Environmental contaminants and cardiovascular risk: a systematic review and meta-analysis of observational studies

Supplementary tables and figures

Table S1 MOOSE checklist

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7
8	Search strategy, including time period included in the synthesis and key words	6,3*
9	Effort to include all available studies, including contact with authors	6
10	Databases and registries searched	6
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	6
13	List of citations located and those excluded, including justification	4-5*
14	Method of addressing articles published in languages other than English	NA
15	Method of handling abstracts and unpublished studies	NA
16	Description of any contact with authors	NA
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	17,7-9*
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	NA
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	7-8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	NA
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7-8
22	Assessment of heterogeneity	7-8
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7-8
24	Provision of appropriate tables and graphics	17-29, 3-26*
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	22-29
26	Table giving descriptive information for each study included	17,7-9*

27	Results of sensitivity testing (eg, subgroup analysis)	10-18*
28	Indication of statistical uncertainty of findings	12,19-24*

Appendix1 Details of search strategy

PubMed strategy:

(("arsenic"[MeSH Terms] OR "arsenic"[All Fields]) OR ("mercury"[MeSH Terms] OR "mercury"[All Fields]) OR ("copper"[MeSH Terms] OR "copper"[All Fields]) OR ("lead"[MeSH Terms] OR "lead"[All Fields]) OR ("cadmium"[MeSH Terms] OR "cadmium"[All Fields]))

AND

("Cardiovascular Diseases"[Mesh] OR "Coronary Artery Disease"[MeSH] OR "Atherosclerosis"[MeSH] OR "Coronary Disease"[MeSH] OR "Myocardial Infarction"[MeSh] OR "Myocardial Ischemia"[MeSH] OR "Stroke"[MeSH] OR "Cardiovascular Disease" [All Fields] OR "Coronary Artery Disease" [All Fields] OR "Atherosclerosis" [All Fields] OR "Coronary Disease"[All Fields] OR "Myocardial Infarction"[All Fields] OR "Myocardial Ischemia"[All Fields] OR "Stroke"[All Fields)

AND

("Cohort Studies"[Mesh] OR "case-control studies"[MeSH Terms] OR "cross-sectional studies"[MeSH Terms] OR "Follow-Up Studies"[Mesh] OR "odds ratio"[All Fields] OR "prospective"[All Fields])

AND

("humans"[MeSH Terms])

EMBASE strategy:

((exp arsenic/ OR exp mercury/ OR exp copper/ OR exp lead/ OR exp cadmium/) OR ((arsenic OR mercury OR copper OR (lead NOT ("lead ECG" OR "12-lead" OR "leads" OR "lead to")) OR cadmium).ab,ti.))

AND

((exp "cardiovascular disease"/ OR exp "Coronary Artery Disease"/ OR exp "Atherosclerosis"/ OR exp "Coronary Disease"/ OR exp "Myocardial Infarction"/ OR exp "Myocardial Ischemia"/ OR exp "Stroke"/) OR (("cardiovascular disease" OR "Coronary Artery Disease" OR "Atherosclerosis" OR "Coronary Disease" OR "Myocardial Infarction" OR "Myocardial Ischemia" OR "Stroke").ab,ti.))

AND
((exp "Cohort Studies"/ OR exp "case-control studies"/ OR exp "cross-sectional studies"/ OR exp "Follow-Up Studies"/ OR exp "odds ratio"/) OR (("Cohort Studies" OR "case-control studies" OR "cross-sectional studies" OR "Follow-Up Studies" OR "odds ratio" OR "prospective").ab,ti.))

NOT (animals NOT humans)

Web of science strategy:

(TS="arsenic" OR TS="mercury" OR TS="copper" OR TS="lead" OR TS="cadmium")

AND

(TS="Cardiovascular Diseases" OR TS="Coronary Artery Disease" OR TS="Atherosclerosis" OR TS="Coronary Disease" OR TS="Myocardial Infarction" OR TS="Myocardial Ischemia" OR TS="Stroke")

AND

(TS="Cohort Studies" OR TS="case-control studies" OR TS="cross-sectional studies" OR TS="Follow-Up Studies" OR TS="odds ratio" OR TS="prospective")

Table S2 List of studies included in the review and meta-analysis

Author, Year	PMID	Study name	Markers
Afridi, 2011	20480400		Arsenic
Chen, 2011	21546419	HEALS	Arsenic
Chen, 1996	8624771		Arsenic
Farzan, 2015	26048586	NHSCS	Arsenic
James, 2015	25350952	SLVDS	Arsenic
Liao, 2012	22569360		Arsenic
Moon, 2013	24061511	SHS	Arsenic
Monrad, 2017	28157645	Diet, Cancer and Health	Arsenic
Ruiz-Navarro, 1998*	9618928		Arsenic
Sohel, 2009	19797964		Arsenic
Wade, 2015	25889926		Arsenic
Wu, 2010	20708634		Arsenic
Chowdhury, 2014	24769120	ABLES	Lead
Khalil, 2009	19344498	SOF	Lead
Kromhout, 1988	3203644	The Zutphen Study	Lead
Lustberg, 2002	12437403	NHANES II	Lead
McElvenny, 2015	25872777		Lead
Menke, 2006	16982939	NHANES III	Lead
Moller, 1992	1462969	Glostrup Population Studies	Lead
Pocock, 1988	3203640	BRHS	Lead
Schober, 2006	17035139	NHANES III	Lead
Weisskopf, 2009	19738141	VA-NAS	Lead
Aoki, 2016	26735529	NHANES III	Lead, Cadmium
Barregard, 2015	26517380	MDCS	Cadmium
Li, 2011*	22340168		Cadmium
Menke, 2009	19270787	NHANES III	Cadmium
Nawrot, 2008	19079711	CadmiBel	Cadmium
Tellez-Plaza, 2013	23514838	SHS	Cadmium
Tellez-Plaza, 2012	22472185	NHANES	Cadmium
Yoshizawa, 2002*	12456851	HPFS	Cadmium
Bergdahl, 2013*	22350276	Gothenburg	Mercury
Daneshmand, 2016*	26991769	KIHD	Mercury
Downer, 2016	28056794	PREDIMED	Mercury
Guallar, 2002	15972934	EURAMIC	Mercury
Hallgren, 2001	11570992		Mercury
Mozaffarian, 2011	21428767	HPFS&NHS	Mercury
Virtanen, 2005	15539625	KIHD	Mercury
Wennberg, 2007*	17537290	NSHDS	Mercury
Wennberg, 2011	21048056	NSHDS	Mercury
Ford, 2000	10905530	NHANES II	Copper

Kok, 1988	3394701	EPOZ	Copper
Leone, 2006	16570028	PPS II	Copper
Marniemi, 2005	15955467		Copper
Reunanen, 1996	8862478		Copper
Salonen, 1991	1877585	KIHD	Copper

*Studies excluded from the meta-analysis. One study reporting on exposure to arsenic which did not adjust for seafood consumption, two studies reporting on exposure to cadmium which did not adjust for smoking and three study reporting on exposure to mercury which did not adjust for seafood consumption or n-3 fatty acids were excluded.

Abbreviations: ABLES = Adult blood lead epidemiology and surveillance; **BRHS** = British regional heart study; **EPOZ** = Epidemiological study of risk factors for cardiovascular diseases; **EURAMIC** = European multicentre cases-control study on antioxidants, myocardial infarction and cancer; **HEALS** = Health effects of arsenic longitudinal study; **HPFS** = Health professions follow-up study; **KIHD** = Kuopio ischemic heart disease risk factor study;;; **NHANES** = National health and nutrition examination survey; **NHS** = Nurses health study; **NHSCS**: New Hampshire Skin Cancer Study; **No.** = number; **NR** = not reported; **NSHDS** = Northern Sweden health and disease study; **PPS II** = Paris prospective study 2; **SHS** = Strong heart study; **SLVDS** = San Luis Valley Diabetes Study; **SOF** = Study of osteoporotic fractures; **VA-NAS** = Veterans affairs normative ageing study.

