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

Rajiv Chowdhury,[1] Anna Ramond,[1] Linda M O'Keeffe,[2,3] Sara Shahzad,[1] Setor K Kunutsor,[4,5,6] Taulant Muka,[7] John Gregson,[8] Peter Willeit,[1,9] Samantha Warnakula,[1] Hassan Khan,[10] Susmita Chowdhury,[1] Reeta Gobin,[11] Oscar H Franco,[7] Emanuele Di Angelantonio[1,12,13]

For numbered affiliations see end of article.

Correspondence to: S Shahzad ss2231@medschl.cam.ac.uk

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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.

REVIEW METHODS

Studies reporting risk estimates for total cardiovascular disease, coronary heart disease, and stroke for levels of arsenic, lead, cadmium, mercury, or copper were included. Two investigators independently extracted information on study characteristics and outcomes in accordance with PRISMA and MOOSE guidelines. Relative risks were standardised to a common scale and pooled across studies for each marker using random effects meta-analyses.

RESULTS

The review identified 37 unique studies comprising 348 259 non-overlapping participants, with 13 033 coronary heart disease, 4205 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 1.30 (95% confidence interval 1.04 to 1.63) 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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In recent years, exposures to environmental toxic metals of hydrogeological origin (eg, arsenic, lead, cadmium, mercury, and copper) have become a major global public health concern

There are increasing suggestions that exposure to toxic metals may be an independent risk factor for cardiovascular disease

WHAT THIS STUDY ADDS

Exposure to arsenic, lead, and cadmium showed a positive and approximately linear association with the risk of cardiovascular disease

Mercury was not associated with any cardiovascular outcomes

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 7] 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,[5] 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.[18 19] 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.[20-23]

Methods

Search strategy

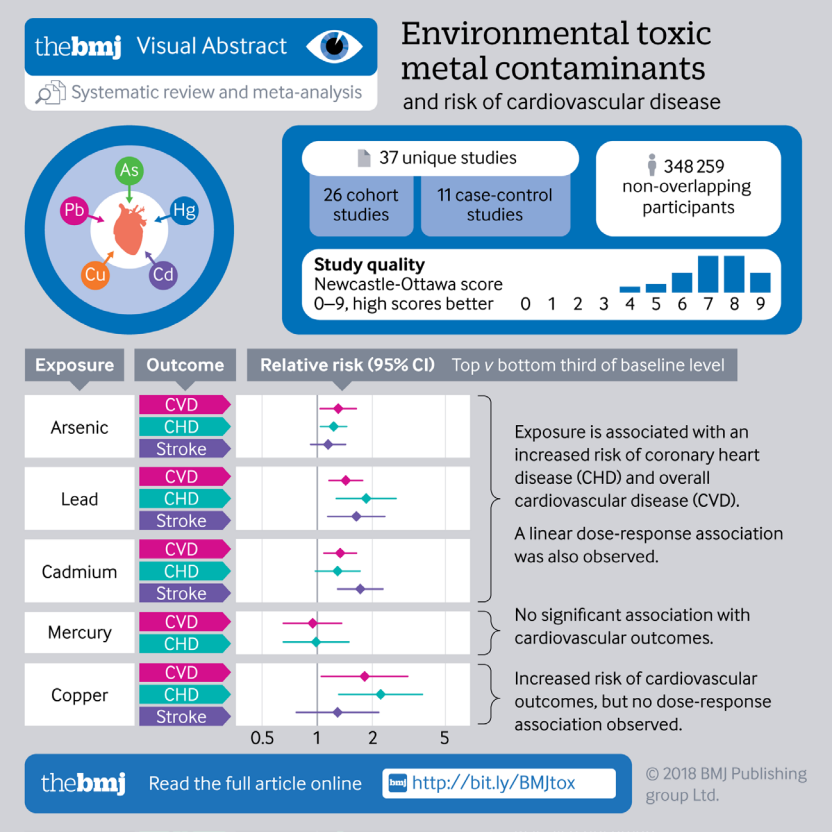
This study was conducted in accordance with the PRISMA and MOOSE guidelines (see fig 1 and supplementary materials, table S1). We comprehensively searched the MEDLINE, Embase, and Web of Science electronic databases to identify studies published until 5 December 2017 (date of last search), which examined 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



