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Review Article

Maternal Infection during Pregnancy and Attention-Deficit Hyperactivity Disorder in Children: A Systematic Review and Meta-Analysis

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Abstract

Background: We aimed to determine the association between maternal infections during pregnancy with risk of Attention-Deficit Hyperactivity Disorder (ADHD) in children.

Methods: A systematic literature search was performed utilizing the online databases PubMed, Scopus, and Web of Sciences up to July 2020. Random-effects meta-analyses were applied to estimate pooled relative risk (RR). Heterogeneity, study quality and publication bias were assessed through I^2 value, Newcastle–Ottawa scale (NOS) and Egger's test, respectively.

Results: Thirteen articles involving 1401904 mother-child pairs were included. The result of meta-analysis showed that the risk of ADHD increased by 30% among children whose mothers took any infections during pregnancy (pooled RR=1.30, 95% CI: 1.14-1.49; I^2=85.5, P<0.001). Overall, the included studies were good in quality and no publication bias was found (*P*=0.23, Egger's test).

Conclusion: Maternal infections during pregnancy might be associated with an increased risk of ADHD in children.

Keywords: Maternal infection; Pregnancy; Disorder; Hyperactivity

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric diagnosis in both children and adults. It affects approximately 5–10% of school-age children (1) with a worldwide prevalence of 7.2% (95% confidence interval [CI]: 6.7 to 7.8) (2). However, it argued that the statistics for the morbidity of ADHD is along with the degree of bias because there is the degree of underestimation and overestimation in these statistics (3, 4). ADHD may be a risk factor for several adverse outcomes in children, youth and adults such as comorbid mood disorders, substance abuse and dependency (5-7), suicidal behavior (8), social and functional impairments

(9), academic performance (10), unintentional injury and mortality (11).

Risk factors of ADHD are the constellation of genetic and environmental factors. Regarding genetic background, several studies aimed to estimate heritability (12) and risk gene identification (13). There are several well-known environmental risk factors for ADHD, e.g. socioeconomic status (14), heavy metals exposures (15), brain injury (16), low birth weight (17) and prenatal smoking (18, 19) and alcohol (20).

One of the prenatal risk factors of ADHD that attracts notable attention is maternal infection during pregnancy (21-23). Several studies have demonstrated that neurodevelopmental disorders may be due to exposure to maternal infection during pregnancy (22, 24, 25). In other words, in utero exposure to infections may influence fetal brain development and following short and long-term effects on function (26). Studies on whether maternal infection during pregnancy may influence the risk of ADHD in children have increased recently and they are still controversial. For example, the findings suggest a null, positive and negative association between maternal infection during pregnancy and ADHD (21-23).

Therefore, we aimed to evaluate the association between maternal infection during pregnancy and the risk of ADHD among children using a systematic review and meta-analysis.

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) (27).

This research was approved by the Research Ethics Committee of Hamadan University of Medical Sciences (Ethical code: IR.UMSHA.REC.1401.662).

Search strategy and Study Selection

Potential articles were retrieved from three electronic databases including PubMed, Scopus and Web of Sciences up to July 2020. The search strategy was created using the following MeSH terms and keywords: ("infection" [Mesh Terms] OR "infection" [All Fields] OR "maternal infection") AND ("Attention Deficit Disorder with Hyperactivity" [Mesh Terms] OR "Attention Deficit Disorder with Hyperactivity" [All Fields] OR "Attention deficit hyperactivity disorder" [All Fields] OR "ADHD" [All Fields] "attention deficit disorder" [All Fields] OR "hyperactivity disorder" [All Fields]) AND ("Pregnancy" [Mesh Terms] OR "Pregnant" [All Fields] OR "Gestational" [All Fields]) AND ("Child" [Mesh Terms] OR "Pediatrics" [Mesh Terms] OR "child" [All Fields] OR "children" [All Fields] OR "children" [All Fields]). Then, this search strategy was modified for search in other electronic databases. The search strategy was restricted to articles in English. The results of initial searches were screened by one author (EA) based on titles and abstract, and then potential eligible articles for inclusion in the systematic review and Meta-analyses were assessed by two authors (EA and KM). Any disagreement was resolved with discussion.

