

Review Article

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Prenatal exposure to persistent organic pollutants as a risk factor of offspring metabolic syndrome development during childhood

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Abstract: Persistent Organic Pollutants (POPs) are exogenous, artificially made chemicals that can disrupt the biological system of individuals and animals. POPs encompass a variety of chemicals including, dioxins, organochlorines (OCs), polychlorinated biphenyl (PCBs), and perfluoroalkyl substances (PFASs) that contain a long half-life and highly resistant to biodegradation. These environmental pollutants accumulate over time in adipose tissues of living organisms and alter various insulin function-related genes. Childhood Metabolic Syndrome (MetS) consists of multiple cardiovascular risk factors, insulin function being one of them. Over the years, the incidence of the syndrome has increased dramatically. It is imperative to explore the role of persistent organic pollutants in the development of Childhood Metabolic Syndrome. Some epidemiological studies have reported an association between prenatal exposure to POPs and offspring MetS development throughout childhood. These findings have been replicated in animal studies in which these pollutants exercise negative health outcomes such as obesity and increased waist circumference. This review discusses the role of prenatal exposure to POPs among offspring who develop MetS in childhood, the latest research on the MetS concept, epidemiological and experimental findings on MetS, and the POPs modes of action. This literature review identified consistent research results on this topic. Even though the studies in this review had many strengths, one major weakness was the usage of different combinations of MetS criteria to measure the outcomes. These findings elucidate the urgent need to solidify the pediatric MetS definition. An accurate definition will permit scientists to measure the MetS as a health outcome properly and allow clinicians to

diagnose pediatric MetS and provide individualized treatment appropriately.

Keywords: fetus; obesity; organochlorines; pediatric; pregnancy.

Introduction

The “syndrome x” was first described by Gerald Reaven as the clustering of cardiovascular disease risk factors, which later evolved as the adult Metabolic Syndrome (MetS) [1]. This syndrome was a framework that described the various pathophysiology outcomes and mechanisms underlying insulin resistance (i.e., dyslipidemia and adipose tissue dysfunction), hyperinsulinemia, blood pressure, and coronary artery disease risk from high refined carbohydrate intake [1]. As syndrome x evolved to become the MetS, the adult definition became more comprehensive and included central or abdominal obesity in addition to hyperglycemia, hypertension, and dyslipidemia as risk factors [1, 2]. The pediatric MetS definition followed a similar course to the adult definition proposed by the International Diabetes Federation (IDF) described in Table 1. In the present paper, the IDF pediatric MetS definition helped to identify articles in the methods section. Components of the MetS definition are cardiovascular disease risk factors frequently associated with obesity, socioeconomics, and environmental exposure to endocrine-disrupting chemicals (EDC) like persistent organic pollutants. Persistent organic pollutants (POPs) are synthetic compounds with lipophilic chemical properties and are highly resistant to degradation, thus persistent in the environment. These pollutants have been hypothesized to disrupt the metabolism by interfering with adipocyte formation [3]. Especially offspring exposed during pregnancy, a critical period of fetal development and epigenetic programming, may be more susceptible to metabolic-related diseases that manifest in the future [2]. Current literature has found multiple associations between POP exposure during gestation and MetS-related components in offspring. The present literature review

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Table 1: International Diabetes Federation pediatric and adolescent metabolic syndrome definition [5].

	Age group, years		
	6–9	10–15	≥16
MetS definition criteria	Cannot diagnose in this age group	Abdominal obesity and at least two other components	Using adult criteria: abdominal obesity and at least two other components
Components			
– Abdominal obesity, WC		≥90th percentile or adult cut-off if lower	≥94 cm (Europid men)* ≥80 cm (Europid women)*
– Triglycerides, mmol/L		≥1.7	≥1.7
– HDL-C, mmol/L		<1.03	<1.03 males <1.29 females Or specific treatment for lipid abnormalities
– Blood pressure, mmHg		Systolic: ≥130 Diastolic: ≥85	Systolic: ≥130 Diastolic: ≥85 Or the treatment of previously diagnosed hypertension
– Glucose, mmol/L or known T2DM		≥5.6 (if ≥5.6 or known t2DM recommend an OGTT)	IFG: FPG=5.6 Or previously diagnosed T2DM

WC, waist circumference; T2DM, type 2 diabetes mellitus; IFG, impaired fasting glucose; FPG, fasting plasma glucose. *According to the IDF Consensus group, ethnic, gender, and age differences are acknowledged, but further research is needed on outcomes to establish risk [5].

aims to compare and contrast the results of recent prospective cohort studies whose goal was to explore the relationship between prenatal POP exposure and the development of offspring MetS.

