Original Article

Serum levels of lead are associated with venous thromboembolism: a retrospective study based on the NHANES database (1999 to 2018)

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Background: Venous thromboembolism (VTE) is a common clinical problem. While lead toxicity is known to affect the nervous, hematopoietic system, skeletal, and cardiovascular system, the relationship between blood lead levels and VTE remains unclear. This study explored whether there is a correlation between the levels of serum lead and VTE through a retrospective analysis based on data from the National Health and Nutrition Examination Survey (NHANES), so as to provide a reference for follow-up research and clinical practice.

Methods: According to the inclusion and exclusion criteria, subjects were enrolled from the NHANES (1999 to 2018) database and divided into a VTE group and a non-VTE group. The factors related to VTE were analyzed by single factor and multiple factor logistic regression analysis.

Results: A total of 31,081 subjects were included, of which 59 had VTE (0.19%). The higher the levels of serum lead, the higher the incidence of VTE. The univariate analysis revealed that age, male sex, history of cigarette use, hypertension, diabetes, and serum lead levels were factors associated with VTE in the population from the NHANES database. Further multivariate analysis revealed that age, history of cigarette use, hypertension, diabetes, and serum lead levels were factors associated with VTE.

Conclusions: The findings of this study suggest that higher serum levels of lead may be associated with VTE.

Keywords: Serum level; lead; predictor; venous thromboembolism (VTE); retrospective study

Submitted Jul 10, 2023. Accepted for publication Aug 10, 2023. Published online Aug 28, 2023.
doi: 10.21037/jtd-23-1071
View this article at: https://dx.doi.org/10.21037/jtd-23-1071

Introduction

Venous thromboembolism (VTE) is a common clinical problem. In clinical practice, VTE mainly refers to deep vein thrombosis (DVT) and pulmonary embolism (PE). Some studies have shown that after major orthopedic surgery, the incidence of DVT in European and American patients is 2.22–3.29%, and the incidence of PE is 0.87–1.99% (1,2). The incidence of DVT and PE in Asian patients is 1.40% and 1.10%, respectively (3). In the general population, the annual incidence of acute VTE is about 1–2 cases per 1,000 people, and increases with age (4-6). The main hazard of DVT is its ability to cause pulmonary embolism, or even sudden death (7,8). Therefore, VTE is very important in clinical practice. Recent research has mainly focused on three aspects. First, the risk factors of VTE have been screened through clinical research to provide reference indicators for identifying high-risk

patients in clinical practice (9,10). The second is VTE prevention, which includes drug therapy and physical therapy. Drug prevention is mainly the use of anticoagulant drugs, while physical prevention mainly involves applying pressure to the lower limbs to promote blood flow (11,12). The third is the treatment of VTE, including drug treatment and surgical treatment (13). As for the risk factors of VTE, however, there are relatively few studies examining the general population and more general risk factors. The main known factors are age and long-term bed rest. Lead is a common metal element in life and work, which can easily enter the human body and be absorbed, leading to lead poisoning (14). Lead poisoning mainly affects the nervous system, hematopoietic system, skeletal system, and kidneys (15). There are few reports on the relationship between the levels of lead in blood and blood coagulation function or thrombosis. Limited studies have shown that lead exposure can lead to vascular endothelial dysfunction, reduced vasodilation function, reduced angiogenesis, reduced damage repair ability, and promote atherosclerosis and thrombosis (16,17). In an early case report, Köklü *et al.* reported a 43-year-old male patient with superior vena cava syndrome due to thrombosis (18). Since no evidence of etiology was found, the authors presumed that chronic lead exposure might be the reason of the thrombosis (18). Later in an experimental study, Jin *et al.* demonstrated lead can cause reactive oxygen species -independent but $[Ca^{2+}]_i$-dependent eryptosis, which might provoke thrombosis (19). However, to date, there have been no studies analyzing the relationship between the levels of lead in the blood and VTE. Moreover, in clinical practice, most patients do not monitor the levels of lead in the blood, and thus, it is difficult to study the relationship between the levels of lead in the blood and VTE through retrospective studies. The National Health and Nutrition Examination Survey (NHANES) is a long-term study on the health and nutrition status of residents in the United States, in which the levels of serum lead has been recorded (20). The NHANES database has been widely used in clinical study and yielded many valuable results. Therefore, this retrospective analysis preliminarily explored whether there is a correlation between the levels of serum lead and VTE using data from the NHANES, so as to provide a reference for follow-up research and clinical practice. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1071/rc).

