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Implications for Prenatal Cadmium Exposure and Adverse Health Outcomes in Adulthood

Jamie L. Young[a], **Lu Cai**[a,b,*]

[a]Department of Pharmacology and Toxicology, University of Louisville School of Medicine, Louisville, KY 40202, USA

[b]Departments of Pediatrics and Radiation Oncology, Pediatric Research Institute, University of Louisville School of Medicine, Louisville, KY 40202, USA.

Abstract

Cadmium is a ubiquitous, non-essential metal that has earned a spot on the World Health Organizations top 10 chemicals of major public health concern. The mechanisms of cadmium-induced adverse health outcomes, such as cardiovascular disease, renal toxicity and cancer, are well studied in adults. However, the implications for early life exposures to low-level cadmium leading to increased risk of developing diseases in adulthood remains elusive. Epidemiological investigation of the long term implications of cadmium-associated adverse birth outcomes are limited and studies do not extend into adulthood. This review will summarize the literature on the non-lethal, adverse health effects associated with prenatal and early life exposure to cadmium and the implications of these exposures in the development of diseases later in life. In addition, this review will highlight possible mechanisms responsible for these outcomes as well as address the inconsistencies in the literature. More recent studies have addressed sex as a biological variable, showing prenatal cadmium exposure elicits sex-specific outcomes that would otherwise be masked by pooling male and female data. Furthermore, researchers have begun to investigate the role of prenatal and early life cadmium exposures in the development of diet-induced diseases with evidence of altered essential metal homeostasis as a likely mechanism for cadmium-enhanced, diet-induced diseases. Although novel experimental models are beginning to be established to study the association between prenatal cadmium exposure and adverse health outcomes in adulthood, the studies are few, highlighting a major need for further investigation.

[*]**Corresponding author at:** Pediatric Research Institute, University of Louisville School of Medicine, 570 S. Preston St., Baxter Building I, Suite 304F, Louisville, KY 40202, USA. lu.cai@louisville.edu.

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Jamie L. Young: Conceptualization, Visualization, Writing - Original Draft

Lu Cai: Writing - Review & Editing, Supervision

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Keywords

Cadmium; prenatal exposure; fetal development; birth outcomes; Developmental Origins of Health and Disease (DOHaD) hypothesis; environmental contaminant

1. Introduction

Cadmium is a naturally occurring, non-essential metal that has been recognized as an occupational and environmental risk factor for decades (ATSDR, 2012; Tinkov et al., 2017). Ranked number 7 on the Agency for Toxic Substances and Disease Registry list of environmental chemical hazards (ATSDR, 2012), cadmium is one of the most common and detrimental metals present in our environment (Jacobo-Estrada et al., 2017). Over the last century, exposure to cadmium has dramatically increased (IPCS, 1992) due to its use in the production of batteries, pigments and plastics. Anthropogenic sources of cadmium include mining, burning of fossil fuels and incineration of household wastes, play a significant role in generating concentrated sources of cadmium and releasing it into the environment (Jarup and Akesson, 2009).

In adults, the association between chronic cadmium exposures and development of adverse health effects such as renal toxicity, cardiovascular disease and cancer is well documented (Jarup and Akesson, 2009; Nawrot et al., 2010). In children, pre- and postnatal exposure to cadmium is associated with reduced birthweight, impaired fetal growth, trace element deficiencies and congenital malformations (Al-Saleh et al., 2014; Hudson et al., 2019; Jin et al., 2016; Kippler et al., 2012; Taylor et al., 2016); however, little is known about the impact of these early life exposures on the development of diseases later in life.

The Developmental Origins of Health and Disease (DOHaD) hypothesis suggests that exposures to environmental stressors during sensitive stages of human development *(in utero* and early childhood) increases susceptibility to adverse health outcomes in adulthood (Barouku et al., 2012; Gluckman et al., 2010; Thayer et al., 2012). Due to the widespread production and use of metals, in parallel with the knowledge that metals can be passed from mothers to offspring via placenta and/or breast milk, concern has risen about prenatal exposure to metals and the long-term adverse health implications (Wang et al., 2014; Young et al., 2018). For some metals, such as arsenic, the connection between *in utero* exposures and increased risk of disease development in adulthood is evident in both human and animal studies (Young et al., 2018); however, for other metals, such as cadmium, this connection remains unclear.

