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RESEARCH ARTICLE

Prenatal maternal infection and risk for autism in offspring: A meta-analysis

Nina Tioleco[1,2] | Anna E. Silberman[2] | Katharine Stratigos[1] | Sharmila Banerjee-Basu[3] | Marisa N. Spann[4] | Agnes H. Whitaker[1,2] | J. Blake Turner[1,2]

[1]Division of Child and Adolescent Psychiatry, Columbia University Irving Medical Center, New York, New York, USA

[2]Division of Child and Adolescent Psychiatry, The New York State Psychiatric Institute, New York, New York, USA

[3]MindSpec Inc., McLean, Virginia, USA

[4]Department of Psychiatry and Pediatrics, Columbia University Irving Medical Center, New York, New York, USA

Correspondence
J. Blake Turner, New York State Psychiatric Institute, 1051 Riverside Drive, Box 78, New York, NY 10032, USA.
Email: blake.turner@nyspi.columbia.edu

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Abstract

While prenatal maternal infection has received attention as a preventable and treatable risk factor for autism, findings have been inconsistent. This paper presents the results of a meta-analysis to determine whether the weight of the evidence supports such an association. Studies with a categorical diagnosis of autism as the outcome and an assessment of its association with prenatal maternal infection or fever (or the data necessary to compute this association) were included. A total of 36 studies met these criteria. Two independent reviewers extracted data on study design, methods of assessment, type of infectious agent, site of infection, trimester of exposure, definition of autism, and effect size. Analyses demonstrated a statistically significant association of maternal infection/fever with autism in offspring (OR = 1.32; 95% CI = 1.20–1.46). Adjustment for evident publication bias slightly weakened this association. There was little variation in effect sizes across agent or site of infection. Small differences across trimester of exposure were not statistically significant. There was some evidence that recall bias associated with status on the outcome variable leads to differential misclassification of exposure status. Nonetheless, the overall association is only modestly reduced when studies potentially contaminated by such bias are removed. Although causality has not been firmly established, these findings suggest maternal infection during pregnancy confers an increase in risk for autism in offspring. Given the prevalence of this risk factor, it is possible that the incidence of autism would be reduced by 12%–17% if maternal infections could be prevented or safely treated in a timely manner.

Lay Summary: This study is a meta-analysis of the association of maternal infection during pregnancy and subsequent autism in offspring. In combining the results from 36 studies of this association we find that a significant relationship is present. The association does not vary much across the types of infections or when they occur during pregnancy. We conclude that the incidence of autism could be substantially reduced if maternal infections could be prevented or safely treated in a timely manner.

KEYWORDS
autism, infections, pregnancy, prenatal, risk factors

INTRODUCTION

The neurodevelopmental bases for the autism syndrome (American Psychiatric Association, 2013), together with marked increases in prevalence in recent years (National

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Center on Birth Defects and Developmental Disabilities, 2020 has stimulated an extensive body of research on early environmental exposures that might be targets for preventive intervention. Among the prenatal maternal exposures that have been studied (Gardener et al., 2009, 2011; Ornoy et al., 2015), maternal infection during pregnancy has been a particular area of interest. This interest has been motivated, in part, by early findings of a strong association of in utero rubella exposure with autistic behaviors (Chess, 1971, 1977). It has also been motivated by evidence that the sequelae of infection (e.g., immune response, inflammation) impact brain development (Meyer et al., 2006; Rudolph et al., 2018; Smith et al., 2007). The inverse association of maternal levels of inflammatory cytokines during pregnancy with early offspring cognition (Rasmussen et al., 2019) also emphasizes the potential importance of intrauterine conditions for the development of neuropsychiatric disorders.

Research on autism risk resulting from maternal infections during pregnancy has included analyses of effect heterogeneity across types of infectious agent and sites of infection. The timing of exposure has also been considered because of the different stages of brain development that occur across gestation—primary neurulation and neural tube formation (early gestation), neuronal proliferation and migration (mid-gestation), and organization (late gestation) (Volpe, 2008).

A few systematic reviews and meta-analyses have attempted to summarize this research. One systematic review (2015) concluded that the risk for autism spectrum disorder (ASD) in offspring did not vary by the agent of infection but did depend upon infection severity, as marked by admission to hospital. A meta-analysis of 11 studies of prenatal maternal infection (Gardener et al., 2009) found a small elevation in the odds of autism and a comparatively large confidence interval (Odds Ratio = 1.18; 95% Confidence Interval = 0.76–1.83). The investigators report a much stronger effect-size in the four studies that adjusted for covariates but did not report which covariates were included, nor which were responsible for the apparent suppression of the maternal infection-autism association. Greater precision was obtained in a later and more comprehensive meta-analysis (Jiang et al., 2016), but the documented association was still quite small (OR = 1.13; 95% CI = 1.03–1.23). This study found little variability in effect sizes across agents or sites of infection but reported some heterogeneity across trimester for infections in general.

This paper presents an up-to-date meta-analysis of studies examining the prenatal maternal infection-autism association. A number of studies have been published since the reviews cited above, and we also included studies that examined fever as a risk factor for autism. Fever is associated with many different types of infection and hyperthermia during pregnancy is known to influence fetal neurodevelopment—severe brain damage has been observed in animal models (Edwards, 1986; Edwards et al., 2003; Hinoue et al., 2001) and neuro tube defects and neurodevelopmental psychopathology has been observed in humans(Kerr et al., 2017; Milunsky et al., 1992; Werenberg Dreier et al., 2016).

Our meta-analysis represents an advancement over previous reviews and meta-analyses in three additional ways: (1) We took care that all effect-sizes combined into a single result were independent of one another; that is, we did not combine effect-sizes computed for different exposures within a single study; (2) We tested for effect heterogeneity across agents of exposure, sites of exposure, timing of exposure, and exposure timing within exposure types; (3) We tested for differences in effect sizes across different methods, particularly differences in the methods of assessment of exposure to maternal infections. Because this meta-analysis spans time periods over which DSM diagnostic definitions have changed and includes research outside of the United States that use International Classification of Diseases definitions, we use the generic term "autism" rather than the DSM-5 designation "Autism Spectrum Disorder."

METHODS

This report is formatted in accordance with the PRISMA statement (Moher, Liberati, Tetzlaff, Altman,, & Group, 2009).

Study selection

We conducted a search of the PubMed and Google Scholar databases, using the search algorithms displayed in Figure S1, and requiring publication in English. Two of us (N. T. and A. E. S.) independently examined each paper to determine eligibility. Selection for inclusion in the meta-analysis required that the study had a categorical diagnosis of autism as the outcome and contained at least one measure of the association of prenatal maternal infection or fever with the diagnosis (or the data necessary to compute this association). Figure 1 displays the PRISMA flow chart documenting the basis for the exclusion of articles. The reference lists of the included articles were manually searched for additional articles meeting our criteria. A total of 36 papers were ultimately used in the meta-analysis, the most recent of which was published in March of 2019.

Data extraction

The information extracted from each paper included study design (cohort or case-control), method of ascertaining exposure, the infectious agent examined and/or the site of the infection, the trimester during which infection occurred, and the operational definition of autism,

