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Prenatal and Perinatal Metabolic Risk Factors for Autism: A Review and Integration of Findings from Population Based Studies

Julia Katz, MD[1], **Abraham Reichenberg, PhD**[1,2,4], **Alexander Kolevzon, MD**[1,2,3]

[1]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, NY, NY

[2]Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, NY, NY

[3]Department of Pediatrics, Icahn School of Medicine at Mount Sinai, NY, NY

[4]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, NY, NY

Abstract

Purpose of review: Given the ongoing rise in prevalence of autism spectrum disorder (ASD) and the challenges in developing and administering interventions to significantly alleviate ASD symptoms, there is an urgent need to identify modifiable risk factors for ASD. The goal of this review is to systematically evaluate the current evidence for an association between conditions related to maternal metabolic syndrome and risk for ASD in offspring focusing on methodically rigorous studies.

Recent findings: In recent years, multiple studies explored the association between various conditions related to maternal metabolic syndrome (obesity, hypertension, or diabetes prior to, or with onset during pregnancy) and ASD risk in the offspring.

Summary: Examining large, sufficiently powered, population-based epidemiological studies that explored the association between maternal metabolic syndrome and ASD, we found consistent evidence for an association between maternal preeclampsia and risk for ASD. Other conditions that are part of maternal metabolic syndrome, including maternal obesity, gestational weight gain, diabetes and gestational diabetes, should be studied further with careful attention paid to potential synergistic effects between different metabolic conditions. These findings highlight the need for rigorous, large, population based epidemiological studies of potentially modifiable ASD risk factors that could inform public health interventions.

Keywords

Autism spectrum disorder; maternal metabolic syndrome; preeclampsia; review; epidemiology

Corresponding Author: Abraham Reichenberg, PhD, Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1230, New York, NY 10029, Tel: 212-659-9177, avi.reichenberg@mssm.edu.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication, and restricted and repetitive patterns of behavior [1]. The prevalence of ASD has been increasing in recent decades and current estimates from the Center for Disease Control (CDC) suggest that 1 in 54 children in the US aged 8 years has ASD [2]. ASD is a leading cause of disability and has a significant public health impact with estimated national costs in the United States between $61–66 billion per year for children and $175–196 billion per year for adults [3,4,5].

The etiology of ASD is thought to be multifactorial and includes a combination of genetic and environmental factors, as well as their interaction [6]. Research confirms a strong causal genetic component, however, monozygotic twin studies report concordance rates less than 100%, suggesting a role for environmental factors as well [22–25,84].

Population-based epidemiological studies have been frequently utilized to explore potential environmental risk factors for ASD. For some risk factors, findings were further refined using systematic reviews and meta-analyses [26–50], and several have been consistently associated with ASD, including advanced maternal and paternal age [26–34,40] and birth complications resulting in fetal hypoxia [32,33,50].

Given the challenges in developing and administering interventions to significantly alleviate ASD symptoms, it is critical to continue exploring modifiable risk factors as a means of primary prevention. Among potential risk factors for ASD, maternal metabolic syndrome consists of several conditions with well-studied preventive and treatment approaches [13]. The metabolic syndrome includes a constellation of pathophysiological states including obesity, insulin resistance, hypertension, and hypercholesterolemia, and predisposes individuals to develop numerous medical conditions including diabetes mellitus (DM) [13,14,17]. According to the CDC, the prevalence of obesity continues to rise and is estimated to be 40% among women aged 20–39 [15]. Further, the incidence of metabolic syndrome has paralleled the incidence of obesity [13]. Human and animal studies have shown that maternal prenatal metabolic syndrome includes increased adiposity and insulin resistance and results in an inflammatory state [18,19] as well as altered leptin signaling [68–72]. These changes have significant impact on fetal neurodevelopment [20] secondary to neuroinflammation and can affect synaptic plasticity, oxidative stress, as well neurotrophic and neuroprotective signaling [14,16,20,21,68–71,73,74–79].

Multiple studies have explored the association of ASD with the various conditions related to maternal metabolic syndrome, including maternal obesity and gestational weight gain (GWG)[56,67, 81,86,89], maternal DM [47,55,58,59,60,61,65,66], gestational DM [55,58,59,60,61,65,66], maternal pregnancy induced hypertension, and preeclampsia [37,53,55,57,61,62,63,64]. However, most studies had methodological limitations including small sample size, inconsistent or unreliable reporting of outcomes (i.e., ASD) or maternal exposure, as well as the use of clinical samples that are prone to ascertainment bias [12]. Several reviews have also discussed the association between specific factors of the metabolic syndrome and its association with ASD [14,16,27,30,35–37,67,94,95].

