Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE
To conduct a systematic review and meta-analysis of epidemiological studies investigating the association of arsenic, lead, cadmium, mercury, and copper with cardiovascular disease.

DESIGN
Systematic review and meta-analysis.

DATA SOURCES
PubMed, Embase, and Web of Science searched up to December 2017.

RESULT
The review identified 37 unique studies comprising 348,259 non-overlapping participants, with 13,033 coronary heart disease, 4,205 stroke, and 15,274 cardiovascular disease outcomes in aggregate. Comparing top versus bottom thirds of baseline levels, pooled relative risks for arsenic and lead were 1.36 (95% confidence interval 1.04 to 1.73) and 1.43 (1.16 to 1.76) for cardiovascular disease, 1.23 (1.04 to 1.45) and 1.85 (1.27 to 2.69) for coronary heart disease, and 1.15 (0.92 to 1.43) and 1.63 (1.14 to 2.34) for stroke. Relative risks for cadmium and copper were 1.33 (1.09 to 1.64) and 1.81 (1.05 to 3.11) for cardiovascular disease, 1.29 (0.98 to 1.71) and 2.22 (1.31 to 3.74) for coronary heart disease, and 1.72 (1.29 to 2.28) and 1.29 (0.77 to 2.17) for stroke. Mercury had no distinctive association with cardiovascular outcomes. There was a linear dose-response relation for arsenic, lead, and cadmium with cardiovascular disease outcomes.

CONCLUSIONS
Exposure to arsenic, lead, cadmium, and copper is associated with an increased risk of cardiovascular disease and coronary heart disease. Mercury is not associated with cardiovascular risk. These findings reinforce the importance of environmental toxic metals in cardiovascular risk, beyond the roles of conventional behavioural risk factors.

Introduction
In recent decades, exposures to environmental toxic metals of hydrogeological origin (eg, arsenic, lead, cadmium, mercury, and copper) have become a global public health concern owing to their potential deleterious health effects in humans.1-5 For example, according to the World Health Organization and the International Agency for Research on Cancer, arsenic and cadmium are group I human carcinogens and arsenic is the world’s second leading water-borne cause of mortality.6-9 Metalloids such as arsenic often fall into the category of heavy metals due to similarity in properties.8 Chronic exposure to high levels of arsenic, cadmium, and other toxic metals has also been associated with higher risk of cancers of the bladder, kidney, liver, lung, and skin.9 Emerging evidence suggests that these toxic metals may have adverse effects on these outcomes even at lower concentrations,3 which might be prevalent in many parts of the world.

Additionally, there are increasing suggestions that exposure to arsenic and other (often co-occurring) toxic metals may be an independent risk factor for cardiovascular disease.10 11 However, despite their well established role as immunotoxicants and carcinogens, the associations between environmental toxic metals and risk of clinical cardiovascular disease outcomes remain less well characterised. Although there are several individual reports published on the topic, they vary greatly in sufficient detail (eg, on associations with diverse cardiovascular outcomes) and in study design (eg, ecological versus individual-level associations). Interpretation of the earlier reviews is difficult, as they were mostly systematic reviews without quantitative synthesis of estimates.12 13 and focused typically on a single toxic metal,14-16 or combined estimates from ecological study designs (which are prone to suffer from substantial bias and confounding).17 Additionally, whether a detrimental association with cardiovascular disease exists in low
or medium levels of exposure (ie, typical for many global regions) remains unclear. Therefore, given the global nature of the toxic metal contamination, accurate characterisation of the associations between these environmental contaminants and cardiovascular disease is essential to understand the aetiology of cardiovascular disease, and critically, to inform public health efforts to reduce toxic metal exposure.

