PROGRESS IN MEDICAL SCIENCES, 2022
VOL 6, NO. 2, PAGE 1 – 8
DOI: doi.org/10.47363/PMS/2022(6)171

REVIEW ARTICLE

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Risk of Autism Spectrum Disorder in Offspring Following Exposure to Maternal Fever during Pregnancy: A Systematic Review and Meta-Analysis

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ABSTRACT

A systematic review and a meta-analysis were performed to assess the association between prenatal fever and autism spectrum disorder (ASD) in exposed offspring. A total of 9 high quality studies were reviewed and meta-analysed. A positive association between fetal exposure to fever and subsequent ASDs was found. For first and second trimesters exposure, the odds ratio was 1.49 (95% CI; 116-1995) and 1.48 (95% CI; 1.22-1.80) respectively. When all nine studies were collapsed, the odds ratio was 1.238 (95% CI; 1.048-1.462). Prenatal exposure to maternal fever was found to be associated with fetal neurotoxicity during critical windows of CNS development and increased risk for ASD. An association of prenatal fever with ASD in genetically predisposed women may aid in early diagnosis, prevention, and management.

ARTICLE HISTORY

Received March 01, 2022
Accepted March 03, 2022
Published March 16, 2022

Keywords: Autism Spectrum Disorder, ASD, Pregnancy, Fever, Hyperthermia, Neurodevelopment.

Introduction

Autism spectrum disorder (ASD) is a group of prenatal neurodevelopmental dysfunctions with early childhood onset, ASD is clinically exemplified by repetitive and restricted behaviours, impairment in reciprocal social interaction, and impairment in verbal and non-verbal communication. ASD has a wide range of clinical presentations and encompasses the previously known entities of classic autistic disorder, Asperger syndrome and pervasive developmental disorder-not otherwise specified (PDD-NOS) under one umbrella term [1].

ASD is the most prevalent and complex inborn neurodevelopmental disorder affecting one in 54 children by age 8 in the United States. Boys are 4 -5 times more likely than girls to demonstrate symptoms and to be impacted and diagnosed [2, 3]. According to the most plausible prevalence of ASD ranges from 1% to 1.5% worldwide, rises universally, and exhibits similar phenotypic expression across races and countries [4]. Equally diversity is its etiology. ASD is thought by researchers to be multifactorial, with the complex interplay between heritable and environmental risk factors contributing to its development [5, 6]. While the genetic basis of ASD is well-established, with a strong heritability in twin studies extending up to 90% no single gene can explain more than 1-2% of ASD cases [4, 7, 8]. A recent exome sequencing study of ASD identified 102 risk genes, with 53 showing higher frequencies in patients diagnosed with ASD [9].

Furthermore, comorbidities ranging from learning disabilities to epilepsy and gastrointestinal morbidity and occur in 70% of individuals with ASD [4, 8]. This heterogeneity begs for further characterization of the role that some perinatal exposures play in the development of ASD. Considering that the genesis of ASD is multifactorial, it is mostly unlikely that a single associated hazard will explain its presentation across the spectrum [6]. Moreover, several large studies have found an association between maternal gestational infection and the risk of autism, supporting a plausible underlying mechanism in which pathogens trigger dysregulated neuroinflammation that adversely impairs fetal development [10, 11]. In support to this hypothesized pathophysiology, maternal fever, often a coincidental entity with gestational infection, has been shown to independently increase the risk of ASD in

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offspring [12-14]. Maternal hyperthermia (caused by fever or environmental heat sources) is elevation of temperature above the normal body core values [15].

Effects of prenatal fever on developing CNS is not sufficiently studied. Studies assessed the association of maternal fever with the ASD presenting conflicting results (not showing association [9, 16, 17] or reporting a significant positive association [2, 3, 7-9, 14]) due to methodological limitations and power issues. Fever is common during early pregnancy, 1 in 5 women will experience at least one episode of fever within the first 12 weeks' gestation [2, 3, 7-9, 14, 16-18]. Fetal safety following prenatal exposure to fever is essential to address. Therefore, the objectives of this research are to assess the association of prenatal fever with increased rates of ASD in exposed pediatric population. We aim to provide a systematic review of existing literature in a meta-analysis.

Methods

Search Strategies

In November 20, 2021 an additional systematic search was conducted. Medline (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials (OVID), and Web of Science (Clarivate Analytics). The search was composed of three broad concepts: (1) autism, (2) fever, and (3) pregnancy. Subject headings specific to each database were included where available. Terms were also searched in the titles, abstract, and keywords fields. The search captured references if there were at least one term in each of the three subject headings. No limits were used in the search.

Selection Criteria

The inclusion and exclusion criteria were agreed upon prior to the searching of the databases. Randomized controlled trials, cohort studies, and case-control studies on humans born at full term were included. Included studies also documented incidence of maternal fever during pregnancy and diagnosis of ASD by clinical experts using validated scales (ADI-R, ADOS) in offspring born of that pregnancy. Following the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), the previous separate entities of childhood schizophrenia, infantile autism, pervasive developmental disorder (PDD), pervasive developmental disorder not otherwise specified (PDD-NOS), autistic disorder, and social communication disorder were included as equivalent to a diagnosis of ASD [1]. A defined control or comparison group must be documented in the study to be included. We excluded studies that included cases that documented antenatal complications, such as pre-eclampsia, and neonatal complications, such as low birth weight, which are already known to be associated with ASD [19]. This review was carried out following the "Preferred Reporting Items for Systematic reviews and Meta-Analyses, PRISMA. The study selection process is presented in Figure 1.