The goal of this review is to systematically evaluate the evidence for the association of factors related to maternal metabolic syndrome and the risk for ASD. In order to minimize bias of results due to methodological limitations, this review will focus on rigorous studies using large, sufficiently powered, population-based epidemiological samples.

Methods

We conducted a systematic literature search in PubMed from inception until June 2020. Medical Subject Headings (MeSH) and relevant key words were used to conduct the search. Key words included Autism/ASD [AND] maternal metabolic syndrome, Autism/ASD [AND] body mass index/BMI, Autism/ASD [AND] weight gain, Autism/ASD [AND] weight, Autism/ASD [AND] obesity, Autism/ASD [AND] gestational weight gain, Autism/ASD [AND] gestational diabetes, Autism/ASD [AND] diabetes, Autism/ASD [AND] hypertension, Autism/ASD [AND] gestational hypertension, Autism/ASD [AND] preeclampsia. In addition, we reviewed references from original papers and review articles to identify additional relevant studies.

In order to meet criteria for inclusion in this review, studies had to have: (1) a well-defined sample of cases drawn from population-based registers or birth cohorts; (2) a population of interest (i.e., individuals with ASD) sample size greater than 1000 ASD cases; (3) use of standardized diagnostic criteria including either the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV [91] or DSM-5 [1]) or the International Classification of Diseases (ICD-9 [93] or ICD-10 [92]); (4) similarly ascertained exposure and outcomes.

All abstracts were reviewed for relevance and excluded if our inclusion criteria were not met. For example, studies were excluded due to lack of population-based samples, too few cases of ASD (<1000), overlapping cohorts with other included studies, or a focus on exposures outside the scope of this review, such as use of medications or complications during labor and delivery (see Figure 1). Full texts of relevant studies were then reviewed by the authors (JK, AR, and AK) to ensure all eligibility criteria were met and 100 percent consensus was reached. Studies used different measures of relative risk to report on the association between maternal conditions and ASD risk, including Odds-Ratio (OR), Relative-Risk (RR) and Hazard-Ratio (HR). When the outcome is rare (as is ASD), then OR and RR are approximately equal and can readily be interchanged. HR is not always interchangeable because risk factors may operate differently to produce the initial manifestation of a disease and its subsequent presentation. For clarity, we summarized study results in terms of the proportion increase in risk. The specific measures of association used in individual studies are listed in the associated Tables.

Results

A total of 562 publications were found in the initial search. After excluding 54 duplicates and 365 with irrelevant topics, we examined 155 relevant studies. 143 were eliminated after not meeting our inclusion criteria. However, in order to be as thorough as possible and for reference and context, we also summarize results from 11 studies [31,80–83,85–90] that met all of our inclusion criteria except that of sample size (see Table 2). Finally, we

identified 12 studies [54–59,61–66] examining the association between aspects of maternal metabolic syndrome and offspring development of ASD (see Figure 1). Study characteristics and summaries of the main findings of individual studies with crude and fully adjusted risk estimates are presented in Table 1 and summarized below. There were three studies from California [58,65,66] with partially overlapping samples (Jo et al., 2019; Xiang et al., 2015 and 2018). All studies were included because they provided additional information relevant to the goals of this review.

All studies were published between 2010–2020. Ten studies were population-based birth cohort studies [54–59,62,64,65,66] and two were case-control studies [61,63]. Seven different geographic locations were represented, including Denmark, Canada, Sweden, California (US), Finland, Western Australia, and Norway.

Pre-Pregnancy Weight

Among the studies that met criteria for our review, both Andersen and colleagues (2018) and Gardner and colleagues (2015) found a significant association between obese mothers and the risk for ASD. Body mass index (BMI) ≥ 30 was associated with a 1.42 to 1.94 fold greater risk of developing ASD (Table 1). Andersen and colleagues (2018) further observed a possible dose-response relationship with the highest risk in severely obese mothers (BMI ≥ 35). In matched sibling analyses, however, Gardner and colleagues (2018) no longer observed a statistically significant association between maternal BMI and ASD risk.