To help clarify the evidence, we aimed to summarise the available population based epidemiological studies in a comprehensive systematic review and meta-analysis to determine the associations of selected metal contaminants (measured at individual level) with the risk of first-ever cardiovascular outcomes (including cardiovascular disease, coronary heart disease, and stroke), and quantify any dose-response relation. For the current study, we focus primarily on five major toxic metals or metalloids, owing to their global public health relevance. We have included arsenic, lead, cadmium, and mercury, which have been included in the World Health Organization’s list of “Ten chemicals of major public health concern” and have potential mechanistic links to cardiovascular diseases. In addition, we have included copper as it appears to promote atherosclerosis by enhancing the oxidation of LDL-cholesterol and may increase the risk of clinical cardiovascular disease outcomes.

**Methods**

**Search strategy**

This study was conducted in accordance with the PRISMA and MOOSE guidelines (see fig 1 and supplementary materials, table S1). We comprehensively searched the MEDLINE, Embase, and Web of Science electronic databases to identify studies published until 5 December 2017 (date of last search), which examined the association between arsenic, lead, cadmium, mercury, and copper with primary outcomes of interest. The primary outcomes were coronary heart disease (defined as non-fatal myocardial infarction, angina, coronary revascularisation (ie, percutaneous transluminal coronary angioplasty or coronary artery bypass surgery, or coronary heart disease death), stroke (defined as fatal or nonfatal stroke), and composite cardiovascular disease (comprised of coronary heart disease and stroke). The computer based searches combined search terms related to the toxic metal exposures (eg, arsenic*, lead*, mercury*, etc) and outcomes of interest (eg, cardiovascular disease*, myocardial infarction*, stroke*, etc), without any language restriction. Further studies were sought by manually searching reference lists of the relevant articles. When relevant information was unavailable, efforts were made to contact corresponding authors. Details of the search strategy are presented in supplementary materials, appendix 1.

**Selection criteria**

We included studies if they met the following initial search criteria: were prospective cohort, case-control, or nested case-control in design; had sampled from healthy (ie, participants or referents, where appropriate, were based on initially healthy participants) or general populations (ie, populations with both healthy and prevalent cases of cardiovascular disease at baseline); assessed toxic metal exposure at individual level rather than aggregate level (eg, individual-level exposure to arsenic in drinking water); or reported risk estimates for cardiovascular disease, coronary heart disease, or stroke, for at least one toxic metal. We excluded studies for the following reasons: they only reported on mean levels and standard deviations of toxic metals in cases and non-cases; they only assessed exposure to toxic metals using a self reported dietary measure; or were cross-sectional or ecological in design. Two independent reviewers screened the search results to assess conformity with selection criteria, with disagreement resolved with a third reviewer. In cases of multiple publications from a single study, we used the most up to date information.

**Data extraction and quality assessment**

Data on the following characteristics were extracted independently by two investigators using standardised protocols: sample size; study design; sampling population; location (defined as Europe, North America, and the Asia-Pacific region); year of baseline survey; study design; age range of participants at baseline; sex; mean levels of environmental contaminants at baseline; sample type (serum, plasma, or adipose tissue); storage temperature; assay methods; duration of follow-up; numbers of disease outcomes of interest and reported effect estimates with
Fig 1 | PRISMA flow diagram of search strategy

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**Fig 1:** PRISMA flow diagram of search strategy

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...log relative risk for a 1 standard deviation increase (or equivalently, as 2.18/2.54 times the log relative risk for a comparison of extreme quarters). Standard errors of the log relative risks were calculated using published confidence limits and were transformed in the same way. For example, the study by Kromhout et al reported a relative risk of cardiovascular disease of 1.06 (95% confidence interval 0.47 to 2.37) comparing the top versus bottom quartile of lead exposure, corresponding to a log relative risk of 0.058 and standard errors (log relative risk) of 0.41.26 The conversion of risk estimates to top versus bottom third exposure of lead in this study is performed as follows: log relative risk, $\log_{\text{base 2}}((\text{top} - \text{bottom third})) = (2.18/2.54) \times 0.058 - 0.05$ and standard errors log relative risk, $\log_{\text{base 2}}((\text{top} - \text{bottom third})) = (2.18/2.54) \times 0.41 - 0.35$.

