

# Early Life Origins of Metabolic Syndrome: The Role of Environmental Toxicants

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**Abstract** Metabolic syndrome (MetS) affects more than 47 million people in the U.S. Even more alarming, MetS, once regarded as an “adult problem”, has become increasingly common in children. To date, most related research and intervention efforts have occurred in the adult medicine arena, with limited understanding of the root causes and lengthy latency of MetS. This review highlights new science on the early life origins of MetS, with a particular focus on exposure to two groups of environmental toxicants: endocrine disrupting chemicals (EDCs) and metals during the prenatal and early postnatal periods, and their specific effects and important differences in the development of MetS. It also summarizes available data on epigenetic effects, including the role of EDCs in the androgen/estrogen pathways. Emerging evidence supports the link between exposures to environmental toxicants during early life and the development of MetS later in

life. Additional research is needed to address important research gaps in this area, including prospective birth cohort studies to delineate temporal and dose–response relationships, important differences in the effects of various environmental toxicants and their joint effects on MetS, as well as epigenetic mechanisms underlying the effects of specific toxicants such as EDCs and metals.

**Keywords** Diabetes · Environmental toxicants · Metabolic syndrome · Obesity · Prenatal exposure

## Introduction

Metabolic syndrome (MetS) consists of a cluster of clinical conditions, including elevations in blood glucose levels and/or insulin resistance, lower levels of high density lipoprotein cholesterol (HDL-C), hypertriglyceridemia and hypertension, and abdominal obesity [1]. MetS affects more than 47 million people in the U.S [2]. Adults with MetS have a threefold higher risk of coronary heart disease and stroke and a five to six times higher risk of mortality [3]. People with MetS are also at high-risk of type 2 diabetes [4]. Even more alarming, MetS and its components, including obesity, diabetes, dyslipidemia and hypertension, once regarded as “adult problems”, have become increasingly common in children at younger and younger ages.

Additional research and public health efforts are needed to improve prevention of MetS. Most related research and intervention efforts have primarily occurred in the adult medicine arena, where there is a limited understanding of the root causes and lengthy latency of MetS. Emerging evidence supports the ‘fetal programming’ hypothesis, which highlights the importance of exposures that occur during the prenatal period in the development of metabolic disorders later in life (Fig. 1) [5, 6]. Observations that maternal malnutrition during pregnancy is associated with type 2 diabetes, cardiovascular disease and MetS in later life [7, 8] have led to the hypothesis that in utero

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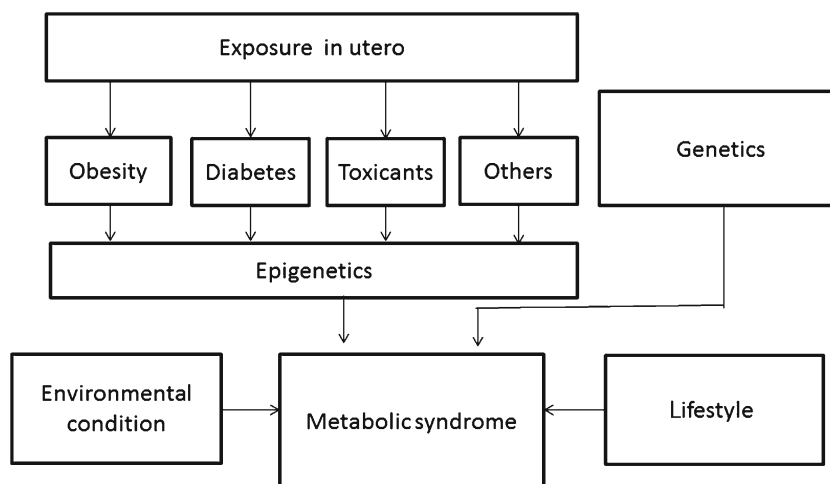
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**Fig. 1** The potential mechanisms underlying the development of metabolic syndrome (MetS)



determinants of birth weight may program the fetus for elevated risk of chronic disease in adulthood. Given the widespread production and use of synthetic chemicals and metals, in parallel with growing epidemics of obesity and type 2 diabetes, recent studies have also examined the potentially detrimental effects of these chemicals on fetal development and health outcomes later in life. For instance, epidemiological studies found that offspring of mothers exposed to endocrine-disrupting chemicals (EDCs) had a higher body mass index (BMI) in adulthood compared with offspring whose mothers had no exposure at all [9]. These findings clearly suggest that, in addition to any genetic transmission, exposure to environmental toxicants in utero and early life may lead to obese or diabetic offspring and contribute to the development of MetS. The purpose of this review is to discuss the early life origins of MetS, and in particular the role of maternal exposure to environmental toxicants including EDCs and metals during pregnancy and early childhood. Furthermore, this review also summarizes available data on the epigenetic effects of exposure to EDCs and metals, and the possible role of epigenetic mechanisms in offspring metabolic risk.