Multiple metabolic conditions often co-occur. Kong and colleagues (2020) examined the association of BMI with ASD risk based on both absence of DM and presence of subtypes of DM. They found an increased risk of ASD among overweight (BMI ≥ 25), and obese (BMI≥ 30) mothers without DM, but no association among severely obese (BMI ≥ 35) mothers without DM (Table 1). BMI was associated with a higher risk of ASD irrespective of other insulin resistance conditions [i.e., insulin dependent DM (IDDM), Type 2 DM (T2DM) and gestational DM].

Gestational Weight Gain

Only Gardner and colleagues (2015) applied methods that met our inclusion criteria and found that excessive GWG independent of pre pregnancy (baseline) BMI was associated with a 1.12 fold greater risk for developing ASD (Table 1). A similar risk was observed for ASD with and without intellectual disability (ID). A matched sibling analysis showed similar results. In addition, a dose response effect was observed where risk increased with each 5 pound increment of weight gained among mothers with normal baseline BMI. Interestingly, Gardner and colleagues (2015) also showed a significant association of insufficient GWG with the risk of ASD.

Pre-gestational diabetes

Among the five studies [55,58,59,65,66] that examined the association between pre-gestational DM and ASD that met our inclusion criteria, the overall increase in risk varied from 1.39 to 1.65 (Table 1). Of note however, 3 of the studies [58,65,66] had overlapping samples. Similarly to their previous work described above, Kong and colleagues (2020)

examined the risk for ASD and pre-gestational T2DM as well as pre-gestational IDDM, stratified according to BMI. A significant association was found between severely obese mothers (BMI ≥ 35) with T2DM or IDDM and the risk for ASD (Table 1). Langridge and colleagues (2013) did not find significant associations between DM and the risk for ASD, however, the type of DM and stage of development (gestational or pre-gestational) were clustered together in this study, making it difficult to compare study results.

Gestational Diabetes

Three studies [55,56,65] evaluated gestational DM as a binary exposure and only one study [56] showed a significant increased risk for ASD among affected mothers. Other studies stratified gestational DM based on gestational age of either 24 weeks [58] (Jo et al., 2019) or 26 weeks [65,66] (Xiang et al., 2015; Xiang et al., 2018) and showed increased risk ranging from 1.24 to 1.63 fold. Kong and colleagues (2018) examined the association of gestational DM with risk for ASD stratified by BMI. A significant association was found among overweight (BMI ≥ 25) and obese (BMI ≥ 30) mothers with DM (Table 1), however, no association was found between severely obese mothers (BMI ≥ 35) with DM and risk for ASD.

Pre-Pregnancy Hypertension

Few studies have reliably examined the association between pre-pregnancy hypertension and offspring development of ASD. Pre-pregnancy hypertension exposure documentation is often lacking or based on maternal self-report and therefore typically clustered with gestational hypertension/preeclampsia in analyses [35]. Among the studies that met our inclusion criteria for review, only Gardner and colleagues (2015) examined the direct association of pre-gestational hypertension with ASD and did not find a significant increase in risk (Table 1). Langridge and colleagues (2013) examined the risk for ASD using clustering of both preeclampsia or essential hypertension and found that risk increased for cases with ASD and ID (Table 1).

When pre-existing hypertension was clustered with pregnancy induced hypertension or pre-eclampsia in other studies, results were inconsistent [80,83]. Maher and colleagues (2020) examined both the effect of pre-gestational hypertension clustered with preeclampsia and preeclampsia alone. They showed decreased effect size resulting in an association that was not statistically significant when preeclampsia was clustered with chronic hypertension (as compared to preeclampsia alone).

Gestational Hypertension/Preeclampsia

Gestational hypertension and preeclampsia are typically clustered together in analyses and consistently found to be associated with increased risk of ASD in offspring. Both large scale studies included in this review (see Table 1) [55,56,57,61,62,63,64] and smaller scale studies (see Table 2) [80,81,83,85,88] support this association. Of the five studies [55,56,57,62,64] to measure gestational hypertension and/or preeclampsia as an exposure that met our inclusion criteria, all five found increased risk of ASD, ranging between 1.25 to 1.49 fold. Langridge and colleagues (2013) found that risk increase was restricted to ASD with ID, a result in part supported by Polo-Kantola and colleagues (2014) who found risk

increasing as a function of severity related to ASD diagnostic subtype (see Table 1). Maher and colleagues also showed that the association between preeclampsia and ASD was present in a sibling matched analysis. However, further stratification of data to examine ASD with and without ID showed the highest risk for ASD with ID and the lowest (but still statistically significant) risk for ASD without ID.

