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Gestational diabetes mellitus and developmental programming

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Abstract

During normal pregnancy, increased insulin resistance acts as an adaptation to enhance materno-foetal nutrient transfer and meet the nutritional needs of the developing foetus, particularly in relation to glucose requirements. However, about one in six pregnancies worldwide is affected by the inability of the mother's metabolism to maintain normoglycaemia, with the combination of insulin resistance and insufficient insulin secretion resulting in gestational diabetes mellitus (GDM). A growing body of epidemiologic work demonstrates long-term implications for adverse offspring health resulting from exposure to GDM *in utero*. The effect of GDM on offspring obesity and cardiometabolic health may be partly influenced by maternal obesity; this suggests that improving glucose and weight control during early pregnancy, or better still preconception, has the potential to lessen the risk to the offspring. The consequences of GDM for microbiome modification in the offspring and the impact upon offspring immune dysregulation are actively developing research areas. Some studies have suggested that GDM impacts offspring neurodevelopmental and cognitive outcomes; confirmatory studies will need to separate the effect of GDM exposure from the complex interplay of social and environmental factors. Animal and human studies have demonstrated the role of epigenetic modifications in underpinning the predisposition to adverse health in offspring exposed to suboptimal hyperglycaemic *in utero* environment. To date, several epigenome-wide association studies in human have extended our knowledge on linking maternal diabetes-related DNA methylation marks with childhood adiposity-related outcomes. Identification of such epigenetic marks can help guide future research to develop candidate diagnostic biomarkers and preventive or therapeutic strategies. Longer-term interventions and longitudinal studies will be needed to better understand the causality, underlying mechanisms or impact of GDM treatments to optimise the health of future generations.

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Keywords

DOHaD; Epigenetics; Gestational Diabetes; Life Course Epidemiology; Non-Communicable Disease

Introduction

Gestational diabetes mellitus (GDM) is a glucose tolerance disorder with onset during pregnancy [1]. GDM has been estimated to affect 14.4% of pregnancies globally, ranging from 7.5% in the Middle East and North Africa region to 27.0% in the South-East Asia region [2]. Although dysglycaemia usually improves after delivery, untreated GDM increases the risk of short-term complications including foetal overgrowth, shoulder dystocia, caesarean delivery, and hypertensive disorders [3]. In the long-term, exposure to GDM will likely predispose both the mother and her child to non-communicable diseases (NCDs) later in life.

NCDs are often seen as diseases of adult lifestyle and are an important public health issue. Their aetiology is likely multifactorial, involving interactions between environmental and genetic factors and multiple risk pathways. Substantial evidence now suggests that NCDs partly originate through environmental exposures before and during pregnancy [4], which have lasting effects on the developing foetus and serve as potential targets in reversing the epidemic of NCDs. It has become apparent that children born to mothers with GDM have an increased lifetime risk for metabolic diseases compared with unexposed children [5]. This concept of lasting consequences of early life nutrition for later disease risk is widely termed ‘developmental programming’ (Figure 1).

There is increasing epidemiological evidence linking the early-life environmental exposures (i.e. maternal malnutrition/overnutrition, environmental chemicals, stress) with later-life health outcomes – conceptualised as the ‘developmental origins of health and disease’ (DOHaD). Compelling studies from animal models have provided strong evidence in support of the DOHaD concept. These have, for example, shown that *in utero* exposure to maternal diabetes and/or obesity disrupts the development and function of hypothalamus, predisposing offspring to obesity [6,7]. Several decades ago Pedersen proposed that foetal adipogenesis can result from foetal hyperinsulinemia induced by maternal hyperglycaemia [8], with more recent evidence suggesting that the mechanisms involved in lasting effects on obesity risk include epigenetic changes [9].

In this review, we highlight some of the latest findings on the long-term health consequences in offspring born to mothers with GDM, specifically relating to body composition, cardiometabolic, allergic, immune/infections and neurobehavioral outcomes, and elaborate the epigenetic changes as one of the major mechanisms linking GDM with long-term “programmed” adverse effects on the offspring.

Offspring Body composition and Cardiometabolic Health

While GDM has been linked with a higher offspring BMI, several studies have suggested that this association is confounded by higher BMI in the mother. Table 1 summarises selected studies that have examined the association of GDM with offspring body composition and cardiometabolic health. In the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) follow-up study of children aged 10-14 years, no association was found between GDM and overweight/obesity defined by BMI after adjusting for maternal BMI during pregnancy [10]. Similarly, a recent population-based retrospective study of 33,157 children aged 1-6 years showed that the significant associations of GDM coupled with large-for-gestational age on childhood overweight were no longer apparent after adjusting for pre-pregnancy BMI [11]. These findings are consistent with those of a meta-analysis [12], suggesting that GDM was not associated with BMI z-scores when accounting for maternal pre-pregnancy BMI, but few studies have accounted for maternal treatment for GDM as a moderating influence [13]. Higher maternal BMI could be associated with higher childhood adiposity through genetic transmission, shared postnatal lifestyle/environment, and the intrauterine environment [14]. Alternatively, since BMI does not distinguish the contributions of fat and lean mass, using direct measures of child adiposity (based on skinfold or simple imaging measurements) could be feasible options in epidemiological studies [10,15,16]. Positive associations between GDM and skinfold thickness have been observed in children at birth and later childhood (aged 5–10 years), with limited evidence in children aged 2–5 years [17].