Definition of pediatric metabolic syndrome

The adult MetS syndrome definition was internationally recognized in 1998. More recently, the IDF proposed a potential definition of pediatric MetS predicated on previous studies using age-specific diagnostic criteria described in Table 1 [4]. According to the IDF, MetS cannot be diagnosed in children younger than 10 years of age. Nonetheless, a weight reduction intervention is suggested for children younger than 10 years should if waist circumference (WC) is ≥90th percentile (considered obese) and present with other relevant risk factors like a family history of MetS, type 2 diabetes mellitus, or hypertension [4, 5]. Children aged from 10 to <16 years with a WC ≥90th percentile and meet two or more of the other MetS components, for instance, elevated triglycerides (TGs), low high-density lipoprotein cholesterol (HDL-C), high blood pressure (BP), and elevated glucose concentrations, are considered to have MetS [4, 5]. The adult criteria are used for children older than 16 years [5]. Although the pediatric MetS criteria have come to a moderate consensus, a concretion of the pediatric MetS definition is difficult to acquire since puberty impacts adipose tissue distribution and hormone regulation, thus misclassifying diagnosis [5].

Definition of persistent organic pollutants

Persistent organic pollutants (POPs) are synthetic compounds that contain similar lipophilic chemical properties. These organic chemicals become widely disseminated throughout the environment via natural processes that involve soil, water, and air. Also, these compounds are highly persistent in the environment and are highly resistant to environmental degradation. Most have a prolonged half-life of about 10 years, leading to bioaccumulation in adipose tissues of living organisms like fish, over time, these chemicals biomagnify in various ecosystems [6, 7]. Biomagnification of POPs can lead to increased POP exposure over time to wildlife and humans, furthermore, increase the risk of toxicity and negative health outcomes [6, 7].

POPs are an umbrella term used to define compounds with similar properties. Some types of POPs include dioxins, polychlorinated biphenyls (PCBs), organochlorine pesticides (OC), and per- and polyfluoroalkyl substances (PFAS) [7, 8]. Dioxins are byproducts of combustion like waste incineration or burning fuels like coal or oil. PCBs, now banned from production in the U.S., are highly resistant to extreme temperature and chemically stable, making them suitable for electrical equipment like capacitors and transformers. OCs are herbicides or insecticides like Dichlorodiphenyltrichloroethane (DDT), an infamous insecticide known to impact individuals' health and the environment negatively. DDT is now banned worldwide. PFASs contain repellent properties with low surface

tension. They are commonly used in commercial applications, particularly materials used to package food, household products like non-stick pans (Teflon), carpets, textiles, and more [7, 9]. The two most widely detected PFASs derivatives in humans are perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS), with half-lives of about four and five years, respectively [9].

Even though manufacturing has been banned for many of these chemicals, a substantial amount of them remains in the environment. They have been associated with diseases, declines in several wildlife species, and adverse health effects in humans [7]. Studies have found inconsistent results between POPs and cardiometabolic-risk factors in people, including insulin resistance, low HDL-cholesterol, elevated triglycerides, and hypertension [8]. In a prospective cohort study conducted in Denmark, investigators reported a modest positive association between prenatal PFOA exposure and overweight and central obesity in 20-year-old female offspring [9, 10]. However, a study reported an inverse relationship between PFAS concentrations and insulin resistance, where higher PFAS concentrations were associated with lower insulin resistance [11]. A longitudinal cohort study conducted in Spain found an increased risk of being overweight and obese in six-year-old children with high exposure to hexachlorobenzene (HCB), an OC. With dioxin exposure, inconsistent results have been found in numerous longitudinal birth cohort studies exploring the relationships between prenatal exposure to dioxin-like compounds and child adiposity [2]. Also, inconsistent sex-specific effects have been observed with POPs in several studies [2].

Studies exploring the relationship between exposure to POPs during gestation and pediatric MetS have been growing during the last decade. The literature concerning pediatric MetS environmental risk factors is emergent, but only a few have been subject to be reviewed. This review aims to explore the role of prenatal exposure to POPs in offspring who develop various risk factors encompassing the MetS in childhood.

