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Review

Understanding the link between different types of maternal diabetes and the onset of autism spectrum disorders☆

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ABSTRACT

Autism spectrum disorders (ASD) encompass a collection of neurodevelopmental disorders that exhibit impaired social interactions and repetitive stereotypic behaviors. Although the exact cause of these disorders remains unknown, it is widely accepted that both genetic and environmental factors contribute to their onset and progression. Recent studies have highlighted the potential negative impact of maternal diabetes on embryonic neurodevelopment, suggesting that intrauterine hyperglycemia could pose an additional risk to early brain development and contribute to the development of ASD. This paper presents a comprehensive analysis of the current research on the relationship between various forms of maternal diabetes, such as type 1 diabetes mellitus, type 2 diabetes mellitus, and gestational diabetes mellitus, and the likelihood of ASD in offspring. The study elucidates the potential mechanisms through which maternal hyperglycemia affects fetal development, involving metabolic hormones, immune dysregulation, heightened oxidative stress, and epigenetic alterations. The findings of this review offer valuable insights for potential preventive measures and evidence-based interventions targeting ASD.

1.Introduction

Autism spectrum disorder (ASD) is a congenital neurodevelopmental disorder (NDD) that typically manifests in early childhood, before the age of 3. It is characterized by repetitive and stereotyped behaviors and social communication disorders [1]. The American Academy of Pediatrics recommends that all infants be clinically assessed for ASD at 18 and 24 months to detect early signs [2]. ASD is associated with a range of clinical and health problems, including mental retardation, electroencephalographic abnormalities, epilepsy, malformations, and magnetic resonance imaging (MRI) abnormalities [3-5]. The prevalence of ASD is approximately 1 % of children worldwide [6]. In China, it is estimated that there may be over 10 million individuals with ASD and over 2 million patients aged 0–14 years by 2020, with an annual growth rate of nearly 200,000, according to a report on the Development of the Autism Education and Rehabilitation Industry.

The exact causes of ASD are not yet fully understood, but it is believed that both genetic and environmental factors play a role [7]. Studies have shown that genetics account for 30–40 % of all autism cases, with standard or rare mutations and copy number variants (CNVs) being identified in some ASD children [8-10]. However, the prevalence of these genetic candidates tends to be low in the population. On the other hand, environmental factors such as maternal disease and drug abuse, air pollution exposure, family life behaviors, and metal exposure during the critical neurodevelopmental period have been found to affect the development of ASD directly [11]. Understanding the role of environmental factors in ASD pathogenesis can develop prevention strategies and effective treatments.

Several studies implicate that early intrauterine environment insults during a critical period are critical for ASD development [12,13]. Many epidemiological studies suggest maternal diabetes during pregnancy is related to an increased ASD risk in offspring [14]. Maternal diabetes, such as pregestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM), are the most frequent complications during pregnancy and have increased in recent decades due to trends in increasing maternal age and obesity [15]. GDM appears typically during pregnancy, especially during the second trimester, as women diagnosed with GDM display no diabetes signs before the pregnancy [16]. PGDM and GDM have been related to slight interference in postnatal growth and development. ASD has been mentioned in several studies on

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neurodevelopmental outcomes in children born to mothers with PGDM or GDM [17-19]. Indeed, most previous studies demonstrated a positive association between GDM, PGDM, and an increased rate of ASD in the offspring [20-23]. Mechanisms underlying the effects of maternal diabetes on the developing fetus may involve metabolic disturbances, immune dysregulation, increased oxidative stress, and epigenetic changes [24,25].

In this review, we aimed to provide a comprehensive summary of the evidence linking various types of maternal diabetes, including type 1 diabetes (T1DM), type 2 diabetes (T2DM), and GDM, to the risk of ASD in their children. Furthermore, the review sheds light on how maternal diabetes affects fetal neurodevelopment by altering the embryonic transcriptional profile and increasing the changes resulting from gene regulation.

2. Maternal diabetes involved in ASD development in patients

2.1. ASD in offspring of diabetic mothers

Most studies show an increased prevalence between maternal diabetes and ASD (Tables 1 and 2). Epidemiological studies have suggested that maternal diabetes during pregnancy is more likely to cause ASD in offspring [26-28]. In 2006, a population-based cohort survey conducted in Australia by Leonard *et al.* found an increased risk of ASD in children of women with diabetes: odds ratio (OR) 2.89 confidence interval (CI) [1.28;6.5] [29]. As in other published cohort and case-control studies, an even more significant trend seems to be associated with ASD. A recent case-control study in Egypt shows several maternal and neonatal risk factors for ASD [30-32]. A History of diabetes (OR 5.98 [1.99;17.97]) was associated with the increased odds of ASD. This risk was further exacerbated in the offspring of diabetic women who gained excess weight during pregnancy [30]. Xu et al. (2014) performed a systematic literature search including three cohorts and nine case-control studies to assess maternal diabetes and ASD risk in the offspring. The meta-analyses of cohorts and case-control studies displayed a 50 % increase in ASD risk when all types of maternal diabetes were pooled [31]. A study conducted by Li using the Boston Birth Cohort showed that maternal diabetes and pre-pregnancy obesity were highly associated with ASD in offspring. Significantly increased risk of ASD in offspring was observed in mothers with PGDM combined with obesity: hazard ratio (HR) 3.91 95 %CI (1.76;8.68]; and in mothers with GDM combined with obesity: HR 3.04 [1.21;7.63] [32]. Consistently, an intergenerational prospective study from the Boston Birth Cohort showed that the risk of ASD was greater among mothers with obesity/diabetes, and this risk was even higher for male children [33]. However, some studies could not demonstrate such associations. A case-control study nested within a national unselected birth cohort by Hultman et al. (2002) investigated possible associations between perinatal measures and the subsequent development of infantile autism [34]. They found an association of ASD with several pregnancy-associated factors but not with maternal diabetes [34]. Cordero et al. found that a US multisite case-control study that enrolled children born in 2003–2006 at 2–5 years of age did not find a strong association between maternal diabetes and ASD: aOR 1.10 [0.77;1.56] after adjustment for covariates [35].

2.2. ASD in offspring according to the type of the mother's diabetes

T1DM is regarded as an autoimmune disease that affects cells, whereas T2DM is marked by progressive β-cell dysfunction and insulin resistance [36]. Gestational diabetes (GDM) is linked to glucose tolerance impairment during pregnancy. Given the different pathogenesis and socio-demographics of diabetic subtypes, it is crucial to examine the association between subtypes of maternal diabetes and ASD risk in offspring. In a large, multiethnic clinical cohort of singleton children born at 28 to 44 weeks gestation in California, T2DM was not significantly associated with ASD risk in offspring (HR 1.21 [0.97;1.52]), but

Table 1
Studies related to the association between different type of maternal diabetes and an autism spectrum disorder in offspring.

