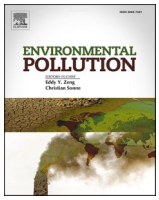
Environmental Pollution 345 (2024) 123462

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol



Review

Cadmium exposure and cardiovascular disease risk: A systematic review and dose-response meta-analysis☆

Pietro Verzelloni [a], Teresa Urbano [a], Lauren A. Wise [b], Marco Vinceti [a,b], Tommaso Filippini [a,c,*]

[a] CREAGEN, Environmental, Genetic and Nutritional Epidemiology Research Center, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy
[b] Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA
[c] School of Public Health, University of California Berkeley, Berkeley, CA, USA

ARTICLE INFO

Keywords:
Cadmium
Cadmium biomarkers
Cardiovascular disease
Coronary heart disease
Heart failure
Stroke

ABSTRACT

Exposure to toxic metals is a global public health threat. Among other adverse effects, exposure to the heavy metal cadmium has been associated with greater risk of cardiovascular disease (CVD). Nonetheless, the shape of the association between cadmium exposure and CVD risk is not clear. This systematic review summarizes data on the association between cadmium exposure and risk of CVD using a dose-response approach. We carried out a literature search in PubMed, Web of Science, and Embase from inception to December 30, 2023. Inclusion criteria were: studies on adult populations, assessment of cadmium exposure, risk of overall CVD and main CVD subgroups as endpoints, and observational study design (cohort, cross-sectional, or case-control). We retrieved 26 eligible studies published during 2005–2023, measuring cadmium exposure mainly in urine and whole blood. In a dose-response meta-analysis using the one-stage method within a random-effects model, we observed a positive association between cadmium exposure and risk of overall CVD. When using whole blood cadmium as a biomarker, the association with overall CVD risk was linear, yielding a risk ratio (RR) of 2.58 (95 % confidence interval-CI 1.78–3.74) at 1 μg/L. When using urinary cadmium as a biomarker, the association was linear until 0.5 μg/g creatinine (RR = 2.79, 95 % CI 1.26–6.16), after which risk plateaued. We found similar patterns of association of cadmium exposure with overall CVD mortality and risks of heart failure, coronary heart disease, and overall stroke, whereas for ischemic stroke there was a positive association with mortality only. Overall, our results suggest that cadmium exposure, whether measured in urine or whole blood, is associated with increased CVD risk, further highlighting the importance of reducing environmental pollution from this heavy metal.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for 32 % of all global deaths corresponding to over 17.9 million people in 2019 (WHO, 2021). Of these, about 50 % are attributed to ischemic heart disease and 34 % to stroke (WHO, 2020). In addition, the American Heart Association reported that in 2018, 126.9 million U.S. adults had CVD, representing the 49.2 % overall (Tsao et al., 2022). Similarly, despite decreasing rates of CVD mortality in most European countries, it remains the leading cause of death, causing 45 % of cases in Europe and 37 % in the overall European Union (Timmis et al., 2020). Such trends have varied across high-, medium- and low-income countries: in the high-income countries, a decline has been registered in both coronary heart disease (CHD) and stroke, while Eastern Europe and Asia have reported a decline in stroke mortality, but not in CHD mortality (Institute of Medicine, 2010).

Many studies demonstrated that environmental pollution plays an important role in human health (Kulick et al., 2023; Tsai et al., 2023), particularly CVD, with increased mortality from ischemic heart disease, dysrhythmia, heart failure (HF), and cardiac arrest (Ayuso-Alvarez et al.,

Abbreviations: AMI, acute myocardial infarction; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; IARC, International Agency for Research on Cancer; PECOS, population exposure comparator outcomes and study design; PRISMA, preferred reporting items for systematic review and meta-analysis; ROBINS-E, risk of bias for non-randomized studies of exposures; RR, risk ratio; WHO, World Health Organization.

☆ This paper has been recommended for acceptance by Da Chen.

* Corresponding author. Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Via Campi 287, 41125, Modena, Italy.

E-mail address: tommaso.filippini@unimore.it (T. Filippini).

https://doi.org/10.1016/j.envpol.2024.123462
Received 19 September 2023; Received in revised form 30 December 2023; Accepted 27 January 2024
Available online 29 January 2024

2022; Pope et al., 2004). Specifically, exposure to toxic heavy metals has become a global health concern (Broomandi et al., 2023; Yang et al., 2020). Cadmium (Cd) is a naturally occurring heavy metal found in a wide range of products and environments. It is produced in various industrial processes and most of the cadmium consumed globally was thought to be used in Nickel-Cd batteries, but relevant other uses included alloys, coatings, pigments, solar cells, and stabilizers (Faroon et al., 2012). Contamination has been reported in air, food, water, and soil (Mititelu et al., 2023; Rocha et al., 2023). In addition to occupational exposure, smoking is a relevant source of exposure, while food is the major source in non-smoking populations (Filippini et al., 2016; Snoj Tratnik et al., 2022; Urbano et al., 2023). For what concerns the exposure biomarkers, whole blood cadmium is typically regarded as an indicator of acute exposure, whereas urinary concentrations are reflective of long-term exposure (Adams and Newcomb, 2014; Goumenou et al., 2021; Julin et al., 2011; Vacchi-Suzzi et al., 2016).

The World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) included cadmium in Group 1 human carcinogens (IARC, 2012) and recent studies indicate an increased risk of cancers of the lung, kidney, bladder, breast, and endometrium (Filippini et al., 2020a; McElroy and Hunter, 2019; Nawrot et al., 2015). Moreover, there are many laboratory and epidemiological findings supporting the hypothesis that cadmium exposure increases the risk of CVD and its risk factors (Filippini et al., 2022; Liu et al., 2022; Suwazono et al., 2021; Tellez-Plaza et al., 2013; Tinkov et al., 2017), although the level of exposure leading to detrimental effects is not fully understood. In fact, a previous meta-analysis investigated the relation between urinary cadmium exposure and CVD mortality and found a strong and consistent evidence of such an association (Larsson and Wolk, 2016). Similarly, a more recent meta-analysis found a positive association between both urinary and whole blood cadmium levels and CVD mortality (Guo et al., 2022), although none of previous reviews performed a dose-response meta-analysis on overall CVD risk.

Our main objective was to review the epidemiological studies that have examined the association between cadmium exposure and CVD risk. The present report builds on previous meta-analyses by including studies examining a broader set of exposure matrices (e.g., urine, whole blood, plasma, and diet), by evaluating CVD risk (including prevalence, incidence, and mortality) as study endpoints, and by assessing CVD overall and according to its subtypes. Finally, this report assesses the shape of these associations, which has been only partially explored previously.

2. Methods

We used the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement (Page et al., 2021) to perform this review registered in PROSPERO database (no. CRD42022360751).

2.1. Study identification and selection

We configured the research and defined the inclusion criteria according to the Population, Exposure, Comparator, Outcomes, and Study design (PECOS) statement: "What is the shape of the association between exposure to cadmium, assessed through urinary concentrations, whole blood concentrations, and dietary intake, and risk of CVD and strokes in adults, in observational studies?" (Morgan et al., 2018).

To find eligible articles, we conducted a systematic literature search for publications available from inception up to December 30, 2023, in the PubMed/MEDLINE, Web of Science, and Embase databases using MeSH terms and keywords linked to "cardiovascular disease", "coronary disease", "heart failure", "stroke", "myocardial infarction" and "cadmium". The full search strategies are reported in Supplementary Table S1. Moreover, we scanned the reference list of included studies and other reviews, as well as we used backward and forward citation retrieval to identify possible additional relevant papers.

We performed a meta-analysis of retrieved observational studies assessing disease risk (as prevalence, incidence, or mortality) of the following cardiovascular outcomes: CVD, HF, CHD (including acute myocardial infarction - AMI), and any stroke (both ischemic and hemorrhagic). We included only the studies measuring cadmium in whole blood, plasma, urine, or dietary intake with specified dose levels divided into different quantiles.

Two authors (PV and TU) reviewed all titles and abstracts independently. If conflicts occurred, they were resolved with the help of a third author (TF). For each included study, we extracted information about country, study period, years of follow-up (for cohort studies), measures of association (odds ratio, hazard ratio, or relative risk) and their 95 % confidence interval (CI) from the most adjusted model, adjustment factors, study design, population size and characteristics, method used to assess cadmium exposure, dose of exposure, and cardiovascular outcomes.

2.2. Quality assessment

We evaluated the quality of the included studies using criteria from the Risk of Bias for Non-randomized Studies of Exposures (ROBINS-E) tool version 2.0 (Morgan et al., 2019). We classified studies as having a low, moderate, or high risk of bias according to the following seven domains of bias: bias due to confounding; bias in selecting participants in the study; bias in exposure classification; bias due to departures from intended exposures; bias due to missing data; bias in outcome measurement; bias in the selection of reported results. In Supplementary Table S2, we reported criteria for risk of bias evaluation performed by two authors (PV and TF). In case of disagreement, a third author helped in the final decision (MV). Each study was considered at a moderate or high risk of bias if at least one domain was judged at moderate or high risk, respectively. Otherwise, it was classified as having a low risk of bias.

2.3. Statistical analysis

We synthesized the evidence through both qualitative and quantitative approaches; in the qualitative approach, we used the inclusion criteria configured through PECOS criteria. In the quantitative synthesis, we compared the different risks in prevalence, incidence and mortality of the main cardiovascular outcomes (see section *2.1. Study identification and selection*) regarding the different levels of cadmium exposure using a restricted maximum likelihood random-effects model (Orsini and Spiegelman, 2021) and whenever possible, we carried out a dose-response meta-analysis of risk of the main cardiovascular outcomes according to increasing cadmium exposure using a one-stage approach (Crippa et al., 2019) as previously implemented in other fields (Filippini et al., 2019; Veneri et al., 2023b; Vinceti et al., 2021). In particular, we used the mean or median value of the intermediate quantile whenever available, while for the highest and the lowest exposure categories in which the mean/median values were not reported, we defined a value 20 % higher or lower than the closest cut-point (Filippini et al., 2022; Iamandii et al., 2023; Veneri et al., 2023a). To assess potential non-linear associations, we used a restricted cubic spline model with knots at 3 fixed points (10th, 50th, and 90th percentiles) of cadmium exposure (Crippa et al., 2019). The reference for the dose-response meta-analysis was set at 0, having no *a priori* assumptions regarding the shape of the association between cadmium exposure and the outcome.

Whenever possible, we carried out additional stratified analyses according to potential confounders including sex and smoking status. We also carried out sensitivity analyses by excluding studies at high risk of bias, and whenever possible we restricted them to studies with cohort design to evaluate incidence only. We used STATA software (v17.0, Stata Corp., College Station, TX, 2021) for all data analyses.

3. Results

3.1. Study selection and characteristics of the included studies

After removal of duplicates, we retrieved 1383 unique studies from which 1270 were excluded after title and abstract screening. We assessed 111 full-text articles excluding 87 with reasons: wrong outcome (N = 46), insufficient data (N = 19), wrong study design (N = 8), overlapping population (N = 7), wrong population (N = 5), and wrong publication type (N = 2). We then added two studies after the screening of a previous meta-analysis on the same topic (Nawrot et al., 2008), and citation chasing (Moon et al., 2023), with a total of 26 eligible studies. The PRISMA flow-chart of the literature search is reported in Fig. 1.

Characteristics of the 26 included studies are summarized in Table 1. All the articles were published between 2005 and 2023; most of the populations are from the US (N = 12) (Agarwal et al., 2011; Chen et al., 2018; Everett and Frithsen, 2008; Ferraro et al., 2012; Kong et al., 2023; Li et al., 2022; Menke et al., 2009; Moon et al., 2023; Tellez-Plaza et al., 2013; Tellez-Plaza et al., 2012; Xing et al., 2023; Xu et al., 2021), Sweden (N = 5) (Barregard et al., 2016; Borne et al., 2015; Julin et al., 2013a; Julin et al., 2013b; Tagt et al., 2022), Denmark (N = 3) (Jeong et al., 2020; Poulsen et al., 2021; Sears et al., 2022; Sears et al., 2021), Japan (N = 2) (Sakurai et al., 2021; Suwazono et al., 2021), South Korea (N = 1) (Jeong et al., 2020), Australia (N = 1) (Deering et al., 2018), China (N = 1) (Wen et al., 2019), and Spain (N = 1) (Domingo-Relloso et al., 2019).