Evidence for an effect of GDM on offspring abnormal glucose tolerance is mixed as data from several meta-analyses have provided somewhat inconsistent findings. Positive associations between GDM and postnatal abnormal glucose metabolism (fasting plasma glucose, postprandial and diabetes mellitus) in the offspring were reported in a systematic review of prospective cohort studies [18]. In a meta-analysis including 11 studies, marginally higher fasting plasma glucose levels were found in offspring exposed to GDM compared with those who were not (standard mean difference: 0.43, 95% confidence interval CI: 0.08–0.77, 6,423 children) [19]. Likewise, in a retrospective matched cohort study of Canadian mother-offspring pairs, incident diabetes in offspring from birth to 22 years was higher in those born to mothers with GDM (hazard ratio HR: 1.77, 95% CI: 1.41–2.22) [20]. However, the aforementioned studies did not account for a potential confounding effect of maternal BMI. In contrast, an earlier meta-analysis showed no association of GDM with childhood diabetes or fasting plasma glucose but a higher level of 2-h plasma glucose from prepubertal to early adulthood (pooled mean difference: 0.43 mmol/L, 95% CI: 0.18–0.69, 890 children) [12]. This finding was independent of maternal pre-pregnancy BMI. Similarly, GDM was associated with higher risk of impaired glucose tolerance (based on 30-min, 1-h, and 2-h plasma glucose) but not impaired fasting glucose in 4,160 children from the HAPO follow-up study [21].

The observed discrepancies in the relation of GDM with impaired glucose tolerance and impaired fasting glucose may result from distinct pathophysiology induced by *in utero* exposure to GDM, in which skeletal muscle function (implicated in the insulin resistance of impaired glucose tolerance), not liver, may be more vulnerable to GDM. Also, the HAPO

follow-up study found that GDM was associated with lower child insulin sensitivity (Matsuda index) and β -cell compensation for insulin resistance (disposition index) [10]. These associations were independent of maternal BMI during pregnancy and child's BMI z-score, reinforcing the hypothesis that intrauterine exposure to hyperglycaemia plays a part in glucose intolerance among offspring. Foetal β -cell insulin dysfunction, arising from intrauterine hyperglycaemia and manifest as a decline in β -cell compensation, is likely to contribute to a progressively increasing metabolic load and an increased risk of impaired glucose tolerance in children of mothers with GDM. This does not preclude the possibility that the above associations could be partly due to some overlap in genetic susceptibility to GDM and type 2 diabetes, given that insulin resistance and/or insulin secretory defects are key players in the pathogenesis of these conditions.

To date there are relatively few studies on the association between GDM and cardiovascular morbidity. Nonetheless, a recent 40-year follow-up study of the Danish population based cohort found an increased rate of early-onset cardiovascular disease (HR: 1.19, 95% CI: 1.07–1.32) and hypertensive disease (HR 1.77, 95% CI: 1.27–2.48) in offspring of mothers with GDM [22]. These associations were independent of sociodemographic status and maternal/paternal history of cardiovascular disease. A 34-year follow-up of the Danish cohort with over 2 million births reported a modest increase in risk of specific congenital heart defects in offspring born to mothers with GDM compared with mothers with pregestational diabetes [23]. Interestingly, a systematic review suggested that the association between GDM and congenital heart defects was evident only in women who had both GDM and pre-pregnancy obesity [24].

The effect of GDM on offspring obesity and cardiometabolic health may be in part influenced by maternal obesity; this has led to the notion that improving glycaemia and weight control during early gestation, or better still before conceiving, have the potential to lessen the risk.

Offspring Allergic Diseases

Children born to mothers with GDM may be at risk of immune dysregulation. Table 2 summarises selected studies that have examined the association of GDM and offspring allergy. A recent US study of 97,554 children (median age 7.6 years) reported evidence that the rate of childhood asthma might be influenced by more severe GDM requiring medication use [25]. Compared with no diabetes during pregnancy, an increased risk of childhood asthma was reported only in GDM cases requiring antidiabetic medications (HR: 1.12, 95% CI: 1.01-1.25), but not in those without requiring medications. These findings were independent of maternal asthma. The Boston Birth cohort found that GDM, independently of maternal pregnancy BMI and foetal growth, was associated with atopic dermatitis and allergen sensitisation (driven primarily by food sensitisation) in term births but not preterm, with speculation that term births had longer exposure to the hyperglycaemic insult at a specific point of immunological development [26]. A meta-analysis did not find an association of maternal diabetes (defined as either chronic diabetes before pregnancy or overt diabetes or glucose intolerance in pregnancy) with ever and recurrent wheezing in early childhood from birth up to 1-2 years of age [27].

