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Article

Association between Blood Lead Levels and Silent Myocardial Infarction in the General Population

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Abstract: Background*:* Although the link between environmental lead exposure and several patterns of cardiovascular disease (CVD) has been reported, its association with silent myocardial infarction (SMI) has not been explored. We aimed to assess the association between blood lead levels (BLL) and risk of SMI. **Methods:** This analysis included 7283 (mean age 56.1±2.52 years, 52.5% women) participants from the Third National Health and Nutrition Examination Survey who were free of clinical CVD. Ascertainment of BLL done using graphite furnace atomic absorption spectrophotometry. SMI defined as ECG evidence of MI without history of MI. Multivariable logistic regression analysis was used to examine the association between SMI and BLL. **Results:** SMI was detected in 120 participants corresponding to an unweighted prevalence of 1.65%. Participants with higher levels of BLL had higher prevalence of SMI (0.4%, 0.9%, and 2.4% across BLL tertiles; p-value <0.001). In a multivariable-adjusted model, participants with BLL levels in the 3rd tertile had more than double the odds of SMI ((OR (95% CI: 3.42 (1.76,6.63)) compared to those with BBL levels in the first tertile. Each 1 µg/dL increase in BLL was associated with a 9% higher risk of SMI ((OR (95%CI: 1.09 (1.05,1.14)). This association was consistent across subgroups stratified by age, sex, and race. **Conclusions:** higher levels of BLL are associated with higher odds of SMI in the general population. Our results emphasize the importance of continued efforts to reduce lead exposure and the importance of screening plans for SMI in high-risk populations.

Keywords: silent myocardial infarction; lead exposure; cardiovascular disease; NHANES-III; Silent myocardial infarction; lead exposure; cardiovascular disease; NHANES-III

1. Introduction

The Lead exposure is estimated to account for nearly 1 million deaths globally in 2019, with 850,000 deaths attributed to its cardiovascular effects [1]. Long-term lead exposure contributes to 4.6% of the global burden of CVD, including coronary heart disease (CHD) and high blood pressure [2,3].Although blood lead levels (BLL) have been decreasing in the past decade, almost half of the US population is at risk of adverse health outcomes caused by high lead levels in their early childhood [4,5].

Human exposure to lead nowadays occurs mainly through food, water, tobacco smoke, and e-cigarettes, either by inhalation, ingestion, and skin contact [6,7]. According to the US Centers for Disease Control and Prevention (CDC), no lead exposure level is safe for adults as adverse health outcomes expected at all exposure concentrations with as low as 2 µg/dL considered a cardiovascular hazard [8,9].

Silent myocardial infarction (SMI) imposes a significant health burden due to its absence of symptoms and the lack of established screening protocols. While prior research has established the adverse effects of lead exposure on cardiovascular health and mortality, the potential link between

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lead exposure and SMI remains unexplored [10,11]. It is believed that the atherogenic effects of lead exposure are attributed to the generation of excessive free radicals, causing oxidative stress and endothelial injury that impairs endothelial growth and repair processes [12,13]. Considering the non-specific symptoms of SMI and the global public health impact of lead exposure, it is crucial to identify effective measures for early detection, screening, and strategies to mitigate the overall burden of lead exposure. This study aims to investigate the possible association between blood lead levels and SMI in the general population, emphasizing the public health implications of this relationship.

2. Materials and Methods

2.1. Study Population:

This study was conducted using data from the Third National Health and Nutrition Examination (NHANES-III) survey 1988-1994. NHANES-III is one of a series of health surveys designed to assess the health and nutritional status of the non-institutionalized United States population. Participants completed a household interview, laboratory measurements, and physical examinations. Details of the survey design, protocol, response rates, and specific data collection methods have been published previously [14]. NHANES III was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB), and written informed consent was obtained from all participants.

For this analysis, we only considered NHANES-III participants who underwent ECG recording (n = 8,561). We excluded participants with missing key covariates or with ECG conditions that prohibit appropriate detection of MI by the Minnesota ECG Classification.[15] This includes the presence of a complete left bundle branch block, pre-excitation, or ventricular pacemaker. We also excluded those with a history of cardiovascular disease, including a history of MI. After all exclusions (n = 1,278) 7,283 participants remained and were included in the analysis.

2.2. Assessment of Covariates:

Age, sex, race/ethnicity, income levels, and smoking status were self-reported during an in-home interview. Hypertension was defined as systolic blood pressure (BP) ≥130 mmHg or diastolic BP ≥85 mmHg or the use of antihypertensive medications. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2. Diabetes was defined as a fasting plasma glucose ≥ 126 mg/dl, hemoglobin A1c values ≥ 6.5%, or previous use of diabetes-related medications. Hyperlipidemia was defined as total cholesterol ≥200 mg/dl or triglycerides ≥150 mg/dl or the use of anti-hyperlipidemic agents.