### Exposure to Endocrine-Disrupting Chemicals

Endocrine-disrupting chemicals (EDCs) are defined as chemicals that act on the body's hormonal systems, such as dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyl dichloroethylene (DDE), polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB), and bisphenol-A (BPA). Emerging evidence suggests that EDCs can affect human fetal development [10, 11]. A common characteristic of DDT, DDE, PCBs and HCB is their persistence in the environment longer than that required for their intended use. For this reason they have been grouped into the category of persistent organic pollutants [11]. In contrast, BPA is categorized as a non-persistent compound [11]. Humans may respond differently

to exposure to EDCs, particularly depending on exposure time, dose and sex. For example, high-dose exposure to EDCs can result in weight loss or growth restriction, whereas normal human environmental exposures at low-moderate levels can result in weight gain [12].

### Persistent Organic Pollutants

DDT was widely used throughout the U.S. and Europe from the 1940s to the 1970s to control insects on agricultural crops and those that carry diseases like malaria and typhus [13]. Although DDT was banned in the U.S. in 1972, it is still used in some areas of the world, primarily in malaria control programs. Animal studies have shown that a low dose of DDT readily passes through the placental barrier to the developing fetus, where it induces embryotoxicity and fetotoxicity, but no teratogenicity [14]. In humans, DDT and its metabolites (DDE) have been found in placental tissue and umbilical cord blood. Furthermore, maternal and newborn blood levels are generally similar [15], suggesting that DDT and DDE may also be able to cross the human blood-placenta barrier. PCBs have been used as lubricants and coolants in electrical appliances [16]. HCB is a synthesized chlorinated monocyclic aromatic compound. HCB was widely used as a pesticide until 1965, but its use is no longer allowed in the U.S. [17]. PCBs and HCB have also been detected in cord blood, again suggesting their ability to transfer across the placenta to the fetus [18, 19].

Results of the impact of prenatal exposure to DDE/DDT, PCBs and HCB on offspring MetS have been inconsistent (Table 1). In the INMA-Sabadell study, a birth cohort recruited in 2004–2005 from Sabadell (Catalonia, Spain), prenatal DDE exposure was associated with an increased risk of rapid growth in the first 6 months of life in 518 infants born to normal weight mothers, as well as with elevated BMI at 14 months [20]. The INMA-Menorca study, with a birth cohort of 344 children recruited in 1997–1998 from the island of Menorca (Spain), evaluated the association between prenatal

**Table 1** Some epidemiologic studies on the association between exposure to endocrine disrupting chemicals and metabolic syndrome components

| Exposure       | Population | Sample size | Age at evaluation | Exposure window      | Exposure Measure                             | Exposure categories   | Outcome and definition  | Estimation of association   | Covariates  | Reference                         |
|----------------|------------|-------------|-------------------|----------------------|--|---|---|---|---|-----------------------------------|
| DDE            | U.S.       | 259         | 20–50 y           | In utero             | Maternal blood DDE ( $\mu\text{g/l}$ )       | 1st quintile<br>2nd<br>3rd<br>4th<br>5th  | BMI   | Mean $\pm$ SD<br>25.8 $\pm$ 4.9<br>26.0 $\pm$ 5.8<br>28.1 $\pm$ 7.7<br>28.0 $\pm$ 5.4<br>28.8 $\pm$ 8.1<br>28.0 $\pm$ 7.1<br>25.1 $\pm$ 4.5<br>26.8 $\pm$ 5.7<br>30.0 $\pm$ 8.6<br>26.4 $\pm$ 4.7 | None  | Karmaus,2008 <sup>9</sup>         |
| HCB            | Spanish    | 482         | 6.5 y             | In utero             | Cord blood HCB (ng/ml)                       | Per log HCB ng/ml   | Overweight:<br>BMI >85th percentile   | OR (95 % CI):<br>1.69 (1.05–2.27)   | Maternal age, height, pre-pregnancy overweight/obesity, education, parity, child's sex, age | Smink,2008 <sup>24</sup>          |
| DDE            | Spanish    | 657         | 6 mo, 14 mo       | In utero             | Maternal blood DDE (ng/g lipid)              | per log ng/g lipid  | Elevated BMI:<br>>85th percentile, among normal-weight mother<br>Rapid weight gain:<br>change of BMI<br>z-score >0.67, among normal-weight mother | RR (95 % CI)<br>1.64 1.24–2.18  | Age, maternal country of birth, maternal age, smoking, parental overweight; rapid growth    | Mendez,2011 <sup>20</sup>         |
| DDE, DDT, PCBs | Spanish    | 344         | 6.5 y             | In utero             | Cord blood DDE (ng/ml)                       | Quartile<br>2nd vs 1st<br>3rd vs 1st<br>4th vs 1st  | Overweight:<br>BMI >85th percentile   | RR (95 % CI)<br>1.67(1.10,2.55)<br>1.28 (0.81,2.03)<br>1.19 (0.76,1.87)<br>1.17 (0.73,1.88)<br>0.97 (0.58,1.62)<br>1.70 (1.09,2.64)   | Birth weight, parity, maternal BMI, education, smoking, maternal age, breast-feeding        | Valvi, 2012 <sup>21</sup>         |
| DDE            | Mexico     | 788         | 14–22 mo          | In utero             | Maternal serum DDE ( $\mu\text{g/g}$ lipid)  | $\leq$ 3.0 (reference)<br>3.01–6.00<br>6.01–9.00<br>>9.00   | BMI SDS   | $\beta$ (95 % CI)<br>–0.11 (–0.29,0.07)<br>–0.18 (–0.45, 0.08)<br>0.07 (–0.15,0.30)   | Maternal BMI, smoking, education, rural residence, gestational age                          | Cupul-Urcab, 2010 <sup>22</sup>   |
| PCBs, DDE      | Denmark    | 656         | 5 y and 7 y       | In utero, early life | Maternal blood PCBs ( $\mu\text{g/g}$ lipid) | PCBs quartile<br>2nd vs 1st<br>3rd vs 1st<br>4th vs 1st<br>2nd vs 1st<br>3rd vs 1st<br>4th vs 1st | BMI at 7 y girl with maternal obesity<br>Change in BMI from 5 y to 7 y<br>BMI at 7 y girl with maternal obesity                                   | $\beta$ (95 % CI)<br>0.76 (–0.63,2.15)<br>0.66 (–0.98,2.29)<br>2.07 (0.59,3.55)<br>0.28 (–0.49,1.04)<br>0.56 (–0.34,1.46)<br>1.23 (0.42–2.05)   | Maternal age-parity   | Tang-Peronard, 2013 <sup>25</sup> |
|                |            |             |                   |                      | Maternal blood DDE ( $\mu\text{g/g}$ lipid)  | DDE quartile<br>2nd vs 1st<br>3rd vs 1st<br>4th vs 1st<br>2nd vs 1st                              |   | –0.06 (–1.49,2.38)<br>–0.09 (–1.91,1.74)<br>1.29 (–0.24,2.81)<br>0.51 (–0.26,1.29)  | Maternal age, parity  |                                   |