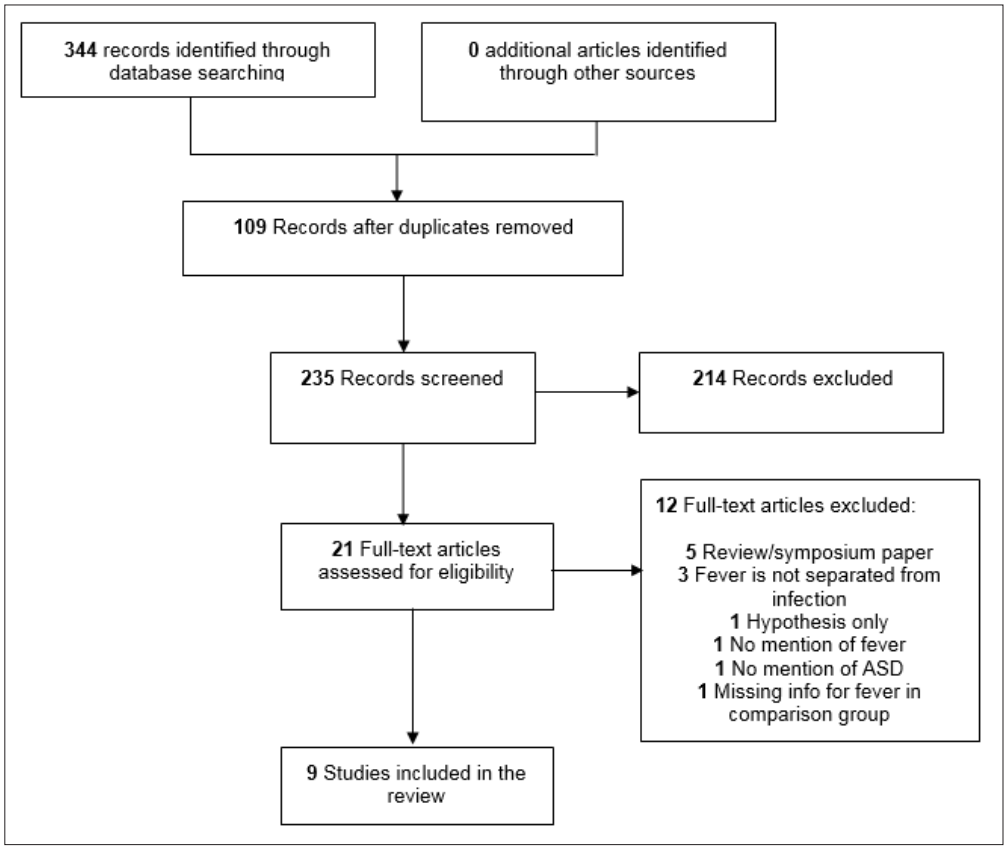


Figure 1: Flow Chart of the Study Inclusion/Exclusion Process

Data Extraction and Study Quality

References were reviewed for further eligible studies. Three reviewers (I. L, E.W, and M.M) independently reviewed the search to identify potentially relevant articles. Disputes were settled by a third reviewer (M.M) and supervisor (I.N). Information including study information, diagnosis and exposure criteria, and characteristics of the participant, and outcomes was extracted from eligible studies.

Data Analysis

Data were analysed with the Comprehensive Meta-Analysis software, version 3.0, using a random-effects model. The odds ratios and 95% confidence intervals were calculated for each outcome. Heterogeneity among studies was assessed using the Q-statistic, which was then quantified by I^2. Risk of ASD after exposure to prenatal maternal fever, as well as risk of ASD based on maternal education, parental education, offspring gender, maternal psychiatric disorder, and maternal and paternal ages was assessed.

Study Selection, Characteristics and Quality

The database search yielded 344 records. Two hundred thirty-four records were screened for eligibility by title and abstract after duplicates were removed. This yielded 21 studies for full-text review. Twelve articles were excluded: 5 were review papers, 3 did not separate the incidence of fever from infection, 1 was a hypothesis, 2 did not meet the inclusion criteria (missing information for fever and missing information of ASD), and 1 was missing fever information in the comparison group.

Study Design

Nine studies underwent data extraction and analysis. Of these 9 studies, 8 were case-control studies and 1 was a prospective cohort study [20]. Exposure was determined through parental structured questionnaire or interviews in all studies and corroboration with hospital records was available in 3 studies [13, 20, 21].

Four studies reported fever by trimester [12-14,22]. Eight studies also analysed effect of potential confounders, such as maternal education and maternal age, on the risk of developing ASD [12-14, 17, 20-23]. Overall, the quality of studies was high. Details of the study characteristics and the quality evaluation of each included study is provided in table 1 below. The results of the present systematic review and meta-analysis suggest that exposure to prenatal, maternal fever during pregnancy is associated with increased risk of ASD among offspring, with a combined OR, 1.238; 95% CI, 1.048-1.462 when compared to the comparison group.