2.3. Ascertainment of SMI:

Resting digital 12-lead ECG was obtained using a Marquette MAC 12 electrocardiograph (Marquette Medical Systems, Milwaukee, Wisconsin) during a physical examination conducted in a mobile examination unit. After visual inspection of the ECGs by trained technicians, automated processing of the tracings was conducted at the Epidemiological Cardiology Research Center (EPICARE Center, Wake Forest School of Medicine, Winston-Salem, NC). ECG abnormalities, including MI, were classified using the Minnesota ECG Classification [15]. SMI was defined as the presence of ECG evidence of MI using the standards of the Minnesota ECG Classification in the absence of a prior history of myocardial infarction.

2.4. Lead Exposure Ascertainment:

During the physical examination, whole-blood specimens were collected by venipuncture for all survey participants ≥1 year of age in NHANES III.[14] Blood specimens are analyzed for lead concentration by the Division of Laboratory Sciences at the National Center for Environmental Health of the Centers for Disease Control and Prevention (CDC). Quantification of blood lead levels (BLL) was done using graphite furnace atomic absorption spectrophotometry. The limit of detection for blood lead levels in NHANES III is 0.07 μg/dL with results below the detection limit reported as a value equal to the detection limit divided by the square root of 2 [16].

 doi:10.20944/preprints202402.1195.v1

2.5. Statistical Analysis:

Demographics and clinical characteristics of the participants were compared across tertiles of BLL using Analysis of variance (ANOVA) for continuous variables and Chi-square for categorical variables. Odds ratios (OR) and 95% confidence intervals (CI) for the risk of SMI were estimated using logistic regression models across tertiles of BLL, with the first tertile as a reference group. Two multivariable-adjusted models were constructed: Model 1 adjusted for age, sex, race, and income levels, and Model 2 adjusted for model 1 plus systolic blood pressure, obesity, diabetes, smoking, total cholesterol, antihypertensive medications, and lipid-lowering medications. Similar models were utilized to examine the odds of SMI associated with each 1 µg/dl increase in BLL. We also examined the effect modification of the association between tertiles and SMI by age (< 65 vs.>65 years), sex (men vs. women), and race (white vs. non-white). Interaction with the main effect was tested in a model adjusted similarly to Model 2.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina), incorporating a complex sampling design (primary sampling units, sampling strata, and weights), and two-sided p -values were considered significant if less than 0.05.

3. Results

After all exclusions (n= 1,278), 7,283 participants (mean age 56.1±2.52 years, 52.5% women, 81% Whites) remained and were included in the analysis. BLL ranged from 0.70 µg/dL to 16.4 µg/dL as follows: 1st tertile (0.70-2.60 µg/dL), 2nd tertile (2.70-4.60 µg/dL), 3rd tertile (4.70-16.4 µg/dL). In our sample, 120 participants had SMI (unweighted percentage = 1.65%). Participants with higher levels of BLL tertiles had a higher prevalence of SMI (p<.001). As shown in (Table 1), participants with higher BLL were more likely to be older, currently smoking, men, with income level <20K annually, and with higher blood pressure levels. In a multivariable logistic regression model adjusted for socio-demographics (age, sex, race, income level) and common CVD risk factors (high blood pressure, obesity, diabetes, smoking, total cholesterol, antihypertensive medications, and lipid-lowering medications), participants with BLL levels in the 3rd tertile had more than double the odds of SMI compared to those with BBL levels in the first tertile ((OR (95% CI): 3.42 (1.76 - 6.63)). Each 1µg/dl increase in BLL was associated with 9% higher odds of SMI ((OR (95% CI): 1.09 (1.05-1.14)) (Table 2). The association between BLL tertile and SMI was consistent among participants stratified by sex (men vs. women), race (white vs. non-white), age (<65 years vs. ≥ 65 years) (Table 3).

Table 1. Baseline Characteristics of the Study Participants.