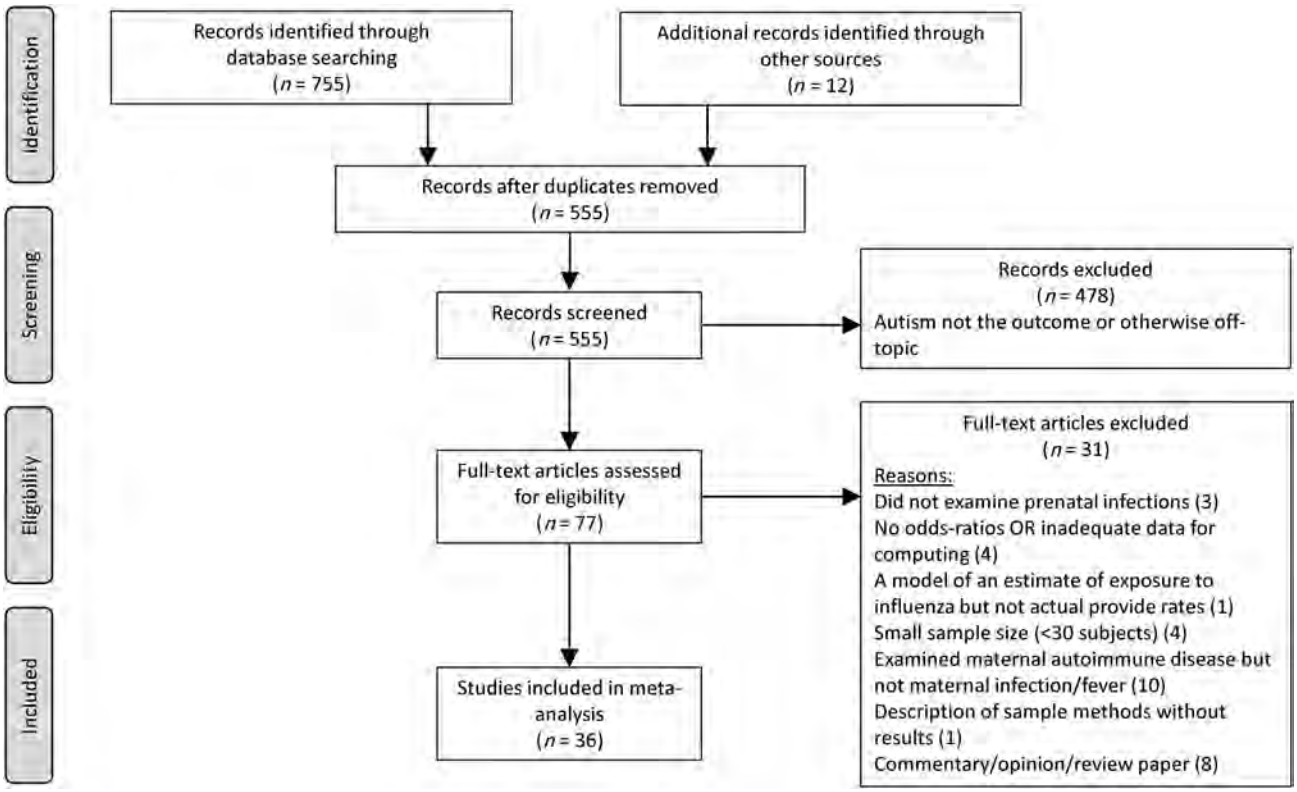

FIGURE 1 PRISMA flow diagram for the article selection process

including whether certain subsets of cases were distinguished (e.g., cases with and without intellectual disability [ID]). Table 1 lists the included studies (Abdallah et al., 2012; Al-Haddad et al., 2019; Atladottir et al., 2010, 2012; Bilder et al., 2009; Brucato et al., 2017; Buchmayer et al., 2009; Christian et al., 2018; Comi et al., 1999; Deykin & MacMahon, 1979; Dodds et al., 2011; Duan et al., 2014; Fang et al., 2015; George et al., 2014; Glasson et al., 2004; Grossi et al., 2016; Guisso et al., 2018; Hisle-Gorman et al., 2018; Hornig et al., 2017; Isaksson et al., 2017; Joseph et al., 2017; Langridge et al., 2013; Lee et al., 2015; Limperopoulos et al., 2008; Lydholm et al., 2018; Maimburg & Vaeth, 2006; Mamidala et al., 2013; Mann et al., 2010; Mrozek-Budzyn et al., 2013; Oerlemans et al., 2016; Spann et al., 2016; Visser et al., 2013; Zerbo et al., 2013, 2015, 2017; Zhang et al., 2010) and summarizes the characteristics abstracted from each. In all tables and figures in the paper, each included study is identified by the surname of the first author and the publication year. Full lists of authorship are, of course, provided in the reference section.

Analysis procedures

Odds ratios and 95% confidence intervals for the association of maternal infection or fever during pregnancy and autism in offspring are graphically displayed using forest plots; odds ratios representing the weighted combination of these associations are also included. Initial analyses pooled all types of exposure into an analysis of the impact of any maternal infection or fever during any point of the pregnancy. When a given study examined multiple exposures, the effects were combined taking care not to let individuals be represented in the exposed group more than once. When maternal fever was one of many exposures examined in a particular paper, we did not include it in the combined analysis under the assumption that one of the other exposures considered may have been the source of the fever. Fever was included in the combined analysis if it was the only exposure considered in a given study. Fever also has its own separate analysis and forest plot as a separate exposure category.

Additional analyses compared effects across subtypes of exposure. Separate plots were generated dividing exposures by agent of infection, site of infection, and trimester of exposure. The analyses of agent of infection and locus of infection are mutually exclusive except in the case of some genitourinary infections for which the agent was also provided. These instances were included in both the "by agent" and "by site" analyses. Design characteristics of the studies (cohort vs. case-control studies), subtypes of autism (e.g., with and without ID), and measure of exposure to infection (e.g., retrospective self-report vs. hospital record) were also considered as potential moderators of the strength of association across studies.

TABLE 1 Characteristics of included studies

Cohort studies								
Author	**Year**	**Study design**	**Total N**	**N of autism cases**	**Timing of exposure**	**Agent/site/fever**	**Autism assessment**	**Age of autism assessment**
Al-Haddad	2019	Cohort	1,337,935	3206	Whole pregnancy	Any infection and urinary tract infection	ICD-9 (299A and 299B) (World Health Organization, 1988) and ICD-10 (F840, F841, F844, F843, F845, F848, F849) (World Health Organization, 2004) diagnosed during an inpatient hospitalization in the Swedish population-based birth registry.	Variable—birth registry linked to medical records followed over time.
Atladottir	2010	Cohort	1,612,342	10,133	Trimester and whole pregnancy	Multiple agent, multiple site	ICD-8 (299.00, 299.01, 299.02, 299.03) (World Health Organization, 1965) and ICD-10 (F84.0, F84.1, F84.5, F84.8, F84.9) in the Danish Psychiatric Central Register. They had been admitted as an inpatient or been in outpatient care with a diagnosis in the autism spectrum. Children, who are suspected to have ASDs, are referred by general practitioners or school psychologists to a child psychiatric clinic where they are diagnosed and treated by a psychiatrist.	Variable—diagnoses from national case registry
Atladottir	2012	Cohort	96,736	976	Trimester and whole pregnancy	Multiple agent, multiple site, fever, use of antibiotic	ICD-10 (F84.0, F84.1, F84.5, F84.8, and F84) in Danish Psychiatric Central Register. Diagnosis made by a psychiatrist.	Variable—diagnoses from national case registry
Dodds	2011	Cohort	129,733	924	Whole pregnancy	Multiple agent, multiple site, fever	ICD-9 (299) or ICD-10 (84) in one of three Nova Scotia administrative health databases—a physician billing database, a hospital discharge database, and an outpatient mental health database. A child with a single ASD code before age 2 was considered a noncase.	Age 2–15 years
Hornig	2017	Cohort	95,754	583	Trimester and whole pregnancy	Fever	MoBa screening (Magnus et al., 2006) and, annual linkages to Norwegian Patient Registry then DSM-IV-TR (American Psychiatric Association, 2000) or ICD-10 F84.	Age(s) 3, 5, and 7 years
Joseph	2017	Cohort	840	59	Whole pregnancy	Multiple site, fever, use of antibiotic	Screened with SCQ (Rutter et al., 2003) with a score greater than or equal to 11, then ADIR (C. Lord et al., 1994) and then ADOS-2 (C Lord et al., 2012). All ADOS-2 administrations were video recorded and independently scored by a second rater who did not have knowledge of the child's SCQ and ADI-R results. In cases of ADOS-2 scoring disagreements, a consensus score was reached after review and discussion.	Age 10 years

(Continues)

TABLE 1 (Continued)