We calculated summary relative risks by pooling the study-specific estimates using a random-effects model that included study heterogeneity (parallel analyses used fixed-effect models). We assessed the consistency of findings across individual studies by standard $\chi^2$ tests and the $I^2$ statistic.27 We assessed heterogeneity between observational cohorts by comparing results from studies grouped according to prespecified study level characteristics (such as study design, location, year of baseline survey, duration of follow-up, numbers of outcomes recorded, outcome definition, degree of statistical adjustment used, and sample type) using meta-regression. In particular, for studies investigating the association of arsenic with cardiovascular disease outcomes, the impact of the measurement source (biomarker v water) on risk estimates was assessed in subgroup analyses. We assessed evidence of publication bias across studies using funnel plots and Egger test for outcomes where at least three studies were available.28

We performed dose-response meta-analyses using generalised least-squares trend estimation (GLST) analysis as described by Greenland and Longnecker.29 We estimated study-specific slopes (linear trends) from the correlated natural logs of the relative risks across toxic metal exposure categories. Only studies that reported the number of cases, non-cases, person years of follow-up, and the relative risks with the variance estimates for at least three quantitative exposure categories were included. The median or mean level of the toxic metal in the original scale was assigned to the corresponding relative risk for each exposure category. If data were not available, we estimated the median using the midpoint of each category. When the highest or lowest category was open, we assumed it to be of the same amplitude as the adjacent category. Potential nonlinear dose-response relations were examined by modelling levels of toxic metals using restricted cubic splines.30 A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero. All statistical tests were two sided and used a significance level of $P<0.05$. We performed all analyses using Stata version 12 (StataCorp, College Station, TX).
Patient involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results
Study level characteristics
A total of 37 unique studies reporting on 348,259 distinct participants were identified, including relevant available data on arsenic (12 studies), lead (11), cadmium (8), mercury (9), and copper (6) (see table 1, fig 1, and supplementary material, table S3).

Overall, 12 of these studies were based in North America, 17 in Europe, and 8 in the Asia-Pacific region. Thirty three studies were prospective (26 cohorts and 7 nested case-control (ie, case-control study nested in a cohort study) or case-cohort studies) and four studies were case-control studies. Environmental contaminant measurement methods used in each study are detailed in supplementary materials, table S4. Primary sources of measurement for arsenic were individual-level drinking water (6 studies), urine (4), and toenails (2). Lead and copper levels in blood were measured in all studies. Cadmium levels in urine were reported in three studies, in blood in four studies, and in toenails in one study. Exposure to mercury levels was measured in hair (2 studies), blood (4), or toenail (3) samples (supplementary material, table S4). Average baseline levels of contaminants in studies reporting baseline exposure ranged from 3.7 μg/L to 4.9 μg/L for arsenic in urine and 0.7 μg/L to 131.1 μg/L for arsenic in drinking water, whereas baseline levels of lead, cadmium, mercury, and copper in blood ranged from 2.6 μg/dL to 44.3 μg/dL, 0.44 μg/L to 1.3 μg/L, 0.004 μg/L to 3.5 μg/L, and 0.96 mg/L to 1.27 mg/L respectively. Table 2 and table 3 show that study quality assessed using the Newcastle-Ottawa scale varied. Most studies were of medium to high quality (score ≥7). Twelve studies (10 cohort, 2 case-control) were of low quality.