Characteristics *	**Blood Lead Levels Tertiles**			
	1st Tertile n= 2369	**2nd Tertile** n= 2451	**3rd Tertile** n= 2463	*p-value*†*
Age (years)	53.3±0.45	56.8± 0.45	58.4± 0.52	<.0001
Men	638 (30.4%)	1166 (47.0%)	1641 (64.4%)	<.0001
Whites	1293 (84.0%)	1267 (81.7%)	1070 (77.7%)	<.0001
Income level <20K	900 (23.6%)	1053 (26.9%)	1308 (38.2%)	<.0001
Systolic Blood Pressure (mmHg)	124.8±0.61	128.9±0.66	131.6±0.67	<.0001
Diastolic Blood Pressure (mm Hg)	75.2±0.28	76.7±0.38	77.1±0.36	<.0001
Antihypertensive Medications	475 (15.8%)	551 (20.1%)	513 (17.3%)	0.01

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Diabetes	315 (8.3%)	300 (8.1%)	277 (8.4%)	0.94
Current smoker	278 (12.7%)	513 (23.0%)	855 (36.1%)	<.0001
Obesity	769 (28.3%)	708 (24.6%)	558 (22.5%)	0.009
Total cholesterol	212.5±1.3	219.9±1.4	219.2±1.3	0.01
Lipid-lowering medications	74 (3.4%)	75(3.3%)	59(3.4%)	0.99
Silent MI	20 (0.4%)	32(0.9%)	68 (2.4%)	<.0001
Continuous variables are presented as mean (standard error) and categorical variables as count (percentage). All percentages and means ±SE are weighted for complex survey design to be nationally representative estimates !p-value by t-test for continuous variable or chi-square for categorical variables				

Table 2. Association of Blood Lead Levels with Silent Myocardial Infarction.

Blood Lead levels	**Events/Participants n (%)**	**Model 1 OR (95% CI)**	**p-value**	**Model 2 OR (95% CI)**	**p-value**
1st Tertile (0.70-2.60 µg/dL)	*20/2369 (0.4%)*	*Ref*	-	*Ref*	-
2nd Tertile (2.70-4.60 µg/dL)	32/2451 (0.9%)	1.51 (0.69 , 3.34)	0.43	1.44 (0.64 , 3.25)	0.42
3rd Tertile (4.70-16.4 µg/dL)	68/2463 (2.4%)	3.73 (1.95 , 7.11)	<.0001	3.42 (1.76 , 6.63)	<.0001
Per 1 µg/dl	120/7283 (1.2%)	1.10 (1.06 , 1.15)	<.0001	1.09 (1.05 , 1.14)	<.0001
OR (95% CI) = Odds ratio (95% Confidence Interval) Model 1 adjusted for age, sex, race, income levels Model 2 adjusted for model 1 plus systolic blood pressure, obesity, diabetes, smoking, total cholesterol, antihypertensive medications, and lipid-lowering medications					

Table 3. Subgroup Analysis for the Association between Tertiles of Blood Lead Levels and Silent Myocardial Infarction.

Subgroups	**BLL Tertiles***	**Silent MI n (%)**	**OR (95% CI) †**	***Interaction p-value***
Men	2nd Tertile	15 (1.2%)	2.83 (0.52 , 15.1)	
	3rd Tertile	49 (2.9%)	7.68 (1.83 , 32.1)	

 doi:10.20944/preprints202402.1195.v1

Women	2nd Tertile	17 (1.3%)	1.05 (0.43 , 2.54)	0.50
	3rd Tertile	19 (2.3%)	2.25 (0.96 , 5.29)	
Whites	2nd Tertile	17 (1.3%)	1.37 (0.55 , 3.38)	0.40
	3rd Tertile	35 (3.2%)	3.78 (1.83 , 7.83)	
Non-Whites	2nd Tertile	15 (1.2%)	1.91 (0.43 , 8.54)	
	3rd Tertile	33 (2.3%)	1.74 (0.51 , 5.90)	
< 65 years	2nd Tertile	13 (0.8%)	1.29 (0.44 , 3.77)	0.75
	3rd Tertile	21 (1.3%)	2.39 (0.90 , 6.36)	
≥ 65 years	2nd Tertile	19 (2.2%)	1.86 (0.65 , 5.33)	
	3rd Tertile	47 (5.1%)	5.83 (2.12 , 15.9)	

* Reference group is BLL first tertiles

†Model adjusted for age, sex, race, income levels, systolic blood pressure, obesity, diabetes, smoking, total cholesterol, antihypertensive medications, and lipid-lowering medications.

4. Discussion

In the United States, around 170 million had BLL above 5 μg/dL during their early life, with lacking evidence of its associated adverse health consequences [1,5]. In this analysis from a large community-based population, we showed that higher levels of BLL are associated with a higher prevalence of SMI. The likelihood of SMI tripled as BLL tertiles increased. This study adds to the growing body of evidence that lead exposure is a risk factor for cardiovascular disease [10,11]. Populations with elevated BLLs may be at increased risk for SMI and more efforts should be directed towards proper screening and preventive interventions.

