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Review of Current Evidence on the Impact of Environmental Chemicals on Gestational Diabetes Mellitus

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Abstract Pregnancy is a naturally insulin-resistant state and may be an important window of susceptibility in determining a woman's lifetime risk of type 2 diabetes. Exposures to environmental chemicals that act as endocrine active compounds may mimic or disrupt hormones that regulate insulin action or maintain glucose homeostasis. In this commentary, we present the animal evidence that explains the biological plausibility for an association between environmental chemicals and gestational diabetes mellitus (GDM). We review the current epidemiological evidence examining the associations between GDM and bisphenol A, phthalates, air pollution, and toxic metals including arsenic and cadmium. We briefly discuss the strengths and limitations of the current evidence and offer recommendations for future studies that attempt to assess the impact environmental chemical exposure has on GDM. Lastly, we discuss the health implications for women that experience GDM during pregnancy and the importance for examining how environmental chemicals may play a role in the etiology of GDM.

Keywords Gestational diabetes · Environmental chemicals · Bisphenol A · Air pollution · Phthalates · Metals

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Introduction

Type 2 diabetes mellitus (T2DM) has become a global epidemic with 382 million people affected worldwide. The number of cases is set to hit 592 million by 2035 [1]. Considerable scientific endeavors have been made recently to understand the role that environmental factors play in the etiology of T2DM. This work has been driven in large part by the global rising burden of T2DM and the lack of identification of genetic factors to explain this excess. More alarming is that gestational diabetes mellitus (GDM), a significant risk factor for T2DM in women has been steadily increasing. Recent data suggest that the prevalence of GDM has increased by 10–100 % in several race/ethnicity groups during the past 20 years [2]. In 2013, an estimated 21 million women with high blood glucose during pregnancy contributed to the global burden of diabetes [1]. For women, pregnancy may be a window of susceptibility where researchers can examine the role that environmental chemicals play in the etiology of GDM and subsequently T2DM.

Pregnancy has been described as a natural stress test requiring anatomical, physiological, and biochemical adaptations to support the maintenance of pregnancy and the growth and development of the fetus [3]. An important adaptation during pregnancy is diabetogenic [4]. This insulin-resistant state begins in the first trimester to support the growth of the placenta. The maternal pancreas increases total insulin to

supplement and support the growth and development of the fetus, particularly in the second trimester. The inability of the maternal system to transition into this diabetogenic state results in glucose intolerance that can lead to GDM. The long-term maternal health implications of this maladaptation is that women who develop GDM during pregnancy are more likely to experience pregnancy complications, recurrent GDM during subsequent pregnancies [5], and an estimated 19–87 % will go on to be diagnosed with impaired glucose tolerance (IGT) or T2DM within 5 years of being diagnosed with GDM [6]. Pregnancy is thought to unmask underlying pancreatic β-cell dysfunction that eventually leads to the development of diabetes. Consensus exists that risk factors for GDM include maternal age, a family history of diabetes, ethnicity, a previous pregnancy with a history of macrosomia, and maternal obesity [7]. The hypothesis that some environmental chemicals could also be related to the etiology of GDM is gaining momentum.

Given the emerging evidence suggesting a positive association between environmental chemicals and T2DM risk, it is important to consider how these associations may differ among pregnant women. Exposures to environmental chemicals that act as endocrine active compounds may mimic or disrupt hormones that regulate insulin action or maintain glucose homeostasis. Given that pregnancy may be a critical window of susceptibility for diabetes, we discuss the animal and human evidence linking environmental chemicals and GDM.

Summary of the Animal Literature

An increasing number of animal studies have emerged indicating a causal relationship between the exposure to environmental contaminants and the occurrence of metabolic disorders. Initial studies focused on examining the contributing role of environmental chemicals in the etiology of T2DM. These studies established the impetus for examining their role in contributing to the risk of GDM (Table 1), the focus of this commentary. Here, we briefly summarize the biological plausibility for the association between environmental chemicals and T2DM or GDM.

Non-Persistent Pollutants

The most potent and important estrogen, 17β-estradiol (E2), plays a key role in the growth and maintenance of the female reproductive system [8]. In addition, it exerts profound effects on the control of energy homeostasis as well as glucose and lipid metabolism [9, 10]. In particular, converging findings from clinical and basic science research indicate that E2 can modulate insulin sensitivity. One of the most relevant aspects of BPA is that it can promote estrogen-like action that is similar or stronger in magnitude than E2 [11, 12].

Environmentally relevant doses of bisphenol A (BPA) have been shown to provoke insulin resistance, a key hallmark in the development of T2DM. Adult mice treated with BPA at a dose of 100 μg/kg/day for 4–8 days exhibited signs of glucose intolerance, insulin resistance, hyperinsulinemia, as well as an impaired insulin signaling cascade [13, 14]. Acute treatment with BPA disrupts pancreatic β cell function altering insulin release and glycemic levels [14]. Similarly, experimental studies in rats fed diets supplemented with di(2-ethylhexyl) phthalate (DEHP) exhibited glucose intolerance [15], decreased insulin, and increased blood glucose levels [16].