We included 15 cohort studies (Barregard et al., 2016; Borne et al., 2015; Deering et al., 2018; Domingo-Relloso et al., 2019; Ferraro et al., 2012; Julin et al., 2013a; Julin et al., 2013b; Li et al., 2022; Menke et al., 2009; Moon et al., 2023; Sakurai et al., 2021; Suwazono et al., 2021; Tagt et al., 2022; Tellez-Plaza et al., 2013; Tellez-Plaza et al., 2012), 6 cross-sectional studies (Agarwal et al., 2011; Everett and Frithsen, 2008; Jeong et al., 2020; Kong et al., 2023; Xing et al., 2023; Xu et al., 2021), 4 case-cohort studies (Chen et al., 2018; Poulsen et al., 2021; Sears et al., 2022; Sears et al., 2021), and 1 case-control study (Wen et al., 2019).

Cadmium concentrations were measured in urine (N = 13) (Chen et al., 2018; Deering et al., 2018; Domingo-Relloso et al., 2019; Everett and Frithsen, 2008; Menke et al., 2009; Poulsen et al., 2021; Sakurai et al., 2021; Sears et al., 2022; Sears et al., 2021; Suwazono et al., 2021; Tagt et al., 2022; Tellez-Plaza et al., 2013; Xu et al., 2021), whole blood

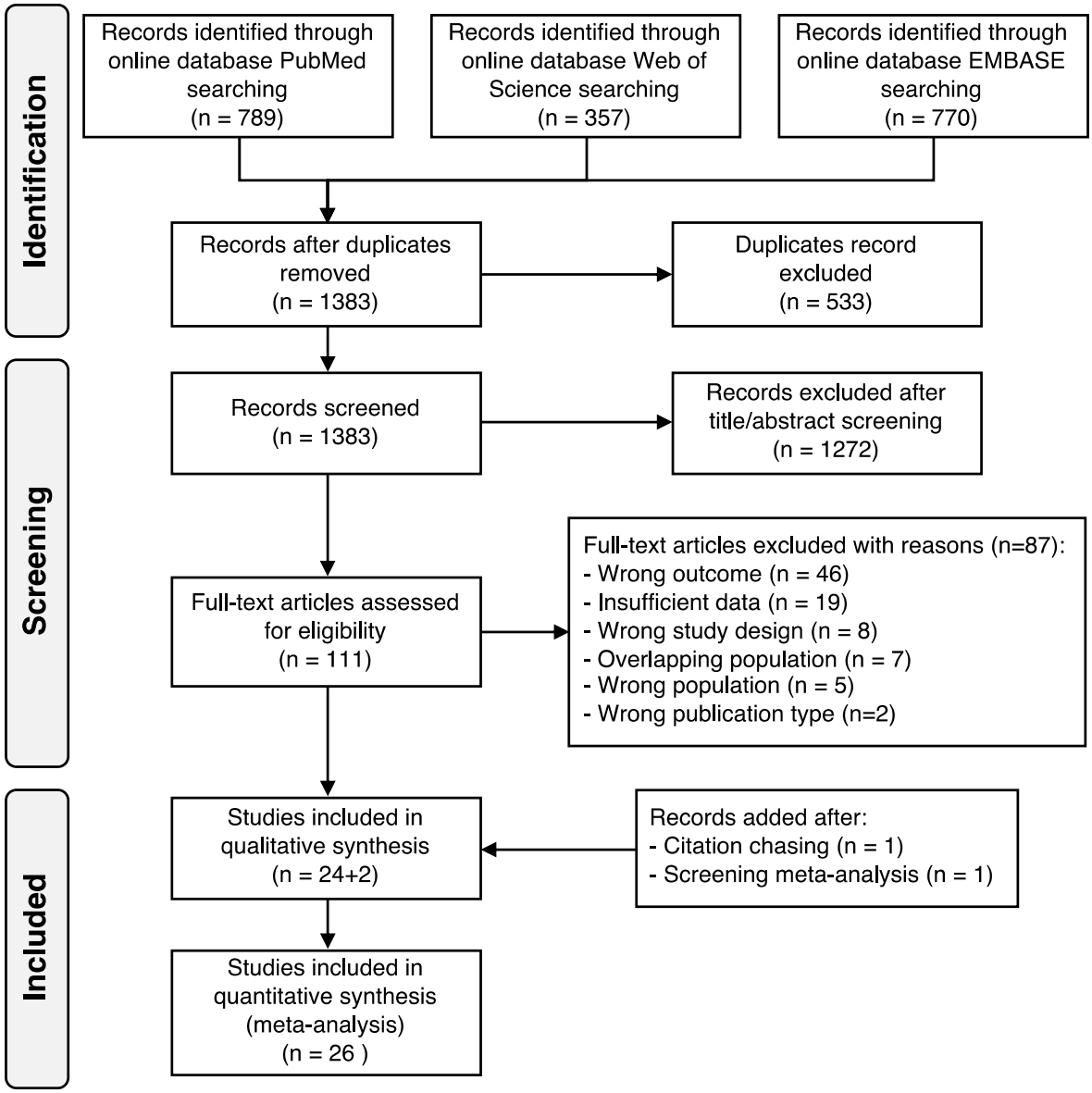


Fig. 1. Flow-chart of systematic literature search through December 30, 2023.

Table 1
Characteristics of included studies.

Reference	Region	Cohort name	Study design	Follow-up	Specimen	Outcome	Risk assessment (highest-lowest)	Cd levels (lowest-highest)	Adjustment factors
Agarwal et al. (2011)	US	NAHNES, 1999–2000; 2001–2002; 2003–2004; 2005–2006	Cross-sectional	NA	Blood (μg/L)	CVD	OR: 1.44 (1.07–1.95)	0.176–0.732	Age, sex, race, education, hypertension, diabetes, hypercholesterolemia, chronic kidney disease, BMI, CRP, smoking, serum cotinine, and lead
Barregard et al. (2016)	Sweden	Malmö Diet and Cancer Study, 1991–1994	Cohort	Until 2010	Blood (μg/L)	AMI, Any stroke, Ischemic stroke, CVD, CHD, CVD mortality	HR: 1.80 (1.20–2.80) 2.10 (1.30–2.80) 2.10 (1.30–2.30) 1.90 (1.30–2.80) 1.90 (1.20–2.90) 1.90 (1.10–3.20)	0.13–1.20	Sex, smoking, waist circumference, low education, low physical activity, alcohol intake, serum triglycerides, HbA1c, CRP, postmenopausal status, hormonal replacement, treatment for hypertension, diabetes mellitus, lipid-lowering medication, DBP, LDL-C, and HDL-C
Borne et al. (2015)	Sweden	Malmö Diet and Cancer Study, 1991–1996	Cohort	Average 17 years	Blood (μg/L)	HF	HR: M 3.91 (1.32–11.54) F 1.18 (0.49–2.82)	0.12–0.98	Age, SBP, use of blood pressure-lowering or lipids-lowering medications, presence of diabetes mellitus, history of a coronary event, waist circumference, smoking status, alcohol intake, LDL-C, HDL-C, hs-CRP, plasma creatinine, marital, and educational status
Chen et al. (2018)	US	REGARDS, 2003–2007	Case-cohort	Until 2012	Urine (μg/g creatinine)	Ischemic stroke	HR: 1.50 (1.01–2.22)	0.18–1.03	Age, sex, race, age-sex and age-race interactions, region, income, BMI, smoking status, alcohol consumption, physical activity, diabetes mellitus, HDL-C/LDL-C ratio, CRP, serum calcium, and urinary arsenic concentrations
Deering et al. (2018)	Australia	Australian electoral roll, 1998	Cohort	15 years	Urine (μg/L)	Any stroke, HF, CHD, Ischemic stroke mortality, HF mortality, CHD mortality	HR: 0.90 (0.61–1.32) 1.35 (0.85–2.16) 0.84 (0.62–1.16) 0.78 (0.44–1.38) 1.77 (0.90–3.48) 0.88 (0.55–1.41)	0.092–0.306	Age at baseline, calcium treatment, BMI, hypertension, eGFR, prevalent ASVD, diabetes, low dose aspirin use and statin use, for urinary specific gravity, urinary creatine, or ever/never smoker and pack-years smoked
Domingo-Relloso et al. (2019)	Spain	Hortega Study, 1997; 1999–2000; 2001–2003	Cohort	Until 2015	Urine (μg/g creatinine)	Any stroke + CHD, CVD, HF	HR: 1.68 (0.92–3.08) 2.31 (1.47–3.65) 3.68 (1.54–8.75)	0.216–0.636	Sex, education, smoking status, cumulative smoking dose, urine cotinine, eGFR, residence, HDL-C , total cholesterol, dyslipidemia treatment, hypertension treatment, diabetes mellitus of type 2 and SBP
Everett and Frithsen (2008)	US	NHANES III, 1988–1994	Cross-sectional	NA	Urine (μg/g creatinine)	AMI	OR: 1.46 (1.01–2.13)	0.516–1.056	Age, sex, total cholesterol, HDL-C, SBP, hypertension medications, smoking status, pack-years of smoking, race-ethnicity, family history of heart attack, and diabetes
Ferraro et al. (2012)	US	NHANES, 1999–2004	Cohort	Until 2006, an	Blood (μg/L)	CVD mortality	HR: M 1.34	0.15–0.84	Age, sex, total cholesterol, HDL-C, SBP, hypertension

(*continued on next page*)

Table 1 (*continued*)

Reference	Region	Cohort name	Study design	Follow-up	Specimen	Outcome	Risk assessment (highest-lowest)	Cd levels (lowest-highest)	Adjustment factors
				average of 57 months			(0.62–2.89) F 2.83 (0.78–10.24)		medications, smoking status, pack-years of smoking, race-ethnicity, family history of heart attack, and diabetes
Jeong et al. (2020)	South Korea	KNHANES, 2008–2013 and 2016	Cross-sectional	NA	Blood (μg/L)	Any stroke, CHD	OR: 2.39 (1.03–5.56) 1.12 (0.56–2.26)	0.8–2.4	Age, sex, current smoking status, education level, income level, alcohol consumption, BMI, glucose level, SBP, survey year, regular walking, and eGFR
Julin et al. (2013a)	Sweden	The Swedish Mammography cohort, 1987–1990 and 1997	Cohort	Until 2010	Food intake (μg/day)	AMI, Any stroke, Ischemic stroke, Hemorragic stroke, CVD	RR: 1.07 (0.88–1.29) 0.90 (0.76–1.05) 0.89 (0.74–1.06) 1.11 (0.68–1.80) 0.96 (0.85–1.09)	10–17	Age, postsecondary education, family history of myocardial infarction before the age of 60 years, high cholesterol, hypertension, ever use of postmenopausal hormones, ever use of aspirin, smoking status, BMI, total physical activity, alcohol consumption, and energy intake, consumption of vegetables and whole grains
Julin et al. (2013b)	Sweden	The cohort of Swedish men (COSM), 1997	Cohort	Until 2010	Food intake (μg/day)	CVD	RR: 0.99 (0.91–1.09)	15–23	Age, postsecondary education, family history of myocardial infarction before the age of 60 years, high cholesterol, hypertension, ever use of postmenopausal hormones, ever use of aspirin, smoking status, BMI, total physical activity, alcohol consumption, and energy intake, consumption of vegetables and whole grains
Kong et al. (2023)	US	NHANES 2007–2018	Cross-sectional	NA	Blood (μg/L)	CVD, CHD	OR: 1.70 (1.47–1.97) 1.74 (1.47–2.07)	0.200–0.576	Age, sex, race and ethnicity, education, income smoking, alcohol use, weight status (BMI), hypertension, hypercholesterolemia, and diabetes history
Li et al. (2022)	US	NHANES 1999–2014	Cohort	Median 9 years	Blood (μg/L)	CVD mortality	HR: 1.72 (1.28–2.30)	0.14–0.72	Survey cycle, age, race, sex, educational level, family income-poverty ratio, alcohol intake, smoking status, marital status, BMI, hypertension, diabetes, cardiovascular disease, and cancer
Menke et al. (2009)	US	NHANES III, 1988–1994	Cohort	Until 2000, Average 9 years above who is still alive, 5.1 years above who is dead	Urine (μg/g creatinine)	CVD mortality, CHD mortality	HR: M 1.33 (0.69–2.56) F 0.82 (0.47–1.42) M 2.48 (0.85–7.27) F 0.45 (0.24–0.83)	M 0.252–0.576 F 0.232–0.816	Age, race/ethnicity, postmenopausal status, urban residence, annual household income, high school education, smoking category, tertile of pack-years, physical activity, diabetes, BMI, alcohol consumption, CRP, total cholesterol, systolic blood pressure, blood pressure–lowering medication, blood lead, and eGFR
Moon et al. (2023)	US	NHANES, 1999–2018	Cohort	Until 2019,	Urine (μg/g creatinine)	CVD mortality	HR: 1.26 (0.81–1.95)	0.112–0.576 0.176–0.720	Age, sex, race/ethnicity, BMI, smoking status,