**Table 1** (continued)

| Exposure  | Population | Sample size | Age at evaluation | Exposure window | Exposure Measure                 | Exposure categories              | Outcome and definition  | Estimation of association  | Covariates  | Reference                           |     |      |                      |  |         |                                   |          |  |                            |
|-----------|------------|-------------|-------------------|-----------------|----------------------------------|----------------------------------|---|--|---|-------------------------------------|-----|------|----------------------|--|---------|-----------------------------------|----------|--|----------------------------|
| PCBs      | U.S.       | 399         | At birth and 5 y  | In utero        | Maternal serum PCBs (ng/g lipid) | 3rd vs 1st                       | Change in BMI from 5 y to 7 y   | 0.14 (0.82,1.10)   | Maternal age, BMI, height, parity, smoking, race, hypertension or preeclampsia, prenatal care, medications associated with intrauterine growth restriction, child's sex | Hertz-Picciotto, 2005 <sup>93</sup> |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | 4th vs 1st                       |   | 1.11 (0.30,1.92)   |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | PCB percentile: 90th vs 10th     |   | $\beta$ (se)<br>-268 (101)<br>-26 (73)                                     |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
| DDE, PCBs | Belgium    | 138         | 1-3 y             | In utero        | Cord blood DDE (ng/g lipid)      | Per ng/g lipid DDE               | Birth length: Boy girl<br>Standardized height at 5 y: Boy girl<br>BMI SDS | 2.6 (1.7)<br>4.1 (2.1)<br>$\beta$ (se)<br>-0.002 (0.001)<br>-0.003 (0.001) | Birth weight  | Verhulst, 2009 <sup>27</sup>        |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | DDE×maternal smoking ever        |   | 0.001 (0.001)  |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | DDE×maternal smoking×child's age |   | 0.003 (0.001)  |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | Per ng/g lipid PCBs              |   | 0.003 (0.001)  |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | PCBs, DDE                        |   | U.S.   |   |                                     | 594 | 14 y | In utero, early life | Cord blood PCBs (ng/g lipid)<br>Maternal blood PCB (ppm fat) | 0-1 ppm | Self-reported weight (kg)<br>Girl | 51.6±1.9 | Birth weight, maternal smoking, maternal BMI, height | Gladen, 2000 <sup>23</sup> |
|           |            |             |                   |                 |                                  |                                  |   |  |   |                                     |     |      |                      |  | 1-2     |                                   | 53.0±0.6 |  |                            |
|           |            |             |                   |                 |                                  |                                  |   |  |   |                                     |     |      |                      |  | 2-3     | Boy                               | 52.9±0.9 |  |                            |
|           |            |             |                   |                 |                                  |                                  |   |  |   |                                     |     |      |                      |  | >3      |                                   | 57.0±1.6 |  |                            |
|           |            |             |                   |                 |                                  |                                  |   |  |   |                                     |     |      |                      |  | 0-1 ppm |                                   | 59.6±2.2 |  |                            |
|           |            |             |                   |                 |                                  |                                  |   |  |   |                                     |     |      |                      |  | 1-2     |                                   | 56.9±0.7 |  |                            |
| 2-3       | 56.8±1.1   |             |                   |                 |                                  |                                  |   |  |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
| >3        | 56.1±1.6   |             |                   |                 |                                  |                                  |   |  |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
| 0-1 ppm   | 54.2±2.1   |             |                   |                 |                                  |                                  |   |  |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
| 1-2       | 52.5±0.8   |             |                   |                 |                                  |                                  |   |  |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 | Maternal blood DDE (ppm fat)     | 2-3                              | Self-reported weight (kg)<br>Girl   | 54.0±0.8   |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | 3-4                              |   | 53.3±1.1   |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | >4                               |   | 51.5±1.4   |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | 0-1 ppm                          |   | 53.7±2.0   |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | 1-2                              | Boy   | 5.61±1.0   |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | 2-3                              |   | 57.4±1.0   |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | 3-4                              |   | 55.6±1.2   |   |                                     |     |      |                      |  |         |                                   |          |  |                            |
|           |            |             |                   |                 |                                  | >4                               |   | 60.6±1.4   |   |                                     |     |      |                      |  |         |                                   |          |  |                            |