Study type	Sample size	Main findings	Ref
ASD in Offspring of Diabetic Mothers			
A population - based study	ASD = 191 Controls = 236,964 (age:7–16years)	ASD risk was increased for children of women with diabetes (OR=2.89; 95 %CI 1.28 - 6.51).	29
A case-control study	ASD = 268 Controls = 504	During conception, exposure to diabetes with pregnancy was linked with the increased odds of ASD (OR=4.68, 95 %CI 2.11–10.36)	30
A prospective birth cohort	ASD = 102 Controls = 1748	Maternal pregnancy obesity and maternal diabetes in combination were significantly associated with increased risk for ASD (HR=3.04, 95 %CI 1.21–7.63).	32
An intergenerational prospective cohort	ASD = 89 TD = 700	Compared to the reference group, BCAAs had markedly joint effects with maternal ob/DM and child male sex on increasing ASD risk (OR=10.79, 95 %CI 4.40, 26.42).	33
A case-control nested within a population -based cohort	ASD = 408 Controls = 2040 (age: ≤9 years)	No association was found between autism and maternal diabetes.	34
A case-control study	ASD = 698 Controls = 979(age: 30–68 months)	Any diabetes during pregnancy was not associated with ASD (aOR = 1.10, 95 %CI 0.77, 1.56).	35
A population -based, case-control investigation	ASD = 517; Controls = 315 (age: 24–60 months)	After adjustment for covariates, the link between diabetes and ASD did not get statistical significance (OR=1.52, 95 %CI 0.82,2.83).	58
A retrospective case-cohort study	ASD = 8760 Controls = 26,280 (age: 2–18 years)	No association between ASD and diagnosed diabetes without pharmaceutically treatment, but medication use (with and without diagnosis) was linked with ASD.	23
ASD in Offspring by type of mother's diabetes			
A retrospective longitudinal cohort study	Maternal T2DM = 6496; GDM = 5035; Controls = 290,792	Exposure to maternal GDM diagnosed by 26 weeks' gestation or earlier increased ASD risk in offspring (HR=1.42; 95 %CI 1.16–1.75).	22
A large prospective population-based cohort study	All = 649,043 PGDM = 4000 GDM = 101,696	PGDM implied marked effects for autism (HR = 6.49; 95 %CI 3.08- 13.69). GDM did not increase the risk highly for offspring disorders.	19

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Table 1 (*continued*)

Study type	Sample size	Main findings	Ref
ASD in Offspring of Diabetic Mothers			
A retrospective cohort study	T1DM = 621;T2DM = 9453; GDM(≤ 26weeks) =11,922; GDM(> 26 weeks) = 24,505	The risk of ASD in offspring was elevated in mothers with T1D, T2D, and GDM diagnosed by 26 weeks' gestation compared with no diabetes.	37
A population-based cohort study	Controls = 541,133 Insulin- treated PDGM= 4000; T2DM = 3724; GDM = 98,242	The offspring of severely obese mothers with T2DM had higher risks of ASD (HR, 2.28; 95 % CI, 1.18–4.41) compared with the normal-weight mothers without diabetes.	38
A national population-based cohort study	Unexposed=2,326,033; T1DM = 17,444;T2DM = 1679;GDM = 21,325; PGDM- NOS = 3199	T2DM most strongly associated with ASD (OR adjusted =1.37, 95 %CI 1.03–1.84). Exposure to GDM diagnosed at 27–30 wkGA was associated with the greatest risk for ASD.	18
A retrospective cohort study	T1DM = 338 T2DM = 8749 GDM = 90,200	T1DM on NDDs was the largest, followed by T2DM, then GDM, linked with an increased ASD risk.	39
A population- based cohort study	T1DM = 22,614;T2DM = 6713;GDM = 26,879 Unexposed = 2,357,129	ASD was associated with prenatal exposure to PGDM type 1 and GDM.	40

ASD, autism spectrum disorder; TD, typically developing; DM, diabetes mellitus; GDM, gestational diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; PGDM, pre-gestational diabetes mellitus; NOS, non-specified; OR, odds ratio; aOR, adjusted odds ratio; HR, hazard ratio; CI, confidence interval; NDDs, neurodevelopmental disorders; wkGA, weeks of gestation.

GDM diagnosed before the 26th week of gestation was associated with ASD risk (HR 1.42 [1.15;1.74]) [22]. The authors noticed that after adjusting for potential confounders, offspring exposed to GDM before the 26th week of gestation were at an increased ASD risk in both the bivariable and multivariable analysis before and after HR adjustment: HR 1.63 [1.35;1.97] and 1.40 [1.14;1.72] respectively [22]. In 2018, Xiang et al. conducted a retrospective birth cohort study that examined the relationship between ASD and maternal T1DM, T2DM, and GDM. This analysis showed an elevated risk of ASD in offspring from mothers with T1DM, T2DM, and GDM diagnosed before the 26th week of gestation compared to mothers with no diabetes. The study found that maternal T1DM was the highest risk of ASD offspring in both adjusted and fully adjusted analyses: HR 2.33 [1.29;4.21] and 2.36 [1.36;4.12] , respectively [37].

Kong et al. assessed the involvement of obesity and diabetic subtype in ASD risk in a large prospective population-based cohort study [19]. They found no association with ASD in their offspring for mothers with PGDM and GDM without obesity and demonstrated that maternal PGDM increased further risk increase for ASD (HR 6.49 [3.08;13.69]) in mothers with severe obesity [19]. In 2020, Kong et al. extended their analysis to examine the association between maternal diabetic subtype and in combination with maternal obesity and psychiatric disorders in offspring [38]. Offspring of severely obese mothers with T2DM had a higher risk of ASD than normal-weight mothers without diabetes: HR 2.28 [1.18;4.41] [38]. The results indicated that the effect sizes for

Table 2
Studies related to the association between PDGM and GDM with an autism spectrum disorder in offspring.

