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Assessing the impact of arsenic, lead, mercury, and cadmium exposure on glycemic and lipid profile markers: A systematic review and meta-analysis protocol

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ABSTRACT

The toxicity of metals presents a significant threat to human health due to the metabolic changes they induce. Thus, it is crucial to understand the impact of exposure to toxic elements on glycemic and lipid profiles. To this end, we developed a systematic review protocol registered in PROSPERO (CRD42023393681), following PRISMA-P guidelines. This review aims to assess environmental exposure to arsenic, cadmium, mercury, and lead in individuals aged over ten years and elucidate their association with glycemic markers such as fasting plasma glucose, glycated hemoglobin, as well as lipid parameters including total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein cholesterol. Articles published in the MEDLINE (PubMed), EMBASE, Web of Science, LILACS, and Google Scholar databases until March 2024 will be included without language restrictions. The modified Newcastle-Ottawa scale will be employed to assess the quality of the included studies, and the results will be presented through narrative synthesis. If adequate data are available, a meta-analysis will be conducted. This review can help understand the metabolic responses to exposure to toxic elements and the associated health risks.

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Specifications table

Subject area:	Environmental Science
More specific subject area:	Endocrinology
Name of your protocol:	Arsenic, lead, mercury and cadmium exposure and glycemic and lipid profile markers: protocol for a systematic review and meta-analysis
Reagents/tools:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to develop the protocol for this systematic review.
Experimental design:	Not applicable
Trial registration:	Not applicable
Ethics:	Not applicable
Value of the Protocol:	1. Identify whether exposure to toxic elements is associated with changes in lipid and glycemic profiles. 2. To contribute to understanding these elements' environmental impact and identify the characteristics of the populations most affected, such as age and geographic region. 3. Highlight the importance of monitoring environmental contamination by toxic elements.

Background

The contamination of the environment with toxic elements poses a global challenge due to its persistent nature and increasing impact on human well-being [1]. Various countries, including the US [2], China [3], India [4], Taiwan [5], France [6], South Korea [7], Canada [8], and Brazil [9], have conducted research to explore the connections between exposure to environmental pollutants and changes in lipid and glycemic profiles.

The general population is exposed to a wide range of metals in their daily lives through the consumption of food and water as well as the inhalation of ambient air [10]. The bioavailability of inorganic arsenic (iAs) in rice is frequently reported to exceed 70% [11]. In a study involving individuals residing in 19 villages in India, where groundwater contamination with As is prevalent, a significantly positive association was found between the concentration of low-density lipoprotein cholesterol (LDL-c) and As in rice [12]. Additionally, a positive correlation was reported between blood lead (Pb) and the weekly consumption of portions of red and white wine, as well as a correlation between mercury (Hg) and the consumption of white wine and fish in Vienna [13].

Furthermore, certain occupational groups are more exposed to environmental contaminant. A study conducted in Ghana revealed that blood Pb concentrations were significantly higher among individuals with occupational exposure to Pb (average of 92.4 μg/L) compared to those without such exposure (average of 40.67 μg/L) [14].

Additionally, metabolic analysis has revealed elevated concentrations of very low-density lipoprotein (VLDL), decreased LDL-c, and increased unsaturated fatty acids in foundry workers exposed to Pb, Cd, and As [15]. Conversely, a study conducted on women in the northern Argentinean Andes showed no indication of adverse effects of As on cardiovascular disease risk markers, including LDL-c [16].

In the non-diabetic population in Taiwan, a significantly positive correlation was found between blood Pb and hemoglobin A1c (HbA1c) [17]. Blood Pb and As may have the potential to predict the risk of diabetes mellitus. However, a study on Mexican students did not find associations between serum Pb and fasting plasma glucose (FPG) [18].

The mechanism underlying the toxicity of these elements is complex, owing to the presence of multiple cellular targets. In general, the production of extracellular reactive oxygen species (eROS), enzyme inactivation, and alterations in antioxidant defense have been proposed as pathways in the mechanism of action of toxic agents, leading to the inhibition of some metabolic pathways [19].