(*continued on next page*)

Table 1 (*continued*)

Reference	Region	Cohort name	Study design	Follow-up	Specimen	Outcome	Risk assessment (highest-lowest)	Cd levels (lowest-highest)	Adjustment factors
				median 110 months	and Blood (μg/L)		HR: 1.75 (1.41–2.17)		alcohol consumption, hypertension, diabetes mellitus, dyslipidemia, history of CVD, and history of cancer
Poulsen et al. (2021)	Denmark	Diet, Cancer, and Health cohort, 1993–1997	Case-cohort	Until 2009	Urine (μg/g creatinine)	Any stroke, Ischemic stroke, Hemorragic stroke	HR: 1.11 (0.79–1.55) 1.12 (0.78–1.62) 1.09 (0.53–2.24)	0.098–0.436	Age as time axis and adjusted for sex, cotinine, BMI, and education
Sakurai et al. (2021)	Japan	Kakehashi River basin's inhabitants, 1981–1996	Cohort	35 years	Urine (μg/g creatinine)	Any stroke mortality, CHD mortality, CVD mortality, HF, Hemorrhagic stroke mortality, Ischemic stroke mortality	HR: M 0.75 (0.30–1.86) F 1.11 (0.66–1.87) M 2.64 (0.99–7.04) F 0.97 (0.35–2.70) M 1.92 (1.08–3.40) F 1.71 (1.07–2.71) M 1.20 (0.47–3.04) F 2.37 (1.31–4.30) M 1.51 (0.66–3.44) F 0.46 (0.09–2.26) M 0.63 (0.15–2.60) F 0.92 (0.46–1.84)	4–12	Age
Sears et al. (2021)	Denmark	Diet, Cancer, and Health cohort, 1993–1997	Case-cohort	Until 2015	Urine (μg/g creatinine)	AMI	HR: 1.16 (0.86–1.56)	0.097–0.430	Age as the time scale, sex, BMI, education, cotinine, menopausal status (for women)
Sears et al. (2022)	Denmark	Diet, Cancer and Health cohort, 1993–1997	Case-cohort	Until 2015	Urine (μg/g creatinine)	HF	HR: 1.30 (0.95–1.80)	0.10–0.45	Age as the time scale, sex, BMI, education, and cotinine
Suwazono et al. (2021)	Japan	Residents in one of three regions without environmental Cd pollution, one being in the south Bosoarea of Chiba Prefecture and other two in the Noto area of Ishikawa Prefecture, 1993–1994	Cohort	19 years	Urine (μg/g creatinine)	Any stroke mortality, Ischemic stroke mortality, CVD mortality, CHD mortality	HR: M 1.50 (0.73–3.10) F 1.08 (0.46–2.52) M 2.08 (0.84–5.12) F 1.61 (0.45–5.77) M 1.59 (0.93–2.71) F 1.34 (0.71–2.53) M 2.17 (0.53–8.85) F 4.95 (0.54–45.65)	0.896–3.816	Age, BMI, mean arterial pressure, present illness of hypertension, region of residence, and smoking and drinking habits
Tellez-Plaza et al. (2012)	US	NHANES, 1999–2004	Cohort	Until 2006	Urine (μg/g creatinine) and blood (μg/L)	CVD mortality, CHD mortality CVD mortality CHD mortality	HR: 1.74 (1.07–2.83) 2.09 (1.06–4.13) HR: 1.69 (1.03–2.77) 1.73 (0.88–3.40)	0.14–0.57 0.22–0.80	Sex, education, annual household income, and race/ethnicity, postmenopausal status for women, BMI, blood lead, CRP, total cholesterol, HDL-C , cholesterol-lowering medication use, hypertension, diabetes, eGFR, smoking status, cumulative smoking dose, and serum cotinine

(*continued on next page*)

Table 1 (*continued*)

Reference	Region	Cohort name	Study design	Follow-up	Specimen	Outcome	Risk assessment (highest-lowest)	Cd levels (lowest-highest)	Adjustment factors
Tellez-Plaza et al. (2013)	US	13 American Indian communities in Arizona, Oklahoma, and North and South Dakota, 1989–1991	Cohort	Until 2008, an average of 15 years	Urine (μg/g creatinine)	Any stroke, CVD, HF, CHD, CVD mortality, CHD mortality	HR: 1.87 (1.22–2.86) 1.48 (1.21–1.80) 1.61 (1.10–2.36) 1.33 (1.05–1.68) 1.87 (1.34–2.60) 1.51 (1.04–2.20)	0.488–1.740	Sex, postmenopausal status for women, education, BMI, total cholesterol, estimated LDL-C, hypertension, diabetes, eGFR, smoking status, and cumulative dose of pack years
Tagt et al. (2022)	Sweden	Swedish Mammography Cohort-Clinical, 2003–2009	Cohort	Until 2019	Urine (μg/g creatinine)	AMI, Ischemic stroke, HF, CVD mortality	HR: 1.24 (0.78–1.97) 0.66 (0.43–1.02) 1.40 (0.93–2.11) 1.48 (0.96–2.29)	0.20–0.54	Age, education, height, weight, history of diabetes, parity, decreased GFR, smoking status, physical activity, Mediterranean diet score, total energy intake, and hypercholesterolemia
Wen et al. (2019)	China	Shenzhen People's Hospital, Shenzhen-China, 2012–2017	Case-control	NA	Plasma (μg/L)	Ischemic stroke	OR: 6.98 (5.09–9.57)	0.024–0.096	BMI, smoking, alcohol drinking, hypertension, diabetes, and hyperlipidemia
Xing et al. (2023)	US	NHANES, 1999–2000; 2003–2004; 2011–2018	Cross-sectional	NA	Blood (μg/L)	HF, CVD mortality	OR: 1.77 (1.34–2.34) 1.56 (1.18–2.06)	0.192–0.576	Age, sex, race, country of birth, education, marital status, drinking, current smoking, SBP, DBP, pulse, total cholesterol, HDL-C, BMI, and glycohaemoglobin
Xu et al. (2021)	US	NHANES, 1999–2016	Cross-sectional	NA	Urine (μg/L)	AMI, Any stroke, CVD, HF, CHD	OR: 2.66 (1.79–3.94) 1.44 (0.93–2.23) 1.83 (1.36–2.47) 2.73 (1.66–4.48) 1.93 (1.22–3.05)	0.104–0.624	Age, sex, race, education level, poverty income ratio, serum cotinine, BMI, total cholesterol, alcohol drinking status, family history of CVD, NHANES cycle, urinary creatinine, and 8 other heavy metals

Abbreviations: AMI: acute myocardial infarction; BMI: body mass index; CHD: coronary heart disease; CRP: C-reactive protein; CV: cardiovascular; CVD: cardiovascular disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; F: females; HDL-C: high-density lipoprotein cholesterol: HF: heart failure; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol; M: males; NA: not available; OR: odds ratio; RR: relative risk; SBP: systolic blood pressure. The underlined outcomes and specimen indicate that it was assessed in the study but not considered in the analysis due to overlapping populations with other included studies.

(N = 8) (Agarwal et al., 2011; Barregard et al., 2016; Borne et al., 2015; Ferraro et al., 2012; Jeong et al., 2020; Kong et al., 2023; Li et al., 2022; Xing et al., 2023), and plasma (N = 1) (Wen et al., 2019), with two studies measuring cadmium in both urine and whole blood (Moon et al., 2023; Tellez-Plaza et al., 2012). Two studies estimated dietary cadmium intake via food frequency questionnaires (Julin et al., 2013a; Julin et al., 2013b).

Among the included articles, the prevalence or incidence of each outcome was assessed as follows: AMI by four studies using urine (Everett and Frithsen, 2008; Sears et al., 2021; Tagt et al., 2022; Xu et al., 2021), one using whole blood (Barregard et al., 2016), and one using food intake (Julin et al., 2013a); any stroke by four studies using urine (Deering et al., 2018; Poulsen et al., 2021; Tellez-Plaza et al., 2013; Xu et al., 2021), one whole blood (Jeong et al., 2020), and one dietary intake (Julin et al., 2013a); ischemic stroke by three studies using urine (Chen et al., 2018; Poulsen et al., 2021; Tagt et al., 2022), one whole blood (Barregard et al., 2016), one food intake (Julin et al., 2013a), and one through plasma (Wen et al., 2019); hemorrhagic stroke by one study using urine (Poulsen et al., 2021), and one food intake (Julin et al., 2013a); CVD has been studied in three studies through urine (Domingo-Relloso et al., 2019; Tellez-Plaza et al., 2013; Xu et al., 2021), in three with whole blood (Agarwal et al., 2011; Barregard et al., 2016; Kong et al., 2023), and one food intake (Julin et al., 2013a); HF by seven studies using urine (Deering et al., 2018; Domingo-Relloso et al., 2019; Sakurai et al., 2021; Sears et al., 2022; Tagt et al., 2022; Tellez-Plaza et al., 2013; Xu et al., 2021), and twice whole blood (Borne et al., 2015; Xing et al., 2023); CHD was assessed using urine in three studies (Deering et al., 2018; Tellez-Plaza et al., 2013; Xu et al., 2021), and using whole blood in other three (Barregard et al., 2016; Jeong et al., 2020; Kong et al., 2023). Regarding the outcome mortality: any stroke was evaluated through urine in three studies (Deering et al., 2018; Sakurai et al., 2021; Suwazono et al., 2021); ischemic stroke by urine in two articles (Sakurai et al., 2021; Suwazono et al., 2021); cardiovascular mortality by urine in seven studies (Menke et al., 2009; Moon et al., 2023; Sakurai et al., 2021; Suwazono et al., 2021; Tagt et al., 2022; Tellez-Plaza et al., 2013; Tellez-Plaza et al., 2012), and by whole blood in six studies (Barregard et al., 2016; Ferraro et al., 2012; Li et al., 2022; Moon et al., 2023; Tellez-Plaza et al., 2012; Xing et al., 2023); HF in two studies through urine (Deering et al., 2018; Sakurai et al., 2021); CHD in five studies with urine (Deering et al., 2018; Menke et al., 2009; Suwazono et al., 2021; Tellez-Plaza et al., 2013; Tellez-Plaza et al., 2012).

Overall, included studies that assessed cadmium exposure through whole blood used μg/L as the unit of measure, while concerning urine 13

studies used μg/g creatinine and two studies used μg/L, although the latter included creatinine as a control variable, so it was considered valid for the purpose of dose-response analyses. Despite the high accuracy of the two types of measurements, because of the formal difference, we performed sensitivity analyses by excluding studies that used μg/L.