Table S3 Major sources of toxic metals

Toxic metals	Sources
Arsenic	*Most common source is groundwater*. Large areas in Argentina, Bangladesh, Chile, China, India, Mexico, and the United States of America have naturally high level of groundwater arsenic[1]. *Food*. For individuals whose primary exposure to arsenic is not from drinking water, exposure primarily comes from food consumption[1]. Globally, these foods may include grains (mainly rice), fruits, and vegetables grown in contaminated soil or water in addition to contaminated seaweed, shellfish, and fish[1,2]. *Human activities*. Mining, ore smelting, and industrial use of arsenic can expose workers and nearby residents via inhalation and can cause soil and water contamination[1].
Cadmium	*Most common source is smoking.* Active and passive inhalation of tobacco smoke is a known route of cadmium exposure[3]. *Food.* Grains and vegetables are the primary exposure to cadmium for those who do not smoke tobacco[4]. Many plants have a high uptake of cadmium from soil[5]. *Human activities*. Metal mining and refining, industrial uses of cadmium, and improper disposal of cadmium household products can expose workers and nearby residents by contaminating the surrounding environment[3].
Lead	*Most common source is food and air.* Humans are exposed to lead by air and food fairly equally world-wide[3]. *Air.* Metal industrial activities, other industrial uses of lead, leaded gasoline, and medical and household products can expose workers and nearby individuals to lead via inhalation and contamination of the surrounding environment[3]. *Water.* Corrosion of plumbing materials containing lead can introduce lead into drinking water[6].
Mercury	*Most common source is food.* High fish consumption is a main route of methyl mercury, especially of certain species of fish in certain areas, and such consumption has been correlated with higher levels of mercury in the blood[7]. *Dental procedures.* Studies have shown that mercury vapour releases from dental amalgams by chewing action. The largest occupational group exposed to mercury is dental care staff[3]. *Human activities.* Metal mining, coal combustion, and other industrial processes release mercury into the environment. Mercury can also be found in older medical devices[3].
Copper	*Most common source is food.* Copper is an essential nutrient for biological processes found naturally in many foods[8]. Additional consumption of copper can come from cookware and dietary supplements[9]. *Drinking water.* Exposure to unsafe amounts of copper in drinking water can occur via corrosion of plumbing materials or naturally high levels in groundwater[9]. *Human Activities.* Man-made exposures to copper include emission from the electric waste burning and metal industrial activities such as smelting[10,11].

Table S 4 Summary of the baseline levels of environmental contaminants and measurement methods in the included studies

Study/Lead Author (Publication Year)	Measurement Method	Definition of levels	Baseline Level (SD)*	CV(%)	LOD	%<LOD
Arsenic						
Levels measured in urine:						
Afridi (2011)	Graphite furnace atomic absorption spectrometry	Concentration	4.9 [Males] μg/l 4.8 [Females] μg/l[Ψ]	NR	15.9pg/g	NR
HEALS	Graphite furnace atomic absorption spectrometry	Creatinine adjusted	199[¶] ug/g	NR	NR	NR
* Ruiz-Navarro (1998)	Hydride generation atomic absorption spectrometry	Concentration	3.68 (2.27) μg/l[Ψ]	NR	NR	0%
SHS	High performance liquid chromatography coupled to mass spectrometry	Creatinine adjusted	9.7[¶] (5.8-15.7[α]) ug/g	6 to 7%	1ug/l	5% (max)
Levels measured in water:						
Chen (1996) **[2]	NR	Well water consumed (Cu)	NR	NR	NR	NR
Liao (2012)**[2]	NR	Well water consumed (Cu)	NR	1 to 3%	0.8 to 1.5ug/l	NR
DCH (2017)	ICP-MS	Household tap water consumed (Cu)	0.7 (0.03-25.34[β]) ug/l	NR	0.03ug/l	NR
Sohel (2009)	Hydride generation atomic absorption spectrophotometer	Household tube well water consumed (Cu)	131.1 (116) μg/l	NR	1ug/l	17%
SLVDS	Ion chromatography and inductively coupled plasma mass spectrometry	Household tap water consumed (Cu)	NR	NR	NR	NR
Wu (2010)**[1]	Hydride generation atomic absorption spectrometry	Well water consumed (Cu)	NR	NR	0.2ug/l	NR
Levels measured in toenails:						
NHSCS	Neutron-activation analysis	Concentration	120 (140) μg/l	NR	0.01ug/g	5%
Wade (2015)	Neutron-activation analysis	Concentration	0.87 (0.18-34.0[β]) ug/g	NR	0.2ug/g	6%
Lead						
Levels measured in blood:						
ABLES	NR	Concentration	NR	NR	NR	NR
BRHS	Flame atomic absorption spectroscopy	Concentration	15.3 μg/dl	NR	NR	NR
McElvenny (2015)	NR	Concentration	44.3 (22.7) μg/dl	NR	NR	NR
Moller (1992)	NR	Concentration	11.5 (5.2) μg/dl	NR	NR	NR
NHANES II	Atomic absorption spectroscopy	Concentration	13[¶] μg/dl	7 to 14%	NR	NR
NHANES III	Graphite furnace atomic absorption spectrophotometer	Concentration	2.58[§] μg/dl	3 to 8%	1ug/dl	8%
NHANES III	Graphite furnace atomic absorption spectrophotometer	Concentration	NR	3 to 8%	1ug/dl	8%
NHANES III	Inductively coupled plasma mass spectrometry	Hematocrit corrected concentration	1.73 (0.02) μg/dl	3 to 8%	1ug/dl	8%

SOF	Graphite furnace atomic absorption spectrometry	Concentration	5.3 (2.3) μg/dl	NR	1ug/dl	NR
Zutphen Study	Electro-thermal atomization atomic absorption spectrometry	Concentration	18.3 (7.4) μg/dl	NR	NR	NR
VA-NAS	Graphite furnace atomic absorption	Concentration	5.6 (3.3) μg/dl	1 to 8%	NR	NR
Levels measured in blood:						
EPOZ	Atomic absorption spectrophotometer	Concentration	1.27 (0.27) mg/l[Ψ]	NR	NR	NR
KIHD	Flame atomic absorption spectrometer	Concentration	1.11 (0.17) mg/l	4%	NR	NR
Marniemi (2005)	Flame atomic absorption spectrophotometer	Concentration	1.18 (0.26) mg/l	NR	NR	NR
NHANES II	Atomic absorption spectroscopy	Concentration	1.23(0.34) mg/l	NR	NR	NR
PPS II	Flame atomic absorption spectrometry	Concentration	0.96 (0.14) mg/l	NR	NR	NR
Reunanen (1996)	Atomic absorption spectrophotometer	Concentration	1.18 mg/l[Ψ]	<5%	NR	NR
Cadmium						
Levels measured in blood:						
CadmiBel	Electrothermal atomic absorption spectrometer	Concentration	1.19[§] (0.80-1.90[α]) μg /l 1.29[§] (0.76-2.20[α]) μg /l	NR	NR	NR
MDCS	Atomic adsorption spectrometer	Concentration	0.46 (0.26) μg/l	7%	0.02ug/l	0%
NHANES	Atomic adsorption spectrometer	Concentration	0.44 (0.02) μg/l	1 to 5%	0.06ug/l	3%
NHANES III	Inductively coupled plasma mass spectrometry	Concentration	0.43 (0.01) μg/l	NR	NR	NR
Levels measured in toenails:						
*HPFS	Neutron-activation analysis	Adjusted for toenail weight	0.63 μg/g	14%	NR	NR
Levels measured in urine:						
* Li (2011)	Atomic absorption spectrophotometer	Concentration	NR	NR	NR	NR
NHANES III	Graphite furnace atomic absorption	Creatinine adjusted	Men: 0.28[§] μg/g Women: 0.4[§] μg/g	3 to 14%	NR	3%
SHS	Inductively coupled plasma mass spectrometry	Creatinine adjusted	0.92 (0.61-1.45 [α]) ug/g	NR	0.02ug/l	0.1%
Mercury						
Levels measured in blood:						
* Gothenburg	Cold vapour atomic fluorescence spectrometry	Concentration	1.4 (1.03-1.89) μg/l	NR	NR	NR
Hallgren (2001)**[3]	Atomic fluorescence technique	Concentration (E)	5.7 (5.9) ng Hg/l[Ψ]	NR	NR	NR
NSHDS**[3]	Cold vapour atomic fluorescence spectrometry	Concentration (E)	0.0038[¶] (0.0037) μg/l	5%	0.1ug/l	NR
* NSHDS**[3]	Cold vapour atomic fluorescence spectrometry	Concentration (E)	3.54[¶] (0.01-87[β]) μg/l	4%	0.2ug/l	NR
Levels measured in hair:						

KIHD**[4]	Atomic fluorescence technique	Concentration	1.9 (1.9) μg/g	7%	NR	NR
* KIHD (2016) **[4]	Atomic fluorescence technique	Concentration	1.9 (1.95) μg/g	NR	NR	NR
Levels measured in toenails:						
EURAMIC	Neutron activation analysis	Concentration	0.25 (0.15-0.40) μg/g[Ψ]	NR	0.1ug/g	5%
HPFS & NHS	Neutron activation analysis	Concentration	0.37 (0.58) μg/g[Ψ]	6%	NR	NR
PREDIMED	Instrumental neutron activation analysis	NR	0.63[§] (0.53) ug/g	NR	NR	NR

Copper

Levels measured in blood:						
EPOZ	Atomic absorption spectrophotometer	Concentration	1.27 (0.27) mg/l[Ψ]	NR	NR	NR
KIHD	Flame atomic absorption spectrometer	Concentration	1.11 (0.17) mg/l	4%	NR	NR
Marniemi (2005)	Flame atomic absorption spectrophotometer	Concentration	1.18 (0.26) mg/l	NR	NR	NR
NHANES II	Atomic absorption spectroscopy	Concentration	1.23(0.34) mg/l	NR	NR	NR
PPS II	Flame atomic absorption spectrometry	Concentration	0.96 (0.14) mg/l	NR	NR	NR
Reunanen (1996)	Atomic absorption spectrophotometer	Concentration	1.18 mg/l[Ψ]	<5%	NR	NR