During late pregnancy, mothers develop severe insulin resistance which becomes necessary to ensure an appropriate supply of nutrients to the fetus. An elevation of estrogen and other maternal hormone levels is thought to be involved in this phenomenon [17, 18]. Despite this insulin-resistant state, the endocrine pancreas adapts and produces extra insulin to maintain glucose levels within the physiological range. However, if this pregnancy adaptation fails then GDM or glucose intolerance develops.

Thus, alterations in estrogen signaling by BPA during pregnancy could potentially have adverse effects on the maternal adaptation to glucose metabolism. In accordance with that, pregnant mice treated with BPA from days 9–16 of gestation developed marked glucose intolerance [19]. In addition, insulin signaling was impaired in the liver and adipose tissue with reduced ability of insulin to promote phosphorylation of Akt, resulting in a worsening of the insulin resistance that characterizes gestation. Increased body weight, higher levels of triglycerides, glycerol, and leptin were also observed in BPA-treated dams, suggesting that lipid metabolism could also be affected. Importantly, the doses used in this study were in the range of human exposure and below the reference dose that has been established to be safe according to the US Environmental Protection Agency (EPA) [19].

Toxic Metals

Experimental animal exposure to toxic metals has also shown a wide range of effects on glucose metabolism and insulin sensitivity. The administration of arsenic in male rats provoked higher fasting plasma glucose levels and glycosylated hemoglobin as well as impaired glucose tolerance [20]. A relationship between arsenic exposure and diabetes has also been suggested with disrupted β cell function and increased gluconeogenesis as the main causes [21]. Another study indicated that arsenic promoted insulin resistance together with impaired glucose tolerance [22]. Similar effects were observed after cadmium exposure in adult rats [23, 24]. Rodent studies suggest that cadmium accumulates in the pancreas and is associated with reductions in serum insulin [25] and damage to pancreatic β-cells [26, 27].

Table 1 Characteristics and results of animal studies examining the association between environmental chemicals and GDM

Author and year	Animal	Exposure vehicle	Time of exposure	Doses tested	Time endpoints measured	Chemicals tested	Main findings
Alonso-Magdalena et al. [19]	OF-1 mice	Corn oil, subcutaneous injection	Days 9–16 of gestation	10 and 100 μg/kg	Days 16–18 of gestation	BPA	Glucose intolerance. Aggravated insulin resistance, hyperinsulinemia, higher levels of triglycerides and leptin
Wan et al. [43]	CD-1 mice	Corn oil, orally administered	From the last day of mating, daily throughout gestation until the end of weaning period	0.3 and 3 mg	Postnatal day 21	PFOS	Increased relative liver weight. Higher fasting serum glucose and insulin levels. Increased HOMA-IR index
Zeng et al. [31]	Wistar rats	Oral, food	5 weeks before breeding	0, 0.3, and 3 mg Se/kg	Day 19 of gestation and day 14 postpartum	Selenium	Elevated fasting plasma glucose. Increased body weight. Glucose intolerance and insulin resistance elevated HOMA-IR index. Alterations of selenoproteins in the pancreas and liver
Hill et al. [28]	LM/Bc/Fnn mice	Water, intraperitoneal injection	Gestational days 7.5 and 8.5 or 8.5–9.5	10 μl/g body weight	After treatment	Arsenic	Higher plasma glucose. Glucose intolerance. Elevated HOMA-IR index
Kim et al. [44]	Sprague-Dawley rats	Corn oil, gavage	Gestational days 14 to 16	100 or 500 mg/kg/day	Gestational day 17	OP	Reduced body weight
Butenhoff et al. [45]	Crl:CD rats	Water, orally by gavage	Gestational day 0 through postnatal day 20	0, 0.1, and 0.3, 1 mg/kg	Postnatal day 4 through the end of lactation	PFOS	Reduced body weight
Tada et al. [46]	ICR mice	Food	Gestational day 0 to postnatal day 27	0, 0.01, 0.1 or 1 %	Postnatal day 27	TBBPA	Higher liver weight and serum cholesterol. Focal necrosis of hepatocytes
Daruich et al. [47]	Wistar rats	Water	Whole pregnancy	0.2–0.4 ml/ml water	Day 21 of gestation	Glyphosate	Decreased body weight and ingestion. Altered activity of certain enzymes in the liver, heart, and brain
Beuret et al. [48]	Wistar rats	Water	Gestational days 1 to 21	0.4 ml/20 ml water	Day 21 of gestation	Glyphosate	Excessive lipid peroxidation
Yoruk et al. [29]	Wistar rats	Isotonic NaCl Subcutaneous injection	Onset of pregnancy throughout the experiment	0.49 mg/kg/day	Day 15 or 20 of gestation	Cadmium	Hyperglycemia. Decreased insulin secretion. Changes of glycogen content of the placenta
Kanter et al. [30]	Wistar rats	Isotonic NaCl Subcutaneous injection	Onset of pregnancy throughout the experiment	0.49 mg/kg/d	Day 15 or 20 of gestation	Cadmium	Hyperglycemia. Decreased insulin secretion. Necrosis, degeneration and degranulation of pancreatic β cells
Alonso-Magdalena et al. [55•]	OF-1 mice	Corn oil, subcutaneous injection	Days 9–16 of gestation	10 and 100 μg/kg	6–7 months after delivery	BPA	Glucose intolerance. Insulin resistance. Decreased insulin secretion. Decreased pancreatic β cell mass and proliferation. Increased β cell apoptosis

