

Association between Blood Lead Levels and Markers of Calcium Homeostasis: A Systematic Review and Meta-Analysis

Kuldip Upadhyay

National Institute of Occupational Health

Ankit Viramgami

National Institute of Occupational Health

Bhavani Shankara Bagepally

National Institute of Epidemiology

Rakesh Balachandar (✉ balachandar.rakesh@gmail.com)

National Institute of Occupational Health

Research Article

Keywords: Calcium homeostasis, Lead exposure, Parathyroid hormone, Vitamin D, Systematic Review

Posted Date: November 16th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1042280/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published at Scientific Reports on February 3rd, 2022. See the published version at <https://doi.org/10.1038/s41598-022-05976-4>.

Abstract

Introduction:

Chronic Pb exposure associated systemic illness are partly posited to involve calcium homeostasis. Present systematic review aims to comprehensively evaluate the association between chronic lead exposure and markers of calcium homeostasis.

Methods:

Observational studies documenting the changes in calcium homeostasis markers (i.e. serum calcium, parathyroid hormone, vitamin D & calcitonin) between occupationally Pb exposed group and control group were systematically searched from digital databases since inception to March 17, 2021. PRISMA guidelines were adhered during execution. Mean differences of calcium homeostasis markers between the groups were analysed using random-effects model. Heterogeneity was assessed by I^2 statistic, while the risk of bias was performed using Newcastle Ottawa Scale. Sub-group, sensitivity and meta-regression analyses were performed where data permitted.

Results:

Eleven studies were (837 Pb exposed vs 739 controls) identified. Pb exposed group exhibited higher mean 36.13 (95%CI 25.88-46.38) $\mu\text{g/dl}$ blood lead level significantly lower serum calcium, and trend of higher parathyroid levels and lower vitamin D levels than controls. Heterogeneity was high among the studies.

Conclusion:

Considering the cardinal role of calcium in multiple biological functions, present observations emphasis the need for periodic evaluation of calcium levels and its markers among those with known cumulative exposure to Pb.

Highlights

- Systematic review confirms the association between chronic lead exposure and aberrations in calcium homeostasis markers
- Serum calcium was significantly lower among chronically lead exposed individuals as compared to control participants
- The evidence was synthesized predominantly from relatively heterogeneous and scarce high-quality primary studies

Introduction

Lead (Pb), a common hazardous heavy metal bioaccumulates in various tissues on chronic exposure, causing serious systemic illnesses. The pathophysiology posited in some Pb-induced health hazards involves direct and indirect interference with calcium metabolism and homeostasis. Despite studies verifying the causal role of perturbations on calcium homeostasis/metabolism is fewer, collective evidence supports the Pb-calcium interactions (1). The availability of calcium in serum for various biological functions are tightly regulated by parathyroid hormone (parathormone), calcitonin and vitamin. Therefore, parathormone, calcitonin, vitamin D, and serum calcium (itself) constitute calcium homeostasis markers (2).

Few mechanisms posited in Pb altering calcium homeostasis include the inhioting of enzymes responsible for vitamin D activation (i.e., 1 α -hydroxylase), thereby reducing serum calcium (3, 4). Given growing reports of Pb among the general population and inconclusive evidence from individual primary studies regarding the association of blood lead levels (BLL) on calcium homeostasis markers (parathyroid and vitamin D) (5-9), there is need to investigate current evidences of association (if any) between the duo.

Individuals employed at workplaces involving Pb and its derivatives commonly exhibit high BLL. Hence, the present study aimed to systematically investigating the association between BLL and calcium homeostasis markers by reviewing those studies comparing calcium homeostasis markers between individuals occupationally exposed to Pb as against those without obvious Pb exposure. In addition the study aimed at exploring the association between BLL and bone resorption / turnover markers (urinary pyridinoline, urinary deoxypyridinoline, osteocalcin, osteopontin).

Methods

The study proposed to employ PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analysis) guidelines during every step of its execution (10) and the protocol was eaelier registered at PROSPERO (ID: CRD42020199503). Observational studies of both cross-sectional or longitudinal design, evaluating calcium homeostasis markers among occupationally Pb exposed participants as compared to those without obvious exposure were systematically searched using key terms from pubmed-Medline, Scopus, and Embase digital repositories. The key terms were constructed on the basis of PICOS approach (i.e., Participants, Intervention (exposure to Pb), Controls (obviously unexposed Pb), Outcome (calcium homeostasis markers), and Study design). Sensitivity and precision maximizing strategy was adopted to identify relevant studies. Detailed search terms and search strategies are reported in the appendix. The search was performed on September 24, 2020 (updated search in Pubmed on March 17, 2021). A lateral search was performed for potential studies using the bibliography of included studies.

Primary literature reporting the differences in calcium homeostasis markers in otherwise healthy individuals occupationally exposed to Pb, as compared to those without a history of occupational Pb exposure, were considered. Calcium homeostasis markers viz. serum calcium, vitamin D, calcitonin, and parathyroid were primarily aimed in addition to bone resorption / turnover markers. Preclinical studies (animal/cell line), studies reporting acute Pb poisoning, involving individuals with congenital/acquired disorders of calcium metabolism or other endocrine disturbances, review articles, commentaries, letters to the editors, editorials, and methodology articles were excluded from the review.

