Journal of Health and Technology
Volume 1, Issue 3, September 2025; pp: 132-136
eISSN: 2455-2852 DOI: 10.65129/health.v1i3.95

RESEARCH ARTICLE

Association of Blood Heavy Metal Levels with Iron Deficiency

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Abstract

Background: Anaemia is a common health issue in India, more so among women. Along with diet and lifestyle, exposure to heavy metals like cadmium, lead, and mercury has also been implicated. However, their link with haemoglobin and iron levels is not well understood. This study aimed to address this lacuna by secondary analysis of the National Health and Nutrition Examination Survey (NHANES) survey data done in the United States (US). **Methods:** The publicly available NHANES database was accessed, and 6296 adult participants (2858 men and 3438 women) for whom basic demographic details and results of blood investigations for heavy metals, iron-related parameters, and other routine investigations were available were included. Anaemic and non-anaemic groups were compared using an independent t-test. Linear regression was used to examine how blood heavy metal levels were associated with haemoglobin, ferritin, and transferrin receptor levels, after adjusting for gender and other potential confounders. **Results:** Anaemia was found in 7.7% of men and 12% of women. The average haemoglobin was 13.9 g/dL, and the mean ferritin was 65 ng/mL. Among the heavy metals, the mean levels of lead, cadmium, and mercury were 0.87 µg/dL, 0.35 µg/L, and 1.00 µg/L, respectively. Surprisingly, mercury levels (both total mercury and methyl mercury) were higher in those without anaemia compared to those with anaemia. Cadmium showed a weak negative correlation with ferritin ($\beta = -0.07$, $p=0.018$), suggesting that cadmium may be associated with lower iron stores. **Conclusion:** In this secondary analysis of data from the US, mercury levels were found to be higher in non-anaemics compared to anaemics, and cadmium was associated with reduced iron stores.

Keywords: Anaemia, Cadmium, Environmental Exposure, Ferritin, Heavy Metals, Iron Deficiency, Lead, Mercury, Transferrin Receptor

1. Introduction

Anaemia continues to be a major public health concern in India, particularly among women and adolescent girls. Anaemia not only affects productivity but also contributes to maternal morbidity, adverse pregnancy outcomes, and impaired cognitive and physical performance[1] Data from the National Family Health Survey (NFHS-5, 2019–21) showed that the prevalence of anaemia among women aged 15–19 years rose to 59%, compared to 54% in NFHS-4 (2015–16), indicating a worsening trend despite national programmes to address the problem[2,3].

While dietary iron deficiency remains the most common cause of anaemia[4], there is increasing evidence that environmental exposure to heavy metals such as cadmium, lead, and mercury may also influence erythropoiesis and iron metabolism, thus increasing the risk of anaemia. Sources of these heavy metals include industrial emissions, water and soil contaminated with pesticides, and some traditional medicines[5]. However, evidence linking heavy metals

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Article Received on: 01 June 2025 Revised on: 5 Aug 2025 Accepted on: 5 Sept 2025

to anaemia in Indian populations is limited. There are no large epidemiological studies available to answer such questions. In view of this limitation, this research utilised the publicly available NHANES survey data from the US to study possible associations of heavy metal exposure with anaemia and iron deficiency.

2. Review of Literature

Anaemia is a major public health concern all over the world due to its high prevalence and adverse consequences on health. It is caused by multiple factors, including nutritional deficiency of iron, vitamin B12, and folic acid. In addition, chronic inflammation, bleeding disorders, parasite infestations (e.g., hookworm), and hemoglobinopathies contribute significantly to the burden of anaemia in India and other low and middle-income countries[6].

As developing countries like India continue to industrialise, exposure to heavy metals from the environment increases[7]. Heavy metals such as lead, mercury, and cadmium are known toxins and pollutants that can result in adverse health consequences. For example, exposure to heavy metals can result in anaemia by multiple mechanisms[8]. Cadmium interferes with red blood cell formation by promoting oxidative stress and impairing erythropoietin regulation[9]. Cadmium is also suspected to cause iron deficiency by inhibiting intestinal absorption of iron[10]. Mercury disrupts haemoglobin synthesis and causes bone marrow toxicity[11], possibly by disrupting sulfhydryl groups in enzymes and oxidative stress[12,13]. Lead toxicity is a known cause of anaemia, especially in children, by inhibiting ALA dehydratase and ferrochelatase, both of which are enzymes involved in heme synthesis[14].

Although these relationships are biologically plausible, the strength and direction of association vary across populations depending on exposure levels, nutritional background, and co-existing health conditions. There are no studies based on large-scale population-level data to answer the questions on the association of heavy metal exposure with anaemia and iron deficiency.