Study eligibility

Observational studies investigating the effect of maternal infection during pregnancy on the ADHD were considered. To be eligible, studies had to report the relative risks (RRs) including odds ratio (OR), risk ratio (RR) and hazard ratio (HR) and their corresponding confidence intervals (CIs) or at least to report data for manually calculating the RRs and CIs. Case reports, small case series, animal and lab studies, reviews, irrelevant original studies, letters and correspondences, editorials, and conference proceedings were excluded.

Data extraction and quality assessment

Data were extracted independently by two authors (EA and KM), with any discrepancies discussed; the extracted data were as follow; first author, year of publication, country, study design, sample size, male % among ADHD cases, age of ADHD cases, type of maternal infection during pregnancy, time of infection ascertainment in the study, the method to confirm maternal infection during pregnancy, the method to ADHD assess-

ment, crude and adjusted RRs and list of confounders in multivariable analyses.

The methodological quality of included cohort and case-control studies was criticized using the Newcastle-Ottawa Scale (NOS) (28) and a modified version of the NOS was used for cross-sectional studies (29). The NOS criticize the quality of each study according to a) selection of study groups (4 items), b) comparability of study groups (2 items) and c) exposure and outcome measurement (3 items). The highest quality study is awarded up to 9 scores. The modified form of NOS assesses the "selection of study groups" in 5 items and the maximum score is 10 for a study. The two authors EA and KM evaluated the quality of included studies separately. Any discrepancies were resolved after discussion and consensus.

Statistical analysis

Heterogeneity across studies was evaluated using I^2 value where I^2 value over 50% was considered as substantial between-study heterogeneity. In case of significant substantial heterogeneity, Pooled RRs with the corresponding 95% CIs were estimated using a random-effects model, otherwise fixed-effect model was used to estimate pooled association. A forest plot was generated to present the results of pooled associations. Since the study outcome was being expected to be rare among both exposed and unexposed, we approximated pooled RRs by ORs and HRs from included studies (30). Publication bias was checked by visual inspection of the funnel plot and Egger's test. All analysis were conducted using Stata SE version 11. P <0.05 was considered as a significant level.

Results

Study selection

Fig. 1 is the PRISMA flow chart of the study selection process. Initial searches yielded 375 potential articles. After removing 42 duplicate records, 333 articles were screened by titles and abstracts, of which 16 articles met the eligibility criteria. Of them, four articles (23, 31-33) were discarded because did not meet eligibility criteria. After an update search, one other article was retrieved and finally, 13 articles (16, 21, 22, 34-43) were considered for the systematic review and of these, 9 articles (16, 21, 22, 36-39, 42, 43) provides adjusted RRs on association between maternal infection during pregnancy and ADHD and they met the criteria for the meta-analysis.

Characteristics of included studies in systematic review

Table 1 present characteristics of included studies in systematic review and meta-analysis. This systematic review included five case control (16, 35, 36, 41, 42), five cohort (21, 22, 37-39) and three cross sectional studies (34, 40, 43) that published in English between 2005 and 2019. The total sample size of included studies in the systematic review was 1401904 with a wide range from 92 (34) to 1,066,956 (38). All of the included studies examined ADHD as the study outcome while in one study (37) considered attention problems as an additional outcome. Five studies (16, 21, 22, 36, 38) ascertained maternal infection in pregnancy period, 6 studies (34, 35, 40-43) at time of ADHD diagnosis, one study (37) at time of delivery, and another in both during pregnancy and postpartum period (39). Maternal infection during pregnancy was assessed with different type of methods e.g. in 9 studies (22, 34-36, 39-43) based on mothers' recall through questionnaires or interviews, in 2 (16, 38) using medical records, in one study (21) with International Classification of Diseases, Ninth Revision (ICD-9) and in another study (36) with examining gestational maternal C-reactive protein (CRP) as a biological marker of maternal infection.