Prevalence of metabolic syndrome

Given the different criteria per age group and limited criteria for younger children to be diagnosed with MetS and the diverse pediatric MetS definitions used in studies, it has become difficult to estimate a prevalence for the MetS in children. One systematic review of 85 papers from Europe, the Middle East, the Far East, and the Americas all published between 2003 and 2011 concluded that the MetS prevalence for the whole population was about 3% [12]

using the National Cholesterol Education Program's Adult Treatment Panel (ATP), the World Health Organization (WHO), and the IDF definitions. It also estimated the MetS among overweight children to be 11.9% (range 2.8–29.3%), and within-study analyses, the median prevalence was higher among boys than girls (5.1 vs. 3.0% respectively) [12]. Using various National Health and Examination Survey (NHANES) cohorts, a representative sample of the U.S. population, a study found the overall U.S. age-adjusted MetS prevalence with the 2001 revised ATP III definition. The age-adjusted prevalence for the NHANES 1988–1994 cohort ($n=6,436$) was 29.2%, NHANES 1999–2002 cohort ($n=1,677$) was 32.3%, NHANES 2003–2006 cohort ($n=3,423$) was 34% [13]. The reported prevalence for MetS in U.S. adolescents was calculated using the pediatric IDF definition within the 1999–2004 NHANES cohort, which was about 4.5% and higher in males (6.7%) than females (2.1%) [4].

Methods

Data sources and search strategy

Two database search engines, MEDLINE via PubMed and Google Scholar, were used to identify studies with a publication date between 2008 and 2019 using multiple combinations of exposure, outcome, and time-variable keywords. The exposure keywords searched included: Persistent Organic Pollutants, Organochlorines, Polychlorinated biphenyls, Perfluoroalkyl substances, Perfluorooctanoate, Perfluorooctane sulfonate, and Dioxins. Outcome keywords used in the search were: metabolic syndrome, obesity, waist circumference, insulin, glucose, hypertension, blood pressure, lipids, dyslipidemia. Time-variable keywords used: prenatal, gestational, perinatal, *in utero*, fetal, child, and children. Eight additional records were identified via searching the references of all applicable papers. No grey literature was part of this review. The last performed search was on 22 April 2019.

Potential articles for screening and review were selected per the inclusion criteria. A flow diagram of the study selection process and citation analysis is depicted in Figure 1.

Study screening and selection

A single reviewer selected articles based on the title and abstract for their inclusion eligibility in the review process.

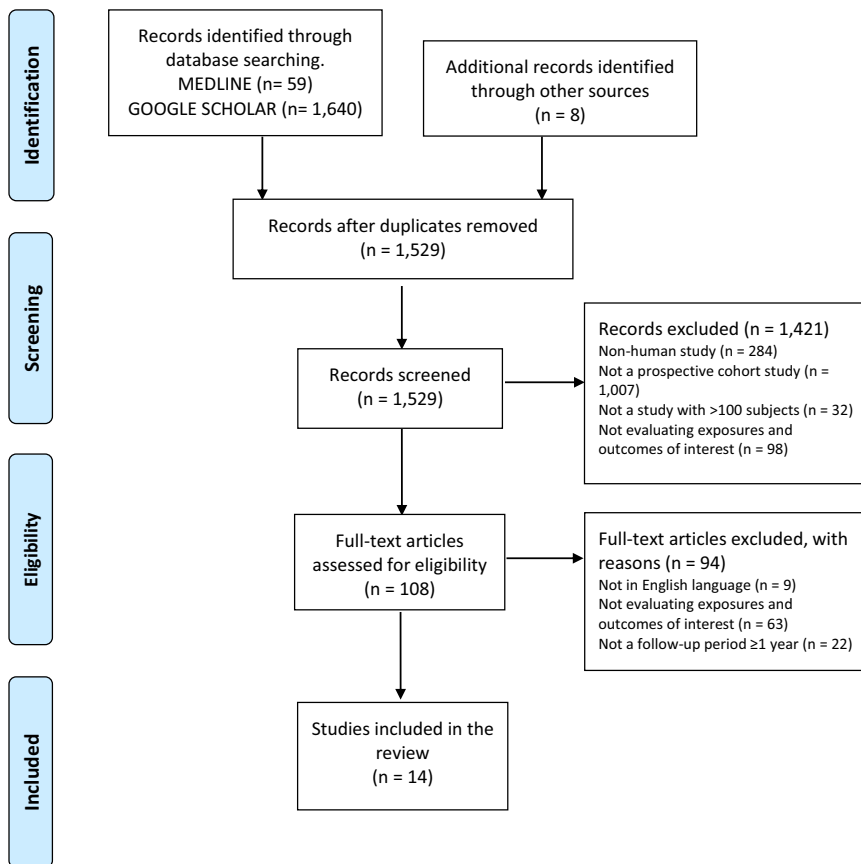


Figure 1: Preferred Reporting Items for Systemic Reviews and Meta-analysis (PRISMA) flow diagram of the study selection process [14].