In vitro and in vivo studies have reported that Cd exposure exacerbates damage to pancreatic β-cells. It also disrupts lipid metabolism within pancreatic β-cells and stimulates the production of pro-inflammatory cytokines [20]. Furthermore, toxic elements can influence processes regulated by the endocrine system, which can result in changes in blood glucose concentrations [21]. Additionally, lifestyle habits such as diet and smoking, along with genetic and gender factors, influence the absorption, distribution, retention, or excretion of toxic elements [22]. This review aims to provide evidence on whether exposure to toxic elements in individuals correlates with changes in lipid and glycemic profiles.

Description of protocol

The systematic review protocol follows the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (PRISMA-P) [23] (Supplementary file 1). Our protocol is registered under the code CRD42023393681 in the International Prospective Register of Systematic Reviews (PROSPERO).

Research question

"Does human exposure to As, Cd, Hg, and Pb is associated with changes in lipid and glycemic profiles?" (Table 1).

Inclusion and exclusion criteria

We will include cohort, cross-sectional, case-control, or mixed design studies with control group not exposed (or with low exposure) to As, Cd, Pb/Hg. Children under ten years of age and pregnant women will be excluded. Systematic reviews, abstracts, comments, correspondence, editorials, as well as animal and in vitro studies will be excluded from the review.

Table 1
Research question structured according to "PECOS".

Description	Abbreviation	Elements
Population	P	Individuals aged 10 years and above, including both healthy and populations with chronic diseases such as diabetes, metabolic syndrome, hypertension, and cardiovascular diseases.
Exposure	E	As, Cd, Pb, and Hg assessed in urine, whole blood, plasma, serum, hair, and nails.
Comparison	C	Control groups not exposed to As, Cd, Pb, and/or Hg.
Outcome	O	FBG (mg/dL), HbA1c (%),TC (mg/dL), LDL (mg/dL), HDL (mg/dL), and TG (mmol/L or mg/dL).
Study design	S	Observational (case-control, cohort, cross-sectional, and combined study designs)

Search strategy

All articles published until March 2024 in MEDLINE (PubMed), EMBASE, Web of Science, LILACS, and Google Scholar databases will be searched. Google Scholar will be used to explore gray literature [24]. Gray literature comprises studies not controlled by commercial publishers. Government, academics, and businesses produce it in print and electronic formats; however, including these reports reduces publication bias [25]. Additionally, the reference lists of all records will be manually scrutinized. This review will cover observational studies conducted with individuals aged ten years and above, including case-control, cohort, cross-sectional, and combined study designs.

The search strategy will blend Medical Subject Headings (MeSH) and additional input terms. These search terms will focus on exposure and will yield components that encompass terms such as "glycemic control," "blood glucose," "glucose tolerance test," "glycated hemoglobin," "disorders of lipid metabolism," "cholesterol," "lipoproteins", ''LDL", "lipoproteins, ''HDL", "triglycerides," "heavy metal poisoning," "heavy metals," "cadmium," "cadmium poisoning," "mercury," "mercury poisoning," "arsenic," "arsenic poisoning," and "lead poisoning." These search components will be amalgamated using Boolean operators (AND, OR, and NOT) (Supplementary file 2) to construct search equations for the databases.

Study selection process

All articles found by the search strategy will be exported to the Rayyan QCRI® (The Systematic Reviews Web App) [26] application for initial selection, considering their titles and keywords. Two independent reviewers will select titles and abstracts to identify studies that satisfy the inclusion criteria. Duplicate studies will be excluded.

Full-text versions of potentially eligible studies will be obtained and independently evaluated for eligibility by two reviewers. Any disagreements on eligibility will be resolved through discussion with a third reviewer. The selection process will follow the flowchart developed by PRISMA recommendations [27] (Fig. 1).