Screening and reviewing of studies: Conventional screening steps of executing the systematic review, including independent screening of the title and abstract of studies, for their potential inclusion were followed by the authors (RB, KU, AV). The final list of studies meeting the inclusion-exclusion criteria for data extraction was prepared ensuring no duplication. Any conflict during the independent review was resolved by mutual consensus.

Data collection, extraction, analysis, and management: All necessary details from the primary literature vital for executing the proposed study were extracted using the data extraction form (Google sheets). The data extraction sheet included details of the participant (age, gender, and duration of employment), occupation/workplace (nature of workplace, location, simultaneous exposure to other heavy metals), and outcome measurements, in addition to details of the article (title, year of publication, journal, authors and contact details of the corresponding author) whenever available.

Data on central tendency (mean / median) and dispersion (standard deviation (SD) / Standard error (SE) / Interquartile range / 95% confidence interval (CI)) for available parameters were independently extracted from the included studies by (AV & RB). Webplot application (11) was used for extracting data when the results were graphically reported (12). The data after confirmation for consistency was used for further analysis. For studies reporting outcome variables other than the conventional units / standard units, the outcome parameters were converted to uniform units using standard conversion factors (3, 6).

When the measures of central tendency (e.g., median, mode) & data dispersion (e.g., 95% confidence interval, interquartile range, standard error of mean) were provided (13) alternate to mean & SD, appropriate conversions were performed (14-16). Lastly, in situations where the primary study reported more than one exposed group (7), grand mean and SD was calculated (17),

Pooled mean difference (95% CI) between the occupationally Pb exposed workers and the control group was estimated using the generic inverse variance method by pooling the mean and SD from individual studies. On anticipating high heterogeneity random-effects model was employed during meta-analysis (18).

Heterogeneity, sensitivity, subgroup, and Risk of Bias Assessment: The heterogeneity among included studies was assessed using visual inspection of forest plots, the Cochran-Q test, and I-squared (I^2) statistics. The $I^2 > 25\%$ or Cochran-Q < 0.1 were regarded as evidence for heterogeneity among the included studies. Further, the sources of heterogeneity were explored by fitting the co-variables (mean age, mean duration of exposure, and percentage of males in the study, whichever was available) individually in the meta-regression model when more than ten primary studies were available. A particular variable exhibiting a 50% reduction in I^2 was regarded as a potential source of heterogeneity.

Publication bias was assessed using funnel plot (asymmetry) and Egger's test ($p < 0.05$) of the effect measures (19, 20). Further, on identifying asymmetry in the funnel plot, the source of asymmetry was explored using a contour-enhanced funnel plot. Lastly, sensitivity & subgroup analysis was performed to investigate the influence of the simultaneous exposure to other heavy metals (yes vs. no/not available) on the outcome variables. However, the sub-group analysis was conducted only if sufficient (i.e., ≥ 2) studies were available for subgroup/sensitivity analysis. The changes in the mean difference and heterogeneity (I^2) were considered to decide (interpret) the influence of a particular subgroup analysis (21).

Data was recorded using a Microsoft Excel sheet (version 2016) and analyzed using Stata version 16 (22). Two-sided $p < 0.05$ was considered statistically significant except for the subgroup analysis and heterogeneity test, wherein $p < 0.10$ was regarded as significant.

Assessment of the risk of bias in included studies: Newcastle Ottawa scale was employed independently by the authors for assessing the risk of bias in the included studies (23). Briefly, the tool was used for rating the risk of bias in participant selection, comparison of cases and controls, and assessing the exposure. Based on agreement with the definition of cases and controls in the individual studies, their representativeness and comparability, and relatively occupational Pb exposure, individual studies were rated with a star(s). Any conflict in the rating was resolved by mutual consensus among the authors.

Results

The electronic search retrieved 12,430 studies. After removal of duplicates, screening of abstract & titles of all studies, 52 of them were considered for full-text review. Full-text scrutiny resulted in eleven studies for the final quantitative data synthesis. Total number of studies excluded and the reasons are described in the PRISMA flowchart (Figure 1).

Description of studies: Details of the individual studies such as sample size, mean age of participants, duration of occupational exposure, type of industry (responsible for occupational Pb exposure), simultaneous exposure to other heavy metals, and the outcome parameters reported are described in table 1. Majority of the included studies reported sample mean of the outcome variables of control groups within the recommended normal values (i.e., Serum calcium: 8.2 - 10.2 mg/dl, ionized Calcium: 4.60 - 5.08 mg/dl, serum PTH: 10-65 pg/ml and vitamin D: 25 - 80ng/ml) (24) suggesting the control group as apparently normal in terms of the outcome parameters (24). However, the mean Vitamin D of the control group from Dongre et al.

