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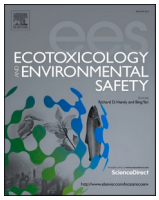

Review

Impact of prenatal exposure to metallic elements on neural tube defects: Insights from human investigations

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ABSTRACT

Metallic elements play a pivotal role in maternal and fetal health. Metals can cross the placental barrier and be absorbed by fetuses, where they may affect closure of the neural tube during embryonic development. Neural tube defects (NTDs), which result from aberrant closure of the neural tube three to four weeks post-conception, have a multifactorial and complex etiology that combines genetic variants and environmental exposure. Recent advances in population-level association studies have investigated the link between maternal environmental exposure and NTDs, particularly the influence of metals on the incidence of NTDs. Herein, we present a broad and qualitative review of current literature on the association between maternal and prenatal metal exposure via the maternal peripheral blood, amniotic fluid, placenta, umbilical cord, and maternal hair, and the risk of developing NTDs. Specifically, we identify the various aggravating or attenuating effects of metallic exposure on the risk of NTD formation. This review provides novel insights into the association between environmental metals and NTDs and has important applications for NTD prevention and mitigating environmental exposure to metals.

1. Introduction

Neural tube defects (NTDs), the second most common type of severe congenital disability after congenital heart defects, result from failure of the neural tube to close during the first trimester. NTDs occur in approximately one per thousand births and lead to fetal loss or disabilities in infants (Copp et al., 2013; Wallingford et al., 2013). NTDs have a multifactorial and complex etiology, whereby both genetic variants and environmental exposure can contribute to the observed range of phenotypes, which include spina bifida, anencephaly, and encephalocele (Finnell et al., 2000). Environmental factors, such as deficiency in folate and other essential trace elements, environmental toxicants, or maternal exposure to drugs during the periconception period have been identified as pivotal risk factors for aberrant closure of the neural tube (Baldacci et al., 2018; Foster et al., 2017). Consequently, it is important to define the relationship between environmental exposure and NTD formation.

Several "inorganic elements" (metallic elements) are vital components of living organisms, particularly human beings (Zoroddu et al., 2019). Approximately 10 metallic elements (calcium, sodium, potassium, magnesium, zinc, copper, iron, manganese, cobalt, and molybdenum) are essential for maintaining basic life activities in the human body but can be toxic at sufficiently high doses (Maret, 2016). Therefore, an optimal balance of essential metallic elements is important for sustaining normal functions in an organism. In contrast, non-essential metallic elements, such as lead, mercury, and cadmium, exhibit an array of negative effects (Jan et al., 2015). Thus, exposure to metallic elements plays an important role in disease occurrence.

Of particular concern is the impact of metallic element exposure during pregnancy on the fetus, as these elements can be transported across the placenta (Michaelis et al., 2022). Over the last few decades, overwhelming evidence has indicated that deficiencies in essential metallic elements are associated with adverse pregnancy outcomes, including NTDs, congenital heart defects, preterm birth, miscarriage, and stillbirth (Cetin et al., 2010). In addition, mounting evidence suggests that non-essential metallic element exposure plays a role in the etiology of NTDs (Tindula et al., 2021). Although previous studies have reviewed the environmental factors contributing to NTDs, including industrial waste, pollutants (e.g., arsenic, pesticides, and polycyclic aromatic hydrocarbons) (Finnell et al., 2021; Yu et al., 2021), and

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pharmaceuticals (e.g., anti-epileptic medications) (Caiaffa et al., 2023; Lo et al., 2021), this is the first to review the association between maternal exposure to specific environmental metals and the risk of NTDs.

Metallic elements have been detected in the peripheral blood, placenta, umbilical cord, amniotic fluid, urine, nail clippings, and maternal hair of pregnant women (Sakamoto et al., 2013; Zhou et al., 2019). These metallic elements can cross the placental barrier and be absorbed by the fetus. However, if the maternal metal content exceeds the placental filtration rate and the requirements of the developing embryo, the accumulation of metal elements in the embryo may induce the formation of NTDs (Liu et al., 2021a). Conversely, the inadequate intake of essential metal elements is also related to the incidence of NTDs (Tian et al., 2021). Therefore, analysis of various metallic element contents in pregnant women may help us understand the risk factors and pathophysiological of NTDs, thereby enabling better prevention and treatment of NTDs. Herein, we conduct a focused scoping review to summarize the links between prenatal exposure to metallic elements in maternal peripheral blood, amniotic fluid, placenta, umbilical cord, and maternal hair and the incidence of human NTDs (Fig. 1). The findings of this review can guide future research and prevention strategies.

2. Methods

In this study, we reviewed previous literature examining the effects of metallic elements during pregnancy, including essential metallic elements (calcium, sodium, potassium, magnesium, zinc, copper, iron, manganese, cobalt, and molybdenum), toxic heavy metals (lead, mercury, chromium, aluminum, silver, nickel, uranium, and cadmium), rare earth elements (lanthanum, cerium, praseodymium, europium, terbium, lutetium, and yttrium), alkali metals (lithium, rubidium, and cesium), and alkaline earth elements (barium and strontium).