Highlight box

Key findings

- Analysis of a population from the National Health and Nutrition Examination Survey (NHANES) database revealed that higher levels of serum lead concentrations are associated with a higher incidence of venous thromboembolism (VTE).

What is known and what is new?

- VTE is a common clinical problem. Lead toxicity mainly affects the nervous sys-tem, hematopoietic system, skeletal system, cardiovascular system, and the kidneys.
- Serum lead levels were found to be associated with VTE in a general population.

What is the implication, and what should change now?

- Clinicians should pay attention to the patient's serum lead levels to further assess the risk of VTE in addition to traditional risk factors.

Methods

Study population

This study was conducted based on the NHANES (1999 to 2018) and all original data of participants included in this study can be accessed from the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). We used data from 10 cycles of survey (1999 to 2018) consisting of 101,316 subjects. The inclusion criteria of participants were as follows: patients aged ≥20 years; the results of serum lead tests were available; and the presence or absence of VTE was confirmed by ultrasonography or computed tomography. VTE was defined as DVT or PE, which was extracted from the NHANES database. The exclusion criteria were as follows: missing data of serum lead levels; and no definite diagnosis of VTE or non-VTE. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data collection

In the NHANES, venous blood was obtained to measure the serum lead levels. Blood samples were stored at –20 ℃. Serum lead level was tested by an Inductively Coupled Plasma Dynamic Reaction Cell Mass Spectrometer (ELAN DRC II, PerkinElmer, Norwalk). When the concentration was not lower than 0.3 μg/dL (1999–2002 survey), 0.28 μg/dL (2003–2004 survey), 0.25 μg/dL (2003–2012 survey), 0.07 μg/dL (2013–2016 survey), and 0.05 μg/dL

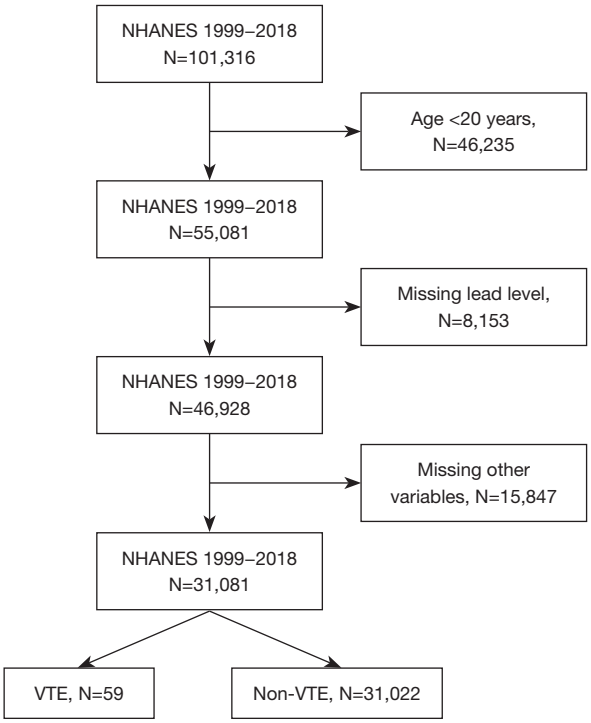

Figure 1 A flowchart showing the participant inclusion and exclusion process. Missing other variables included: information about whether there was DVT or PE; information about history of cigarette or alcohol use; information about medical history; information about education. NHANES, National Health and Nutrition Examination Survey; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.

(2017–2018 survey), the level of serum lead can be determined (21).

Statistical processing

SPSS statistical software (version 25.0, IBM, Chicago, USA) was used for statistical analyses. The associated variables were expressed as mean ± standard deviation, the comparison between two groups was conducted using the Student's *t*-test, and comparison between multiple groups was conducted using the F test. Categorical variables were expressed by quantity (percentage), and inter-group comparisons were performed using chi-square test or Fisher's exact test. The factors related to VTE were analyzed using single factor and multiple factor logistic regression analysis. A two-side P value <0.05 was considered statistically significant.