2013 was lower than the recommended values (7). None of the studies reported calcitonin levels, while a single study reported bone turnover/resorption markers (5). Briefly, all studies recruited 100% male participants, except Batra et al. 2014 (4), where 11.3% were female participants. The sources of occupational Pb exposure among the exposed group varied across Pb battery and its allied industries, Pb smelting process, e-waste recycling process, welding, and paint industries. The duration of occupational Pb exposure was not available for a majority of the studies, while few reported the exposure duration ranging from 5 to 34 years. The studies were restricted to Asian (India, China, and Bangladesh), European (Croatia, Austria, Turkey, and Israel), and African (Nigeria) countries, while no studies from Australia or American (both Latin and North) countries were available.

Risk of Bias assessment: The risk of bias during participant selection, ascertainment of exposure, and outcome parameters were evaluated using Newcastle Ottawa scale (23) (Table 2). Notable risk of bias in the participant selection included convenient sampling, inadequate representativeness of the exposed and control participants (in view of absence of precise records on exposure), non-description of precise source of control participants in some of the studies (7, 9, 25) and incomplete description of control participants (i.e., occupation, confirmation of their non-exposure) (4, 7, 9, 25). Additionally, as the interviewer(s) were non-blinded to the participant status (as either exposed or unexposed), the exposure assessment could have been potentially biased. Therefore, none of the included studies was comparable to that of a well-conducted RCT.

Meta-analysis results of individual outcome parameters

Blood lead levels: Current systematic search identified eleven studies that reported BLL among occupationally Pb exposed & control workers (3-9, 12, 13, 25, 26). All identified studies reported significantly ($p < 0.05$) higher BLL among occupationally exposed workers as compared to control subjects. The results were congruent with the current pooled quantitative analysis, wherein individuals with occupational exposure to Pb had a mean BLL of 36.13 $\mu\text{g}/\text{dl}$ (95% CI, 25.88 to 46.38, $I^2=99.75\%$, $p<0.05$) higher than controls (Figure 2). Subgroup analysis of studies involving Pb exposed participants with history of co-exposure to other heavy metal(s) did not alter the results (Supplement Figure 1). Explorative uni-variate meta-regression with participants' mean age as the moderator did not significantly reduce the heterogeneity / alter results. Further, the asymmetric funnel plot suggests publication bias ($p=0.425$), while the contour enhanced funnel plot suggests the presence of other biases as well. (Supplement Figure 2).

Urinary lead levels: Two studies reported Urine Pb levels among occupationally Pb exposed & unexposed workers. The pooled mean difference between the groups was 10.89 $\mu\text{g}/\text{dl}$ (95% CI, -1.01 to 22.79, $I^2=96.71$). Subgroup, meta-regression and funnel plot analysis were not possible in view of fewer studies.

Serum calcium: Ten of the included studies reported serum calcium levels, while seven of them observed significantly lower calcium levels among occupationally Pb exposed group compared to control group (3, 4, 6-9, 12, 13, 25, 26). The Pb exposed group exhibited -0.72 mg/dl (95% CI -0.36 to -1.07, $I^2=95.12\%$) lower calcium levels as compared to the control group. (Figure 3A). Subgroup analysis of studies involving Pb exposed participants with a history of co-exposure to other heavy metal(s), did not significantly reduce the heterogeneity, however reduced the magnitude of the difference between the duo (-0.39 mg/dl, 95% CI -0.64 to -0.15, $I^2=72.04\%$) (3, 6, 8, 12, 13) (Supplement Figure 3). Meta-regression analysis with participant's mean age as moderator, did not significantly change the results. Further, the asymmetric funnel plot was suggestive of publication bias ($p=0.779$) and the contour enhanced funnel plot suggested the presence of other biases as well (Supplement Figure 4).

Serum ionized Calcium: Four of the included studies reported ionized serum calcium levels. All but one study reported statistically significant lower ionized calcium levels among occupationally Pb exposed group compared to control group (3, 7, 8, 26). The results were consistent with that of the serum calcium levels, i.e., the pooled mean difference revealed lower ionized calcium levels among occupationally Pb exposed group as compared to the control group (-1.20 mg/dl with 95% CI -2.38 to -0.02 and $I^2=99.76\%$) (Figure 3B). In view of limited studies, subgroup, meta-regression and funnel plot analysis were not executed.

Parathyroid hormone (PTH) (Parathormone): Five included studies reported parathormone levels; all but one observed lower serum PTH levels among occupationally Pb exposed as compared to the control group (4, 5, 7, 8, 26). Occupationally Pb exposed group exhibited mean 37.97pg/ml (95% CI -14.36 to 90.29 and $I^2=99.80\%$) lower parathormone levels as compared to the control group, with high levels of heterogeneity (Figure 4A). However, the results were statistically not significant. Subgroup and meta-regression analyses weren't taken up, given fewer available studies reporting parathormone levels.

Vitamin D: Five studies reported Vitamin D levels, and all but one reported significantly lower Vitamin D levels among occupationally Pb exposed group compared to control group (4, 5, 7, 8, 25, 26). The pooled mean difference between the duo was -12.26 (95% CI -25.36 to 0.84, $I^2=99.10\%$) ng/dl with high heterogeneity (Figure 4B). Although the results indicate the point estimate of the effect measure for Vitamin D was lower among Pb exposed, the result was statistically not significant. Due to the limited number of studies, subgroup and meta-regression analysis were not executed.