Eligible studies were subject to full-text review using the following inclusion criteria:

- (1) The study must be a prospective cohort of ≥ 100 participants with a follow-up period of at least one year.
- (2) The study must have a prenatal exposure measurement.
- (3) Study outcome(s) of interest must include at least one component of the IDF MetSyn criteria mentioned in Table 1.

Articles in non-English language were excluded from the selection process, in addition to non-human studies.

Data collection and synthesis

One reviewer extracted the data into a standardized format based on study type, study population, exposure, and outcome. A comparative analysis was performed to compare and contrast environmental exposures and MetS components found on the offspring of mothers exposed during pregnancy. The 14 studies that fit the aforementioned inclusion criteria are summarized in Table 2.0 in the Supplementary Materials.

Results

POPs & MetS risk factors

According to the IDF definition (Table 1), the risk factors or components of childhood MetS include obesity or increased WC, elevated triglycerides, low levels of HDL-C, high blood pressure, and elevated glucose levels or insulin resistance. Most studies that look at prenatal exposure to POPs and offspring MetS development in childhood use obesity or overweight as an outcome measurement [15–20], where obesity and overweight pertain to age and sex-specific body mass index (BMI) *z*-scores. Other studies have used insulin resistance as an outcome measurement for pediatric MetS with BMI measurements [11, 21]. In contrast, other studies have innovated methods of measuring MetS risk by utilizing calculations involving various MetS risk factors [2, 22].

Several studies have explored the relationship between prenatal exposure to POPs and childhood MetS. The major POP categories explored in the literature include OC, PFASs, PCBs, and Dioxins.

Organochlorines & MetS risk factors

Obesity/overweight

Over time, evidence has emerged showing an increased risk of obesity in individuals exposed to organochlorines. Of the included studies, the following examined the relationship between exposure to POPs and pediatric MetS. Mendez et al. [18] conducted a prospective mother–child pair cohort study in Spain. They observed an association with an elevated BMI and risk ratio (RR) of being overweight at the age of 14 months equal to 1.5 (95% Confidence Interval [CI]: 1.11, 2.03) when mothers are prenatally exposed to 1,1-Dichloro-2,2-bis(p-chlorophenyl) ethylene (DDE).

Furthermore, Cupul-Uicab et al. [19] studied child–mother pairs throughout the United States who were part of the U.S. Collaborative Perinatal Project. Cupul-Uicab et al. [19] found a nonlinear dose–response between obesity and dieldrin, an OC, with an odds ratio of 3.6 (95% CI: 1.3, 10.5) at the fourth quintile (0.92–1.18 µg/L) and 2.3 (95% CI: 0.8, 7.1) for the highest dieldrin quintile (>1.18 µg/L) compared with the lowest quintile (dieldrin, <0.5 µg/L).

Valvi et al. [20] studied a Spanish birth prospective cohort whose mothers were exposed to various POPs *in utero*. They observed that at 14 months of age, the adjusted RR for being overweight when prenatally exposed to DDE equal to 1.15 (95% CI: 1.03, 1.28); the RR for HCB and being overweight was 1.19 (95% CI: 1.05, 1.34). Demonstrating a slight association between prenatal exposure to DDE and HCB and infant overweight.

Vafeiadi et al. [15] found that among The Rhea study participants in Greece, both HCB and DDE increased the risk of abdominal obesity to 3.49 (95% CI: 1.08, 11.28) and 3.76 (95% CI: 1.70, 8.30), respectively. In the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) birth prospective cohort study, Warner et al. [17] found the odds of nine-year-old boys of being overweight/obese when prenatally exposed to o,p'-DDT and p,p'-DDT to be 2.5 (95% CI: 1.0, 6.3) and 2.1 (95% CI: 1.0, 4.5) respectively; when exposed to p,p'-DDE the odds were 1.97 (95% CI: 0.94, 4.13). Contingent to the CHAMACOS study cohort, Warner et al. [16] later reported DDT (o,p'-DDT and p,p'-DDT) and DDE prenatal exposure were associated with an increased risk of overweight/obesity in 12-year-old boys.