Associations between environmental contaminants and the risk of cardiovascular disease outcomes
Thirty five studies were included in the meta-analysis of environmental contaminants and cardiovascular disease outcomes. Six studies (one reporting on arsenic, two on cadmium, three on mercury) which did not use an appropriate assessment of heavy metal exposure (ie, use of cadmium levels in toenails) or did not adjust for important confounders of heavy metal exposure (eg, smoking for cadmium or seafood intake for mercury) were excluded from the analysis (table 1). In total, 14,706, 12,033, and 3613 cases of cardiovascular disease, coronary heart disease, and stroke, respectively, across 35 contributing studies were included in the meta-analysis. The total follow-up duration ranged from five to 36 years in the prospective studies. Twenty three studies adjusted for conventional risk factors for cardiovascular disease including age, sex, and sociodemographic factors (ethnicity, education, income) as well as additional risk factors such as smoking status, blood pressure, lipids, and medical history. Thirteen studies adjusted for age, sex, and sociodemographic factors. Three studies adjusted for age and sex only. Figure 2 shows the summary plot for cardiovascular disease, coronary heart disease, and stroke comparing participants in the top third with those in the bottom third of various environmental contaminants. Figure 3, figure 4, and figure 5 show the forest plots for each separate outcome.

Arsenic, lead, cadmium, and copper were significantly associated with the risk of coronary heart disease, with respective relative risks of 1.23 (95% confidence interval 1.04 to 1.45), 1.85 (1.27 to 2.69), 1.29 (0.98 to 1.71), and 1.72 (1.29 to 2.28). There was no association of mercury levels with coronary heart disease, relative risk of 0.99 (0.65 to 1.49). There was evidence of heterogeneity in coronary heart disease estimates across studies for most environmental contaminants (I²=78%, P<0.001 for arsenic; I²=66%, P=0.005 for lead; I²=52%, P=0.08 for cadmium; I²=85%, P<0.001 for mercury; and I²=67%, P=0.03 for copper).

Similar to the risk of coronary heart disease, arsenic, lead, cadmium, and copper were also associated with an increased risk of cardiovascular disease (relative respective risks of 1.30, 95% confidence

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**Table 1**

<table>
<thead>
<tr>
<th>Metals</th>
<th>No of studies</th>
<th>No of participants</th>
<th>No of events</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>Cardiovascular disease</td>
<td>7</td>
<td>135,943</td>
<td>3208</td>
<td>1.30 (1.04 to 1.63)</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease</td>
<td>8</td>
<td>190,816</td>
<td>4640</td>
<td>1.15 (0.92 to 1.43)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>4</td>
<td>134,526</td>
<td>961</td>
<td>1.43 (1.16 to 1.76)</td>
</tr>
<tr>
<td>Lead</td>
<td>Cardiovascular disease</td>
<td>10</td>
<td>110,382</td>
<td>4970</td>
<td>1.85 (1.27 to 2.69)</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease</td>
<td>8</td>
<td>91,779</td>
<td>2228</td>
<td>1.63 (1.14 to 2.34)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>6</td>
<td>89,494</td>
<td>518</td>
<td>1.33 (1.09 to 1.64)</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Cardiovascular disease</td>
<td>6</td>
<td>50,674</td>
<td>3756</td>
<td>1.29 (0.98 to 1.71)</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease</td>
<td>5</td>
<td>32,070</td>
<td>1651</td>
<td>1.72 (1.29 to 2.28)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>3</td>
<td>9123</td>
<td>601</td>
<td>0.94 (0.66 to 1.36)</td>
</tr>
<tr>
<td>Mercury</td>
<td>Cardiovascular disease</td>
<td>4</td>
<td>11,410</td>
<td>4866</td>
<td>0.99 (0.65 to 1.49)</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease</td>
<td>5</td>
<td>9169</td>
<td>3838</td>
<td>0.94 (0.66 to 1.36)</td>
</tr>
<tr>
<td>Copper</td>
<td>Cardiovascular disease</td>
<td>4</td>
<td>5385</td>
<td>538</td>
<td>1.22 (1.31 to 3.74)</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease</td>
<td>4</td>
<td>7299</td>
<td>492</td>
<td>1.29 (0.77 to 2.17)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>2</td>
<td>728</td>
<td>100</td>
<td>1.81 (1.05 to 3.11)</td>
</tr>
</tbody>
</table>