Calcitriol: Two of the included studies reported differences in calcitriol levels (active form of vitamin D), with one study reporting higher (8) while the other (5) reported contrastingly lower serum calcitriol levels among occupationally Pb exposed group compared to control group. The pooled mean difference between the duo was -5.98 (95% CI -8.40 to 20.35, $I^2=91.20\%$) pg/dl with high heterogeneity. The results are suggestive of lower calcitriol among Pb-exposed as compared to the control group; however, the result was statistically not significant. Due to a limited number of studies, subgroup and meta-regression analysis were not carried out.

Other outcome parameters: Akbar et al. (2014) alone compared serum osteocalcin (bone resorption marker), urinary deoxypyridinoline, and urinary hydroxyproline values between the two groups(5). Both bone turnover markers in urine (deoxypyridinoline and hydroxyproline) and bone resorption markers (osteocalcin) were higher among the Pb exposed as compared to the non-exposed control; however, the results of urinary bone turnover markers (deoxypyridinoline and hydroxyproline) were statistically significant ($p < 0.05$).

Discussion

Present study systematically pooled existing evidence to determine the association between occupational Pb exposure and calcium homeostasis markers. Therefore studies comparing calcium homeostasis markers among occupationally Pb exposed workers as against unexposed control participants were systemically reviewed. Salient observations include, chronic Pb exposure (mostly occupational) was associated with derangement of calcium homeostasis markers. However, these observations were derived by pooling relatively heterogeneous studies.

Occupationally Pb exposed workers exhibited significantly higher BLL as compared to control participants without a history of occupational Pb exposure. The results were supported by most of the included studies irrespective of the duration of exposure or type of workplace employed. Interestingly, the occupationally unexposed subjects too had Pb in their blood, however with significantly lower levels as compared to exposed participants. As Pb has no known biological functions, there was no absolutely safe / recommended BLL. Though the average acceptable BLLs among the general population earlier documented was 1.2 micrograms/dl (27), however, based on observations from the “Adult Blood Lead Epidemiology and Surveillance” program, the Center for Disease Control has relaxed the levels and designated < 10 micrograms/dl as reference levels for adults (28). Surprisingly six of the eleven included studies reported mean BLL > 10 micrograms/dl among the unexposed control group (3, 6, 7, 12, 26). Reasons for such high BLL among the control group was possibly with exposure to environmental Pb contributed by leaded fuel, Pb-based paints, leaded plumbings, etc. Considering the potential hazardous nature of Pb and no known physiological role, the possible sources of environmental Pb exposure should be meticulously investigated and control strategies to be employed.

Pooled results suggest the occupational Pb exposure was significantly associated with lower serum calcium (total Calcium and ionized Calcium) and a trend of higher parathormone and lower vitamin D levels. Current observations require cautious interpretation, in view of results being synthesized by pooling relatively heterogeneous primary literature (unacceptably high heterogeneity i.e., $I^2 > 95\%$), probably biased by publication bias as inferred by the funnel plots. Lastly, for fewer primary studies in this regard, meta-regression, subgroup, and sensitivity analyses were restricted.

Lead, a biochemical analogue of calcium, was posited to impair the activation of vitamin D (i.e., formation of calcitriol) and thereby perturbs calcium metabolism (i.e., reduction in serum calcium) (3, 4). Parathormone, known to regulate the serum calcium levels by feedback mechanisms, was in turn elevated by lower calcium levels. Consistent with the posited mechanisms, occupationally Pb exposed individuals exhibited significantly lower serum calcium levels and trend of higher parathormone levels and lowered vitamin D levels in the present study. Based on current observations and previous inferences confirming the association between chronic Pb exposure and reduced prolactin levels, Pb may be regarded as an endocrine disruptor (29).

Observations from the present study was perhaps the earliest to confirm the association between occupational Pb exposure and derangement in calcium homeostasis markers (particularly calcium) via systematic review and meta-analysis. However, the limitations inherent to systematically pooling results from primary literature such as heterogeneity among them, absence of high-powered studies, non-uniform reporting of results, and other unknown factors, should be considered while interpreting the current results. Future longitudinal studies, investigating the role of vitamin D intervention in alleviating the aberrations in the calcium homeostasis markers and estimating the bone turnover/resorption markers would throw more light in this regard. In view of the vitality of the trace element (Calcium) in physiologic functions (viz. musculoskeletal system and second messenger) and the influence of parathormone on bones (calcium mobilization to regulate serum calcium), current study recommends their evaluation as part of the periodic worker examination protocol in occupationally Pb exposed workers.

Conclusion: Current results support the inverse relationship between chronic Pb exposure and calcium homeostasis markers (particularly reduction in serum calcium). However, considering the lack of evidence from high-quality studies, further evidences from multicentred longitudinal studies, including additional investigations (vitamin D metabolites, bone turnover/ resorption markers) is warranted for a precise understanding of the relation between the duo. Present observations perhaps suggest the need to draft regulations for periodic examination of calcium homeostasis markers among those chronically exposed to lead.