Studies that met all of the following criteria were included in the review: (1) original articles; (2) assessments of metal exposure during pregnancy using maternal samples (e.g., maternal blood, maternal hair) or tissues that transport substances between the mother and the fetus (e.g., amniotic fluid, placenta, umbilical cord); (3) assessments of NTDs, as well as subtypes of NTDs, following metal exposure; (4) published prior to 2023. We excluded studies that met the following criteria: (1) experiments on animals and non-human studies; (2) letters, case reports, and reviews; (3) studies not written in English; (4) and studies with no mention of metallic elements or NTDs/adverse pregnancy outcomes in the title or abstract.

The PubMed database was searched using the following terms: (NTDs OR neural tube defects OR neural tube malformation OR neural tube anomalies OR spina bifida OR anencephaly OR encephalocele OR meningomyelocele) AND (metal OR metallic elements or environmental exposure) AND (maternal blood or maternal hair or amniotic fluid or placenta or umbilical cord).

3. Results

3.1. Metallic elements in maternal blood and associations with NTD risk

3.1.1. Essential macro metallic elements

Metallic elements in maternal serum are convenient indicator of recent maternal exposure which can be used to assess the risk of fetal NTDs (Tindula et al., 2021; Wei et al., 2020). Many xenobiotics, especially metallic elements, rapidly infiltrate maternal blood and pass through the placental barrier into the fetus across the placental barrier, which may be concerned in the risk of fetal NTDs. A deficiency of essential metallic elements may also contribute to fetal NTDs (Pi et al., 2022). A series of studies have shown that the macrometallic elements calcium, sodium, and potassium are required for maternal health and normal fetal development; however, abnormal levels of these elements have a critical impact on development of the nervous system in early embryos, which is associated with the occurrence of NTDs (Hughes, 1975; Komiya and Runnels, 2015; Webb and Miller, 2003). Notably, one study found that maternal serum calcium levels were considerably lower in pregnant women with NTDs than those in healthy women (Daglar

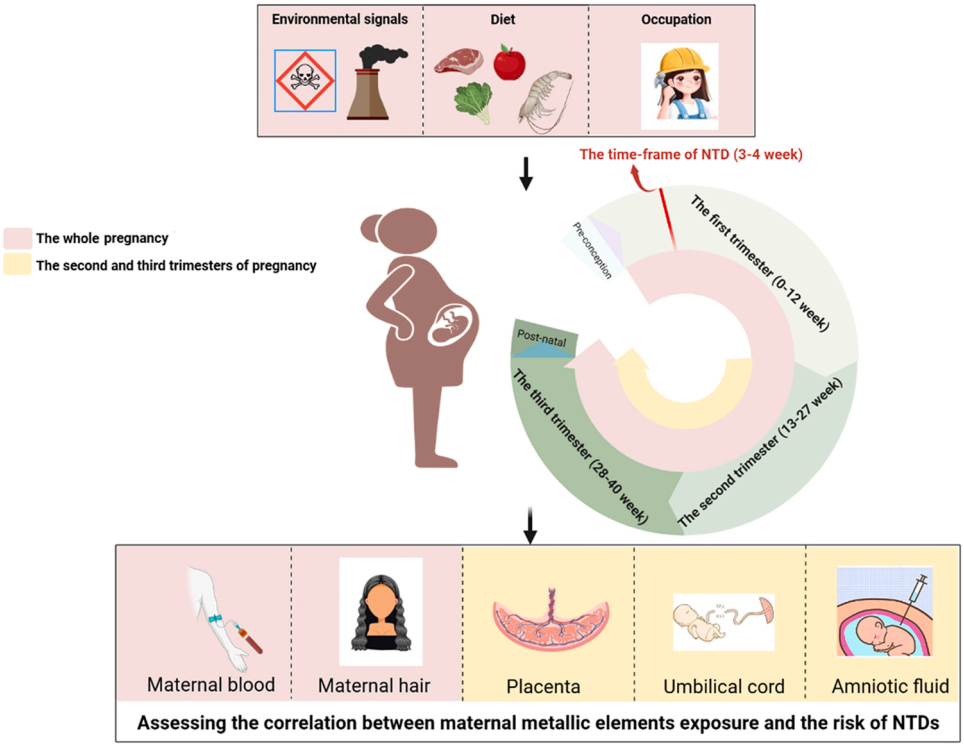

Fig. 1. Overview of the correlation between maternal metal exposure and the risk of fetal NTDs. The analysis of environmental metal exposure and metallic elements in maternal peripheral blood, amniotic fluid, placenta, umbilical cord, and maternal hair is crucial for assessing the risk of fetal NTDs.

et al., 2016), whereas another study with a relatively small sample size found no significant changes in calcium levels in the serum of mothers with or without NTDs (Sirinoglu et al., 2018). Sodium is another metallic element that maintains normal cellular physiological activity and function. Pi et al. reported higher sodium concentrations in the maternal serum of an NTD group than in that of a control group, but they observed no significant differences in potassium concentrations between the two groups (Pi et al., 2022). These studies imply that both overexposure and underexposure of essential major metallic elements may affect the closure of neural tubes and be related to the risk of NTDs. However, considering the inconsistent findings, determining the exact roles of calcium and potassium in fetal NTDs is a key area for future research.