BMI/body mass index, DDT dichlorodiphenyltrichloroethane, DDE dichlorodiphenyl dichloroethylene, PCBs polychlorinated biphenyls, HCB hexachlorobenzene, mo months, y years, ppm parts per million

exposure to DDT, DDE and PCBs measured in cord blood with weight during childhood. Compared with the first tertile, the third tertile of PCB exposure increased the risk of overweight in childhood by 1.7-fold, and the second tertile of DDE by 1.67-fold, but DDT was associated with overweight only in boys [21]. However, in a study of male children from Chiapas, Mexico, there was no apparent association between high prenatal exposure to DDE and height or BMI in the first years of life [22]. In a North Carolina cohort study, 594 children with prenatal and lactational exposures to PCBs or DDE, prenatal and early life PCBs exposures were associated with increased weight in girls at puberty [23]. In terms of the relationship between early life exposures and obesity in adulthood, a study of DDE and PCBs levels in maternal blood during pregnancy in a U.S. cohort from Michigan found that offspring who were exposed to higher prenatal levels of DDE had higher BMI at age 20–50 years, but found no association between prenatal exposure to PCBs and BMI in adulthood (Table 1) [9]. In terms of exposures to HCB, analysis of cord blood from 482 children from the INMA-Menorca (Spain) study showed that those in the higher HCB exposure group had a 2.5- and 3.0-fold increased risk of being overweight and obese, respectively [24].

Some, although limited, studies have evaluated the role of factors such as gender, maternal obesity and maternal smoking in modifying the association between EDCs and later obesity. To evaluate the modification effects of sex and maternal obesity on the association between prenatal exposure to EDCs and later obesity, Tang-Peronard et al. [25] recruited 656 pregnant women from Denmark and measured PCBs and DDE levels in maternal serum and breast milk. Researchers found a significant gender difference between exposure to DDE and PCBs and BMI at age 5 and 7 years. In girls with overweight mothers, PCBs levels were associated with an increased BMI at age 7 years, and PCBs and DDE levels were associated with an increased change in BMI from 5 to 7 years of age and waist circumference at age 7. No association was found for girls with normal-weight mothers or in boys, suggesting that maternal obesity and sex are important mediators. In addition, substantial epidemiologic and toxicologic evidence, and more than 80 studies in human populations and almost 20 animal studies also support a positive association between maternal smoking and increased risk of obesity or overweight later in life [26]. In a birth cohort from Belgium, maternal smoking enhanced the relationship between prenatal exposure to DDE and BMI at age 3 years, while prenatal exposure to PCBs was associated with an increase in BMI in early childhood between 1 and 3 years of age independent of maternal smoking [27]. To date, most such studies have been conducted outside of the U.S. It will be important to confirm if the associations found in other populations are relevant to a U.S. population, which is typically exposed to lower levels of EDCs, and to what degree infant gender and maternal characteristics (such as BMI and

smoking) modify the association between EDCs and offspring obesity, diabetes and MetS.

### Bisphenol-A

BPA is an endocrine-disrupting chemical used in the production of plastic food and beverage containers, leading to ubiquitous low-dose human exposure. Available data suggest widespread human exposure to BPA [28–33]. Both U.S. children and pregnant women have shown nearly universal exposure to BPA [32, 33]. The 2005–2006 National Health and Nutrition Examination Survey (NHANES) urinary BPA data showed that median daily intake for the overall population is approximately 34 ng/kg-day [34]. Importantly, BPA is rapidly absorbed and can easily cross the placental barrier to the fetus [35–38]. BPA may also accumulate in the fetus [37] and is measurable in cord blood [36, 37, 39, 40], amniotic fluid [35, 41], meconium and placental tissues [37].