Although the immune system is a complex network affected by various environmental and genetic factors, the potential role of the human microbiota in influencing the host immune system has drawn considerable attention. It has been proposed that GDM triggers gut microbiota dysbiosis (i.e. altered gut microbial ecosystem) in both mother and neonate [28], which could lead to alteration of T-cell subpopulations, in turn implicated in maintaining immune tolerance. Indeed, mothers with GDM exhibited higher levels of peripheral Th2, Th17 and regulatory T cells, with these remaining unchanged from the third trimester of pregnancy up to six months postpartum [29]. Hence, it is plausible that altered levels of T-cells in the mother have an epigenetic impact on the immunological function of the offspring.

Offspring Neurocognitive Development and Behavioural Outcomes

While more is known about the association between maternal diabetes (regardless of the type) and offspring neurodevelopmental outcomes, evidence on the adverse effect of GDM is currently inconclusive.

A systematic review reported that while overall intellectual function may be within the normal range in children born to mothers with GDM, they may have an increased risk for problems related to fine and gross motor coordination, attention span and activity level compared to children born to mothers without GDM [30]. A number of important confounding factors, such as socioeconomic status, parental educational level and family upbringing, contribute to children's cognitive performance [31]. Table 3 summarises selected cohort studies and meta-analyses that have examined the association of GDM and offspring neurodevelopmental outcomes. In a meta-analysis adjusting for parental educational attainment, a deleterious effect of maternal diabetes (encompassing GDM, type 1 and type 2 diabetes) on lower IQ score was observed in children aged 3-12 years, but the authors cautioned against drawing conclusions due to significant heterogeneity in included studies [32]. It is plausible that women with pre-existing diabetes may have received monitoring and counselling prior to pregnancy, and therefore have better controlled glucose levels. Offspring born to mothers with GDM may have a higher exposure to a greater level of circulating glucose during the early stages of pregnancy than those with pre-existing diagnosed diabetes.

An increased risk for deficit/hyperactivity disorder (ADHD) in children born to mothers with GDM (risk ratio: 2.00, 95% CI: 1.42–2.81, 985,984 children) has been shown in a meta-analysis [33]. Notably, a large-sample US study suggests that severe GDM requiring antidiabetic medications was associated with increased ADHD risk (HR: 1.26, 95% CI: 1.14–1.41) in children (median age: 4.9 years) compared to the non-exposed group [34]. Neither GDM requiring no medications nor gestational age at GDM diagnosis was associated with offspring ADHD risk. These associations were independent of sociodemographic factors, smoking and alcohol use, maternal history of ADHD and maternal pre-pregnancy BMI.

There are a number of observational epidemiologic studies published on offspring autism spectrum disorders outcome. A meta-analysis detected a positive association between GDM

and child autism spectrum disorders even after adjustment for important covariates such as obesity, maternal age and gestational age [35]. However, a Finnish cohort of 649,043 births followed-up to 11 years reported no increased risk of child's autism spectrum disorders in women with GDM and normal weight, after adjusting for important covariates including maternal psychiatric disorder, maternal age at delivery, maternal smoking and maternal systemic inflammatory disease [36]. Of note, more pronounced risk effects for child autism spectrum disorders were reported in obese mothers with GDM and/or maternal pregestational diabetes [36,37]. Joint effects of maternal obesity and pregestational diabetes were also observed on conduct disorders with onset in childhood as well as mixed disorders of conduct and emotions, disorders of social functioning and tic disorders with onset in childhood and adolescence [36]. Possible explanations for the joint effects between obesity and maternal pregestational diabetes are the stronger neural impact of long-term exposure to concomitant contribution of lipotoxicity, inflammation, metabolic stress and hyperglycaemia.

Limited data exists regarding other offspring neuropsychiatric disorders, with some showing either higher rates [38] or null associations [36] with eating disorders, and positive associations of sleep disorders [36,38] in children exposed to GDM.

Developmental Programming by Epigenetic Mechanisms

In the context of foetal programming, epigenetic processes are thought to be an important mechanism underpinning lasting effects on the offspring [9]. Epigenetic modifications are cell type and tissue-specific, which involve changes in gene expression and genomic structure without altering the DNA sequence. Epigenetic processes include DNA methylation, histone post-translational modifications and expression of non-coding RNAs. GDM, as an example of maternal environmental trigger, can play a role in influencing offspring outcomes through epigenetic regulation of genes. DNA methylation is the classic and most studied epigenetic measure, primarily found in the CpG (cytosine followed by a guanine) sequence contexts. The identification of DNA methylation patterns related to adverse health-related outcomes in offspring is a potentially useful tool to assess individuals at risk for health problems in early life exposed to GDM, representing an important window of opportunity for early interventions during childhood.

