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A REVIEW OF SEX DIFFERENCES IN VULNERABILITY TO HEAVY METALS

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ABSTRACT

Heavy metal exposure has been linked to several detrimental health outcomes, including cancer, neurotoxicity and cardiovascular diseases. Recent research suggests that the sensitivity to heavy metal toxicity may vary by gender. This review summarizes scientific research on sex-specific vulnerability to heavy metal toxicity. Several studies have shown that women may be less likely than men to have cardiovascular illness brought by exposure to heavy metals. This could be partly attributed to estrogen's preventive properties, which have been shown to mitigate the harmful cardiovascular consequences of heavy metal intake. Contrarily, testosterone has been found to negatively affect the cardiovascular system and may make men more susceptible to cardiovascular illness brought by heavy metals. Disparities in heavy metal absorption, distribution, metabolism, and excretion as well as variances in lifestyle and exposure patterns, may also play a role in sex disparities and vulnerability to heavy metals. The results as a whole point to the possibility that gender variations may significantly affect the susceptibility to heavy metal toxicity, particularly in connection to cardiovascular diseases. To appreciate the underlying mechanisms, develop specific preventive and treatment measures for both men and women, further research is still required.

***Keywords**:* Heavy metal exposure, vulnerability, toxicity, gender variation

1.0 INTRODUCTION

Heavy metals are a sort of environmental pollutant that can be dangerous to human health and is present in many different environments. Lead, mercury, cadmium, and arsenic exposure has been

related to a number of harmful health outcomes, including cancer, kidney damage, cardiovascular disease, and neurodevelopmental abnormalities (Agency for Toxic Substances and Disease Registry, 2019). Heavy metal exposure can have an impact on both sexes, although research indicates that the health effects may differ depending on sex (Ali *et al*. 2018).

In this review, we explore the relationship between heavy metal exposure and sex-based variations in susceptibility to adverse health effects. We explore current studies on the many mechanisms, such as variations in how the body absorbs, metabolizes, and excretes these compounds, that may explain sex differences in heavy metal toxicity. The effects of heavy metal exposure on reproductive and developmental health in both men and women are also examined, as well as the potential impact of sex hormones on the effects of heavy metals on the body.

2.0 HEAVY METALS AND SEX DIFFERENCES

A group of hazardous substances called heavy metals are found all over the environment. These chemicals are present in the food we consume, the water we drink, and the air we breathe (USEPA 2018). People can be exposed to heavy metals in a variety of ways, including as through their profession, contact with contaminated dust or soil, or through some consumer products (Giacomello *et al.* 2019). Numerous detrimental health effects, such as cancer, renal damage, neurodevelopmental issues, and cardiovascular disease have been related to heavy metal intake (WHO, 2010). Although both sexes are affected by heavy metal exposure, current research has indicated that the effects on each gender's health may be different (Li *et al.* 2018). Numerous studies have suggested that some heavy metals, such as lead and mercury, may have more of a negative impact on females. For instance, studies have shown that, even after accounting for exposure levels at work, women tend to have greater blood levels of lead than men. Sexes may differ in their vulnerability to heavy metals for a variety of reasons. The fact that women often have a higher percentage of body fat than men, which can serve as a storage space for heavy metals, is one theory (Campagnolo *et al.* 2019). Additionally, as women are often targeted by marketers more than men, they may be exposed to heavy metals through jewelry, personal care products, and cosmetics (Genuis & Kelln, 2012). Furthermore, sex hormones like estrogen and testosterone may also have an impact on the impacts of heavy metals. While testosterone has been found to lessen the negative effects of some heavy metals, research has shown that estrogen can increase the body's absorption of lead and other heavy metals (Martin, *et al.* 2007 and Li *et al.* 2014). Understanding the differences in gender-specific sensitivity to heavy metals is essential for public health measures

focused at preventing and reducing exposure (Huang *et al.* 2021). It is crucial to identify at-risk groups and execute targeted treatments to lessen exposure and improve adverse health effects.