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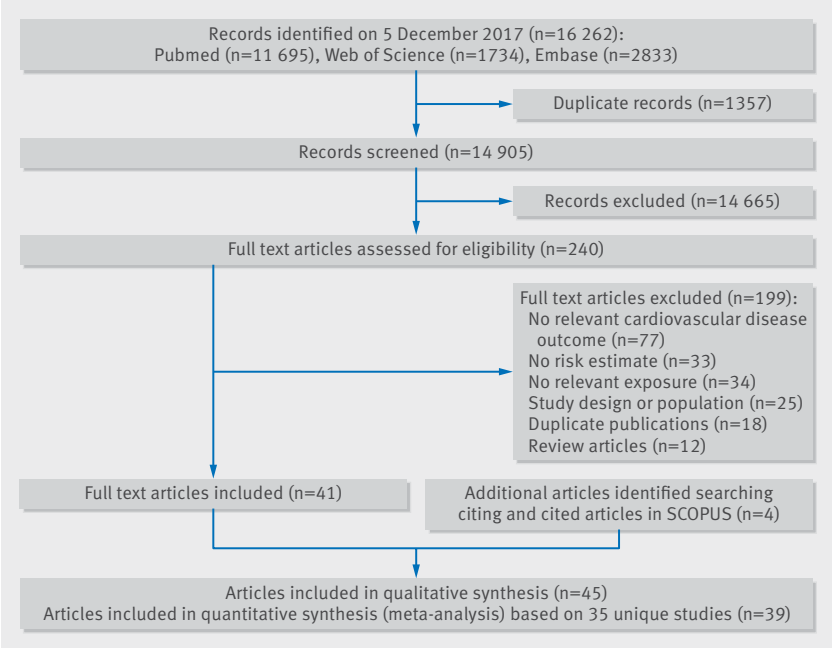

Fig 1 | PRISMA flow diagram of search strategy

each marker for each outcome; and degree of statistical adjustment used (defined as '+' when relative risks were adjusted for age and sex only; '++' when adjusted for established vascular risk factors (eg, age, sex, smoking status, lipids, hypertension, history of cardiometabolic disease); and '+++' when adjusted other additional factors (eg, social status)). Adequate adjustments for these factors are essential to control for the potential confounding effect by these factors in influencing both levels of toxic metals and the risk of cardiovascular disease, resulting in a spurious association. Two independent reviewers used the Newcastle-Ottawa scale to assess the quality of the included studies.[24] This scale uses a star system (with a maximum of nine stars) to assess the quality of a study in three domains: selection of participants; comparability of study groups; and the ascertainment of outcomes of interest. Studies that scored nine stars were considered to be of high quality, studies that scored seven or eight stars were considered to be of medium quality, and studies that scored less than seven stars were considered to be of low quality.

Data synthesis and analysis

To enable a consistent approach to meta-analysis and interpretation of findings in this review, relative risk estimates for the association of toxic metals and cardiovascular disease, coronary heart disease, and stroke were transformed to consistently correspond to the comparison of the top versus bottom third of the distribution in each study, using methods previously described.[25] Briefly, log risk estimates were transformed assuming a normal distribution, with the comparison between top and bottom thirds being equivalent to 2.18 times the 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$_{(\text{top } v \text{ bottom third})}$ =(2.18/2.54)*0.058=0.05 and standard errors log relative risk$_{(\text{top } v \text{ bottom third})}$=(2.18/2.54)*0.41=0.35.

We calculated summary relative risks by pooling the study-specific estimates using a random- effects model that included between study heterogeneity (parallel analyses used fixed-effect models). We assessed the consistency of findings across individual studies by standard χ^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 patients 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.

Metals	No of studies	No of participants	No of events	Relative risk (95% CI)
Arsenic				
Cardiovascular disease	7	135 943	3208	1.30 (1.04 to 1.63)
Coronary heart disease	8	190 816	4640	1.23 (1.04 to 1.45)
Stroke	4	134 526	961	1.15 (0.92 to 1.43)
Lead				
Cardiovascular disease	10	110 382	4970	1.43 (1.16 to 1.76)
Coronary heart disease	8	91 779	2228	1.85 (1.27 to 2.69)
Stroke	6	89 494	518	1.63 (1.14 to 2.34)
Cadmium				
Cardiovascular disease	6	50 674	3756	1.33 (1.09 to 1.64)
Coronary heart disease	5	32 070	1654	1.29 (0.98 to 1.71)
Stroke	3	9123	601	1.72 (1.29 to 2.28)
Mercury				
Cardiovascular disease	4	11 410	4866	0.94 (0.66 to 1.36)
Coronary heart disease	5	9169	3838	0.99 (0.65 to 1.49)
Copper				
Cardiovascular disease	4	5385	538	1.81 (1.05 to 3.11)
Coronary heart disease	4	7299	492	2.22 (1.31 to 3.74)
Stroke	2	728	100	1.29 (0.77 to 2.17)