Several studies have also addressed how toxic metals may adversely affect glucose homeostasis during pregnancy or impact glucose metabolism on diabetic pregnant animals. During pregnancy, arsenic has been shown to alter glucose tolerance and insulin sensitivity [28]. A study performed by Yoruk et al. [29] examined the effect of cadmium intake on streptozocin-induced diabetic pregnant rats and non-diabetic pregnant rats. Hyperglycemia as well as lower insulin levels was found in both non-diabetic and diabetic pregnant mice when compared to controls; the effect was more pronounced on the diabetic group. In the cadmium diabetic-treated group, changes in glycogen content localization were observed with increased glycogen content in both labyrinth and maternal part of placenta [29]. In a similar manner, cadmium has been shown to provoke higher levels of glycemia and decreased insulin release in diabetic pregnant rats which was related to degeneration, necrosis, and weak degranulation caused in pancreatic β-cell by cadmium exposure [30]. Overall, these results show that cadmium exposure during pregnancy aggravates diabetes.

Metabolic abnormalities have also been observed in gestating rats exposed to high doses of selenium. Studies performed by Zeng et al. [31] show how Wistar rats fed a basal diet supplemented with 3 mg of Se/kg during 5 weeks before breeding were found to have an increased fasting plasma glucose and body weight on day 19 of gestation. At this time point, they also displayed glucose intolerance and aggravated insulin resistance with elevated homeostatic model assessment of insulin resistance (HOMA-IR) index. Interestingly, altered hepatic insulin signaling including decreased messenger RNA (mRNA) levels of major insulin signaling protein insulin receptor (IR) 1 (Irs1), Irs2, Insr, and serine/threonine protein kinase 2 (Akt2) was observed in the dams 14 days postpartum. All these metabolic changes have been proposed to be related to the overexpression of some selenoprotein genes such as Gpx1 which could modulate the intracellular redox state and thus interfere with insulin secretion and signaling [31].

Persistent Organic Pollutants

Persistent organic pollutants (POPs) have also been found to disrupt glucose homeostasis. Rats exposed to POPs through the consumption of a high fat diet containing salmon oil showed exacerbated high fat diet-induced insulin resistance, abdominal obesity, and hepatosteatosis or fatty liver [32]. When assessing the joint effects of POPs, using a diet supplemented with farmed Atlantic salmon, the addition of a high fat diet or a western diet, it was concluded that in all cases, POPs contribute to the development of glucose intolerance, insulin resistance, and obesity [33]. Rats orally treated with a mixture of POPs and other chemicals common in Artic populations provoked loss of pancreatic β and α cells resulting in decreased insulin and glucagon levels [34]. Flame retardants like hexabromocyclododecane (HBCD) or polybrominated diphenyl ethers (PBDE) may also impair glucose and lipid metabolism [35] by aggravating the effects of a high fat diet [36]. The chronic administration of some organophosphate pesticides (OPs) like malathion, monocrotophos, or diazinon among others is associated with the development of insulin resistance and oxidative stress [37, 38].

While limited, animal evidence has also demonstrated that POPs can act as endocrine disruptors and impact energy metabolism during pregnancy. The increased glycogen content found in pregnant mice treated with the dioxin TCDD was accompanied by an upregulation of Glut3 mRNA levels, resembling that glucose kinetics could be affected [39]. The peroxisome proliferator-activated receptor (PPAR) system, a group of receptors that play a critical role in lipid metabolism and adipogenesis, has been identified as a target for endocrine disruption. For instance, perfluoroalkyl acids (PFAAs) [40, 41] and also the non-persistent phthalates [42] have been proposed to alter energy metabolism through PPAR receptors. Female pregnant mice orally fed with 0.3 or 3 mg/kg of perfluorooctanesulfonate (PFOS) by gavage during gestation and lactation periods were reported to show higher fasting glycemia levels at the end of the weaning period. Importantly, these mothers exhibited elevated homeostatic model assessment of insulin resistance (HOMA-IR) index, a common method used for the estimation of insulin resistance [43].

Lipid metabolism has also been reported to be affected by 4-tert-octylphenol (OP) or PFOS. Gestational exposure to OP or PFOS was found to result in altered body weight [44, 45], histological changes in adipose tissue, and altered transcriptional levels of lipogenesis-associated genes [44]. Other non-persistent flame retardants such as tetrabromobisphenol A (TBBPA) did not produce changes in body weight during pregnancy but the treated dams showed higher levels of cholesterol and liver weight and focal necrosis of hepatocytes [46]. Maternal exposure to the herbicide glyphosate resulted in the alterations of the activity of certain antioxidant enzymes with possible negative effects for the antioxidant defense system [47, 48].

Air Pollution

Several rodent studies have proposed that exposure to air pollution may induce profound metabolic effects through oxidative stress. In particular, exposure to fine particular matter ($PM_{2.5}$) was found to promote glucose intolerance, decrease insulin sensitivity, and altered hepatic glucose and lipid metabolism [49–51]. Acute exposure to ozone in rats resulted in decreased glucose tolerance and a marked trend of altered insulin signaling in liver and adipose tissue [52].