Results

Baseline characteristic

A total of 98,306 adult participants from the NHANES (1999 to 2018) database was analyzed and 129 cases with VTE were identified, resulting in a rough prevalence of 0.13%. After excluding participants according to exclusion criteria, there remained 31,081 individuals, among which 59 participants had VTE, with a prevalence of 0.19% (*Figure 1*). To observe the preliminary association between lead and health status, we divided participants into four groups according to serum lead levels using four quartiles (*Table 1*). The results showed that the group with the highest serum lead levels had the highest average age, prevalence of VTE, hypertension, and history of cigarette, as well as the highest percentage of male sex and lowest body mass index (BMI). The race distribution, education status, and rate of alcohol use also differed among these four groups. The rate of individuals with diabetes and cancer did not differ between groups.

A comparison of the characteristics between individuals with and without VTE

We compared the baseline characteristics of individuals with and without VTE (*Table 2*). The results demonstrated that when compared with individuals without VTE, individuals with VTE were older, more likely to be male, presented with hypertension, diabetes, and a history of cigarette use, and had higher mean serum lead levels. Race distribution, education level, BMI, and rate of cancer and alcohol use did not differ between individuals with and without VTE.

Univariate and multivariate logistic regression analysis

We used variables with statistical difference in *Table 2* as independent variables, and VTE as the dependent variable for univariate and multivariate logistic regression analysis. Univariate analysis revealed that age, male sex, history of cigarette use, hypertension, diabetes, and serum lead levels were factors associated with VTE in the population from the NHANES database. Using these factors as independent variables and VTE as dependent variable, further multivariate logistic analysis revealed that age, history of cigarette use, hypertension, diabetes, and serum lead levels were factors associated with VTE (*Table 3*).

Table 1 Characteristics of patients divided by serum levels of lead (n=31,081)

Characteristics	Q1 (n=7,663)	Q2 (n=7,745)	Q3 (n=7,916)	Q4 (n=7,757)	t/χ^2 value	P value
Age (years)	38.4±14.7	48.2±16.8	53.9±17.1	58.6±16.3	2,205.639	<0.001
Male, n (%)	2,318 (30.2)	3,481 (44.9)	4,243 (53.6)	4,936 (63.6)	2,019.791	<0.001
Cigarette use, n (%)	2,281 (29.8)	3,158 (40.8)	3,947 (49.9)	4,625 (59.6)	1,519.620	<0.001
Alcohol use, n (%)	6,367 (83.1)	6,574 (84.9)	6,681 (84.4)	6,516 (84.0)	1,222.882	<0.001
BMI (kg/m^2)	30.2±8.0	29.5±6.9	28.9±6.4	28.1±5.7	133.028	<0.001
Hypertension, n (%)	2,912 (38.0)	3,956 (51.1)	4,702 (59.4)	5,096 (65.7)	3,573.789	<0.001
Diabetes, n (%)	643 (8.4)	667 (8.6)	654 (8.3)	677 (8.7)	1.336	0.721
Cancers, n (%)	259 (3.4)	258 (3.3)	282 (3.6)	271 (3.5)	0.783	0.854
Serum lead levels (μg/dL)	0.56±0.13	0.98±0.14	1.61±0.19	3.60±1.92	14,934.559	<0.001
Race, n (%)						<0.001
Non-Hispanic White	3,471 (45.3)	3,573 (46.1)	3,872 (48.9)	3,607 (46.5)	22.770	
Non-Hispanic Black	1,449 (18.9)	1,513 (19.5)	1,488 (18.8)	1,739 (22.4)	42.248	
Mexican American	1,257 (16.4)	1,231 (15.9)	1,369 (17.3)	1,458 (18.8)	26.515	
Other Hispanic	757 (9.9)	720 (9.3)	562 (7.1)	411 (5.3)	141.386	
Other race	729 (9.5)	708 (9.1)	625 (7.9)	542 (7.0)	40.693	
Education, n (%)						<0.001
> High school	4,783 (62.4)	4,267 (55.1)	3,903 (49.3)	3,010 (38.8)	921.158	
High school	1,661 (21.7)	1,797 (23.2)	1,916 (24.2)	1,971 (25.4)	32.059	
< High school	1,219 (15.9)	1,681 (21.7)	2,097 (26.5)	2,776 (35.8)	873.302	
VTE, n (%)	6 (0.08)	10 (0.13)	17 (0.21)	26 (0.34)	15.447	0.002

Data are expressed as n (%) or mean ± standard deviation. Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; BMI, body mass index; VTE, venous thromboembolism.