3. Objectives

The present study was carried out with the following objectives:

1. To compare the blood levels of heavy metals (lead, cadmium, and mercury) between anaemic and non-anaemic individuals.
2. To examine the association of heavy metals (lead, cadmium, and mercury) with haemoglobin and iron markers.

4. Methods

4.1 Study Design and Setting

This is a cohort study based on data collected from a large community-based NHANES from August 2021 to August 2023. The NHANES contains a series of nationally representative cross-sectional surveys conducted by the US Centres for Disease Control and Prevention (CDC). This survey collects data about the health of adults and children in the United States. It conducts interviews about the dietary intake of the participants. These dietary interviews and blood tests help us measure the nutritional status of adults and children in the US. The data is publicly available on the CDC's official website.

4.2 Study Population

For the present study, we chose NHANES participants aged 18 years or more (n = 6296) who could provide complete data on heavy metals, haemoglobin, serum ferritin, and high-sensitivity C-reactive protein (hsCRP).

4.3 Definition of Anaemia

Anaemia was defined based on the WHO cut-offs[15] as given below.

- Hemoglobin <13.0 g/dL for men
- Hemoglobin <12.0 g/dL for non-pregnant women

4.4 Statistical Analysis

Data was analysed using SPSS version 21.0 software.

Descriptive statistics were applied to summarise baseline variables and heavy metal levels.

- Independent samples t-tests were used to compare heavy metal concentrations between anaemic and non-anaemic groups.
- Linear regression models were applied to assess the relationship between lead, cadmium, mercury (total,

inorganic, ethyl, and methyl), and haematological markers (haemoglobin, ferritin, transferrin receptor).
- Categorical variables, including gender, were presented as frequencies and percentages.
- A p-value < 0.05 was considered statistically significant.

5. Results

The present analysis provides a detailed account of the baseline clinical features, heavy metal exposure levels, and their association with anaemia and iron-related parameters in the study cohort.

5.1 Baseline Characteristics

The basic demographic and biochemical indicators of the study population are shown in Table 1. A total of 6,296 participants were enrolled, with 2,858 males and 3,438 females. The mean age at screening was 52.5 years (SD 18). Mean haemoglobin concentration was 13.9 g/dL (SD 1.5), while the average ferritin level was 65 ng/mL (SD 72). The data also include transferrin receptor, red blood cell folate, C-reactive protein, and red cell indices.

5.2 Heavy Metal Levels in Blood

The levels of various heavy metals in blood are presented in Table 2. These findings provide the background exposure profile of the population.

5.3 Heavy Metal Levels and Anaemia Status

Independent-samples t-tests were performed to compare heavy metal concentrations between anaemic and non-anaemic participants. As shown in Table 3, blood heavy metal concentrations were not different between the two groups except for higher methyl and total mercury levels in non-anaemic participants.

5.4 Regression Analysis

The regression models (Table 4) were applied to assess the association of cadmium and other metals with haemoglobin and iron markers. Cadmium showed a statistically significant positive association with haemoglobin; however, the effect size was small. At the same time, cadmium was negatively associated with ferritin and positively associated with transferrin receptor, consistent with iron deficiency. Total mercury

Table 1. Baseline characteristics of the study population

Variable	N	n(%)/Mean (SD)
Gender	6,296	
Male		2,858 (45%)
Age in years at screening	6,296	52.47 (18.25)
Haemoglobin (g/dL)	5,967	13.90 (1.48)
Red Blood Cell Count (million cells/µL)	5,967	4.66 (0.49)
Mean Cell Volume (fL)	5,967	88.65 (5.73)
Mean Cell Haemoglobin Concentration (g/dL)	5,967	33.72 (0.91)
Mean Cell Haemoglobin (pg)	5,967	29.91 (2.31)
Red Cell Distribution Width (%)	5,967	13.86 (1.36)
Ferritin(ng/mL)	1,301	65.01 (71.85)
Transferrin Receptor (mg/L)	1,301	3.55 (2.13)
RBC Folate (ng/mL)	5,918	533.22 (249.56)
HS C-Reactive Protein (mg/L)	5,785	3.82 (7.33)
Anaemia	6,296	636 (10%)

Table 2. Heavy metal levels in blood (overall population)