Long-Term Health Risks for Mothers

Gestational diabetes may not simply be a transient metabolic alteration that occurs during pregnancy but a problem leading to overt T2DM. Women diagnosed with GDM have a significantly higher risk of developing diabetes in the future [53]. Long-term follow-up studies indicate that approximately 10 % of women with GDM will have diabetes soon after delivery, rising to 20–60 % within 5–10 years [54]. Under this paradigm, the metabolic disturbances produced by EDC exposure during pregnancy may predispose mothers to suffer diabetes later in life. In accordance with that, it has been shown that mice treated with BPA during gestation developed abnormal glucose tolerance, insulin resistance, and increased body weight several months after delivery [19, 55•]. In addition to that, a more rapid deterioration of the pancreatic β-cell with aging occurs in the exposed mothers [55•]. They exhibited impaired pancreatic β-cell function with decreased insulin secretion and β-cell mass which was associated with important alterations of the proliferation capacity as well as the rate of apoptosis. Importantly, both pregnancy and BPA exposure were required for this outcome. Non-pregnant female mice exposed to BPA during the same period do not present any metabolic alteration later in life. Overall, these findings suggest that pregnancy is a critical window of susceptibility for BPA effects on the mothers and increases future risk of developing metabolic abnormalities. Whether or not this is the case for other EDCs has not yet been studied but merits further investigation [55•]. In addition, these findings suggest that BPA may be obesogenic [56], possibly providing another potential mechanism for an increased risk of metabolic disorders among mothers and their offspring exposed to BPA.

Summary of Epidemiologic Evidence: Environmental Chemicals and GDM

We now summarize and discuss the epidemiological evidence that suggests an association between environmental chemical exposures and GDM (Table 2). Environmental chemicals discussed include bisphenol A, phthalates, toxic metals, and air pollution.

Bisphenol A and GDM

A recent systematic review and meta-analysis summarizes literature linking urinary concentrations of phthalate metabolites and bisphenol A to the risk of T2DM [57]. Only two studies, a small case-control study [58] in Oklahoma City, OK, USA ($n=94$; 22 GDM cases and 72 controls) and a large Canadian prospective cohort [59•] that recruited participants from 10 sites across six provinces ($n=1274$; 49 IGT and 44 GDM), have examined the relationship between BPA exposure during pregnancy and GDM risk. In both studies, pregnant women underwent GDM screening using a 50-g glucose challenge test. GDM diagnoses were assigned when glucose levels exceeded thresholds for screening test or follow-up 75 g or 100 g oral glucose tolerance tests. Additionally, the assessment of BPA exposure preceded GDM screening in the second trimester. Neither study reported a statistically significant association between BPA urinary concentrations and GDM [58, 59•] or impaired glucose tolerance [59•].

Null findings may be the result of several limitations. The number of GDM cases in both studies was small and may have limited the ability to detect associations between urinary concentrations of BPA and GDM risk. In addition, a single urine specimen during the first trimester was used to measure BPA exposure. Due to its short biological half-life, a single spot urine sample has been shown to be inadequate in capturing within person variability in BPA exposure in non-pregnant and pregnant populations [60–62]. It should also be noted that in both studies, BPA urinary concentrations among pregnant women were found to be lower than the general populations of women in the USA and Canada. While preliminary evidence does not suggest a link between exposure to BPA and GDM risk during pregnancy, further studies are needed. Future studies would be improved by assessing BPA exposure multiple times across pregnancy to allow the identification of potential windows of susceptibility. In addition, conducting studies within and across populations experiencing more variability in BPA exposures are warranted.

Phthalates and GDM

Exposures to phthalates, synthethic diester compounds, are assessed by measuring the urinary concentrations of monoester metabolites resulting from metabolized parent compounds. Preliminary evidence supports associations between urinary phthalate metabolite concentrations during pregnancy and GDM. A small pilot study ($n=110$) conducted in Oklahoma City, OK, USA that measured nine phthalate metabolites during early pregnancy reported changes in blood glucose among women ($n=72$) for whom results for a 50-g glucose challenge test administered during routine GDM screening could be obtained [63]. Of the 72 women, 15 had a GDM screening value that exceeded the threshold of 135 mg/dL. Mean blood glucose levels among pregnant women with urinary concentrations of mono-iso-butyl phthalate (MiBP) and monobenzyl phthalate (MBzP) in the highest tertile of exposure (MiBP ≥15.30 μg/L and MBzP ≥30.31 μg/L) were approximately 18 mg/dL lower when compared to those in the first tertile of exposure (MiBP <8.70 μg/L and MBzP <10.01 μg/L). These estimates were adjusted for urinary creatinine, race/ethnicity, and gestational age at enrollment (MBzP only).