Discussion

This study systematically evaluated the evidence for the association between maternal metabolic syndrome around pregnancy and risk for ASD in offspring. By focusing on large population based studies, we endeavor to limit potential biases and draw evidence-based conclusions.

The most consistent association across studies was observed for preeclampsia and ASD. This is further supported by a sibling analysis [62], suggesting limited familial confounding factors. Additional sub-analyses [61,62] showed even greater effects for preeclampsia when restricting analysis to offspring with ASD and ID compared to ASD without ID. Sun and colleagues [64] examined whether pre-term birth contributes to the observed risk, as delivery is considered a treatment for preeclampsia. They found only minimal difference in risk (OR of 1.29 for term only vs 1.31 for all births including pre-term) suggesting that pre-term birth is not a strong factor in the relationship between preeclampsia and ASD.

While the etiology of how preeclampsia contributes to the risk of ASD is not fully elucidated, several mechanisms have been repeatedly proposed. Preeclampsia, a condition associated with chronic immune activation, contributes to an increase in the circulation of pro-inflammatory cytokines such as IL-6 and CRP, which can impact the development of the hypothalamic-pituitary-adrenal (HPA) axis as well as neurotransmitter pathways in the developing fetus [16,97]. In addition, the placental dysfunction seen with preeclampsia can result in reduced placental perfusion, causing fetal hypoxia and oxidative stress [37,57,62,74,94].

Inflammation has been suggested as a primary contributor to the adverse effects of the metabolic syndrome, and one potential mechanism through which pre-eclampsia as well as the other metabolic conditions contribute to the development of ASD. A chronic low grade inflammatory state is thought to be present in obese mothers, which accompanies the fetus during its intrauterine development [18]. Animal studies suggest that low grade inflammation and release of pro-inflammatory cytokines from adipose tissue play a role in the development of insulin resistance [16,96]. This in turn can impact the developing fetus by inducing a chronic state of inflammation via circulating cytokines that are able to cross the placenta and impact the inflammatory profile of the fetus, as well as its brain development [19,20]. In addition, the fetus' intrauterine exposure to a modified nutrient environment with high concentrations of glucose and leptin, can also contribute to alteration in its brain development. Leptin signaling, similarly to pro-inflammatory cytokines, was found to have effects on the HPA axis, synaptic plasticity, and BDNF signaling [14,16,59,60,98]. Furthermore, these intrauterine effects can be perpetuated by alteration in brain development as well as epigenetic mechanisms [14].

Given that other conditions comprising the maternal metabolic syndrome are significant factors contributing to maternal gestational inflammation and the potential mechanisms associated with the risk of developing ASD, it is important to continue investigating the association between those factors and ASD risk. In this review, we include at least one study supporting an association with ASD risk for each of the conditions comprising the maternal metabolic syndrome (pre-gestational DM, GDM, pre-pregnancy weight and GWG). However, this is not sufficient to draw definitive conclusions.

In summary, current evidence from large scale population-based epidemiological studies support an association between preeclampsia and ASD. Evidence for other maternal conditions which are part of the metabolic syndrome was limited due to a paucity of studies. Given the frequent co-occurrence of the conditions comprising the metabolic syndrome, potential synergistic effects should be systematically studied. The use of multiple study designs, especially those that control for potential familial confounding (e.g., sibling control studies), and examining the effects of medical interventions (e.g., pharmaco-epidemiological studies) are imperative for evaluating potential mechanisms and preventive approaches in the future.