The prevalence of lead exposure peaked in the late 1970s, particularly among children aged 1-5 years with BLLs greater than or equal to 10 μg/dL [17]. While there has been a steady decline in BLLs over the past decades, socioeconomic status and racial inequalities still continue to influence population exposure to environmental hazards, albeit to a lesser extent compared to the late 1970s [18,19]. At that time, African Americans had higher national BLLs compared to whites, with a mean blood lead level of 23 μg/dL in low-income black children [20]. Moreover, certain occupations such as mining, construction, and manufacturing, particularly battery manufacturing, involve significant exposure to environmental hazards including lead [6]. Despite this progress, the long-term health consequences of lead exposure are still being investigated, and it is imperative to continue efforts to reduce exposure and minimize its adverse effects.

The asymptomatic nature of SMI and the absence of formal screening protocols contribute significantly to its health burden. Prevalence rates of SMI are influenced by age groups and socioeconomic status, and it is frequently associated with comorbidities such as hypertension, diabetes, and previous coronary heart disease (CHD) [21,22].In the general population, SMI has been linked to an increased risk of sudden cardiac death and heart failure [23,24].

Our study revealed that individuals in the highest tertile of BLL tended to be older men with a higher incidence of SMI. This, in conjunction with the gradual onset of CHD and the typical age group affected, might contribute to the association between elevated BLLs and the incidence of ischemic events in older participants. Furthermore, individuals in this age group may have experienced higher lead exposure during their early childhood.[5] Furthermore, lead can remain in the human bones for up to 30 years, potentially serving as a source of continuously circulating lead long after cessation of external exposure emphasizing the cumulative and long-term effects of lead exposure on CVD [25].

Prior research has demonstrated a significant association between lead exposure and CVD, with unfavorable outcomes in cases of myocardial infarction (MI). For instance, Afridi et al. conducted a study wherein they observed elevated levels of lead in hair samples collected from MI patients in comparison to control subjects. Importantly, the lead levels displayed a progressive increase

 doi:10.20944/preprints202402.1195.v1

corresponding to the severity of the disease, with the highest concentrations identified in individuals experiencing their third episode of MI [26]. Additionally, a systematic review of more than 300,000 participants revealed an 85% increased risk for the development of coronary heart disease (CHD) among individuals in the high tertile of lead exposure, underscoring lead's significance as a potential risk factor for CHD [27].

The perception of anginal pain during myocardial ischemia involves intricate interactions between the myocardium and the nervous system [28]. Autonomic neuropathy, variations in pain thresholds, and altered neural processing in the peripheral and central nervous systems contribute to the pathophysiology of asymptomatic myocardial ischemia [29–31]. The adverse effects of lead exposure on both the cardiovascular and nervous systems could possibly explain these findings. First, lead exposure induces oxidative stress and chronic inflammation, leading to endothelial dysfunction and accelerated atherosclerosis [13,32]. Second, it promotes the development of atherosclerosis and plaques, as demonstrated in animal models exposed to low-level lead [33]. Furthermore, lead impairs the release of tissue plasminogen activator (t-PA) and increases plasminogen activator inhibitor-1 release, which can lead to coagulation abnormalities and a heightened risk of thrombosis, especially in the presence of endothelial injury [34]. Moreover, lead exposure-related neurological dysfunctions, such as peripheral neuropathy and cortical dysfunction, can alter the perception of anginal pain in affected individuals [35,36]. Another important consideration regarding SMI and lead exposure is the influence of socioeconomic status and education levels [37]. Populations with socioeconomic disadvantage tend to have higher levels of toxic metals exposure including lead, and lead exposure has been associated with cognitive decline and cortical dysfunction [38]. Adverse cognitive effects of lead exposure further impact the health literacy in this population and thus poor comprehension of symptoms related to myocardial infarction [49].

Given the combined impact of lead exposure and the significant health and economic burden associated with SMI, effective screening and preventive measures are imperative for this high-risk population. Our findings highlight the importance of recognizing low-level environmental lead exposure as a crucial cardiovascular risk factor. Incorporating lead exposure into risk stratification strategies can aid in identifying high-risk groups and promoting targeted screening for CHD.

Our results should be read in the context of certain limitations. Like other observational cross-sectional studies, we cannot conclude causality or ascertain temporality. Also, despite adjusting for several factors, residual confounding remains a possibility. Finally, several covariates were assessed by self-report, which is liable for recall bias. Key strengths include the large sample size and standardized ascertainment of variables. In conclusion, we demonstrated that higher BLL was linked to higher odds of developing SMI. Promoting screening plans for SMI in populations with high lead exposure and advocating for decreased BLL could have a significant favorable impact on CVD prevention.

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Data Availability Statement: Data used in this study is publicly available at: https://wwwn.cdc.gov/nchs/nhanes/nhanes3/datafiles.aspx

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