3.1.2. Essential trace metallic elements

Apart from the macroelements, the maternal blood contents of several trace metallic elements, including zinc, copper, iron, manganese, cobalt, and molybdenum, play a pivotal role in fetal health during pregnancy (Lewicka et al., 2017). Similarly, both deficient and excess amounts of these elements are related to fetal malformations (Ou et al., 2017; Yin et al., 2020).

Several studies have reported significantly lower levels of zinc in the maternal serum of patients with NTDs than in controls (Buamah et al., 1984; Cavdar et al., 1983, 1988; Cengiz et al., 2004; Demir et al., 2019; Dey et al., 2010; Golalipour et al., 2009; Hinks et al., 1989; Zeyrek et al., 2009). Zinc is a central component of several enzymes and proteins; thus, zinc deficiency during critical periods of neural tube closure may elevate the incidence of NTDs. However, Jiang (1991) suggested that low zinc levels in maternal serum were not particularly diagnostic of NTDs, and instead, are a trait shared by all pregnant women. Several other studies also exhibit inconsistent results, which has sparked debate over the true causal nature of this correlation (Hambidge et al., 1993; Nikolov et al., 1993; Tian et al., 2022). McMichael et al. (1994) suggested that the deficient maternal-to-fetal transfer of zinc in women with very high serum zinc levels may be related to the risk of NTDs. Undoubtedly, heterogeneity in the methodologies, sample collection time, and sources for assessing zinc concentrations may have contributed to the contrasting results of previous studies. Thus, it is crucial to establish a large-scale early-pregnancy zinc intervention cohort to confirm the relationship between maternal serum zinc levels and the risk of NTDs.

Cobalt plays a biologically essential role as a metallic ingredient of vitamin B12, whereas molybdenum assists in the processing of aldehyde oxidase, sulfite oxidase, and xanthine oxidase, but both trace elements exhibit a protective effect against NTDs. For example, Tian et al. (2021) reported that the median concentrations of cobalt and molybdenum were significantly lower in NTD samples than in controls, suggesting that deficiency of these essential trace elements in maternal blood is strongly associated with the risk of NTDs. However, in another study with a relatively small sample size, no significant relationship was observed between maternal blood cobalt or molybdenum levels and the development of NTDs (Demir et al., 2019; Tian et al., 2022). Iron is a crucial nutrient during pregnancy, and thus, pregnant women are vulnerable to iron deficiency. Low iron intake is associated with a significantly increased risk of NTDs (Kakebeen and Niswander, 2021). Nevertheless, researchers have found no significant difference in the concentrations of iron between NTD and control samples of maternal blood (Tian et al., 2022, 2021). Therefore, it remains unclear whether cobalt, molybdenum, or iron deficiency in maternal blood is associated with NTD risk.

Copper, another common heavy metal, is critical for maintaining cellular biological functions in humans; however, the accumulation of copper in human cells induces copper toxicity, which leads to the occurrence of disease (Chen et al., 2022; Tsvetkov et al., 2022). In human studies, copper levels in the blood of mothers with NTD fetuses were significantly higher than those in healthy controls (Cengiz et al., 2004; Demir et al., 2019; Jiang, 1991; Zeyrek et al., 2009), which indicates that high levels of copper may be associated with NTD development. Cengiz et al. suggested that the interaction between zinc and copper during intestinal absorption might contribute to a relative increase in copper in patients with NTDs (Cengiz et al., 2004). In addition, a study with a large sample size that investigated the association between maternal blood metal element contents and NTDs reported higher copper concentrations in the NTD group (Tian et al., 2021). However, several other studies have reported no differences in serum copper concentrations between patients with and without NTDs (McMichael et al., 1994; Tian et al., 2022). Furthermore, excess manganese intake can be hazardous to embryonic development and can impair neural cell differentiation (Pinsino et al., 2011). For example, Ozel et al. demonstrated that high levels of manganese in maternal blood are associated with the risk of NTDs (Ozel et al., 2019), which is consistent with the findings of Tian et al. (2021). However, Jiang (1991) showed that NTD fetuses are positively correlated with manganese deficiency in maternal serum. Therefore, the relationship between excess copper and manganese levels in maternal blood and NTD risk requires further clarification.

In summary, too much or too little of essential trace metallic elements can impair the neurodevelopment of an embryo. Thus, disturbances to the homeostasis of these trace metallic elements are critical for fetal NTD development. Nevertheless, the relationship between trace metallic element exposure and NTD risk requires further investigation.