Declarations

Data availability statement:

Not applicable,

Funding statement:

No funding support for this work

Conflict of interest disclosure:

None

Ethics approval statement:

Not applicable

Patient consent form:

Not applicable

Any other permissions:

Not applicable

Acknowledgments:

None

Authors Contribution:

Upadhyay K: Conceptualization, Data curation, Investigation, Methodology and Review.

Viramgami A: Conceptualization, Data curation, Investigation, Methodology, Original draft and Review

Bagepally BS: Data curation, Formal analysis, Investigation, Methodology, Software, Original draft & Review.

Balachandar R: Conceptualization, Data curation, Investigation, Methodology, Original draft & Review.

References

1. Pounds JG. Effect of lead intoxication on calcium homeostasis and calcium-mediated cell function: a review. *Neurotoxicology*. 1984;5(3):295-331.
2. Medicine) Ilo. Dietary Reference Intakes for Calcium and Vitamin D. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): The National Academies Press; 2011.
3. Anetor J I ATS, Adeniyi F A, Taylor G O. Decreased. Decreased total and ionized calcium levels and haematological indices in occupational lead exposure as evidence of the endocrine disruptive effect of lead. *Indian Journal of Occupational & Environmental Medicine*. 2005;9:7.
4. Batra J, Thakur A, Meena SK, Singh L, Kumar J, Juyal D. Blood lead levels among the occupationally exposed workers and its effect on calcium and vitamin D metabolism: A case-control study. *J Family Med Prim Care*. 2020;9(5):2388-93.
5. Akbal A, Tutkun E, Yilmaz H. Lead exposure is a risk for worsening bone mineral density in middle-aged male workers. *Aging Male*. 2014;17(3):189-93.
6. Anetor JI, Ajose OA, Adebisi JA, Akingbola TS, Iyanda AA, Ebesunu MO, et al. Decreased thiamine and magnesium levels in the potentiation of the neurotoxicity of lead in occupational lead exposure. *Biol Trace Elem Res*. 2007;116(1):43-51.
7. Dongre NN, Suryakar AN, Patil AJ, Hundekari IA, Devarnavadagi BB. Biochemical effects of lead exposure on battery manufacture workers with reference to blood pressure, calcium metabolism and bone mineral density. *Indian J Clin Biochem*. 2013;28(1):65-70.
8. Kristal-Boneh E, Fromm P, Yerushalmi N, Harari G, Ribak J. Calcitropic hormones and occupational lead exposure. *Am J Epidemiol*. 1998;147(5):458-63.
9. Osterode W, Ulberth F. Increased concentration of arachidonic acid in erythrocyte membranes in chronically lead-exposed men. *J Toxicol Environ Health A*. 2000;59(2):87-95.
10. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-12.
11. Rohatgi A. WebPlotDigitalizer: HTML5 based online tool to extract numerical data from plot images. 3 ed 2012.
12. Wang Y, Sun X, Fang L, Li K, Yang P, Du L, et al. Genomic instability in adult men involved in processing electronic waste in Northern China. *Environ Int*. 2018;117:69-81.

13. Pizent A, Jurasovic J, Telisman S. Serum calcium, zinc, and copper in relation to biomarkers of lead and cadmium in men. *J Trace Elem Med Biol.* 2003;17(3):199-205.
14. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* 2005;5:13.
15. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Statistical Methods in Medical Research.* 2018;27(6):1785-805.
16. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology.* 2014;14(1):135.
17. Altman DG MD, ; Bryant TN; Gardner MJ. *Statistics with Confidence, Second Edition: BMJ Books; 2000.*
18. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials.* 2015;45(Pt A):139-45.
19. Deeks JJ, Altman DG. Effect Measures for Meta–Analysis of Trials with Binary Outcomes. *Systematic Reviews in Health Care*2001. p. 313-35.
20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629-34.
21. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ,. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0.* July 2019.
22. StataCorp. . *Stata Statistical Software Release 16.* College Station, TX: StataCorp LLC.; 2019.
23. Wells G SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses Ottawa2013*
24. values Lr. Lab reference values [updated 5th Jan 2020. Available from:<https://education.endocrine.org/system/files/ESAP%202015%20Laboratory%20Reference%20Ranges.pdf>.
25. Himani, Kumar R, Ansari JA, Mahdi AA, Sharma D, Karunanand B, et al. Blood Lead Levels in Occupationally Exposed Workers Involved in Battery Factories of Delhi-NCR Region: Effect on Vitamin D and Calcium Metabolism. *Indian J Clin Biochem.* 2020;35(1):80-7.
26. Mazumdar I, Goswami K, Ali MS. Status of Serum Calcium, Vitamin D and Parathyroid Hormone and Hematological Indices Among Lead Exposed Jewelry Workers in Dhaka, Bangladesh. *Indian J Clin Biochem.* 2017;32(1):110-6.
27. CDC lead document. CDC web document 2015 [cited 2015. Available from:https://www.cdc.gov/niosh/topics/ables/pdfs/Reference%20Blood%20Levels%20for%20Adults-2015-12-18_508.pdf.
28. Centers for Disease C, Prevention. Very high blood lead levels among adults - United States, 2002-2011. *MMWR Morb Mortal Wkly Rep.* 2013;62(47):967-71.
29. Balachandar R, Bagepally BS, Kalahasthi R, Haridoss M. Blood lead levels and male reproductive hormones: A systematic review and meta-analysis. *Toxicology.* 2020;443:152574.