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Conflicts of interest:

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Key points:

- Multiple studies explored the association between various conditions related to maternal metabolic syndrome and ASD risk with mixed results
- Current evidence from large scale population based epidemiological studies support an association between preeclampsia and ASD
- Given the frequent co-occurrence of the conditions comprising the metabolic syndrome, potential synergistic effects should be systematically studied

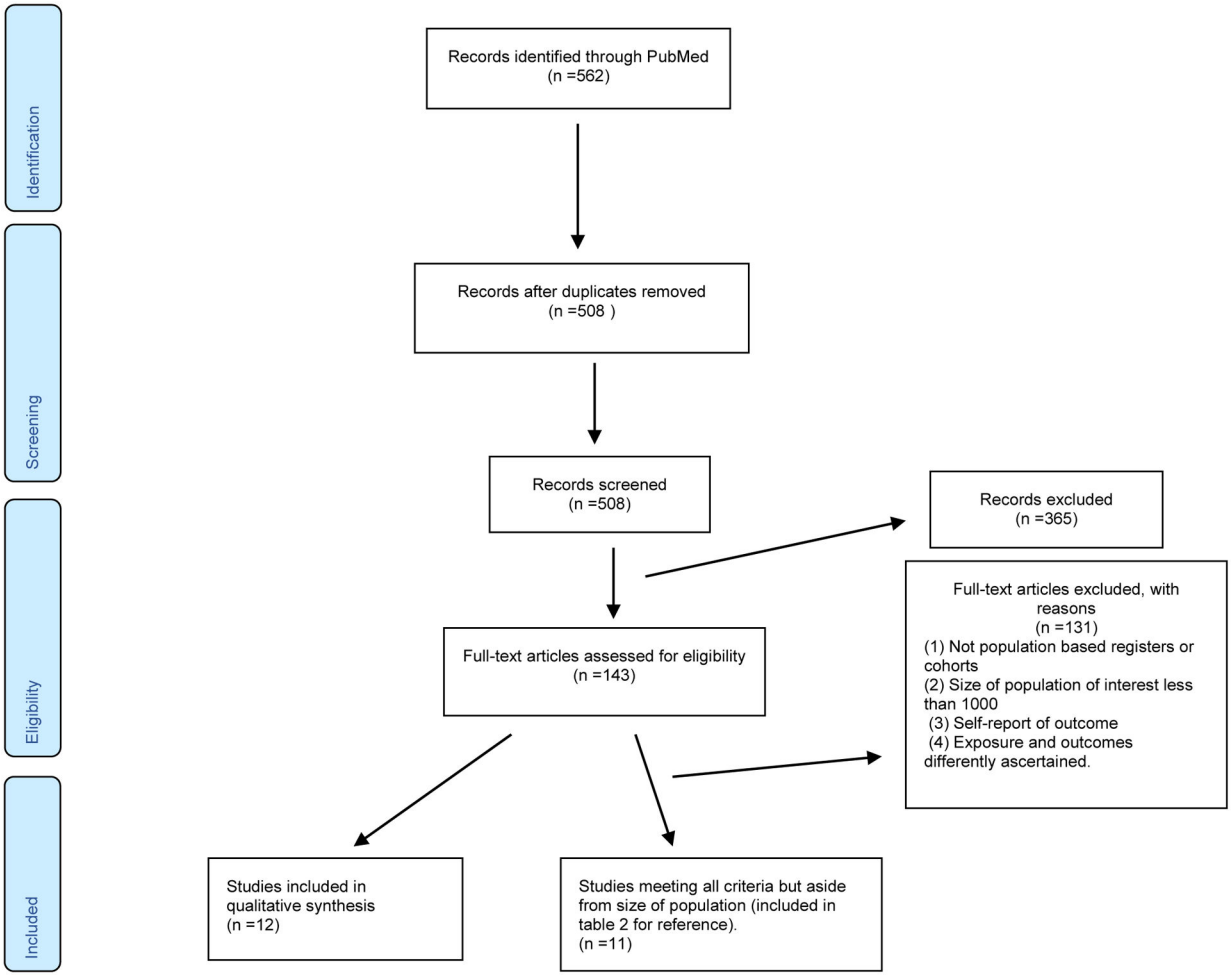

Figure 1.
PRISMA flow diagram

Table 1.