3.1.3. Non-essential metallic elements

In addition to essential metallic elements, the human body may absorb a variety of non-essential metallic elements through diet and the environment that are harmful to human health. Heavy metal toxicity has been reported as a risk factor for NTD development. In experimental animal studies, maternal exposure to mercury or methylmercury, cadmium, chromium and aluminum during pregnancy can contribute to NTDs or vertebral malformations in mice and chicken (Robinson et al., 2010; Zhang et al., 2016; Iijima et al., 1983; Lin et al., 1997). An epidemiological study showed that the offspring of women living in areas with drinking water levels of lead exceeding 10 mg/L were more likely to have NTDs in their offspring (Bound et al., 1997). Another cohort study showed that Norwegian parents potentially exposed to lead in the workplace were 2.9 times more likely than non-exposed women to have offspring with an NTD (Irgens et al., 1998). However, a study conducted by Macdonell et al. failed to verify a correlation between drinking water lead levels and the prevalence of NTDs in Glasgow (Macdonell et al., 2000). An investigation in Mexican–American women showed that the maternal environmental and occupational exposure to lead did not appear to be risk factors for NTDs in offspring; however, a strong association was found between mercury levels and NTD risk among the highest socioeconomic group with exposure to inorganic/elemental mercury in the workplace and via drinking water (Brender et al., 2006). Given the inconsistencies in the above studies, in addition to monitoring heavy metal levels in the environment, analyzing heavy metal levels in maternal samples is essential for assessing the association between heavy metals and NTD risk.

A case–control study reported that high maternal blood levels of lead during the second trimester are associated with NTDs (Ozel et al., 2019). Moreover, maternal plasma or serum levels of lead and cadmium were significantly higher in NTD samples than control samples (Demir et al., 2019; Jiang, 1991). Jin et al. (2014) discovered that prenatal exposure to mercury, lead, and cadmium is associated with the concentration of these metals in maternal blood and an increased risk of fetal NTDs. Subsequently, Tian et al. (2021) reported that the risk of NTDs is associated with a higher concentration of several toxic elements, specifically cadmium, chromium, mercury, and lead, with lead being a key contributor to NTD risk. Exposure to aluminum, which is widespread in nature, may be linked to a variety of human diseases, including NTDs. Liu et al. (2021a) explored the association between prenatal aluminum exposure and the risk of NTDs by detecting aluminum concentrations in

maternal serum and found that increased aluminum concentration is a risk factor for fetal NTDs. Toxic heavy metal elements are mainly produced by industrial processes, especially coal-related industries. These operations pollute the air, water, and soil in the natural environment. Pregnant women are then exposed to these toxic metallic elements from polluted farmland soil, air, water, and food via ingestion, inhalation, and the cutaneous route. In the studies mentioned above, participants were recruited from areas with abundant coal reserves and developed coal-related industries, where the incidence of NTDs was high. Thus, coal mining may be a major source of environmental metal exposure in the population. As a common characteristic of the study subjects was long-term exposure to toxic heavy metals, the avoidance of toxic metals is a key requirement for the prevention of NTDs.

Wei et al. (2020) demonstrated that the median maternal serum concentrations of rare earth elements such as lanthanum, cerium, praseodymium, europium, terbium, lutetium, and yttrium were higher in NTD samples than in controls, which implies that the risk of NTDs is related to the overall concentration of rare earth elements. Fertilizers that combine chemical rare earth elements can increase the concentrations of these metals in crops, which may be a source of maternal environmental exposure of rare earth elements. The role of alkali metals in the development of NTDs is poorly understood; however, recent studies have suggested that the alkali metal lithium may affect neural tube development, with high lithium concentrations observed in controls but not in NTDs (Pi et al., 2022). However, a case study considered that in utero exposure to lithium may be associated with the presence of NTDs and found that the intake of lithium carbonate drugs increased the risk of NTDs in fetuses (Grover and Gupta, 2005). Nevertheless, the relationship between lithium levels in maternal blood and the risk of NTDs remains unclear.

The above studies demonstrate that the concentration of metal elements in maternal blood is helpful for assessing the risk of NTDs and exploring the pathogenesis of NTDs. Nevertheless, the use of maternal blood to evaluate the incidence of NTDs remains limited. The relatively short turnover of metallic elements in maternal blood may only reveal recent metallic exposure; thus, several metals present in maternal blood may not reflect the exposure profile during development of the neural tube. In addition, several delivery complications may influence the levels of metallic elements in maternal blood. Thus, in addition to considering the influence of gestational age, delivery complications and other factors should be excluded in subsequent research.

3.2. Metallic elements in amniotic fluid and associations with NTD risk

Fetal exposure to environmental substances occurs through the amniotic fluid. Researchers have widely demonstrated that a range of metallic elements penetrate the placental barrier and enter the amniotic fluid for uptake by the fetus (Caserta et al., 2013). Therefore, the amniotic fluid represents a delicate equilibrium between fetal and maternal compartments and can be considered a valuable indicator of prenatal exposure to exogenous factors. Similar to the results in maternal blood, previous studies have shown that the amniotic fluid contents of essential metallic elements (calcium, zinc, and molybdenum) are lower in NTDs than in controls (Dawson et al., 1999; Groenen et al., 2003; Ovayolu et al., 2020). In addition, non-essential trace metallic elements and heavy metals, such as aluminum, tin, antimony, lead, and mercury, may be elevated in the amniotic fluid of pregnancies complicated with NTDs (Dawson et al., 1999; Ovayolu et al., 2020), implying that these elements are correlated with the occurrence of NTDs. Observed changes in some of the metallic element concentrations of the amniotic fluid are consistent with those of maternal blood, such as calcium, zinc, aluminum, molybdenum, mercury, and lead. However, several studies have reported that the amniotic fluid levels of zinc, cadmium, manganese, cobalt, nickel, copper, and lead are not significantly different between NTD and control groups (Ancona et al., 1977; Ovayolu et al., 2020). The contrasting results between maternal blood and amniotic fluid can be attributed to the limitations of these studies. Specifically, differences in the distribution of metallic elements between the amniotic fluid and maternal blood, sample collection times, and living environments may all contribute to the observed variability. Another limitation is that metallic element concentrations in the amniotic fluid were measured later than the early embryogenesis period of the neural tube because of the clinical difficulty of obtaining amniotic fluid during early pregnancy. Hence, the link between exposure to these metallic elements in the amniotic fluid and the risk of NTDs requires further validation in samples from early pregnancy.