*Mean level (SD) or median (inter-quartile range) of entire cohort unless specified otherwise

**Same study

[¶]Median level

[Ψ]Control subjects

[§]Geometric mean

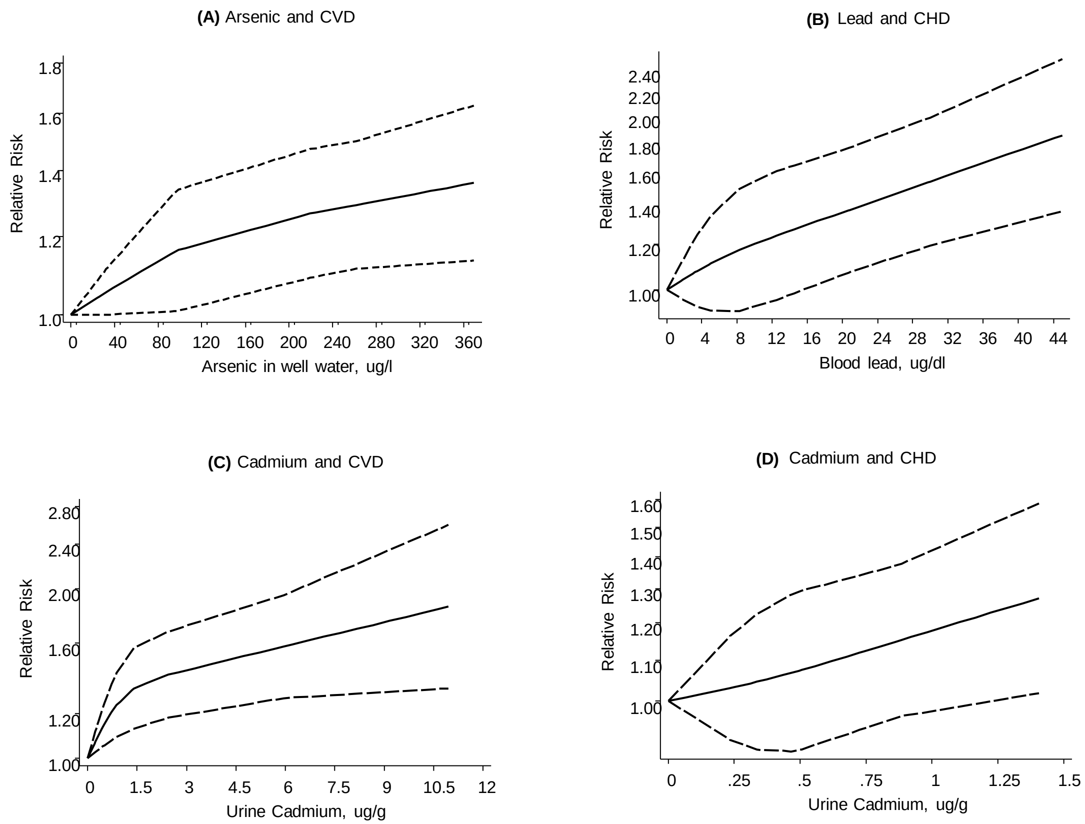
[α]Inter-quartile range

[β]Range

Abbreviations: BRHS = British regional heart study; **Cu** = cumulative; **CV**: coefficient of variation, **E** = erythrocytes; **EPOZ** = Epidemiological study of risk factors for cardiovascular diseases; **EURAMIC** = European multicentre cases-control study on antioxidants, myocardial infarction and cancer; **HEALS** = Health effects of arsenic longitudinal study; **HPFS** = Health professions follow-up study; **KIHD** = Kuopio ischemic heart disease risk factor study; **LOD**: limit of detection; **NHANES** = National health and nutrition examination survey; **NHS** = Nurses health study; **NHSCS**: New Hampshire Skin Cancer Study; **NR** = not reported; **NSHDS** = Northern Sweden health and disease study; **PPS II** = Paris prospective study 2; **SD** = standard deviation; **SHS** = Strong heart study; **SLVDS**: San Luis Valley Diabetes Study; **SOF** = Study of osteoporotic fractures; **VA-NAS** = Veterans affairs normative ageing study.

*studies were not included in the meta-analysis

Figure S1 Dose-response relations between levels of toxic metals and relative risks of cardiovascular outcomes

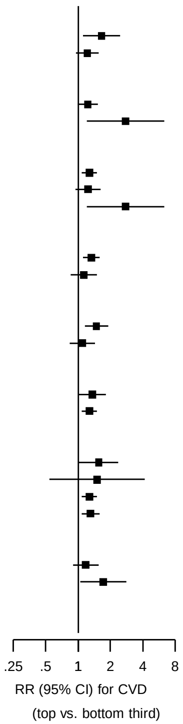


Data were modelled with restricted cubic splines in dose-response models. Studies contributing to (A) n=2, (B) n=4, (C) n= 3, (D) n=3.

Figure S 2 Subgroup analyses for the association of arsenic with CVD outcomes

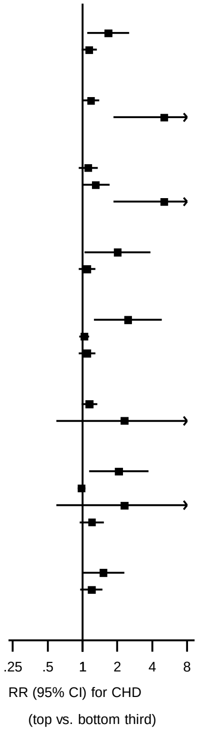
Arsenic: CVD Outcomes

Group	No. of studies	No. of participants	No. of events	RR for CVD (95% CI)	P-value
Study size					
< 250 cases	3	11993	224	1.65 (1.11, 2.46)	0.286
>= 250 cases	4	123950	2984	1.22 (0.96, 1.55)	0.286
Study design					
Prospective	6	135410	2931	1.23 (0.99, 1.53)	0.140
Retrospective	1	533	277	2.76 (1.21, 6.32)	0.140
Type of event					
Both	1	3575	1184	1.27 (1.08, 1.49)	0.362
Fatal	5	131835	1747	1.23 (0.94, 1.62)	0.362
Non-fatal	1	533	277	2.76 (1.21, 6.32)	0.362
Total follow-up					
<= 10 Years	3	127392	1413	1.33 (1.11, 1.59)	0.332
> 10 Years	3	8018	1518	1.13 (0.85, 1.49)	0.332
Location					
Asia Pacific	5	128429	1712	1.48 (1.15, 1.90)	0.155
North America	2	7514	1496	1.09 (0.83, 1.43)	0.155
Study Population					
General	6	132368	2024	1.35 (1.01, 1.82)	0.802
Healthy	1	3575	1184	1.27 (1.08, 1.49)	0.802
Measurement Source					
NR	1	11109	192	1.55 (1.01, 2.37)	0.978
Toenails	2	4472	589	1.50 (0.54, 4.16)	0.978
Urine	1	3575	1184	1.27 (1.08, 1.49)	0.978
Water	3	116787	1243	1.31 (1.08, 1.58)	0.978
Adjustment factor					
++/+/*	3	130951	1715	1.18 (0.90, 1.55)	0.305
+++	4	4992	1493	1.71 (1.04, 2.81)	0.305



Arsenic: CHD Outcomes

Group	No. of studies	No. of participants	No. of events	RR for CHD (95% CI)	P-value
Study size					
< 250 cases	5	17482	448	1.67 (1.10, 2.52)	0.346
>= 250 cases	3	173334	4192	1.14 (0.98, 1.33)	0.346
Study design					
Prospective	6	190142	4486	1.18 (1.00, 1.39)	0.129
Retrospective	1	119	58	5.06 (1.85, 13.83)	0.129
Type of event					
Both	2	57431	3553	1.12 (0.92, 1.35)	0.248
Fatal	5	133266	1029	1.30 (0.99, 1.71)	0.248
Non-fatal	1	119	58	5.06 (1.85, 13.83)	0.248
Total follow-up					
<= 10 Years	3	128772	779	2.00 (1.04, 3.86)	0.215
> 10 Years	3	8069	1096	1.09 (0.93, 1.29)	0.215
Location					
Asia Pacific	4	128891	837	2.47 (1.25, 4.87)	0.206
Europe	1	53856	2707	1.03 (0.93, 1.14)	0.206
North America	3	8069	1096	1.09 (0.93, 1.29)	0.206
Study Population					
General	6	187122	3736	1.14 (0.98, 1.34)	0.498
Healthy	2	3694	904	2.30 (0.59, 8.94)	0.498
Measurement Source					
NR	1	11109	101	2.06 (1.14, 3.72)	0.800
Toenails	1	3939	154	0.98 (0.91, 1.06)	0.800
Urine	2	3694	904	2.30 (0.59, 8.94)	0.800
Water	4	172074	3481	1.20 (0.94, 1.53)	0.800
Adjustment factor					
++/+/*	4	131070	952	1.51 (0.99, 2.29)	0.735
+++	4	59746	3688	1.19 (0.96, 1.49)	0.735