A systematic review and meta-analysis by Cano-Sancho et al. [23] examined the association between p,p'-DDT and its metabolite p,p'-DDE, and obesity. They reported an observed risk of obesity among human populations exposed to p,p'-DDE, mainly during the prenatal period [23].

However, from the studies included in this review, the study conducted by Cupul-Uicab et al. [24] in Chiapas, Mexico, found no association between exposure and MetS components. Cupul-Uicab et al. recruited participants between 2002 and 2003 to explore prenatal exposure to DDE and BMI in male offspring. In this study, Cupul-Uicab et al. obtained an exposure measurement within a day of delivery. Cupul-Uicab et al. found no significant association between DDE and childhood height or BMI patterns after a year of follow-up [24]. Both unadjusted and adjusted models showed no significant associations between DDE and BMI in male offspring. Furthermore, the exposure was measured after delivery and not during pregnancy, thus limiting prenatal exposure measurement. The window of exposure measurement is crucial during prenatal development because fetal programming occurs during this period and may lead to the offspring's intergenerational health effects [25].

Waist circumference

Increased WC is one of the MetS risk factors according to the IDF. Several studies included WC as an outcome. Warner et al. [17] observed that prenatal DDT and DDE concentrations were associated with higher odds of elevated WC z-score (o,p'-DDT adj. OR=1.98 [0.95, 4.11]; p,p'-DDT adjusted OR=2.05 [1.10, 3.82]) only among nine-year-old boys in the CHAMACOS Study [17]. Tang-Péronard et al. [26] reported a significant association between DDE and increased WC in girls with overweight mothers ($\beta=2.21$).

PFASs & MetS risk factors

Obesity/overweight

Braun et al. [27] explored the association between PFASs *in utero* exposure and obesity in the prospective cohort in Cincinnati, OH (HOME) study. The study reported a higher risk of being overweight or obese at eight years of age of children born to mothers exposed to the second tertile (4.4–6.7 ng/mL) of PFOA, with a reported RR of 1.84 (95% CI: 0.97, 3.50), and an RR of 1.54 (95% CI: 0.77, 3.07) for the third tertile (6.8–26 ng/mL) of PFOA compared to children born to women in the first tertile (0.5–4.3 ng/mL).

A longitudinal cohort study conducted by Chen et al. [28] in Taiwan explored the association between fetal PFASs exposure and childhood growth indicators (weight, height, and BMI). Chen et al. [28] found a modest susceptibility to prenatal exposure to PFOS and weight gain in girls, the adjusted coefficient by PFOS weight in girls at

measured intervals of 6–12 months of age was $\beta = -0.25$ (95% CI: $-0.47, -0.04$) and at 12–24 months of age $\beta = -0.24$ (95% CI: $-0.41, -0.06$).

In The Avon Longitudinal Study of Parents and Children from the United Kingdom, a cohort study of mother–female offspring pairs, Hartman et al. [29] studied the association between *in utero* PFAS exposure and various metabolic syndrome components in female offspring at the age of nine. In this study, the investigators observed a modification by the mother's education status for PFOA; henceforth, they stratified the mother's education results to allow for a different slope across the three educational categories [29]. Hartman et al. found that exposure to PFOA and PFOS during *in utero* was associated with female offspring total percent body fat within some strata of maternal education status. Low education status was determined as not attaining any General Certificates of Secondary Education (GCSE). Obtaining a GCSE was considered middle education status, and high education status was coded as completing a GCSE with additional education (i.e., university) [29]. The study results showed gestational PFOA concentrations (ng/mL) to be 1.41 (95% CI: 0.28, 2.54) higher for each one-unit increase of total body fat among girls whose mothers reported a middle education status compared to mothers reporting a higher educational status (-0.58 ; 95% CI: -1.12 to -0.04).

In the Project Viva, Mora et al. [30] investigated the association between various PFASs in a mother–child cohort study of a total of 876 mother–child pairs. The study results comprised of each interquartile range increment of prenatal PFOA having a modest association with 0.21 kg/m² (95% CI: $-0.05, 0.48$) higher body mass index and with 0.17 kg/m² (95% CI: $-0.02, 0.36$) higher dual X-ray absorptiometry total fat mass index among girls in mid-childhood (median years of age 7.7) [30]. These results show a slightly higher risk of obesity among girls in mid-childhood when exposed to PFAS *in utero*. No associations were found among boys.