Study type	Sample size	Main findings	Ref
ASD in Offspring of mothers with PGDM			
A comparative study	ASD = 61; Controls = 46 (age: 3–28 years)	21 % of the ASD group reported having relatives with T1DM, compared to 13 % of the controls.	45
A cohort study	ASD = 3325 All = 689,196	Increased risk of infantile ASD in children with a family history of T1DM. [95 %CI 1.11–2.81]	47
A nationwide birth cohort study	ASD = 4506 All = 708,517 family triads	No association between maternal autoimmune disease and offspring ASD risk, including T1DM (HR=0.30, 95 %CI 0.04–2.15)	43
A retrospective chart review	ASD = 9 All = 984 (age: 3.3–6.8 years)	There is a higher prevalence of ASD in pediatric patients with T1DM in Toronto than in the general population.	48
A population-based case-control study	ASD = 1237 Controls = 30,925	Maternal T1DM was associated with a higher risk of ASD in children (OR=1.8, 95 % CI 1.0–2.9).	49
A prospective cohort study	T1DM = 8003 Controls = 1,398,647	Increased ASD risk in offspring of T1DM mothers (HR=1.40, 95 %CI 1.21–1.61). Higher HbA1c was not associated with higher ASD risk.	50
A nationwide population-based cohort study	T1DM = 6226 Controls = 62,260	The HR of ASD was increased in patients with T1DM compared with controls (HR = 14.52).	51
ASD in Offspring of mothers with GDM			
A prospective birth cohort study	ASD = 426 GDM = 419 All = 3260	A 48.6 % increased risk of autistic traits was among offspring born to mothers with GDM (OR=1.49, 95 % CI: 1.11–2.00).	59
A Randomized Controlled Trial	Infants of diabetic mothers = 23; Controls = 20	GDM-induced hyperglycemia of pregnancy may affect the ability to process emotional prosodies in the neonatal brain, indicating an increased risk of ASD.	60
A prospective national cohort	ASD mothers = 793; Controls = 65,652	GDM was linked with a markedly increased ASD risk in primary and sensitivity analyses (OR=1.76, 95 %CI 1.34, 2.32, $P < 0.0001$).	62
A population- based cohort study	GDM A_1 = 10,076 GDM A_2 = 2566 Controls = 218,629	GDM exposure was an independent ASD risk factor in hospitalized offspring ($OR_{adjusted}$=4.44; 95 %CI 1.55–12.69).	21
A cohort study	ASD = 503 Controls = 38,810	GDM was positively and markedly linked with having a ASD child compared to controls (OR= 1.56, 95 %CI 1.14–2.11).	64
A retrospective cohort study	ASD = 2471 Controls = 243,949	Increased ASD risk was associated with first trimester O_3 among mothers with GDM < 24 weeks' gestation [$HR_{adjusted}$=1.50 (95 %CI 1.08–2.09)].	65
A cohort study	GDM = 1073 Controls = 2050	GDM was not associated with an increased risk of ASD ($HR_{adjusted}$ =1.46; 95 %CI 0.74–2.84).	26
A population-representative birth cohort	GDM = 8 Controls = 691	No significant associations between diabetes and autistic symptoms in children	27
A population- based case- control study	ASD = 227 Controls = 58 (age: 2–5 years)	Among mothers of children with severe ASD symptoms, GDM was associated with a 3.2-fold increased Ab^+ prevalence (95 %CI 1.2, 8.6).	44

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ASD, autism spectrum disorder; ID, intellectual disability; TD, typically developing; DM, diabetes mellitus; GDM, gestational diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; PGDM, pre-gestational diabetes mellitus; NOS, non-specified; OR, odds ratio; aOR, adjusted odds ratio; HR, hazard ratio; CI, confidence interval; NDDs, neurodevelopmental disorders; Ab, anti-fetal brain autoantibodies; HbA1c, glycated hemoglobin; GDM A1, GDM controlled by diet and exercise; GDM A2, GDM requiring insulin or oral hypoglycemic agents.

T2DM among mothers with severe obesity were smaller than those for insulin-treated PGDM, which was associated with offspring ASD. However, the effect sizes for ASD were more significant in severely obese mothers with T2DM compared to those with GDM [38]. In a Swedish population-based cohort study, Chen et al. investigated the correlation between maternal exposure to T1DM, T2DM, or GDM and the risk of ASD. The findings revealed that T2DM had the strongest correlation with any ASD diagnosis: adjusted OR 1.37 [1.03;1.84] [18]. Another retrospective cohort study by Chen et al. in Taiwan explored the relationship between maternal exposure to T1DM, T2DM, or GDM and NDDs, including ASD, attention deficit hyperactivity disorder, developmental delay, intellectual disability, cerebral palsy, and epilepsy/infantile spasms. The results indicated that T1DM had the most significant impact on NDDs, followed by T2DM and GDM, with both T2DM and GDM linked to a higher risk of ASD [39].

One population-based cohort study containing 2413,335 live births in Denmark from 1978 to 2016 showed that ASD was associated with prenatal exposure to T1DM and GDM. This finding aligns with previous research indicating that offspring exposed to GDM, T1DM, or T2DM had a greater likelihood of being diagnosed with ASD [40].

2.3. ASD in offspring of the mother with PGDM

The incidence of T1DM or T2DM is steadily increasing in women of childbearing age, affecting approximately 1 % of all pregnancies. PGDM onset exerts adverse effects on the mother, fetus, and child and continues throughout pregnancy [17]. PGDM is poorly treated before conception and in the first trimester of pregnancy and might increase the risk of neurodevelopmental dysplasia in the offspring [41,42]. Several studies have shown that parental autoimmune disease is positively associated with the risk of ASD in offspring [43,44].

In one study conducted by Comi *et al.*, they used maternal self-reports of autoimmune diseases to examine the frequency of autoimmune disorders in autism. Using questionnaires, they assessed prenatal and postnatal events in 61 autistic and 46 healthy families. The results showed an increase in autoimmune disease incidence, such as T1DM, in mothers with autistic offspring compared to control mothers [45]. Another study, a retrospective longitudinal case-control study by Mouridsen et al., examined rates and types of autoimmune disease in parents of 111 individuals with infantile autism (IA) and 330 controls. They used data from the nationwide Danish National Hospital Register (DNHR) covering 27 years. They found that mothers with ulcerative colitis and fathers with T1DM appeared more frequently among parents of children with IA compared to control parents [46]. One study cohort contained all children born in Denmark from 1993 through 2004 (689, 196 children). Atladóttir *et al.* (2009) found no altered prevalence of ASD in T1DM. However, infantile autism was markedly more prevalent in T1DM, with an incidence rate ratio (IRR) of 2.14 ($P < 0.05$) [47]. Utilizing the Taiwan National Health Insurance Research Database, Lee et al. selected 708,517 family triads (father-mother-child) from 2001 to 2008 and followed them until the end of 2011 [43]. They confirmed that only paternal autoimmune diseases were associated with ASD risk in offspring, with no association between any maternal autoimmune disease and ASD risk [43].