BPA is usually metabolized via the uridine 5-diphosphoglucuronosyltransferase (UGT) system to BPA glucuronide, which does not bind to the estrogen receptor [42]. However, the role of BPA glucuronidation in protecting the fetus and infant from BPA toxicity during early life is unclear [43]. Relatively few epidemiological studies have examined the relationship between prenatal exposure to BPA and MetS in later life. However, animal studies provide important evidence. In a mouse model, pregnant animals were treated with either vehicle or BPA during days 9–16 of gestation. At 6 months of age, male offspring exposed to BPA in utero had reduced glucose tolerance and increased insulin resistance [44]. In another animal study, pregnant Wistar rats were exposed to different levels of BPA, and offspring were fed a normal diet or a high-fat diet after weaning. On a normal diet, perinatal exposure to a modest dose of BPA resulted in increased body weight, elevated serum insulin, and impaired glucose tolerance in adult offspring. Meanwhile, on a high-fat diet, such detrimental effects were accelerated and exacerbated. Furthermore, severe MetS, including obesity, dyslipidemia, hyperleptinemia, hyperglycemia, hyperinsulinemia, and glucose intolerance, was observed in high-fat-fed offspring perinatally exposed to BPA [45]. Taken together, these results support the hypothesis that the fetus is highly vulnerable to exposure to environmental chemicals, resulting in a metabolic profile that shows increased risk for and susceptibility to type 2 diabetes and MetS later in life. Most studies to date were conducted in animals. Human research is needed to evaluate the role of prenatal BPA exposure and MetS in offspring.

### Exposure to Metals

Metals have drawn great attention because of their widespread exposure worldwide, trans-placental and trans-breast milk

passage, evidence of fetotoxicity, multi-organ adverse effects, and ability to interact with the genome and the epigenome [46, 47]. Our results in the Boston Birth Cohort showed a high degree of maternal to fetal transfer for mercury, lead and selenium, and that their transfer was a major source of early life exposure to these metals [48]. To date, most human studies on the association of metals with obesity, diabetes and MetS have been conducted in adults. A recent systematic review of the epidemiologic evidence concluded that the available evidence is suggestive of but not sufficient for a relationship between arsenic and diabetes, and is insufficient for mercury [49].

The primary source of exposure to inorganic arsenic is through drinking water contaminated by natural mineral deposits or improperly disposed chemicals. In addition, rice represents a major dietary source of inorganic arsenic both for adults and children [50]. In a cross-sectional study of 788 adults aged 20 years or older who participated in the 2003–2004 National Health and Nutrition Examination Survey (NHANES) and had urine arsenic determinations, the odds ratios for type 2 diabetes was 3.58-fold (95 % CI, 1.18–10.83) higher in participants within the 80th percentile of total arsenic than subjects within the 20th percentile [51]. In a cross-sectional study from Wisconsin, subjects who drank water with high levels of arsenic had higher risk of hypertension than those with low levels [52]. In NHANES 2003–2008, however, total arsenic and dimethylarsinate (DMA) were not associated with hypertension or blood pressure levels, although a weak association between DMA and hypertension could not be ruled out [53]. In a study of 660 Taiwan residents, hair arsenic levels were associated with the risk of MetS, and with increased levels of plasma glucose, lipids, and blood pressure [54]. Exposure to arsenic in utero has been related to an increased risk of cancer and cardiovascular disease both experimentally [55] and in human populations [56]. Arsenic also has been associated with epigenetic effects [57]. Thus, it is important to evaluate the effect of early life arsenic exposures in the development of MetS including its individual components.

Regarding mercury, recently conducted research is evaluating its relationship with diabetes in adult populations. A large prospective study in young-middle aged men and women from different communities in the U.S. found that toenail mercury levels were associated with increased diabetes risk [58]. In a large cross-sectional study including 6,213 adults in Korea, results showed a significant correlation between serum mercury concentrations and hypertension in both men ( $r=0.193$ ,  $P<0.001$ ) and women ( $r=0.145$ ,  $P<0.001$ ) [59]. In two recent prospective cohort studies of health professionals in the U.S., however, toenail mercury level was not associated with diabetes risk in either men or women [60]. While selenium has been used as an antioxidant supplement, large cross-sectional studies and interventional trials revealed that high selenium status was associated with an increased risk of diabetes [61, 62]. In a large prospective study in Italy, where

the women were followed up a median of 16 years, dietary selenium intake was measured using a semi-quantitative food-frequency questionnaire at the baseline examination (1987–1992) and categorized into quintiles [63]. The risk of type 2 diabetes in the highest quintile of selenium intake increased 2.39-fold (95 % CI, 1.32–4.32) (Table 2). Lead levels are an established risk factor of hypertension and may be related to additional metabolic abnormalities [64]. A large study in Korea evaluated the joint effect of exposure to lead, mercury and cadmium as measured in blood. Serum lead levels, but not mercury and cadmium, were associated with a higher prevalence of MetS. Moreover, the sum of heavy metals exposures was associated with hypertension and elevated triglycerides [65]. For cadmium, the epidemiologic evidence does not seem to support an association with diabetes [49].