Table 1: Characteristics and quality assessment of the included studies

Study name (year)	Study location	Study design	Mode of reporting fever exposure	Cohort size	No. of cases exposed to fever	No. of cases and controls exposed to fever	No. of cases unexposed to fever with ASD	No. of cases and controls unexposed to fever	Diagnostic Criteria	OR (95% CI)
Juul-Dam (2001)	USA	case-control	Medical records and parental interviews.	64	17	1392	47	6760	DSM-IV, ADI-R, CARS, ADOS	1.766 (1.011-3.085)
Atladottir (2001)	Denmark	prospective cohort	Telephone interviews during pregnancy and early postpartum	96736	234	23128	620	61482	ICD-10	1.003 (0.863-1.167)
Zerbo (2014)	USA	case-control	Telephone interviews, and outcomes were clinically confirmed	1122	97	191	441	931	ADI-R, ADOS-G	1.147 (0.840-1.566)
Maimburg (2006)	Denmark	population-based matched case-control	Midwives collected information throughout pregnancy from the Danish Medical Birth Register	5203	25	53	391	772	ADI-R, ADOS-G	0.870 (0.498-1.519)
Brucato (2018)	USA	case-control	Interviewed 24–72 hours after delivery using a standardized postpartum questionnaire to gather information about pregnancy	1104	15	93	86	892	ICD-9-CM	1.802 (0.993-3.270)
Guisso (2018)	Lebanon	case-control	Questionnaire through telephone interviews	314	22	35	112	277	DSM-IV, DSM-V	2.493 (1.206-5.155)
Hornig (2017)	Norway	case-control	Questionnaires completed around gestational weeks 17 and 30, and 6 months postpartum.	95754	98	13607	376	65499	DSM-IV-TR	(1.256 (1.005-1.570)
Saunders (2019)	Canada	case-control	Telephone Survey Questions	215	20	31	85	182	DSM-IV, DSM-V	2.075 (0.940-4.578)
Croen (2019)	USA	case control	Telephone interview with the mother and maternal prenatal and labor/delivery medical records.	2258	105	367	501	1891	ADOS	1.112 (0.867-1.425)

Systematic Review

Hornig et al. reported a small but significant association between prenatal fever and development of ASD (aOR 1.26; 95% CI, 1.01-1.57) [12]. However, when data was stratified by trimester, second trimester exposure to prenatal fever was more strongly associated with ASD (aOR, 1.40; 95% CI, 1.09-1.79). Furthermore, the risk increased markedly with exposure to three or more fever episodes after 12 weeks gestation (aOR, 3.12; 1.28-7.63).

Croen et al. separately analysed exposure to infection and fever during pregnancy and reported that maternal fever with or without infection during the second trimester is associated with an increased risk of ASD [13]. After adjusting for covariates such as medication use, the adjusted OR was 2.11 with a 95% confidence interval of 1.04–4.25.

Zerbo et al. analysed data from the Childhood Autism Risks from Genetics and Environment (CHARGE) study in California in a retrospective case-control design [14]. Prenatal fever exposure in the second trimester doubled the risk of ASD in offspring (OR 2.60, 95% CI (1.14-5.94). This study further showed that the risk of ASD was attenuated in mothers who took antipyretic medications to control their fever but remained elevated in mothers who did not.

Saunders et al. analysed data from local pediatricians and separately recruited participants. They reported risk of ASD with various prenatal environmental exposures and found the association between prenatal fever and ASD just shy of statistical significance (OR 2.075, 95% CI (0.940-4.578) [17]. However, after regression analysis with other potential covariates, no significant correlation was found.

Atladottir et al. did not find a significant association between episodes of fever (defined as 37.5C and greater) and development of ASD [20]. However, upon stratifying their data based on number of episodes, highest recorded temperature, trimester of exposure, and duration of fever, a strong elevation in autism risk was associated with prolonged episodes of fever (≥7 episodes and more than 7 days) during second trimester (aHR: 1.6; 95% CI: 1.0–2.5). A significant association between second trimester fever exposure and infantile autism was also found (aHR: 3.2; 95% CI: 1.8–5.6).

Juul-Dam et al. examined 28 pre-, peri-, and neonatal factors in their association with the risk of developing ASD and did not find a significant association between prenatal fever exposure and ASD [21].

Brucato et al. assessed the risk of ASD in a nested sample Boston Birth Cohort (BBC) sample of 116 ASD cases and 988 typically developing controls in a crude or adjusted analysis [22]. Prenatal exposure to fever was associated with increased ASD risk (aOR, 2.02; 95% CI, 1.04-3.92) after adjustment for educational attainment, marital status, race, child sex, maternal age, birth year, gestational age and maternal smoking. The study also stratified fever exposure by trimester and noted that fever in the third trimester was associated with risk of ASD (aOR, 2.70; 95% CI, 1.00-7.29).