The previously described Canadian prospective cohort by Shapiro et al. [59•] also examined the association between

Table 2 Characteristics and results of epidemiological studies examining the association between environmental chemicals and GDM

Author and year	Study design and population	Exposure	Outcome	Analyses and confounders included	Main findings
Shapiro et al. [59•]	Longitudinal birth cohort 10 sites in 6 Canadian provinces $n = 1274$	1st trimester urinary levels of total BPA and 9 phthalate metabolites	IGT ($n = 59$) and GDM ($n = 48$) assessed using 50 g glucose challenge test and 75 or 100 g OGTT (Canadian Diabetes Association)	Logistic regression estimated ORs adjusted for specific gravity, age at delivery, pre-pregnancy BMI, parity, household income, education, race, and smoking.	No statistically significant associations observed between BPA or phthalate metabolites and GDM.
Robledo et al. [58]	Case-control Oklahoma City, OK GDM cases ($n = 22$) and GDM controls ($n = 72$)	1st trimester urinary levels of total BPA	GDM assessed using 1-h 50 g OGTT and subsequent 3-h 100 g OGTT (Metzger and Coustan)	Logistic regression estimated ORs adjusted for specific gravity and race/ethnicity.	No statistically significant associations observed between BPA and fasting blood glucose levels or GDM.
Robledo et al. [63]	Cohort Oklahoma City, OK $n = 72$	1st trimester urinary levels of 9 phthalate metabolites	Fasting blood glucose assessed using 1-h 50 g OGTT	Multiple linear regression estimated association between phthalate metabolites and blood glucose levels; models adjusted for creatinine, race/ethnicity, and gestational age at enrollment.	Pregnant women with urinary levels of MiBP ($\beta = -18.30$ 95 % CI, −35.41 to −1.19) and MBzP ($\beta = -17.26$ 95 % CI, −34.12 to −0.40) in the highest tertile had mean blood glucose levels approximately 18 mg/dl lower when compared to those in the 1st tertile of exposure.
Fleisch et al. [71]	Cohort Boston, MS $n = 2093$; 65 IGT, 118 GDM	2nd trimester $PM_{2.5}$ and black carbon, proximity to roads, traffic-related air pollution	IGT and GDM assessed using 50 g OGTT and subsequent 3-h 100 g OGTT per American Diabetes Association 2008 criteria	Multinomial logistic regression estimated association with air pollution exposures and IGT and GDM; models adjusted for maternal age, pre-pregnancy BMI, pregnancy weight gain, race/ethnicity, education, smoking, season, history of GDM or diabetes, and household income.	IGT is more prevalent in women in the highest quartile of exposure to $PM_{2.5}$ (OR = 2.63, 95 % CI 1.15, 6.01) and traffic density (OR = 2.66, 95 % CI 1.24, 5.71) compared to those in the lowest quartile. No associations observed with GDM.
Malmqvist et al. [73•]	Cohort Sweden $n = 81{,}110$	Average 1st, 2nd, and 3rd trimester exposures to NO_X, proximity to roads, combustion-related air pollution	GDM; 75 2-h OGTT, plasma glucose > 10 mmol/L if IGT results repeated to make GDM diagnosis	Estimated ORs for association between GDM and increasing quartiles of exposures; models adjusted for pre-pregnancy BMI, smoking, ethnicity, parity, type 1 DM, and maternal age.	Odds of GDM increased for increasing quartiles of NO_X exposure in the 2nd trimester.
Robledo et al. [72•]	Longitudinal cohort USA $n = 220{,}264$; 11, 334 GDM	Average daily exposure for 3 months prior to conception, 1st trimester, gestational weeks 1–28 of $PM_{2.5}$, PM_{10}, CO, O_3, SO_2, and $PM_{2.5}$ subspecies	GDM diagnoses in medical record or discharge records (ICD-9: 648.8)	Binary regression models with link function estimated RRs for GDM per IQR increase in air pollutants adjusted for maternal age, race/ethnicity, and study site.	Preconception exposures of NO_X and SO_2 and during early pregnancy associated with GDM/preconception O_3 associated with lower GDM risk but increased later during pregnancy.
Romano et al. [81•]	Case-cohort Seattle-Tacoma, WA, USA $n = 621$	Cd and total As in early pregnancy urine (~15 gw) ICP-MS	GDM = 140 50 g GCT/100 g OGTT (24–28 weeks gestation) (American Diabetes Association 2003)	Logistic regression: age, pre-pregnancy body mass index, race/ethnicity, nulliparity, preeclampsia, chronic hypertension, family history of diabetes, family history of hypertension, total urinary arsenic, and fish consumption.	Women in the high tertile of urinary cadmium had 2.07 times the risk of GDM (95 % CI 1.15, 3.73) versus women in the low tertile; p trend = 0.015).
Ettinger et al. [77]	Cross-sectional Tar Creek Superfund Site, Ottawa County, OK $n = 532$	As in blood and hair (delivery) ICP-MS	IGT = 140 (>140 mg/dL) after 1 h, 50 g OGTT (24–28 weeks gestation)	Logistic regression: age, race, pre-pregnancy BMI, Medicaid use, and marital status.	Women in the highest quartile for blood arsenic had 2.8 times the odds of IGT compared to women in the lowest quartile (95 % CI 1.1, 6.9; p trend = 0.008).
Peng et al. [78]	Nested case-control Xiamen, China 327	As, Hg, Pb, Cd, and Cr in meconium (delivery) ICP-MS	GDM = 137 Routine antenatal screening (24–28 weeks)	Logistic regression: age pre-pregnancy BMI, gravidity, parity, hepatitis B infection, and newborn sex.	Higher levels of meconium As, Hg, Cr, and Cd were associated with maternal GDM. The odds ratios (95 % CI; p trend) comparing the highest to lowest quartile for meconium metals were as follows As = 5.25 (1.99,