There is a particular lack of prospective birth cohort studies on the metabolic consequences of exposure to metals, including arsenic, mercury, selenium and lead in utero and in early childhood. Given the available evidence on the role of some metals in diabetes and MetS in adults, the recognition of early life as a vulnerable period for environmental exposures and epigenetic alterations and for adipose tissue development and metabolic programming, it is important to evaluate the role of early metal exposure and subsequent risk of MetS.

### Epigenetic Mechanisms

Epigenetic mechanisms may be the critical biological links between genetic vulnerability, in utero exposures and the development of MetS via the regulation of gene expression through DNA methylation, histone modifications, chromatin remodeling, and/or regulatory feedback by way of microRNAs. Epigenetic alterations are heritable and reversible changes in gene expression with no change in the underlying DNA code, and are believed to regulate cell differentiation and organogenesis, and be a key molecular process underlying human responses to environment and gene-environment interactions [66]. Some studies have shown that prenatal conditions, such as fetal growth restriction as well as nutrient restriction, can epigenetically modify gene expression by altering the DNA methylation level in promoter regions [67, 68]. Our work in the Boston Birth Cohort demonstrated considerable individual variation in DNA methylation, which is detectable at birth and dynamic in the first 2 years, and offered an epigenetic insight into this trans-generational effect [69••]. We also found that maternal obesity can alter offspring DNA methylation in multiple genes that may have important implications for future chronic diseases [70]. These findings highlight the presence of in utero mechanisms that are available to respond to nutritional, hormonal, or other metabolic cues by possibly altering the timing and direction of methylation events during fetal development.

**Table 2** Some epidemiologic studies on the association between heavy metals and metabolic syndrome

| Exposure               | Study design    | Study population | Sample size | Age range (years) | Outcome definition   | Exposure assessment                        | Exposure categories  | Estimation of associations   | Covariates   | References                      |
|------------------------|-----------------|------------------|-------------|-------------------|--|--|--|--|--|---------------------------------|
| Arsenic                | Cross sectional | Serbia           | 746,202     | Around 60         | Type 2 diabetes: FPG $\geq 7.8$ mmol/l, OGTT $\geq 11.1$ mmol/l, National Registry of Type 2 Diabetes  | Drinking water arsenic ( $\mu\text{g/l}$ ) | Unexposed vs exposed   | OR (95 % CI)<br>Men: 1.52 (1.30–1.77)<br>Women: 1.71 (1.49–1.97)                             | None   | Jovanovic, 2013 <sup>54</sup>   |
| Arsenic                | Cross sectional | U.S.             | 788         | >20               | Type 2 diabetes: FPG $\geq 126$ mg/dl, self-reported physician diagnosis or use of insulin or oral hypoglycemic medication   | Urine arsenic ( $\mu\text{g/l}$ )          | 80th vs 20th percentiles   | OR (95 % CI)<br>3.58 (1.18–10.83)  | Sex, age, race and ethnicity, urine creatinine, education, body mass index, serum cotinine, use of antihypertensive medication, urine arsenobetaine, blood mercury | Navas-Acien, 2008 <sup>51</sup> |
| Arsenic                | Cross sectional | U.S.             | 1,185       | >20               | Hypertension: Self-reported  | Drinking water arsenic ( $\mu\text{g/l}$ ) | >10 $\mu\text{g/l}$ vs <2 $\mu\text{g/l}$                        | OR (95 % CI)<br>1.68 (1.13, 2.49)  | Gender, age, smoking status, and body mass index   | Zierold, 2004 <sup>52</sup>     |
| Arsenic                | Cross sectional | Taiwan           | 660         | 35–64             | MetS: with 3 or more following factors: FPG >110 mg/dl, TG >150 mg/dl, HDL >40 mg/dl (men), 50 mg/dl (women)<br>SBP >130 mmHg, DBP >85 mmHg, BMI >27 kg/m <sup>2</sup> (men), 25 (women) | Hair arsenic ( $\mu\text{g/g}$ )           | Tertile<br>2nd vs 1st<br>3rd vs 1st                              | OR (95 % CI)<br>2.54 (1.20–5.39)<br>2.35 (1.02–5.43)   | Gender, work, alcohol, betel nut, smoking, and groundwater use   | Wang, 2007 <sup>54</sup>        |
| Mercury                | Longitudinal    | U.S.             | 3,875       | 20–32             | Type 2 diabetes: FPG $\geq 7.8$ mmol/l, OGTT $\geq 11.1$ mmol/l, HbA1C $\geq 6.5$ %, use of antidiabetes medication  | Toenail mercury ( $\mu\text{g/g}$ )        | Quintile<br>2nd vs 1st<br>3rd vs 1st<br>4th vs 1st<br>5th vs 1st | HR (95 % CI)<br>1.05 (0.72–1.53)<br>1.23 (0.85–1.78)<br>1.18 (0.79–1.77)<br>1.65 (1.07–2.56) | Age, sex, ethnicity, study center, BMI, education, family history of diabetes, smoking, alcohol, physical activity, LCn3PUFAs, magnesium, toenail selenium         | He, 2013 <sup>58</sup>          |
| Mercury                | Cross sectional | Korea            | 6,213       | >20               | Hypertension: self-reported or use of hypertension medication  | Serum mercury (nmol/l)                     | Tertile  | <i>p</i> for trend <0.01   | None   | Chio, 2013 <sup>59</sup>        |
| Selenium               | Longitudinal    | Italy            | 7,182       | 34–70             | Type 2 diabetes: self-reported   | Food frequency questionnaire               | Quintile<br>2nd vs 1st<br>3rd vs 1st<br>4th vs 1st<br>5th vs 1st | OR (95 % CI)<br>1.42(0.87–2.34)<br>1.43(0.86–2.38)<br>1.65(0.98–2.78)<br>2.39(1.32–4.32)     | Age, education, menopausal, BMI, smoking, alcohol, energy intake, saturated/polyunsaturated fatty acids ratio, animal proteins, total carbohydrates, weight change | Stranges, 2010 <sup>63</sup>    |
| Lead, mercury, cadmium | Cross sectional | Korea            | 3,850       | >20               | MetS: at least three of the following: (1) SBP >130 mmHg, DBP >85 mmHg, use of blood   | Serum lead ( $\mu\text{g/dl}$ )            | Quartile<br>2nd vs 1st<br>3rd vs 1st<br>4th vs 1st               | OR (95 % CI)<br>0.84 (0.62–1.13)<br>1.21 (0.90–1.62)<br>1.07 (0.79–1.45)                     | Age, sex, region, smoking, alcohol, regular exercise, BMI  | Moon, 2013 <sup>65</sup>        |