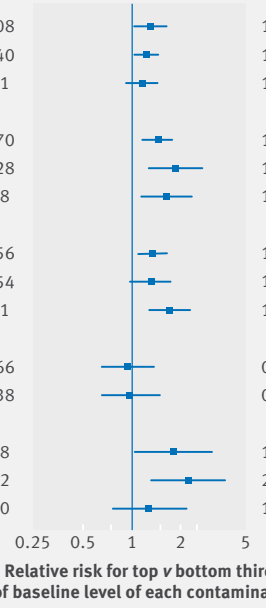

Fig 2 | Summary of the association of environmental contaminants with cardiovascular outcomes. Pooled risk estimates were calculated using random effects meta-analyses. The relative risk compares the risk for each outcome in individuals in the top third with those in the bottom third of baseline levels 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)

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 2.22 (1.31 to 3.74). 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 (I^2=78%, P<0.001 for arsenic; I^2=66%, P=0.005 for lead; I^2=52%, P=0.08 for cadmium; I^2=85%, P<0.001 for mercury; and I^2=67%, P=0.03 for copper;).

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

Table 1 | Summary of the studies included in the systematic review

Study or lead author (Publication year)	Country	Population source	Study design	Baseline survey	Mean age	Male (%)	Total follow-up (Years)	No of participants	No of cases		
									CVD	CHD	Stroke
Arsenic											
Afridi (2011)[31]	Pakistan	Hospital records	Case-control	2007-2008	45-60*	52	NA	119	0	58	0
Chen (1996)†[2 32]	Taiwan	General	Prospective cohort	1988-1989	NR	46	7	1760	0	39	0
DCH (2017)[33]	Denmark	Cancer register	Prospective cohort	1993-1997	50-64*	46.9	14.8	53 856	0	2707	0
HEALS[34]	Bangladesh	General	Prospective cohort	2000-2002	18-75*	43	9	11 109	192	101	82
Liao (2012)†[2 35]	Taiwan	General	Case-control	2002	61	43	7	676	10	0	0
NHSCS[36]	USA	Cancer register	Prospective Cohort	1993-1995	59	56	20	3939	312	154	43
Ruiz-Navarro (1998)[37]	Spain	Hospital records	Case-control	NR	NR	39	NA	78	0	29	0
SHS[38]	USA	Health survey	Prospective Cohort	1989-1991	45-74*	40	19	3575	1184	846	264
SLVDS[39]	USA	Hospital based	Case-cohort	1984-1998	57‡	48	14	555	0	96	0
Sohel (2009)[40]	Bangladesh	Health survey	Prospective cohort	1991-2000	>15	50	9	115 903	1211	639	572
Wade (2015)[41]	China	Hospital records	Case-control	NR	21-70*	69	NA	533	277	0	0
Wu (2010)†[1 42]	Taiwan	Household records	Prospective cohort	1991-1994	>40	47	11	504	22	0	0
Lead											
ABLES[43]	USA	Health survey	Prospective cohort	1987-2005	39	100	17	58 368	692	569	123
BRHS[44]	UK	Registers	Prospective cohort	1978-1980	40-59	100	7	7379	382	316	66
McElvenny (2015)[45]	UK	Health survey	Prospective cohort	1975-1979	35	85	36	9122	941	792	149
Moller (1992)[46]	Denmark	Hospital records	Prospective cohort	1976	40	48	14	1045	54	40	0
NHANES II[47]	USA	Health survey	Prospective cohort	1976-1980	54	47	16	4190	424	0	0
NHANES III†[4 48]	USA	Health survey	Prospective cohort	1988-1994	58	48	12	9757	1189	0	0
NHANES III†[4 49]	USA	Health survey	Prospective cohort	1988-1994	44	47	12	13 946	0	367	141
NHANES III†[4 50]	USA	Health Survey	Prospective cohort	1999-2010	58	47.6	12	18602	985	0	0
SOF[51]	USA	General	Prospective cohort	1990-1991	70	0	13	533	54	23	21