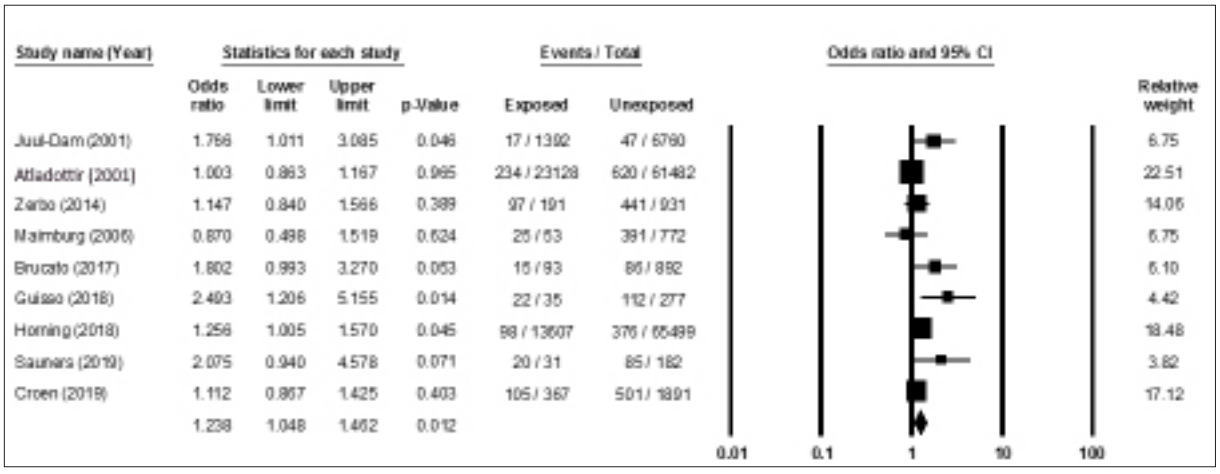
Guisso et al. is the only study identified through our search whose population is primarily non-Caucasian [23]. In a retrospective case-control design, 314 Lebanese children from a large university health centre were analyzed for pre-, post-, and neonatal exposures which may have contributed to the risk of developing ASD. Prenatal fever was found to be associated with ASD (OR 2.5 (1.2-5.2) p 0.012) [24].

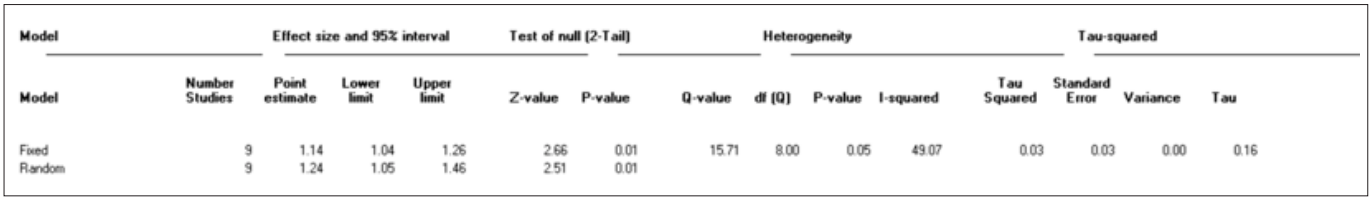
Maimburg et al. analysed pre- and perinatal factors in 504 children diagnosed with infantile autism between 1990 and 1999 [25]. They found no significant correlation between fever, which was defined as >37.7 C, and risk of ASD.

Meta-Analytic Results

A summary of all the meta-analysis performed is provided in Table 2. The cumulative effect of the nine studies analysed showed a positive association between prenatal fever exposure and development of ASD in offspring (OR, 1.238; 95% CI (1.048-1.462) with heterogeneity (I^2) of 49% (Figure 2). In this meta-analysis, out of the 9 studies, 4 studies stratified prenatal fever exposure by trimester. There was a combined total of 214 616 patients, of which 39,747 pregnant women experienced fever throughout pregnancy and 190,372 women did not.