Arsenic: Stroke Outcomes

Group	No. of studies	No. of participants	No. of events	RR for Stroke (95% CI)	P-value
Study size					
< 250 cases	2	15048	125	0.97 (0.87, 1.09)	0.122
>= 250 cases	2	119478	836	1.35 (1.08, 1.68)	0.122
Type of event					
Both	1	3575	264	1.39 (0.98, 1.98)	0.447
Fatal	3	130951	697	1.08 (0.86, 1.36)	0.447
Total follow-up					
<= 10 Years	2	127012	654	1.27 (0.99, 1.65)	0.676
> 10 Years	2	7514	307	1.12 (0.79, 1.58)	0.676
Location					
Asia Pacific	2	127012	654	1.27 (0.99, 1.65)	0.676
North America	2	7514	307	1.12 (0.79, 1.58)	0.676
Study Population					
General	3	130951	697	1.08 (0.86, 1.36)	0.447
Healthy	1	3575	264	1.39 (0.98, 1.98)	0.447
Adjustment factor					
++/+/*	3	130951	697	1.08 (0.86, 1.36)	0.447
+++	1	3575	264	1.39 (0.98, 1.98)	0.447

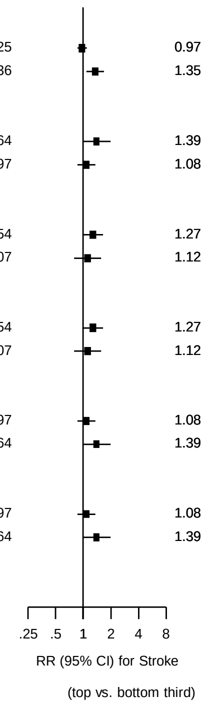


Figure S 3 Subgroup analyses for the association of lead with CVD outcomes

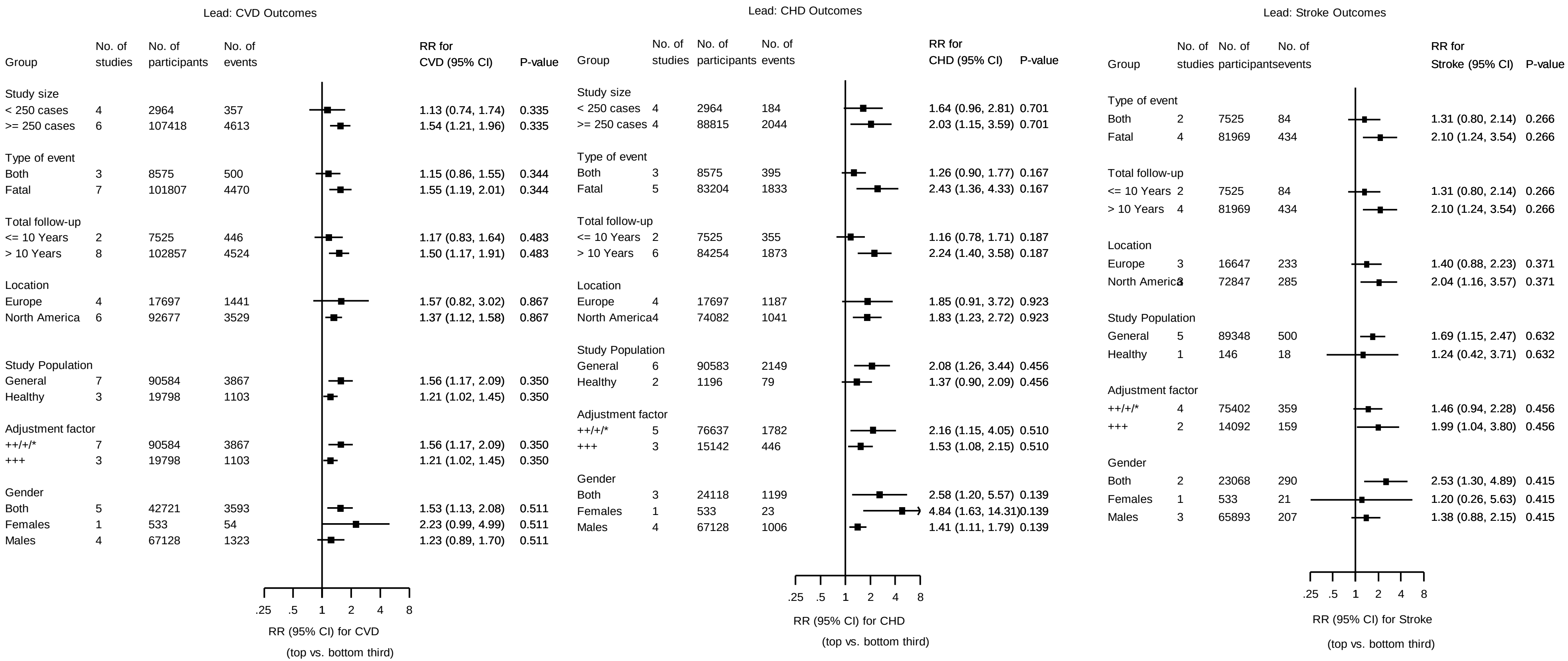
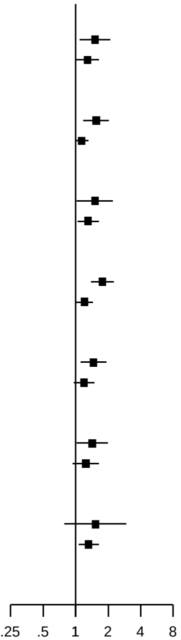


Figure S 4 Subgroup analyses for the association of cadmium with CVD outcomes

Cadmium: CVD Outcomes

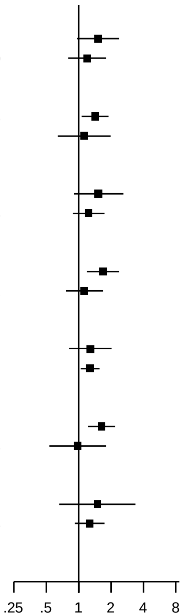
Group	No. of studies	No. of participants	No. of events	RR for CVD (95% CI)	P-value
Study size					
< 250 cases	2	9945	279	1.51 (1.08, 2.11)	0.572
>= 250 cases	4	40727	3477	1.29 (1.02, 1.64)	0.572
Type of event					
Both	2	8167	1723	1.55 (1.18, 2.04)	0.155
Fatal	4	42505	2033	1.14 (0.99, 1.32)	0.155
Total follow-up					
<= 10 Years	1	8989	191	1.51 (1.02, 2.21)	0.671
> 10 Years	5	41683	3565	1.31 (1.05, 1.64)	0.671
Location					
Europe	2	5775	801	1.77 (1.40, 2.25)	0.101
North America	4	44897	2955	1.21 (1.02, 1.44)	0.101
Study Population					
General	4	28722	1761	1.47 (1.12, 1.92)	0.340
Healthy	2	21950	1995	1.20 (0.96, 1.50)	0.340
Measurement Source					
Blood	4	33366	1977	1.42 (1.02, 1.98)	0.569
Other	2	17306	1779	1.24 (0.94, 1.65)	0.569
Adjustment factor					
++/+/*	1	956	88	1.52 (0.78, 2.95)	0.744
+++	5	49716	3668	1.32 (1.07, 1.64)	0.744



RR (95% CI) for CVD
(top vs. bottom third)

Cadmium: CHD Outcomes

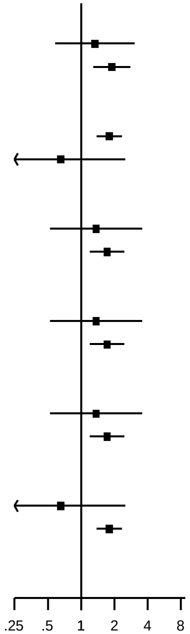
Group	No. of studies	No. of participants	No. of events	RR for CHD (95% CI)	P-value
Study size					
< 250 cases	2	9945	144	1.52 (0.98, 2.37)	0.584
>= 250 cases	3	22125	1510	1.20 (0.80, 1.81)	0.584
Type of event					
Both	2	8167	1143	1.42 (1.07, 1.90)	0.481
Fatal	3	23903	511	1.13 (0.64, 1.99)	0.481
Total follow-up					
<= 10 Years	1	8989	88	1.53 (0.91, 2.60)	0.674
> 10 Years	4	23081	1566	1.24 (0.88, 1.75)	0.674
Location					
Europe	2	5775	433	1.69 (1.20, 2.38)	0.319
North America	3	26295	1221	1.13 (0.76, 1.68)	0.319
Study Population					
General	4	28722	888	1.29 (0.82, 2.01)	0.986
Healthy	1	3348	766	1.28 (1.04, 1.56)	0.986
Measurement Source					
Blood	3	14764	521	1.64 (1.23, 2.19)	0.214
Other	2	17306	1133	0.98 (0.53, 1.80)	0.214
Adjustment factor					
++/+/*	1	956	56	1.49 (0.66, 3.38)	0.794
+++	4	31114	1598	1.27 (0.92, 1.75)	0.794