Cohort studies								
Author	**Year**	**Study design**	**Total N**	**N of autism cases**	**Timing of exposure**	**Agent/site/fever**	**Autism assessment**	**Age of autism assessment**
Langridge	2013	Cohort	383,153	1179	Whole pregnancy	Urinary tract infection	DSM-IIIR (American Psychiatric Association, 1987), DSM-IV (American Psychiatric Association, 1994) and DSM-IV-TR in (1) the Disability Services Commission of Western Australia (WA) (the government agency that is the primary service provider and assessment agency for children with ASD and/or ID); (2) the WA Register of Autism Spectrum Disorders, a prospective surveillance system of newly diagnosed cases since 1999 [52]; and (3) a retrospective data set based on a comprehensive audit and individual case note review of all ASD cases born in WA between 1984 and 1995 and diagnosed by 1999.	Variable—diagnoses from case registries
Lee	2015	Cohort	2,371,403	24,414	Trimester and whole pregnancy	Multiple agent, multiple site	ICD-9 (299), ICD-10 (F84), and DSM-IV (299) in (1) the National Patient Register; and regional registers including (2) the Habilitation Register; (3) the Clinical Database for Child and Adolescent Psychiatry; (4) the VAL database recording all inpatient and outpatient health services usage in Stockholm County since 1997.	Variable—diagnoses from case registries
Limperopoulos	2008	Cohort	91	23	Whole pregnancy	Fever, chorion/amnion	M-CHAT (Robins et al., 2001) cutoff ≥2 critical items or 3+ total items.	Age 18–24 months adjusted for prematurity
Lydholm	2018	Cohort	NA	NA	Whole pregnancy	Any infection	ICD-10 (F84.0, F84.1, F84.5, F84.8, F84.9) from the Danish Psychiatric Central Research Registry. Diagnosis from an inpatient admission, outpatient contact or psychiatric emergency department contact.	Variable—followed national cohort
Mahic	2017	Cohort	348	338	Whole pregnancy	Influenza	Parent questionnaire screening, professional and parental referrals, annual linkages to the Norwegian Patient Register, or diagnosed at the Autism Birth Cohort Clinic nested within the Norwegian Mother and Child Cohort Study (MoBa).	Parent questionnaire screening done at 3, 5, and 7 years
Mann	2010	Cohort	87,677	472	Whole pregnancy	Genitourinary	ICD-9 (299, 299.0, 299.1, 299.8, 299.9) in Medicaid billing data and receiving services from the South Carolina Department of Disabilities and Special Needs (DDSN) for autism. The diagnosis of ASD had to be from at least two different healthcare professionals.	Not reported

(Continues)

TABLE 1 (Continued)

Author	Year	Study design	Total N	N of autism cases	Timing of exposure	Agent/site/fever	Autism assessment	Age of autism assessment
Cohort studies								
Zerbo	2017	Cohort	196,929	3101	trimester and whole pregnancy	influenza	ICD-9 (299.0, 299.8, 299.9) on at least 2 occasions in Kaiser Permanente medical record over follow-up period.	Variable - oldest subjects age 15 at end of follow-up.
Case-control studies								
Abdallah	2012	Case-control	820	414	Whole pregnancy	Any infection	ICD-10 (F84.0, F84.1, F84.5, F84.8, F84.9) and ICD-8 (299.00, 299.01, 299.02, 299.03) in Danish Psychiatric Central Register.	Variable—diagnoses from national case registry
Bilder	2009	Case-control—nested	100	132	Whole pregnancy	Genital herpes	Two-stage procedure. (1) Trained abstractors identified potential cases from two record sources—health records and school records for the subset of children receiving special educational services. (2) A team of clinicians reviewed the selected records and made diagnoses using DSM-IV-TR criteria for autistic disorder, Asperger disorder, and pervasive developmental disorder, not otherwise specified.	Age 8 years
Brucato	2017	Case-control—nested	988	116	Trimester and whole pregnancy	Influenza, fever, genitourinary	ICD-9 (299.00, 299.01, 299.80, 299.81, 299.90, or 299.91) at least once in the child's medical record. Sensitivity analysis: ASD had to be recorded on at least two separate occasions.	Variable—study nested within a longitudinal birth cohort
Buchmayer	2009	Case-control	6080	1216	Whole pregnancy	Any infection	ICD-9 or ICD-10 in the Hospital Discharge Registry.	Before 10 years old
Christian	2018	Case-control—one-to-one matched	298	298	Whole pregnancy	Fever or infection	Cases identified from University of West Indies Jamaica Autism Database (diagnoses based on DSM-IV_TR and CARS; Schopler et al., 2002). Each case was reassessed using the ADOS and the ADI-R.	Age 2–8 years old
Comi	1999	Case-control	46	61	Whole pregnancy	Any infection	Self-identified and were associated with the East Tennessee Chapter of the Autism Society of America.	Not reported

Author	Year	Study design	N of controls	N of autism cases	Timing of exposure	Agent/site/fever	Autism assessment	Age of autism assessment
Duan	2014	Case-control	286	286	Whole pregnancy	Any infection	Children were screened for autism using the Autism Behavior Checklist (ABC) (Krug et al., 1980). Those children identified by the screen (scoring at least a 53 on the ABC) were then evaluated by two experienced clinicians. Diagnosis was confirmed using DSM-IV criteria and obtaining the childhood autism diagnostic critical value on the Child Autism Rating Scale (CARS).	Age 3–7 years old
Deykin	1979	Case-control—sibling matched	355	183	Whole pregnancy	Multiple agent, multiple site, fever with infection	Retrospective report of parents about child's behavior before the age of six. Children exhibiting impairments in relatedness to the environment, stereotypy, and impairments in language development were classified as totally autistic; those whose symptoms were limited to one or two areas were classified as partially autistic.	Before 6 years old
Fang	2015	Case-control	16,734	4184	Trimester and whole pregnancy	Multiple agent, multiple site	Cases identified from a national insurance database; ICD-9 (299.0X) diagnosed at two or more outpatient visits.	Average ages at the first ASDs diagnosis for children with birth year of 2000–2004 were 3.98, 3.67, 3.27, 2.99, and 2.58.
George	2014	Case-control	200	143	Whole pregnancy	Multiple site, use of antibiotics	Patients in a single autism clinic who had a CARS score greater than or equal to 30.	Age 2–6 years old
Glasson	2004	Case-control	1313	465	Whole pregnancy	Urinary tract infection	Cases identified from one of five diagnostic centers. Cases identified prior to 1997 were reassessed by a 1997 were reassessed by a pediatric registrar using DSM criteria. Cases identified between June 1997 and 1999 required agreement from multiple clinicians so were not independently reassessed.	Not reported
Grossi	2016	Case-control	68	45	Whole pregnancy	Fever	Clinician diagnosis using DSM-5 (American Psychiatric Association, 2013) criteria, independently confirmed by child psychiatrist.	Not reported
Guisso	2018	Case-control	178	136	Whole pregnancy	Any infection, fever, influenza, use of medication	Clinician diagnosis of DSM-IV or DSM -V; Pervasive Developmental Disorder-Not Otherwise Specified and Asperger's excluded.	Not reported

(Continues)

TABLE 1 (Continued)

Author	Year	Study design	N of controls	N of autism cases	Timing of exposure	Agent/site/fever	Autism assessment	Age of autism assessment
Hisle-Gorman	2018	Case-control	26,280	8760	Whole pregnancy	Any infection	Cases identified from family medical records in a military health system database. ICD-9 code for ASD required on two separate encounters with the system to be included.	Age 2–18 years
Isaksson	2017	Case–control - sibling matched	209	206	whole pregnancy	viral and bacterial infections, use of antibiotic	Parent reported	Before 10 years
Maimburg	2006	Case-control	4730	473	Whole pregnancy	Fever, urinary tract infection	ICD-8 and ICD-10 diagnosis of infantile autism in Danish Psychiatric Central Register.	Average age at diagnosis for infantile autism was 4.57 years
Mamidala	2013	Case-control	942	471	Whole pregnancy	Multiple site	Case ascertainment from cooperating psychiatry departments and autism treatment centers across India.	Age 2–10 years old
Mrozek-Budzyn	2013	Case-control	192	96	Whole pregnancy	Any infection, fever, vaginitis, use of antibiotic	ICD-10 (F84.0 and F84.1) in the medical records from a psychiatric outpatient clinic for children by a child psychiatrist.	Not reported
Oerlemans	2016	Case-control	408	288	Whole pregnancy	Any infection	Case families recruited from child psychiatric and pediatric clinics, and from the Dutch Autism Association. Cases and controls subsequently phenotyped using the ASQ (Squires et al., 1997) and the ADI-R.	Not reported
Spann	2016	Case-control—one-to-one matched	874	874	Whole pregnancy	Toxoplasmosis	ICD-10 (F84.0) during psychiatric hospital admissions and outpatient visits from the Finnish Hospital and Outpatient Discharge Registry.	Variable—diagnoses from registry
Visser	2013	Case-control	311	196	Whole pregnancy	Any infection	Screening using ESAT (Swinkels et al., 2006) (score greater than or equal to 3) and/or for whom there were major concerns regarding social and communicative development. Diagnostic protocol consisted of medical and developmental history, semi-structured parent–child play observation, psychiatric evaluation, ADOS and ADIR were used by at least two highly experienced clinicians, a child psychiatrist and a psychologist, achieved consensus best-estimate clinical diagnostic classifications.	Screening of enrolled children between 12 and 40 months. Diagnosis between 43–98 months.