Population based studies not included in the review

Author	Publication date	study location	ASD cases / Non cases	study design	diagnostic criteria	Relevant exposure	Crude data	Fully adjusted
Andersen et al. [54]	Feb-18	Denmark (Danish national birth cohort (DNBC)	1,116 / 81,892	population based cohort	ICD-10	maternal pre-pregnancy BMI self report	ASD+ADHD HR: 30 ≤ BMI < 35: 1.43 (1.06;1.92), BMI ≥ 35: 2.11 (1.43;3.13)	ASD+ADHD HR: BMI<18.5: 1.09 [0.75–1.58] 30 ≤ BMI < 35: 1.42 [1.05–1.92] BMI ≥ 35: **2.08** [1.40–3.08]
Burstyn et al. [55]	Sep-10	Alberta, Canada,between January 1, 1998, and December 31, 2004.	1,138/218,890	population based cohort	ICD-9	pre pregnancy DM, GDM, preeclampsia		RR Prepregnancy DM **1.65** (1.01–2.71) GDM RR 1.24 (0.94–1.65) preeclampsia RR 1.49 (1–2.23)
Gardner et al. [56]	Jun-15	sweden (Stockholm Youth Cohort (SYC), a prospective register-based cohort consisting of all individuals born 1984–2007 and resident in Stockholm County)	6,420/333,057	population based cohort	ICD-9, ICD-10, DSM-IV	(BMI) at first antenatal visit, GWG, pre gestatonal HTN, pre gestational DM, GDM and preeclampsia	OR: BMI ≥25 & < 30: 1.34 (1.24 – 1.45) BMI ≥ 30: 2.07 (1.85 – 2.32)	OR: Pre gestational HTN 1.16 (0.85–1.58) Preeclapsia 1.25 (1.07–1.47) Pre gestationl DM 1.53 (1.07–2.2) Gestational DM 1.49 (1.09–2.07)BMI ≥25 & < 30 1.31 (1.21–1.41) BMI ≥ 30 **1.94** (1.72–2.17) ALL mother/child pairs: Insufficient GWG-> 1.17 (1.04 – 1.31) Excessive GWG-> 1.12 (1.01 – 1.25) mothers w/normal baseline BMI: Insufficient GWG-> 1.22 (1.07 – 1.40) excessive GWG-> 1.23 (1.08 – 1.40)
Getahun et al. [57]	Feb-17	Kaiser Permanente Southern California hospitals between 1991 and 2009	6,255/594,638	retrospective cohort study	DSM-IV	preeclampsia (ICD-9-CM codes 642.x)	HR 1.38 (1.23, 1.54)	HR 1.26 (1.13, 1.41)
Jo et al. [58]	Dec-19	246,420 singleton children born in Kaiser Permanente Southern California hospitals in 1999–2009	2,471/246,420	retrospective cohort study	ICD-9	maternal diabetes during index pregnancy. GDM exposure was further categorized as diagnosis before or after 24 weeks' gestation.	GDM <24 weeks' gestation HR 1.40 (1.08–1.81), Pre-existing type 2 diabetes HR 1.65 (1.26–2.16)	GDM <24 weeks' gestation HR 1.24 (0.95–1.62) Pre-existing type 2 diabetes HR 1.45 (1.11–1.91)
Kong et al. [59]	Feb-20	nationwide registries in Finland 2004–2014	2,346/649,043	population-based cohort study	*ICD-10*	Maternal pre pregnancy body mass index, insulin-treated		HR: No DM: BMI ≥25 & < 30 1.14 (1.02–1.28), BMI ≥30 & < 35 1.29 (1.07–1.56), BMI ≥35 1.21