3.0 MECHANISMS OF HEAVY METAL TOXICITY

Heavy metals are dangerous substances that can adversely affect people's health. Through environmental contamination, occupational exposure, or consumption of tainted food or water, people may come into contact with heavy metals (WHO, 2010). Cancer, neurological issues, and cardiovascular disease are just a few of the detrimental health effects that heavy metals can have (Agency for Toxic Substances and Disease Registry (2007). According to studies, the sensitivity to heavy metal toxicity varies between the sexes, with women often showing more risk than men.

One aspect that leads to the disparities in toxicity between the sexes is variances in the absorption and distribution of hazardous heavy metals. Females typically have a higher percentage of body fat than males, which can serve as a storage space for heavy metals. Females may therefore circulate more heavy metals, which increases the likelihood of poisoning (Agency for Toxic Substances and Disease Registry (2007). In addition, women typically ingest more calcium, iron, and other micronutrients, which can compete with heavy metals for absorption in the digestive system. In contrast to men, females may absorb fewer heavy metals as a result of this rivalry (Rothenberg, 2016). Differences in the metabolism and excretion of heavy metals may also have an impact on sex differences in susceptibility to poisoning. Compared to men, women often have lower amounts of glutathione, a vital antioxidant molecule that aids in the body's removal of heavy metals (Klaassen *et al*. 2009). This can make females more susceptible to the harmful effects of heavy metals and result in higher levels of oxidative stress (Smith & Johnson, 2021). The metabolism and excretion of heavy metals can be impacted by sex hormones including estrogen and testosterone (Wu *et al.,* 2019). Studies have revealed that testosterone can lessen the harmful effects of some heavy metals whereas estrogen can enhance the absorption of lead and other heavy metals. Estrogen and testosterone, two sex hormones, can affect how well heavy metals are metabolized and eliminated. According to studies, testosterone can lessen some heavy metals' damaging effects while estrogen can enhance the absorption of lead and other heavy metals (Pappas & Kotampasi, 2019). In relation to the toxic effects of heavy metals, estrogen can have both beneficial and detrimental consequences. Despite the fact that estrogen possesses antioxidant properties that may help shield against the harmful effects of heavy metals, it has been observed that estrogen increases the absorption of these substances (Jomova & Valko, 2011). Contrarily, testosterone has been demonstrated to lessen several heavy metals' harmful effects (Hu, & Aro,

2002). Serum testosterone and heavy metals in female pubertal growth. In addition, estrogen receptors are found in a variety of tissues and organs, including as the liver, kidneys and brain, and they may be involved in regulating the harmful effects of heavy metals on females (Silva *et al.* 2011).

To summarize, a variety of factors, including differences in the absorption, distribution, metabolism, and excretion of these toxic substances, genetic and epigenetic factors, as well as hormonal factors, impact sex differences in susceptibility to heavy metal toxicity. Understanding these pathways is essential for creating therapies that particularly aim to reduce exposure and minimize detrimental effects on health. Understanding these pathways may also provide insight into sex differences in disease and environmental toxin vulnerability.

3.1 SEX DIFFERENCES IN HEAVY METAL ABSORPTION, DISTRIBUTION, AND EXCRETION

Heavy metal exposure has been associated with harmful effects on male reproductive function, including reduced sperm quality and quantity, testicular damage, and hormonal imbalances. The toxic effects of heavy metals on the testes and sperm, as well as the disruption of hormone production and regulation, are believed to be the underlying causes of these effects (Jurewicz & Hanke 2006). Women's menstrual cycle irregularities, decreased fertility, and poor pregnancy outcomes have all been linked to heavy metal exposure. Similar to the effects seen in males, heavy metals can impair ovarian function and influence hormone synthesis and control (Sallmen & Rahman, 2004).

Due to variations in anatomy, physiology, and hormonal regulation, studies have revealed that females may be more vulnerable to the reproductive effects of heavy metal exposure than males (Järup, 2003). Inhibiting the harmful effects of heavy metal poisoning on the female reproductive system may be possible with the protective action of estrogen (Sen & Shukla 2001). To completely comprehend the processes underlying these impacts and create efficient strategies to lower exposure and attenuate unfavorable health outcomes, more study is required.