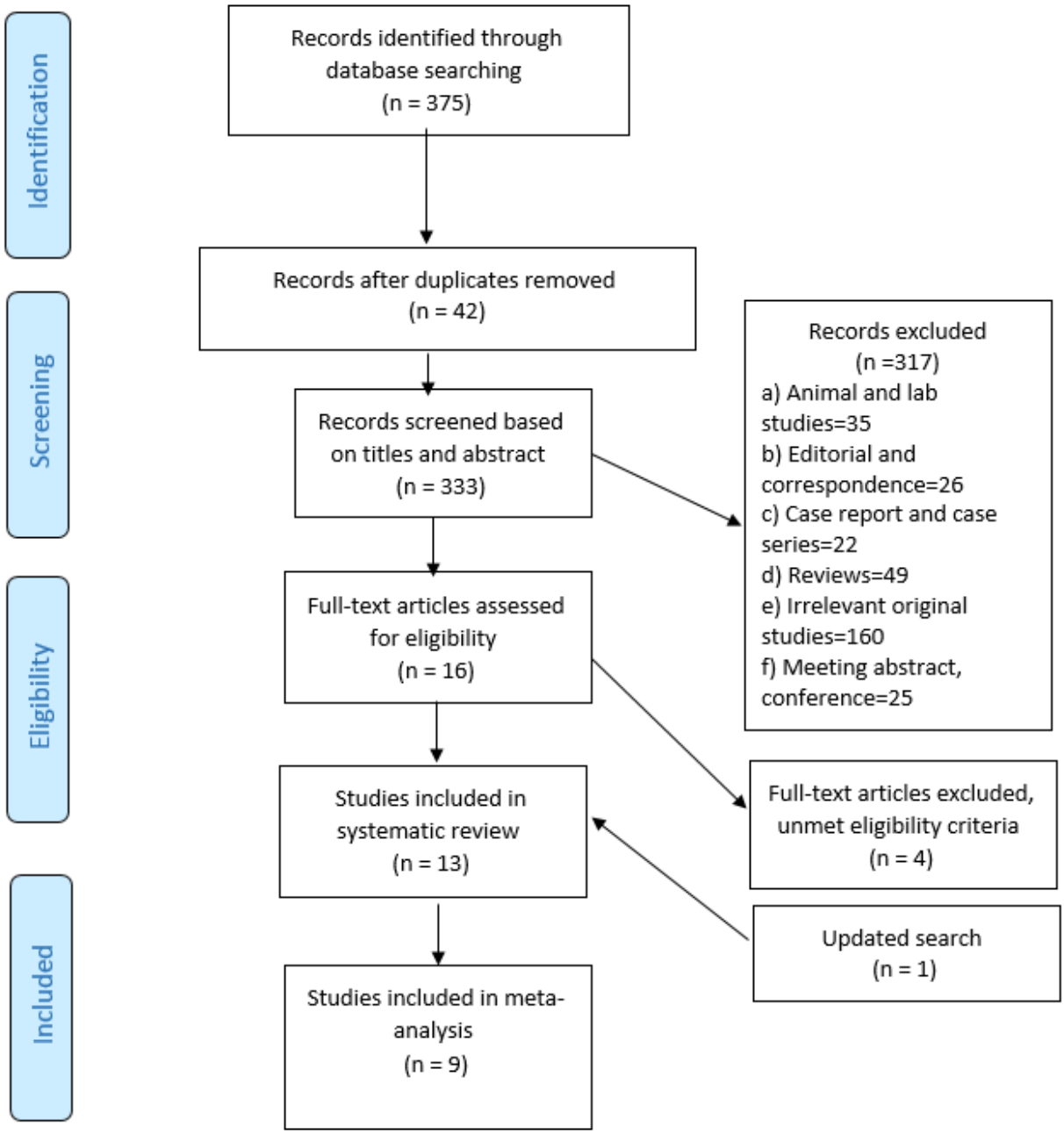

Fig. 1: PRISMA flow diagram showing study selection process

Table 1: Characteristics of included studies in systematic review and meta analyses