3.3. Metallic elements in the placenta and associations with NTD risk

The placenta is a transitory organ that participates in fetal growth by mediating the quality of the intrauterine environment, which has a critical influence on fetal health. Specifically, the placenta provides an adequate supply of nutrients for fetuses and removes waste products to ensure that the pregnancy progresses harmoniously (Punshon et al., 2019). Recently, many studies have investigated the association between placental exposure to essential metallic elements and the risk of NTDs. For example, Pi et al. (2022) found that the median concentrations of potassium were lower in NTD samples than in controls, whereas the median concentrations of sodium exhibited no significant difference between the two groups. According to a multiple-metal regression model, which included five alkali metals (sodium, potassium, lithium, rubidium, and cesium), sodium was positively and significantly associated with the occurrence of NTDs; however, when considering potential confounders, such as education status, occupation, and gestational age, the association between sodium and NTDs was no longer significant (Pi et al., 2022). Similarly, Wang et al. (2021b) showed that the median concentration of magnesium was considerably higher in NTDs than controls, whereas calcium levels showed no significant differences. When logistic regression revealed no correlation between placental magnesium or calcium concentrations and the risk of NTDs, Wang et al. (2021b) quantified the effect of a multiple-metal mixture on the NTD risk and identified the contribution of individual metallic elements to the mixture effect through Bayesian kernel machine regression (BKMR) models. The results indicated a beneficial effect of calcium on NTDs (Wang et al., 2021b). Therefore, instead of estimating the effect of metallic elements independently through traditional logistic analysis, the effects of metal concentrations on the NTD risk may be more effectively evaluated by considering the interactions within metal mixtures.

Additionally, Yin et al. (2020) investigated essential trace metallic elements in the placenta and observed that the median concentrations of manganese, molybdenum, and zinc were substantially higher in NTD groups and associated with greater NTD risk, whereas the cobalt concentration was significantly lower in NTD groups, which reduced the NTD risk (Yin et al., 2020). Furthermore, according to the BKMR model, manganese and zinc are risk factors for NTDs, whereas cobalt is a protective factor for NTDs (Yin et al., 2020). Another study confirmed that increased manganese concentrations are likely associated with the risks of NTDs (Liu et al., 2013). Environmental exposure to manganese has recently attracted substantial interest considering its multiple sources, which include paint, fungicides, gasoline, and seed protectants. High exposure to ambient manganese is positively correlated with high maternal and fetal blood manganese levels (Lin et al., 2011; Takser et al., 2004); thus, future research should identify potential sources of manganese to determine the effect of manganese exposure on subsequent fetal development. The median concentrations of copper and zinc were also significantly higher in an NTD group than in a control group (Yin et al., 2022). This variability of zinc results may be attributed to the influence of the length of gestation, that is the NTD group had a shorter gestational period than the control group (Liu et al., 2013). Additionally, different types of tissue may affect the concentrations of metal elements. Moreover, the ability of the placenta to transfer metals to the fetus can be impacted in NTDs, which results in the accumulation of copper and

zinc in the placenta.

Apart from essential metallic elements, non-essential metallic elements, such as the toxic heavy metals aluminum and mercury, are important exposure indicators of NTDs (Jin et al., 2016; Liu et al., 2013, 2021a; Tong et al., 2021), which is consistent with the results for these elements in maternal blood. Conversely, in these studies, the median cadmium concentrations in NTDs were lower than those in the controls; however, the association between placental levels of cadmium and NTD risk was no longer present after adjusting for the gestational age, which proves that the length of gestation is the most important confounding variable when assessing the risk of NTDs. In addition, researchers considered that lower lead exposure may explain the lack of differences in lead concentrations between NTD and control groups (Jin et al., 2013). In another study, other types of non-essential trace elements with lower concentrations in NTD groups than in controls (e.g., the alkali metals rubidium and cesium) were negatively associated with the occurrence of NTDs; however, lithium levels showed no difference between the two groups (Pi et al., 2022). In addition, the alkali earth metal barium was significantly more abundant in NTD samples than controls, with BaCl2 exposure inducing the presence of NTDs in animal models, which suggests that Ba is a likely risk factor for NTDs (Wang et al., 2021b). Barium exposure mainly occurs through food and water intake and inhalation of ambient air polluted by coal combustion and the disposal of fly ash emitted during coal burning. Moreover, Yin et al. (2022) investigated the association between prenatal exposure to uranium and the risk of NTDs and found that uranium exposure in the NTD group was significantly higher than that in the control. Another study revealed that exposure to silver was associated with an elevated risk of NTDs and that higher silver concentrations were positively correlated with a maternal diet being polluted by silver (Yin et al., 2022). Although inconsistent results between blood and placenta may be attributed to the barrier function of placentas, the placenta is more closely related to fetal exposure than maternal blood. Furthermore, although placenta samples cannot be obtained before or during closure of the neural tube, the level of metallic elements in the placenta during the second and third trimester of pregnancy may reflect exposure to metallic elements in the critical period of fetal neural tube closure because the dwelling environment, daily habits, and occupation of pregnant women are relatively stable factors. Nevertheless, it is essential to further validate the association between placental exposure to metallic elements and the risk of NTDs in early-pregnancy specimens.