Animal Studies

Evidence from non-human animal models suggests that *in utero* GDM exposure leads, for example, to developmental and functional alterations of the hypothalamus [6,39], heightening the risk of developing overweight/obesity in the offspring. Animal models of developmental programming have to date mainly involved nutritional, toxin exposure, selective breeding and direct genetic manipulations.

A study of streptozotocin-induced maternal diabetes in mice showed an inhibitory effect of intrauterine hyperglycaemia exposure on the development of brown adipose tissue (BAT) in offspring, thereby impairing the glucose uptake function of BAT in adulthood [40]. The authors found a down-regulation of BAT-associated genes, *Ucp1*, *Cox5b*, and *Elovl3*, which

are accompanied by disorganised ultrastructural of mitochondria in BAT, probably contributing to intracellular lipid accumulation and fat-induced insulin resistance [40]. Another GDM mouse model showed altered DNA methylation patterns in pancreatic tissues, manifested as dyslipidaemia, impaired glucose tolerance and insulin resistance with advancing age [41]. The authors rationalised that the pancreas has a direct role in regulating blood glucose levels, and should hence serve as an important target tissue to demonstrate the role of DNA methylation as opposed to the more widely studied samples such as placenta, umbilical cord blood or maternal peripheral blood.

However, animal models using chemical approaches such as streptozotocin to induce permanent pancreatic damage with impaired insulin secreting function and irreversible diabetes may be of limited relevance to GDM, which is transient in nature and usually returns to euglycemia after childbirth. A recent mice experiment studied the induction of transient glucose tolerance in pregnant mice with an insulin receptor antagonist (*S96I*), reporting that mice born from *S96I*-treated dams showed no susceptibility to physical or reflexes development in early neonatal period, but had long-term metabolic (glucose intolerance) and cognitive impairment consequences in adulthood when administered a high-fat-diet [42]. The administration high-fat-diets in mice mimics typical energy rich diets in both developing and industrialised countries, implicating epigenetic alterations as an important mechanism underpinning the induction of altered phenotypes in response to environmental cues.

Human Studies

The mechanistic pathways underlying long-term morbidity in offspring exposed to GDM are incompletely understood so far, but a growing number of studies have supported involvement of epigenetic mechanisms in the association of GDM with offspring health. Most human studies on epigenetic mediation examined the associations of *in utero* GDM exposure and DNA methylation in placentas, offspring cord or infant blood, as summarised in a recent review [43]. Several differentially methylated genes in foetal tissues of babies born to mothers with GDM have been identified using a candidate gene approach; these include loci related to the leptin (*LEP*), adiponectin (*ADIPOQ*), mesoderm-specific transcript (*Mest*), the ATP-binding cassette transporter A1 (*ABCA1*), *SLC2A1/GLUT1* and *SLC2A3/GLUT3* genes. Epigenetic modifications at these loci in response to impaired glucose homeostasis during pregnancy might lead to lifelong susceptibility to adiposity development in offspring.

Two epigenome-wide association studies (EWAS) using Illumina 450k methylation arrays have reported associations of maternal diabetes-related DNA methylation marks with childhood adiposity-related outcomes [44,45]. One of these studies included data from two prospective cohorts - the EPOCH (Exploring Perinatal Outcomes in Children) and the Colorado Healthy Start - which identified six GDM-exposure-associated DNA methylation marks that were linked to measures of childhood adiposity and fat distribution [44]. Peripheral/cord blood samples of GDM-exposed and non-GDM-exposed offspring (n=285, aged 10.5 years) were profiled, revealing that DNA methylation of the *SH3PXD2A* gene was associated with BMI, waist circumference, skinfold thicknesses, subcutaneous adipose

tissue and leptin levels, after adjustment for cell proportions [44]. In the second study of 388 Pima Indian children of Arizona (aged 13.0 years) [45], the observed DNA methylation marks altered by intrauterine exposure to maternal diabetes and linked to offspring BMI and insulin secretory were different from those detected by the EPOCH study. The discrepancies in DNA methylation hits could be due to the different population studied, covariates adjusted for, and outcomes of interest.