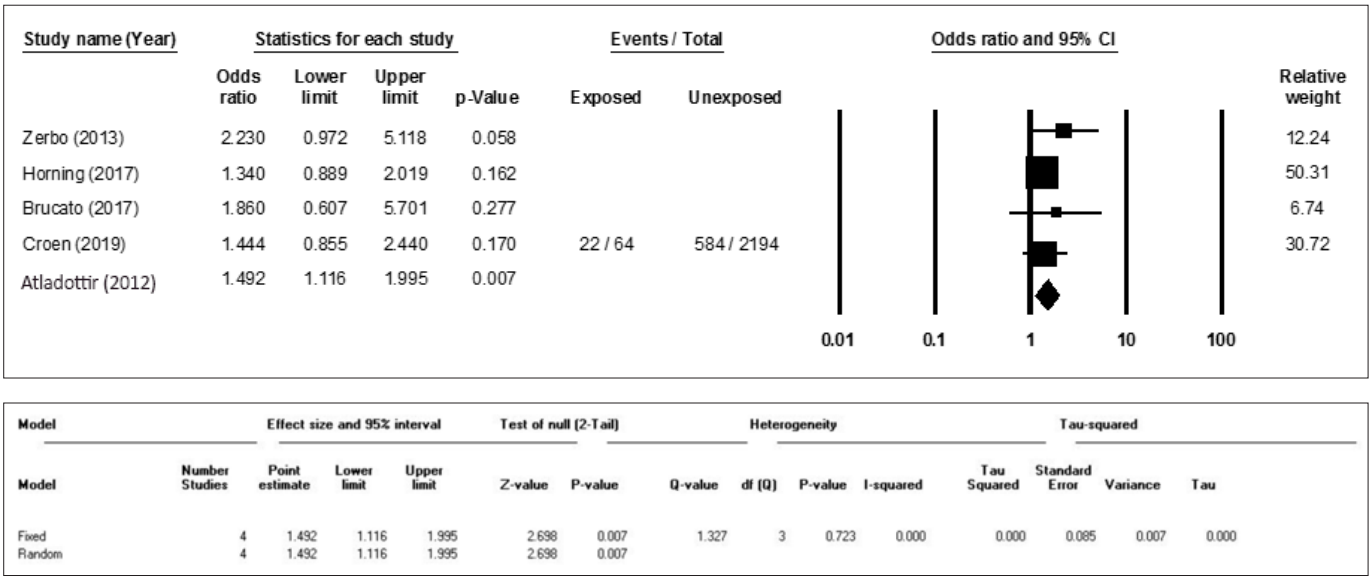
There was significant association between first-trimester fever exposure and diagnosis of ASD (OR 1.49; 95% CI (1.116-1.995), I^2 of 0%) (Figure 3). Second-trimester prenatal fever exposure was also significantly associated with development of ASD in offspring (OR 1.48; 95% CI (1.22-1.80), I^2 of 0%) (Figure 4). Third-trimester prenatal fever exposure was not significantly associated with risk of ASD (OR 1.18; 95% CI (0.83-1.67), I^2 of 34.9%) (Figure 5).





Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	9	1.14	1.04	1.26	2.66	0.01	15.71	8.00	0.05	49.07	0.03	0.03	0.00	0.16
Random	9	1.24	1.05	1.46	2.51	0.01								

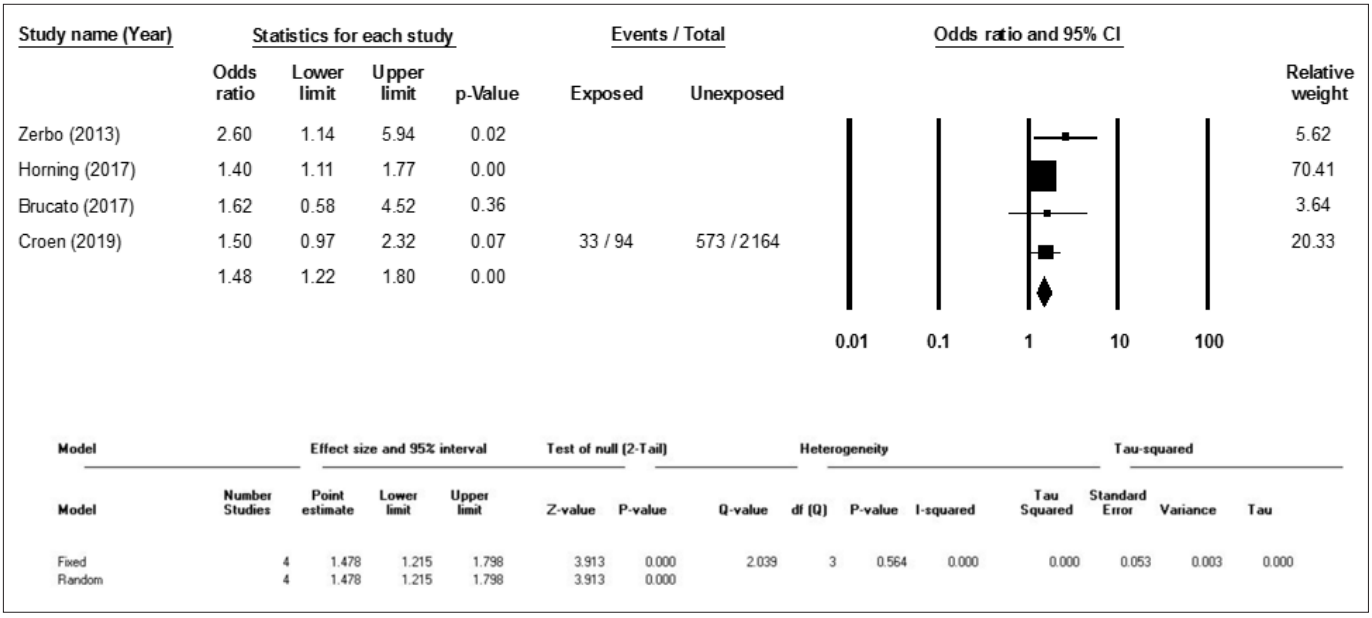
Figure 2: Forest plot of the association between maternal fever during pregnancy and ASD in offspring



Study name (Year)	Odds ratio	Lower limit	Upper limit	p-Value	Exposed	Unexposed	Relative weight
Zerbo (2013)	2.230	0.972	5.118	0.058			12.24
Horning (2017)	1.340	0.889	2.019	0.162			50.31
Brucato (2017)	1.860	0.607	5.701	0.277			6.74
Croen (2019)	1.444	0.855	2.440	0.170	22 / 64	584 / 2194	30.72
Atladottir (2012)	1.492	1.116	1.995	0.007			