3.4. Metallic elements in the umbilical cord and associations with NTD risk

The umbilical cord tissue belongs to fetus-side tissue, and the umbilical cord blood represents the fetal blood circulating in the fetal body. Moreover, compared with maternal blood, umbilical cord is an effective means of detecting the elemental input to the fetus via the placenta and amniotic fluid (Aylward et al., 2014; Jagodic et al., 2022). Thus, the umbilical cord is a good indicator of fetal environmental exposure. Liu et al. (2020) found that cobalt and molybdenum concentrations were significantly lower in the umbilical cord of patients with NTDs than in controls, whereas nickel levels were significantly higher in NTDs than in controls. However, when considering the effect of gestational age, only cobalt levels were significantly associated with NTD risk. Moreover, using the BKMR model to assess multiple exposure revealed that a co-exposure mixture of zinc, manganese, cobalt, molybdenum, and nickel reduced the NTD risk (Liu et al., 2020). The reciprocal consistency of logistic analysis results and BKMR model results strengthen the confirmation of the protective effect of cobalt on NTDs. The concentration of zinc in umbilical cord blood is inversely related to that in maternal blood and the placenta, suggesting that the placenta may act as a strong barrier against zinc and could contribute to fetal zinc insufficiency (Yin et al., 2020).

In contrast to these other tissues, heavy metallic elements in the umbilical cord may also be significant in patients with NTDs. A study showed that umbilical cord serum copper levels were significantly higher in an NTD group than a control group (Zeyrek et al., 2009). Additionally, prenatal exposure to the heavy metals cadmium and mercury in the umbilical cord has been implicated in the incidence of NTDs (Liu et al., 2021b; Tong et al., 2021). The umbilical cord is an embryonic part of the fetus; thus, compared with maternal blood, amniotic fluid, and placenta, metallic element levels in the umbilical cord should be more informative of the true exposure status of the fetus and a more direct indicator of fetal exposure. Furthermore, umbilical cord samples for patients with NTDs are collected at pregnancy termination, whereas most control samples are only collected at delivery, which is substantially outside the window for neural tube development, suggesting that measured metallic element levels may not match the levels observed during neural tube closure. This limitation can also explain the observed differences in these studies. Thus, although metallic elements are more stable in umbilical cord tissue and could reflect long-term exposure in the fetus (Liu et al., 2020), the above findings should be verified using samples collected in the early trimester of pregnancy.

3.5. Metallic elements in maternal hair and associations with NTD risk

Human hair has been used as a substitute for blood and urine in biomonitoring analyses of environmental and occupational exposure to various pollutants, owing to its low invasiveness, minimal risk, and ease of storage and transport. Contaminant levels might reflect exposure over a long period of time, and certain components may be present in high quantities in human hair, making it a valuable assessment tool. Metal levels in hair have proven to be an effective for determining internal accumulation in individuals. Notably, hair may be used to represent the exposure level over a certain time span (Wang et al., 2009). Li et al. (2017) found that the median concentrations of magnesium and calcium were significantly lower in the maternal hair of NTD groups than in that of the controls, which is generally consistent with previous studies in other tissues (Dawson et al., 1999; Groenen et al., 2004). Thus, the collection of hair samples early in pregnancy can indicate the level of maternal intake of essential metal elements during neural tube closure. Specifically, lower levels of calcium and magnesium in maternal hair may have negative consequences on neural development in offspring. The same researchers also observed that the essential trace metals nickel and molybdenum were significantly lower in NTDs than in controls, whereas a deficiency of zinc and tin was related to spina bifida and anencephaly development, respectively (Yan et al., 2017). Other groups have also demonstrated that zinc insufficiency is associated with the risk of NTDs (Bergmann et al., 1980; Cavdar et al., 1991, 1988; Srinivas et al., 2001; Zhang et al., 2005). In addition, the alkaline earth elements barium and strontium may exhibit protective effects against NTD risk (Li et al., 2017). Therefore, high-frequency supplementation with essential trace elements is critical for embryonic development. In contrast, thorium exposure detected in maternal hair and caused by indoor air pollution from the combustion of coal is associated with the risk of NTDs (Wang et al., 2021a), which suggests that toxic environmental exposure is closely related to the occurrence of NTDs.