According to study by Gruia *et al.* (2021), exposure to heavy metals can alter the epigenome of male and female reproductive cells, which could pass these effects on to future generations. Additionally, exposure to heavy metals may harm fetal development, postpartum health outcomes, egg and sperm quality, fertility, and pregnancy outcomes (Kapka-Skrzypczak *et al*. 2015).

The usage of antioxidants and other dietary components has been recommended as a preventative approach to lessen the effects of heavy metal exposure on reproduction (Flora and Mittal, 2021). To completely understand the processes underlying these effects and to create efficient exposure reduction and health consequence prevention methods, more research is nonetheless required.

3.2 REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF HEAVY METALS

Reactive oxygen species (ROS), which are produced as a result of oxidative stress caused by heavy metals, can be damaging to the organism (Davies, 2016). According to Gill & Tuteja (2010), ROS have the potential to harm biological elements like proteins, lipids, and DNA, which can result in cell death, inflammation, and other health issues. Numerous illnesses, including cancer, cardiovascular disease, and neurological disorders all of which are correlated with oxidative stress have been linked to heavy metal exposure (Flora, 2011).

In addition to oxidative stress, heavy metals can damage cells by interfering with their signaling pathways. Heavy metals can obstruct normal cellular function when they bind to proteins and enzymes involved in signaling cascades. This interference may result in faulty cell differentiation, growth, and death processes, which may result in aberrant cell growth and the development of cancers. Jomova & Valko (2011) added that heavy metals can harm by altering how genes involved in numerous biological processes are expressed. According to Kippler *et al.* (2017), exposure to heavy metals like arsenic and cadmium can change how some genes related to DNA damage, oxidative stress, and inflammation are expressed. To effectively prevent and cure the negative health impacts brought on by heavy metal exposure, preventative and treatment measures must take into account how heavy metals induce toxicity (Flora, 2009). Future studies may concentrate on discovering novel toxicological pathways, creating specialized defense mechanisms, and discovering biomarkers of heavy metal exposure and toxicity (Chen *et al.,* 2017).

It may be possible to understand the apparent differences in sensitivity to heavy metal exposure between males and females by investigating the mechanisms of heavy metal toxicity. According to research, the body's capacity to metabolize and remove heavy metals may be impacted by differences in hormone levels and metabolism between the sexes (Chen *et al.*, 2017). Furthermore, differences in the gene expression of the enzymes involved in heavy metal metabolism and detoxification may affect how these processes differ across the sexes.

An important area of research is identifying populations that may be more susceptible to the negative effects of heavy metals. Li *et al* (2019) opined that heavy metal exposure at work may be

higher for certain occupational groups, such as miners and workers in the manufacturing industry, making them more vulnerable to negative health impacts. Järup (2003) stated that people who have illnesses like kidney disease, which affects excretion, may be more vulnerable to the negative effects of heavy metals.

3.3 SEX HORMONES AND HEAVY METAL TOXICITY

Estrogen and testosterone, which are sex hormones, may play a part in moderating the effects of heavy metals. Important hormones including testosterone, progesterone, and estrogen control many physiological functions like metabolism, immunological response, and reproduction (Vidaeff and Severino, 2010). Heavy metals such cadmium, lead and mercury can build up in many tissues and organs and cause cellular injury and dysfunction.

According to studies, there are a variety of ways that sex hormones and heavy metals might interact. For instance, estrogen can attach to metal ions and interact with them, creating complexes that can build up in tissues and be harmful (López-Espinosa *et al.* 2016). The production of antioxidant molecules can also be increased and the expression of enzymes involved in heavy metal detoxification can be affected by testosterone, potentially providing protection from the toxicity of heavy metals.

In addition to these direct interactions, sex hormones may affect how heavy metals are taken in, circulated, and expelled from the body (Rogers and Haswell, 2014). For instance, by boosting the production of transport proteins in the stomach, estrogen can increase the absorption of some heavy metals, such as cadmium (Roggenbeck *et al.* 2018). Contrarily, testosterone can increase the excretion of heavy metals by boosting the expression of liver detoxifying enzymes (Gurer, 2001).