VA-NAS[52]	USA	Health screening	Prospective cohort	1991-1999	67	100	16	1235	185	82	0
Earlier randomised[26]	Netherlands	Health survey	Prospective cohort	1977-1978	57-76*	100	8	146	64	39	18
Cadmium											
CadmiBel[53]	Belgium	Population registers	Prospective cohort	1985-1989	47	45	22	956	88	56	21
HPFS[54]	USA	Health professionals	Nested case-control	1987	62‡	100	5	884	0	442	0
Li (2011)[55]	Japan	Health survey	Prospective cohort	1981-1982	>50	45	22	3119	267	0	217
MDCS[56]	Sweden	Health study	Prospective cohort	1991-1994	46-67*	41	17	4819	713	377	336
NHANES (1999-2004)†[3 57]	USA	Health survey	Prospective cohort	1999-2004	>20	48	7	8989	191	88	0
NHANES III[58]	USA	Health survey	Prospective cohort	1988-1994	>20	47	12	13 958	769	367	0
NHANES III[50]	USA	Health survey	Prospective cohort	1999-2010	58	48	12	18602	985	0	0
SHS[59]	USA	Health survey	Prospective cohort	1989-1991	56	40	19	3348	1010	766	244
Mercury											
EURAMIC[60]	Multinational	Population registers and hospital records	Case-control	1991-1992	≤70	100	NA	1408	0	684	0
Gothenburg[61]	Sweden	Health study	Prospective cohort	1968-1969	38-60*	0	32	1391	301	128	173
Hallgren (2001)†[5 62]	Sweden	Health survey	Nested case-control	1985-1994	55	79	9	234	0	78	0
HPFS and NHS[63]	USA	Health professionals	Nested case-control	1976 and 1986	56	35	15.3	6854	3427	2363	1064
KIHD†[6 64]	Finland	General	Prospective cohort	1984-1989	52	100	17.8	1871	414	282	0
KIHD (2016)†§[6 65]	Finland	General	Prospective cohort	1984-1989	42-60*	100	21.2	2682	0	0	202
NSHDS†§[5 66]	Sweden	Health surveys	Nested case-control	1994-1999	NR	75	5	930	0	431	0
NSHDS†§[5 67]	Sweden	Health surveys	Nested case-control	1985-2000	55	60	15	2271	878	0	369
PREDIMED[68]	Spain	Primary care centres	Nested case-control	2003-2009	55-80*	59	4.8	414	147	0	0
Copper											
EPOZ[69]	Netherlands	Health survey	Nested case-control	1975-1978	68	53	9	186	62	0	0
KIHD[70]	Finland	General	Prospective cohort	1984-1988	52	100	5.75	1666	0	51	0
Marniemi (2005)[71]	Finland	Health survey	Prospective cohort	1986-1987	65-99*	48	10	660	200	130	70
NHANES II[72]	USA	Health survey	Prospective cohort	1976-1980	48	46	12	4574	0	151	0
PPS II[73]	France	Public employees	Prospective cohort	1980-1985	43	100	21	4035	56	0	0
Reunanen (1996)[74]	Finland	Screening programme	Nested case-control	1981	15-69*	100	10	504	220	160	30
Overall total¶								348 259	15 274	13 033	4205

NA=not applicable; NR=not reported
*Age range.
†Same study or subset of main study.
‡Median age.
§For NSHDS (1985-2000), we combined Wennberg 2011 and Hallgren 2001 using random effects meta-analyses as study populations differ slightly and follow-up is different.
¶Estimated unique number of participants and cases of cardiovascular disease, coronary heart disease, or stroke.