Studies were considered for this review if they were published between 1970 and 2020 (last 50 years); however most of the studies discussed in this review were published after 2000 as the topic is new to the field and still emerging. Both Google Scholar and PubMed were searched using key terms (cadmium, prenatal exposure, early life exposure, fetal development, birth outcomes, Developmental Origins of Health and Disease (DOHaD) hypothesis, sex differences and sexual dimorphism). The most representative studies for each discussion point were then chosen for discussion in this review article.

2. Maternal Cadmium Exposure and Placental Toxicology

The main route of cadmium uptake in humans is by inhalation and ingestion, with 10–50% of inhaled cadmium being absorbed (dependent on particle size) and 5–10% of ingested cadmium being absorbed (dependent on an individuals' essential metal load) (Friberg 1983; Nordberg et al., 2007; Röllin et al., 2015). Cadmium primarily accumulates in the kidneys and liver, with an estimated half-life of 6 to 38 years and 4–19 years, respectively (Jacobo-Estrada et al., 2017; Kjellstrom and Nordberg, 1978); however, cadmium also accumulates in the placenta with limited direct transfer to the fetus. (Kippler et al., 2010; Korpela et al., 1986; Osman et al., 2000). During pregnancy, the absorption of cadmium is enhanced as a result of physiological changes that occur to ensure nutritional needs of the mother and fetus are met during gestation (Astbury et al., 2015; Moya et al., 2014). For example, the divalent metal transporter 1 (DMT1) is abundantly expressed in the placenta throughout gestation. The major function of DMT1 is iron uptake and transfer; however DMTs also readily facilitate cellular uptake of other divalent cations, such as cadmium (Bressler et al., 2004; Chong et al 2005; Georgieff et al., 2000).

Effects of placental cadmium accumulation on the developing embryo include decreased uteroplacental blood flow, altered trophoblast cell integrity and cell migration, reduced synthesis and metabolism of placental hormones (Alvarez et al., 2011; Chertok et al., 1984; Lin et al., 1997; Stasenko et al., 2010). In addition, cadmium can interfere with placental transport of key micronutrients to the fetus/embryo, such as calcium and zinc (Lin et al., 1997; Wier et al., 1990). Wier *et al* (1990) showed impaired transfer of zinc from maternal to fetal circulation in human placentas perfused with 10 nmol/ml of cadmium. Mechanistically, cadmium accumulation in the placenta induces synthesis of the metal binding protein metallothionein (MT) and subsequent formation of cadmium-MT complexes in order to avoid transfer of cadmium to the fetus, although some cadmium crosses the placenta via DMTs. High concentrations of MT can reduce the amount of free, available zinc in the placenta through the formation of zinc-MT complexes, and reduce zinc transfer to the fetus (Kippler et al., 2010; Ronco et al., 2006). Since it is evident that placental cadmium accumulation can disrupt fetal growth and development (Cheng et al., 2017, Jacobo-Estrada et al., 2017) the relationship between prenatal cadmium exposure and birth outcomes has received growing interest.