First author Year of publication	*Study design*	*Sample size*	*Male % among ADHD cases*	*Age of ADHD cases*	*Infection during pregnancy*	*Method to confirm infection*	*Method to ADHD assessment*	*uRR (95% CI)*	*aRR (95% CI)*
Afsharpaiman 2016 (35)	Cross sectional	92	66.7%	Mean (SD): 8.12 (3.25) years	Unknown infections	questionnaire	DSM-IV-TR	1.00* (0.06, 16.48)	
Arpino 2005 (36)	Case control	189	77.5%	range= 6-11 years	Exanthematic infection (i.e. measles, varicella, or rubella)	questionnaire	DSM-IV-TR	5.26* (0.81, 34.23) ††	
Chudal 2019 (37)	Nested case control	2158	85.4%	Mean (SD): 7.3 (1.9), range: 2-14	Unknown infection	C-reactive protein (CRP) assayed in stored maternal sera	ICD-10 codes F90.0, F90.1, F90.8, F90.9	1.03* (0.95, 1.11)	1.05* (0.96, 1.11)
Downey 2015 (38)	Cohort	826	58%	range: 0-2	Mycoplasma recovered from placenta	interview	DSM-IV-TR		2.3*** (1.1, 4.8)
					Fever			14.83* (4.4, 50.00)	
					Urinary tract infection			16.85* (8.09, 35.07)	
					Vaginal/cervical infection			26.01* (12.48, 54.22)	
					Periodontal disease			24.03* (4.31, 133.76)	
					One organism recovered from placenta	Interview	Child Behavior Checklist (CBCL)-defined attention problem †		2.2*** (1.3, 3.8)
					2+ organisms recovered from placenta		Child Behavior Checklist (CBCL)-defined attention problem †		0.9*** (0.5, 1.7)

					Fever		Child Behavior Checklist (CBCL)-defined attention problem †	14.66* (4.68, 45.88)	
					Urinary tract infection		Child Behavior Checklist (CBCL)-defined attention problem †	17.05* (8.48, 34.28)	
					Vaginal/cervical infection		Child Behavior Checklist (CBCL)-defined attention problem †	12.38* (5.85, 26.16)	
					Periodontal disease		Child Behavior Checklist (CBCL)-defined attention problem †	12.98* (2.14, 156.52)	
Ginsberg 2019 (39)	Cohort	1066956	51.3%		Unknown infections	Medical records	ICD-9 code 314.00, ICD-10 code F90		1.03** (0.76, 1.41)
Gustavson 2019 (40)	Cohort	99947		Mean:11 range (7-17	Fever	questionnaire	ICD-10 code F90.0	1.45 (1.29, 1.62)	1.30 (1.15-147)
Mann 2011 (21)	Cohort	84721	Mean: 6.49	71.9%	Genitourinary infections	ICD-9 codes	ICD-9 codes 314.00 314.01	1.12* (1.07, 1.17)	1.29* (1.23, 1.35)
					Candidiasis			1.01* (0.9, 1.13)	1.22 (1.08, 1.37)
					Chlamydia/NGU			1.1* (0.85, 1.43)	1.47 (1.12, 1.92)
					Gonorrhea			0.83* (0.63, 1.08)	0.99 (0.75, 1.31)
					Trichomoniasis			0.97* (0.85, 1.1)	1.26 (1.10, 1.45)
					Urinary tract infection			1.17* (1.11, 1.24)	1.25 (1.18, 1.33)
					genitourinary infections and preeclampsia				1.53* (1.32, 1.77)
Mellins 2009 (47)	Cross sectional	340			perinatally HIV-infected	questionnaire	DSM-IV-TR	2.45* (1.2, 4.99)	