Author	Publication date	study location	ASD cases / Non cases	study design	diagnostic criteria	Relevant exposure	Crude data	Fully adjusted
						pregestational diabetes, pre gestational type 2 diabetes and gestational diabetes without insulin treatment. all date obtained from database (no self report)		(0.88–1.66). IDDM: BMI ≥25 & < 30 0.43 (0.11–1.72), BMI ≥30 & < 35 **3.61** (1.61–8.07), BMI ≥35 **5.93** (2.81–12.52). T2DM: BMI ≥25 & < 30 **1.68** (0.75–3.75), BMI ≥30 & < 35 1.14 (0.43–3.05), BMI ≥35 **2.28** (1.18–4.41). GDM: BMI ≥25 & < 30 1.28 (1.07–1.53), BMI ≥30 & < 35 **1.57** (1.26–1.95), BMI ≥35 1.29 (0.95–1.74)
Lagridge et al. [61]	Jan-13	Western Australia (WA) between January 1984 and December 1999	1,179/383,153	case contol?	DSM-IIIR, DSM-IV, DSM-IV-TR	Maternal diabetes during pregnancy (gestational diabetes or pre-existing diabetes), Pregnancy hypertension (preeclampsia or essential hypertension).	univarate*: Maternal pre pregnancy DM and GDM: ASD+ID 1.38 (0.86–2.2), ASD−ID 1.35 (0.74–2.46) pregnancy HTN (preeclampsia or essential) ASD+ID 1.34 (1.07–1.67), ASD−ID 0.81 (0.58–1.74)	Multivariate*: Maternal pre pregnancy DM and GDM: ASD+ID 1.03 (0.62–1.69), ASD−ID 1.3 (0.69–2.45) pregnancy HTN (preeclampsia or essential) ASD+ID 1.34 (1.05, 1.71), ASD−ID 0.73 (0.5–1.07)
Maher et al. [62]	Feb-20	Sweden from 1982 to 2010	54,071/2,842,230	population-based cohort study	ICD-9 and ICD-10	preeclampsia	Preeclampsia HR 1.36 (1.31–1.43)	HR Preeclampsia 1.25 (1.19, 1.30) Preeclampsia and SgA **1.66** (1.49, 1.85) Preeclampsia without SGA 1.20 (1.14, 1.26) SGA only **1.60** (1.53, 1.67)
Polo-Kantola et al. [63]	Feb-14	Finland from 1990–2005	4,713 /total amount of cases not available	Registry-based case-control	ICD-9 and ICD-10	maternal high blood pressure included both pre-eclampsia and pregnancy induced hypertension	OR: childhood autism 1.56 (1.–2.1) PDD 1.36 (1.04–1.8) Asperger syndrome 1.3 (1–1.7)	OR: childhood autism **1.6** (1.1.–2.2) PDD 1.3 (1–1.7) Asperger syndrome 1.03 (0.8–1.4)
Sun et al. [64]	Apr-20	Norway's Medical Birth Registry January 1, 1991, through December 31, 2009, and followed up through December 31, 2014	3,548/980,560	prospective, population-based cohort study	ICD-9 and ICD-10	Preeclampsia	term birth: OR 1.37 (1.15–1.62) pre-term+term: OR 1.37 (1.19–1.59)	term birth: OR 1.29 (1.08–1.54) pre-term+term: OR 1.31 (1.12–1.52)
Xiang et al. [65]	Apr-15	1995–2009 at Kaiser Permanente Southern California (KPSC) hospitals.	3,388/322,323	Retrospective longitudinal cohort study	ICD-9	Maternal preexisting type 2 diabetes and GDM	Bivariable: T2DM HR 1.59 (1.29–1.95) GDM HR 1.18 (1.04–1.33) GDM ≤ 26wks HR 1.63 (1.35–1.97)	Multivariable adjused: T2DM HR 1.3 (1.04–1.62) GDM HR 1.03 (0.9–1.17) GDM ≤ 26wks HR 1.4 (1.14–1.72) GDM>26wks HR 0.86 (0.73–1.02)

Author	Publication date	study location	ASD cases / Non cases	study design	diagnostic criteria	Relevant exposure	Crude data	Fully adjusted
							GDM >26 &<30 HR 0.94 (0.76–1.15) GDM >30 HR 1.04 (0.81–1.32)	
Xiang et al. [66]	Jul-18	Kaiser Permanente Southern California (KPSC) hospitals from January 1, 1995, through December 31, 2012	5,827/419,425	Retrospective cohort study	ICD-9	T1DM, T2DM, GDM	T1DM HR 2.36 (1.36–4.12) T2DM HR 1.45 (1.24–1.7) GDM ≤ 26wks HR 1.3 (1.12–1.51) GDM >26wks HR 0.99 (0.88–1.12)	T1DM HR **2.33** (1.29–4.21) T2DM HR 1.39 (1.18–1.62) GDM ≤ 26wks HR 1.26 (1.08–1.47) GDM >26wks HR 0.98 (0.87–1.1)

Table 2.

