

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-1071>

Review Comments

This is an interesting article, which 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). I would suggest a more comprehensive overview of the research question in the background /introductory section and additional explanation to be included in the materials and methods and results sections. This will assist the reader in obtaining a more comprehensive overview of the data.

Suggested major corrections:

1) Introduction:

a) Lines 66-67: “There are few reports on the relationship between the levels of lead in blood and blood coagulation function or thrombosis”.

Although very limited, there is scientific literature to suggest that lead levels may be associated with thrombosis and hypothesis as to the possible mechanism. In addition, there is also conflicting literature suggesting lead is not thrombogenic. It would be of value to include an overview of this literature debate in the introduction to contextualize the findings of this study and to add to the body of literature evidence. Possible references to review follow:

• Köklü S, Aksoy DY, Altundag K, Usalan C. Superior Vena Cava Thrombosis in Chronic Lead Exposure: A Case Report. *Angiology*. 2003;54(4):481-483. doi:10.1177/000331970305400413

• Shin JH, Lim KM, Noh JY, Bae ON, Chung SM, Lee MY, Chung JH. Lead-induced procoagulant activation of erythrocytes through phosphatidylserine exposure may lead to thrombotic diseases. *Chem Res Toxicol*. 2007 Jan;20(1):38-43. doi: 10.1021/tx060114+. PMID: 17226925.

• Jin Q, Yao C, Bian Y, Pi J. Pb-Induced Eryptosis May Provoke Thrombosis Prior to Hemolysis. *International Journal of Molecular Sciences*. 2022; 23(13):7008. <https://doi.org/10.3390/ijms23137008>

• Nielsen, V.G. Lethal concentrations of mercury or lead do not affect coagulation kinetics in human plasma. *J Thromb Thrombolysis* 48, 697–698 (2019). <https://doi.org/10.1007/s11239-019-01921-x>

REPLY: We added some discussion in the INTRODUCTION section (manuscript, page 3, line 77-82).

b) Lines 74-76: “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”.

It would be of value to expand the information on this database (how and what data were collected) and include a description in the introduction of normal lead reference ranges, toxicity levels and whether ranges are stable over differing age groups.

REPLY: We added some information on NHANES (manuscript, page 3, line 80-90). However, level (normal and abnormal) of lead is associated with testing methods and reagents. We prefer not discuss in detail the levels of lead. Thank you.

2) Materials and Methods:

a) Lines 87-91: “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 using relative information. The exclusion criteria were as follows: missing data of serum lead levels; and no definite diagnosis of VTE or non-VTE”.

This information needs to be explained in more detail and clarified. How was the presence or absence of VTE confirmed using relative information? How is information on VTE captured in the database? Refer also to Figure 1: Lines 325-329. 15 487 participants were excluded because of missing variables (in addition to 8153 excluded because of missing lead levels). What were those missing variables? This needs to be documented in the exclusion criteria. Does the exclusion of these individuals introduce a bias in the data?

REPLY: We added some description in the METHODS section (manuscript, page 4, line 104-106). Thanks.

3) Results:

a) Line 121-123: “To observe the preliminary association between lead and health status, we divided participants into four groups according to serum lead levels using four quartiles”.

A discussion of normal peripheral blood lead levels is warranted in the introduction as well as an overview / definition of lead level quartile cut-offs in the materials and methods.

REPLY: Dear reviewer, normal level of peripheral blood lead is different in different medical center, even in the same center in different time.

b) Line 140 and Table 3: Suggest include more comprehensive explanation of the regression models used for multivariate analysis.

REPLY: We added some description in this section (manuscript, page 6, line 161-162).

Minor Corrections:

1) Abstract

- Line 33: Amend to “analysis revealed that age, male sex, history of cigarette use....”
- Line 38: Conclusion is too broad a generalisation. Would reword to: “The findings of this study suggest that higher serum levels of lead may be associated with VTE”.

Reply: We revised these in the Abstract section. Thanks.

2) Introduction

- Lines 45,47,48: Standardize abbreviation - pulmonary embolism as PE or PTE.
- Lines 59-61: “As for the risk factors of VTE, most studies are based on the same category, using common clinical parameters for analysis, and the results are often highly targeted”. Please reword to clarify meaning – uncertain what you are trying to convey here.

Reply: We revised these in the Introduction section. Thanks.

3) Results:

- Line 124 and 127: Contradictory information with regards to Diabetes.
- Line 125: Amend to “the highest percentage of male sex and.....”
- Lines 133-138: Amend “VTE individuals with that of non-VTE individuals” to “individuals with and without VTE”.
- Line 144: Amend to “analysis revealed that age, male sex, history of cigarette use....”

Reply: We revised these in the Result section. Thanks.

4) Table 2: Line 335: Amend title to “Characteristics of individuals with and without VTE”

Reply: We revised this. Thanks.

Although this is an interesting article with potential scientific merit it is difficult to assess the validity of some of the data because the information provided is not comprehensive enough. I would suggest that major revisions are undertaken to improve the robustness of the paper. In particular, the introduction needs to include debate about the role of lead and the coagulation system - there is some literature evidence which has not been addressed. In addition, normal and toxic lead levels warrant discussion as does the association of age and lead levels. The nature of the database used has not been comprehensively discussed and it is unclear how evidence of VTE is captured in this database, nor is it clear why a substantial number of patients were excluded based on a lack of evidence of presence or absence of VTE. Finally the data around the multiple regression analysis models utilized is not clear and the presentation should clarify whether lead is independently associated with VTE.^[1]