A causal relation between maternal hyperglycaemia and epigenetic regulation of the leptin gene (with biological relevance to long-term programming of offspring excessive adiposity) in offspring cord blood has been reported based on a 2-step epigenetic Mendelian randomised approach [46]. The epigenetic adaptations triggered by maternal glycaemia, resulted in an association between lower DNA methylation levels at CpG site cg12083122 (in leptin gene of the offspring) and higher cord blood leptin levels [46]. Using mediation analysis, higher DNA methylation levels of the key genes responsible for glycaemic/lipid metabolism (*PPARGC1a*) were correlated with higher cord blood leptin levels in offspring exposed to maternal hyperglycaemia [47]. DNA methylation (increased methylation of *PYGO1* and *CLN8*) has also been reported to mediate effects of *in utero* GDM exposure on adverse offspring cardiometabolic traits (increased VCAM-1 levels) [48].

For neurodevelopmental outcome, a recent meta-analysis of EWAS data published by the Pregnancy and Childhood Epigenetics Consortium (with 3677 mother-neonate pairs from seven pregnancy cohorts) showed that GDM was associated with offspring cord blood hypomethylation of the *OR2L13* promoter, a gene associated with autism spectrum disorder [49]. Notably, the study accounted for numerous potential confounding influences, including cord blood cell heterogeneity, which is one of the potential sources of variability in DNA methylation.

In a human placenta study [50], maternal dysglycaemia in pregnancy was associated with altered DNA methylation of the serotonin transporter gene (*SLC6A4*), a principal regulator of serotonin homeostasis. Serotonin, a neurotransmitter, is involved in neurodevelopmental disorders (e.g. depression, anxiety, autism). *SLC6A4* methylation levels were negatively associated with maternal glucose levels (both fasting and 2-h plasma glucose) in the 24–28 weeks of gestation, after adjustment for maternal pre-pregnancy BMI and gestational weight gain. Further, placental *SLC6A4* methylation was inversely associated with *SLC6A4* mRNA levels, suggesting a functional role of the CpG sites in regulating *SLC6A4* gene expression, and that epigenetic changes predominates over genetic mechanism in the human placenta. A separate study has shown differential *SLC6A4* methylation as a predictive epigenetic marker of adiposity from birth to adulthood [51]. Such studies provide valuable information on epigenetic marks that can guide future research in developing potential diagnostic biomarkers and predictive/treatment strategies for adverse health events.

Transgenerational Epigenetic Inheritance

Increasing research on animal models, mainly in mice and rats, suggests that developmental programming is a transgenerational phenomenon. The programmed phenotype is passed on through several possible mechanisms including persistence of the adverse environmental

exposures in subsequent generations, altered maternal phenotype, and inheritance of epigenetic modifications via alteration of the epigenome (germline and/or somatic line). Whilst most literature on transgenerational transmission of traits have focused on the maternal contributions to offspring, impacts of paternal contributions have also been observed [4].

A GDM mice model of intrauterine hyperglycaemia induced by streptozotocin showed a pattern of dysregulation at key methylation sites in the placenta (reflected by down-regulation and up-regulation of *Dlk1* and *Gtl2* genes, respectively) of the F1 and F2 generations [52]. A reduction in placental weight was found to be transmitted paternally to the F2 offspring, but not maternally, which was believed to be linked to the susceptibility of the sperm under a suboptimal intrauterine environment.

While the transgenerational transmission of traits has been reported through to F2 offspring, evidence on the transmission through to F3 and subsequent generations remains unclear [53]. Studying F3 and succeeding generations is important to eliminate the possible confounding effects by the initial adverse maternal insults on the embryo.

Although there is substantial evidence on the transgenerational inheritance of epigenetic modifications in mice and rats, the application of this concept in humans has been challenged by others [54], mainly due to a complex sum of many confounding factors including ecological and cultural inheritance [55]. Well-controlled experiments in mammalian animal models and large-scale cohorts/well-characterised epidemiological studies are required in the future.

Do GDM treatment interventions improve long-term offspring health?

Infants born to mothers receiving treatment of GDM in the form of dietary advice, blood glucose monitoring and insulin therapy have improved perinatal outcomes compared with those born to women receiving routine care [56]. However, evidence from a Cochrane review of long-term follow-up studies of GDM treatment interventions suggests that treatment may not reduce childhood obesity [13]. In two follow-up studies of children whose mothers participated in pregnancy trials for the treatment of mild GDM, there was no difference in child's BMI (aged 4-10 years) by treatment and control groups [57,58]. A possible reason for the null finding is that more-pronounced GDM might be necessary to program long-term treatment effects on the development of offspring obesity. Nonetheless, female offspring of mothers treated for mild GDM had lower fasting glucose levels, suggesting a beneficial effect of treatment of mild GDM in relation reducing the risk of offspring insulin resistance in females [57].