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 (I^2 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

Table 2 | Newcastle-Ottawa scale for assessing cohort study quality

Author, year (Pubmed ID)	Selection (Max=4)	Comparability (Max=2)	Outcome (Max=3)	Overall quality score (Max=9)
Aoki, 2016 (26735529)	3	2	3	8
Barregard, 2015 (26517380)	3	2	3	8
Bergdahl, 2013 (22350276)*	2	2	3	7
Chen, 2011 (21546419)	3	2	3	8
Chen, 1996 (8624771)	1	2	3	6
Chowdhury, 2014 (24769120)	1	1	3	5
Daneshmand. 2016 (26991769)*	3	2	3	8
Farzan, 2015 (26048586)	2	2	3	7
Ford, 2000 (10905530)	4	2	3	9
Khalil, 2009 (19344498)	2	2	3	7
Kromhout 1988, (3203644)	3	2	1	7
Leone, 2006 (16570028)	2	2	2	6
Li, 2011 (22340168)*	3	1	3	7
Liao, 2012 (22569360)	1	2	2	5
Lustberg, 2002 (12437403)	3	2	3	8
Marniemi, 2005 (15955467)	3	2	2	7
McElvenny, 2015 (25872777)	2	1	2	5
Menke 2006, (16982939)	3	2	3	8
Menke, 2009 (19270787)	4	2	3	9
Moller, 1992 (1462969)	4	2	1	7
Monrad, 2017 (28157645)	2	2	2	6
Moon, 2013 (24061511)	3	2	3	8
Nawrot, 2008 (19079711)	3	2	3	8
Pocock, 1988 (3203640)	3	1	3	7
Salonen, 1991 (1877585)	3	2	2	7
Schober, 2006 (17035139)	3	2	2	7
Sohel, 2009 (19797964)	2	1	1	4
Tellez-Plaza, 2013 (23514838)	3	2	3	8
Tellez-Plaza, 2012 (22472185)	3	2	1	6
Virtanen, 2005 (15539625)	4	2	3	9
Weisskopf, 2009 (19738141)	2	2	2	6
Wu, 2010 (20708634)	1	2	3	6

*Studies not included in the meta-analysis of cardiovascular disease outcomes

risks of 1.63, 95% confidence interval 1.14 to 2.34 and 1.72, 1.29 to 2.28) with no evidence of heterogeneity across studies (I^2=0%, P=0.76 and I^2=10%, P=0.33). There was no evidence of an association of arsenic with risk of stroke, with little to no evidence of heterogeneity in stroke estimates across studies for either contaminant (I^2=56%, P=0.08).

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).

Table 3 | Newcastle-Ottawa scale for assessing case-control study quality

Author, year (Pubmed ID)	Selection (Max=4)	Comparability (Max=2)	Exposure (Max=3)	Overall quality score (Max=9)
Afridi, 2011 (20480400)	4	1	2	7
Downer, 2016 (28056794)	4	2	3	9
Guallar, 2005 (11570992)	2	2	2	6
Hallgren, 2001 (11572934)	3	2	3	8
James, 2015 (25350952)	4	2	2	8
Kok, 1988 (3394701)	3	2	3	8
Mozaffarian, 2011 (21428767)	3	2	3	8
Reunanen, 1996 (8862478)	2	2	3	7
Ruiz-Navarro, 1998 (9618928)*	1	1	2	4
Wade, 2015 (25889926)	2	2	2	7
$Wennberg, 2007 (17537290)*	4	2	3	9
Wennberg, 2011 (21048056)	4	2	3	9
Yoshizawa, 2002 (12456851)*	4	2	3	9