Waist circumference

The INUENDO cohort study, conducted by Høyer et al. [10] in Greenland and Kharkiv (Ukraine), followed pregnant women and their offspring up to nine years to explore the relationship between prenatal PFASs exposure and offspring risk of being overweight ($>85\%$ BMI z-score) and having a high (>0.5) waist-to-height ratio (WHtR). Høyer et al. [10] reported an adjusted RR of having a high WHtR ratio to be 1.30 (95% CI: 0.97, 1.74) for each ln-unit increase of offspring prenatally exposure to PFOA. The adjusted RR of having a high WHtR was 1.38 (95% CI: 1.05, 1.82) for each

ln-unit increase of offspring prenatally exposed to PFOS. These results suggest that offspring prenatally exposed to PFOA and PFOS may have a high risk of having a high waist-to-height ratio at the ages of 5–9 years.

Additionally, Braun et al. [27] reported a higher WC among children exposed to PFOA in the second tertile with an adjusted RR of 4.3 (95% CI: 1.7, 6.9) and for the third tertile an adjusted RR of 2.2 (95% CI: $-0.5, 4.9$) relative to children in the first tertile. Another previously mentioned study, The Avon Longitudinal Study of Parents and Children, Hartman et al. [29] found that for every one increment of prenatal PFOA concentration (ng/mL), resulted in a 1.16 cm (95% CI: 0.11, 2.21) increase of WC among girls with mothers who reported a middle education status compared to girls with mothers who reported higher education (-0.82 ; 95% CI: $-1.32, -0.32$).

A study conducted in Denmark examined the association between PFOA prenatal exposure and the risk of offspring being overweight at 20 years of age. The study results showed the adjusted relative risk comparing the highest with the lowest quartile of maternal PFOA concentration to be 3.0 (95% CI: 1.3, 6.8) for WC >88 cm and an estimated increase of 4.3 cm (95% CI: 1.4, 7.3) in average WC among female offspring only [9]. Thus, the findings suggest low-dose prenatal exposure of PFOA is associated with a risk of high WC among female offspring at 20 years of age [9].

PCBs & MetS risk factors

Obesity/overweight

In a Spanish birth cohort study, Valvi et al. [31] found an adjusted RR of becoming overweight with a PCB exposure in the third tertile (>0.9 ng/mL) of 1.7 (95% CI: 1.09, 2.64) relative to the lowest tertile (<0.6 ng/mL). Where the observed associations between overweight and PCB were stronger in girls than in boys [31].

Waist circumference

Pregnant women from the Faroe Islands were recruited for a study conducted by Tang-Péronard et al. [26] to investigate the association between PCBs and offspring obesity risk at the age of five and seven. Tang-Péronard et al. [26] found a significant and positive dose–response relationship between prenatal exposure to PCBs and WC in girls with overweight mothers. Investigators reported that for every one-unit increment of prenatal PCB concentration, there was 1.37 cm (95% CI: 0.13, 2.61), 2.20 cm (95% CI:

0.74, 3.65), and 2.48 cm (95% CI: 1.10, 3.85) higher WC among girls with overweight mothers for the second, third and fourth quartile respectively [26]. Thus, in this study, prenatal PCB exposure was associated with increased female offspring WC at low exposure levels.

Other POPs

Insulin

A few studies have explored the association between fetal exposure to POPs and insulin as an endpoint. Tang-Péronard et al. [21] found that only in girls, the odds of high non-fasting insulin from prenatal exposure to PCBs in the fourth quartile was 3.71 (95% CI: 1.36, 10.01); for DDE in the fourth quartile OR=2.75 (95% CI: 1.09, 6.90); for HCB in the fourth quartile OR=1.98 (95% CI: 1.06, 3.69) compared to the lowest quartile. However, Fleisch et al. [11] found no evidence of an adverse effect of early-life PFAS exposure on metabolic function in mid-childhood. Fleisch et al. [11] reported that children with higher PFAS concentrations had lower insulin resistance.