3.2. Risk of bias assessment

Quality assessments of the studies are provided in Supplementary Table S3. Overall, we considered three of the included studies at high risk of bias (Jeong et al., 2020; Kong et al., 2023; Xu et al., 2021) because they used a self-reported questionnaire to assess the outcome. One of these three studies (Xu et al., 2021) was considered biased due to >20 % missing data. Two articles were considered to have a moderate risk of bias regarding confounding due to missing important adjustment factors, namely age (Domingo-Relloso et al., 2019), and smoking (Sakurai et al., 2021). Although four studies did not adjust for smoking (Poulsen et al., 2021; Sears et al., 2022; Sears et al., 2021; Xu et al., 2021), they were still considered at low risk because they adjusted for cotinine, which is an indirect method to evaluate smoking status. Of all the articles, only one had a moderate risk of bias in terms of participant selection, as it included a population known to be exposed to cadmium from the environment (Sakurai et al., 2021). Nine of the articles were deemed to have a moderate risk of bias due to missing data, higher than 10 % (Agarwal et al., 2011; Borne et al., 2015; Deering et al., 2018; Everett and Frithsen, 2008; Ferraro et al., 2012; Kong et al., 2023; Menke et al., 2009; Moon et al., 2023; Xing et al., 2023). Two studies were deemed to be at moderate risk because the outcome assessment was based on self-report through questionnaire data subsequently validated (Agarwal et al., 2011; Chen et al., 2018).

Combining the various sources of bias, we considered three studies at high risk of bias (Jeong et al., 2020; Kong et al., 2023; Xu et al., 2021), ten at moderate risk (Agarwal et al., 2011; Borne et al., 2015; Chen et al., 2018; Deering et al., 2018; Everett and Frithsen, 2008; Ferraro et al., 2012; Menke et al., 2009; Moon et al., 2023; Sakurai et al., 2021; Xing et al., 2023), and thirteen at low risk (Barregard et al., 2016; Domingo-Relloso et al., 2019; Julin et al., 2013a; Julin et al., 2013b; Li et al., 2022; Poulsen et al., 2021; Sears et al., 2022; Sears et al., 2021; Tagt et al., 2022; Tellez-Plaza et al., 2013; Tellez-Plaza et al., 2012; Wen et al., 2019).

3.3. Dose-response meta-analysis

3.3.1. Cardiovascular disease

Risk of CVD was studied in three included articles with whole blood as a biomarker (Agarwal et al., 2011; Barregard et al., 2016; Kong et al., 2023), in two through food intake (Julin et al., 2013a; Julin et al., 2013b), and three using urinary concentrations (Domingo-Relloso et al., 2019; Tellez-Plaza et al., 2013; Xu et al., 2021).

We performed a dose-response meta-analysis for urine and whole blood only because only two studies evaluated dietary intake. The dietary studies indicated no increased risk comparing the highest versus the lowest quartile (Q4 vs. Q1) among both males (with RR = 0.99, 95 % CI 0.91–1.09) and females (RR = 0.96, 95 % CI 0.85–1.09) (Table 1). Concerning urine, two studies used μg/g creatinine as the unity of measure (Domingo-Relloso et al., 2019; Tellez-Plaza et al., 2013), while one used μg/L adjusted for creatinine (Xu et al., 2021). We found a positive non-linear association with CVD risk reaching a plateau above 0.5 μg/g creatinine of cadmium exposure, with a RR of 2.79 (95 % CI 1.26–6.16). The dose-response curve performed using whole blood levels showed a positive linear association, reaching a RR of 2.58 (95 % CI 1.78–3.74) at 1 μg/L (Fig. 2). Exclusion of studies at high risk of bias yielded a positive linear association reaching a RR of 2.33 (95 % CI 1.63–3.33) at 1 μg/L. In contrast to the previous curve, the slope decreased slightly when the concentration was above 0.3 μg/L (Supplementary Fig. S1).

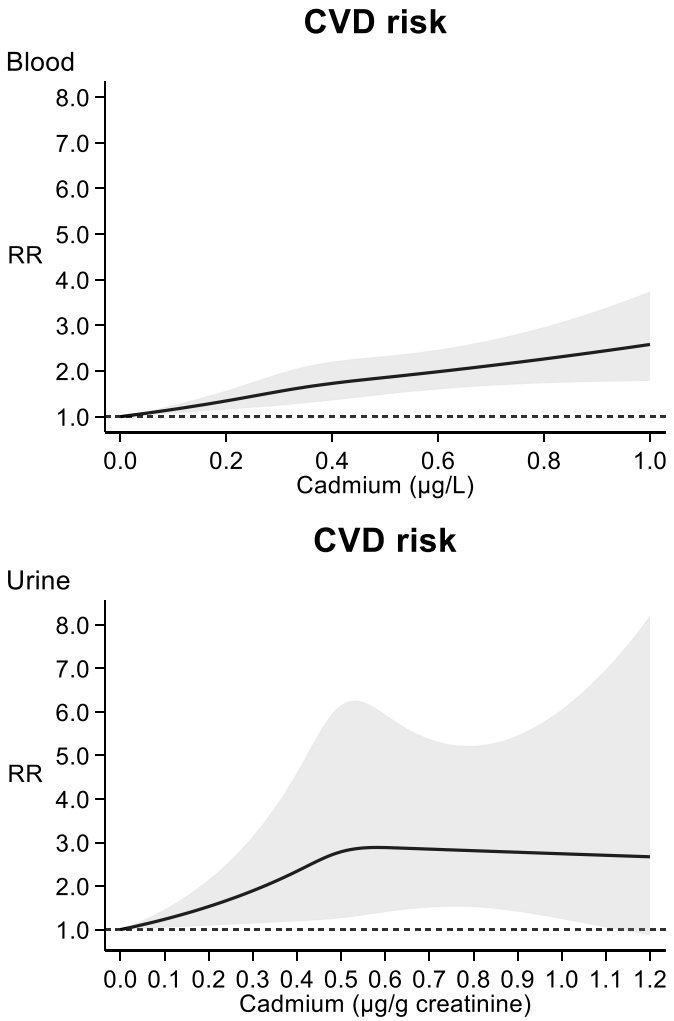
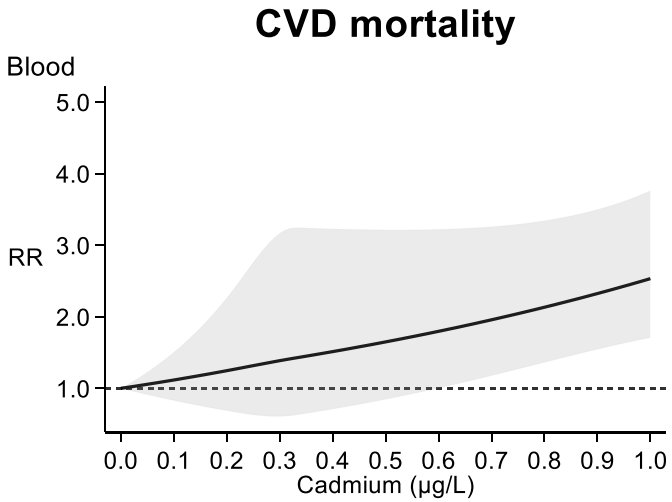


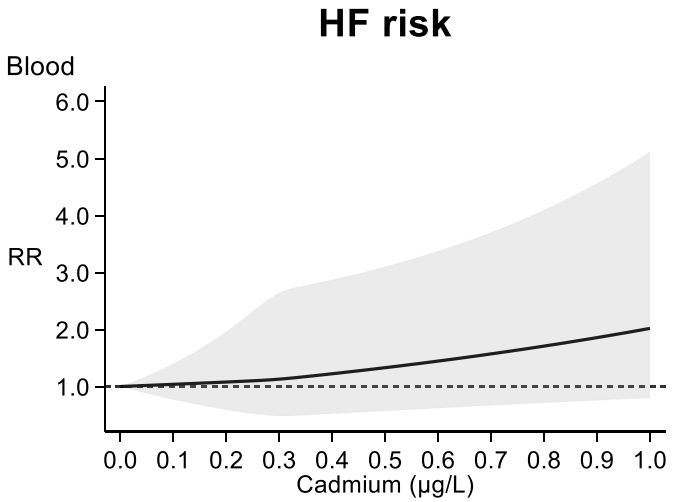
Fig. 2. Dose-response curves for cardiovascular disease (CVD) risk and cadmium exposure measured through blood and urine. Spline curve (solid black line) with 95 % confidence limits (gray area). RR: risk ratio.

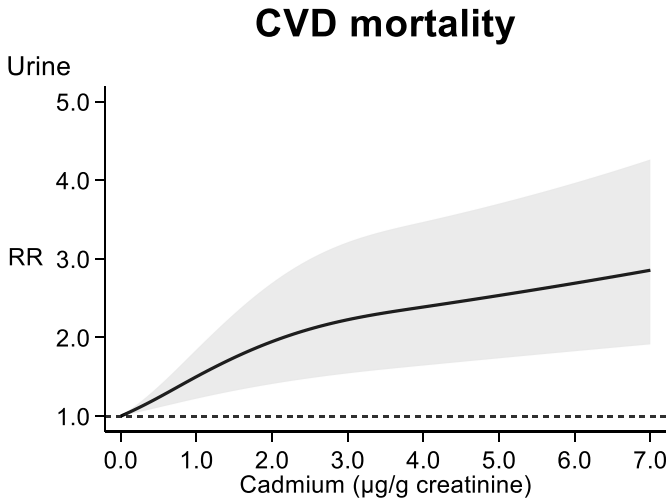
With respect to CVD mortality, we included six articles using whole blood concentrations (Barregard et al., 2016; Ferraro et al., 2012; Li et al., 2022; Moon et al., 2023; Tellez-Plaza et al., 2012; Xing et al., 2023), but four have been excluded from the dose-response analysis for overlapping populations (Ferraro et al., 2012; Moon et al., 2023; Tellez-Plaza et al., 2012; Xing et al., 2023). The dose-response curve showed a linear positive association that reach a RR of 2.53 (95 % CI 1.71–3.76) at 1 μg/L. Seven articles evaluated CVD mortality using urinary cadmium concentrations (Menke et al., 2009; Moon et al., 2023; Sakurai et al., 2021; Suwazono et al., 2021; Tagt et al., 2022; Tellez-Plaza et al., 2013; Tellez-Plaza et al., 2012), but one was excluded for overlapping populations (Tellez-Plaza et al., 2012). We observed a positive relation between urinary cadmium excretion and the risk of CVD mortality, although the association was not entirely monotonic and the slope was less steep above 3 μg/g creatinine of cadmium exposure, where it reached a RR of 2.23 (95 % CI 1.54–3.21), increasing to a RR of 2.86 (95 % CI 1.91–4.26) at 7 μg/g creatinine (Fig. 3).

3.3.2. Heart failure

The risk of HF has been studied as an outcome in two studies that measured whole blood concentrations of cadmium (Borne et al., 2015; Xing et al., 2023). The dose-response curve showed a slightly positive association up to 0.3 μg/L (RR = 1.13, 95 % CI 0.48–2.64) and steeper slope thereafter reaching a threshold at approximately 1 μg/L (RR = 2.02, 95 % CI 0.80–5.12) (Fig. 4). Seven articles used urine as a







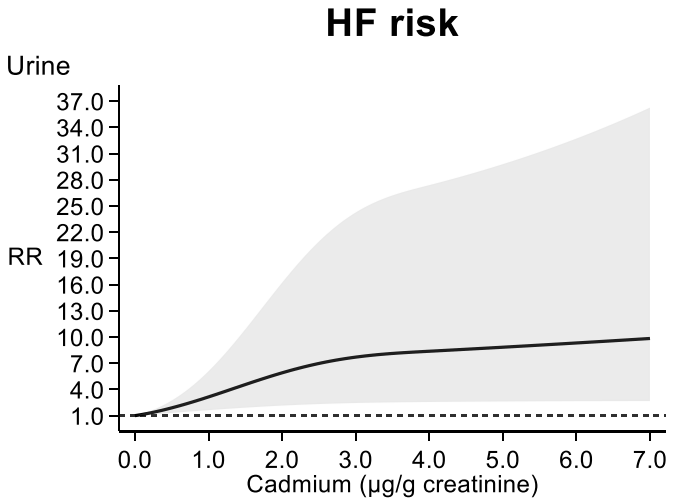


Fig. 3. Dose-response curves for cardiovascular disease (CVD) mortality and cadmium exposure measured through blood and urine. Spline curve (solid black line) with 95 % confidence limits (gray area). RR: risk ratio.