(Continues)

TABLE 1 (Continued)

Author	Year	Study design	N of controls	N of autism cases	Timing of exposure	Agent/site/fever	Autism assessment	Age of autism assessment
Zerbo	2013	Case-control	421	538	Trimester and whole pregnancy	Any infection, fever, multiple agent, use of medication	Cases identified from state developmental services centers and multiple clinical settings. Cases and controls subsequently assessed using the ADOS and the ADI-R.	Age of initial diagnosis not reported. Cases and controls assessed with ADOS and ADI-R between 2 and 5 years of age.
Zerbo	2015	Case-control	2075	407	Trimester and whole pregnancy	Multiple agent, multiple site	ICD-9 (299.0, 299.8) in outpatient clinical databases in at least one occasion.	Age up to 7 years old
Zhang	2010	Case-control	95	95	Whole pregnancy	Influenza	ICD-10 diagnosed by the major hospitals in Tianjin and Beijing. Evaluated by a pediatric psychologist at entry to the study using CARS; all cases had a score greater than or equal to 30.	Age of initial diagnosis not reported. CARS assessment at 3–21 years old

Abbreviations: ADIR, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; ASQ, Autism Spectrum Quotient; CARS, Childhood Autism Rating Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; EAST, Early Screening of Autistic Traits Questionnaire; ICD, International Classification of Diseases; ID, intellectual disability; ISAA, Indian Scale for Assessment of ASD; M-CHAT, Modified Checklist for Autism in Toddlers; SCQ, Social Communication Questionnaire.

Four prospective studies (Al-Haddad et al., 2019; Atladottir et al., 2010, 2012; Zerbo et al., 2017) followed cohorts of children born over the course of a number of years and who thus varied considerably in the length of time for which they were at risk for autism. The investigators in these studies appropriately used person-years as the level of analysis and computed hazard ratios comparing the exposed and unexposed. In order to keep the effect sizes statistically comparable when combining, we computed simple odds ratios from the data provided in these papers, ignoring the variable periods of follow-up. One study (Lydholm et al., 2018) included only an adjusted odds ratio and did not provide the information necessary to compute an unadjusted figure, so is not included in the unadjusted analysis.

The data were pooled using a random-effects model. Heterogeneity was assessed using the *Q*-statistic—both within and between different types and periods of exposure. Funnel plots were examined to assess the possibility of publication bias. The analysis was performed using Comprehensive Meta-Analysis software (Borenstein et al., 2005).

RESULTS

Any infection during pregnancy and autism in offspring

Figure 2 summarizes the results of the 35 studies that included an unadjusted assessment of the effect of any

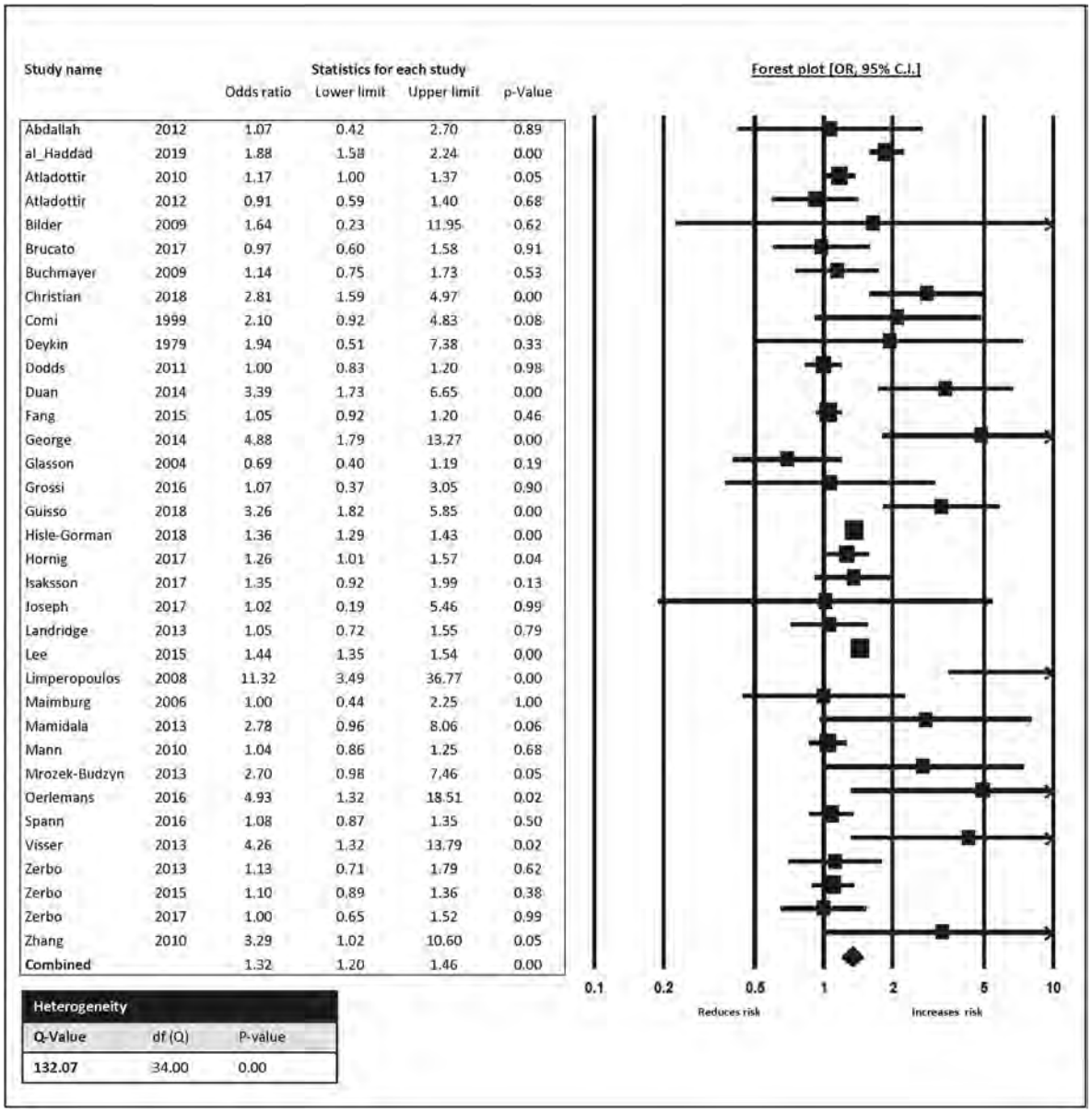

FIGURE 2 Forest plot for the association of any maternal infection during pregnancy with autism in offspring. "Lower limit" and "upper limit" refer to the ends of the 95% CI. CI, confidence interval

type of prenatal maternal infection or fever and autism in the offspring. The combined effect (OR = 1.32, 95% CI = 1.20–1.46) is modest but stronger that those reported in earlier meta-analyses. The *Q*-statistic indicates substantial heterogeneity across the effects sizes which subsequent analyses attempt to explain.

Publication bias

Figure S2 displays a funnel plot of the odds ratios from the 35 studies against the precision of the estimates. The studies reporting large odds ratios in the context of low precision are at the bottom right hand of the plot. The absence of matching studies at the lower left of the plot is an indication of publication bias in this body of literature.

The "trim and fill" process (Duval & Tweedie, 2000) can determine the impact of bias on the combined estimate by imputing effect sizes that should have been present in the absence of bias. When this method is applied to the data in Figure 2, the combined estimate is slightly reduced (OR = 1.25, CI = 1.12–1.39) but is still statistically significant. We note that, in all but one of these small N, large effect studies, the exposure variable was either "any infection" or a collapsed single variable reflecting any of a number of infections. Thus, these studies were not involved in subsequent analyses that grouped studies by type and/or timing of exposure.

Adjustment for potential confounders

Eighteen of the studies presented adjusted odds ratios though the potential confounders included in the adjustments varied considerably (see Table S1). In six of these studies, at least one of either the unadjusted or adjusted odds ratios had 95% confidence intervals that did not encompass 1.0. The impact of adjustment in these six studies is displayed in Table S2. For four of the six, the ORs were reduced by adjustment. In the remaining two, the putative confounders had a net suppression effect, and the ORs increased after adjustment. There is considerable variation across the four studies in terms of the potential confounders considered. Furthermore, with one exception, the associations of the putative confounders with the exposure were not reported making it impossible to identify the confounders having the greatest influence. In the one study that reported these associations (Hornig et al., 2017), parity appears to exert a suppression effect on the association because it is positively associated with the probability of maternal fever during pregnancy, but inversely associated with the probability of autism.