Freeman et al. found an increased ASD prevalence in T1DM patients in Toronto than in the general population: 0.9 % [0.3;1.5] versus [0.34;0.67] [48]. Keil *et al.* studied 1237 ASD child-parent pairs and 30, 925 control pairs and found that maternal T1DM was related to a higher ASD risk in children [49]. The study also displayed that the prevalence in T1DM children and adolescents was 1.1 % [0.8;1.5], higher than the global ASD prevalence in the general population in 2019, indicating that T1DM impacts the prevalence of ASD [49]. In a nationwide, prospective cohort investigation of 1.4 million live births in Sweden, Persson et al. conducted a nationwide, prospective cohort investigation of 1.4 million live births in Sweden. They found that the offspring of mothers with T1DM had an increased risk of ASD (HR 1.40 [1.21;1.61]) that persisted after adjusting for individual and familial confounding [50]. A nationwide population-based cohort investigation by Chen et al. recruited 6226 T1DM patients and 62,260 age- and sex-matched controls between 2001 and 2010, followedup until the end of 2011 [51]. Cox regression analysis showed an increased HR of ASD (14.52) in T1DM patients compared with controls [51].

Wu *et al.* (2015) conducted a meta-analysis and found that autoimmune diseases were related to higher ASD risk in children: 28[12;48]%. Moreover, ASD risk in children is associated with T1DM: OR 1.49 [1.23;1.81] [52]. Yamamoto et al. performed a systematic review and found that previous cohort studies revealed that a higher incidence of ASD was linked to greater severity of PGDM: HR 1.98 [1.19;1.55] [53]. One meta-analysis by Xie et al. (2022) displayed that the prevalence of ASD in children and adolescents with T1DM was 1.2[0.9;1.6]% higher than the global prevalence of ASD in the general population in 2019 [54]. Eletri and Mitanchez conducted a systematic review and showed that ASD risk was markedly augmented after in-utero exposure to T1DM, followed by T2DM [55]. Similarly, in-utero exposure to preexisting maternal diabetes showed an increased risk of ASD and poorer neurocognitive and behavioral outcomes, according to another meta-analysis [53].

2.4. ASD in offspring of mothers with GDM

Glucose intolerance during pregnancy, known as GDM, has become increasingly prevalent in the last two decades. It has an approximate 6 % to 10 % prevalence [56]. There is evidence showing the relationship between GDM and adverse neurobehavior in children, such as ASD [57]. Several cohort studies found that GDM increases ASD risk in children, especially in mothers with an earlier diagnosis of GDM. Krakowiak *et al.* found that among ASD cases, GDM is associated with language expression deficits [58]. Zhu et al. found that 419 of 3260 children (12.85 %) were exposed to GDM, and the prevalence of autistic traits was 13.86 %. Among offspring born to mothers with GDM, a 48.6 % increased risk of autistic traits was observed (OR 1.49 [1.11;2.00]) [59]. Sun *et al.* found that GDM-induced hyperglycemia during pregnancy may affect the neonatal brain's ability to process emotions, as reflected in decreased mismatch response amplitude in response to fearful prosody, which indicates an increased risk of ASD [60]. On the other hand, one cohort study included singleton GDM pregnancies > 22 weeks' gestation with live newborns between 1991 and 2008, which showed that GDM was not associated with an increased risk of ASD ($HR_{adjusted}$ 1.46 [0.74;2.84]) [26]. A population-representative birth cohort revealed no significant associations between GDM and autistic symptoms in children [27].

In a comprehensive evaluation of 40 studies exploring the relationship between prenatal factors and ASD, Gardener *et al.* discovered a potential correlation between various maternal factors and ASD. Among these factors, maternal diabetes emerged as a leading contributor to ASD: OR 2.07 [1.24;3.47] [61]. In a separate study involving a large population-based cohort of 66,445 pregnant individuals, Lyall et al. investigated the potential link between maternal GDM and ASD in 793 children with ASD. Their results indicated a significant association between GDM and an increased risk of all types of ASD, with consistent findings in both primary and sensitivity analysis: primary analysis OR 1.76 [1.34;2.32] $P < 0.0001$ [62]. A population-based study conducted by Nahum et al. analyzed neuropsychiatric morbidity in offspring of 12, 642 GDM women compared to those of 218,629 non-diabetic women

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[21]. They showed a possible relation between in-utero exposure to GDM and ASD offspring ($OR_{adjusted}$ 4.44 [1.55;12.69] that remained significant after controlling for potential confounders including time-to-event, maternal age at delivery, gestational week, and offspring weight at birth [21]. Similarly, Wan *et al.* found that an association between maternal diabetes and ASD was higher for GDM (RR 1.62 [1.36;1.94]) without significant heterogeneity in the studied population [14]. A recent meta-analysis by Rowland and Wilson culled 15 studies to assess the association between ASD and GDM. Eight of these studies were included in a meta-analysis of ORs, in which an increased ASD risk was observed: OR 1.42 [1.22;1.65] [63].

Connolly *et al.* (2016) evaluated patient data from Cincinnati Children's Hospital Medical Center (CCHMC) and correlated it with data from birth certificates to identify risk factors [64]. They found that both obesity and GDM in mothers significantly increased the risk of ASD in their offspring by approximately 1.5-fold [64]. Compared to controls, the association with having a child with ASD was 2-fold greater in mothers with both GDM and obesity [64]. Kong and colleagues analyzed the association of GDM with ASD risk stratified by body mass index (BMI) and found that there was a significant association between diabetes and ASD risk among overweight (BMI $\geq$ 25) and obese (BMI $\geq$ 30) mothers with diabetes but not among highly obese mothers (BMI $\geq$ 35) with diabetes [19]. A retrospective cohort study containing singleton children born in Kaiser Permanente Southern California hospitals from 1999 to 2009 showed that exposure to PM2.5 during preconception, the first and third trimesters, and the first year of life was associated with an increased risk of ASD [65]. An interaction was found between maternal diabetes and ozone (O_3) exposure during the first trimester and first year of life, with a higher risk of ASD among mothers with GDM < 24 weeks' gestation who were exposed to O_3: adjusted HR 1.50 [1.08;2.09] per 15.7 ppb O_3 [65].

3. Maternal diabetes is involved in ASD development in animals

Evidence shows that maternal diabetes is involved in ASD development in rodent models (Table 3). Therefore, it is critical to interpret how maternal diabetes is involved during rodent pregnancy when assessing the validity of utilizing these studies in humans.

3.1. Autism-like behavior in diabetic rodent offspring of mothers with GDM

Leprdb/Leprdb (db/db) Bl/KS mice have a mutation for the leptin receptor (ObR). During pregnancy, db/+ females display a GDM phenotype with moderate glucose intolerance [66]. Offspring of db/+ mothers also display characteristics widely reported for infants of GDM mothers [67]. BKS *db/+* females develop GDM while pregnant, and Greene et al. showed that male BKS *db/+* mice exhibited a lower preference for social interaction and repetitive behaviors. However, BKS strain significantly contributes to BKS *db/+* behaviors [68]. However, it is difficult to use the BKS *db/+* model to study the contributions of GDM exposures to offspring autistic behaviors due to BKS confusing the behavioral results. Yang et al. found depleted embryonic and adult neural precursor cells (NPCs) in db/db murine offspring. In line with this, human genetic variants of Glo1 increased in diabetes are associated with ASD [69].