Compared with insulin treatment, findings from the Metformin in Gestational diabetes: The Offspring Follow-Up (MiG TOFU) cohort reported no differences in the body fat percent and metabolic measures in children (aged 7-9 years) whose mothers had been randomised to metformin and insulin GDM-treatment [59]. However, metformin-exposed children at 9 years of age were larger than the insulin-exposed group [59]. In line with this, a meta-analysis including three follow-up studies of RCTs reported that children prenatally exposed

to metformin-treatment for GDM were heavier than those whose mothers received insulin-treatment [60]. Larger studies with longer follow-up will be needed to better understand the health impact of GDM treatments on offspring to optimise the health of future generations.

There is also evidence for the periconceptual period as an early window for which poor environmental exposures can induce adverse health effects in offspring [4]. Interventions delivered during pregnancy may only partly alter foetal growth and development, and therefore studies examining interventions that begin preconception are warranted. A large multi-centre RCT is underway to investigate the effectiveness of a nutritional (containing myo-inositol, probiotics and additional micronutrients) intervention commencing before conception and continuing during pregnancy to maintain good maternal glycaemic control, with the aim of improving offspring health outcomes [61].

Conclusion

Overall, there is increasing evidence for an impact of *in utero* GDM exposure on lifetime health in the offspring. However, whether maternal GDM contributes directly to childhood adiposity remains to be elucidated, given that maternal BMI and gestational weight gain are also linked with childhood adiposity. Other observed long-term offspring adverse consequences include cardiovascular abnormalities, glucose/insulin dysfunction, allergic/respiratory health and neurodevelopmental outcomes. Most evidence is based on observational prospective cohorts, and further studies are required to advance our knowledge of the effect of GDM and its treatment on development, function and health in the offspring. Taken together, the adverse health impacts of *in utero* GDM exposure on offspring may rely upon epigenetic changes in selected genes. Notably, many of these epigenetic modifications may not be reversible and may persist throughout the offspring's life course. More studies in both animal and human models are needed to replicate the epigenetic findings, with careful consideration of the selection of cell or tissue types for epigenetic analysis because epigenetic mechanisms are generally tissue-specific. There is also a need for larger studies with long-term follow-up to understand the health impact of GDM treatments in preventing adverse programming of health outcomes in offspring.

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Key Messages (2-3 messages)

- A mother's glycaemic status and weight during preconception and pregnancy influence the long-term health of the offspring.
- The offspring's future health can be programmed through the role of epigenetic changes induced by a hyperglycaemic environment *in utero*.
- More longitudinal studies are warranted to investigate the causality and underlying mechanisms of GDM on offspring's long-term health to provide a basis for developing effective interventions during this critical period, with the aim of improving lifelong health and wellbeing.