3. Prenatal Cadmium Exposure and Non-lethal Birth Outcomes

Although several studies have reported associations between prenatal cadmium exposure and impaired fetal growth (low birth weight, small for gestation age and preterm birth) (Huang et al., 2017; Ikeh-Tawari et al., 2013; Lou et al., 2017; Salpietro et al 2002; Röllin et al., 2015; Sun et al., 2014; Wang et al., 2016; Zhang et al., 2018), the findings are inconsistent likely because they heavily rely on correlative measurements of cadmium at birth. For example, in a prospective pregnancy cohort study of 1027 women from Durham, North Carolina maternal blood samples collected at the time of delivery had a mean cadmium level of 0.46 μg/L (<0.08 – 2.52 μg/L) and infants born to women with blood cadmium levels in the highest tertile of exposure were more likely to have low birthweight and be small for gestational age (Salpietro et al., 2002). Similarly, a cross-sectional study of pregnant women

in Saudi Arabia designed to evaluate the association between heavy metal exposure during pregnancy and adverse outcomes at birth showed cadmium in umbilical cord blood (median = 0.704 μg/L) taken at delivery was associated with low birth weight, reduced crown-heel length and were at greater risk of being small for gestational age (Al-Saleh et al., 2014).

In contrast, other studies have not observed associations between maternal cadmium levels and size at birth (Osman et al., 2000; Thomas et al., 2015); however these studies report cadmium levels much lower than the aforementioned studies. For example, a Canadian study of 1835 pregnant women found no association between average maternal blood concentrations from the first and third trimester (0.2 μg/L) and risk for small for gestational age (Thomas et al., 2015). Osman *et al* (2000) measured cadmium in the placenta, cord blood and maternal blood (median concentration: 5.17, 0.02 and 0.157 μg/L, respectively) at gestational week 36 in 106 Swedish women and found no association between cadmium and birth length, height or head circumference.

Furthermore, some studies have observed limited associations between birth outcomes and cadmium concentrations in umbilical cord blood, but not maternal blood, urine or placental tissue. For example, a study by Zhang *et al* (2004) of 44 pregnant women from a cadmium polluted area in the Hubei province of China found no association between maternal blood (0.80 to 25.20 μg/L) or placental cadmium (0.084 to 3.97 μg/g) levels and pregnancy outcomes (neonatal asphyxia or premature labor), neonatal birth weight or neonatal birth height. However, cord blood cadmium levels >0.40 μg/L were negatively associated with birth height (Zhang et al., 2004). In another agriculturally polluted area of China, the Jiangsu Province, a birth cohort study of 1073 mother-newborn pairs found no association between maternal urinary cadmium levels (median = 0.19 μg/L) and birth outcomes including birth weight, length, head circumference and ponderal index (a measure of leanness based on the relationship between height and mass) but did find cord blood cadmium levels (median = 0.40 μg/L) to be negatively associated with ponderal index in male newborns only (Guo et al., 2017). Overall, those studies that report associations between prenatal cadmium exposure and impaired fetal growth report the cadmium effects at levels of 0.40 ug/L and above. Thus, suggesting a potential threshold for cadmium-associated fetal growth impairment.

Variability in cadmium exposure, analytical methods and timing of fetal cadmium exposure and specimen collection likely all play a role in these inconsistent epidemiological findings. To begin to address the inconsistent findings in the literature Cheng *et al* (2017) assessed trimester-specific effects of prenatal cadmium exposure on birth weight, birth length and ponderal index using creatinine adjusted urinary cadmium levels which are thought to be more reflective of whole-body burden than blood samples which are more reflective of recent, transient exposures (Cheng et al., 2017; Hays et al., 2008). More specifically, urinary cadmium levels were collected during each trimester in 282 pregnant women from the Wuhan Women and Children Medical Center in China (Cheng et al., 2017). Urinary creatinine, which is excreted at a relatively contestant rate in the urine, was measured and used to control for variations in spot urine sample dilutions. The creatinine adjusted urinary cadmium levels during the first, second and third trimesters were 0.51, 0.59 and 0.61 μg cadmium/g creatinine, respectively. Birth size in males was not associated with maternal

cadmium levels in any trimester. In contrast, female birth size was inversely associated with high maternal cadmium levels in the first trimester only, suggesting that the critical window of susceptibility to cadmium-associated adverse effects on birth size can occur during earlier periods of pregnancy and can be sex-specific. The sex-dependent outcome of this study is consistent with other studies investigating *in utero* cadmium exposure (Kippler et al., 2012; Röllin et al., 2015; Vahter et al., 2007) and provides insight into the variability surrounding the literature.