Another way to assess the importance of these statistical adjustments is to repeat the analysis that generated Figure 2 for the subset of studies that report adjusted ORs. The combined weighted OR for these adjusted analyses is 1.22 with a 95% CI of 1.14–1.32 (Figure S3). This is somewhat smaller than the combined unadjusted effect for all of the studies but is still statistically significant. Because of substantial variability across these studies in the potential confounders considered, it is difficult to interpret this small difference. Thus, in order to use all of the available data, the subsequent subgroup comparisons present only unadjusted ORs and all appropriate studies are included.

Heterogeneity in the effect of infection during pregnancy on autism by characteristics of exposure

Figure 3 displays variation in the effect of maternal infection during pregnancy across types of infectious agent. The combined ORs for viral (1.25, CI = 1.04–1.50) and bacterial agents (1.24, CI = 1.00–1.52) are quite similar. Both are higher than infections in the "other" category, which includes fungal infections and toxoplasmosis (1.13, CI = 0.94–1.35). However, this between-group heterogeneity is not statistically meaningful as indicated by the *Q*-value for the mixed effects model.

Figure 4 divides studies into four categories by the site of infection—genitourinary, gastrointestinal, respiratory, and other. Genitourinary and respiratory infections have modest combined effect sizes—genitourinary, OR = 1.19, 0.99–1.42; respiratory, OR = 1.20, 0.95–1.52. Gastrointestinal infections have the largest effect in the combined analysis, but there are only three such studies, so the confidence interval is wide—OR = 1.29, 0.87–1.91. Finally, the effect for the omnibus "other" category (OR = 1.20, 0.88–1.64), is difficult to interpret given the range of infection sites within this category. Again, as is clear from the between-groups *Q*-statistic there is not significant variation in effects across infection sites.

Figure 5 displays the 11 studies that examined maternal fever during pregnancy and autism. The combined odds ratio is somewhat larger than for infections in general (1.40, CI = 1.06–1.84).

Infection and autism by trimester of exposure

Ten of the studies documented the timing of exposure to infection during pregnancy. Table 2 summarizes variation in the effects of maternal infection on autism risk across trimester of exposure—both for any infection and within types of infection. In the analysis for any infection, the combined odds ratio for exposure during the first trimester is the smallest (OR = 1.16, CI = 1.00–1.33). The effects in the second and third trimester are somewhat larger (second trimester—OR = 1.27, CI = 1.13–1.43; third trimester—OR = 1.21, CI = 1.07–1.37). Nonetheless, as indicated by the *Q*-statistic, these differences across trimester are not statistically significant (forest plot presented in Figure S4).

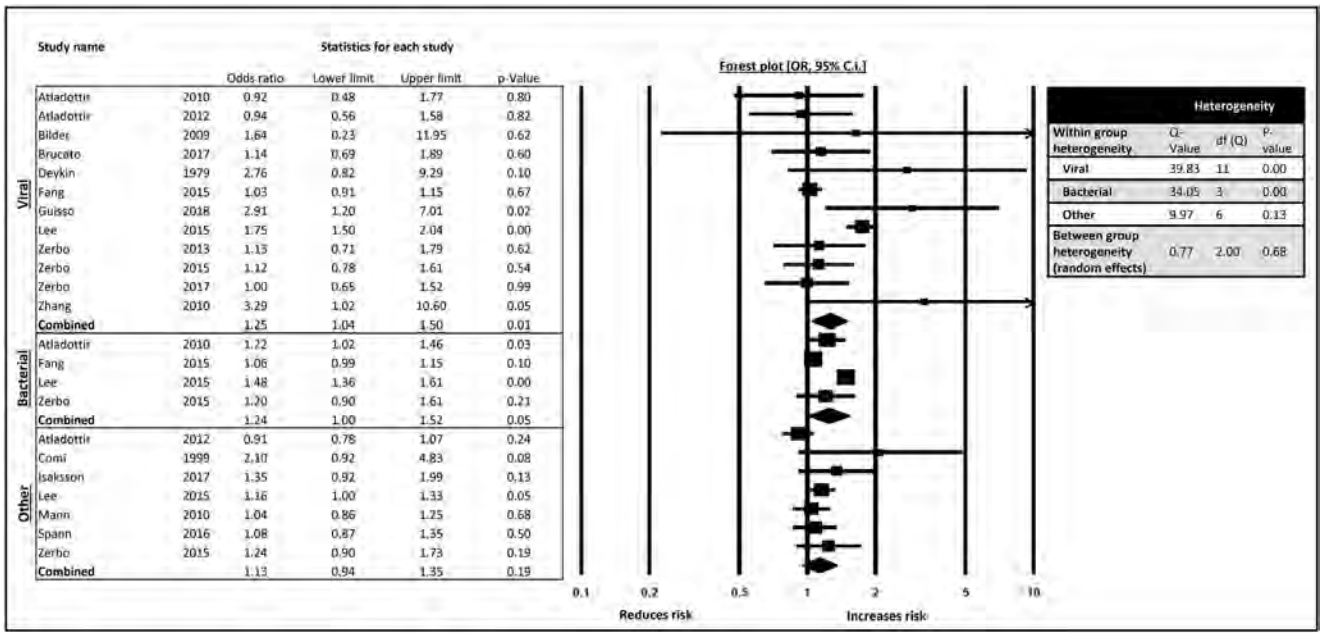

FIGURE 3 Forest plot for the association of maternal viral, bacterial, and other types of infection with autism in offspring

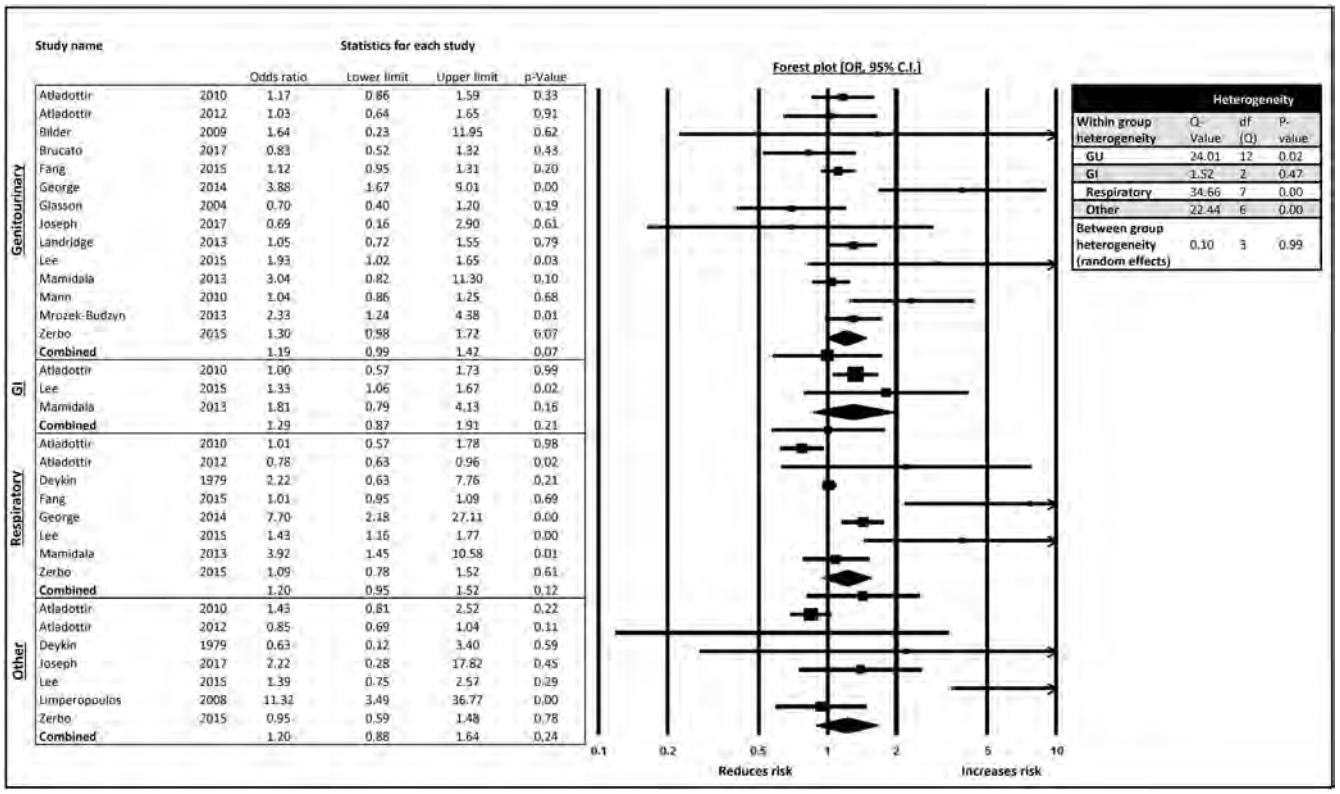

FIGURE 4 Forest plot for the association of maternal genitourinary, gastrointestinal (GI), respiratory, and infections at other sites with autism in offspring