The effects of the interplay between sex hormones and heavy metals on human health may be profound. For instance, those with diseases like polycystic ovarian syndrome (PCOS) or hypogonadism that disrupt sex hormone levels may be more vulnerable to the hazardous effects of heavy metals (Ognjanović *et al.* 2008). Likewise, treatments that regulate sex hormone levels, such hormone replacement therapy, may be advantageous for people who are exposed to heavy metals at work or in their environment (Wang *et al.,* 2023)

Additionally, gender-specific variations in the toxicity of heavy metals may affect the risk and development of disease. For instance, research points to the possibility that women who have been exposed to more heavy metals may be at higher risk for breast cancer (Acharya and Misra 2019). This may be because heavy metals may interact with estrogen receptors to promote tumor growth.

Similar to how testosterone is known to offer protection against heavy metal toxicity, males with low testosterone levels may be more vulnerable to the negative health effects of heavy metal exposure (Yurdakok-Dikmen *et al.* 2013 and Shen *et al.* 2017).

There is mounting evidence that suggests the interaction between sex hormones and heavy metals may play a key role in the sex-specific variations in toxicity. The fundamental processes and therapeutic ramifications of this association, however, remain largely unknown. Future studies in this field may focus on elucidating the processes underlying the connection between sex hormones and heavy metals as well as creating therapies that can control hormone levels in order to prevent or lessen the toxicity of heavy metals.

3.4 HEAVY METALS AND CARDIOVASCULAR HEALTH

Exposure to heavy metals has been linked to a range of cardiovascular health outcomes, including hypertension, atherosclerosis, and heart failure (González-Muse *et al.* 2021). Heavy metal exposure is a global public health issue that affects millions of people worldwide. Cardiovascular diseases (CVDs) are the leading cause of death globally, accounting for an estimated 17.9 million deaths in 2019 (WHO 2021). There is mounting evidence to suggest that heavy metal exposure can lead to cardiovascular damage, which can ultimately lead to CVDs. However, recent research suggests that there may be sex differences in the impact of heavy metal exposure on cardiovascular health.

One of the most well-studied heavy metals in relation to CVDs is lead. Lead exposure has been linked to a range of cardiovascular outcomes, including hypertension, atherosclerosis, and coronary heart disease (Navas-Acien, 2007). Studies have found that men with higher levels of lead in their blood are more likely to develop hypertension than women with similar levels of lead exposure (Navas-Acien, 2004). This suggests that men may be more vulnerable to the cardiovascular effects of lead than women.

Cadmium is another heavy metal that has been linked to cardiovascular damage. Cadmium exposure has been associated with endothelial dysfunction, which is a key risk factor for CVDs (Liu *et al.,* 2018). One study found that men who were exposed to high levels of cadmium had an increased risk of developing CVDs while women with similar levels of cadmium exposure did not have an increased risk (Barregard *et al.* 201). This suggests that men may be more vulnerable to the cardiovascular effects of cadmium than women.

Mercury is another heavy metal that has been linked to cardiovascular damage. Mercury exposure has been associated with hypertension, atherosclerosis, and other cardiovascular outcomes. Sun *et al* (2019) found that men with higher levels of mercury in their blood had a greater risk of developing hypertension than women with similar levels of mercury exposure. This suggests that men may be more vulnerable to the cardiovascular effects of mercury than women.

The mechanisms underlying sex differences in the impact of heavy metal exposure on cardiovascular health are not yet fully understood. However, it is thought that sex hormones may play a role. Estrogen, for example, has been shown to have protective effects on the cardiovascular system. Some studies have suggested that estrogen may protect against the cardiovascular effects of heavy metal exposure. Testosterone, on the other hand, has been shown to have negative effects on the cardiovascular system. Some studies have suggested that testosterone may increase the vulnerability of men to the cardiovascular effects of heavy metal exposure (Smith *et al.,* 2021).

There is mounting evidence to suggest that there may be sex differences in the impact of heavy metal exposure on cardiovascular health. Men may be more vulnerable to the cardiovascular effects of lead, cadmium, and mercury than women. The mechanisms underlying these sex differences are not yet fully understood, but sex hormones are thought to play a role. Further research is needed to better understand the mechanisms underlying these sex differences and to develop effective strategies for reducing the cardiovascular impact of heavy metal exposure in both men and women.