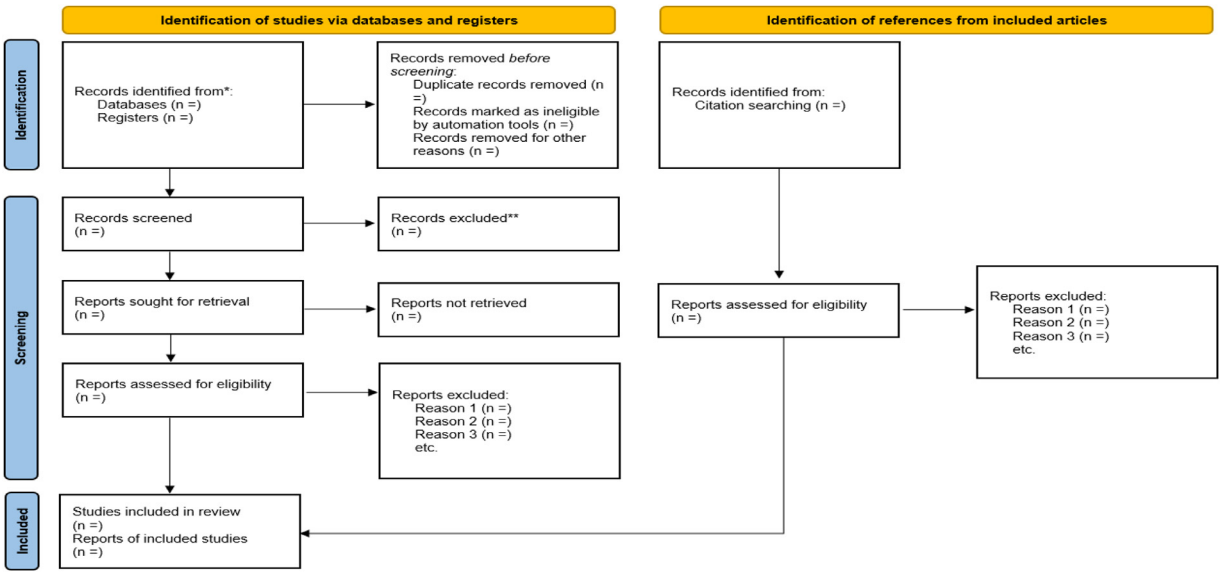

Fig. 1. The flowchart provides a clear view of the comprehensive nature of the systematic study selection process. In the identification phase, duplicate records or for other reasons are excluded. In the screening phase, titles and abstracts are examined to exclude records not meeting the selection criteria. Subsequently, the articles are checked against the inclusion criteria, encompassing the study reports found in the included articles. This thorough process ensures that only articles that meet the requirements of these steps will then be incorporated into the systematic review, providing a high level of assurance of the review's quality. Adapted from Page MJ, et al. (2021) (27).

Data extraction

Two independent reviewers will collect data from primary studies, including authors' names, publication year, country, study design, sample size, population, data on toxic elements exposure, outcomes, type of biological matrix used to assess exposure (urine, whole blood, plasma, serum, hair, and nail) and statistical analyses (Supplementary file 3). We will contact the study authors to acquire the missing data if the results are unclear or incomplete. The first or corresponding author or co-author will be contacted via email. If the requested information is not received, the data will be omitted from our analysis, which will be addressed in the discussion section.

Data synthesis

The results of the eligible studies will be described in a narrative summary considering study characteristics according to author, publication year, study design, sample size, exposure, outcomes, and results [28]. If possible, a meta-analysis will combine and analyze the results of at least two studies using Stata statistical software (Stata Corp., College Station, TX, USA) [29]. The results will be analyzed separately, consistent with the type of study (cross-sectional, prospective cohort, or case-control), grouping them according to toxic elements, observed outcomes, and age (10 - 18 years and over 18 years).

Cochran's Q test will be employed to evaluate the existence of heterogeneity for each outcome and effect measure, while the I^2 statistics will be used to estimate the extent of heterogeneity [30]. A random effects model will compute pooled effect sizes for each outcome [31]. The selection of effect measures is contingent upon the particular study design.