Table 2 (continued)

Author and year	Study design and population	Exposure	Outcome	Analyses and confounders included	Main findings
					13.86; <0.001), Hg = 1.75 (0.76, 4.03; 0.004), Cr = 4.48 (1.40, 14.31; 0.002), and Cd = 11.95 (2.97, 48.04; <0.001).
Roverso et al. [79]	Case control Padua, Italy $n = 47$	Placental Al, As, Ba, Ca, Cd, Ce, Co, Cr, Cs, Cu, Fe, Ga, Gd, K, La, Mg, Mn, Mo, Na, Ni, P, Pb, Rb, Sb, Se, Sn, Sr, Ta, Ti, V, Zn, and Zr (delivery) ICP-MS	GDM = 19 (diagnostic criteria not described)	Student's *t* test and principle component analysis.	GDM placentas contained less Cd and more Se than non-GDM placentas.
Shapiro et al. [59•]	Longitudinal birth cohort 10 sites in 6 Canadian provinces $n = 1274$	Blood As, Cd, Hg, Pb (first trimester) ICP-MS	IGT ($n = 59$) and GDM ($n = 48$) assessed using 50-g glucose challenge test and 75 or 100 g OGTT (Canadian Diabetes Association)	Logistic regression and restricted cubic splines: Each chemical was examined separately, and models were adjusted for maternal age, race, pre-pregnancy BMI, and education.	Women in the highest quartile of blood As had increased risk of GDM (OR = 3.7, 95 % CI = 1.4, 9.6; p trend < 0.01) and of GDM/IGT combined (OR = 1.9, 95 % CI = 1.1–3.5; p trend = 0.01) compared to those in the lowest quartile. Odds of GDM were elevated in the highest quartile of blood Cd compared to the lowest, but the OR and trend were not statistically significant (OR = 2.5 (1.0–6.4; p trend = 0.13).

IGT and GDM with urinary concentrations of seven phthalate metabolites detected in >75 % of their study populations, including MBzP. MiBP exposure levels were not examined in this population. Women in the third and fourth quartiles of MBzP exposure (4.9 to 420 μg/L) were approximately three times more likely to be IGT compared to women in the bottom quartile of exposure (0.1–2.1 μg/L). After adjustment for maternal age, race, pre-pregnancy BMI, education, and specific gravity, odds ratios for IGT were no longer statistically significant. No associations were observed between urinary concentrations of other phthalate metabolites and GDM risk. Phthalate metabolites are highly correlated and may share the same parent compound. Associations between phthalate metabolites and outcomes are often examined separately. However, both studies also examined the associations of interest between outcomes and summed metabolite concentrations by parent compound or molecular weight (high or low). No statistically significant associations were observed for these exposure variables in either study.

Inverse associations between MBzP and fasting blood glucose observed by Robledo et al. [63] are consistent with findings for MBzP and self-reported type 1 or 2 diabetes in a Mexican non-pregnant population of women ($n = 255$) [64]. However, these results contradict findings by Shapiro et al. that suggest that the increasing levels of MBzP during pregnancy are associated with increased IGT and other epidemiological evidence linking phthalate exposure to diabetes in adult populations [64–67]. Similarly as with BPA, variability in phthalate exposure is an issue when a single urine specimen is used to measure exposure during pregnancy [62, 68, 69]. Again, future studies can be improved by examining phthalate exposure multiple times across pregnancy to allow the identification of potential windows of susceptibility. In addition, the high correlation among phthalate metabolites warrants investigation into their joint action or similar mechanisms of action in potentially increasing GDM risk.

Air Pollution and GDM

A recent systematic review and meta-analysis of European and North American studies ($n = 13$) concluded that current evidence supports a positive association between air pollution and diabetes [70]. Literature is also mounting to suggest a positive association between specific air pollutants and IGT during pregnancy [71] and GDM [72•, 73•, 74]. The most comprehensive of these studies utilized data obtained from the Air Quality and Reproductive Health (AQRH) study [72•]. The AQRH study estimated maternal air pollutant exposures for the Consortium of Safe Labor ($n = 228, 562$), a population-based retrospective cohort of US pregnancies (2002–2008). Information on maternal residence was not available, and air pollutant exposures were estimated for hospital referral regions where the deliveries took place. Hourly

exposures for the following pollutants were estimated: particulate matter (PM) with an aerodynamic diameter ≤2.5 mm ($PM_{2.5}$) and ≤10 mm (PM_{10}), nitrogen dioxides (NO_X), sulfur dioxides (SO_2), carbon monoxide (CO), ozone (O_3), and constituents of $PM_{2.5}$ including elemental carbon, organic compounds, ammonium ion, dust, sulfate, and nitrate. Hourly estimates were averaged across several potential windows of susceptibility to examine GDM risk. Exposure windows included the 3 months prior to pregnancy (91 days before last menstrual period (LMP)), the first trimester (LMP to 13 weeks gestation), and gestational weeks 1 through 24. GDM diagnoses ($n = 11,334$) were reported in electronic medical records or discharge data using the International Classification of Diseases, Ninth Revision (ICD-9).