3.5 HEAVY METALS AND CANCER

Heavy metal exposure has been linked to a number of cancers, including kidney, bladder and lung cancer. Furthermore, exposure to heavy metals has been linked to a number of unfavorable health effects, including cancer. According to certain research, a person's sex may have an impact on how exposure to heavy metals affects their chance of acquiring cancer.

Heavy metals have the potential to induce numerous types of cancer and have carcinogenic qualities. Mercury, lead, cadmium, and arsenic are a few of the frequent heavy metals related to cancer. These metals may progressively accumulate in the body, raising the risk of cancer.

Many of the research that have looked into the connection between heavy metal exposure and cancer risk have suggested that there are sex differences in this association. For instance, a Chinese study found that exposure to cadmium was associated with a greater risk of lung cancer in women but not in men (Lin *et al.,* 2008). According to a different study (Gallagher *et al.*, 2010), exposure

to lead raised the risk of developing breast cancer in women but not in men. It is still unclear how heavy metal intake affects cancer risk differently depending on a person's gender. But it's thought that sex hormones could be at play. As an illustration, research has shown that estrogen promotes the absorption of heavy metals in female tissues, which may raise the risk of cancer (D'Ilio and Falcioni, 2008). In contrast, testosterone has been demonstrated to protect against heavy metal toxicity, possibly lowering the incidence of cancer in men (Awadallah *et al.,* 2012).

The influence of heavy metal intake on cancer risk may vary depending on the sex, depending on a number of other factors than sex hormones. Men and women may have different cancer risks for various reasons, including different lifestyle choices like smoking and drinking (Jones *et al.,* 2022). Additionally, variations in occupational exposure to heavy metals can be important.

The evidence that is now available suggests that the effect of heavy metal exposure on cancer risk varies depending on the sex. Although, further investigation is required to fully understand the precise mechanisms underlying these variations, it is clear that exposure to heavy metals increases the risk of developing cancer. Therefore, it is essential for the public's health to put emphasis on initiatives to reduce exposure to these dangerous compounds.

4.0 ENVIRONMENTAL JUSTICE AND HEAVY METAL EXPOSURE

Inequitable distribution of environmental dangers and pollutants, such as heavy metals, that have a disproportionate negative impact on underserved communities is referred to as environmental injustice (Marco *et al.,* 2010). As a result, men and women may be more or less susceptible to the toxicity of heavy metals. Due to biological differences, exposure to heavy metals might have distinct effects on men and women. For instance, lead's neurotoxic effects, which can impair cognition and induce sadness and anxiety, are more likely to affect women. Additionally, heavy metal exposure has been related to reproductive issues like infertility and difficult pregnancies, which can have a more severe impact on women. This is due to the fact that heavy metals can build up in the reproductive system and interfere with hormonal signals, causing irregular menstrual cycles and issues with ovulation. On the other hand, because of variations in their toxin metabolism, men might be more vulnerable to cancer brought on by heavy metals (Al-Saleh and Shinwari, 2019). Environmental injustice can expose women to higher levels of heavy metals, making them more susceptible to their harm. Women are frequently engaged in fields including agriculture, battery manufacturing, and electronics manufacturing that have high exposure rates to heavy metals (Khan *et al.,* 2018). Women may also be more exposed to heavy metals as a result of their domestic responsibilities, such as using cookware that contains lead or residing close to

sources of heavy metal pollution (Khna *et al.,* 2008). As heavy metals can pass through the placenta or breast milk to the fetus or newborn, pregnant and breastfeeding women are also more likely to be exposed to heavy metals.

As a result of environmental injustice, social and economic variables may make the negative health effects of heavy metal exposure on women worse. Access to protective gear, healthcare, and reproductive services may be restricted for women who work in industries that are heavily polluted by heavy metals. Mohai *et al* (2009) opined that oppressed women who already struggle because of their color, immigrant status, or poverty may suffer from additional disadvantages as a result of environmental injustice because they may reside in locations with higher pollution levels and have fewer resources to safeguard their family.