**Fig 2** | Summary of the association of environmental contaminants with cardiovascular outcomes. Pooled risk estimates were calculated using random effects meta-analyses. The relative risk compares the risk for each outcome in individuals in the top third with those in the bottom third of baseline levels of the environmental contaminants (ie, extreme thirds). Risk estimates from separate studies were typically adjusted for basic demographics (eg, age, sex, systolic blood pressure, smoking, history of diabetes, etc)
there was significant evidence of heterogeneity in cardiovascular disease (0.94, 0.66 to 1.36). However, of an association of mercury levels with the risk of cardiovascular disease estimates across studies (I² ranging from 68%, P=0.001 for lead to 84%, P<0.001 for mercury).

Lead and cadmium were also associated with a significantly increased risk of stroke (respective relative interval 1.04 to 1.63; 1.43, 1.16 to 1.76; 1.33, 1.09 to 1.64; and 1.81, 1.05 to 3.11). There was no evidence of an association of mercury levels with the risk of cardiovascular disease (0.94, 0.66 to 1.36). However, there was significant evidence of heterogeneity in cardiovascular disease estimates across studies (I² ranging from 68%, P=0.001 for lead to 84%, P<0.001 for mercury).
Dose-response meta-analyses

The dose-response relations between levels of toxic metals and cardiovascular outcomes, based on available relevant data are shown in supplementary materials, figure S1. Only two studies reporting on exposure to arsenic in drinking water, three studies reporting on exposure to cadmium, and four studies reporting on exposure to lead, provided sufficient information to perform the dose-response analysis. In summary, for baseline arsenic levels in well water and risk of cardiovascular disease, there was evidence of a linear association across the full spectrum of arsenic levels (0 μg/L to 369.5 μg/L, P=0.31 for nonlinearity; see supplementary material, fig S1A). Similarly, there was evidence of a linear association between lead levels in blood and the risk of coronary heart disease (P=0.677 for nonlinearity; see supplementary material, fig S1B), with a pooled relative risk for risk of coronary heart disease per 5 μg/dL increment in lead levels being 1.07 (95% confidence interval 1.04 to 1.10). By contrast, for the association between cadmium levels in urine and the risk of cardiovascular disease, an initial steep increase in risk (within urine cadmium levels of 0.11 μg/g to 1.41 μg/g) was followed by a weaker increase in risk beyond 1.41 μg/g. The relative risk of cardiovascular disease for each 0.75 μg/g increment of cadmium was 1.21 (95% confidence interval 1.09 to 1.33, P=0.656 for nonlinearity; see supplementary materials, fig S1C). There was a significant linear association between cadmium levels in urine and the risk of coronary heart disease (P=0.865 for nonlinearity; see supplementary materials, fig S1D).

Subgroup analyses and assessment of publication bias

Little of the variation in risk estimates across contaminants was explained by any of the recorded study level characteristics (P>0.05 for most factors investigated; see supplementary materials, fig S2-S6). For example, there was no significant difference in relative risks for cardiovascular disease across the types of individual exposures (eg, blood v other measurement sources; P=0.05). Additionally, pooled relative risks were all generally similar regardless of the level of adjustment for possible confounding factors considered in the included studies, by geographical location, baseline health, or size of the studies. In analyses investigating the effect of arsenic measurement source (urine and toenails v water) on risk estimates of cardiovascular disease, coronary heart disease, and stroke, risk estimates were comparable between studies with no evidence of significant heterogeneity between studies measuring arsenic in drinking water versus biomarkers (see supplementary materials, fig S7). Subgroup analyses comparing the risk of cardiovascular disease, coronary heart disease, and stroke in never-smokers compared to current and former smokers produced similar results for arsenic and cadmium exposure (see supplementary materials, fig S8 and S9). Funnel plots (see supplementary materials, fig S10-S14) and tests for publication bias for other markers and outcomes were non-significant for most contaminants (P>0.05), however, there was
evidence of publication bias for studies reporting on arsenic association with cardiovascular disease (P=0.01) and coronary heart disease (P<0.001) (see supplementary materials, table S5).75