**Table 2** (continued)

| Exposure | Study design | Study population | Sample size | Age range (years) | Outcome definition  | Exposure assessment                              | Exposure categories  | Estimation of associations   | Covariates | References |
|----------|--------------|------------------|-------------|-------------------|---|--|--|--|------------|------------|
|          |              |                  |             |                   | pressure medication; (2) HDL <40 mg/dl (men) and 50 mg/dl (women); (3) TG >150 mmHg or use of antidiabetic medication; (4) FPG >100 mg/dl or use of antidiabetic medication; (5) WC >90 cm (men) and >85 cm (women) | Serum mercury (µg/l)<br><br>Serum cadmium (µg/l) | Quartile<br>2nd vs 1st<br>3rd vs 1st<br>4th vs 1st<br>Quartile<br>2nd vs 1st<br>3rd vs 1st<br>4th vs 1st | 1.24 (0.94-1.64)<br>1.08 (0.82-1.42)<br>1.13 (0.86-1.49)<br><br>0.71 (0.52-0.97)<br>0.82 (0.64-1.05)<br>0.92 (0.73-1.14) |            |            |

OR odds ratio, HR hazard ratio, CI confidence interval, FPG fasting plasma glucose, TG triglycerides, HDL high density lipoprotein, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, LCN3PUFAs long-chain n-3 polyunsaturated fatty acids, WC waist circumference, OGTT oral glucose tolerance test, MetS metabolic syndrome

Epigenetic changes provide a ‘memory’ of developmental plastic responses to the early environment and are central to the development of phenotypes and their stability throughout the life course. There is a growing recognition that epigenetic mechanisms may contribute to MetS [71–73]. Some studies have tested epigenetic changes as a result of exposure to unfavorable in utero environments. For example, Ruchat et al. measured DNA methylation at >485,000 CpG sites in placental tissue and cord blood and found that 3,271 and 3,758 genes in the placenta and cord blood, respectively, were differentially methylated between samples exposed or not to gestational diabetes. Among the differentially methylated genes, 326 in placental tissue and 117 in cord blood were also associated with newborn weight [74]. Another similar study showed that increased methylation of the pygopus homolog 1 (PYGO1) and ceroid-lipofuscinosis, neuronal 8 (epilepsy, progressive with mental retardation) (CLN8) genes had a relative mediation effect on the impact of exposure to maternal diabetes in utero on vascular adhesion molecule-1 (VCAM-1) levels in the offspring [75].

Increasing evidence provides support for the epigenetic effects of environmental chemicals in the development of MetS. For instance, a recent study found that PCBs activate androgen receptor transcriptional activity by inducing Jarid1b, a histone demethylase that catalyzes the removal of trimethylation of lysine 4 on histone H3 [76]. A similar in vitro experiment showed that BPA, HCB and PCBs induce a modest decrease in global DNA methylation [77]. Animal study has also provided evidence that early-life exposure to PCBs modifies the epigenome in the offspring liver, via inducing androgen receptor transcriptional activity [78]. Animal studies also have supported that exposure to EDCs induces epigenetic alteration. For example, in utero exposure to BPA is associated with decreased methylation in the promoter and intron of Hoxa10 in CD-1 mice, which has been shown to persist after birth. BPA may exert its function partly through epigenetic alteration of estrogen response element (ERE) sensitivity to estrogen [79]. In addition, plasma DDT and DDE were found to be inversely associated with global methylation levels [80, 81].