4. Sex-Specific Effects

The contradictory results in the effects of prenatal cadmium exposure on birth outcomes is likely to be due to studies pooling male and female data, which masks the sex-specific effects, a phenomenon observed with the pharmacokinetics and toxicity studies of other metals (Vahter et al., 2007). Thus, the experimental study design has shifted to account for sex as a biological variable in order to more accurately and informatively address research questions. For example, Romano *et al* (2016) showed a negative association between maternal urinary cadmium levels (0.31 μg/g creatinine) and female offspring birth length, but a positive association with male offspring birth length in a subset of 396 women form a prospective cohort study in Seattle, Washington. In another study using whole blood samples collected in the first trimester from 4191 pregnant women enrolled in the Avon Longitudinal Study for Parents and Children, Taylor *et al* (2016) found an adverse association between maternal blood cadmium levels (mean, 0.56 μg/L) and birthweight, head circumference and crown-heel length in females, but not males. Similarly, maternal urinary cadmium (median, 0.63 μg/L with 75% < 1 μg/L) collected during early gestation (on average gestation week 8) from 1616 women in rural Bangladesh was negatively associated with birth weight and head circumference in female, but not male neonates (Kippler et al., 2012).

The “moderate” cadmium levels found in maternal blood and urine [defined by the Human Biomonitoring Commission of the German Federal Environment Agency as anything below the 1 μg/L reference level (Schulz et al., 2007)], in the aforementioned studies are similar to those reported in other developed countries (Taylor et al., 2014). Interestingly, the sex-specific associations between maternal cadmium levels and adverse birth outcomes continue to be evident at even lower cadmium concentrations. Specifically, Röllin *et al* (2015) found a negative association between lower birth weight in female, but not male neonates, and maternal blood cadmium levels (mean: 0.25 μg/L) half that of previously reported studies correlating cadmium with sex-specific adverse outcomes (Kippler et al., 2012; Röllin et al., 2015; Taylor et al., 2016).

Of the three epigenetic mechanisms involved in regulating gene expression (DNA methylation, histone modifications and gene silencing mediated by non-coding RNAs), cadmium research has focused exclusively on DNA methylation (Paul and Bhattacharje, 2016; Vilahur et al., 2015). Sex-specific effects have been reported in DNA methylation patterns associated with prenatal cadmium exposure in both epidemiological and animal studies, providing a possible mechanism by which birth size is correlated to maternal cadmium exposure (Castillo et al., 2012; Kippler et al., 2013; Mohanty et al., 2015). In a study of 24 maternal-infant pairs, Mohanty *et al* (2015) found sex-specific associations

between placental genome-wide DNA methylation and placental cadmium levels. In females, differentially methylated sites were near transcriptional start sites for cell damage response genes whereas in males the sites were close to transcriptional start sites involved in organ development, cell differentiation and angiogenesis (Mohanty et al., 2015). More specifically, in female infants cadmium was associated with hypomethylation of cell damage genes SIAH3, HS3ST4, and TP53G1 where as in male infants cadmium was associated with hypomethylation of MECOM, and hypermethylation of SALL1. Whether these genes were upregulated or downregulated by the observed altered methylation patterns was not addressed in this study.

In another study, Kippler *et al* (2013) found altered DNA methylation patterns in mononuclear cells from cord blood were associated with maternal blood cadmium levels taken at gestational week 14 (mean of 1.3 μg/kg) and the associations were sex-specific. Of the top 500 CpG sites, 96% of the sites showed positive correlations between cadmium exposure and cord blood methylation in males where as in females only 29% were positively correlated, with most associations being inverse. Cadmium exposure was associated with more global hypermethylation in males and hypomethylation in females. The top 6 genes with differential DNA methylation associated with cadmium exposure were hypomethylated in females and hypermethylated in males. In females, methylation changes were reported to be associated with genes involved in morphology and mineralization of bone as well as organ development. In males, methylation changes were associated with genes related to cell death (Kippler et al., 2013).