Variable	N	n(%)/Mean (SD)
Blood Lead (µg/dL)	5,969	0.97 (1.13)
Blood Cadmium (µg/L)	5,969	0.42 (0.51)
Blood Mercury, total (µg/L)	5,969	1.16 (1.96)
Mercury, Inorganic (µg/L)	5,966	0.19 (0.32)
Mercury, Ethyl (µg/L)	5,966	0.05 (0.00)
Mercury, Methyl (µg/L)	5,966	1.03 (1.71)

Table 3. Comparison of heavy metal levels between anaemic and non-anaemic participants

Variable	Non-anemic N = 5,660[1]	Anemic N = 636[1]	p-value[2]
Blood Lead (µg/dL)	0.96 (0.94)	1.08 (2.15)	0.2
Blood Cadmium (µg/L)	0.41 (0.52)	0.42 (0.40)	0.7
Blood Mercury, Total (µg/L)	1.20 (2.03)	0.81 (1.12)	<0.001
Mercury, Inorganic (µg/L)	0.19 (0.34)	0.18 (0.11)	0.14
Mercury, Ethyl (µg/L)	0.05 (0.00)	0.05 (0.00)	0.8
Mercury, Methyl (µg/L)	1.07 (1.77)	0.71 (1.01)	<0.001

[1] Mean (SD)
[2] Two-sample t-test

Table 4. Linear regression analysis for heavy metals and iron parameters

Heavy Metal	Hemoglobin			Ferritin			Transferrin Receptor		
	β	P-value[2]	Model R^2	β	P-value	Model R^2	β	P-value	Model R^2
Lead	-0.001	0.902	0.259	-0.021	0.33	0.026	-0.001	0.98	0.000
Cadmium	0.092	<0.001	0.268	-0.07	0.018	0.029	0.089	<0.01	0.007
Total Mercury	0.037	<0.001	0.261	0.026	0.513	0.026	-0.033	0.413	0.001
Inorganic Mercury	-0.007	0.545	0.260	0.043	0.368	0.026	-0.001	0.991	0.000
Ethyl Mercury	-0.002	0.833	0.260	Data not available					
Methyl Mercury	0.042	<0.001	0.262	0.025	0.528	0.026	-0.041	0.302	0.001

[1] Standardised beta coefficients represent the change in outcome (in standard deviations) per 1 standard deviation increase in heavy metal exposure.
[2] All models adjusted for age and gender. P-values <0.05 indicate statistical significance.

and methyl mercury were positively associated with haemoglobin.

6. Discussion

This study was done as a secondary data analysis of the NHANES survey conducted by the CDC in the United States, and it adds to the various studies on the role of heavy metals in anaemia. A large dataset of 6,296 individuals was analysed and used to compare heavy metal levels between anaemic and non-anaemic groups, while also modelling the relationship of heavy metals with iron status and haemoglobin.

A key finding was that cadmium showed a negative association with ferritin but a positive association with haemoglobin. Cadmium competes with iron for transporters in the gut and interferes with storage proteins, leading to lower ferritin[16]. The small positive correlation with haemoglobin in our study suggests that cadmium may not directly reduce haemoglobin concentrations.

Previous reports indicate that women with low iron stores are more likely to have higher cadmium levels due to increased gastrointestinal absorption[17]. Environmental exposures may therefore worsen the iron status or blunt the response to dietary interventions. For example, women exposed to cadmium may continue to have low iron stores despite compliance with iron tablets, as cadmium interferes with iron absorption[18].

Lead, though considered a strong contributor to anaemia through inhibition of δ-aminolevulinic acid dehydratase and ferrochelatase[19], did not emerge as a dominant factor in this dataset, possibly due to minimal exposure to lead in the US population, as shown in Table 2.

Interestingly, blood methyl mercury levels were higher in non-anaemics and were associated with higher haemoglobin and ferritin levels. Methyl mercury is commonly acquired from seafood due to bioaccumulation in the marine food pyramid. At the same time, a fish-based diet is often an iron-rich diet as well. Therefore, it is possible that those who consume seafood have higher iron stores and higher blood levels of methyl mercury. This may be an explanation for the association seen between mercury and haemoglobin.

6.1 Limitations

* This is a secondary analysis of data from the US. It may have limited applicability to India. Nevertheless, it highlights the relevance of heavy metals to anaemia.
* This was a cohort study, and therefore, the nature of the association between heavy metals and haemoglobin is not clear.

6.2 Strength

The large sample size, standardised assays, and inclusion of multiple metals provide important insights.

7. Conclusion

In summary, the study showed that cadmium correlates with depleted iron stores. Lead levels were less influential in this dataset. Mercury tended to be associated with higher haemoglobin levels. These findings highlight the need for studies on environmental exposures to heavy metals in the Indian population.

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