A high-fat diet (HFD) can destroy β-cell function and cause insulin resistance, and feeding high-fat to pregnant animals is used to induce GDM [70]. Liang *et al.* gave HFD to mice beginning from one month before pregnancy and continued throughout gestation, and an evident GDM phenotype appeared by the end of gestation day (GD) 20. Consistent with other HFD models, the treatment caused increased blood glucose and insulin levels during pregnancy [71]. In line with this, using this HFD murine model, Furlan et al. recapitulated that GDM causes social deficits in offspring, evidenced by three-chamber tests and reciprocal social interaction analyses [72]. Gawlińska et al. found that maternal HFD during pregnancy and lactation in Wistar rats induced male-specific social interaction deficits and repetitive behavior. They further confirmed significant changes in ASD-related gene expression in the male frontal cortex [73]. Moreover, evidence also indicates that male Cc2d1a conditional knockout mice fed with HFD display an aggravated autistic-like behavior, evidenced by increased restricted repetitive behaviors and impaired social memory [74]. Similarly, BTBR

Table 3
Studies related to the association between maternal diabetes and an autism spectrum disorder in animals.

Animal models	Intervention	Main findings	Ref
GDM mouse model db /+(BKS-gDock7$^{m+/+}$ Lepdb/J)	develop GDM during pregnancy	Social deficits, restrictive-repetitive behaviors, and increased social dominance in db/$^{+}$ offspring	68
STZ-induced TIDM mouse model (Cyp 27b1$^{-/-}$, sh Cyp 27b1)	STZ(35 mg/kg) after 8-h fasting; vehicle alone as a control	Prenatal VDD potentiates maternal diabetes induced autism-related phenotypes.	71
Maternal HFD C57 mouse model	HFD for 14 weeks	Male offspring showing social deficits in the three-chamber test and reciprocal social interaction analyses.	72
Maternal HFD (Wistar Han rats)	Maternal HFD during pregnancy and lactation	Male-specific social interaction deficits and increased repetitive behavior during adolescence.	73
Male Cc2d1a conditional knockout mice	HFD from weaning onwards and via the experimental period	Increased restricted repetitive behaviors and impaired performance in the preference for social novelty.	74
BTBR mice	HFD from weaning onwards and via the experimental period	Marked aggravation in increased cognitive rigidity and diminished preference for social novelty.	75
STZ-induced GDM C57 mouse model	STZ(120 mg/kg) a single ip after initiation of pregnancy	Male offspring of GDM mothers displayed increased repetitive behaviors.	77
STZ-induced TIDM rat model	STZ(65 mg/kg) a single injection	Neonatal rats from mothers with T1DM may develop autism-relevant biochemical autistic features.	79
STZ-induced TIDM rat model (SD rats)	STZ(50 mg/kg) after 8-h fasting	Male offspring displayed decreased USVs impaired sociability and social novelty.	80
STZ-induced TIDM C57 mouse model	STZ(35 mg/kg) after 8-h fasting	Male offspring displayed decreased USVs, impaired sociability and social novelty.	81
STZ-induced TIDM mouse model (Vil1-cre- RORA$^{fl/fl}$)	STZ(35 mg/kg) after 8-h fasting	Intestine-specific RORA deficiency does not affect maternal diabetes-mediated ALBs.	84
STZ-induced TIDM mouse model (Otp^{Cre} - *RORA*$^{fl/fl}$)	STZ(35 mg/kg) after 8-h fasting	Neuron specific RORA deficiency mimicked similar maternal diabetes -mediated ALBs in male offspring except for decreased USVs.	83
STZ-induced TIDM mouse model (OXTR$^{-/-}$)	STZ(35 mg/kg) after 8-h fasting	potentiates maternal diabetes-mediated ALB, while it has little effect on ALB in male offspring.	82

STZ, streptozotocin; i.p. injected intraperitoneally; USV, ultrasonic vocalization; HFD, high-fat diet;T1DM, type 1 diabetes mellitus; GDM, gestational diabetes mellitus; VDD, vitamin D deficiency; RORA, retinoic acid-related orphan receptor alpha; ALB, autism-like behavior.

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mice with HFD displayed significantly aggravated autism-related behaviors, manifested in augmented cognitive rigidity and decreased preference for social novelty [75]. In line with this study, Deng et al. have confirmed that ten-week HFD-fed mice showed aggravated repetitive behaviors in the self-grooming test and social deficits in the three-chamber sociability test [76].

Aviel-Shekler et al. (2020) have specifically induced GDM in mice with streptozotocin (STZ) a day after pregnancy initiation [77]. Increased glucose levels between E7 and E14 in pregnancy were due to diabetic levels in a subset of the pregnant animals, and male offspring of GDM mothers showed increased repetitive behaviors without altering social interaction [77]. Chen et al. recently constructed a rat model of GDM combining a high-fat and high-sugar diet with the intraperitoneal injecting 25 mg/kg STZ for the nonspontaneous model of experimentally induced GDM, similar to those of GDM patients [78]. Moreover, the model was stable and reliable and provided a basis for constructing a GDM rat model for studying the prevention and treatment of GDM [78].

3.2. Autism-like behavior in offspring in rodent models of T1DM

A single dose of 65 mg/kg STZ was administrated to female Wistar rats to cause

T1DM [79]. Aljumaiah et al. discovered that the offspring of T1DM rats could exhibit biochemical autistic features. However, they also found a glimmer of hope that insulin treatment could potentially alleviate oxidative stress, weak detoxification, neuroinflammation, and excitotoxicity, all of which are implicated in the pathogenesis of autism [79].

Wang et al. induced T1DM by injecting 50 mg/kg STZ into female Sprague–Dawley rats after an 8-h fasting period. The blood glucose > 300 mg/dl in animals was positive [80]. Male offspring displayed autistic behaviors with some core symptoms of ASD, such as decreased ultrasonic vocalizations and social recognition and interaction [80]. Similarly, T1DM was caused in female mice by injecting 35 mg/kg STZ, and animals with blood glucose > 250 mg/dl for three days continuously were considered to have T1DM [81]. Male offspring displayed autistic behaviors, such as impaired ultrasonic vocalizations, social recognition, and interaction [81].