Oerlemans 2016 (45)	Case control	493	Mean (SD): 11.8 (2.4), range:4 - 20	87.1%	Unknown infections	questionnaire	standardized questionnaires and diagnostic interviews	1.41* (0.31, 6.37)	
Pineda 2007 (43)	Case control	486	Mean (SD): 7.9 (1.5), range:6 -11	74.5%	urinary infections along other physical illness	questionnaire	Diagnostic Interview for Children and Adolescents (DICA) and the Behavior Assessment System for Children (BASC	4.20 *(1.70, 10.0)	5.0 *(2.0, 12.9)
					Severe maternal respiratory infection (flu)			3.3* (1.7, 6.4)	3.1* (1.5, 6.3)
					Syphilis			1.43* (0.14, 13.90)	
					Measles, Varicella, Rubella			2.40* (0.31, 18.35)	
					toxoplasmosis			1.43* (0.14, 13.9)	
Schmitt 2012 (48)	Cross sectional	13488	Mean (SD): 9.8 (4.3), range:3 - 17	78.8%	Unknown infections along other perinatal health problems	Interview	ICD-10 hyperkinetic disorder	1.88* (1.6, 2.22)	1.69* (1.40, 2.03)
Silva 2014 (16)	Case control	43062		77.1%	Urinary tract infection	Medical records	ICD-10 and DSM-IV-TR	1.37* (1.21, 1.54) for male	1.26* (1.11, 1.44) for male
								1.51* (1.21, 1.90) for female	1.33* (1.04, 1.70) for female
Werenberg Dreier 2016 (22)	Cohort	89146			Fever	Interview	ICD-10 codes DF90.0 DF90.9	1.09 (0.99, 1.19)	1.03 (0.93, 1.13)
					Any infection			1.09** (0.99, 1.19)	1.01 ** (0.92, 1.11)
					Genitourinary infections (cystitis, pyelonephritis, vaginal symp-			1.22** (1.11, 1.34)	1.14 ** (1.03, 1.25)

	toms)		
	Persistent viral infections (orofacial herpes infection, genital herpes, condylomas)	1.03** (0.91, 1.16)	1.01 ** (0.89, 1.14)
	Prolong Cough	1.15 (1.03, 1.29)	1.05 ** (0.94, 1.19)
	Diarrhea	1.09 (0.99, 1.20)	0.98 ** (0.89, 1.09)
	Other infection	0.99 ** (0.87, 1.13)	0.97** (0.84, 1.11)

* odds ratio
** hazard ratio
*** risk ratio
† outcome studied is attention problem
†† odds ratio was estimated using adding 0.5 to each cell of 2×2 contingency table

In the all included studies, ADHD was assessed using ICD or Diagnostic and Statistical Manual of Mental Disorders (DSM) while in 2 studies (41, 42) ADHD was confirmed using standardized questionnaires and diagnostic interviews. The results of the quality assessment have demonstrated that overall, the quality of the included study was good e.g., the NOS score of studied included in the meta-analyses was equal to or above 7. The detail of quality assessment is presented in Table 2.

Association between maternal infection during pregnancy and ADHD

Using a random-effects model with adjusted RRs from 8 eligible studies (16, 21, 22, 36-38, 42, 43) that aimed to evaluate association between maternal infection during pregnancy and ADHD (not including fever), a pooled RR (95% CI of 1.30 (1.14, 1.49) have been yielded (I^2=85.5%, p<0.0001) (Fig. 2) and evidence of symmetric funnel plot and no publication bias (p=0.23, Egger's test, *P*-value=0.23 and Begg's test, *P*-value=0.32) (Fig. 3). The pooled effect estimate did not change when adding adjusted RR for fever during pregnancy from Gustavson et al. (39) to the meta-analysis (overall RR=1.30; 95% CI=1.15, 1.46; I^2=84.1%, *P*-value<0.001) (Forest plot not shown).