Fig. 4. Dose-response curves for heart failure (HF) risk and cadmium exposure measured through blood and urine. Spline curve (solid black line) with 95 % confidence limits (gray area). RR: risk ratio.

biomarker to evaluate the risk of HF. Of these, five used µg/g creatinine as a unit of measurement (Domingo-Relloso et al., 2019; Sakurai et al., 2021; Sears et al., 2022; Tagt et al., 2022; Tellez-Plaza et al., 2013), while two used µg/L (Deering et al., 2018; Xu et al., 2021) adjusting for creatinine in the model. The overall analysis including all studies showed a positive association between urinary cadmium concentrations and risk of HF, with a less steep curve after 3 µg/g creatinine where it reaches a RR of 7.70 (95 % CI 2.44–24.25), going up to a RR of 9.83 (95 % CI 2.67–36.26) at 7 µg/g creatinine (Fig. 4). Sensitivity analysis excluding the two studies with different units of measurement, both of which were cohort studies, yielded comparable results (Supplementary Fig. S2). Regarding the analysis excluding one study with a high risk of bias, we found similar shape of the curve as with all studies, reaching a RR of 6.97 (%95 CI 1.86–26.04) at 7 µg/g creatinine (Supplementary Fig. S3).

3.3.3. Stroke

Only two studies evaluated the risk of any stroke through whole blood cadmium exposure (Barregard et al., 2016; Jeong et al., 2020), reporting an increased risk for the highest compared to the lowest exposure, respectively with RRs of 2.10 (95 % CI 1.30–3.30) and 2.39 (95 % CI 1.03–5.56) (Table 1). Four articles analyzed the association of cadmium exposure with risk of stroke using urine as a biomarker: two with µg/g creatinine as a unit of measurement (Poulsen et al., 2021; Tellez-Plaza et al., 2013), two with µg/L (Deering et al., 2018; Xu et al., 2021) adjusting the analysis for creatinine. The dose-response curve highlighted a slightly positive monotonic association between cadmium exposure and the risk of any stroke, with RR of 1.56 (95 % CI 1.12–2.15) at 1 µg/g creatinine. When restricted to cohort studies without a high risk of bias, there was a positive linear association between urinary cadmium concentration and the incidence of stroke with a RR of 1.47 (95 % CI 0.91–2.36) at 1.0 µg/g creatinine (Supplementary Fig. S4). Any stroke mortality was assessed in two studies (Sakurai et al., 2021; Suwazono et al., 2021) using urine as a biomarker and µg/g creatinine as a unit of measurement. The dose-response curve showed a positive non-monotonic association with a plateau at 3.5 µg/g creatinine reaching a RR of 1.58 (95 % CI 0.88–2.83) (Fig. 5).

Ischemic stroke was investigated in six studies with different biomarkers: three through urine (Chen et al., 2018; Poulsen et al., 2021; Tagt et al., 2022), one through whole blood (Barregard et al., 2016), one using plasma (Wen et al., 2019), and one through dietary intake (Julin et al., 2013a). The risk evaluated through whole blood and plasma demonstrated an increased risk comparing the highest versus the lowest exposure with RRs of 2.10 (95 % CI 1.30–3.30) and 6.98 (95 % CI 5.09–9.57), respectively. Conversely, dietary cadmium intake, estimated through food-frequency questionnaires, showed no association with a RR comparing the highest versus the lowest quartile of 0.89 (95 % CI 0.74–1.06) (Table 1). We performed the association with a dose-response curve only for urine as a biomarker because of the lack of enough studies for the other assessments. The figure showed a null

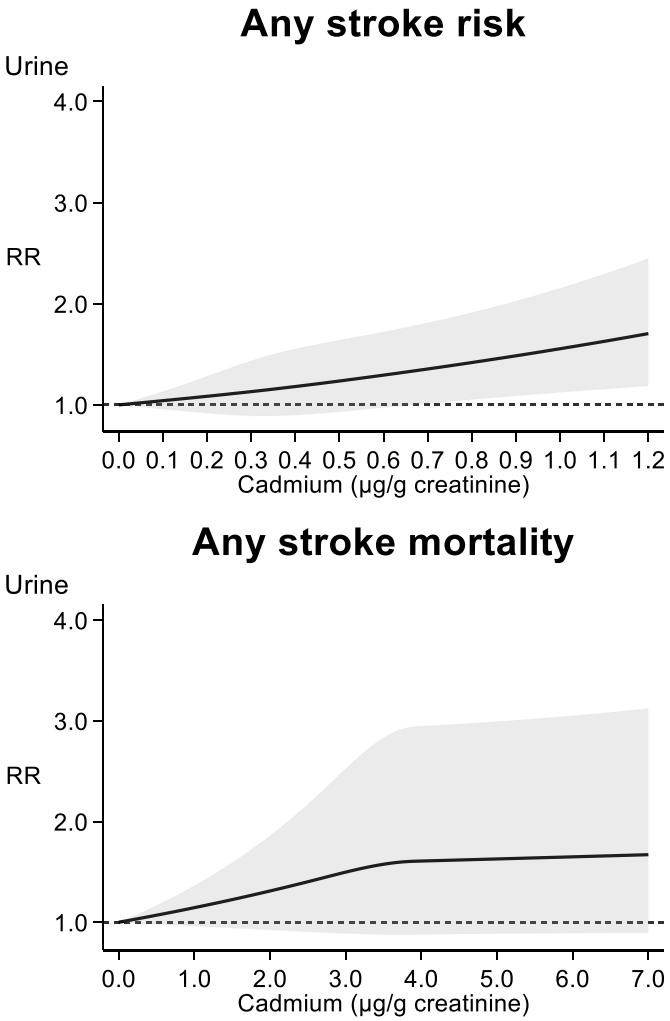


Fig. 5. Dose-response curves for any stroke risk and mortality, and cadmium exposure measured through urine. Spline curve (solid black line) with 95 % confidence limits (gray area). RR: risk ratio.

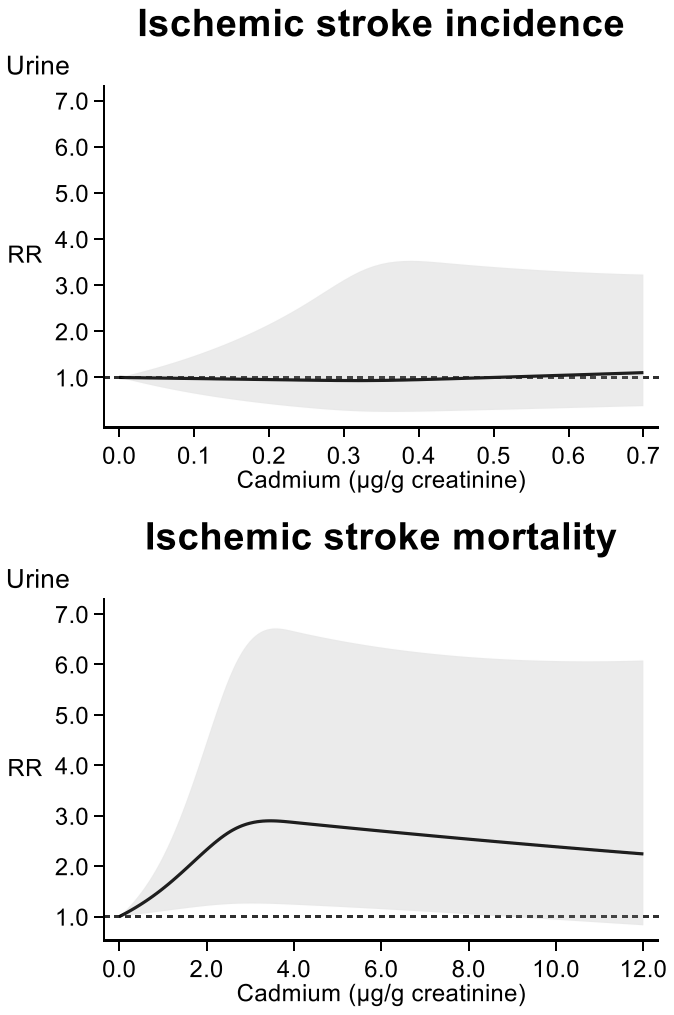


Fig. 6. Dose-response curves for ischemic stroke risk and mortality, and cadmium exposure measured through urine. Spline curve (solid black line) with 95 % confidence limits (gray area). RR: risk ratio.

association, with null RR over the entire range of cadmium exposure.

The association between urinary cadmium concentrations and ischemic stroke mortality was evaluated in three articles: two used µg/g creatinine as a unity of measurement (Sakurai et al., 2021; Suwazono et al., 2021), one µg/L adjusted for creatinine (Deering et al., 2018). The figure showed a nonlinear positive association reaching a plateau at 3 µg/g creatinine (RR = 2.85, 95 % CI 1.26–6.47) (Fig. 6).

Only two studies analyzed hemorrhagic stroke as an outcome through urine: one found a very little increase in incidence (RR = 1.09, 95 % CI 0.53–2.24) comparing the highest versus the lowest quartile (Poulsen et al., 2021) (Table 1). The second study found an inverse U-shape relation between urinary cadmium concentrations and risk of mortality in females; elevated risk was observed at intermediate exposure levels (RR = 2.05, 95 % CI 0.82–5.11) comparing the second versus the first tertile, but a lower risk was observed at high exposure levels (RR = 0.46, 95 % CI 0.09–2.26) comparing the highest versus the lowest tertile, while a RR of 1.51 (95 % CI 0.66–3.44) was reported in males comparing the second versus the first tertile (no analysis was done for the third tertile) (Sakurai et al., 2021) (Table 1).

3.3.4. *Coronary heart disease*

Three studies evaluated the association between whole blood cadmium concentrations and risk of CHD (Barregard et al., 2016; Jeong et al., 2020; Kong et al., 2023) and the dose-relation curve showed a positive linear association with a less steep curve above 0.5 µg/L with a RR of 1.99 (95 % CI 1.50–2.63), going up to 2.49 (95 % CI 1.70–3.65) at 1.0 µg/g creatinine (Fig. 7). Likewise, three studies evaluated urinary cadmium concentrations and risk of CHD: one using µg/g creatinine as

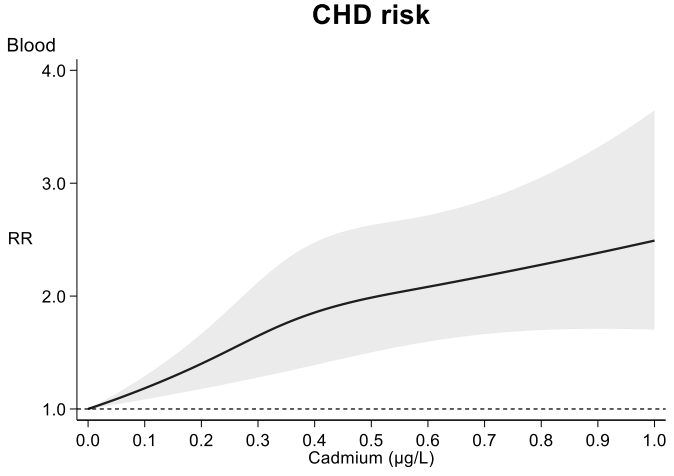


Fig. 7. Dose-response curves for coronary heart disease (CHD) risk, and cadmium exposure measured through blood. Spline curve (solid black line) with 95 % confidence limits (gray area). RR: risk ratio.

the unit of measurement (Tellez-Plaza et al., 2013), two using μg/L and adjusting for creatinine (Deering et al., 2018; Xu et al., 2021). Three additional studies assessed the association between urinary cadmium exposure and AMI, which is the main manifestation of CHD; therefore, we included these studies in the overall CHD analysis (Everett and Frithsen, 2008; Sears et al., 2021; Tagt et al., 2022). The curve showed a monotonic positive association with a RR of 1.82 (95 % CI 1.16–2.86) at 1 μg/g creatinine. (Fig. 8). When we excluded studies that used μg/L as a unit of measurement, we found no differences in the shape of the curve, with a RR of 1.73 (IC 95 % 1.15–2.62) at 1.0 μg/g creatinine (Supplementary Fig. S5).