To conclude, women are more vulnerable to heavy metal toxicity due to environmental injustice, which exposes them to heavy metals and worsens the health impacts of exposure. It is vital to address environmental injustice to safeguard public health and ensure equitable access to a safe environment. Strategies may include enhancing workplace regulations, offering better protective equipment and healthcare for workers, reducing pollution in communities, and tackling social and economic disparities that contribute to environmental injustice. These efforts can mitigate the negative health outcomes of heavy metal exposure in women and promote a more fair and just society.

4.1 HEAVY METAL EXPOSURE IN THE WORKPLACE

Numerous studies have been conducted on the effects of heavy metal exposure on employees, with an emphasis on those who work in industrial environments. For instance, a study by Li *et al* (2020) examined the levels of heavy metal exposure among staff members working in a battery production facility and was published in the Journal of Occupational Health. According to the study, workers had much higher blood levels of lead, cadmium, and zinc than a control group. The study also emphasized a number of variables that could raise the risk of exposure to heavy metals, including the type of work done, the duration of employment, and the use of personal protective equipment.

The risk of heavy metal exposure among welders in the construction industry was evaluated in a study published in the Journal of Environmental Health Science and Engineering. Researchers found that compared to a control group, welders had significantly higher blood levels of chromium,

nickel, and cadmium (Zarei *et al*., 2017). The study also found a number of risk factors related to heavy metal exposure in the welding sector, including the kind of welding, employment duration and use of protective equipment.

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An investigation of the impact of workplace interventions on heavy metal exposure in workers at a battery manufacturing factory was published in the Journal of Occupational and Environmental Medicine. A study by Xiao *et al* (2019) showed that the levels of lead and cadmium in the employees' blood were significantly lowered by a complete intervention program that included improved ventilation, routine air quality monitoring and the use of personal protective equipment.

The scientific literature is becoming more and more interested in figuring out how gender affects exposure to heavy metals at work. Although, exposure to heavy metals can affect both male and female employees, the effects of this exposure differ for each gender.

The relationship between sex and exposure to heavy metals in professional contexts has been investigated in a number of research. For instance, a study examined the blood levels of heavy metals in male and female workers at a battery manufacturing facility and was published in the Journal of Occupational and Environmental Medicine. Despite similar exposure, the study found that male workers' blood levels of lead and cadmium were greater than those of female workers. The study suggests that the varied effects of heavy metal exposure on men and women may be due to sex-specific factors, such as hormonal differences.

An investigation into the effects of sex on the neurobehavioral effects of lead exposure on workers in a battery manufacturing factory was published in the Journal of Occupational Health. Even at lower exposure levels, the study found that female workers were more susceptible to the neurobehavioral consequences of lead exposure than male workers. According to the study, sex-specific characteristics including variations in lead metabolism may increase the vulnerability of female employees to the neurobehavioral effects of lead exposure. Several characteristics that are particular to each sex and may contribute to the various consequences of heavy metal exposure

were found by a literature study that was published in the Journal of Toxicology and Environmental Health. These variables include variations in hormones, body composition, and the metabolization and excretion of heavy metals.

The effect of sex on the association between cadmium exposure and kidney function was investigated in a study published in the Journal of Occupational and Environmental Medicine. Even at low exposure levels to cadmium, female workers exhibited a larger decrease in kidney function than male workers, according to the study. This suggests that the way cadmium affects kidney function may depend on sex-specific variables.

The connection between sex, workplace exposure to heavy metals and oxidative stress was examined in a study published in the Journal of Environmental Health Sciences and Engineering. According to the study, after being exposed to heavy metals, male workers had higher levels of oxidative stress than female workers. According to the study, there may be disparities in how employees react to the oxidative stress brought on by exposure to heavy metals.

In conclusion, the research shows how important it is to consider sex-specific characteristics when assessing workplace exposure to heavy metals. Although, both male and female workers are exposed to heavy metals, there may be disparities in the health impacts of exposure depending on how each biological system of any sex processes these metals and reacts to exposure. Additional research in this area may clarify the sex-specific elements contributing to the negative effects of heavy metal exposure on health and contribute to the creation of strategies to protect workers' health.

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