Table 2: Results of the quality assessment

Author (yr)	***Items***								***Total NOS stars***
	Selection				Comparability	Outcome/exposure			
Cohort	1	2	3	4	5	6	7	8	
Downey (2015)	*	*	*	*	*	*	*		*******
Ginsberg (2019)	*	*	*	*	**	*	*	*	**********
Gustavson (2019)	*	*		*	**	*	*	*	********
Mann (2011)	*	*	*	*	**	*	*		********
Werenberg Dreier (2016)	*	*		*	**	*	*		*******
Case controls									
Oerlemans (2016)	*	*	*	*	**	*	*		********
Pineda (2007)	*	*	*	*	**		*		*******
Silva (2014)	*	*	*	*	**	*	*	*	*********
Arpino (2005)	*	*	*	*	*		*		******
Chudal (2019)	*	*	*	*	**	*	*		********
Cross sectional studies									
Afsharpaiman (2016)				**	*	*			****
Mellins (2009)		*		*	**	*	*		******
Schmitt (2012)	*	*		*	**	**	*		********

Cohort studies: 1. Representativeness of the exposed cohort, 2. Selection of the non-exposed cohort, 3. Ascertainment of exposure, 4. Demonstration that outcome of interest was not present at start of study, 5. Comparability of cohorts on the basis of the design or analysis controlled for confounders, 6. Assessment of outcome, 7. Was follow-up long enough for outcomes to occur, 8. Adequacy of follow up of cohorts

Case control studies: 1.Is the case definition adequate?, 2. Representativeness of the cases, 3. Selection of Controls, 4. Definition of Controls, 5. Comparability of cases and controls on the basis of the design or analysis, 6. Ascertainment of exposure, 7. Same method of ascertainment for cases and controls, 8. Non-Response rate

Cross sectional studies: 1. Representativeness of the sample, 2. Sample size, 3. Non-respondents, 4. Ascertainment of the exposure (risk factor), 5. The subjects in different outcome groups are comparable, based on the study design or analysis, 6. Assessment of the outcome, 7. Statistical test