In the sensitivity analysis among cohort studies (Deering et al., 2018; Sears et al., 2021; Tagt et al., 2022; Tellez-Plaza et al., 2013), we found a monotonic positive association between cadmium exposure and CHD incidence with a RR of 1.35 (95 % CI 0.91–2.01) at 1.0 μg/g creatinine, less steep than the general analysis (Supplementary Fig. S6). When we excluded studies that used μg/L as a unit of measurement (Sears et al., 2021; Tagt et al., 2022; Tellez-Plaza et al., 2013), the shape of the curve was similar to the other analysis, with a linear positive association reaching a RR of 1.32 (95 % CI 0.96–1.81) at 0.3 μg/g creatinine, above which the curve was less steep and reached a RR of 1.60 (95 % CI 1.09–2.34) at 1.0 μg/g creatinine (Supplementary Fig. S7). Excluding the study with a high risk of bias (Xu et al., 2021) yielded a positive linear association, with a shape that resembled the general curve (Supplementary Fig. S8).

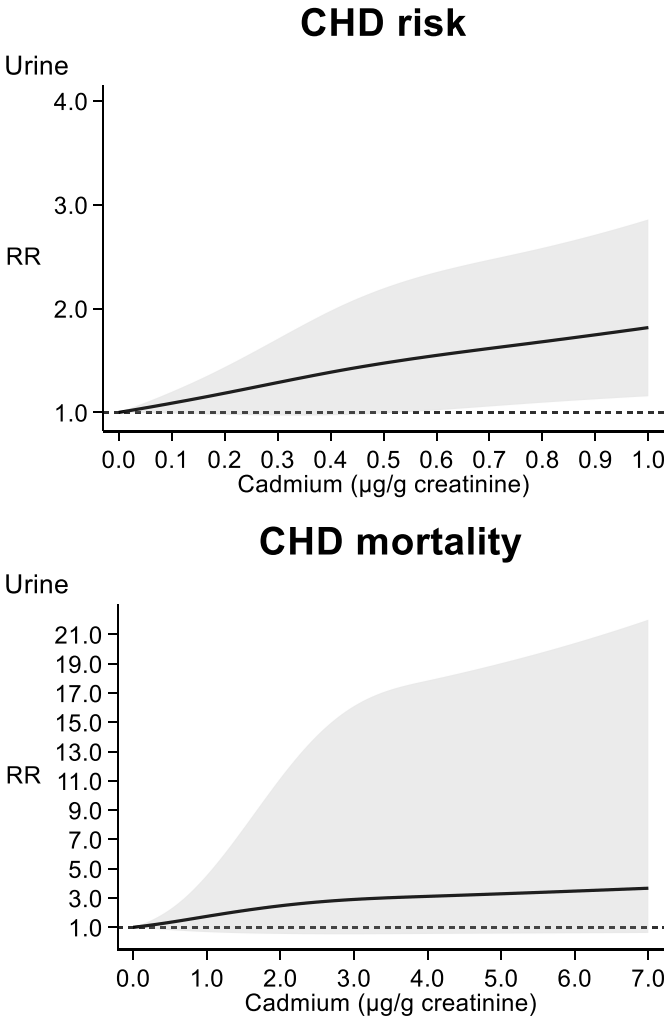


Fig. 8. Dose-response curves for coronary heart disease (CHD) risk and mortality, and cadmium exposure measured through urine. Spline curve (solid black line) with 95 % confidence limits (gray area). RR: risk ratio.

CHD mortality has been examined using urine as a biomarker in five studies: four using μg/g creatinine as a unit of measurement (Menke et al., 2009; Sakurai et al., 2021; Suwazono et al., 2021; Tellez-Plaza et al., 2013; Tellez-Plaza et al., 2012), and one using μg/L adjusting the model for creatinine concentrations (Deering et al., 2018). Only one of these studies analyzing CHD mortality also used whole blood as a biomarker reporting a RR of 1.73 (95 % CI 0.88–3.40) comparing the 80th percentile of exposure compared to the 20th (Tellez-Plaza et al., 2012) (Table 1). The dose-response curve representing the association between urinary cadmium concentrations and CHD mortality was performed with data from all five studies and showed a monotonic positive association with a RR of 1.51 (95 % CI 0.47–4.83) at 1.5 μg/g creatinine and 2.84 (95 % CI 0.86–9.37) at 3 μg/g creatinine (Fig. 8). After excluding studies that used μg/L as a unit of measurement, we found no differences in the shape of the curve, except higher imprecision due to the lower number of studies (Supplementary Fig. S5).

3.3.5. *Other outcomes*

Owing to the lack of sufficient data among included studies, it was not possible to perform a dose-response meta-analysis for other outcomes, namely acute myocardial infarction, stroke mortality overall or by subtype (ischemic vs. hemorrhagic), and HF mortality.

3.3.6. *Stratified analyses*

Overall, thirteen studies stratified by sex (Barregard et al., 2016; Borne et al., 2015; Chen et al., 2018; Everett and Frithsen, 2008; Ferraro et al., 2012; Menke et al., 2009; Poulsen et al., 2021; Sakurai et al., 2021; Sears et al., 2022; Sears et al., 2021; Suwazono et al., 2021; Tellez-Plaza et al., 2012; Wen et al., 2019) and eight studies stratified by smoking status (Barregard et al., 2016; Chen et al., 2018; Poulsen et al., 2021; Sears et al., 2022; Sears et al., 2021; Tagt et al., 2022; Tellez-Plaza et al., 2012; Wen et al., 2019). However, due to the limited number of studies, the dose-response meta-analysis was feasible for studies evaluating sex-specific data using urine as a biomarker. In both males and females, cadmium exposure was positively related to CVD mortality. At about 2.0 μg/g creatinine, the curve was less steep, reaching a RR of 2.19 (95 % CI 1.00–4.82) in males and 2.13 (95 % CI 0.82–5.53) among females, respectively (Supplementary Fig. S9).

Regarding HF, it was possible to perform an additional analysis only in females because of the lack of enough studies for males. This outcome showed a slightly positive non-monotonic association with urinary cadmium excretion, reaching a plateau at about 0.3 μg/g creatinine of urinary cadmium, with a RR of 1.55 (95 % CI 0.99–2.44) (Supplementary Fig. S10).

For CHD, the sex-stratified analysis – which was feasible among females only – showed a positive and almost linear association above 0.4 μg/g creatinine of cadmium exposure, reaching a RR of 1.99 (95 % CI 1.04–3.80) at 1.0 μg/g creatinine (Supplementary Fig. S11).

4. Discussion

This meta-analysis found evidence to support strong positive associations between increasing levels of cadmium and risk of CVD. All dose-response curves assessing CVD outcomes through whole blood biomarkers showed a linear positive association. In addition, the association with urinary cadmium concentrations was positive but not entirely linear for almost all investigated outcomes.

Our results are consistent with previous meta-analyses that revealed an increased risk of overall CVD, stroke, and CHD associated with exposure to cadmium (Chowdhury et al., 2018; Tinkov et al., 2018), although no dose-response analysis was previously feasible for individual outcomes and for both whole blood and urinary cadmium concentrations. In contrast, the availability of a larger number of studies allowed us to assess the shape of the association for both biomarkers and CVD subtypes, namely HF and ischemic stroke not previously investigated. It is noteworthy that a previous dose-response meta-analysis

indicated a positive association between cadmium exposure and stroke (Bao et al., 2022). Our results confirm such association, adding new studies along with specific results divided by any stroke and ischemic stroke incidence and mortality, and showed increased risk, with the exception of the incidence of ischemic stroke that showed null association with cadmium exposure.

In our meta-analysis, both biomarkers of cadmium exposure, whole blood and urine, were associated with an increased risk of CVD, though with different shape of such association. Despite both biomarkers reflecting cumulative exposure to cadmium (Martinez-Morata et al., 2023; Tellez-Plaza et al., 2012), whole blood cadmium is generally considered an indicator of recent exposure (i.e., weeks or months), while urinary concentrations reflect long-term exposure (i.e., years or decades) (Adams and Newcomb, 2014; Julin et al., 2011; Vacchi-Suzzi et al., 2016). These different features of the biomarkers may explain the different shape of the relation with CVD. In particular, at low levels of exposure, both biomarkers showed linear association, while at higher levels, urinary concentrations are likely to be affected by the cadmium accumulation and subsequent slow release from kidney with half time 10–30 years (Jarup and Akesson, 2009). Conversely, it should be noted that the two studies assessing cadmium exposure through dietary intake found no support for an association with CVD risk (Julin et al., 2013a; Julin et al., 2013b). Despite several studies generally reported a good correlation between dietary intake and biomarkers (Amzal et al., 2009; Julin et al., 2011), we cannot rule out risk of exposure misclassification due to changes over time of dietary habits and the ability of dietary assessment to accurately evaluate cadmium exposure (Filippini et al., 2020b). Therefore, possible risk of misclassification of the exposure is higher when estimated dietary intake was used compared to biomarkers of exposure. In addition, due to the limited number of studies using dietary intake, we could not perform a dose-response meta-analysis concerning such biomarkers. Especially urinary concentration is frequently used in biomonitoring studies for long-term cadmium exposure, with a high correlation with total body burden (Akerstrom et al., 2013; Meliker et al., 2019).

Whenever possible, we performed stratified analyses by relevant effect measure modifiers, in particular by sex. The curves of the dose-response analysis showed a similar pattern between males and females with a substantial positive association, although some differences can be noted. With reference to CHD risk in females, we found a linear positive association above 0.4 μg/g creatinine, quite different from the curve of both sexes in which the risk starts to increase immediately from zero. Concerning the risk of HF, the curve for females shows a positive association with a flattening of the curve above 0.3 μg/g creatinine, while in the general analysis, the curve is steeper. The differential pattern of associations may relate to the higher absorption of cadmium in females (Amzal et al., 2009; Berglund et al., 1994; Jarup and Akesson, 2009), although the limited number of studies hamper the implementation of such analysis for all the outcomes considered and especially sex-stratified analysis in both males and females.

Even if the mechanisms by which cadmium exposure increases the risk of CVD are not fully understood, there is a strong biological plausibility for cadmium having adverse effects on the cardiovascular system. Once absorbed by the organism, cadmium is transported to soft tissues (specifically, the liver and kidneys) bound to albumin, transferrin, and red blood cell membranes (Genchi et al., 2020; Lamas et al., 2021). Hence, both free cadmium and protein-bound cadmium are released into the circulation or transported to target tissues, potentially leading to adverse effects such as mitochondrial damage, cell death, inflammation, and fibrosis. Previous studies suggested that cadmium affects the vascular system through increased oxidative stress, inflammation, and endothelial cell damage (Wu et al., 2016). Specifically, cadmium is known to induce DNA and mitochondrial damage, and increase oxidative stress, which could lead to cell apoptosis and tissue damage (Genchi et al., 2020; Urbano et al., 2022). Several *in vivo* and *in vitro* studies revealed the toxic effects of cadmium on cardiomyocytes, smooth muscle cells, and vascular endothelial cells (Ghosh and Indra, 2018; Messner et al., 2016; Shen et al., 2018). In a recent animal study, cadmium induced cardiomyocyte apoptosis by damaging sarcomeres and myofibrils, and caused myocardial fibrosis and focal necrosis in mice (Chou et al., 2023). In addition, cadmium has been positively associated with atherogenesis via the same mechanisms of increased oxidative stress and inflammation, endothelial dysfunction, enhanced lipid synthesis, upregulation of adhesion molecules, prostanoid dysbalance, and altered glycosaminoglycan synthesis (Buha et al., 2018; Nakagawa et al., 2006; Tinkov et al., 2018).

Our study has strengths and limitations. This is the first comprehensive systematic review and meta-analysis including several cardiovascular-related outcomes assessing the shape of the association with cadmium exposure. In particular, we performed all dose-response analyses using data on cadmium exposure measured through objective biomarkers, whole blood and urinary concentrations. Therefore, we were able to perform several analyses using for the first time both biomarkers. In addition, our findings were similar when we excluded studies at high risk of bias, strengthening the evidence of such association.

Regarding study limitations, due to data incompleteness in some studies using urine as a biomarker, we cannot rule out exposure misclassification when studies reported exposure using μg/L instead of μg/g creatinine, although all studies adjusted for creatinine in the multivariable model. In addition, there were insufficient studies to perform stratified analyses by sex or smoking status for some relevant outcomes (i.e., stroke and CVD incidence). Nonetheless, all but one (Sakurai et al., 2021) of the included studies adjusted for smoking or cotinine levels. Finally, we were not able to compare specific sources of cadmium, e.g., smoking or food (Filippini et al., 2018), limiting our ability to recommend remediation strategies to decrease cadmium exposure (Li et al., 2023a; Li et al., 2023b), especially in vulnerable populations (Lamas et al., 2023; Ouyang et al., 2015).