The remainder of Table 2 examines heterogeneity in effects across trimester separately by types and sites of infection, and for fever generically. The number of studies that could be broken down in this way are few and, in general, there is little effect heterogeneity across trimester. One exception seems to be for genitourinary infections—the effect of these infections on ASD risk appears to be largely limited to the last trimester

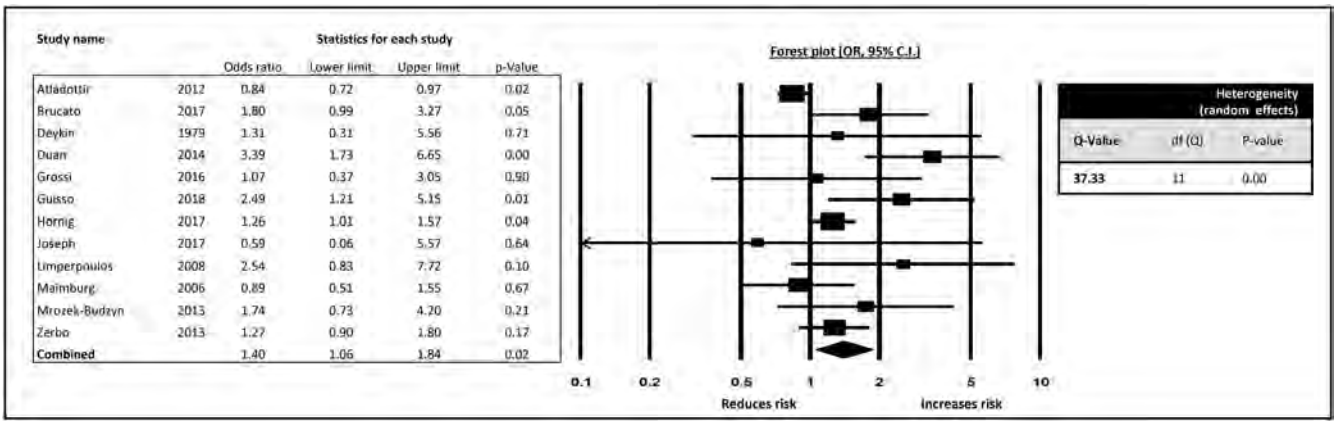

FIGURE 5 Forest plot for the association of maternal fever during pregnancy with autism in offspring

TABLE 2 Effects of maternal infection during pregnancy on autism by trimester of exposure

	First trimester		Second trimester		Third trimester		Heterogeneity across trimesters	
	OR	95% CI	OR	95% CI	OR	95% CI	*Q*	*p* value
Any infection	1.13	1.01–1.27	1.26	1.16–1.41	1.29	1.21–1.38	1.00	0.61
By infectious agent								
Viral	1.26	0.94–1.68	1.11	0.83–1.49	1.22	0.94–1.58	0.39	0.82
Bacterial	1.07	0.86–1.33	1.28	1.05–1.55	1.22	1.02–1.47	1.59	0.45
Other	1.00	0.82–1.23	1.27	1.07–1.51	1.22	1.07–1.40	3.41	0.18
By site of infection								
Genitourinary	0.98	0.80–1.19	1.00	0.83–1.19	1.32	1.08–1.63	5.53	0.06
Respiratory	0.99	0.91–1.08	1.02	0.94–1.11	0.97	0.89–1.05	0.78	0.68
Other	1.33	0.83–2.12	1.22	0.58–2.56	1.32	0.67–2.60	0.04	0.98
Fever	1.30	0.92–1.85	1.31	0.95–1.81	1.23	0.72–2.11	0.04	0.98

Abbreviations: CI, confidence interval; OR, odds ratio.

(OR = 1.32, CI = 1.08–1.63). In terms of variation by agent of infection, there appears to be a trend toward greater impact in the second and third trimesters in the case of nonviral infections. However, statistical power is too limited to be definitive about this observation. Forest plots for these analyses are presented in Figures S5–S7.

Variation in effects by subtype of autism

Three studies examined the effects of maternal infection on different categories of autism—these have been collapsed in the analyses conducted thus far. Two studies (Joseph et al., 2017; Langridge et al., 2013) separately considered ASD with and without ID. One study (Langridge et al., 2013) failed to find an effect of a prenatal maternal urinary tract infection on ASD, either with or without ID. The other (Joseph et al., 2017) did find elevated odds of ASD with ID in offspring of mothers who had such an infection (OR = 2.70; CI = 1.20–6.01). No effect was found for ASD without ID.

The third study (Atladottir et al., 2012) considered separately the impact of maternal infection on "infantile autism," defined as an ICD-10 code of F84.0 (childhood autism) in the Danish Psychiatric Registry, in addition to looking at the effect for any autism diagnosis (including infantile autism, atypical autism, Asperger's, and other Pervasive Developmental Disorders). The effects of maternal exposure to infection and fever during pregnancy were consistently stronger for infantile/childhood autism (equivalent to autistic disorder in DSM-IV) than for the autism spectrum as a whole.

Variation in effects by autism assessment procedure

As is evidenced in Table 1, there is substantial variation across studies in the operational definitions of an autism diagnosis. The clearest distinction is between studies that used an existing diagnosis, either from medical records or because of the recruitment in a clinical setting, and

studies in which the investigators made their own diagnoses upon entry of each study participant. The latter procedure usually occurred in case-control studies in which cases identified from clinical settings and controls were independently diagnosed using instruments such as the ADOS or the ADI-R. Figure S8 displays a comparison of these two groups of studies. Studies in which the investigators arrived at diagnoses independently of initial case status have a combined effect size (OR = 2.58; CI = 1.89–3.51) that is substantially and significant greater than the effect size than studies that used existing diagnoses (OR = 1.23; CI = 1.11–1.36). Although the Limperopoulos et al. (2008) is a substantial outlier, it is not particularly influential due to its small sample size. If this study is removed, the effect-size is similar (OR = 2.32; CI = 1.69–3.19). The studies that applied their own diagnostic procedure did not provide figures as to changes made to the original case status—thus making it difficult to interpret the differences in results between these two groups of studies.

Variation in exposure severity: Length of febrile episode

It is likely that infection severity varies considerably, even within specific types of exposures. For example, the category of influenza encompasses both brief experiences of 24 h or less and prolonged severe illnesses requiring medical intervention. Similarly, fevers can be very high or comparatively mild, and febrile episodes can be brief or lengthy.

Information on variation in severity was largely unavailable in the studies examined here. One exception (Atladottir et al., 2012) broke down febrile episodes in terms of three different indicators of severity: level of fever at its highest point, number of febrile episodes during pregnancy, and length of the longest febrile episode. These investigators found little variation in impact across the first two of these dimensions. However, febrile episodes of 7 days or longer during pregnancy conferred more than a threefold risk in childhood autism; a marked contrast to the small elevations in risk associated with shorter episodes.

Medications in response to infection

Six studies examined the effects of antibiotic medication on risk for autism. In combination, these studies show an elevated risk of autism in children whose mothers took antibiotics during pregnancy (OR = 1.72, 95% CI = 0.93–3.20). It should be noted that none of these studies examined antibiotic use conditioned on the presence of infection. Thus, any observed effect is an amalgamation of the effects of exposure to bacterial infection and the effects—possibly salutary, possibly iatrogenic—of the drugs.

Three studies examined the effect of antipyretic use during pregnancy but only one (Zerbo et al., 2013) conditioned this comparison on the presence of maternal fever. Fever resulted in significant elevation in autism risk in the absence of antipyretic use— adjusted OR = 2.55 (1.30–4.99), but not when mothers used these medications—adjusted OR = 1.30 (0.59–2.84).