4. Discussion

Although NTDs caused by environmental factors have multiple biological mechanisms, evidence is increasingly indicating that exposure to metallic elements may contribute to NTD development. Fetal metal exposure occurs from environmental metals accumulating in the maternal body followed by placental transfer. However, because fetal exposure is difficult to determine directly, it is generally measured by determining the concentration of metals in maternal matrices as a surrogate or by measuring levels in the umbilical cord, placental tissue, and amniotic fluid. Thus, this review outlines the contribution of various metallic elements in the maternal blood, placenta, umbilical cord, and

maternal hair of patients with NTDs to investigate the relationship between metal exposure and the occurrence of fetal NTDs (Table 1). Determining the links between these metals and NTDs may contribute to a better understanding of the pathophysiological underlying aberrant closure of the neural tube.

Among the many metallic elements analyzed in these samples, several exhibit a consistent association with NTD risk. For example, toxic heavy metals, such as mercury, aluminum, lead, and cadmium, have been linked to an elevated risk of NTD development. Higher concentrations of copper that induce copper toxicity are also related to the risk of fetus NTDs. Moreover, cobalt exhibits a protective effect against NTDs by assisting in the processing of cobalamin. However, the concentration of several metal elements exhibit a highly inconsistent association with NTD risk according to the different sources of the sample. For example, manganese deficiency in maternal blood is linked to NTDs, which is consistent with the hypothesis that manganese deficiency may weaken antioxidant capacity and the free radical scavenging effect during fetus development. Conversely, excess manganese intake measured in the placenta and maternal blood can be hazardous in fetuses. Moreover, NTD fetuses exhibit a lower molybdenum concentration in maternal blood but a higher molybdenum concentration in placenta.

It is worth noting that zinc has been investigated in all tissue samples included in this review, with the majority of evidence suggesting that zinc deficiency is linked to NTDs. Zinc is present in numerous enzyme systems and is required for the production of a series of molecules during embryo development. Animal investigations have revealed that a shortage of zinc during gestation can promote apoptosis and result in NTD phenotypes in offspring (Jankowski et al., 1995; Li et al., 2018). This is consistent with reports from a series of small-sample-size studies that lower concentrations of zinc in maternal serum, hair, and amniotic fluid are associated with the risk for NTDs. A meta-analysis by Cheng and Gao (2022) highlighted zinc deficiency in pregnant women as a risk factor for NTDs in offspring. However, Yin et al. (2020) showed that higher concentrations of zinc in placental tissue are associated with NTD risk. This apparent contradiction may be attributed to the fact that affected placentas are hampered in their ability to transfer metals to the fetus, which leads to zinc accumulation in the placenta and zinc deficiency in the umbilical cord and fetus.

The inconsistent findings across the above studies is due to the many limitations in assessing the association between metallic elements and NTDs. Heterogeneity in the methodologies, sample sources, timing of sample collection, amount of sample, living environment, nutritional habits of pregnant women, and patient ethnicity can substantially influence the results. One of the greatest limitations is the sampling time is later than the critical period of fetal neural tube closure, as well as inconsistent sampling time. Gestational age can also greatly affect the detection of metal levels, especially for essential metallic elements, which are critical for the development of neural tubes. Thus, metal concentrations in NTD and control groups should be compared at the same gestational age. Furthermore, the sample size of some studies is limited, and differences in the place of residence, ethnicity, parental occupation, and intake of various nutrients during pregnancy are considered to influence fetal metal exposure. Therefore, multi-center, large-sample-size studies are required to better evaluate the impact of metal exposure on NTDs. Additionally, although amniotic fluid, placental tissue, and umbilical cord specimens are closer to the fetal side and more likely to precisely reflect the metal exposure of fetuses, these samples can only be collected during the mid-to-late stage of pregnancy. Hence, it is hard to assess metal exposure in these tissues during the early stage of NTDs, which can lead to inaccurate evaluation of the impact on NTD formation. Maternal blood and hair are easy to obtain throughout pregnancy and can reflect maternal exposure to various metals during pregnancy. Thus, concentrations of metallic elements in maternal blood and hair collected during early pregnancy can represent maternal intake characteristics during this decisive period of neural tube

Table 1
Case-control studies evaluating the risk of fetal NTDs in association with metallic elements in maternal blood, placenta, umbilical cord, and maternal hair.