The findings of the AQRH study suggest [72•] that GDM risk increases with each interquartile (IQR) increase in NO_X and SO_2 exposures during the 3 months prior to pregnancy (NO_X: RR = 1.09; 95 % CI 1.04, 1.13 and SO_2: RR = 1.05; 95 % CI 1.01, 1.09), the first trimester (NO_X: RR = 1.06; 95 % CI 1.01, 1.10 and SO_2: RR = 1.04; 95 % CI 1.00, 1.08), and during the first 7 weeks of pregnancy. Ozone exposure during the 3 months prior to pregnancy was associated with decreased GDM risk (RR = 0.93, 95 % CI 0.90, 0.96). However, upon further examination of the association between O_3 exposure and GDM risk by gestational week, GDM risk was observed to increase after the 13th week of pregnancy. No associations were seen for $PM_{2.5}$, PM_{10}, CO, elemental carbon, organic compounds, ammonium ion, or dust components during any of the exposure windows examined.

These results are consistent with other studies that have examined associations between NO_X, $PM_{2.5}$, and GDM [73•, 74]. A Swedish Medical birth study ($n = 81,110$) observed an association between the increasing quartiles of NO_X exposure at maternal residence during the first and second trimesters with GDM prevalence ($n = 1599$). When compared to women in the lowest quartile of NO_X exposure (2.5–8.9 μg/m^3), women in the highest quartile (>22.7 μg/m^3) were almost two times more likely to have been diagnosed with GDM during their pregnancy (OR = 1.98; 95 % CI 1.41, 2.03). This study also observed that women living within 200 m of a road with traffic density >10 vehicles/min were at increased odds of GDM (OR = 1.23; 95 % CI 1.05, 1.51) compared to those not living within 200 m. However, in a study of Japanese pregnant women ($n = 19,077$) [75], women living ≤200 m from major roads that experienced a much larger traffic volume (50,000 per 24 h on weekday) were not found to be at an increased risk of GDM (OR = 1.2, 95 % CI 0.5, 2.5). Authors noted that the small prevalence of GDM ($n = 100$) in their study may have hindered their ability to detect an association between markers of traffic-related air pollution and GDM.

Other studies have found associations between air pollutants and $PM_{2.5}$ and O_3 with IGT and GDM. Findings from a cohort ($n = 2093$) of pregnant women from Boston, MA, USA [71] suggest that the second trimester $PM_{2.5}$ exposure at maternal residence is associated with IGT ($n = 65$) but not GDM ($n = 118$). Women in the highest quartile of $PM_{2.5}$ exposure (12.8–15.9 μg/m^3) were almost three times (OR = 2.63; 95 % CI 1.15, 6.01) more likely to be IGT during pregnancy. A population-based study conducted in FL, USA using vital statistics records with complete covariate data ($n = 406,334$) suggests that $PM_{2.5}$ and O_3 exposure at maternal residence during pregnancy is associated with GDM ($n = 13,943$) [74]. Women were found to be at an increased odds of GDM with each 5-μg/m^3 increase in $PM_{2.5}$ concentrations during the first trimester (OR = 1.16, 95 % CI 1.11, 1.21), second trimester (OR = 1.15, 95 % CI 1.10, 1.20), and throughout the entire pregnancy (OR = 1.20, 95 % CI 1.13, 1.26). Similar associations were observed for each 5 part per billion (ppb) increase in O_3 exposure during the first trimester (OR = 1.09, 95 % CI 1.07, 1.11), second trimester (OR = 1.12, 95 % CI 1.10, 1.14), and the entire pregnancy window (OR = 1.18, 95 % CI 1.15, 1.21).

While not all evidence is confirmatory, accumulating evidence supports a positive association between GDM and increasing exposures to NO_X, SO_2, O_3, and $PM_{2.5}$. Inconsistent findings across populations may be attributed to the differences in composition or variability in air pollution across geographic areas or near air monitors, methods, or models used to estimate air pollutant concentrations or even the choice in geographic location used to assign exposures (e.g., maternal residence, hospital referral regions). Future studies could be improved by examining the association between GDM and specific pollutants, exploring the impact on GDM risk using multi-pollutant models, and exploring the risk of GDM across various exposure windows to help identify the windows of susceptibility for GDM risk. Future studies should also attempt to examine the association between air pollution exposures before pregnancy and GDM risk.