RR (95% CI) for CHD
(top vs. bottom third)

Cadmium: Stroke Outcomes

Group	No. of studies	No. of participants	No. of events	RR for Stroke (95% CI)	P-value
Study size					
< 250 cases	2	4304	265	1.33 (0.58, 3.05)	0.685
>= 250 cases	1	4819	336	1.89 (1.28, 2.78)	0.685
Type of event					
Both	2	8167	580	1.79 (1.38, 2.34)	0.386
Fatal	1	956	21	0.65 (0.17, 2.52)	0.386
Location					
Europe	2	5775	357	1.36 (0.52, 3.57)	0.816
North America	1	3348	244	1.71 (1.19, 2.47)	0.816
Study Population					
General	2	5775	357	1.36 (0.52, 3.57)	0.816
Healthy	1	3348	244	1.71 (1.19, 2.47)	0.816
Measurement Source					
Blood	2	5775	357	1.36 (0.52, 3.57)	0.816
Other	1	3348	244	1.71 (1.19, 2.47)	0.816
Adjustment factor					
++/+/*	1	956	21	0.65 (0.17, 2.52)	0.386
+++	2	8167	580	1.79 (1.38, 2.34)	0.386

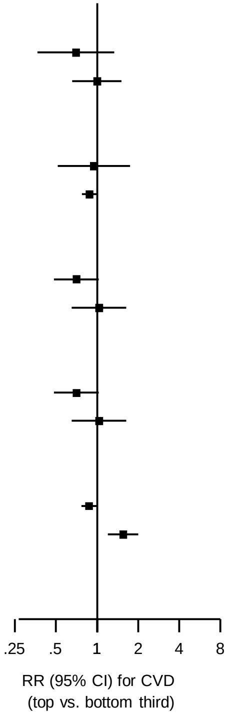


RR (95% CI) for Stroke
(top vs. bottom third)

Figure S 5 Subgroup analyses for the association of mercury with CVD outcomes

Mercury: CVD Outcomes

Group	No. of studies	No. of participants	No. of events	RR for CVD (95% CI)	P-value
Study size					
< 250 cases	1	414	147	0.70 (0.37, 1.34)	0.589
>= 250 cases	3	10996	4719	1.00 (0.66, 1.51)	0.589
Location					
Europe	3	4556	1439	0.95 (0.51, 1.74)	0.896
North America	1	6854	3427	0.88 (0.77, 1.01)	0.896
Measurement Source					
Blood	1	2271	878	0.71 (0.48, 1.03)	0.500
Other	3	9139	3988	1.03 (0.65, 1.63)	0.500
Adjustment factor					
++/+/*	1	2271	878	0.71 (0.48, 1.03)	0.500
+++	3	9139	3988	1.03 (0.65, 1.63)	0.500
Gender					
Both	2	7268	3574	0.87 (0.77, 0.99)	0.159
Males	1	1871	414	1.56 (1.20, 2.01)	0.159



Mercury: CHD Outcomes

Group	No. of studies	No. of participants	No. of events	RR for CHD (95% CI)	P-value
Study size					
< 250 cases	1	234	78	0.43 (0.19, 0.95)	0.243
>= 250 cases	4	8935	3760	1.11 (0.73, 1.71)	0.243
Study design					
Prospective	4	7761	3154	0.86 (0.56, 1.34)	0.316
Retrospective	1	1408	684	1.82 (1.07, 3.11)	0.316
Type of event					
Both	2	5656	2794	0.79 (0.59, 1.05)	0.468
Non-fatal	3	3513	1044	1.19 (0.59, 2.38)	0.468
Total follow-up					
<= 10 Years	2	1164	509	0.61 (0.45, 0.83)	0.216
> 10 Years	2	6597	2645	1.19 (0.64, 2.23)	0.216
Location					
Europe	4	4443	1475	1.00 (0.53, 1.89)	0.877
North America	1	4726	2363	0.88 (0.75, 1.03)	0.877
Measurement Source					
Blood	2	1164	509	0.61 (0.45, 0.83)	0.112
Other	3	8005	3329	1.34 (0.80, 2.27)	0.112
Adjustment factor					
++/+/*	2	1164	509	0.61 (0.45, 0.83)	0.112
+++	3	8005	3329	1.34 (0.80, 2.27)	0.112
Gender					
Both	3	5890	2872	0.72 (0.52, 1.00)	0.035
Males	2	3279	966	1.71 (1.30, 2.25)	0.035

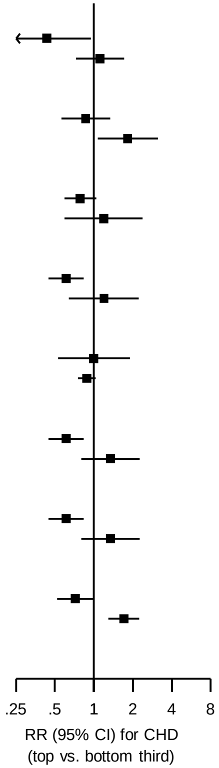
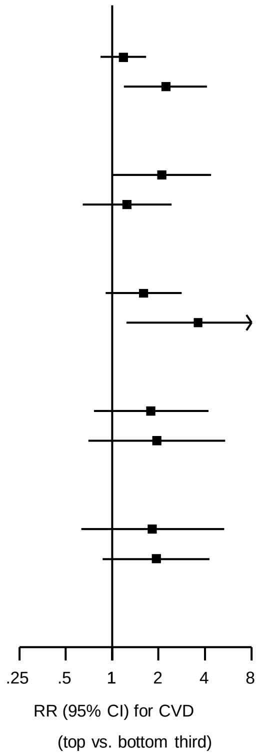


Figure S 6 Subgroup analyses for the association of copper with CVD outcomes

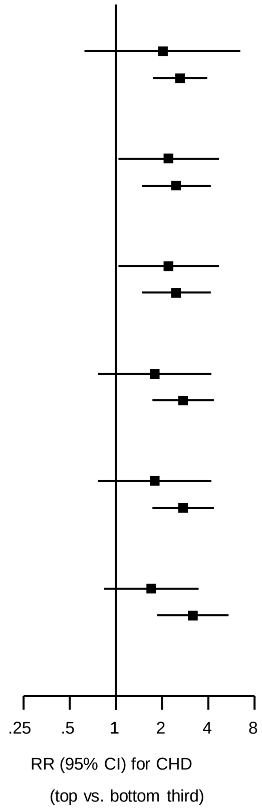
Copper: CVD Outcomes

Group	No. of studies	No. of participants	No. of events	RR for CVD (95% CI)	P-value
Type of event					
Both	1	660	200	1.18 (0.84, 1.67)	0.363
Fatal	3	4725	338	2.22 (1.20, 4.13)	0.363
Total follow-up					
<= 10 Years	3	1350	482	2.10 (1.00, 4.38)	0.554
> 10 Years	1	4035	56	1.25 (0.65, 2.43)	0.554
Study Population					
General	3	5199	476	1.60 (0.91, 2.82)	0.388
Healthy	1	186	62	3.61 (1.24, 10.51)	0.388
Adjustment factor					
++/+/*	2	1164	420	1.79 (0.76, 4.20)	0.912
+++	2	4221	118	1.95 (0.70, 5.42)	0.912
Gender					
Both	2	846	262	1.83 (0.63, 5.34)	0.919
Males	2	4539	276	1.93 (0.87, 4.29)	0.919