Variation in effects by study design and exposure assessment

Eleven of the 35 studies employed a cohort design. Two of these (Atladottir et al., 2012; Hornig et al., 2017) relied upon maternal report of exposure to infection or fever, but both were prospective studies—assessment of exposure took place immediately after pregnancy, well before symptoms of autism might appear in the offspring. Of the 24 case-control studies, 13 assessed infection exposure independent of parent report (usually using medical records or registry data). The combined result for these 13 studies (OR = 1.17; CI = 0.95–1.45) is similar to the combined result for the cohort studies (OR = 1.25; CI = 1.05–1.48).

The remaining 11 case-control studies relied on the retrospective self-report of the mothers to assess exposure to infection and fever during pregnancy. The forest plot displayed in Figure 6 contrasts the results for these studies with those of the remaining case-control studies and the cohort studies (collapsed together). The effect in the studies using retrospective report (OR = 1.88; CI = 1.50–2.37) is substantially stronger than the effect in the remaining studies (OR = 1.22; CI = 1.09–1.37), and the difference is statistically significant. This appears to indicate that, in the studies using retrospective self-report, parental recall bias associated with the offspring's status on the outcome variable leads to differential misclassification of exposure status.

DISCUSSION

Our meta-analysis demonstrated a modest but statistically significant association of prenatal maternal infection, defined as infection of any type, and risk of autism in offspring. Although there was evidence of publication bias, adjustment for this bias did not have a substantial impact on the magnitude of the association.

We found little heterogeneity in the effect of maternal infection across agent or site of infection. The combined effect of maternal fever during pregnancy was somewhat stronger than the effect for "any infection," perhaps indicating that fever is more proximal to autism in the causal chain and an important mediator of the impact of infection. We found slight (though nonsignificant) variation in the effects of infection across trimester of exposure with greater effects in the second and third trimesters relative

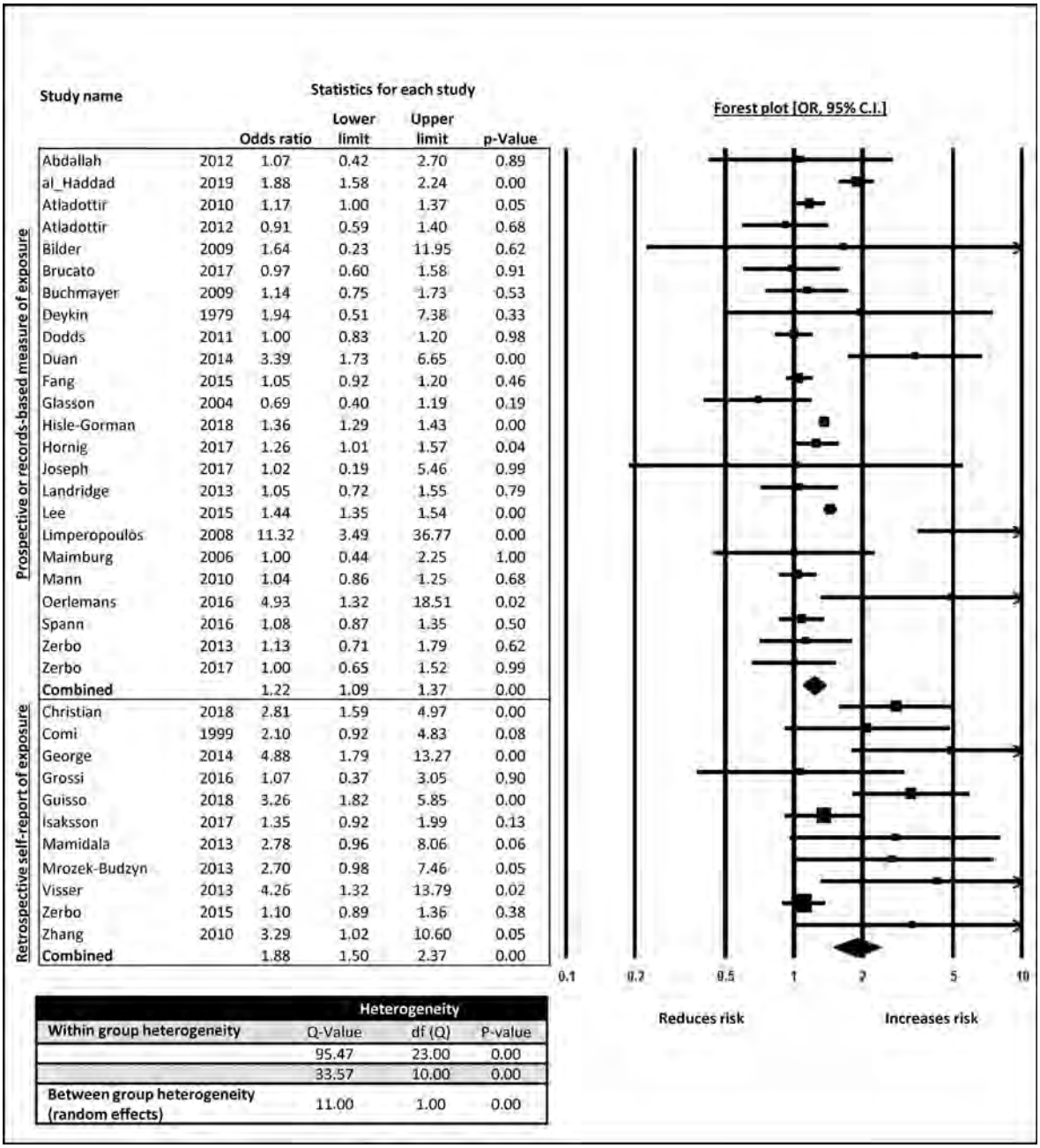

FIGURE 6 Forest plot contrasting the strength of the association of maternal infection with autism in studies using retrospective self-reports of infection during pregnancy with prospective cohort studies or studies using records-based measures of exposure

to the first—particularly for nonviral infections. These differences are clearest in the case of genitourinary infection which has a comparatively strong association with autism risk, but only for exposures that occur in the third trimester.

Atladottir et al. (2012) reported a very strong elevation in autism risk associated with febrile episodes of 7 days or longer. Together with the findings regarding the benefits of antipyretic use in the context of fever (Zerbo et al., 2013), this suggests a possible intervention for the prevention of autism. Type of antipyretic was not distinguished in this study, so the finding may need to be tempered with respect to acetaminophen. Acetaminophen use during pregnancy has been linked to Attention-Deficit/Hyperactivity Disorder and behavioral problems in offspring (Brandlistuen et al., 2013; Liew et al., 2014), though the causal basis for this association is still in doubt (Masarwa et al., 2020).

The newest study of those included in the meta-analysis (Al-Haddad et al., 2019) provides indirect evidence that offspring risk for autism elevates with increasing severity of maternal infections. This study examined the hospitalization records of over 1.7 million women in Sweden during pregnancy and linked them to registry-

based records of psychopathology in the offspring. Exposure to maternal infection in utero elevated the risk of a diagnosis of autism by 79%, adjusting for a range of maternal health status and health behavior variables. The strength of this association relative to the total combined effect we obtained in our meta-analysis may reflect the fact that the exposures in this study would have been either severe enough or persistent enough to result in treatment seeking.

We also found important method effects. First, the studies that administered their own diagnostic protocol for autism disorders reported significantly stronger associations, on average, than did the studies that used existing case definitions either in the clinics from which subjects were recruited, national case registries, or other medical records. It is difficult to speculate on the reasons for this difference because the studies that administered diagnostic instruments did not report the changes in cases relative to the initial clinical status. Second, the 11 studies that used retrospective maternal reports for the assessment of infection during pregnancy had definitively larger odds ratios for the association with autism than were found in prospective cohort studies or studies that used a records-based approach for exposure assessment. This suggests the presence of strong recall bias, perhaps driven by "effort after meaning" (Auble & Franks, 1978; Bartlett, 1932). Parents of children with autism may make an enhanced effort to recall events that are possible explanations for the condition.

This meta-analysis was completed well before the onset of the current COVID-19 pandemic. The findings presented here indicate the potential for a substantial increase in the incidence of neurodevelopmental problems in the cohort of births occurring during the pandemic—the early months of 2020, and perhaps beyond. While data on these potential consequences will not be available for some time, considerable effort has been made during the pandemic to document the effects of COVID-19 on pregnancy and birth characteristics. Early data document a very high prevalence of preterm birth in women who were hospitalized with COVID-19 in the latter stages of pregnancy (Dashraath et al., 2020; Di Mascio et al., 2020; Mullins et al., 2020). A substantial body of research conducted during earlier outbreaks of coronavirus infections (SARS and MERS) documents elevated rates of intrauterine growth restriction (IUGR) in infants born to mothers with these diseases (Schwartz & Graham, 2020). Preterm birth and IUGR are both established risk factors for a subsequent diagnosis of autism (Agrawal et al., 2018; Lampi et al., 2012).