Discussion
Principal findings
We have conducted a systematic review and meta-analysis, using non-overlapping data from approximately 350,000 participants from 37 studies, to help clarify available evidence on the associations of environmental toxic elements with the risk of cardiovascular disease. Overall, our results indicate that exposures to arsenic, lead, cadmium, and copper are each positively and importantly associated with cardiovascular disease and coronary heart disease, cardiovascular disease and stroke, or all cardiovascular outcomes. By contrast, mercury was not significantly associated with cardiovascular risk. Additionally, based on relevant available data, the shape of associations for levels of arsenic, lead, and cadmium were approximately linear.
Comparison with other studies

Findings observed in this review may have several potential explanations. We found a positive association of arsenic, an environmental toxic metal found in large quantities in rice and groundwater in many parts of the world, with the risk of coronary heart disease.\(^86\)\(^76\) Arsenic exposure has been reported to accelerate and exacerbate atherosclerosis in apolipoprotein E-knockout mice.\(^78\)\(^79\) Clinical and experimental studies of arsenic exposure have reported the production of reactive oxygen species in endothelial cells, up regulation of inflammatory signals, and higher blood pressure.\(^82\)\(^84\) These findings extend several previous epidemiological studies that reported striking associations with Blackfoot disease (a severe peripheral vascular disease) in people exposed to extremely high cumulative doses of arsenic.\(^85\)\(^86\)

Although circulating levels of lead seem to be in decline in the developed world,\(^87\) owing principally to the concomitant decrease in the usage of leaded gasoline and leaded paint, lead exposure remains considerably high in many areas.\(^5\)\(^88\) The strong positive association found in our review between lead and the risk of cardiovascular disease, reinforces lead
which have been suggested to induce endothelial mechanism for the potential deleterious effects of several in vivo and in vitro studies. Another possible mediated lipid peroxidation has been demonstrated in by generation of reactive oxygen species. Copper, albeit based on limited data, the potentially linear dose-response relation that we have observed indicates that even at lower average exposure levels (common in many global regions), these toxic metals may have a detrimental impact on vascular health.

We also observed a positive association between levels of cadmium and cardiovascular disease, which was independent of several potential risk of cardiovascular disease factors (including smoking status). Cadmium's adverse effects on the vascular system are thought to be mediated by oxidative stress, inflammation, and endothelial cell damage, which can result in atherosclerosis. This is important as cadmium is widely prevalent in groundwater and common plant-based foods (eg, rice and vegetables).

Conversely, mercury, a potentially toxic trace metal that humans are exposed to primarily through fish consumption, was not significantly associated with the risk of cardiovascular disease in the current review. Although some individual studies have observed inverse relations between mercury levels and the risk of cardiovascular disease, there is currently no accepted biological explanation that supports such a link.

Strengths and limitations of the study

Strengths and limitations of this work merit careful consideration. This is the first comprehensive meta-analysis of several key environmental toxic metals in relation to the risk of cardiovascular disease. We have focused solely on individual-level assessments of exposure to toxic metals, and performed our analyses based primarily on toxic metals measured directly using an objective biomarker or well established measures of individual level exposure such as arsenic in drinking water. However, it should be noted that the biological determinants, precision of measurements and exposure as a major public health concern.

Two key pathways by which lead has been implicated in the risk of cardiovascular disease are mediation through accelerated systolic blood pressure and damage to renal function. Previous studies have also suggested an association of lead with atherosclerosis as a result of lead-induced oxidative stress and inflammation after exposure.