Furthermore, one study by Liu et al. showed that maternal diabetes leads to oxytocin receptor (OXTR) inhibition; prenatal OXTR loss mimics and augments maternal diabetes-mediated anxiety-like behaviors, but autistic behaviors were not altered [82]. Additionally, postnatal infusing OXTR partly reverses maternal diabetes-induced social impairments. It implied that maternal diabetes-induced OXTR inhibition contributes to social impairments in offspring [82]. Recent studies suggest that gastrointestinal symptoms often occur in ASD. RORA loss in the intestine is involved in maternal diabetes-mediated symptoms in mouse offspring but does not influence maternal diabetes-mediated autistic behaviors [83,84].

3.3. Autism-like behavior in offspring in rodent models of T2DM

The obese BTBR (ob/ob BTBR) mice are considered a model of T2DM. The BTBR strain cannot adaptively promote the proliferation of pancreatic islet cells and up-regulate insulin levels in response to obesity and insulin resistance [85,86]. Due to these features, the ob/ob BTBR mice can serve as a valuable model to explore the pathogenesis of T2DM development and its associated complications [87].

4. Possible mechanisms linking maternal diabetes and autism

Understanding the potential correlations between maternal diabetes and the occurrence of neurodevelopmental and psychiatric disorders in offspring can be challenging due to the influence of parental genetic and familial environmental factors. The mechanisms exploring maternal hyperglycemia influencing fetus development may include metabolic hormones, immune dysregulation, increased oxidative stress, mitochondria dysfunction, neuroendocrine, and epigenetic changes (Figs. 1 and 2).

4.1. Hormones

4.1.1. Insulin

Insulin, a hormone synthesized in pancreatic beta cells, is in response to physiological triggers, predominantly peripheral glucose levels. Abnormal insulin secretion is involved in GDM development, which causes an increased incidence of impaired glucose tolerance and hyperinsulinemia in the general population [88,89]. Increased peripheral insulin leads to insulin resistance and has a significant association with ASD in youth [90]. Although insulin does not cross the placenta, glucose can freely cross the blood-fetal barrier, increasing fetal insulin secretion and triggering a hypermetabolic state that can cause chronic intrauterine tissue hypoxia [91]. Chronic intrauterine hypoxia may cause fetal iron deficiency. Both fetal hypoxia and iron deficiency might have inhibitory effects on neural development, including loss of myelin, alterations in cortical connectivity, and abnormalities in hippocampal neurons, contributing to ASD development [92]. It is interesting to note that some initial studies have suggested that a "ketogenic diet" could be therapeutic due to its strong suppression of insulin secretion [93]. Additionally, our research has shown that metformin, a drug used to treat T2DM, can significantly improve social approach, reduce repetitive grooming, and decrease marble-burying in BTBR mice when administered early [94]. Another study conducted by Aljumaiah et al. found that neonatal rats born to mothers with T1DM developed biochemical features relevant to ASD. Interestingly, insulin therapy in these rats may have potential benefits in mitigating oxidative stress, poor detoxification, inflammation, and excitotoxicity, which are mechanisms involved in the etiology of ASD [79].

4.1.2. Leptin

Leptin is a protein hormone secreted by adipocytes, encoded by the obesity gene (*ob*) [95]. Its receptors are mainly in several critical brain regions in humans, which play a central role in eating behavioral regulation, such as the cortex, hippocampus, amygdala, thalamus, and hypothalamus [96]. When body fat increases, the level of leptin in serum increases, which regulates the homeostasis of body fat and energy by neurons in the hypothalamic arcuate nucleus (ARC), which inhibits eating, accelerates metabolism ,and decreases blood glucose [96]. Leptin can inhibit the expression of proinsulin mRNA, reduce the transcriptional activity of insulin gene promoters, and inhibit insulin synthesis; insulin can up-regulate *ob/ob* gene expression and promote leptin secretion [97]. “Resistance” often appears in the body of people with GDM or obesity, manifested as high levels of leptin [98]. When subjected to high concentrations of leptin, the reactivity of the islet β-cell receptor diminishes, resulting in hyperinsulinemia and the establishment of a harmful cycle [99]. Clinical observation showed that infants of mothers with T1DM have significantly higher levels of leptin at birth compared to infants of normal mothers [100]. Compared with normal children, higher levels of leptin were also detected in the plasma of children with ASD, suggesting that leptin may be a critical mediator involved in ASD development [101]. A cohort study in Boston showed that elevated leptin levels were related to a higher incidence of ASD [102].

4.2. Oxidative stress

Oxidative stress refers to an imbalance between the production of reactive oxygen species (ROS) and the body’s ability to neutralize and eliminate them. This heightened state of ROS may adversely affect fetal brain development and function. Under normal conditions, endogenous antioxidants, including glutathione (GSH), catalase, and glutathione peroxidase (GPx), play a crucial role in neutralizing ROS and protecting

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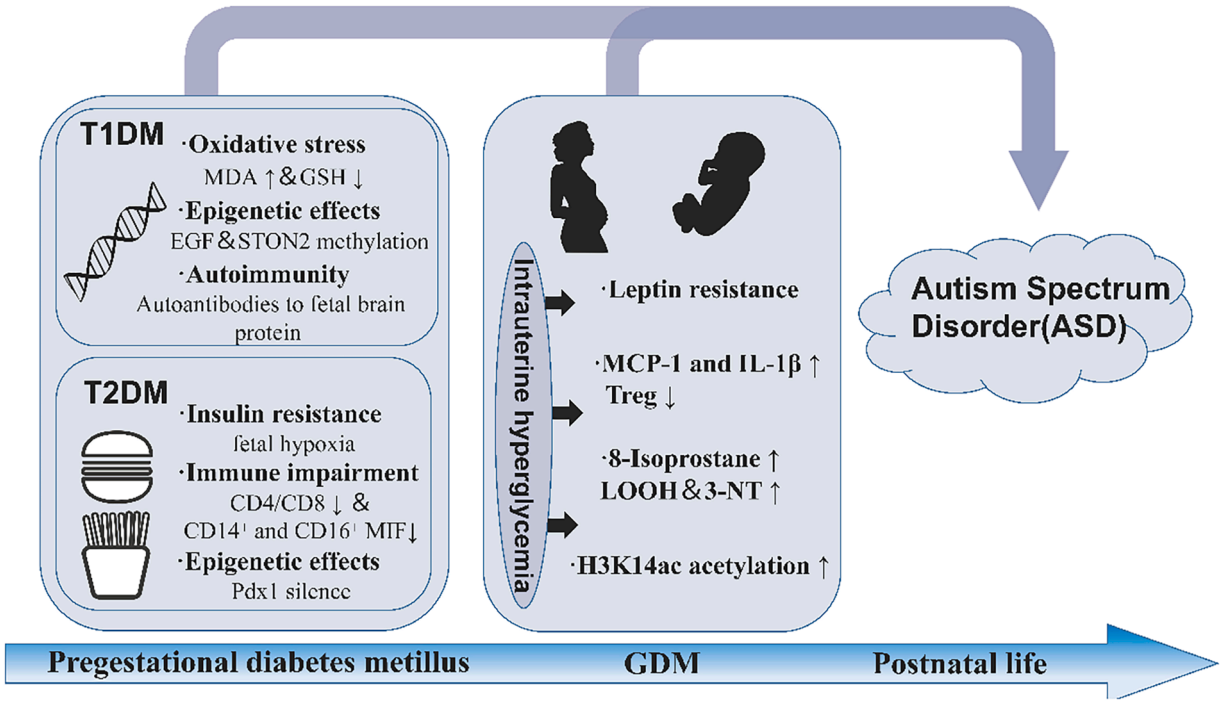