Other POPs & MetS

A limited amount of studies have explored the MetS as an outcome of prenatal exposure to POPs. Warner et al. [2] explored the relationship between 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), dioxin, and MetS. They defined MetS as possessing three or more of the following: (1) waist circumference ≥ 80 cm for females, or ≥ 94 cm for males; (2) elevated triglycerides ≥ 150 mg/dL or report of the current use of drug treatment for elevated triglycerides; (3) low HDL-C < 50 mg/dL for female, or < 40 mg/dL for male, or report of the current use of drug treatment for reduced HDL-C; (4) increased systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg, or report of the current use of antihypertensive medication; (5) elevated fasting glucose ≥ 100 mg/dL or report of the current use of diabetes medication [2]. After adjusting for various confounders, they observed a risk ratio of 2.09 (95% CI: 1.09, 4.02) in male offspring from the Seveso Second Generation Study in Italy. In a second study, Manzano-Salgado et al. [22] utilized a cardiometabolic-risk (CM-risk) score to assess the risk of getting pediatric MetS (described in Table 2.0 under Supplementary Materials). However, Manzano-Salgado et al. [22] found that prenatal PFAS concentrations were not associated with individual outcomes or the combined CM-risk score.

Discussion

Possible mechanisms

The Developmental Origins of Health and Disease was first introduced by David Barker and his colleagues, proposing the hypothesis of a critical window during fetal development that may be disrupted by environmental exposures and influence genetic changes resulting in increased risks to diseases later in the offspring's life [3]. Such diseases include diabetes, cardiovascular disease, asthma, cancer, osteoporosis, and neuropsychiatric disorders [32]. A major unresolved question is whether different environmental exposures mentioned in this review cause different components of the MetS to arise in an individual and result in the development of MetS, and if so, what are the mechanisms of action of these toxins?

Obesity & increased waist circumference

Obesity is a proinflammatory condition in which the body's cells produce and release chronic low levels of proinflammatory cytokines responsible for a spectrum of signaling events within cells. These cytokines are associated with cellular apoptosis, insulin resistance, and T2D [33].

During the first trimester of gestation, the brain begins to develop and plays a key role in regulating energy balance in the neuroendocrine hypothalamus [3]. Various anabolic and catabolic pathways connect the body to the brain. One important anabolic pathway found in the hypothalamic arcuate nucleus is the neuropeptide Y (NPY)/agouti-related neuropeptide (AgRP) neuron [34]. These neuropeptides are associated with food intake and energy expenditure. They show high concentrations of binding sites for many hormonal and metabolic signals like insulin and leptin-hormones important in regulating glucose and satiety, respectively. Some studies have displayed that an increase in NPY release develops into increased food intake, decreased energy expenditure, and increased body weight [3, 34]. Thus, the NPY/AgRP neuron's disturbances in the arcuate nucleus have consequences involving obesity and T2D in humans [3, 34].

Dyslipidemia

Maternal exposures to xenobiotics like OC, PCBs, and Dioxins have been associated with altered hepatic metabolism and steatosis in offspring. Chronic gestational

exposure to such chemicals exacerbates steatohepatitis symptoms in animal offspring fed a high-fat diet throughout gestation. The mechanism of action of these xenobiotics includes disruption in different stages of the hepatic lipid metabolism. These metabolism disruptors are associated with increased lipogenic gene expression with mitochondrial dysfunction and decreased beta-oxidation; microRNA changes; increased oxidative stress with a reduction in hepatic antioxidant enzymes; and increased inflammation [3]. Overall, the liver is a target for some xenobiotics that may lead to metabolism disruptions, altering insulin signaling expression, and increasing the risk of developing the MetS.

Elevated glucose levels & insulin resistance

The endocrine pancreas comprises various islet cells, the majority being β -cells, whose major responsibility is to release insulin. The second most abundant islet cell type is the α -cell. Unlike β -cells, α -cells are responsible for secreting glucagon. Other cells within the pancreas are pancreatic polypeptide-producing cells (PP cells), δ -cells, and ϵ -cells. The PP cell produces pancreatic polypeptides, the δ -cells produce somatostatin, and the ϵ -cells synthesize ghrelin. These hormones are crucial for maintaining gastrointestinal regulation.

Throughout the utero and neonatal periods, β -cells quickly proliferate; infancy is the period with the greatest growth [35]. However, once the offspring reaches adolescence and soon adulthood, the replication of β -cells slows down and limiting the number of β -cells produced [3]. It is important to maintain sufficient β -cells to maintain proper insulin levels; a β -cell deficiency may contribute to type 1 or type 2 diabetes onset [35].