Discussion

In clinical practice, VTE can cause important adverse events. Screening the factors related to VTE is helpful in identifying high-risk patients with VTE. In this study, we analyzed the factors related to VTE in the general population based on the NHANES database. The results demonstrated that the incidence of VTE was 0.13% in the general adult population. To the best of our knowledge, this study is the first to identify an association between the levels of serum lead and clinical VTE. In the general population, the factors related to clinical VTE include age, smoking history, hypertension history, and diabetes history. In this study, we divided patients into four groups according to different levels of serum lead. The results revealed that the higher the levels of serum lead, the higher the incidence of VTE. We also found that blood lead levels may be related to age, gender, smoking history, drinking history, BMI, hypertension history, diabetes history, race, and education level.

Previous data related to risk factors of VTE have mainly been derived from case-control studies conducted for clinical patients (2,3,10). By analyzing the clinical data of two groups of patients with and without VTE, we herein explored the factors related to the occurrence of VTE in specific patients. To date, the factors associated with VTE mainly cover three aspects (7,22,23). The first aspect includes factors related to the slowing down of venous blood flow, such as long-term immobilization, especially after major abdominal or lower limb surgery, obesity, etc. The second relates to the increase of procoagulant properties, such as antiphospholipid syndrome, nephrotic syndrome, pregnancy, oral contraceptives, etc. The third relates to

Table 2 Characteristics of individuals with and without VTE

Characteristics	VTE patients (n=59)	Non-VTE patients (n=31,022)	t/χ^2 value	P value
Age (years)	58.7±14.6	49.8±15.9	4.296	<0.001
Male, n (%)	39 (66.1)	14,939 (48.2)	7.596	0.006
Cigarette use, n (%)	37 (62.7)	13,974 (45.0)	7.423	0.006
Alcohol use, n (%)	44 (74.6)	24,674 (79.5)	0.890	0.345
BMI (kg/m^2)	30.6±6.4	29.2±6.0	1.790	0.073
Hypertension, n (%)	47 (79.7)	18,039 (58.1)	11.201	0.001
Diabetes, n (%)	11 (18.6)	2,630 (8.5)	7.828	0.005
Cancers, n (%)	4 (6.8)	1,066 (3.4)	1.102	0.294
Serum lead levels (μg/dL)	3.14±0.35	1.69±0.14	79.093	<0.001
Race, n (%)			1.426	0.840
Non-Hispanic White	31 (52.5)	14,492 (46.7)		
Non-Hispanic Black	9 (15.3)	6,180 (19.9)		
Mexican American	11 (18.6)	5,304 (17.1)		
Other Hispanic	4 (6.8)	2,446 (7.9)		
Other race	4 (6.8)	2,600 (8.4)		
Education, n (%)			1.076	0.584
> High school	27 (45.8)	15,936 (51.4)		
High school	14 (23.7)	7,331 (23.6)		
< High school	18 (30.5)	7,755 (25.0)		

VTE, venous thromboembolism; BMI, body mass index.

Table 3 Logistic regression analysis of factors associated with venous thromboembolism

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.107	1.035–1.240	0.031	1.104	1.052–1.226	0.035
Male	1.062	1.021–1.137	0.044	1.047	0.983–1.110	0.194
Cigarette use	1.115	1.049–1.273	0.025	1.108	1.048–1.239	0.043
Hypertension	1.148	1.072–1.319	0.027	1.113	1.067–1.285	0.037
Diabetes	1.114	1.055–1.262	0.033	1.092	1.024–1.251	0.040
Serum lead levels	1.191	1.084–1.405	0.016	1.185	1.075–1.390	0.026

OR, odds ratio; CI, confidence interval.