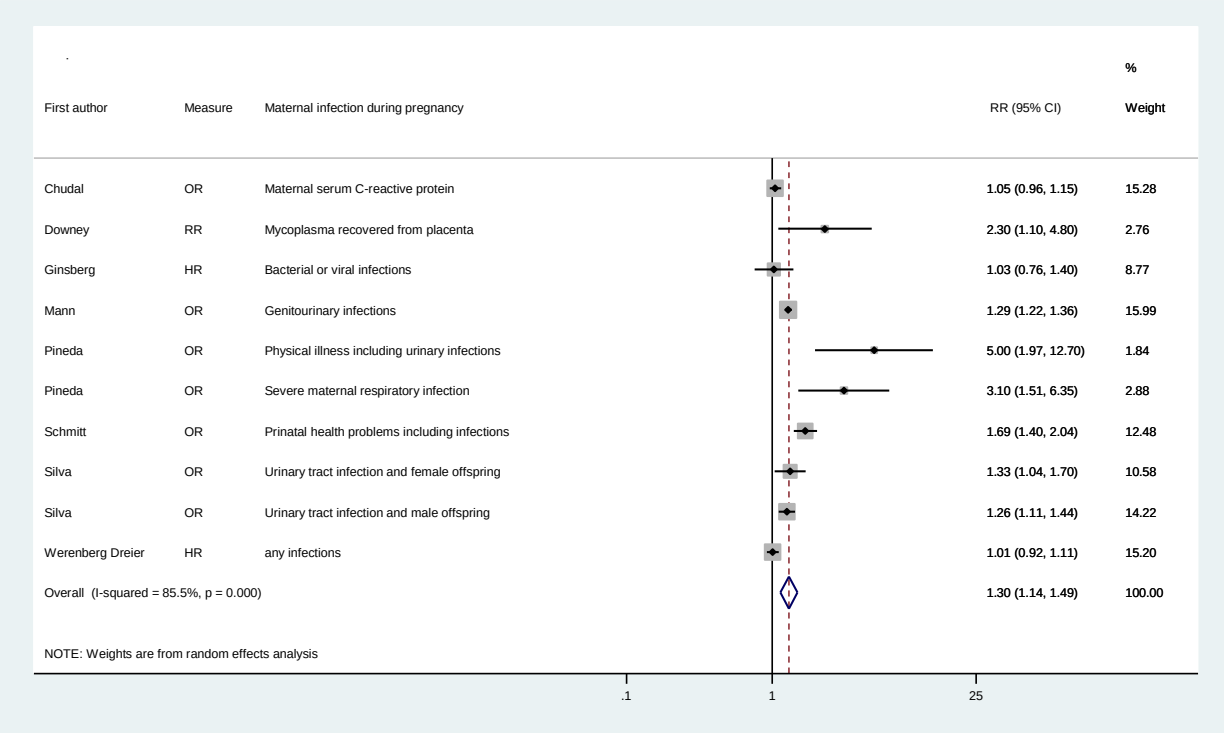

Fig. 2: The overall effect of maternal infection during pregnancy on the risk of ADHD in children

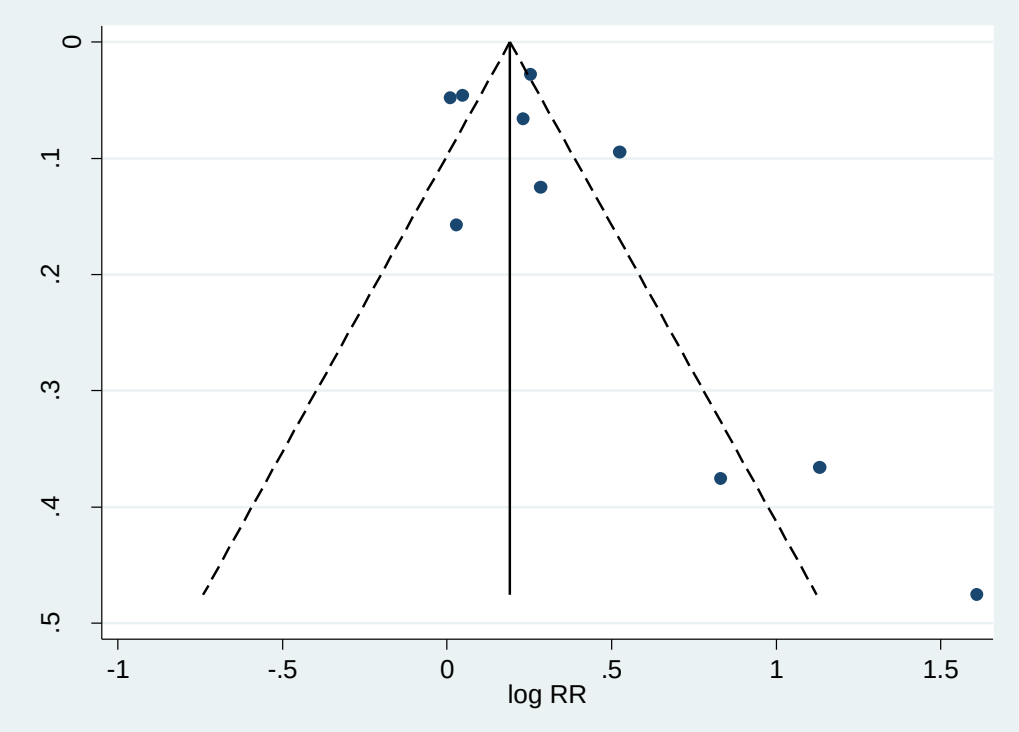

Fig. 3: Funnel plot assessment of publication bias

Discussion

The present study aimed to review systematically and meta-analysis published studies evaluating the effect of maternal infection during pregnancy on the risk of ADHD in children. Our pooled analysis from observational studies results suggests that maternal infection during pregnancy was significantly associated with a 30% increased risk of ADHD in the children.

Although the biological mechanisms underlying the association between maternal infection during pregnancy and ADHD still not completely defined, however, the finding from both animal studies (26) and observational studies on the association between maternal infection during pregnancy and neurodevelopmental disorders (24, 25) suggested that maternal infection during pregnancy might disrupt some aspects of fetal brain development and the children's function.