Limitations

Although we have used the terms "association" and "effect" interchangeably, it is important to acknowledge that we have only demonstrated the former. An important limitation imposed by the literature is the inconsistent inclusion of potential confounders of the association of maternal infection and autism. Only half of the studies we considered adjusted in any way for potential confounders and, among those that did, the choice of variables differed considerably. Thus, little can be said about the role of confounders in the association. At the same time, it is important to remember that some prenatal confounders (e.g., parity) may actually be suppressing the association between maternal exposure and offspring autism outcomes. Future research will need to consider plausible confounders and take advantage of designs (e.g., comparisons of siblings discordant on in utero exposure to infection) that can effectively isolate the impact of maternal infection during pregnancy.

There are a number of other limitations in the content of the existing literature that place limits on what can be concluded from the meta-analysis. First, existing studies make only very gross divisions in the types of infectious agents being compared. Distinctions between different types of bacterial infections might be important for understanding the pathophysiological mechanisms through which in utero effects on offspring neurodevelopment occur. Further, genetically informative designs are absent from the literature on prenatal paternal infection, as is any consideration of variable impact of infection by offspring sex, characteristics of the immune system, or other known risk factors such as paternal age. Studies of potential environmental moderators are also lacking. Clearly research is needed to determine the contexts within which maternal exposure to infection in pregnancy is the most dangerous.

Another limitation is the absence of information on exposure severity. While the finding regarding long periods of fever (Atladottir et al., 2012) invites speculation, this single finding is inadequate to sustain any useful conclusions about severity. The literature also offers very little in terms of variation in the effect of maternal infection across autism phenotypes or levels of functioning among those with the diagnosis. Clearly more attention needs to be paid to these issues in future research.

The literature is also largely lacking in terms of explicit tests of mediating mechanisms for the impact of maternal infection on autism in offspring. As noted above with respect to coronaviruses, birth characteristics like pre-term birth and low birthweight could be intervening factors. Further, a template for the effects of maternal immune activation on neurodevelopmental disorders is well established in the literature (Estes & McAllister, 2016), Notably, pregnant women with COVID-19 have been shown to have higher levels of the inflammatory cytokine interleukin-6 than non-pregnant woman suffering from the disease (Yin et al., 2020). This suggests an important mechanism for the effects of intrauterine exposures that may extend to other infectious agents.

There are also limitations associated with our attempts to understand the role of timing of maternal

infection during pregnancy. There is likely to be considerable measurement error in the assessment of trimester of exposure. Dates of conception are often uncertain, and periods of exposure may overlap the trimester boundaries. It should also be noted that trimester is merely a stand-in for the fetal developmental periods across which vulnerability to maternal infection may vary. It is quite possible that the relevant developmental periods for enhanced vulnerability to maternal infection do not correspond to the arbitrary division of pregnancy into trimesters. Thus, using trimester as an operational definition of relevant fetal developmental periods could result in misclassification error that biases findings in the direction of the null—that is, toward a lack of variability across period of exposure.

Finally, a very important limitation is imposed by our search strategy. It is possible that the neurodevelopmental consequences of maternal infection during pregnancy are not specific to autism disorders. Because we required studies to have a diagnosis of autism as at least one of the outcome variables considered, we cannot address this issue. Four of the included studies examined the association of other neurodevelopmental problems in addition to autism. Lydholm et al. (2018) report an association of maternal infection with developmental disorders in general (ICD-10, F80-89)(World Health Organization, 1993) that is similar in magnitude to its association with ASD alone. Zerbo et al. (2013) found a more than twofold increased risk of both ASD and developmental delay associated with maternal influenza during pregnancy. Langridge et al. (2013), who did not find an association of maternal urinary tract infection with autism, did find a significant association with mild–moderate ID. In contrast, the strong association of maternal infections with ASD documented by Oerlemans et al. (2016) did not extend to ADHD. Although not as strong as the associations with autism, Al-Haddad et al. (2019) also found a significant association of severe maternal infection with an offspring diagnosis of depression. Clearly, it would be worthwhile to examine the offspring developmental and mental health consequences of maternal infection during pregnancy more broadly.

Public health and clinical implications

Assuming a causal connection, a 32% elevation in autism risk as a result of maternal infection during pregnancy represents a significant impact from a public health perspective. This is because such infections are very common. In the National Birth Effects Prevention Study (1997–2003), 63.6% of women reported at least one infection during pregnancy (Collier et al., 2009). Based on this figure, a relative risk for autism of 1.32 translates into a population-attributable risk (PAR) of 17%. The more conservative estimate that results from removing studies potentially tainted by recall bias (OR = 1.22) still results in a PAR of 12%. This suggests that 12%–17% of incident cases of autism could be prevented by the elimination of maternal infection during pregnancy—or, perhaps, the relevant downstream consequences of infection (fever, inflammation, etc.).

From a clinical point of view, however, this increase in risk is modest and suggests that maternal infection affects autism risk in conjunction with risk factors that are comparatively rare in the population. Genetically informative designs will allow for the assessment of gene-by-maternal infection interactions. The relevant interactions might be with one or more rare genetic variants with a demonstrated association with autism (Buxbaum, 2009). Alternatively, they might be with the presence of multiple common variants (as indicated using polygenic risk scores) that are comparatively rare in combination (Serdarevic et al., 2020). If certain genetic vulnerabilities can be identified, then we might expect the effect of maternal infection, conditional on these vulnerabilities, to be substantially greater than what we uncovered in our meta-analysis. At the same time, the fact that prolonged fever may be accompanied by particularly dramatic increases in autism risk suggests that, at higher levels of severity, a wider range of causal partners (vulnerabilities) are sufficient to result in the disorder—or, alternatively, causal partners that are more prevalent in the population.

Continued investigation of the factors that condition the effects of maternal investigation will be important from the point of view of preventative intervention. As we have experienced during the course of the COVID-19 pandemic, the measures necessary to prevent infectious transmission are often invasive and arduous. Prescription of such measures to expectant mothers would ideally be limited to those whose genetics and medical history indicate a high risk of adverse child outcomes resulting from exposure to infection.

The caveats noted above suggest that caution is necessary in interpreting the results of this study. Nonetheless, the important elevation in risk of autism in offspring with prenatal exposure to maternal infection is worthy of further investigation. The meta-analysis presented expands upon previous efforts to summarize findings in this area, both in terms of the range of research included, and in terms of our more extensive consideration of factors that influence effect heterogeneity. The analysis also makes clear that further understanding of the role of maternal infection and autism risk will require research designs that consider both infection severity and potential moderators—that is, the conditions under which infection poses the greatest risk. Findings from such designs will have the potential to identify fruitful avenues for intervention to reduce the incidence of autism.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

AUTHORS CONTRIBUTION

Dr. Tioleco and Ms. Silberman were involved in planning the study, helped develop the search algorithm, selected the articles based on the inclusion criteria, edited the figures, and reviewed drafts of the manuscript. They have given final approval of the version to be published and agree to be accountable for the accuracy and integrity of the contents.

Dr. Stratigos was involved in planning the study, helped develop the search algorithm and reviewed drafts of the manuscript. She has given final approval of the version to be published and agrees to be accountable for the accuracy and integrity of the contents.

Dr. Banjeree-Basu was involved in planning the study, helping to conceptualize its design. She reviewed each draft of the manuscript. She has given final approval of the version to be published and agrees to be accountable for the accuracy and integrity of the contents.

Dr. Spann reviewed drafts of the manuscript and contributed insights in interpreting the data. She has given final approval of the version to be published and agrees to be accountable for the accuracy and integrity of the contents.

Dr. Whitaker was involved in planning the study, helping to conceptualize its design. She assisted Dr. Turner in supervising the article search and the data extraction, reviewed drafts of the manuscript, and contributed insights in interpreting the results. She has given final approval of the version to be published and agrees to be accountable for the accuracy and integrity of the contents.

Dr. Turner was involved in planning the study and conceptualized its design. He supervised all aspects of the article search and data extraction. He also conducted all of the data analysis, drafted the initial manuscript, and prepared the final draft. He has given final approval of the version to be published and agrees to be accountable for the accuracy and integrity of the contents.

ORCID

J. Blake Turner https://orcid.org/0000-0001-8575-0705

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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