Toxic Metals and GDM

Biologically plausible mechanisms by which arsenic could induce T2DM have been previously described [76], and chronic exposure to arsenic has been suggestively associated with GDM risk. In a US based study ($n = 532$), Ettinger et al. observed that women with the highest blood arsenic levels (2.09–24.07 μg/L) had almost three times the odds (OR = 2.8; 95 % CI 1.1–6.9) of IGT (>140 mg/dL) compared to the women with the lowest levels (0.23–0.92 μg/L) [77]. It is important to note that blood for arsenic analysis was collected at delivery (after outcome assessment) in this study, though similar results were observed among a subset of women that provided hair for arsenic analysis [77]. In the Canadian

prospective cohort study described above [59•], women in the fourth quartile of blood arsenic (1.3–34.5 μg/L) had nearly four times the odds of GDM (OR = 3.7; 95 % CI = 1.4, 9.6; *p* trend <0.01) and twice the odds of GDM and IGT combined (OR = 1.9, 95 % CI = 1.1–3.5; *p* trend = 0.01), compared to those in the first quartile (0.3–11.0 μg/L). The association between blood arsenic and GDM was further supported by a dose-response cubic spline model ($p < 0.01$) [59•]. A Chinese case-control study ($n = 327$) observed 5.25 greater odds of GDM among women whose newborns were in the fourth quartile for the concentration of arsenic in meconium (95 % CI = 1.99, 13.86; *p* trend <0.001) versus those in the first quartile [78]. However, a small case-control study ($n = 47$) in Italy [79] assessed several placental metals and observed no association between placental arsenic and GDM. The estimates in this study were not adjusted for any potential confounding factors, though [79]. Speciated arsenic was not assessed in any of these studies [59•, 77, 78], so the toxicologically relevant form of arsenic (organic v. inorganic) is currently unknown. Regardless, these studies indicate that arsenic is a potentially important environmental risk factor for GDM across diverse populations of women.

Previous research suggests that cadmium is associated with T2DM in the US general population [80]. Although studies have not been entirely consistent across biomarkers of exposure, cadmium also appears to be associated with elevated risk of GDM. A US based case-cohort study ($n = 621$) observed that women in the third tertile (≥0.43 μg urinary Cd/g Cr) had 2.07 times the risk of GDM (95 % CI 1.15, 3.73) versus women in the first tertile (<0.29 μg urinary Cd/g Cr; *p* trend = 0.015) [81•]. In a Chinese case-control study ($n = 327$), women whose newborns were in the fourth quartile for the concentration of cadmium in meconium had 11.95 times the odds of GDM (95 % CI = 2.97, 48.04; *p* trend <0.001) versus those in the first quartile [78]. These results are quite striking despite the wide confidence interval and the fact that the correlation between meconium cadmium concentrations and the etiologically relevant maternal cadmium exposure is somewhat unclear, given that cadmium accumulates in the placenta and transplacental transfer of cadmium is quite limited [82]. Alternatively, in a small metallomic study ($n = 47$), placental cadmium was lower among women with GDM than among women without GDM [79]. However, the small sample size may have limited statistical power in this study, and the reported estimates were not adjusted for any confounding factors [79]. Though not statistically significant, Shapiro et al. observed that women in the fourth quartile of blood cadmium (0.3–5.1 μg/L) had 2.5 times the odds of GDM compared to women with blood cadmium <0.1 μg/L (95 % CI = 1.0, 6.4) [59•]. Differences in the choice of biomarker of exposure across studies of cadmium and GDM may explain some of the variability in results across studies. Blood cadmium more closely reflects recent cadmium exposure, whereas, urinary cadmium quantifies body burden of cadmium [83]. Additionally, the control of confounding was not consistent across studies. In particular, only the study by Romano et al. controlled for maternal total urinary arsenic in the analyses, though no association between total urinary arsenic and GDM was observed in that study [81•]. Collectively, these studies suggest that cadmium may be a risk factor for GDM. Future research should assess the influence of underlying deficiencies on nutrient metals and potential interactions between toxic and nutrient metals, as well as interactions among toxic metals.

Conclusions

This commentary underlies the importance of studying the role that environmental chemicals play in the etiology or exacerbation of GDM. Evidence on the association between air pollutants and GDM risk also underscores the importance of examining the preconception period, an often understudied critical exposure window for the effects of environmental chemical exposure. Long-term prospective studies that evaluate whether gestational exposures to environmental chemicals play an important role in the development of T2DM in women after pregnancy are also needed.

One important challenge to consider when conducting future studies is the cost of assays to measure environmental chemical exposure which can impact the ability to carry out studies large enough to give rise to an adequate number of GDM cases. Banked biological specimens from pregnancy cohorts or pooling resources across pregnancy cohorts could provide valuable information regarding the environmental determinants of GDM and T2DM in women. Also, in environmental epidemiology, there is the inherent difficulty in singling out the effect of a single chemical from those of unknown or unmeasured co-exposures, as humans are exposed daily to complex mixtures of toxic substances. As methodology related to studying mixtures continues to develop [84], the potential for synergistic and antagonistic relations among possible environmental exposures should be carefully explored in the GDM literature. Despite the challenges, increased knowledge of environmental risk factors for GDM, especially those that may be modifiable through either policy change or behavioral interventions, will assist in identifying women at higher risk of GDM and prevention of long-term morbidities associated with GDM during pregnancy.

Compliance with Ethical Standards

Conflict of Interest C. Robledo, M. E. Romano, and P. Alonso-Magdalena declare no conflict of interest.

Human and Animal Rights and Informed Consent All animal studies by P. Alonso-Magdalena and human studies by C. Robledo and M. Romano were performed after approval by the appropriate institutional review boards. When required, informed consent was obtained from all participants.

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