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	4	1.492	1.116	1.995	2.698	0.007	1.327	3	0.723	0.000	0.000	0.085	0.007	0.000
Random	4	1.492	1.116	1.995	2.698	0.007								

Figure 3: Forest plot of the association between maternal fever in first trimester and ASD in offspring



Study name (Year)	Odds ratio	Lower limit	Upper limit	p-Value	Exposed	Unexposed	Relative weight
Zerbo (2013)	2.60	1.14	5.94	0.02			5.62
Horning (2017)	1.40	1.11	1.77	0.00			70.41
Brucato (2017)	1.62	0.58	4.52	0.36			3.64
Croen (2019)	1.50	0.97	2.32	0.07	33 / 94	573 / 2164	20.33
	1.48	1.22	1.80	0.00			

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	4	1.478	1.215	1.798	3.913	0.000	2.039	3	0.564	0.000	0.000	0.053	0.003	0.000
Random	4	1.478	1.215	1.798	3.913	0.000								

Figure 4: Forest plot of the association between maternal fever in the second trimester and ASD in offspring

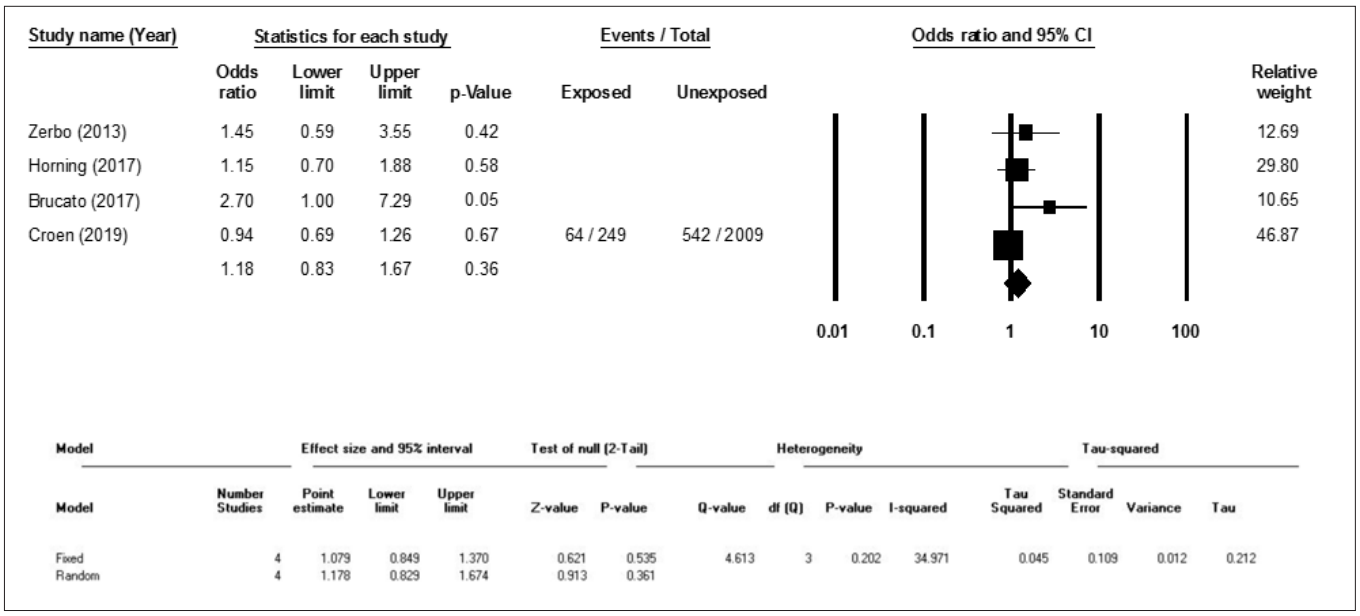


Figure 5: Forest plot of the association between maternal fever in the third trimester and ASD in offspring

Discussion

The present meta-analysis and systematic review provides an evidence-based association of prenatal maternal fever with ASD in offspring. For obvious ethical reasons randomized control trials have not been conducted to assess the perinatal and long-term outcomes following prenatal fever. Therefore, a meta-analysis of 9 high-quality research studies presents more powerful evidence of teratogenicity of prenatal maternal fever pertaining to ASD. Even stronger association with ASD was found following exposure during the first and second trimester, the vulnerable windows of fetal development.

Fever is common during human pregnancy. The ramification of fever action depends on the extent of its elevation, duration, and timing during embryo-fetal development. Knowledge of the effects of hyperthermia on perinatal and long-term human pregnancy outcomes in very limited. Human embryos and fetuses are very sensitive to thermal injuries during vulnerable stages of development and during neuronal migrations, leading to non-restorable neuronal loss. Research supports these findings, reporting adverse outcomes following exposure to “any fever”, suggesting that the risk of detrimental effects of hyperthermia is significant and still, have not been sufficiently studied [18]. In presented meta-analysis investigators presented a significant association of fever with increased risk for ASD, separately from other effects, pointing on significance of timing in gestation, and duration of fever [17, 23].