These studies provide clear evidence that prenatal cadmium exposure alters DNA methylation patterns in a sex-specific manner with cadmium-related hypomethylation more prominent in females and hypermethylation more prominent in males. Further studies are needed to elucidate the consequences of these altered DNA methylation patterns on child health and development. In addition, the cadmium-induced epigenetic modifications during fetal development may cause persistent alternations in gene expression that increase the risk for long-term adverse health effects, a phenomenon observed with prenatal exposure to other metals, such as arsenic (Vilahur et al., 2015; Wang et al., 2012; Young et al., 2018). In addition, the altered DNA methylation patterns observed in the placenta and newborns of cadmium exposed mothers may, at least in part, explain the sex-specific differences adverse birth outcomes, as sex-specific differences in methylation patterns are generated early after fertilization (Gabory et al., 2013).

Castillo et al (2012) designed an animal study to investigate the impact of maternal cadmium exposure (50 ppm in drinking water) during pregnancy on altered fetal methylation patterns in the liver, focusing on altered glucocorticoid metabolism, a phenomenon linked to increased risk of cardiometabolic disorders in adulthood (Ronco et al., 2009; Seckl, 2004). Prenatal cadmium exposure resulted in increased expression of fetal DNA methyltransferase 3a (an enzyme involved in de novo methylation in embryonic development) in males and decreased expression in females. This sex-specific outcome correlated with hypomethylation of the hepatic glucocorticoid receptor in female fetuses and hypermethylation in male fetuses (Castillo et al., 2012). Although informative, it remains unclear if these altered methylation patterns remain throughout life or result in long-term health effects. Relative to

cadmium exposure, hypomethylation of repetitive sequences has been reported in adult women suggesting implications for long term health effects such as hormone-related cancers (Hossain et al., 2012).

However, few epidemiological studies have followed cohorts of *in utero* cadmium exposed children past birth, and of those that do, follow-up ends before puberty (most ending before age 10). The adverse effect of cadmium exposure on fetal growth, including weight and height appear to remain until at least 5 years of age and are more apparent among females (Gardner et al., 2013). Kippler *et al* (2013) identified several CpG sites associated with cadmium exposure in newborns that persisted in 4.5-year old children. In children 9 years of age, Malin Igra *et al* (2019) correlated early life cadmium exposure with increases in bone-related biomarkers associated with osteotoxicity. Recently, Moynihan *et al* (2019) conducted a study that emphasized the sex-dependent effects of prenatal exposure to cadmium, observing a negative association between exposure to cadmium *in utero* and both peripheral and abdominal adiposity in females, but not males (median age 10).

Although it is well documented that prenatal exposure to cadmium is associated with adverse effects on child health and development, the implication for long term health remain elusive (Fig. 1) Few studies have considered the possibility that prenatal cadmium exposure may reprogram an individual to be more susceptible to pathologies later in life including cancer, type 2 diabetes and cardiovascular diseases, a concept known as the DOHaD hypothesis (Heindel et al., 2017; Vilahur et al., 2015).

5. Evidence for Increased Risk of Developing Adult Diseases

Epidemiologically, the link between early-life cadmium exposures and increased risk for adult diseases remains to be explored. Experimentally, researchers have begun to develop models to study the impact of early life cadmium exposure on disease development later in life. For instance, Hudson *et al* (2019) investigated the impact of maternal cadmium exposure on cardiovascular changes in offspring at birth or after 6 months of age (Fig. 2). Maternal cadmium exposure was associated with a hypertensive phenotype in adult female mice, but not in male mice; however, there were no differences in markers of circulating reactive oxygen species or essential trace element levels between control and exposed adult female mice. Thus, the authors focused on neonate tissues to identify possible early-life, cadmium-induce molecular changes (via RNA-*seq*) that may be sufficient to program adulthood hypertension (Hudson et al., 2019). RNA-seq was performed on the hearts of female neonates only as the females showed evidence of hypertension while the males did not. In association with maternal cadmium exposure, RNA-seq identified differentially expressed genes enriched for functions in cardiovascular disease, hypertension, enlarged hearts, hypoxic stress, cellular energy. Overall, the results of this study suggests maternal cadmium exposure causes changes during critical windows of development (perturbed trace element homeostasis and gene expression) that increases risk of hypertension in adulthood (Hudson et al., 2019). However, empirical evidence is still needed to strengthen these observations both in animal models and prospective birth cohort studies in humans.