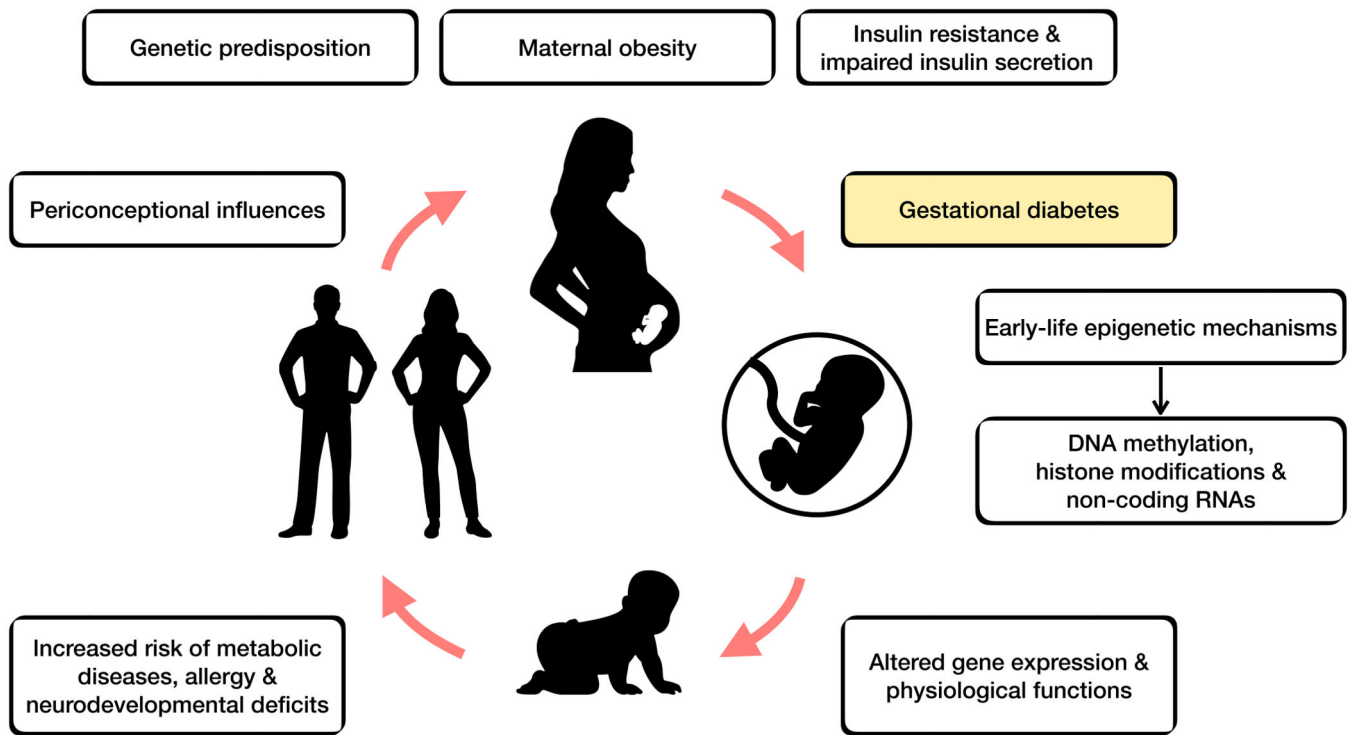


Figure 1. Gestational diabetes mellitus and developmental programming

Table 1
Selected studies linking GDM with offspring body composition and cardiometabolic health

Study	Design	Cohort	Sample size	GDM criteria	Offspring age (years)	Major outcomes for GDM-exposed offspring
Body composition						
Chen et al. (2020) [11] China	Cohort	Medical Birth Registry of Xiamen, China; a population-based retrospective cohort	33,157	International Association of Diabetes and Pregnancy Study Groups (IADPSG)	Range: 1–6	GDM and large-for-gestational age not associated with overweight (OR: 1.27, 95% CI: 0.96–1.68), adjusted for maternal pre-pregnancy BMI
Kawasaki et al. (2018) [12] Japan	Meta-analysis	Included two cohort studies adjusting for maternal BMI; UK, USA	5,941	Carpenter-Coustan, questionnaire	Range: 3–15.5	Not associated with BMI z-scores (pooled MD: -0.11, 95% CI: -0.33–0.12), adjusted for covariates including maternal pre-pregnancy BMI
Lowe et al. (2018) [10] USA	Cohort	Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study	4,832	International Association of Diabetes and Pregnancy Study Groups (IADPSG)	Mean (SD): 11.4 (1.2)	Not associated with overweight/obesity (OR: 1.21, 95% CI: 1.00–1.46), adjusted for maternal BMI at OGTT during pregnancy
Glucose metabolism						
Blotsky et al. (2019) [20] Canada	Matched cohort	A combination of health administrative data with birth registry information from Quebec, Canada	36,590 mother-child pairs with GDM and matched 1:1 with controls	Two abnormal values on a 75-g OGTT or a 50-g glucose screen 10.3 mmol/l	From birth to 22	Associated with incident diabetes (HR: 1.77, 95% CI: 1.41–2.22), not adjusted for maternal BMI
Kawasaki et al. (2018) [12] Japan	Meta-analysis	Included four cohort studies adjusting for maternal BMI; Denmark, Hong Kong SAR, USA	890	Self-report, questionnaire, WHO criteria 1999, OGTT	Range: 7–20	Associated with 2-h plasma glucose (pooled MD: 0.43 mmol/L, 95% CI: 0.18–0.69), adjusted for maternal pre-pregnancy BMI
Lowe Jr et al. (2019) [21] USA	Cohort	HAPO Follow-up Study (FUS)	4,160	International Association of Diabetes and Pregnancy Study Groups (IADPSG)	Mean (SD): 11.4 (1.2) Range: 10–14	<ul style="list-style-type: none"> Associated with IGT (OR: 1.96, 1.41–2.73), insulin sensitivity (adjusted MD: -76.3, -130.3 to -22.4) and oral disposition index (adjusted MD: -0.12, -0.17 to -0.064), adjusted for family history of diabetes, maternal BMI, and child BMI z score Not associated with IFG (OR: 1.09, 95% CI: 0.78–1.52)
Pathirana et al. (2020) [19] Australia	Meta-analysis	Included 11 cohort studies; China, Denmark, Greece, USA	6,423	NDDG, self-reported/confirmed with hospital records, Carpenter-Coustan, WHO criteria 1999, IADPSG, based on GDM risk	Range: 7–27	Associated with fasting glucose (standardized MD: 0.43, 95% CI 0.08–0.77), not adjusted for maternal BMI

Study	Design	Cohort	Sample size	GDM criteria	Offspring age (years)	Major outcomes for GDM-exposed offspring
				factors followed by OGTT		
Cardiovascular outcomes						
Øyen et al. (2016) [23] Denmark	Cohort	Data linkage of Denmark's nationwide registers	2,025,727	Medical record	From birth to 34	<ul style="list-style-type: none"> GDM in third trimester associated with any type of congenital heart defects (adjusted relative risk: 1.36, 95% CI 1.07–1.69) No association for GDM in second trimester
Yu et al. (2019) [22] Denmark	Cohort	Danish national health registries	26,272	Medical record	From birth to 40	Associated with overall CVD (HR: 1.19, 95% CI 1.07–1.32), hypertensive disease (HR 1.77, 1.27–2.48), adjusted for sociodemographic status and maternal/paternal history of cardiovascular disease