A recent BMJ meta-analysis reported that prenatal exposure to high environmental temperatures (that may raise the core body fever) is specifically associated with stillbirth and prematurity, risk factors, leading to ASD [26]. Authors display concerns about the increase in global temperatures and population health, but more research is needed to replicate and confirmation these results. Hyperthermal teratogenicity of MRI and ultrasound is of increased interest in view of knawel technology [27].

A resent meta-analysis of Tioleco et al. assessed an association of prenatal maternal fever and risk for autism in offspring and found that the combined effect of maternal fever during pregnancy was stronger than the effect for “any infection” [28].

Rossman et al. found that prenatal exposure of 107 fetuses to greater mean depth of ultrasonographic penetration (associated with increased heat) during first and second trimesters was consequently associated with higher rates of ASD when compared with two comparison groups of healthy controls and children with developmental delay [29]. This study was not included in the present meta-analysis because the extent of the thermal index was not reported. The editorial discussion was focused on complex environmental and genetic etiology of ASD where the ultrasonography is acting as an environmental stressor and modifier.

It should be stated that not every pregnant woman exposed to prenatal fever will deliver a child with ASD. Pregnant women who are exposed to a single or multiple risk factors, as well as showing a genetic predisposition may have a child with ASD. Prenatal fever may act as such a risk. Bai et al., reported that strongly heritable genetic factors are associated with 81.2% of the variance in ASD occurrence [10, 12, 22, 30]. The established nongenetic factors contributing independently to genetic risk are parental age, prematurity, pregnancy complications, male fetus, and infections.

The mechanism by which fever in pregnant mothers increases the risk of ASD in offspring has been described. Fever is mediated by several proinflammatory cytokines, most notably IL-1, IL-6, and TNFa. These are among the cascade of cytokines produced in response to infection or other inflammatory processes collectively referred to as maternal immune activation (MIA). There is strong evidence in murine models that this cytokine-rich environment in utero causes dysregulation in gene transcription of the developing fetal brain.

In recent years, the concept of copy number variation (CNV) and its implications on several neuropsychiatric conditions including ASD, schizophrenia, and bipolar disease has contributed to a better biomolecular understanding of the disease etiology. CNVs are structural variations of the genome. Common and recurring CNVs have been discovered in individuals with ASD and their unaffected family members. This indicates their likely contribution to the development of ASD. Given that both ASD-related CNVs and MIAs affect gene expression and lead to an altered environment for the developing fetal brain, both are documented aetiologies in the development of ASD.

The large portion of ASD-related CNVs that are heritable make CNV testing a valuable tool in providing genetic counseling, especially for those with a positive family history of psychiatric disorders, advanced parental age or an older child with ASD. CNV testing is done by chromosomal microarray (CMA) and would allow parents and medical care providers for an evidence-based decision-making process. A finding of heritable ASD-related CNVs associated with prenatal fever in concert with environmental risk factors would indicate higher risk of ASD in exposed children and consequently plan primary prevention or appropriate management.

Limitations

Limitations of a meta-analysis and search strategy. The studies which fit the inclusion criteria, are mostly reporting correlational association. Methodological limitations with associated biases, including retrospectivity. Potential multiple confounders (parental age, infections, family history of psychiatric disorders, prematurity, prenatal exposures to neurotoxins) were not considered and not reported.

Strengths

This is the first meta-analysis assessing fetal effect of fever independent of maternal infection. First attempt to assess conflicting outcomes pertaining to association of prenatal fever with increased risk of ASD in exposed offspring. High quality case-control studies included. Obtained meaningful results, discussed scientific evidence of main outcomes, proposed testing encourages future research.

Conclusion

The meta-analysis suggests fetal neurotoxicity during critical windows of CNS development following prenatal exposure to fever. Fever during pregnancy may be considered an additional risk factor associated with ASD in susceptible offspring. Our findings support existing knowledge on fever/hyperthermia teratogenicity which together with genetic factors may ask for consideration of prevention or early management. Future studies should collect and evaluate more detailed information on prenatal fever linking to ASD, with guidelines development objectives.

Dr. Nulman had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study Design: Ilana Leshtsinski, Irena Nulman, Mitko Madjunkov, Ellen Wong, Quenby Mahood, Fatma Etwel

Data Collection: Ilana Leshtsinski, Mitko Madjunkov, Ellen Wong, Quenby Mahood.

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Data Interpretation, Acquisition, Analysis: Ilana Leshtsinski, Irena Nulman, Mitko Madjunkov, Ellen Wong, Quenby Mahood, Fatma Etwel

Manuscript Preparation: Irena Nulman, Ilana Leshtsinski, Ellen Wong.

Critical revision of the manuscript for important intellectual content: Ilana Leshtsinski, Irena Nulman, Mitko Madjunkov, Ellen Wong, Quenby Mahood, Fatma Etwel

Literature Search: Quenby Mahood, Ilana Leshtsinski.

Funds Collection: Not externally funded.

References

[1] Vahia VN. Diagnostic and statistical manual of mental disorders 5: A quick glance. Indian journal of psychiatry. 2013; 55: 220.

[2] Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, et al. The changing epidemiology of autism spectrum disorders. Annual review of public health. 2017; 38: 81-102.

[3] Werling DM, Geschwind DH. Sex differences in autism spectrum disorders. Current opinion in neurology. 2013; 26: 146.