6. Potential Role of Cadmium-Diet Interactions

Of growing interest is the role of diet-environment interaction in the initiation, progression and development of human metabolic diseases. Dietary factors, such as excessive fat intake, contribute to the formation of adult metabolic pathologies including type 2 diabetes, non-alcoholic fatty liver disease and cardiovascular disease, all of which increase susceptibility to a second hit which may promote progression to more severe pathologies (De Long and Holloway, 2017). Animal studies have been published investigating the relationship between diet and low level cadmium exposure, showing that the combination of high fat or high cholesterol diets with cadmium exposure results in increased risk of heart failure and altered bone quality (Türkcan et al., 2015; Zhang et al., 2020); however these studies do not consider the role of prenatal or early-life exposures as a potential "second hit" influencing susceptibility to chronic metabolic disease in adulthood.

Liang *et al* (2019) used a model of early life (*in utero* through 10 weeks post weaning) exposure to environmentally relevant doses of cadmium (0.5 and 5 ppm in drinking water) combined with post-weaning high fat diet (HFD), to investigate the combined effects on mouse cardiac remodeling. A second study, using the same cadmium exposure model, investigated whole-life exposure (*in utero* through 24 weeks post-weaning) on metal distribution in the blood, heart, kidney and liver in HFD-fed adult mice (Young et al., 2019). Based on these two studies using same animal model, the following key features can be obtained (Table 1).

These findings suggest that cadmium interacts with HFD to alter essential metal homeostasis in the liver and kidney, a phenomenon that may contribute to the underlying mechanism responsible for the development of obesity-associated pathologies in multiple organs. Additionally, the data suggests the mechanisms for cadmium-enhanced, diet-induced heart hypertrophy in female mice is independent of both oxidative stress and metal dyshomeostasis (Liang et al., 2019; Young et al., 2019). Although possibly more reflective of true environmental exposures where the offspring continues to be exposed to the same toxicant as the parents (either through food, water or air), these studies do not separate *in utero* and post-natal exposure and therefore conclusions on prenatal exposure alone cannot be deduced from these results.

7. Conclusions

It is evident that although the placenta acts as a significant barrier to cadmium during fetal development, there are several indirect effects implicated in the non-lethal, adverse birth outcomes related to *in utero* cadmium exposure. The implication of these outcomes in the development of diseases later in life remains elusive with little to no epidemiological investigation. Recently, however, the ability of cadmium to alter DNA methylation patterns and disrupt essential metal homeostasis has highlighted the need to investigate the effects of early-life cadmium exposure and increased susceptibility to disease in adulthood. Experimental models have just begun to address this very large knowledge gap and provide novel insights into mechanism by which prenatal cadmium exposure may increase the risk of adverse health complications later in life.

Future studies must continue to address sex as a risk factor as it has become clear that cadmium elicits sex-specific outcomes that are otherwise masked in mixed-sex studies (those that do not separate males and females). In addition, future studies should consider the implications of prenatal, low-dose cadmium exposure in the development of not only metabolic syndrome and cardiovascular disease, but also neurobehavioral disorders and cancers. Furthermore, it remains unclear if the increased risk of disease development seen in the first generation of offspring prenatally exposed to low-dose cadmium can be generationally transmitted. To address this important question, systemic mechanistic studies investigating epigenetic modifications and generational transition of diseases must be implemented. Subsequently, epidemiologic studies should include the collection of trimester specific biosamples and information, not just at birth, to address the gaps and variability in the data.