Fig. 1. Causal relations linking maternal diabetes to ASD development in patients.
Methylation of EGF and STON2 and oxidative stress are involved in the exacerbated autism-like behavior in the offspring of mothers with T1DM. The pathological mechanism of T2DM is insulin resistance, and excessive insulin links to placental hypoxia. Abnormal activation and imbalance in the ratio of immune cells is a unique manifestation of T2DM, and silencing of Pdx1 expression is somewhat associated with T2DM. The fetus of a mother with GDM is affected by intrauterine hyperglycemia, which generates pathological responses, such as leptin resistance, immune cell apoptosis, and inflammatory activation.

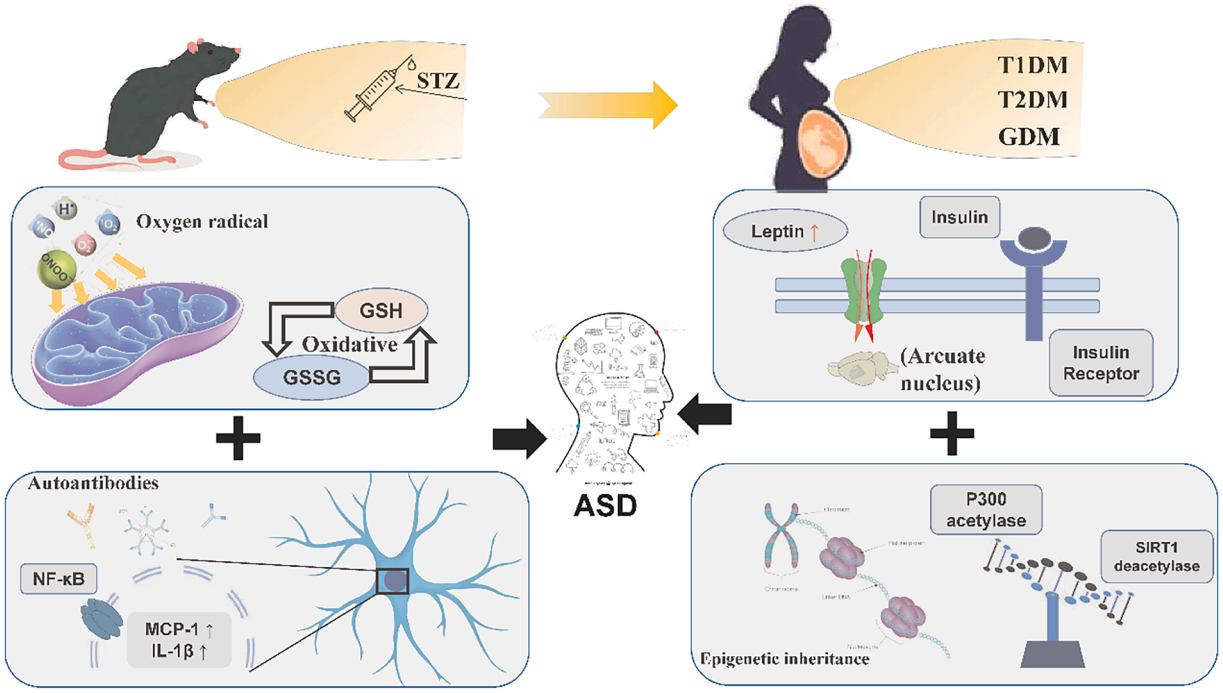

Fig. 2. Potential mechanisms of PGDM and GDM involved in the ASD development in maternal diabetic mouse models.
Diabetic mouse models suggest maternal hyperglycemia is involved in ASD development through metabolic hormones, immune dysregulation, increased oxidative stress, mitochondria dysfunction, and epigenetic changes.

human tissues from excessive damage [103]. However, hyperglycemia can induce oxidative stress by increasing respiratory chain activity and stimulating ROS production [104]. Clinical evidence showed that secreted 8-isoprostane was in the placenta, which accurately and consistently reflects the status and level of oxidative stress in vivo and is commonly used to assess the extent of oxidative stress injury. Its elevation indicates that uncontrolled insulin secretion would increase lipid peroxidation factors while inhibiting the secretion of antioxidants,

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which is also a vital source of ROS [105].

Recent studies suggest that maternal diabetes may impact the development of ASD through oxidative stress. Children with ASD have been found to have low levels of antioxidants like serum GSH, leaving their brains more vulnerable to free radical damage. Additionally, markers of brain oxidative stress, such as lipid peroxides (LOOH), malondialdehyde (MDA), protein carbonyl, and 3-nitrotyrosine (3-NT) have been observed in ASD children [106-109]. Additional research has shown that oxidative stress induced by T1DM is a crucial factor in the development of autism [110]. A study conducted by Aljumaiah *et al.* utilized pregnant mice given STZ to create an animal model of T1DM. This resulted in offspring with decreased levels of GSH and increased levels of MDA in the brain, exhibiting similar biochemical characteristics to autism mouse models [79]. Furthermore, oxidative stress caused by T1DM in pregnant rats has been shown to damage GABA neurons, leading to altered behavior in their offspring [111].

4.3. Immune dysregulation

According to the study by Shanmugam *et al.* (2003), excessive blood glucose induced by hyperglycemia can disrupt immune homeostasis, which may harm neurodevelopmental processes, potentially increasing the risk or susceptibility to NDDs [112]. During the intrinsic immune response, hyperglycemia negatively regulates the development and chemotaxis of neutrophils by modulating myeloperoxidase (MPO) activity [20]. Studies on cultured cells have revealed that when monocytes are exposed to high glucose conditions, their CD33 expression is down-regulated, producing TNF-α and other inflammatory factors like MCP-1 and IL-1β [113]. Recent research suggests that hyperglycemia can cause abnormalities in the immune process by altering the phenotype of dendritic cells and affecting their antigen-presenting function [114]. GDM, in combination with excessive obesity, can lead to chronic inflammation, with mediators like TNF-α and IL-1β crossing the placental barrier and interfering with fetal neurodevelopment [115, 116].