Copper: CHD Outcomes

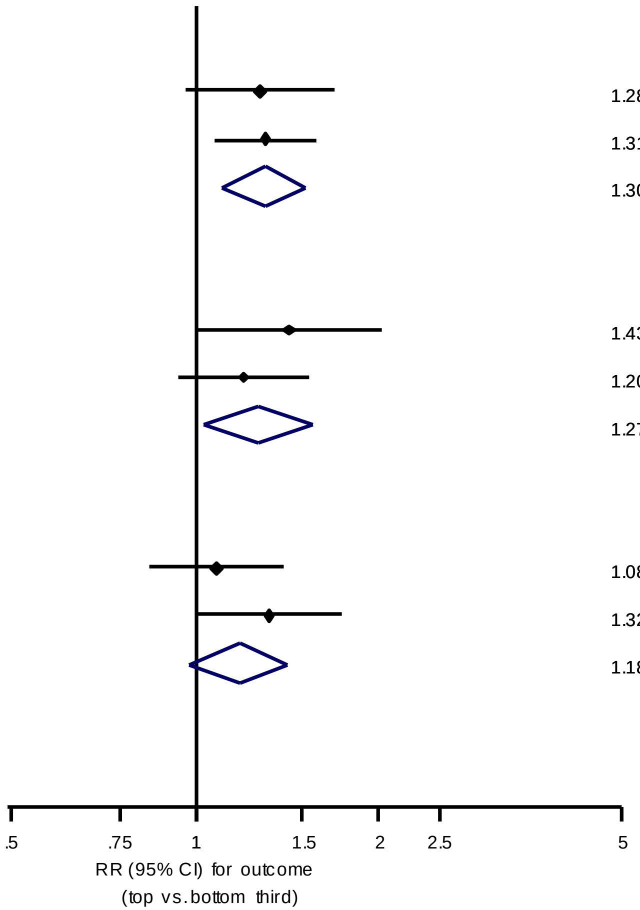
Group	No. of studies	No. of participants	No. of events	RR for CHD (95% CI)	P-value
Type of event					
Both	2	2355	181	2.01 (0.63, 6.46)	0.570
Fatal	2	4944	311	2.62 (1.75, 3.92)	0.570
Total follow-up					
<= 10 Years	3	2725	341	2.20 (1.04, 4.67)	0.880
> 10 Years	1	4574	151	2.47 (1.47, 4.15)	0.880
Location					
Europe	3	2725	341	2.20 (1.04, 4.67)	0.880
North America	1	4574	151	2.47 (1.47, 4.15)	0.880
Study Population					
General	2	1059	290	1.79 (0.77, 4.18)	0.435
Healthy	2	6240	202	2.74 (1.73, 4.34)	0.435
Adjustment factor					
++/+/*	2	1059	290	1.79 (0.77, 4.18)	0.435
+++	2	6240	202	2.74 (1.73, 4.34)	0.435
Gender					
Both	2	5263	281	1.70 (0.84, 3.44)	0.304
Males	2	2036	211	3.16 (1.84, 5.42)	0.304



*The subgroup analysis of copper with stroke was not possible as there were only two studies with small number of participants and cases.

Figure S 7 Subgroup analysis for the association of arsenic with cardiovascular outcomes by measurement source

Measurement Source	No. of studies	No. of participants	No. of events	RR for outcome (95% CI)
CVD				
Urine/Toenail	4	19156	1965	1.28 (0.96, 1.70)
Water	3	116787	1243	1.31 (1.08, 1.58)
Subtotal (I-squared = 0.0%, p = 0.902)				1.30 (1.11, 1.52)
CHD				
Urine/Toenail	4	18742	1159	1.43 (1.00, 2.03)
Water	4	172074	3481	1.20 (0.94, 1.53)
Subtotal (I-squared = 0.0%, p = 0.430)				1.27 (1.04, 1.55)
Stroke				
Urine/Toenail	3	18623	389	1.08 (0.85, 1.39)
Water	1	115903	572	1.32 (1.00, 1.74)
Subtotal (I-squared = 7.9%, p = 0.297)				1.18 (0.98, 1.42)



Pooled risk estimates were calculated using random effects meta-analyses. The Relative Risk (RR) compares the risk for each outcome in individuals in the top third with those in the bottom third of baseline levels of arsenic (i.e. extreme thirds). Abbreviations: CI=confidence interval; CVD= cardiovascular disease; CHD=coronary heart disease

Figure S 8 Subgroup analysis for the association of arsenic with CHD by smoking

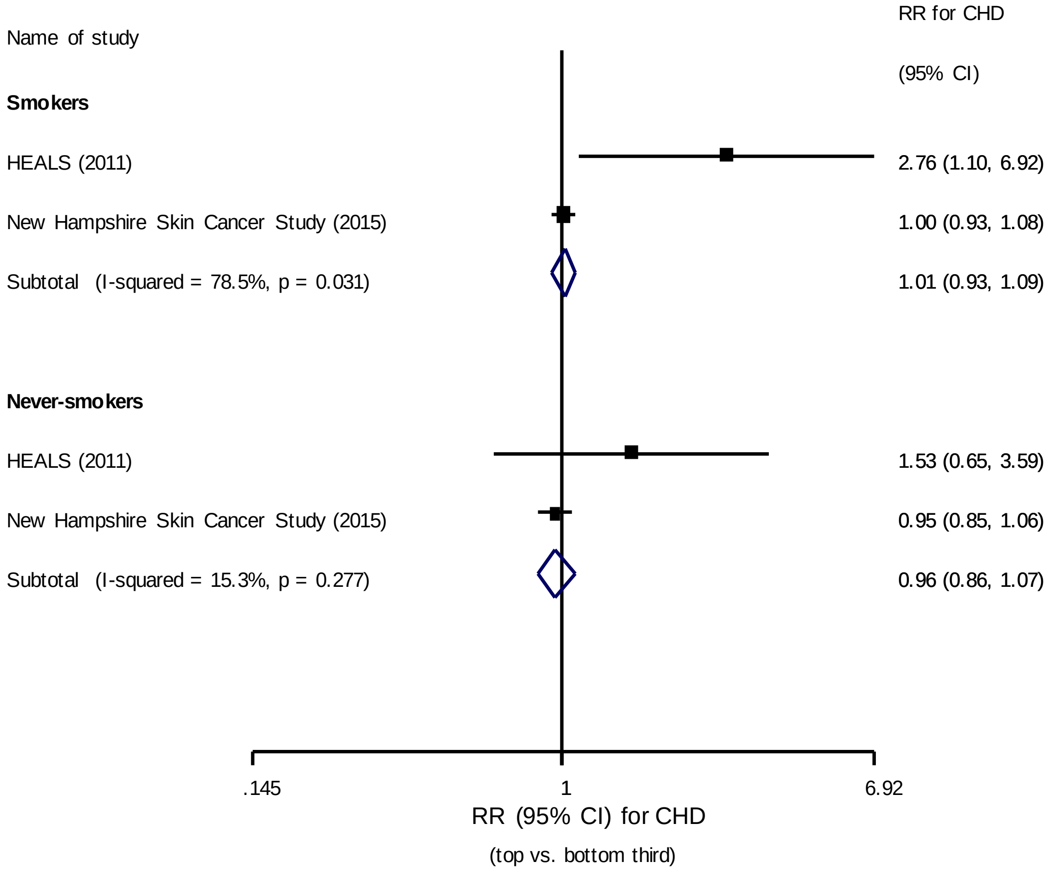


Figure S 9 Subgroup analysis for the association of cadmium with cardiovascular outcomes by smoking

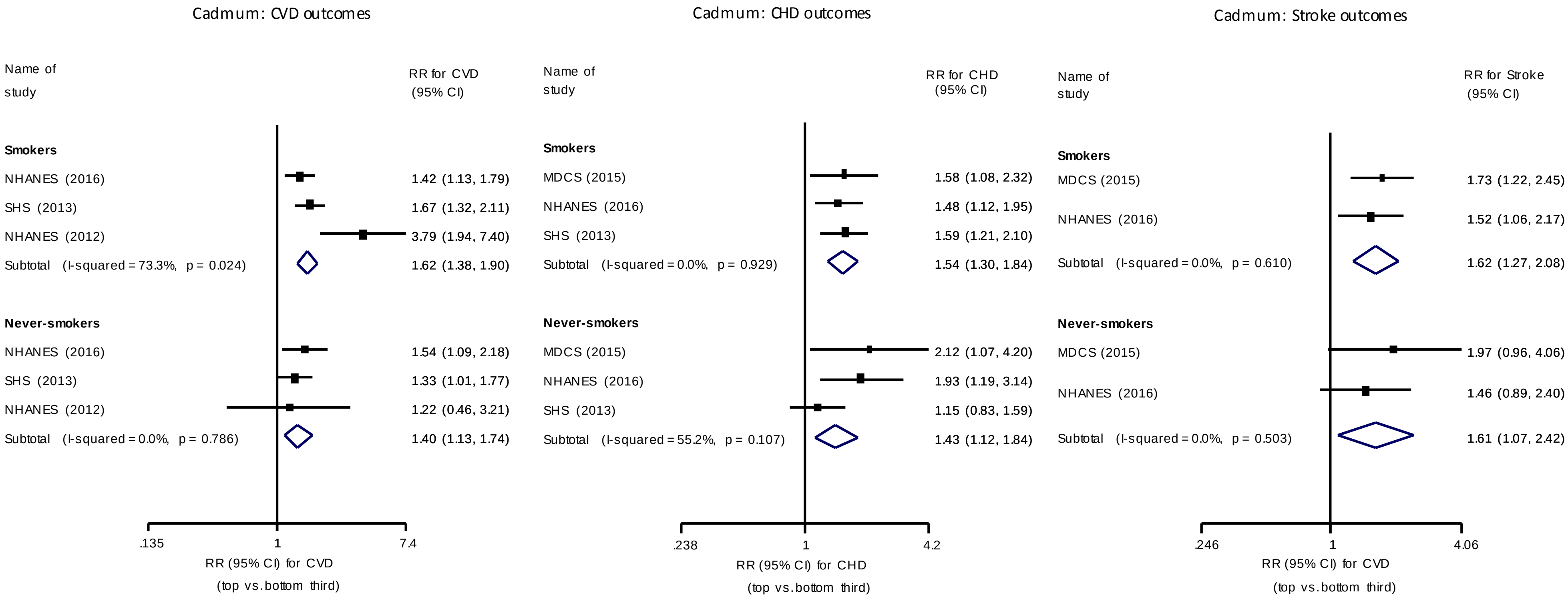
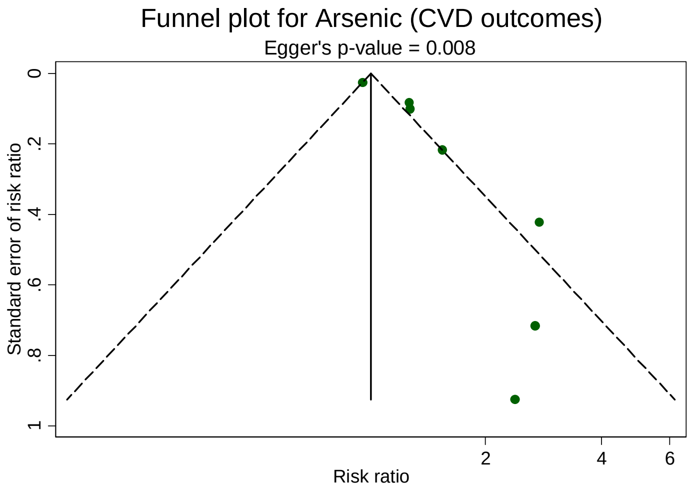