Exposure	Major Findings	Samples	Study
zinc	A decreased risk for zinc: OR 5.06; 95 % CI: 1.51–16.94	maternal blood	(Golalipour et al., 2009)
zinc	A increased risk for zinc: AOR 1.46; 95 % CI: 0.58–3.67	maternal blood	(McMichael et al., 1994)
essential trace elements and heavy metals	A increased risk for lead: OR 1.94; 95 % CI:1.76–2.13 A increased risk for manganese: OR 1.25; 95 % CI:1.14–1.38 A decreased risk for molybdenum: OR 0.87; 95 % CI:0.90–0.94	maternal blood	(Tian et al., 2021)
heavy metals	A increased risk for mercury: AOR 2.00; 95 % CI:1.24–3.23 AOR 3.96; 95 % CI:1.68–9.33 AOR 2.79; 95 % CI:1.41–5.52 A increased risk for cadmium: AOR 0.43; 95 %CI: 0.24–0.77	maternal blood	(Jin et al., 2014)
aluminum	A increased risk for aluminum: AOR 2.42; 95 %CI: 1.23–4.87	maternal blood	(Liu et al., 2021a)
rare earth elements	A increased risk for lanthanum: AOR 2.78; 95 %CI: 1.25–6.17 AOR 4.31; 95 %CI: 1.93–9.62 A increased risk for cerium: AOR 1.52; 95 %CI: 0.70–3.31 AOR 4.73; 95 %CI: 2.08–10.76	maternal blood	(Wei et al., 2020)
aluminum	A increased risk for aluminum: AOR 1.60; 95 %CI: 0.94–2.70	placenta	(Liu et al., 2021a)
alkali metals	A decreased risk for cesium: AOR 0.58; 95 % CI: 0.36–0.91	placenta	(Pi et al., 2022)
alkaline earth metals	A increased risk for barium: AOR 1.6; 95 % CI: 1.06–2.43	placenta	(Wang et al., 2021b)
Essential trace elements	A increased risk for manganese: AOR 3.17; 95 % CI: 2.35–4.28 A increased risk for molybdenum: AOR 3.73; 95 % CI: 2.74–5.07 A increased risk for zinc: AOR 2.85; 95 % CI: 2.13–3.83 A decreased risk for	placenta	(Yin et al., 2020)

(continued on next page)

Table 1 (*continued*)

Exposure	Major Findings	Samples	Study
	cobalt: AOR 0.18; 95 % CI: 0.14–0.25		
manganese	A increased risk for manganese: AOR 4; 95 % CI: 1.23–14.79	placenta	(Liu et al., 2013)
mercury	A increased risk for mercury: AOR 8.80; 95 % CI: 3.80–20.36	placenta	(Jin et al., 2013)
Me mercury	A increased risk for Me mercury: AOR 3.64; 95 % CI: 1.66–7.99	placenta	(Jin et al., 2016)
T-mercury	A increased risk for T-mercury: AOR 1.76; 95 % CI: 1.13–2.76	placenta	(Tong et al., 2021)
uranium	A increased risk for uranium: AOR 2.52; 95 % CI: 1.47–3.25	placenta	(Yin et al., 2022)
silver	A increased risk for silver: AOR 1.92; 95 % CI: 1.11–3.32	placenta	(Pi et al., 2022)
essential trace elements	A decreased risk for cobalt: AOR 0.37; 95 % CI: 0.15–0.91	umbilical cord	(Liu et al., 2020)
cadmium	A increased risk for cadmium: AOR 1.55; 95 % CI: 1.00–2.38	umbilical cord	(Liu et al., 2021b)
alkaline earth elements	A decreased risk for magnesium: AOR 0.44; 95 % CI: 0.28–0.68 A decreased risk for calcium: AOR 0.56; 95 % CI: 0.36–0.87 A decreased risk for strontium: AOR 0.45; 95 % CI: 0.28–0.70 A decreased risk for barium: AOR 0.41; 95 % CI: 0.26–0.65	maternal hair	(Li et al., 2017)
essential trace metals	A decreased risk for nickel: AOR 0.53; 95 % CI: 0.34–0.81 A decreased risk for molybdenum: AOR 0.64; 95 % CI: 0.42–0.98	maternal hair	(Yan et al., 2017)
Thorium	A increased risk for thorium: AOR 1.80; 95 % CI: 1.23–2.63	maternal hair	(Wang et al., 2021a)

development. However, variations in the transmission of different elements across the placental barrier and their half-life period mean that correlations between metallic element concentrations in maternal blood or hair and the occurrence of NTDs requires further verification. Furthermore, information on delivery procedures and delivery complications should also be considered, as they may have an impact on metallic element concentrations.

Humans are inevitably exposed to various environmental metals. Considering the various correlations among metallic components, investigations that include all metals simultaneously in a typical regression model may ignore potentially meaningful relationships between mixture components and the studied health outcomes. Therefore, in addition to comparing the effects of exposure to a single metal element on NTD risk using conventional logistic regression, the combined effect of metal mixtures should be analyzed through the BKMR statistical approach to consider the impact of multiple factors, as well as the influence of each component in the mixture. Furthermore, the exposome-wide association study paradigm has the potential to provide a more in-depth understanding of the association between environmental exposure and clinical outcomes via an integrated approach to investigate the impact of perinatal exposure to metals in different cohorts for the assessment of the effects of prenatal and early life exposure to metals on NTDs. This approach reveals the complex interactions that occur as a consequence of diverse physical, chemical, and biological exposures, as well as nutritional and sociodemographic variables in utero life. Furthermore, animal studies are crucial for understanding the direct effects of metal exposure on NTDs, which can further elucidate the pathogenesis of NTDs. In summary, abundant scope remains for continued exploration of the impact of metal exposure on human NTD formation at the clinical level. Further discovery of new relationships between metallic elements and NTD risk will also provide novel insights into fetal NTD occurrence, thereby contributing to important advances in preventing NTDs and mitigating environmental metal exposure.

Declaration of Competing Interest

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.

Data Availability

No data was used for the research described in the article.

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