Tables

Table 1

Description of the studies

Study	Country	Outcome parameters reported	Sample Size (n) [Exposed: controls]	Age in years (mean ± SD) [Exposed Vs Controls]	Duration of Pb exposure (in years) [mean ± SD]	Exposure to other heavy metals	Industry type of exposed
Akbalet et al (2014) (5)	Turkey	PTH, Calcitriol, UDP* HYP* and OC	30 : 32	39.4 ± 8.7 vs 37.9 ± 8.2	NA	NA	Lead batteries,
Anetor et al (2005) (3)	Nigeria	Ca*	86 : 51	NA	NA	Copper	Lead factory
Anetor et al (2007) (6)	Nigeria	Ca	47 : 25	33.0±8.2 Vs. 36.0±2.5	NA	Magnesium	Welding (n = 9), Printing (n = 10), Paint (n = 14) and Battery (n = 14)
Batra et al (2020) (4)	India	Ca*, PTH*, Vit-D*	80 : 80	30.9±5.75 Vs. 30.2±6.01	8.57±3.81	NA	Lead battery
Dongre et al (2013) (7)	India	Ca, PTH, Vit-D	90 : 30	Range: 20 to 45	30 each with 1-5, 6-10 and >10 years	NA	Lead battery
Estela Kristal Boneh et al (1998) (8)	Israel	Ca, PTH, Vit-D, Calcitriol*	56 : 90	43.4±11.2 Vs. 41.5±9.3	5.3±4.0	Magnesium	Lead battery and recycling
Himani et al (2018) (25)	India	Ca*, Vit-D*	100 : 100	32.6±10.3 Vs. 34.7±7.9	14.8±9.5	NA	Lead battery
Mazumder et al (2016) (26)	Bangladesh	Ca*, PTH*, Vit-D*	47 : 42	NA	NA	NA	Jewellery
Osteroid et al (2010) (9)	Austria	Ca	12 : 12	42.8±5.0 Vs. 40.1± 5.0	NA	NA	Pb smelting
Pizent et al (2003) (13)	Croatia	Ca*	143 : 156	34.0 Vs. 35.0	8 (range 2-34)	Cadmium	Lead battery
Wang et al (2018) (12)	China	Ca*	146 : 121	35.8 Vs. 34.9	NA	Copper	Electronic waste
<p>Ca-Calcium, HYP- hydroxyproline, NA-Not available, OC- osteocalcine, PTH-parathyroid hormone, UDP- Urinary deoxyypyridinoline, Vit-D -Vitamin D</p> <p>*studies reporting significant difference between the occupationally Pb exposed group and control group</p>							

Table 2

Newcastle Ottawa scale for assessing the risk of bias in the included studies.

	Adequacy of case definition	Case representativeness	Selection of controls	Definition of controls	Comparability of groups	Ascertainment of exposure	Similarity in the method of ascertainment	Non-response rate	Total*
Akbal et al 2014 (5)	*	-	*	*	*	*	-	-	5
Anetor et al 2005 (3)	-	-	*	*	*	-	*	-	4
Anetor et al 2007(6)	-	-	*	*	**	-	*	-	5
Batra et al 2020(4)	-	-	*	-	**	-	*	-	4
Dongre et al 2013(7)	-	-	-	-	-	-	*	-	1
Estela Kristal Boneh et al 1998 (8)	-	*	*	*	-	-	*	*	5
Himani et al 2020 (25)	-	-	-	-	*	-	*	-	2
Mazumder et al 2016 (26)	-	-	*	*	-	-	*	-	3
Osteroid et al 2010 (9)	-	-	-	-	-	-	*	-	1
Pizent et al 2003 (13)	-	*	*	*	*	-	*	*	6
Wang et al 2018 (12)	-	-	*	*	**	-	*	-	5
* Total number of stars obtained									