The pooled effect measures from meta-analysis of observational studies should be interpreted with caution due to ignoring the many possible sources of biases. Here, we acknowledge that the estimated pooled RR for the association between maternal infection during pregnancy and ADHD may be different from that in reality due to several reasons. First, among the included studies especially in case-control studies, the information about maternal infection during pregnancy was measured by mothers' recall. This increase the risk of a special type of misclassification bias, known as recall bias. In other words, mothers of children with ADHD are likely to remember infections they took during pregnancy differently than mothers of normal children. Second, the multivariable model across the included studies for evaluating the association between maternal infection during pregnancy and ADHD were heterogonous and most of them did not consider all potential covariates in maternal infection during pregnancy-ADHD pathway.

It argued that potential covariates in maternal infection during pregnancy-ADHD pathway can be as follow; maternal education, calendar year of birth, pre-pregnancy body mass index (BMI), children in household, maternal history of psychiatric disease, maternal age, maternal stress, maternal smoking, birth weight, gestational age at birth, antipyretics (22). Some of them are potential confounders; covariates affecting both maternal infections during pregnancy and ADHD e.g. maternal age and pre-pregnancy BMI, and some others are mediators; covariates that are more likely affected by the maternal infection during pregnancy e.g. birth weight. Of included studies, some studies e.g. Ginsberg et al. (38) and Werenberg Dreier et al. (22) have attempted to adjust possible potential covariates. Finally, in some cases, maternal infection included in meta-analyses as a composite variable. For example in Pineda et al. study (42) maternal infection was evaluated with other exposures e.g. with other physical illness. Here, it is not known how large a proportion of the exposed is truly exposed to infections.

We considered fever during pregnancy from Gustavson et al. study (39) because they have mentioned that infection is the most common cause of fever and they have no attempted to identify microbial causes of fever. Hence, we still believe that the association between fever and other maternal infection indicators during pregnancy and ADHD in children should be evaluated in an independent and comprehensive systematic review with considering issues such as dose response association, episodes in different trimester etc.

Among the included studies, most infection during pregnancy was genitourinary infection. In a study (44), maternal genitourinary infections during pregnancy were important risk factors for autism spectrum disorders in children. Genitourinary infection is a composite variable; however, the risk of ADHD may be different across various genitourinary infections because various pathogens may have specific effects on the risk of ADHD. Since most genitourinary infections are bacterial, general immune activation measures including CRP and cytokines (interleukins) may be more trigged and those resulted in changes in brain morphology (45). On the other hands, genitourinary infections may mediate several factors

such as low birth weight (LBW) (46) which is well-established risk factor for ADHD (47).

We found the association between maternal infection during pregnancy and ADHD to be similar to other meta-analysis that evaluated the association of maternal infection during pregnancy with adverse outcomes in children such as with autism spectrum disorders (pooled OR=1.13, 95% CI: 1.03-1.23) (44) type 1 diabetes mellitus (pooled OR=1.31, 95% CI: 1.07, 1.62) (48), fetal congenital heart diseases (pooled OR, 2.28; 95% CI: 1.54, 3.36) (49), stillbirth (pooled RR=2.36, 95% CI: 1.05-5.31) and low birth weight (RR=1.71, 95% CI: 1.03-2.84) (50).

Our study had several strengths: The systematic review and meta-analysis include over 1,400,000 mother-child pairs that resulted in pooled measures with high precision. However, our study has several limitations that should be considered. The degree of selection bias may exist in this systematic review because the initial search may not be comprehensive coverage of all potential literature. For example, of included studies, there were few studies from low and middle-income countries or we included only literature in English. Moreover, it is needed the results to be updated with including published articles during 2020 and 2021. Another limitation is that no information was available on several important variables such as type of infection, maternal infection during the different trimester etc. Finally, pooled estimates from Meta-analysis of observational studies do not necessarily reflect causal associations.

Conclusion

There was a significant increase in the risk of ADHD among children whose mothers took infections during pregnancy. Future larger and unbiased researches are needed to explore the association between various infectious agents and risk of ADHD separately. Moreover, the association between maternal infection during pregnancy and other neurodevelopmental disorders should be studied.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interests

The authors declare that they have no competing interests.

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