CI, confidence interval; CVD, cardiovascular disease; GDM, gestational diabetes mellitus; HR, hazard ratio; md, mean difference; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NDDG, National Diabetes Data Group; OGTT, oral glucose tolerance test; OR, odds ratio; SD, standard deviation, WHO, World Health Organisation

Table 2
Selected studies linking GDM with offspring allergy

Study	Design	Cohort	Sample size	GDM criteria	Offspring age (years)	Major outcomes for GDM-exposed offspring
Kumar et al. (2009) [26] USA	Cohort	Boston Birth Cohort	680	Medical record	Mean (SD): 3.2 (2.3)	In term births, GDM associated with atopic dermatitis (OR: 7.2, 95% CI: 1.5-34.5), allergen sensitization (5.7, 1.2-28.0), food sensitization (8.3, 1.6-43.3)
Martinez et al. (2020) [25] USA	Cohort	Kaiser Permanente Southern California hospitals (retrospective birth cohort)	97,554	Carpenter-Coustan	Median age: 7.6	GDM requiring antidiabetic medications associated with childhood asthma (HR: 1.12, 95% CI: 1.01-1.25), adjusted for maternal asthma
Zugna et al. (2015) [27] Italy	Meta-analysis	11 European birth cohorts participating in the CHICOS (Developing a Child Cohort Research Strategy for Europe) project	85,509	Exposure: maternal diabetes	From birth to 1-2	Maternal diabetes (regardless of type) associated with ever wheezing (pooled RR: 1.02, 95% CI: 0.98-1.06) and recurrent wheezing (1.24, 0.86-1.79)

CI, confidence interval; GDM, gestational diabetes mellitus; HR, hazard ratio; SMD, standardised mean difference; RR, risk ratio

Table 3
Selected studies linking GDM with neurodevelopmental outcomes

Study	Design	Cohort	Sample size	GDM criteria	Offspring age (years)	Major outcomes for GDM-exposed offspring
Kong et al. (2018) [36] Sweden	Cohort	Data linkage of Finland's nationwide registers	649,043	Medical record	From birth to 11	<ul style="list-style-type: none"> GDM + maternal obesity associated with autism spectrum disorders (HR: 1.56, 95% CI: 1.26–1.93) Non-significant increase in GDM + normal weight for autism, adjusted for maternal psychiatric disorder, maternal age at delivery, maternal smoking and maternal systemic inflammatory disease
Nahum Sacks et al. (2016) [38] Israel	Cohort	A university medical center which serves the entire population of the Southern region of Israel	231,271	Medical record	Not specified (study population included all patients who delivered between the years 1991 through 2014 and their offspring)	<ul style="list-style-type: none"> Associated with autistic spectrum disorder (OR: 4.44; 95% CI: 1.55–12.69), adjusted for maternal age, obesity, gestational week
Robles et al. (2015) [32] Spain	Meta-analysis	Included 7 cohort studies; USA, Israel	6,140	Exposure: maternal diabetes (regardless of type)	1–2 years for mental and psychomotor development; 3–12 years for Intelligence Quotient (IQ)	Maternal diabetes associated with mental development (SMD: -0.41, 95% CI: -0.59 to -0.24), psychomotor development (-0.31, -0.55 to -0.07) and IQ (-0.78, -1.42 to -0.13)
Wan et al. (2018) [35] China	Meta-analysis	Included 16 case-control/cohort studies; USA, Canada, Sweden, Israel, Australia, Egypt	Not specified	Exposure: Maternal diabetes	Not specified	Associated with autism spectrum disorders (relative risk: 1.48; 95% CI: 1.26–1.75), adjusted for obesity, maternal age, gestational age
Xiang et al. (2018) [34] USA	Cohort	Kaiser Permanente Southern California hospitals (retrospective birth cohort)	29,534	Carpenter-Coustan	Median age: 4.9	<ul style="list-style-type: none"> GDM requiring antidiabetic medications associated with ADHD (HR: 1.26, 95% CI: 1.14–1.41) No association for GDM not requiring medications
Zhao et al. (2019) [33] China	Meta-analysis	Included 4 cohort studies; Denmark, Greece, USA, China	985,984	Medical record, self-report, ADA criteria	Range: 4–19	Associated with ADHD (RR: 2.00, 95% CI 1.42–2.81)

ADHD, Attention deficit hyperactivity disorder; CI, confidence interval; GDM, gestational diabetes mellitus; HR, hazard ratio; OR, odds ratio; RR, risk ratio