Figures

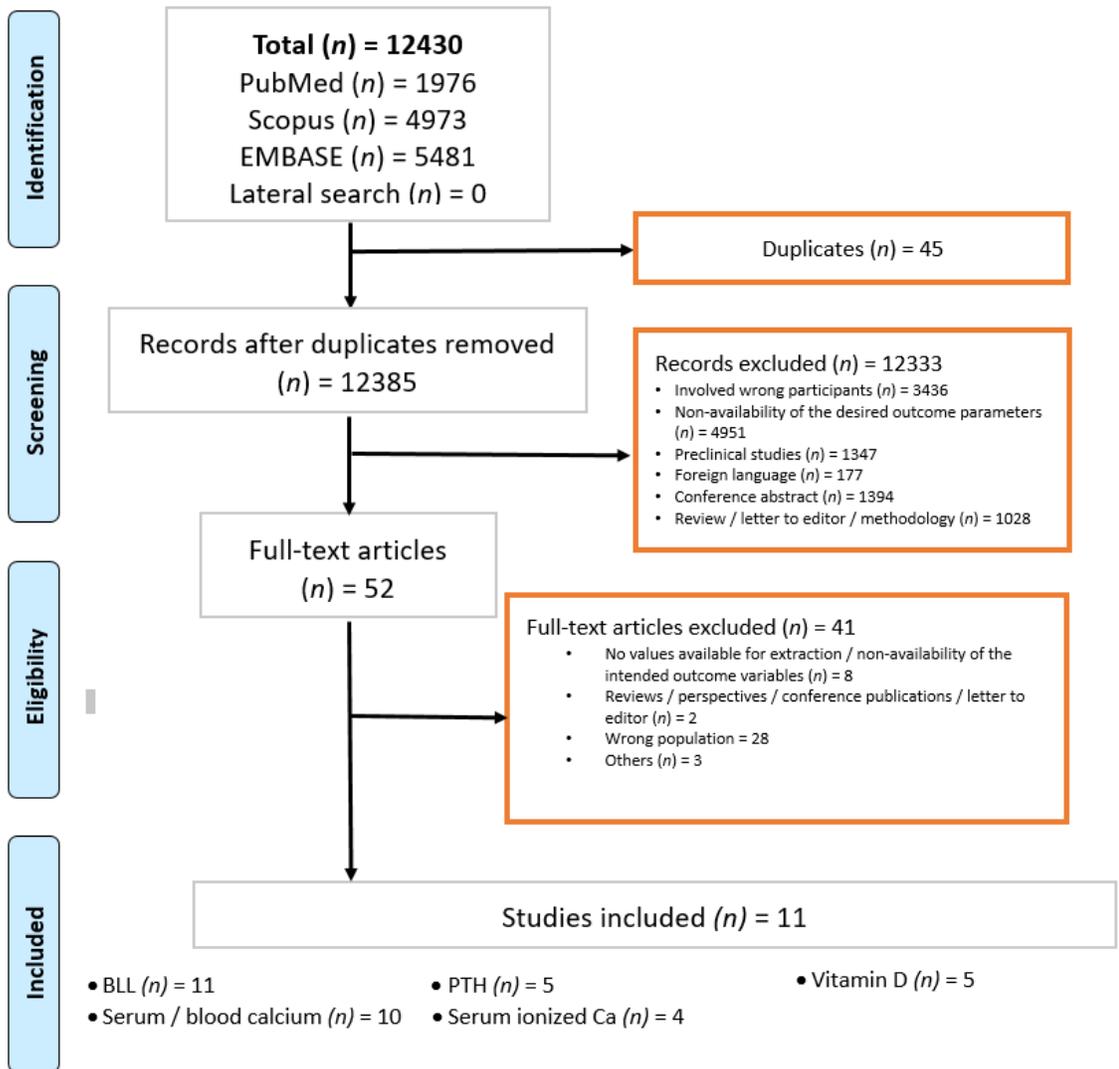
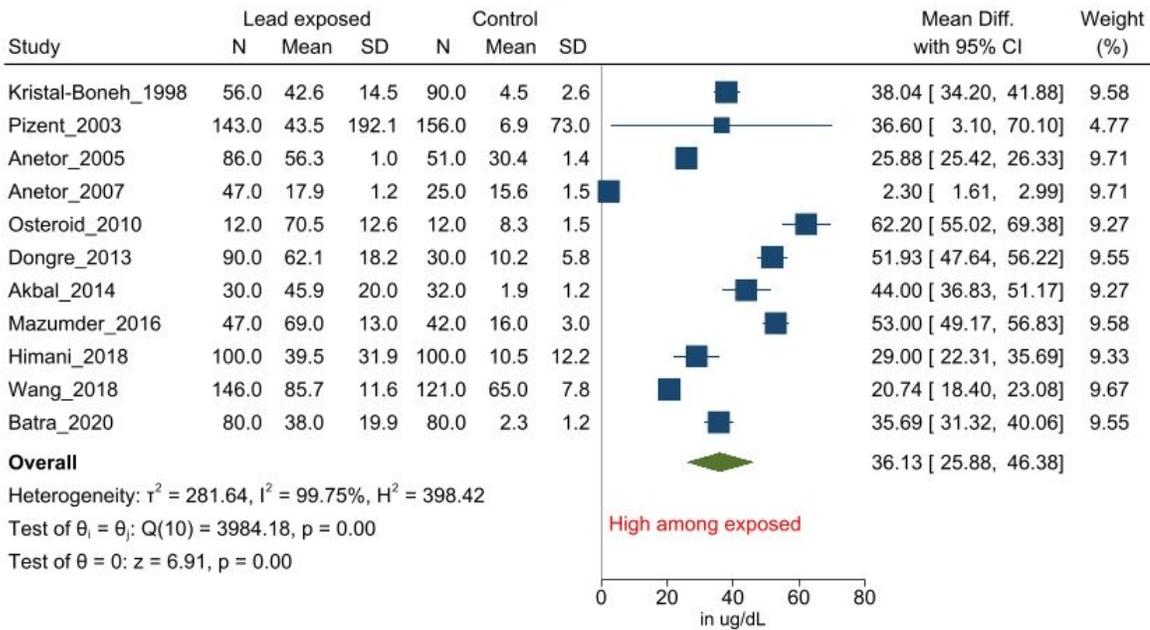