Evidence indicates that dysregulated inflammation links maternal diabetes and ASD [117]. Studies have shown that dysregulated inflammation, which can be caused by maternal diabetes, may contribute to the development of ASD. Furthermore, Modabbernia *et al.* (2017) reported increased inflammation in both children with ASD and animal models of autism [118]. Individuals with ASD also exhibit abnormal and heightened inflammatory responses, as evidenced by several inflammatory molecules, such as IL-1β, IL-6, TNF, elevated activated microglia, and enhanced macrophage M1 polarization [119]. Furthermore, clinicopathological samples tested indicate that hyperglycemia can increase helper T cell number and cytotoxic T lymphocytes, which are features of ASD [120]. Research suggests that maternal autoimmune disease may increase the risk of ASD in offspring by affecting fetal neurodevelopment through inflammatory mediators and autoantibodies [121]. T1DM, a common familial autoimmune disease, may also have a potential link to autism at the etiological level [122]. Studies in non-obese diabetic (NOD) mice have shown that multiple interactions between macrophages, dendritic cells, natural killer (NK) cells, NKT cells, and lymphocytes occur during the development of T1DM [123]. Maternal autoantibodies against fetal cerebral proteins can cross the placental barrier and cause inflammation in the brain, indirectly disrupting neurodevelopment [124]. Autoantibodies to fetal brain proteins have been found in the blood of pregnant women with T1DM or GDM, suggesting a potential role for autoimmune processes in the susceptibility to autism. In addition to maternal autoimmunity affecting fetal brain development, the presence of high levels of autoantibodies in the plasma of children with ASD suggests that the persistence of autoimmunity in children after birth is an independent mechanism for the development of ASD [125]. Hyperglycemia and insulin deficiency contribute to immune cell activity and impaired immune function, manifested by reduced expression of $CD14^{+}$ and $CD16^{+}$monocyte inflammatory factors [126]. The hyperglycemic environment also reduces the resistance of memory CD8+ *T* cells to external infections [127]. A decrease in $CD4^{+}$ *T* cells was frequently observed in ASD patients, with a consequent alteration in the CD4/CD8 ratio. Moreover, previous studies have shown that GDM can exacerbate immune activation effects during brain development [128].

4.4. Epigenetic effects

It is now well established that epigenetic modifications of the DNA and histones play a critical role in the normal development and functioning of the human brain and that aberrations in the epigenetic machinery can cause NDDs, such as embryonic neural tube defects, ASD, Down's syndrome, Rett syndrome, and later onset of neuropsychological deficits [129]. It has been documented that epigenetics are involved in childhood neuropsychiatric disorders induced by GDM [130]. Maternal diabetes induces epigenetic alterations in the fetal genome, and an animal study found altered regulation of gene expression in mouse embryos exposed to GDM [131]. A study of brain samples from ASD patients by Ladd-Acosta et al. found four regions with significant differences in DNA methylation in the temporal cortex and cerebellum. These alterations were associated with abnormal behavioral manifestations in patients with ASD [132]. One study conducted by Rich-Edwards et al. in 1999 confirmed a link between intrauterine growth retardation and the development of T2DM [133]. Another study by Park et al. in 2008 found that epigenetically linked intrauterine growth retardation and T2DM to the silencing of Pdx1, a transcription hyperglycemia-induced epigenetic modification implicated in the pathogenesis of ASD [134].

It has been found that high levels of glucose during embryonic development can disrupt the balance between histone acetylase and histone deacetylase SIRT1, leading to increased acetylation levels of lysine 14 (H3K14ac) at the Ngn1 and NeuroD2 promoters. This, in turn, can lead to compromised neurological function [135,136]. Additionally, a study by Wang et al. (2019) has shown that maternal diabetes can lead to autism-like behavior as a result of oxidative stress and epigenetic modifications on the SOD2 promoter [80].

In line with this study, it was found that SOD2 mRNA levels in peripheral blood mononuclear cells are reduced in autistic subjects when compared to typically developing children [137]. The report by Zeng et al. also found that transient hyperglycemia caused persistent epigenetic alterations and suppressed tight junction genes related to maternal diabetes-mediated gastrointestinal dysfunction and autism-like behavior in chronic diabetic mice [81]. It is worth noting that maternal diabetes was found to suppress the mRNA expression of several genes, including estrogen-related receptor α (ERRα), SOD2, G protein-coupled estrogen receptor (GPER), and RORA, which has been associated with ASD diagnosis [81].

Vitamin D is essential for brain development, neuroprotection, and gene expression regulation [138]. When this vitamin is deficient during critical periods of brain development, such as prenatal and early childhood, it can lead to neurodevelopmental deficits [139]. The VD/VDR signaling pathway also plays a role in the expression of Nrf2 and its target antioxidant genes, including SOD2 and heme oxygenase1 [71]. According to a report by Liang et al., VDD exacerbates hyperglycemia-induced Nrf2 suppression, leading to oxidative stress and inflammation in human NPCs. Additionally, prenatal VDD can worsen maternal diabetes-induced autism-like behavior by amplifying epigenetic changes in the SOD2 promoter [71].

Conclusions

Understanding the link between maternal diabetes and ASD in offspring remains a significant challenge. However, it is crucial to comprehend the disease and design treatment plans accordingly. Clinical studies and animal models have shown that GDM diagnosed before 26 weeks of gestation is significantly related to a higher incidence of

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autism in offspring. It is believed that intrauterine hyperglycemia may interfere with fetal neurodevelopment through oxidative stress, immunodeficiency, neuroendocrine, and epigenetic modalities, leading to autistic-like behaviors such as repetitive stereotypic behaviors and deficits in social interactions in offspring. Nutritional factors or elevated hormone levels related to GDM may interact with genetic susceptibility to ASD, which might be confounded. A large multicenter prospective cohort study with a large sample helps us understand the biological mechanisms behind maternal diabetes and its link to ASD, enabling us to provide early intervention and treatment for children who have maternal diabetes-mediated autism.

CRediT authorship contribution statement

Wenyu Shao: Writing – original draft, Conceptualization. **Yichun Su:** Writing – original draft. **Jiayin Liu:** Writing – original draft. **Yulong Liu:** Writing – original draft, Conceptualization. **Jinghui Zhao:** Writing – review & editing, Writing – original draft, Conceptualization. **Xiaotang Fan:** Writing – review & editing, Writing – original draft, Supervision, Investigation.

Declaration of competing interest

These authors have no conflicts of interest to declare.

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