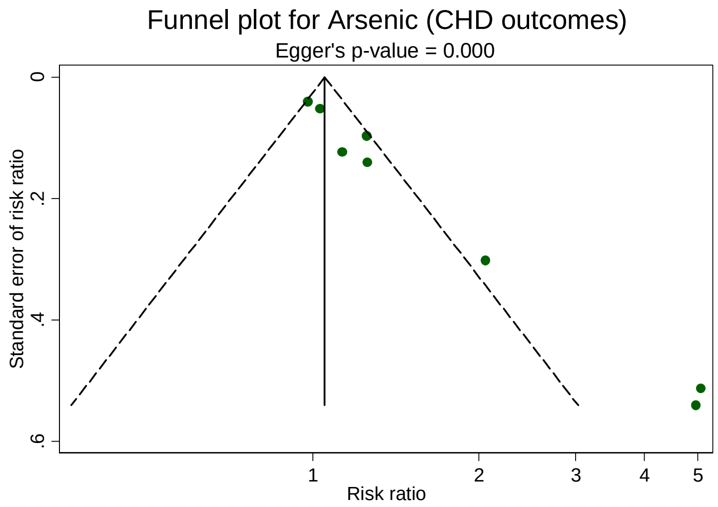
Table S 5 Tests for publication bias

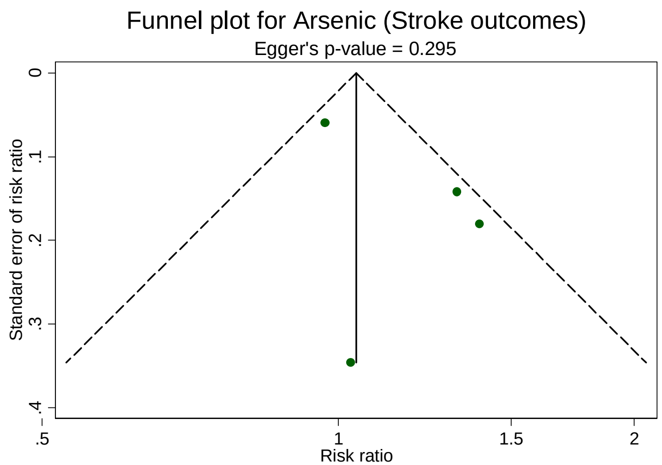
Contaminant	Disease Outcome	No. of studies	Egger's p-value
Arsenic	CVD	7	0.01
	CHD	8	$<10^{-3}$
	Stroke	4	0.30
Lead	CVD	10	0.65
	CHD	8	0.46
	Stroke	6	0.76
Cadmium	CVD	6	0.13
	CHD	5	0.92
	Stroke	3	0.19
Mercury	CVD	4	0.99
	CHD	5	0.86
	Stroke	2	NA
Copper	CVD	4	0.36
	CHD	4	0.18
	Stroke	2	NA

Abbreviations: CHD = coronary heart disease; **CVD** = cardiovascular disease; **NA** = not applicable; **No.** = number