Population based studies included in the review

Author	Publication Date	Study Location	Cohort Size	Study Design	Diagnostic Criteria	Relevant Exposure	Findings
Connolly et al. [31]	Aug-16	Cincinnati Children's Hospital Medical Center's 2009–2014	503	case control	ICD9	pre pregnancy weight/ BMI, GDM	Maternal obesity (BMI≥ 30) and GDM were associated with approximately 1.5-fold increased odds of having a child with an ASD. For mothers with both GDM and obesity, the association was twofold.
Cordero et al. [80]	Jun-19	The Study to Explore Early Development (SEED) is a U.S. multisite. California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania	698	case control	ADOS and ADI-R	pre pregnancy DM, GDM and HTN prior and during pregnancy	Hypertension (pre pregnancy and PIH/preeclampsia) was associated with ASD (aOR = 1.69 [95% CI 1.26, 2.26]). Diabetes (pre gestational an GDM clustered) during pregnancy was not associated with ASD (aOR = 1.10 [95% CI 0.77, 1.56]).
Dodds et al. [81]	Jul-11	1990 and 2002 in Nova Scotia	924	cohort	ICD-9 or ICD-10	pregnancy wt gain, pre pregnancy weight, pre pregnancy HTN, HTN during pregnancy	Univariate: Pregnancy weight gain ≥18 kg RR 1.26 (1.08–1.47), Pregnancy induced hypertension (PIH) RR 1.24 (1.02–1.52), pre pregnancy weight >90kg RR 1.72 (1.39–2.13), pre gestational DM RR1.98 (0.94–4.16), materal weight at delivery >120kg RR 2.18 (1.1–3.16), GDM RR 1.29 (0.9–1.83). Multivariate: Pre-pregnancy weight ≥90 kg RR 1.58 (1.26–1.98), Pregnancy weight gain ≥18 kg RR 1.19 (1.02–1.39), no other data.
Getz et al. [82]	Sep-16	General Practice Research Database from 1993 through 2008 ("about 6% of the population of England, Nortern Ireland, Scotland and Wales"	889	case control	E140.00 Infantile autism, *diagnostic source was not reported	maternal pre-pregnancy BMI	ORs for maternal obesity 1.54 [95% CI: 1.26, 1.89]
Krakowiak et al. [83]	May-12	CHARGE (Childhood Autism Risks from Genetics and the Environment) study in California, January 2003 and June 2010	517	case control	ADOS and ADI-R	maternal T2D or GDM in the index pregnancy. Other conditions of interest were hypertension and obesity, defined as BMI >30 with onset before index pregnancy	The association between diabetes (T2DM or GDM) and ASD did not reach statistical significance, the association between hypertension (during pregnancy and before) and ASD was not signinficant. The risk of having a child with ASD to TD, was significantly increased among obese women (ASD, OR: 1.67 [95% CI: 1.10–2.56],
Mann et al. [85]	May-10	South Carolina, 1996 through 2002	472	case control	ICD-9	Pre-eclampsia/eclampsia	OR 1.69 (1.26–2.28)
Shen et al. [86]	Jan-18	Han Chinese population.	705	case control	DSM-IV-TR	maternal pre-pregnancy BMI, GWG	Excessive GWG was associated with autism risk (OR = 1.327, 95% CI: 1.021–1.725) Excessive GWG increased the risk of autism in overweight/obese mothers (OR = 2.468, 95% CI: 1.102–5.526)
Surén et al. [87]	May-14	Norwegian Mother and Child Cohort Study	419	case control	DSM-IV-TR	Maternal and paternal height and weight were recorded in a questionnaire completed	Maternal BMI <18.5: OR 1.39 (0.79–2.46) BMI 25.0–29.9 : 1.29 (0.99–1.69) BMI >30.0: 1.17 (0.81–1.7)

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Author	Publication Date	Study Location	Cohort Size	Study Design	Diagnostic Criteria	Relevant Exposure	Findings
						by the mothers during week 18 of pregnancy	
Walker et al. [88]	Feb-15	California January 29, 2003, through April 7, 2011, (CHARGE) study	517	case control	ADOS and ADI-R	Preeclampsia	OR 2.36; 95% CI, 1.18–4.68);”
Windham et al. [89]	Feb-19	Study to Explore Early Development (SEED), a multi-site case-control study of children born in 2003–2006. California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania	540	case control	ADOS and ADI-R	Maternal height, weight, and GWG were self-reported	BMI ≥25 & < 30 1.25 (0.94–1.68), BMI>30 OR 1.37 (0.98–1.92). GWG 35–44lb OR 1.52 (1.05–2.22) GWG >44lb OR = 1.58 (1.08–2.31)
Xiang et al. [90]	Jun-19	Kaiser Permanente Southern California (KPSC) hospitals between January 1, 2012, and December 31, 2013	707	cohort	ICD-9	HbA1c screening in the early prenatal period	HbA1c > 6.5% (n-15) HR 1.79 (1.06–3.00)