[4] Bai D, Yip BH, Windham GC, Sourander A, Francis R, et al. Association of genetic and environmental factors with autism in a 5-country cohort. JAMA psychiatry. 2019; 76: 1035-1043.

[5] Muhle RA, Reed HE, Stratigos KA, Veenstra-VanderWeele J. The emerging clinical neuroscience of autism spectrum disorder: a review. JAMA psychiatry. 2018; 75: 514-523.

[6] Hisle-Gorman E, Susi A, Stokes T, Gorman G, Erdie-Lalena C. Prenatal, perinatal, and neonatal risk factors of autism spectrum disorder. Pediatric research. 2018; 84: 190-198.

[7] Tick B, Bolton P, Happé F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. Journal of Child Psychology and Psychiatry. 2016; 57: 585-595.

[8] Sztainberg Y, Zoghbi HY. Lessons learned from studying syndromic autism spectrum disorders. Nature neuroscience. 2016; 19: 1408-1417.

[9] Satterstrom FK, Kosmicki JA, Wang J, Breen MS, De Rubeis S, et al. Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. Cell. 2020; 180: 568-584.

[10] Jiang HY, Xu LL, Shao L, Xia RM, Yu ZH, et al. Maternal infection during pregnancy and risk of autism spectrum disorders. Brain Behav Immun. 2016; 58: 165-172.

[11] Matta SM, Hill-Yardin EL, Crack PJ. The influence of neuroinflammation in Autism Spectrum Disorder. Brain Behav Immun. 2019; 79: 75-90.

[12] Hornig M, Bresnahan MA, Che X, Schultz AF, Ukaigwe JE, et al. Prenatal fever and autism risk. Molecular Psychiatry. 2018; 23: 759-766.

[13] Croen LA, Qian Y, Ashwood P, Zerbo O, Schendel D, et al.

Infection and fever in pregnancy and autism spectrum disorders: findings from the study to explore early development. Autism Research. 2019; 12: 1551-1561.

[14] Zerbo O, Iosif AM, Walker C, Ozonoff S, Hansen RL, et al. Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) study. Journal of autism and developmental disorders. 2013; 43: 25-33.

[15] Miller MW, Nyborg WL, Dewey WC, Edwards MJ, Abramowicz JS, et al. Hyperthermic teratogenicity, thermal dose and diagnostic ultrasound during pregnancy: implications of new standards on tissue heating. International journal of hyperthermia. 2002; 18: 361-384.

[16] Sandin S, Hultman CM, Kolevzon A, Gross R, MacCabe JH, et al. " Advancing maternal age is associated with increasing risk for autism: A review and meta-analysis". J Am Acad Child Adolesc Psychiatry. 2012; 51: 477-486.

[17] Saunders A, Woodland J, Gander S. A comparison of prenatal exposures in children with and without a diagnosis of autism spectrum disorder. Cureus. 2019; 11: e5223.

[18] Edwards MJ. Hyperthermia and fever during pregnancy. Birth Defects Research Part A: Clinical and Molecular Teratology. 2006; 76: 507-516.

[19] Lombardo MV, Lai MC, Baron-Cohen S. Big data approaches to decomposing heterogeneity across the autism spectrum. Molecular psychiatry. 2019; 24: 1435-1450.

[20] Atladóttir HÓ, Henriksen TB, Schendel DE, Parner ET. Autism after infection, febrile episodes, and antibiotic use during pregnancy: an exploratory study. Pediatrics. 2012; 130: e1447-1454.

[21] Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. Pediatrics. 2001; 107: e63.

[22] Brucato M, Ladd-Acosta C, Li M, Caruso D, Hong X, et al. Prenatal exposure to fever is associated with autism spectrum disorder in the boston birth cohort. Autism Research. 2017; 10: 1878-1890.

[23] Guisso DR, Saadeh FS, Saab D, El Deek J, Chamseddine S et al. Association of autism with maternal infections, perinatal and other risk factors: a case-control study. Journal of autism and developmental disorders. 2018; 48: 2010-2021.

[24] Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. Acta Psychiatrica Scandinavica. 2006; 114: 257-264.

[25] Chersich MF, Pham MD, Areal A, Haghighi MM, Manyuchi A, et al. Associations between high temperatures in pregnancy and risk of preterm birth, low birth weight, and stillbirths: systematic review and meta-analysis. bmj. 2020; 4: 371.

[26] Ziskin MC, Morrissey J. Thermal thresholds for teratogenicity, reproduction, and development. International Journal of Hyperthermia. 2011; 27: 374-387.

[27] Tioleco N, Silberman AE, Stratigos K, Banerjee-Basu S, Spann MN, et al. Prenatal maternal infection and risk for autism in offspring: A meta-analysis. Autism Research. 2021; 14: 1296-1316.

[28] Rosman NP, Abbott J, Vassar R. The Association of Prenatal Ultrasonography and Autism Spectrum Disorder—Reply. JAMA pediatrics. 2018; 172: 786-787.

[29] Hultman CM, Sandin S, Levine SZ, Lichtenstein P, Reichenberg A. Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. Molecular psychiatry. 2011; 16: 1203-1212.

[30] Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Molecular autism. 2017; 8: 1-6.