fetal brain and are inversely associated with fetal brain development [32]. Previous study proved that microglia activated on different degrees in 9 of 13 cases with autism [33]. Even if those efforts mentioned above have been achieved, mechanism concerning association between maternal autoimmune disease and ASD in offspring is not conclusive.

Results from current study showed that maternal autoimmune diseases developed during pregnancy were associated with a 30% increased risk of ASD in offspring. This finding more specifically supported that in utero exposure to abnormal immune mediators resulted from maternal autoimmune diseases may be associated with an elevated risk of ASD in offspring. Maternal autoimmune diseases developed before pregnancy exposure could not be evaluated in this study because only one eligible study [6] could provide enough valid data. The study demonstrated that maternal autoimmune diseases developed before pregnancy was not associated with a materially decreased or increased risk of ASD in offspring after adjusting for several potential risk factors including maternal age, maternal education, maternal race/ethnicity, and plurality (OR, 1.0; 95% CI, 0.6–1.7).

Our findings indicated that maternal autoimmune thyroid disease was associated with an increased risk of ASD in offspring, whereas there were no substantial associations in several other specific kinds of maternal autoimmune diseases including SLE, IBD, ITP, psoriasis and rheumatoid arthritis. However, several pooled results were based on a small number of eligible studies, which should be treated with caution because meta-analysis included small number of studies might undermine its credibility. Future studies are needed to make it clear whether specific maternal autoimmune diseases are associated with ASD in offspring.

There were several strengths in this meta-analysis including no substantial publications bias, robustness across sensitivity analyses and inclusion of 9775 ASD cases and 952,211 controls. However, some potential limitations should be discussed. First of all, eligible studies in this meta-analysis were mostly case-control design, which cannot avoid potential selection bias and recall bias. Second, our findings might be affected by the misclassification of ASD

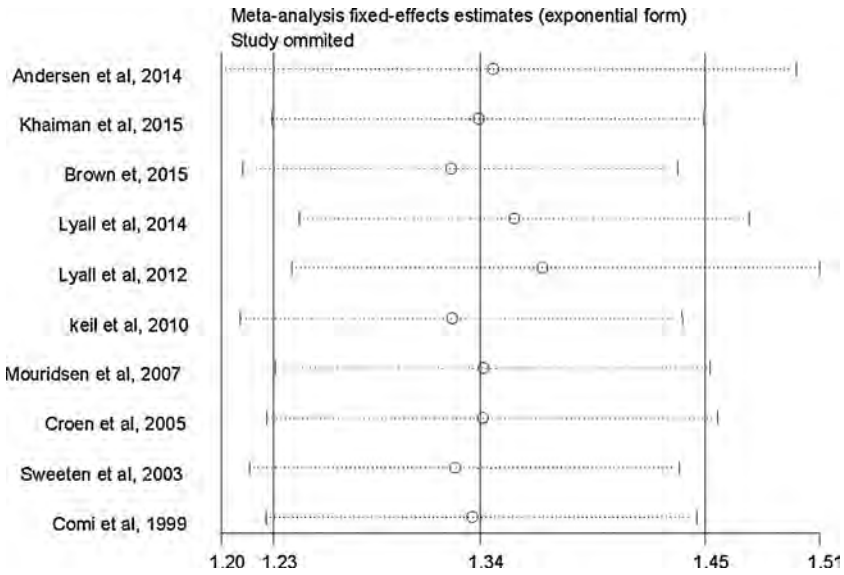

Fig. 6. Plot of sensitive analysis of autism spectrum disorders risk in offspring with maternal autoimmune diseases exposure.

cases because several diagnostic criteria were used for ascertainment of ASD cases in included studies. The criteria for ASD were vacillated over the years and lack of adequate consistence [2]. In addition, we failed to obtain enough data to evaluate the association between specific kinds of maternal autoimmune diseases and ASD in offspring, except for autoimmune thyroid disease.

Two aspects should be attached great importance in future studies. The potential influence of maternal autoimmune diseases developed before pregnancy on ASD in offspring is needed to verify. What is more, because maternal autoimmune diseases consist of numerous kinds of specific diseases, the individual effect of them should be uncovered and confirmed.

In summary, the meta-analysis based on observational studies showed a positive association between maternal autoimmune diseases and ASD in offspring. Maternal autoimmune disease is likely to be an independent risk factor of ASD in offspring. In consideration of methodological weaknesses of case-control studies, additional studies, especially prospective population-based cohort studies, are needed to verify the impact of specific maternal autoimmune diseases on children with ASD.

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