Blood glucose is first transported by β -cells, creating a cellular signaling pathway that leads to the closure of resting membrane-potential channels (ATP-sensitive K^+ channels). This closure results in cellular depolarization and insulin release. Insulin binds to its receptor tyrosine kinase, a surface membrane protein, on target cells to assist in signaling pathways leading to glucose uptake and catabolism.

The development of diabetes can occur from impaired β -cell insulin production. Xenobiotics can disrupt the insulin production pathway by inducing β -cell dysfunction or further destruction. Thus resulting in either T1D or T2D [3].

Endocrine disruption

The endocrine system is composed of the hypothalamus, pineal body, pituitary gland, thyroid and parathyroid glands, the thymus, the adrenal gland, the pancreas, the ovaries, and the testicles. This multi-organ system's role is to maintain the body's hormone levels for proper growth, metabolism, energy expenditure, and more.

Exogenous chemicals that interfere with the endocrine system's proper function are EDC, much like DDT, DDE, and PCBs. EDCs have been found to have harmful effects on humans, especially fetal and child growth development [36]. For example, early life exposure to EDCs is associated with abnormalities in the hypothalamus and thyroid, thus affecting various body systems [36]. These chemicals can disrupt various levels within the endocrine system by interfering with hormone production, metabolism, and transportation [3]. Various EDCs have been found to bioaccumulate in tissues, specifically adipose tissues, which can act as obesogens. Obesogens are xenobiotics that induce fat accumulation and obesity by disrupting critical lipid and metabolic pathways in early life, resulting in permanent changes in fat storage and metabolic homeostasis [37].

Conclusion

The MetS is a complex syndrome, often involving multiple criteria, variable definitions, and unknown mechanisms of action. Many studies included in this review have shown prenatal exposure to POPs to be associated with offspring MetS development during childhood.

This review's studies contain various strengths, including the long follow-up periods in prospective cohort studies, presenting prenatal exposure measurements, and biochemical measures of metabolic function in childhood (i.e., insulin, glucose, leptin). There are limitations to many of the included studies, which consist of generalizability of study results to only the study cohort demographics. However, many studies were globally diverse, meaning that the studies took place in multiple locations worldwide. Even though some studies did adjust for the race, there is limited evidence to suggest differences among ethnic and racial groups in the MetS. However, some literature states that youth who identify as black non-Hispanic demonstrate lower rates of dyslipidemia but greater insulin resistance and higher blood pressure than white non-Hispanic and Hispanic youth [1]. Despite the increased prevalence of obesity and greater risk for type 2 diabetes

mellitus in black non-Hispanic youth, by definition, Black non-Hispanic youth have a lower prevalence of MetS than white non-Hispanic or Hispanic youth due to lower rates of dyslipidemia in Black non-Hispanic youth. The major consequence of not fitting into the pediatric MetS definition is underestimating the MetS risk [1]. Another limitation is the limited adiposity measurement types. Most studies measured MetS risk factors using BMI z-scores to determine obesity/overweight, and others had the resources to measure direct adiposity using Bioelectrical impedance analysis. Lastly, it is difficult to adjust for POP exposure throughout childhood.

Future recommendations

Current research on this topic lacks a true representation of populations who are most affected by POP exposure. Future research should focus on populations experiencing environmental injustice and highly exposed to POPs, especially OC pesticides, for example, agricultural workers, particularly child-bearing women in such environments.

As childhood obesity has been increasing over time, it is highly crucial to obtain a reliable and accurate measurement of adiposity and exposure throughout childhood. Obtaining an environmental exposure measurement throughout childhood can allow researchers to establish an exposure baseline for prenatal and childhood periods. Hence, non-invasive repeated measurements of exposure during pregnancy and postnatal period are highly suggested. I propose using cerumen to measure POP exposure considering its lipophilic characteristics and previous Blue whales usage, to reveal lifetime contaminant exposures [38]. Most importantly, further research to find when in pregnancy exposure has its highest effects on offspring MetSyn is highly needed.

As mentioned before, obesity increases the risk of developing other MetS components that could develop MetS in childhood and carry out through adulthood. Thus, solidifying the pediatric MetS definition should be a priority for public health providers. Acquiring a concrete definition will not only permit scientists to measure the MetS as a health outcome in an accurate manner, but it will also allow clinicians to diagnose pediatric MetS and create treatments properly. Even further, a clear definition will permit the innovation of interventions early in childhood to reduce the risk and prevent children from developing the MetS.

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