In cross-sectional studies featuring a binary exposure variable coupled with a binary or continuous outcome, the effect measures will typically be the odds ratio (OR) or prevalence ratio (PR). Similarly, we will also utilize OR or PR as effect measures in studies reported with continuous exposure variables and binary outcomes. However, when both the exposure variable and outcome are continuous, the effect measures employed will be Pearson's correlation coefficient or the partial regression coefficient [32].

In case-control studies, the odds ratio (OR) will be the effect measure when dealing with a binary exposure variable. Conversely, the standardized mean difference (SMD) effect will be used when the exposure variable is continuous [33].

In cohort studies, the regression coefficient will be the effect measure for binary and continuous outcomes. Analytical cohort studies encompass exposed and non-exposed groups will utilize the incidence rate ratio (IRR) as the effect measure for binary outcomes [32]. At the same time, the regression coefficient will be the effect measure for continuous outcomes. The findings will be displayed in forest plots [33].

Publication bias will be assessed visually through funnel plots. The Egger and Begg tests will be utilized if the review encompasses ten or more studies [34,35]. The Grading, Development, and Evaluation of Recommendations (GRADE) approach will be employed to evaluate the certainty of the evidence using GRADE PRO software (https://gdt.gradepro.org) [36].

Risk of bias and quality assessment

The modified Newcastle-Ottawa scale will be utilized to evaluate the methodological quality of the cohort and case-control studies [37]. Each study will be assessed based on three primary aspects: selection of study groups, comparability of groups, and ascertainment of the exposure or outcome of interest for case-control or cohort studies. The evaluation of cross-sectional studies will be conducted using the JBI Critical Appraisal Tool, considering the criteria for sample selection, definition of exposure, identification of confounding factors, measurement of outcomes, and the statistical analysis method employed [38].

Papers that attain 60% or more of the maximum possible stars will be considered high quality. Two authors will independently review all the included articles. In case of disagreements between the reviewers, a third reviewer will be called upon to resolve the disputes.

Analysis of subgroups

Meta-regression will be employed to examine factors or study characteristics that contribute to the heterogeneity of results [39]. However, this analysis will depend on specific considerations related to the studies, such as study location, type of population (gender, age, health condition), type of exposure, and number of articles identified.

Additional information

The relationship between exposure to toxic elements and detrimental effects on human health, including metabolic alterations, has been widely examined. Nevertheless, knowledge gaps exist, including the exposure response and the inter- and intra-individual variations in the onset of metabolic changes due to exposure to toxic elements. The findings will offer insights to predict the risk of lipid and glycemic profile changes, helping to monitor populations exposed to occupational hazards and varied lifestyles. Furthermore, these results will enhance understanding of the exposure-response relationship to toxic elements and the underlying risk factors that characterize the diverse human phenotypes.

Limitations

This protocol review relies on observational studies, which excludes the possibility of inferring causality. Furthermore, a high degree of heterogeneity is expected regarding study participants' socio-demographic and environmental characteristics and between the analytical methods of toxic elements. To mitigate this condition, we intend to perform subgroup analyses. Observational studies often also present methodological limitations that make it challenging to establish comparator groups defined in the research question and quantitative analysis procedures; however, we will evaluate the risk of bias and the methodological quality of the studies.

This protocol's strengths include applying the PRISMA guidelines, which promote transparency, quality, and replicability in the study. Furthermore, the design involves analyzing exposure to four toxic elements through various biomarkers and across a wide age range, helping to provide evidence that will explain potential changes in the lipid and glycemic profiles of populations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Geovanna Beatriz Oliveira Rosendo: Conceptualization, Methodology, Investigation. **Julia Curioso Padovam:** Conceptualization, Methodology, Investigation. **Rannapaula Lawrynhuk Urbano Ferreira:** Conceptualization, Methodology, Investigation. **Antonio Gouveia Oliveira:** Conceptualization, Methodology, Writing – review & editing. **Fernando Barbosa:** Validation, Writing – review & editing. **Lucia Fatima Campos Pedrosa:** Conceptualization, Methodology, Investigation, Supervision, Validation, Project administration.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mex.2024.102752.

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