*Studies not included in the meta-analysis of cardiovascular disease outcomes

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

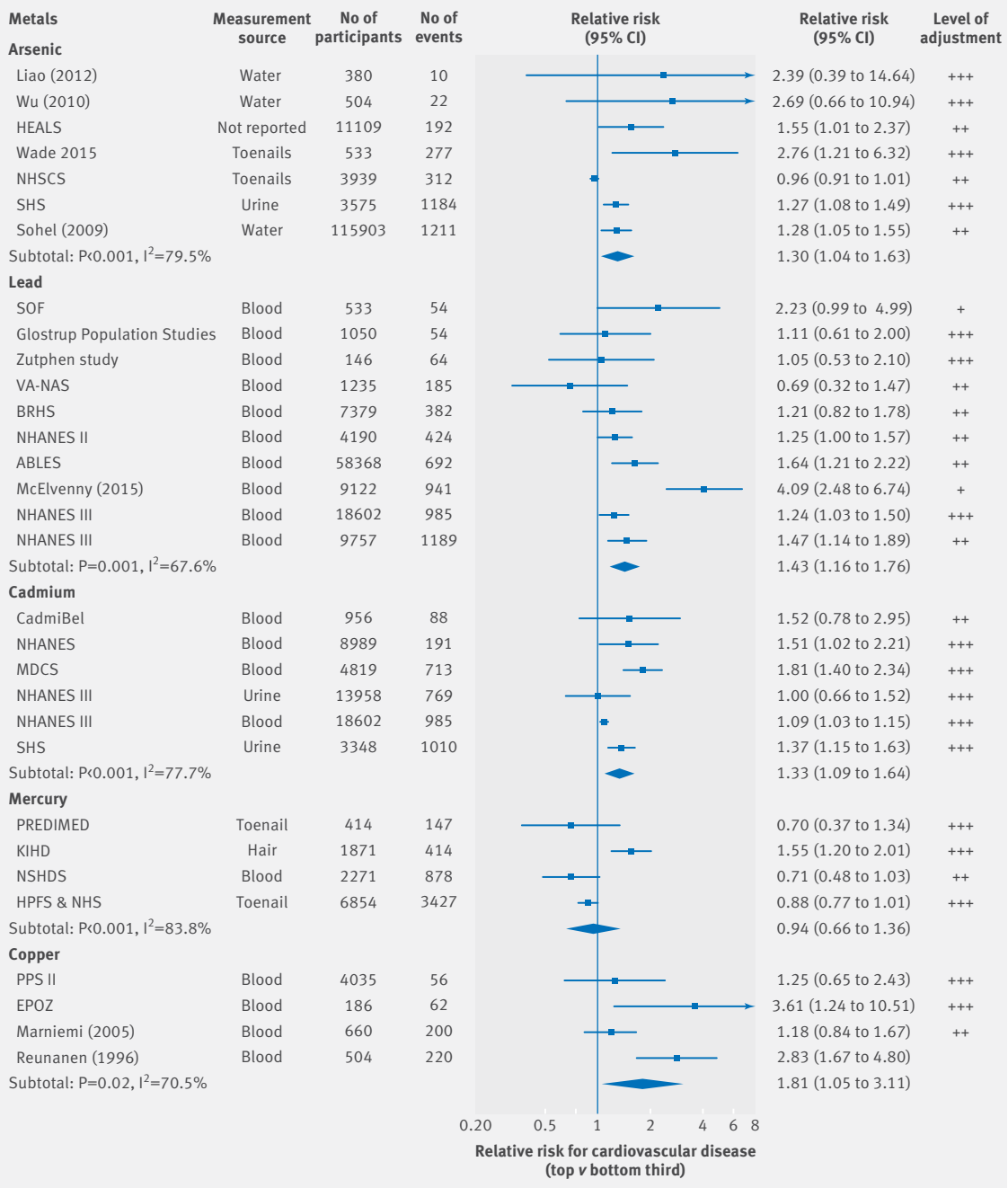

Fig 3 | Association between environmental contaminants and cardiovascular disease. NR=not reported; +=minimally adjusted (typically adjusted for age and sex only); ++=adjusted for at least one non blood based cardiovascular risk factor (eg, systolic blood pressure, body mass index, history of diabetes, etc); +++=additionally adjusted for at least one blood based cardiovascular risk factor (eg, total cholesterol, c-reactive protein, etc)

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 with cardiovascular outcomes was approximately linear.