Figure S 10 Funnel plots for association of arsenic with cardiovascular outcomes

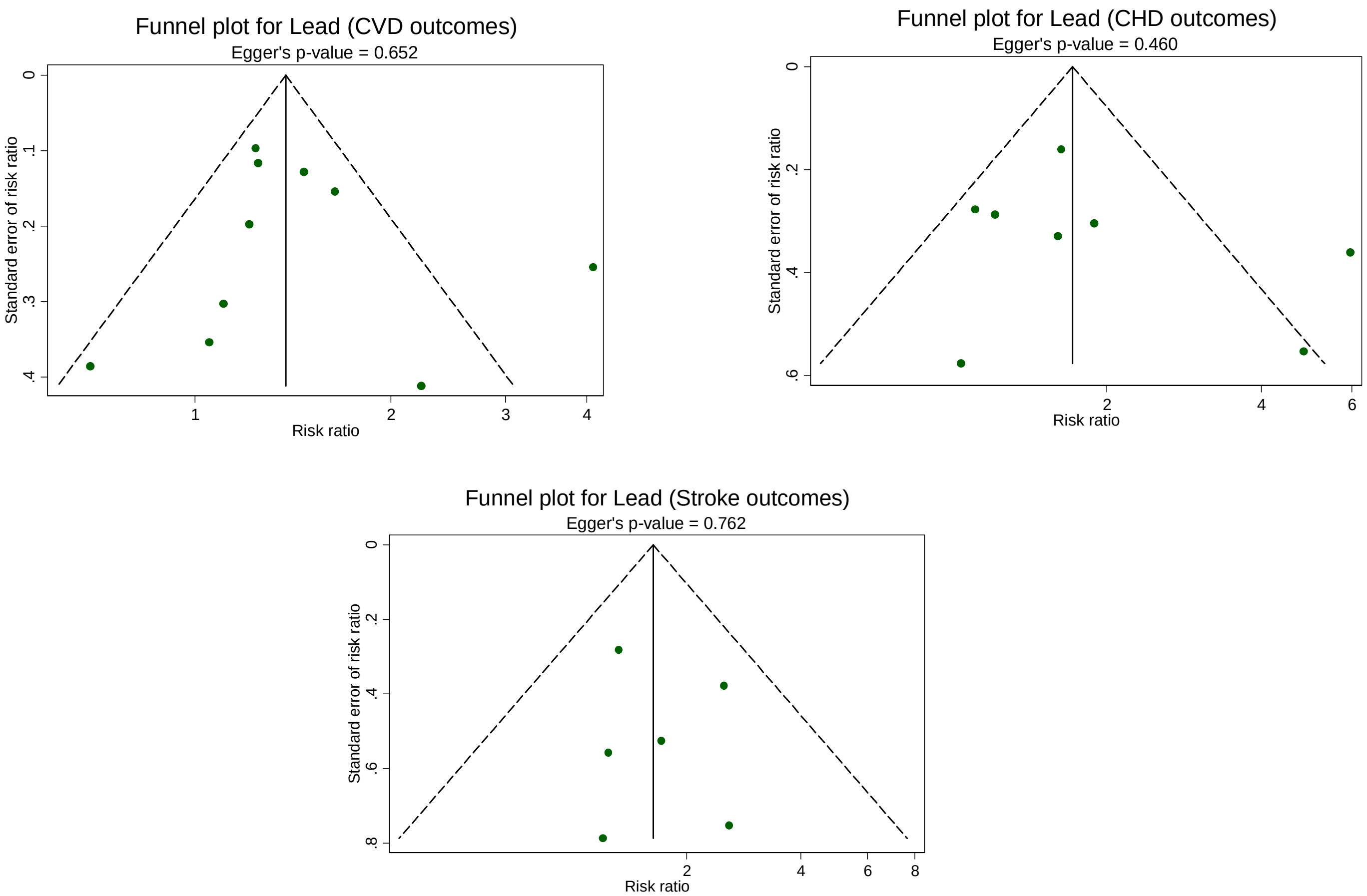






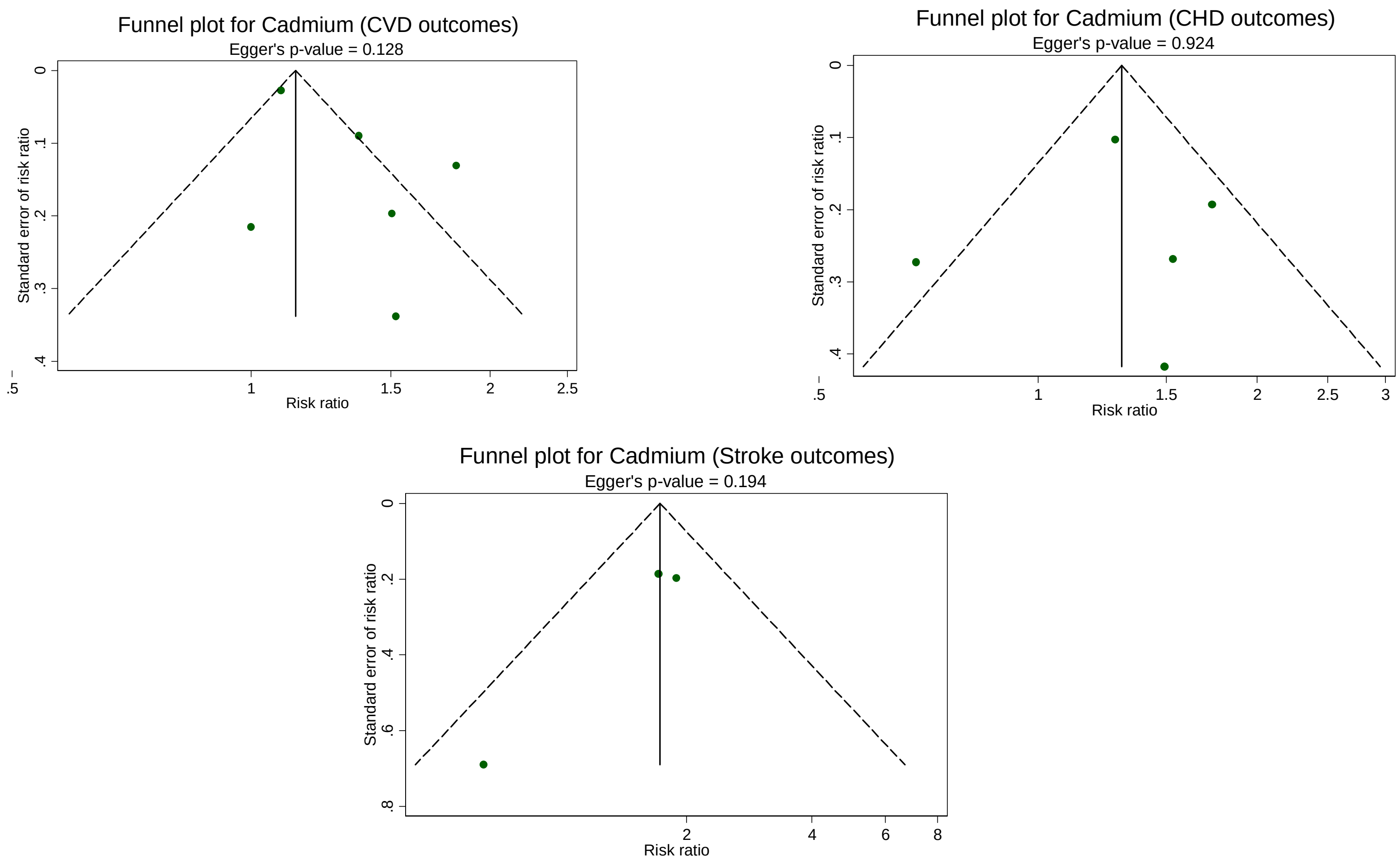
Dotted lines show 95% confidence intervals around the overall summary estimate. Reported p-values are from Egger's asymmetry test of associations.

Figure S 11 Funnel plots for association of lead with cardiovascular outcomes



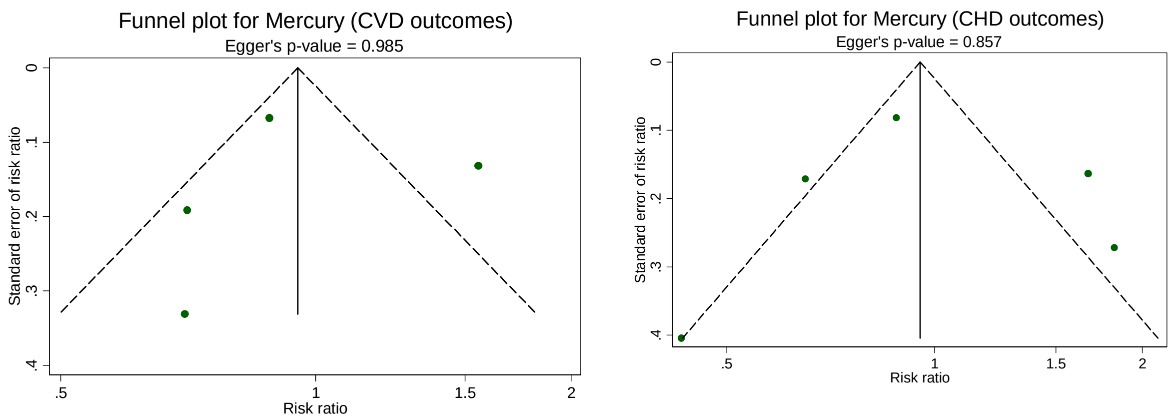
Dotted lines show 95% confidence intervals around the overall summary estimate. Reported p-values are from Egger's asymmetry test of associations.

Figure S 12 Funnel plots for association of cadmium with cardiovascular outcomes



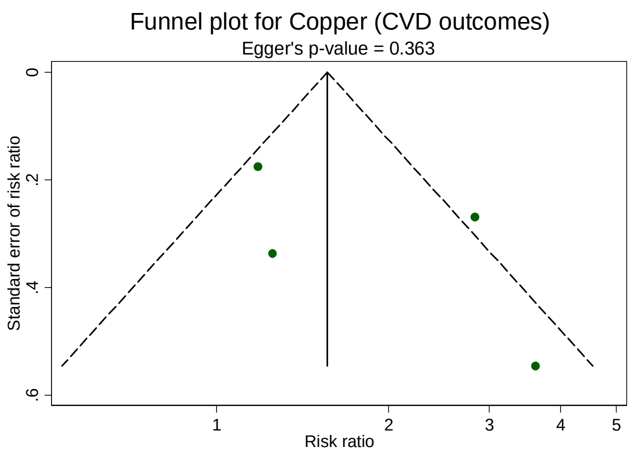
Dotted lines show 95% confidence intervals around the overall summary estimate. Reported p-values are from Egger's asymmetry test of associations.

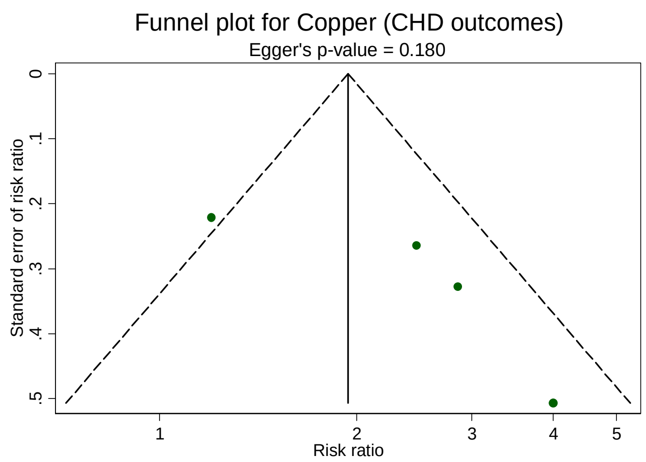
Figure S 13 Funnel plots for association of mercury with cardiovascular outcomes



Dotted lines show 95% confidence intervals around the overall summary estimate. Reported p-values are from Egger's asymmetry test of associations.

Figure S 14 Funnel plots for association of copper with cardiovascular outcomes





Dotted lines show 95% confidence intervals around the overall summary estimate. Reported p-values are from Egger's asymmetry test of associations.

Table S6 Definitions of terms used in the review

Terms	Definitions
Nested case control study	In this study you begin with a defined cohort of cases. Then for each case, a specified number of controls is selected from among those in the cohort who are free of the disease. It is case-control study nested in a cohort study[12].
Linear (dose-response) relationship	In linear associations, when one variable increases the other also increases, or similarly when one variable decreases the other also decreases. For example, a linear association between blood lead level and heart disease risk means if the levels of lead toxicity increases, the risk for heart disease also increases.
"Threshold" or "plateau" effect	This occurs when one variable increases, but other increases only at a certain point.
Publication bias	Publication bias is a well-known term in clinical literature in which positive results have a better chance of being published. Conclusions exclusively based on published studies, therefore, can be misleading[13].

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