In conclusion, our results provide epidemiological evidence that cadmium has detrimental effects on cardiovascular health over the entire range of exposure with an approximately linear association at low exposure levels. Nonetheless, our findings warrant more detailed research to define individuals at higher risk and trigger appropriate action.

Funding

TF, TU and MV were supported by grant 'Dipartimenti di Eccellenza 2018–2022″ to the Department of Biomedical, Metabolic and Neural Sciences of the University of Modena and Reggio Emilia from the Italian Ministry of Education, University and Research. TF was also supported by grants PRIN 2022 (no. 2022MHMRPR) and PRIN 2022 PNRR (no. P20229KSXB) from the Italian Ministry of University funded by European Union - Next Generation EU, and by grant "UNIMORE FAR 2023" from the University of Modena and Reggio Emilia.

CRediT authorship contribution statement

Pietro Verzelloni: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Teresa Urbano:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Lauren A. Wise:** Supervision, Writing – original draft, Writing – review & editing. **Marco Vinceti:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Tommaso Filippini:** Conceptualization, Methodology, Software, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing

interestsThe authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Lauren Wise receives in-kind donations from Kindara.com (fertility apps) and Swiss Precision Diagnostics (home pregnancy tests). She also serves as consultant for Gates Foundation and AbbVie, Inc. All of these relationships are for work unrelated to this manuscript. All other authors have nothing to disclosure.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2024.123462.

References

Adams, S.V., Newcomb, P.A., 2014. Cadmium blood and urine concentrations as measures of exposure: NHANES 1999-2010. J. Expo. Sci. Environ. Epidemiol. 24, 163–170. https://doi.org/10.1038/jes.2013.55.

Agarwal, S., Zaman, T., Tuzcu, E.M., Kapadia, S.R., 2011. Heavy metals and cardiovascular disease: results from the national health and nutrition examination survey (NHANES) 1999-2006. Angiology 62, 422–429. https://doi.org/10.1177/0003319710395562.

Akerstrom, M., Barregard, L., Lundh, T., Sallsten, G., 2013. The relationship between cadmium in kidney and cadmium in urine and blood in an environmentally exposed population. Toxicol. Appl. Pharmacol. 268, 286–293. https://doi.org/10.1016/j.taap.2013.02.009.

Amzal, B., Julin, B., Vahter, M., Wolk, A., Johanson, G., Akesson, A., 2009. Population toxicokinetic modeling of cadmium for health risk assessment. Environ. Health Perspect. 117, 1293–1301. https://doi.org/10.1289/ehp.0800317.

Ayuso-Alvarez, A., Nunez, O., Martin-Mendez, I., Bel-Lan, A., Tellez-Plaza, M., Perez-Gomez, B., Galan, I., Fernandez-Navarro, P., 2022. Metal and metalloid levels in topsoil and municipal cardiovascular mortality in Spain. Environ. Res. 204, 112395 https://doi.org/10.1016/j.envres.2021.112395.

Bao, Q.J., Zhao, K., Guo, Y., Wu, X.T., Yang, J.C., Yang, M.F., 2022. Environmental toxic metal contaminants and risk of stroke: a systematic review and meta-analysis. Environ. Sci. Pollut. Res. Int. 29, 32545–32565. https://doi.org/10.1007/s11356-022-18866-z.

Barregard, L., Sallsten, G., Fagerberg, B., Borne, Y., Persson, M., Hedblad, B., Engstrom, G., 2016. Blood cadmium levels and incident cardiovascular events during follow-up in a population-based cohort of Swedish adults: the Malmo Diet and Cancer study. Environ. Health Perspect. 124, 594–600. https://doi.org/10.1289/ehp.1509735.

Berglund, M., Akesson, A., Nermell, B., Vahter, M., 1994. Intestinal absorption of dietary cadmium in women depends on body iron stores and fiber intake. Environ. Health Perspect. 102, 1058–1066. https://doi.org/10.1289/ehp.941021058.

Borne, Y., Barregard, L., Persson, M., Hedblad, B., Fagerberg, B., Engstrom, G., 2015. Cadmium exposure and incidence of heart failure and atrial fibrillation: a population-based prospective cohort study. BMJ Open 5, e007366. https://doi.org/10.1136/bmjopen-2014-007366.

Broomandi, P., Rodriguez-Seijo, A., Janatian, N., Fathian, A., Tleuken, A., Mohammadpour, K., Galan-Madruga, D., Jahanbakhshi, A., Kim, J.R., Satyanaga, A., Bagheri, M., Morawska, L., 2023. Health risk assessment of the European inhabitants exposed to contaminated ambient particulate matter by potentially toxic elements. Environ. Pollut. 323, 121232 https://doi.org/10.1016/j.envpol.2023.121232.

Buha, A., Matovic, V., Antonijevic, B., Bulat, Z., Curcic, M., Renieri, E.A., Tsatsakis, A.M., Schweitzer, A., Wallace, D., 2018. Overview of cadmium thyroid disrupting effects and mechanisms. Int. J. Mol. Sci. 19, 1501. https://doi.org/10.3390/ijms19051501.

Chen, C., Xun, P., Tsinovoi, C., McClure, L.A., Brockman, J., MacDonald, L., Cushman, M., Cai, J., Kamendulis, L., Mackey, J., He, K., 2018. Urinary cadmium concentration and the risk of ischemic stroke. Neurology 91, e382–e391. https://doi.org/10.1212/WNL.0000000000005856.

Chou, S.H., Lin, H.C., Chen, S.W., Tai, Y.T., Jung, S.M., Ko, F.H., Pang, J.S., Chu, P.H., 2023. Cadmium exposure induces histological damage and cytotoxicity in the cardiovascular system of mice. Food Chem. Toxicol. 175, 113740 https://doi.org/10.1016/j.fct.2023.113740.

Chowdhury, R., Ramond, A., O'Keeffe, L.M., Shahzad, S., Kunutsor, S.K., Muka, T., Gregson, J., Willeit, P., Warnakula, S., Khan, H., Chowdhury, S., Gobin, R., Franco, O.H., Di Angelantonio, E., 2018. Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 362, k3310. https://doi.org/10.1136/bmj.k3310.

Crippa, A., Discacciati, A., Bottai, M., Spiegelman, D., Orsini, N., 2019. One-stage dose-response meta-analysis for aggregated data. Stat. Methods Med. Res. 28, 1579–1596. https://doi.org/10.1177/0962280218773122.

Deering, K.E., Callan, A.C., Prince, R.L., Lim, W.H., Thompson, P.L., Lewis, J.R., Hinwood, A.L., Devine, A., 2018. Low-level cadmium exposure and cardiovascular outcomes in elderly Australian women: a cohort study. Int. J. Hyg Environ. Health 221, 347–354. https://doi.org/10.1016/j.ijheh.2017.12.007.

Domingo-Relloso, A., Grau-Perez, M., Briongos-Figuero, L., Gomez-Ariza, J.L., Garcia-Barrera, T., Duenas-Laita, A., Bobb, J.F., Chaves, F.J., Kioumourtzoglou, M.A., Navas-Acien, A., Redon-Mas, J., Martin-Escudero, J.C., Tellez-Plaza, M., 2019. The association of urine metals and metal mixtures with cardiovascular incidence in an adult population from Spain: the Hortega Follow-Up Study. Int. J. Epidemiol. 48, 1839–1849. https://doi.org/10.1093/ije/dyz061.

Everett, C.J., Frithsen, I.L., 2008. Association of urinary cadmium and myocardial infarction. Environ. Res. 106, 284–286. https://doi.org/10.1016/j.envres.2007.10.009.

Faroon, O., Ashizawa, A., Wright, S., Tucker, P., Jenkins, K., Ingerman, L., Rudisill, C., 2012. Toxicological Profile for Cadmium, Atlanta (GA).

Ferraro, P.M., Sturniolo, A., Naticchia, A., D'Alonzo, S., Gambaro, G., 2012. Temporal trend of cadmium exposure in the United States population suggests gender specificities. Intern. Med. J. 42, 691–697. https://doi.org/10.1111/j.1445-5994.2011.02627.x.

Filippini, T., Cilloni, S., Malavolti, M., Violi, F., Malagoli, C., Tesauro, M., Bottecchi, I., Ferrari, A., Vescovi, L., Vinceti, M., 2018. Dietary intake of cadmium, chromium, copper, manganese, selenium and zinc in a Northern Italy community. J. Trace Elem. Med. Biol. 50, 508–517. https://doi.org/10.1016/j.jtemb.2018.03.001.

Filippini, T., Hatch, E.E., Rothman, K.J., Heck, J.E., Park, A.S., Crippa, A., Orsini, N., Vinceti, M., 2019. Association between outdoor air pollution and childhood leukemia: a systematic review and dose-response meta-analysis. Environ. Health Perspect. 127, 46002 https://doi.org/10.1289/EHP4381.

Filippini, T., Michalke, B., Malagoli, C., Grill, P., Bottecchi, I., Malavolti, M., Vescovi, L., Sieri, S., Krogh, V., Cherubini, A., Maffeis, G., Modenesi, M., Castiglia, P., Vinceti, M., 2016. Determinants of serum cadmium levels in a Northern Italy community: a cross-sectional study. Environ. Res. 150, 219–226. https://doi.org/10.1016/j.envres.2016.06.002.

Filippini, T., Torres, D., Lopes, C., Carvalho, C., Moreira, P., Naska, A., Kasdagli, M.I., Malavolti, M., Orsini, N., Vinceti, M., 2020a. Cadmium exposure and risk of breast cancer: a dose-response meta-analysis of cohort studies. Environ. Int. 142, 105879 https://doi.org/10.1016/j.envint.2020.105879.

Filippini, T., Upson, K., Adani, G., Malagoli, C., Baraldi, C., Michalke, B., Vinceti, M., 2020b. Comparison of methodologies to estimate dietary cadmium intake in an Italian population. Int. J. Environ. Res. Publ. Health 17, 2264. https://doi.org/10.3390/ijerph17072264.

Filippini, T., Wise, L.A., Vinceti, M., 2022. Cadmium exposure and risk of diabetes and prediabetes: a systematic review and dose-response meta-analysis. Environ. Int. 158, 106920 https://doi.org/10.1016/j.envint.2021.106920.

Genchi, G., Sinicropi, M.S., Lauria, G., Carocci, A., Catalano, A., 2020. The effects of cadmium toxicity. Int. J. Environ. Res. Publ. Health 17, 3782. https://doi.org/10.3390/ijerph17113782.

Ghosh, K., Indra, N., 2018. Cadmium treatment induces echinocytosis, DNA damage, inflammation, and apoptosis in cardiac tissue of albino Wistar rats. Environ. Toxicol. Pharmacol. 59, 43–52. https://doi.org/10.1016/j.etap.2018.02.009.

Goumenou, M., Djordjevic, A.B., Vassilopoulou, L., Tsatsakis, A.M., 2021. Chapter 14 - endocrine disruption and human health risk assessment in the light of real-life risk simulation. In: Tsatsakis, A.M. (Ed.), Toxicological Risk Assessment and Multi-System Health Impacts from Exposure. Academic Press, pp. 147–162. https://doi.org/10.1016/B978-0-323-85215-9.00041-6.

Guo, X., Su, W., Li, N., Song, Q., Wang, H., Liang, Q., Li, Y., Lowe, S., Bentley, R., Zhou, Z., Song, E.J., Cheng, C., Zhou, Q., Sun, C., 2022. Association of urinary or blood heavy metals and mortality from all causes, cardiovascular disease, and cancer in the general population: a systematic review and meta-analysis of cohort studies. Environ. Sci. Pollut. Res. Int. 29, 67483–67503. https://doi.org/10.1007/s11356-022-22353-w.

Iamandii, I., De Pasquale, L., Giannone, M.E., Veneri, F., Generali, L., Consolo, U., Birnbaum, L.S., Castenmiller, J., Halldorsson, T.I., Filippini, T., Vinceti, M., 2023. Does fluoride exposure affect thyroid function? A systematic review and dose-response meta-analysis. Environ. Res. 242, 117759 https://doi.org/10.1016/j.envres.2023.117759.