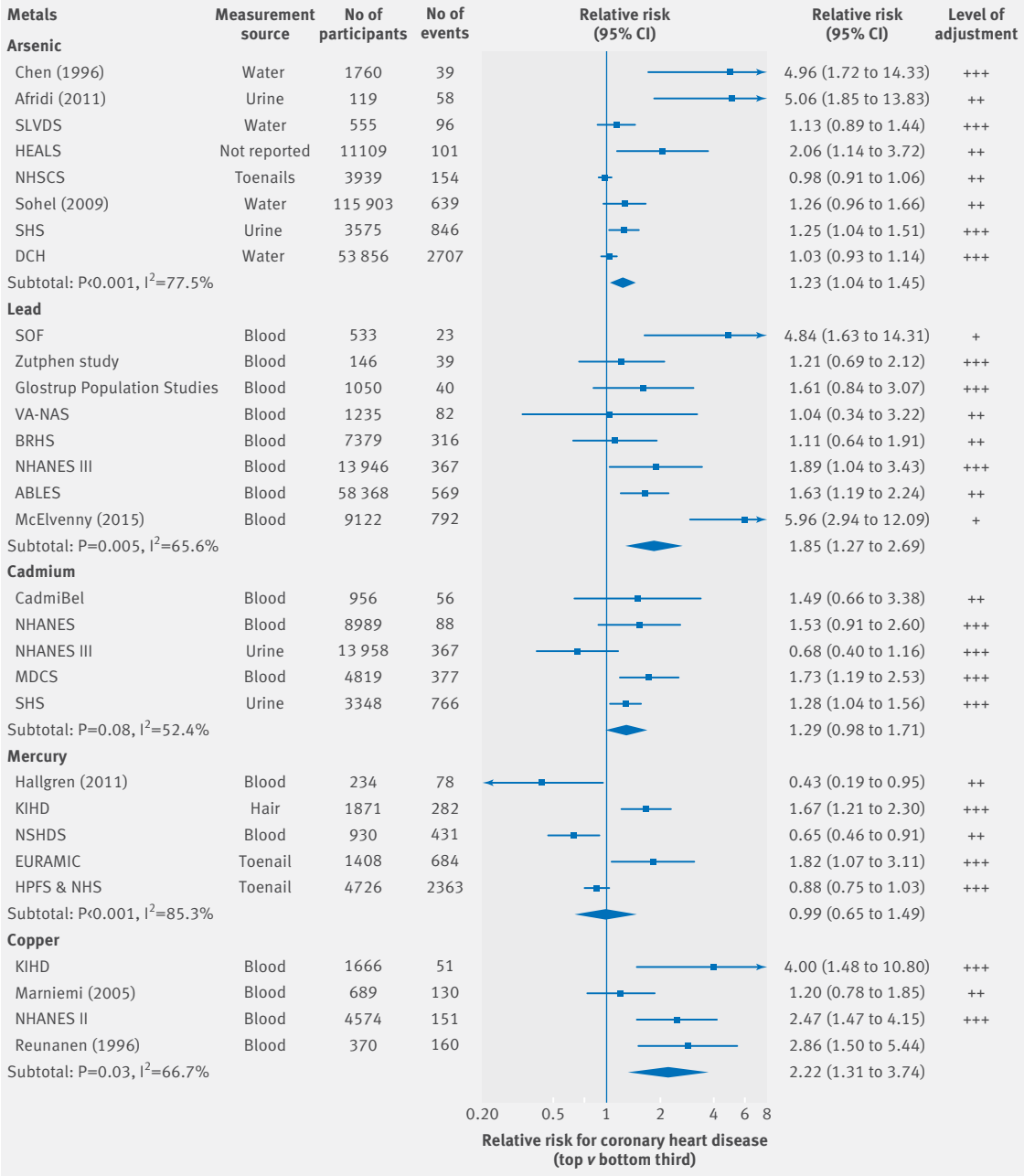

Fig 4 | Association between environmental contaminants and coronary heart disease. NR=not reported; +=minimally adjusted (typically adjusted for age and sex only); ++=adjusted for at least one non blood based cardiovascular risk factor (eg, systolic blood pressure, body mass index, history of diabetes, etc); +++=additionally adjusted for at least one blood based cardiovascular risk factor (eg, total cholesterol, c-reactive protein, etc)

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.[76 77] 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,[80] up regulation of inflammatory signals,[81] 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