The present review also shows a positive association of copper with cardiovascular disease, as suggested in previous studies. While copper is an essential trace element, excess copper can induce oxidative stress by generation of reactive oxygen species. Copper-mediated lipid peroxidation has been demonstrated in several in vivo and in vitro studies. Another possible mechanism for the potential deleterious effects of copper is through a copper-homocysteine complex which have been suggested to induce endothelial dysfunction and vascular injury.

For both arsenic and copper, albeit based on limited data, the potentially linear dose-response relation that we have observed indicates that even at lower average exposure levels (common in many global regions), these toxic metals may have a detrimental impact on vascular health.

<table>
<thead>
<tr>
<th>Metals</th>
<th>Measurement source</th>
<th>No of participants</th>
<th>No of events</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (95% CI)</th>
<th>Level of adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHSCS</td>
<td>Toenails</td>
<td>3939</td>
<td>43</td>
<td>0.97 (0.86 to 1.09)++</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>HEALS</td>
<td>Not reported</td>
<td>11 109</td>
<td>82</td>
<td>1.03 (0.52 to 2.03)++</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>SHS</td>
<td>Urine</td>
<td>3575</td>
<td>264</td>
<td>1.39 (0.98 to 1.98)+++</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Schel (2009)</td>
<td>Water</td>
<td>115 903</td>
<td>572</td>
<td>1.32 (1.00 to 1.74)++</td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>
| Subtotal: P=0.08, I²=56.0%  

| Lead  |                    |                    |             |                       |                       |                     |
| Zutphen study | Blood   | 146                | 18          | 1.24 (0.42 to 3.71)+++ |                       | +++                 |
| SOF    | Blood              | 533                | 21          | 1.20 (0.26 to 5.63)++  |                       | +                   |
| BRHS   | Blood              | 7379               | 66          | 1.32 (0.76 to 2.30)++  |                       | ++                  |
| ABLES  | Blood              | 58 368             | 132         | 1.72 (0.61 to 4.81)++  |                       | ++                  |
| NHANES III | Blood    | 13 946             | 141         | 2.51 (1.20 to 5.26)+++ |                       | +++                 |
| McElvenny (2015) | Blood   | 9122               | 149         | 2.59 (0.59 to 11.31)++ |                       | ++                  |
| Subtotal: P=0.76, I²=0%  

| Cadmium |                    |                    |             |                       |                       |                     |
| CadmiBel | Blood              | 956                | 21          | 0.65 (0.17 to 2.52)++  |                       | ++                  |
| SHS    | Urine              | 3348               | 244         | 1.71 (1.19 to 2.47)+++ |                       | +++                 |
| MDCS   | Blood              | 4819               | 336         | 1.89 (1.28 to 2.78)+++ |                       | +++                 |
| Subtotal: P=0.33, I²=9.5%  

| Copper |                    |                    |             |                       |                       |                     |
| Reunanen (1996) | Blood  | 68                 | 30          | 2.26 (0.65 to 7.88)++  |                       | ++                  |
| Marniemi (2005) | Blood  | 660                | 70          | 1.15 (0.65 to 2.03)++  |                       | ++                  |
| Subtotal: P=0.34, I²=0%  