vascular endothelial injury, such as trauma, intravascular catheterization, etc. However, there are relatively few studies on VTE risk factors for the general population. As mentioned earlier, there are many occasions in work and life where one may be exposed to lead, and the impact of lead on VTE remains unclear. A small number of studies have suggested that lead poisoning may increase the risk of thrombosis (14,16,17). However, there is no corresponding clinical research to support this. The NHANES database provides a sample of the whole population, and also records

the levels of lead in the serum of subjects. Based on this database, we analyzed, for the first time, the relationship between the levels of lead serum and the occurrence of VTE in the general population. Indeed, increased serum lead levels were closely related to VTE. However, in our study, VTE occurred at the same time or before the detection of serum lead. Therefore, it is unclear whether there is a chronological sequence between the increase of serum lead levels and the incidence of VTE. Furthermore, we cannot definitively conclude that the increase of serum lead levels is a risk factor leading to VTE. However, our results suggested that there is a correlation between the increase of serum lead levels and clinical VTE, and the nature of the correlation warrants further clarification in future studies.

Previous investigation have shown that long-term exposure to lead compounds can lead to decreased vasodilation function, affect the formation and repair of blood vessels, and promote atherosclerosis and thrombosis (24,25). The migration and proliferation of endothelial cells is the key to angiogenesis and repair. Exposure to lead compounds can inhibit the proliferation of vascular endothelial cells and promote the proliferation of vascular smooth muscle cells, thus inhibiting the formation and repair of blood vessels (25). Vascular oxidative stress induced by lead compounds has also been shown to reduce the biological availability of nitric oxide (NO) and cause vascular endothelial dysfunction (26,27). Moreover, vascular inflammation caused by exposure to lead compounds is related to the activation of nuclear factor (NF)-κB (28), which is a universal transcription factor of many pro-inflammatory cytokines, chemokines, and adhesion molecules. Oxidative stress can promote the activation of NF-κB, cause vascular inflammation, vascular fibrosis, and vascular cell apoptosis, which may be closely related to venous thrombosis (29,30). Therefore, there may be some potential mechanisms between the increase of serum lead levels and the formation of VTE, which is worthy of further investigation.

Our research results also demonstrated that individuals with high serum lead levels tended to be older, males, and have a history of hypertension and smoking. Furthermore, their ethnic distribution and education level were also different from other individuals. We speculate that the older age may be related to more opportunities for lead exposure. The high rate of males may be related to the fact that men tend to be engaged in more lead-related occupations. The high rate of smoking history may be related to the high rate of males, but may also be related to the content of lead in tobacco, but this speculation warrants further research and observation. The differences in ethnic distribution are difficult to explain at present, and may be related to eating habits, occupation, etc. In terms of education, our results showed that the rate of receiving education above high school level was the greatest among individuals with the lowest serum lead levels. It is suggested that the higher the level of education, the lower the level of lead in the individual's serum and this may be related to the fact that individuals receiving higher education are engaged in occupations that have less lead expose.

There were certain limitations to this investigation. First, this was a retrospective study based on the NHANES database. A large number of patients were not included in the final analysis due to a lack of data availability, which may lead to differences between the observed incidence of VTE and the actual incidence. Second, this study could not comprehensively analyze the causal relationship between the increase of serum lead levels and the occurrence of VTE, only suggesting that there is a correlation between the two. Third, other clinical indicators were not included in this study, and remain unclear whether certain indicators might have affected the research results. Fourth, the present study was based on individuals from the United State, which had significant ethnic difference from individuals with Asian, especially Chinese ethnic. Therefore, future prospective cohort studies should be conducted to further examine the relationship between serum lead levels and the development of clinical VTE, especially in Asian people.

Conclusions

Based on NHANES (1999 to 2018) database, the present retrospective study demonstrated that higher serum levels of lead may be associated with VTE in general population. This finding suggests that lead level might be used as a routine test in clinical practice.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1071/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1071/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1071/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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(English Language Editor: J. Teoh)

Cite this article as: Xiao M, Li D, Wang X, Zhang J, Wang X, Gao J. Serum levels of lead are associated with venous thromboembolism: a retrospective study based on the NHANES database (1999 to 2018). J Thorac Dis 2023;15(8):4426-4433. doi: 10.21037/jtd-23-1071