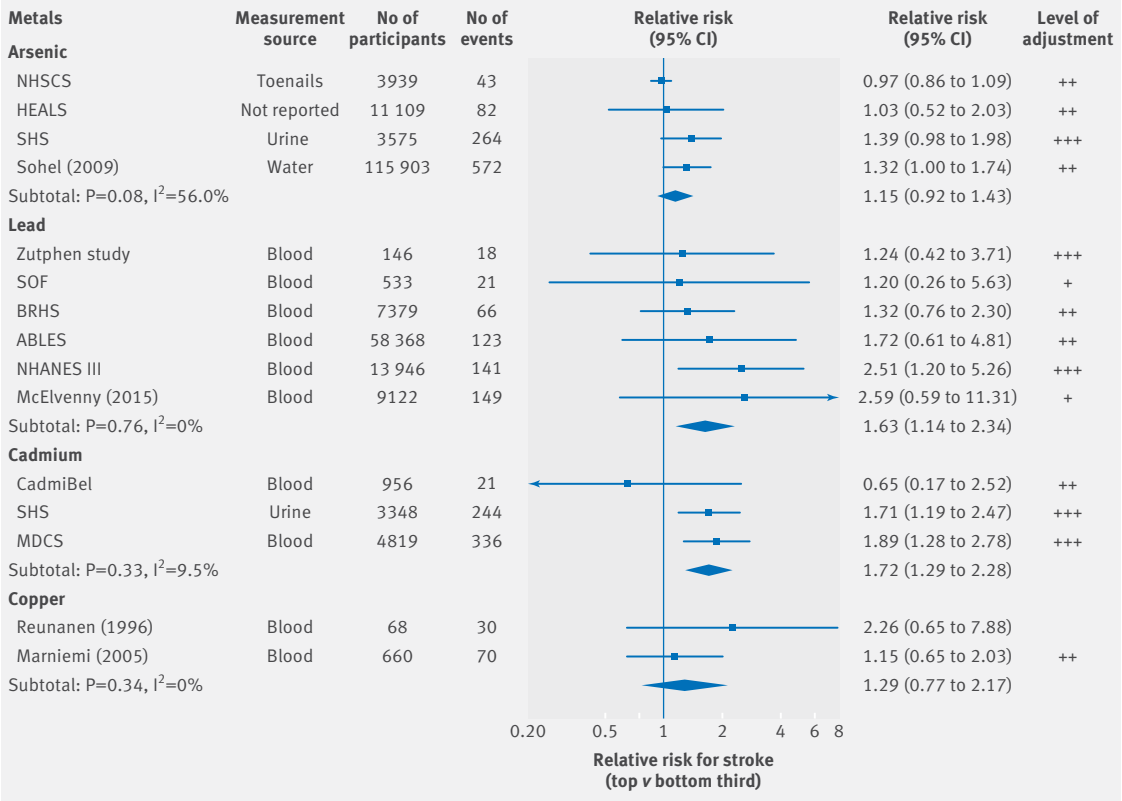

Fig 5 | Association between environmental contaminants and stroke. NR=not reported; +=minimally adjusted (typically adjusted for age and sex only); ++=adjusted for at least one non blood based cardiovascular risk factor (eg, systolic blood pressure, body mass index, history of diabetes etc); +++=additionally adjusted for at least one blood based cardiovascular risk factor (eg, total cholesterol, c-reactive protein, etc)

exposure as a major public health concern.[89] 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.[90] Previous studies have also suggested an association of lead with atherosclerosis as a result of lead-induced oxidative stress and inflammation after exposure.[11 15]

The present review also shows a positive association of copper with cardiovascular disease, as suggested in previous studies.[91 92] While copper is an essential trace element, excess copper can induce oxidative stress by generation of reactive oxygen species.[11] Copper-mediated lipid peroxidation has been demonstrated in several in vivo and in vitro studies.[21] Another possible mechanism for the potential deleterious effects of copper is through a copper-homocystein complex which have been suggested to induce endothelial dysfunction and vascular injury.[93] 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.

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).[94]

Conversely, mercury, a potentially toxic trace metal that humans are exposed to primarily through fish consumption,[95] 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,[62 66] there is currently no accepted biological explanation that supports such a link.[66]

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

ability to reflect long term exposure may differ across various biomarkers.[96] 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)[97] should be considered in future studies.[55] 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,[98] 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.[99 100] 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 occured after intravenous chelation therapy (which facilitates urinary excretion of heavy metals)[101] 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),[102-104] may also allow future investigations of potential causal associations with disease using instrumental variable analysis (ie, mendelian randomisation analyses).[105]

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)[106] 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.[107] 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.[108] However, since efficacy and response of these therapies vary greatly,[109] 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.

AUTHOR AFFILIATIONS

[1]Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge CB1 8RN, UK
[2]MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK
[3]Bristol Population Health Science Institute, Bristol Medical School, Bristol, UK
[4]National Institute for Health Research Bristol Biomedical Research Centre, Bristol, UK
[5]University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[6]Translational Health Sciences, Bristol Medical School, Musculoskeletal Research Unit, University of Bristol, Bristol, UK
[7]Institute of Social and Preventive Medicine, Bern, Switzerland
[8]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK
[9]Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria
[10]Emory University, Atlanta, Georgia, USA
[11]University of Guyana, Georgetown, Guyana
[12]National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
[13]NHS Blood and Transplant, Cambridge, UK

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