Future studies should also address how prenatal exposure to cadmium in combination with other metals impacts disease initiation and progression as cadmium is found in combination with many other metals, such as zinc, lead and copper in the environmental. Additionally, many of the hazardous waste sites, including Superfund sites, around the United States are contaminated with mixtures of metals and present with ideal metal mixture exposure scenarios for future studies.

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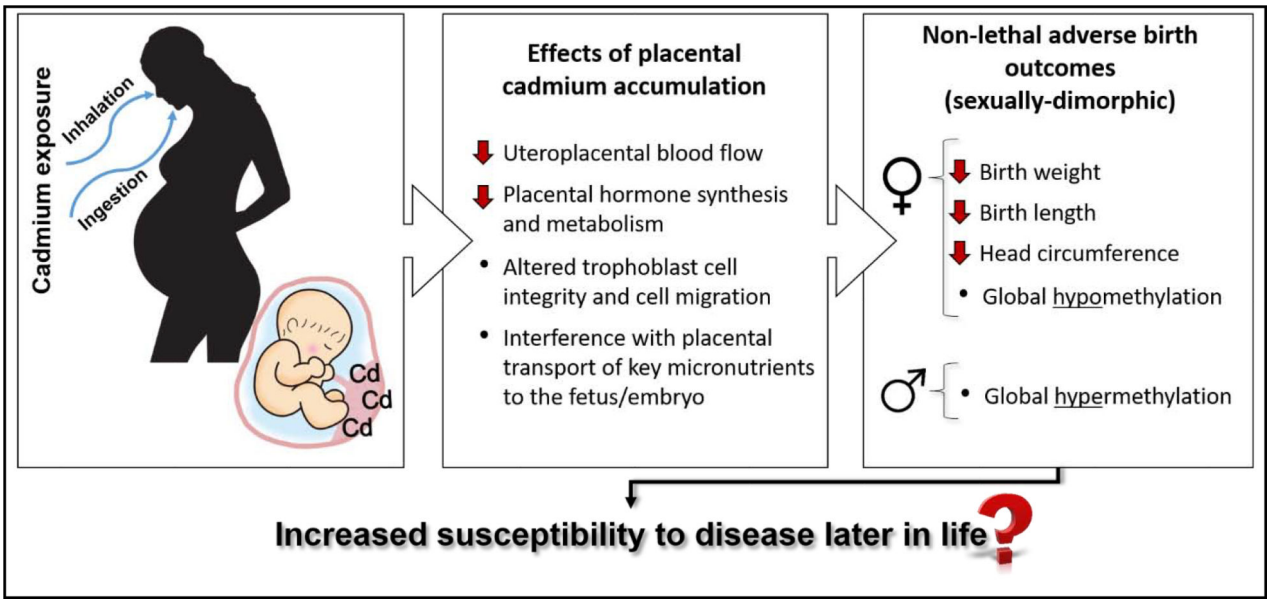

Fig 1.

Summary of the effects of placental cadmium accumulation and the non-lethal adverse birth outcomes that may lead to increased susceptibility of disease development in adulthood.