Figure 1

PRISMA flow chart Legends: The flow chart illustrates the number of articles included and excluded at various steps

Blood Lead Levels



Random-effects DerSimonian-Laird model
 Sorted by: year

Figure 2

Forest plot for Blood lead levels (Legends / footnotes) Group differences in blood lead levels (BLL) between the occupationally Pb exposed and unexposed control workers.

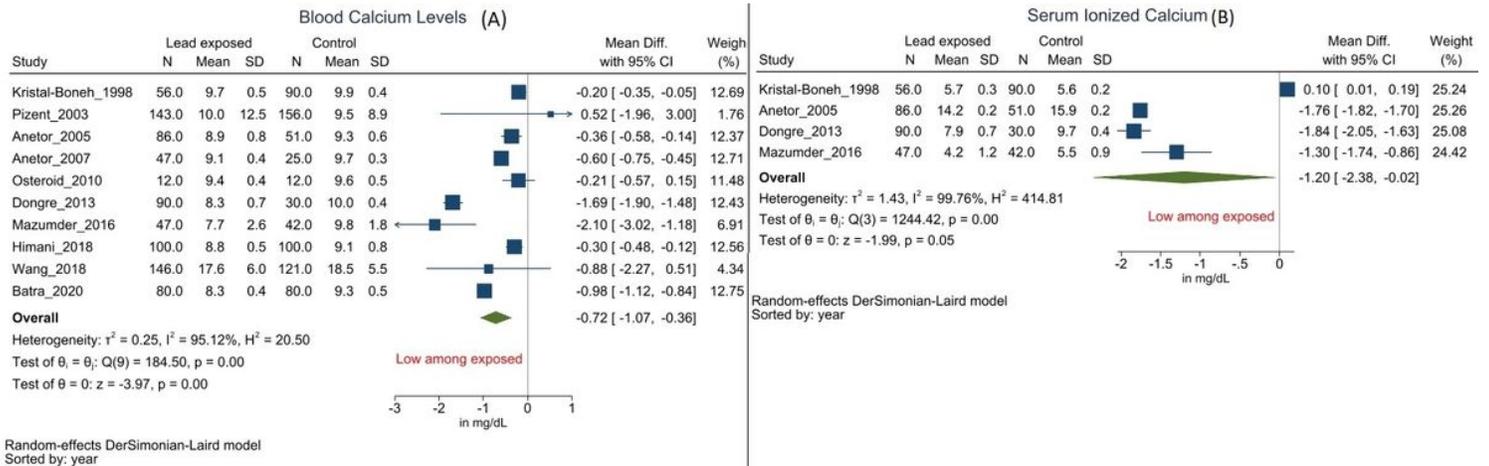


Figure 3

Forest Plot for blood calcium (Legends / footnotes) Group differences in serum calcium (A) and Ionized Calcium (B) between the occupationally Pb exposed and unexposed control workers.

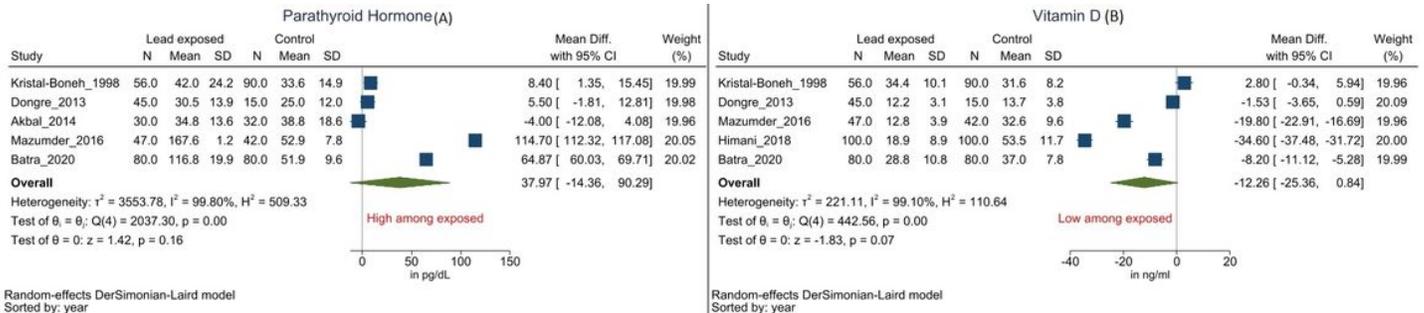


Figure 4

Forest Plot for parathormone (A) and Vitamin D (B) (Legends / footnotes) Group differences in paratharmone (A) and vitamin D (B) between the occupationally Pb exposed and unexposed control workers.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterial.pdf](#)