Fig 5 | Association between environmental contaminants and stroke. NR=not reported; ++=minimally adjusted (typically adjusted for age and sex only); +++=adjusted for at least one non blood based cardiovascular risk factor (eg, systolic blood pressure, body mass index, history of diabetes etc); ++++=additionally adjusted for at least one blood based cardiovascular risk factor (eg, total cholesterol, C-reactive protein, etc)
ability to reflect long term exposure may differ across various biomarkers. Therefore, to ensure consistent long term exposure assessment, the use of repeated measurements over time that accounts for any potential individual variation in levels (ie, regression dilution) should be considered in future studies. Furthermore, most studies that measured arsenic and cadmium levels in urine were based on spot or first morning void samples, which might be limited by the fact that they reflect the hydration status of the individual at the time of collection, and therefore, may differ markedly in dilution owing to differences in urinary flow rate, and differences in stability and reproducibility of metals measured in them. Additionally, although over half the risk estimates for urinary arsenic and cadmium from all included studies were creatinine adjusted, some were unadjusted for any marker of urinary dilution. While this review is limited to published findings, the use of individual participant data, in future large-scale primary studies, would allow a more detailed and specific assessment of the association between the considered environmental toxic metals and cardiovascular disease, including: assessing the role of routes of exposure (eg, environmental v occupational); a standardised adjustment for confounders (eg, smoking status); reduce heterogeneity resulting from meta-analysis of diverse study populations; and a more consistent characterisation of any potential dose-response relation. Such comprehensive assessments are currently underway. Equally, our review was solely based on observational data which might be affected by unmeasured confounders – making a causal inference difficult. In this regard, an earlier randomised trial, based on people with pre-existing cardiovascular disease, suggested that moderate reduction of cardiovascular events occurred after intravenous chelation therapy (which facilitates urinary excretion of heavy metals) compared with placebo. However, further conclusive trials, especially those involving general populations, are needed. Additionally, the identification of polymorphisms influencing circulating levels of these toxic metals which can be used as proxies for circulating levels (such as polymorphisms near AS3MT, MT1A/B), may also allow future investigations of potential causal associations with disease using instrumental variable analysis (ie, mendelian randomisation analyses).

Implications for clinicians and policy makers
Our findings may have important policy and scientific implications. Firstly, these findings highlight the importance of environmental toxic metals in enhancing cardiovascular risk, beyond the roles of conventional behavioural risk factors (such as tobacco use and unhealthy diet). These results may have a key policy implication given that current global noncommunicable disease prevention strategies (eg, WHO 2018 Report) are focused primarily on tackling behavioural determinants. Recognising environmental factors (such as toxic metals) as additional priorities, therefore, will help gain wider sociopolitical support for setting up appropriate legislation, preventive strategies and standards, and investment to tackle these major global determinants of cardiovascular diseases. Secondly, the observed associations appeared approximately linear for arsenic, lead, and cadmium levels with cardiovascular disease outcomes, indicating the risk of adverse health consequences even at a relatively low exposure of these toxic metals. Nonetheless, these current findings warrant further detailed research to reliably quantify suboptimal levels to define individuals at risk and to trigger appropriate clinical action. Presently, in clinical practice, toxicity for these metals, if suspected, are established through a range of diagnostic investigations including blood and 24-hour urinary analyses and typically involving an inductively coupled plasma mass spectrometry analytical technique for elemental determinations. Treatment options for heavy metal toxicity include various antidotes and chelating agents (which enhance the elimination of metals from the body) such as succimer (DMSA), unithiol (DMPS), sodium calcium edetate, and dimercaprol. However, since efficacy and response of these therapies vary greatly, primary prevention, by developing evidence based public health guidelines and innovative low cost, scalable interventions to reduce human exposure to these contaminants, should be prioritised.

Conclusion
Results of this meta-analysis indicate that exposure to arsenic, lead, cadmium, and copper is associated with an increased risk of cardiovascular disease and coronary heart disease. By contrast, mercury was not associated with cardiovascular risk. These findings reinforce the (often under-recognised) importance of environmental toxic metals in cardiovascular risk, beyond the roles of conventional behavioural risk factors. Further detailed work, however, to better characterise these associations and to assess causality, is needed.

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Contributors: RC and ED designed the study. AR, LMO, SS, SKK, RC, and ED acquired, analysed, and interpreted the data. RC, AR, SS, and ED drafted the manuscript. AR and SKK performed the statistical analysis. RC and ED supervised the study. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. RC is the guarantor.

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Transparency: The manuscripts guarantor (RC) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/


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Supplementary materials: Appendix 1, figures S1-S14, and tables S1-S6.