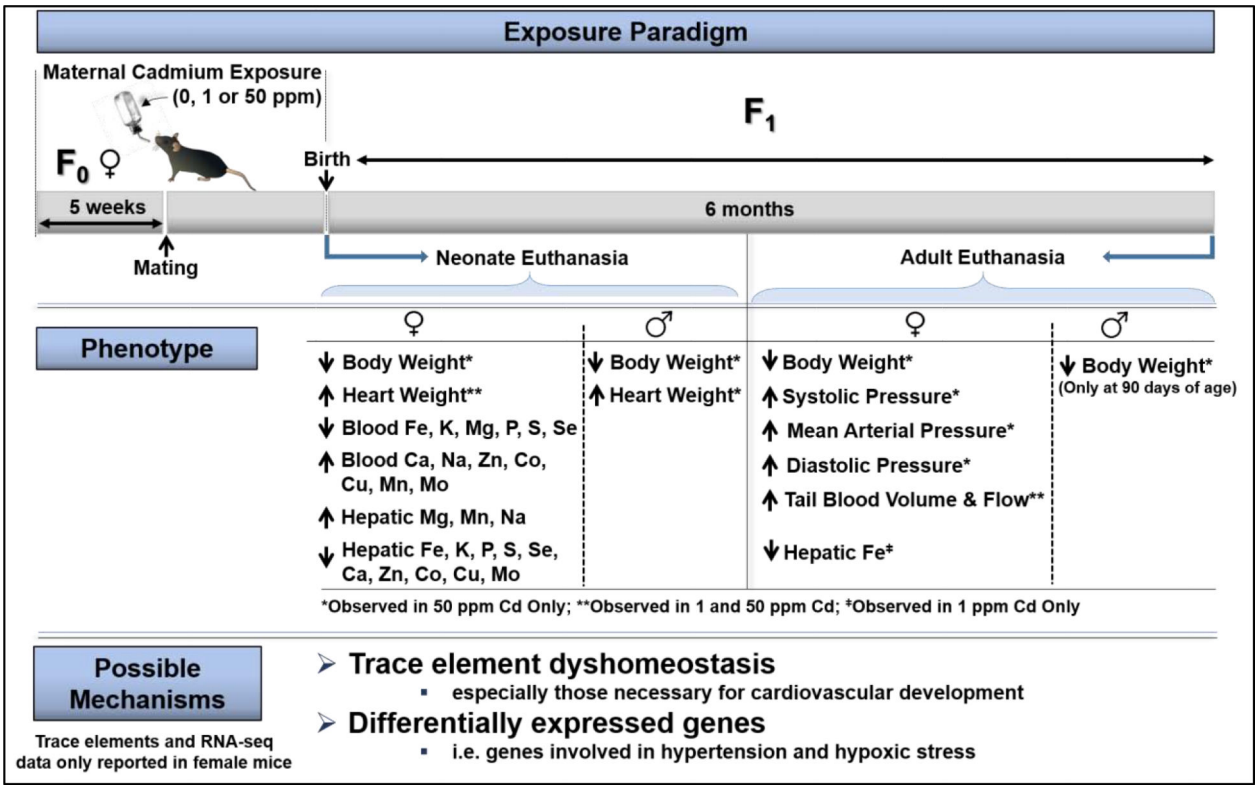

Fig 2.

Summary of the findings in "*Maternal cadmium exposure in the mouse leads to increased heart weight at birth and programs risk to hypertension in adulthood*" (Hudson et al., 2019). The illustration was created by the authors based on the published work by Hudson *et al* (2009). **NOTE:** results summarized in this figure are from BxC mice only. Hudson et al (2019) used two different mating strategies creating B×C (B mother × C father) and C×B (C mother × B father) offspring (B = C57BL/6J and C = CAST/EiJ) to facilitate a study not yet published. Transcriptomics, essential trace metal levels and circulating reactive oxygen species levels were only determined in BxC offspring. In addition, these three endpoints were only measured in female BxC mice as they showed evidence of hypertension while the male mice did not.

Table 1.

Key results from two studies using the same animal model of early life exposure to cadmium combined with post-weaning HFD (Liang et al. 2019; Young et al. 2019)

• Over time, cadmium exposure alone reduced body weight gain in female, but not male mice.
• Cadmium exposure combined with HFD reduced body weight gain in male mice only.
• Females accumulate more cadmium in liver and kidney compared to males.
• HFD increased cadmium levels in liver, kidney and heart tissue in both sexes.
• The combination of cadmium with HFD significantly altered essential metal levels in the blood, liver and kidney, but not the heart.
• The combined exposure induced cardiac hypertrophy and fibrosis in female mice only.
• Cardiac hypertrophy and fibrosis in female mice was independent of oxidative stress.