One in vitro study showed gene-specific hypermethylation in a mouse cell culture with mercury levels equal to human maternal and cord blood samples [82]. A study in women undergoing oocyte retrieval showed a relationship between blood mercury concentration and gene-specific hypermethylation [83]. Specifically, methylation of the glutathione S-transferase mu 1 (GSTM) 1/5 promoter was increased among women with higher mercury exposure. In a cohort of Bangladesh residents, serum selenium levels were inversely related to methylation of leukocyte DNA [84]. In another study, maternal lead exposure was found to correlate with diminished Alu and long interspersed nuclear element-1 (LINE-1) methylation in umbilical cord blood [85].



Furthermore, the Hanna et al. study also showed a relationship between blood lead and gene-specific hypomethylation [83]. They detected reduced methylation in the collagen, type I, alpha 2 (*COL1A2*) promoter in women with higher exposure to lead. Interestingly, a mouse study found that pre- and post-natal lead exposure resulted in a shift in the expression of hundreds of genes [86]. Based on this expanding list of studies, there is growing critical recognition that epigenetic mechanisms may contribute to complex human diseases [87] including MetS [88]. Taken together, these findings suggest that specific epigenetic modifications during key developmental periods may influence metabolic phenotypes in later life.

### The Need for Future Research

Though we have learned to *treat* MetS using increasingly sophisticated technologies and agents, we have not been able to *cure or prevent* MetS. Previous research has been confined by disciplinary boundaries and specific age groups. Often, there is a disjoint that exists between our understanding of what comprises women's health, child health and adult health. To date, while most related research and intervention efforts continue to primarily occur within the adult medicine arena, there is still a limited understanding of the root causes and lengthy latency of MetS. The future direction for medicine and public health is to use precise molecular knowledge to detect disease at the preclinical stage, and intervene *before* clinical disease occurs. By doing so, we will not only achieve preemptive prevention, but we will also reduce disease burden, improve population health and quality of life, and minimize health care costs by an order of magnitude [89]. In order to realize this new paradigm, there is a critical need to deepen our understanding of the early life origins and natural history of disease, explore new paradigms using a life course perspective, and put humankind on a long-range strategic and economically sustainable path to better health.

The prenatal period is particularly vulnerable to environmental exposures because of rapid cellular differentiation and development. Developmental programming and the establishment of the epigenome (regulation of gene expression) is most sensitive during the prenatal period [69••]. Advances in a wide range of biological, behavioral, and social sciences are expanding our understanding of how early environmental influences and genetic predispositions affect adult diseases. The new science suggests that epigenetic mechanisms could be an important interface that links genetic factors, environmental factors, and phenotypic expression [90, 91]. Yet, further studies are needed to determine whether the measurements of epigenetic marks in early life can be used as biomarkers to identify individuals who have experienced environmental perturbations during development, and thus who are more likely to develop obesity and metabolic disease in later life.

Longitudinal studies, in particular birth cohort studies, are lacking, yet critically needed to identify the links among early life factors, genetics, and the development of metabolic disorders in children, adolescents, and adults. The value of birth cohorts has received great attention from the scientific community [92]. Compared with cross-sectional or case-control studies, birth cohorts can be used for testing a wide range of hypotheses on risk factors and outcomes, and exploring temporal, dose-response and causal relationships to gain important insights into the epigenetic mechanisms by which environmental exposures and genetic predisposition interact to affect growth, development and disease over the life course and across generations.

### Conclusion

There is limited and inconsistent evidence regarding the relationship between early life exposure to specific environmental toxicants and MetS in later life. Available studies on prenatal exposure to EDCs and their association with later obesity and MetS had small sample sizes and were performed mostly in non-U.S. populations. The study findings were often inconsistent, which may be due to variations in length of exposure, dose, sex and other confounders (e.g., exposure to other unmeasured toxicants). The data are particularly lacking on prenatal exposure to metals and the development of MetS later in life. Even less data are available on early life exposure to toxicants and epigenetic alterations in the offspring that may regulate gene expression throughout the life course. Given that an individual is often exposed to a mixture of environmental toxicants, there is a particular need for prospective birth cohort studies on the metabolic consequences of multiple exposures, including EDCs and metals (e.g., arsenic, mercury, selenium and lead), in utero and in early childhood. Prospective birth cohort studies could help to delineate temporal and dose-response relationships, evaluate differences in the effects of various environmental toxicants and their joint effect on MetS, and identify epigenetic mechanisms underlying the trans-generational effects of specific toxicants such as EDCs and metals.

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### Compliance with Ethics Guidelines

**Conflict of Interest** Guoying Wang, Zhu Chen, Tami Bartell, and Xiaobin Wang declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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