IARC, 2012. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Arsenic, Metals, Fibres and Dusts.

Institute of Medicine, 2010. In: Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health, Washington (DC). https://doi.org/10.17226/12815.

Jarup, L., Akesson, A., 2009. Current status of cadmium as an environmental health problem. Toxicol. Appl. Pharmacol. 238, 201–208. https://doi.org/10.1016/j.taap.2009.04.020.

Jeong, J., Yun, S.M., Kim, M., Koh, Y.H., 2020. Association of blood cadmium with cardiovascular disease in Korea: from the Korea national health and nutrition examination survey 2008-2013 and 2016. Int. J. Environ. Res. Publ. Health 17, 6288. https://doi.org/10.3390/ijerph17176288.

Julin, B., Bergkvist, C., Wolk, A., Akesson, A., 2013a. Cadmium in diet and risk of cardiovascular disease in women. Epidemiology 24, 880–885. https://doi.org/10.1097/EDE.0b013e3182a777c9.

Julin, B., Vahter, M., Amzal, B., Wolk, A., Berglund, M., Akesson, A., 2011. Relation between dietary cadmium intake and biomarkers of cadmium exposure in premenopausal women accounting for body iron stores. Environ. Health 10, 105. https://doi.org/10.1186/1476-069X-10-105.

Julin, B., Wolk, A., Thomas, L.D., Akesson, A., 2013b. Exposure to cadmium from food and risk of cardiovascular disease in men: a population-based prospective cohort study. Eur. J. Epidemiol. 28, 837–840. https://doi.org/10.1007/s10654-013-9841-8.

Kong, B., Chen, Y., Cheng, S., Ma, H., Liu, Q., Wang, Y., Bai, B., Liu, F., Geng, Q., 2023. Physical activity attenuates the association between blood cadmium exposure and cardiovascular disease: findings from the National Health and Nutrition Examination Survey 2007-2018. Environ. Sci. Pollut. Res. Int. 30, 81008–81018. https://doi.org/10.1007/s11356-023-27598-7.

Kulick, E.R., Eliot, M.N., Szpiro, A.A., Coull, B.A., Tinker, L.F., Eaton, C.B., Whitsel, E.A., Stewart, J.D., Kaufman, J.D., Wellenius, G.A., 2023. Long-term exposure to ambient particulate matter and stroke etiology: results from the Women's Health Initiative. Environ. Res. 224, 115519 https://doi.org/10.1016/j.envres.2023.115519.

Lamas, G.A., Bhatnagar, A., Jones, M.R., Mann, K.K., Nasir, K., Tellez-Plaza, M., Ujueta, F., Navas-Acien, A., American Heart Association Council on, Prevention, E., Council on, C., Stroke, N., Council on, L., Cardiometabolic, H., Council on Peripheral Vascular, D., Council on the Kidney in Cardiovascular, D., 2023. Contaminant metals as cardiovascular risk factors: a scientific statement from the American Heart Association. J. Am. Heart Assoc. 12, e029852 https://doi.org/10.1161/JAHA.123.029852.

Lamas, G.A., Ujueta, F., Navas-Acien, A., 2021. Lead and cadmium as cardiovascular risk factors: the burden of proof has been met. J. Am. Heart Assoc. 10, e018692 https://doi.org/10.1161/JAHA.120.018692.

Larsson, S.C., Wolk, A., 2016. Urinary cadmium and mortality from all causes, cancer and cardiovascular disease in the general population: systematic review and meta-analysis of cohort studies. Int. J. Epidemiol. 45, 782–791. https://doi.org/10.1093/ije/dyv086.

Li, Y., Rahman, S.U., Qiu, Z., Shahzad, S.M., Nawaz, M.F., Huang, J., Naveed, S., Li, L., Wang, X., Cheng, H., 2023a. Toxic effects of cadmium on the physiological and biochemical attributes of plants, and phytoremediation strategies: a review. Environ. Pollut. 325, 121433 https://doi.org/10.1016/j.envpol.2023.121433.

Li, Y., Xu, R., Ma, C., Yu, J., Lei, S., Han, Q., Wang, H., 2023b. Potential functions of engineered nanomaterials in cadmium remediation in soil-plant system: a review. Environ. Pollut. 336, 122340 https://doi.org/10.1016/j.envpol.2023.122340.

Li, Z., Fan, Y., Tao, C., Yan, W., Huang, Y., Qian, H., Xu, Q., Wan, T., Chen, Y., Qin, Y., Lu, C., 2022. Association between exposure to cadmium and risk of all-cause and cause-specific mortality in the general US adults: a prospective cohort study. Chemosphere 307, 136060. https://doi.org/10.1016/j.chemosphere.2022.136060.

Liu, J., Li, Y., Li, D., Wang, Y., Wei, S., 2022. The burden of coronary heart disease and stroke attributable to dietary cadmium exposure in Chinese adults. Sci. Total Environ. 825, 153997 https://doi.org/10.1016/j.scitotenv.2022.153997.

Martinez-Morata, I., Sobel, M., Tellez-Plaza, M., Navas-Acien, A., Howe, C.G., Sanchez, T. R., 2023. A state-of-the-science review on metal biomarkers. Curr Environ Health Rep 10, 215–249. https://doi.org/10.1007/s40572-023-00402-x.

McElroy, J.A., Hunter, M.I., 2019. Cadmium: a new risk factor for endometrial cancer? Expert Rev. Anticancer Ther. 19, 355–358. https://doi.org/10.1080/14737140.2019.1596029.

Meliker, J.R., Vacchi-Suzzi, C., Harrington, J., Levine, K., Lui, L.Y., Bauer, D.C., Orwoll, E., Kado, D.M., 2019. Temporal stability of urinary cadmium in samples collected several years apart in a population of older persons. Int. J. Hyg Environ. Health 222, 230–234. https://doi.org/10.1016/j.ijheh.2018.10.005.

Menke, A., Muntner, P., Silbergeld, E.K., Platz, E.A., Guallar, E., 2009. Cadmium levels in urine and mortality among U.S. adults. Environ. Health Perspect. 117, 190–196. https://doi.org/10.1289/ehp.11236.

Messner, B., Turkcan, A., Ploner, C., Laufer, G., Bernhard, D., 2016. Cadmium overkill: autophagy, apoptosis and necrosis signalling in endothelial cells exposed to cadmium. Cell. Mol. Life Sci. 73, 1699–1713. https://doi.org/10.1007/s00018-015-2094-9.

Mititelu, M., Udeanu, D.I., Docea, A.O., Tsatsakis, A., Calina, D., Arsene, A.L., Nedelescu, M., Neacsu, S.M., Bruno Stefan, V., Ghica, M., 2023. New method for risk assessment in environmental health: the paradigm of heavy metals in honey. Environ. Res. 236, 115194 https://doi.org/10.1016/j.envres.2022.115194.

Moon, S., Lee, J., Yu, J.M., Choi, H., Choi, S., Park, J., Choi, K., Kim, E., Kim, H., Kim, M. J., Park, Y.J., 2023. Association between environmental cadmium exposure and increased mortality in the U.S. National Health and Nutrition Examination Survey (1999-2018). J. Expo. Sci. Environ. Epidemiol. 33, 874–882. https://doi.org/10.1038/s41370-023-00556-8.

Morgan, R.L., Thayer, K.A., Santesso, N., Holloway, A.C., Blain, R., Eftim, S.E., Goldstone, A.E., Ross, P., Ansari, M., Akl, E.A., Filippini, T., Hansell, A., Meerpohl, J. J., Mustafa, R.A., Verbeek, J., Vinceti, M., Whaley, P., Schunemann, H.J., Group, G. W., 2019. A risk of bias instrument for non-randomized studies of exposures: a users' guide to its application in the context of GRADE. Environ. Int. 122, 168–184. https://doi.org/10.1016/j.envint.2018.11.004.

Morgan, R.L., Whaley, P., Thayer, K.A., Schunemann, H.J., 2018. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ. Int. 121, 1027–1031. https://doi.org/10.1016/j.envint.2018.07.015.

Nakagawa, H., Nishijo, M., Morikawa, Y., Miura, K., Tawara, K., Kuriwaki, J., Kido, T., Ikawa, A., Kobayashi, E., Nogawa, K., 2006. Urinary cadmium and mortality among inhabitants of a cadmium-polluted area in Japan. Environ. Res. 100, 323–329. https://doi.org/10.1016/j.envres.2005.08.014.

Nawrot, T.S., Martens, D.S., Hara, A., Plusquin, M., Vangronsveld, J., Roels, H.A., Staessen, J.A., 2015. Association of total cancer and lung cancer with environmental exposure to cadmium: the meta-analytical evidence. Cancer Causes Control 26, 1281–1288. https://doi.org/10.1007/s10552-015-0621-5.

Nawrot, T.S., Van Hecke, E., Thijs, L., Richart, T., Kuznetsova, T., Jin, Y., Vangronsveld, J., Roels, H.A., Staessen, J.A., 2008. Cadmium-related mortality and long-term secular trends in the cadmium body burden of an environmentally exposed population. Environ. Health Perspect. 116, 1620–1628. https://doi.org/10.1289/ehp.11667.

Orsini, N., Spiegelman, D., 2021. Meta-analysis of dose-response relationships. In: Schmid, C.H., Stijnen, T., White, I. (Eds.), Handbook of Meta-Analysis, first ed. Chapman and Hall/CRC, New York. https://doi.org/10.1201/9781315119403.

Ouyang, P., Gottlieb, S.H., Culotta, V.L., Navas-Acien, A., 2015. EDTA chelation therapy to reduce cardiovascular events in persons with diabetes. Curr. Cardiol. Rep. 17, 96. https://doi.org/10.1007/s11886-015-0656-y.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hrobjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLoS Med. 18, e1003583 https://doi.org/10.1371/journal.pmed.1003583.

Pope 3rd, C.A., Burnett, R.T., Thurston, G.D., Thun, M.J., Calle, E.E., Krewski, D., Godleski, J.J., 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 109, 71–77. https://doi.org/10.1161/01.CIR.0000108927.80044.7F.

Poulsen, A.H., Sears, C.G., Harrington, J., Howe, C.J., James, K.A., Roswall, N., Overvad, K., Tjonneland, A., Wellenius, G.A., Meliker, J., Raaschou-Nielsen, O., 2021. Urinary cadmium and stroke - a case-cohort study in Danish never-smokers. Environ. Res. 200, 111394 https://doi.org/10.1016/j.envres.2021.111394.

Rocha, G.S., de Palma Lopes, L.F., de Medeiros, J.F., Montagner, C.C., Gaeta Espindola, E.L., 2023. Environmental concentrations of cadmium and fipronil, isolated and combined, impair the survival and reproduction of a Neotropical freshwater copepod. Environ. Pollut. 336, 122415 https://doi.org/10.1016/j.envpol.2023.122415.

Sakurai, M., Suwazono, Y., Nishijo, M., Nogawa, K., Watanabe, Y., Yoneda, K., Ishizaki, M., Morikawa, Y., Kido, T., Nakagawa, H., 2021. The relationship between the urinary cadmium concentration and cause-specific mortality in subjects without severe renal damage: a 35-year follow-up study in a cadmium-polluted area of Japan. Int. J. Environ. Res. Publ. Health 18, 7747. https://doi.org/10.3390/ijerph18157747.

Sears, C.G., Eliot, M., Raaschou-Nielsen, O., Poulsen, A.H., Harrington, J.M., Howe, C.J., James, K.A., Roswall, N., Overvad, K., Tjonneland, A., Meliker, J., Wellenius, G.A., 2022. Urinary cadmium and Incident heart failure: a case-cohort analysis among never-smokers in Denmark. Epidemiology 33, 185–192. https://doi.org/10.1097/EDE.0000000000001446.

Sears, C.G., Poulsen, A.H., Eliot, M., Howe, C.J., James, K.A., Harrington, J.M., Roswall, N., Overvad, K., Tjonneland, A., Raaschou-Nielsen, O., Wellenius, G.A., Meliker, J., 2021. Urine cadmium and acute myocardial infarction among never smokers in the Danish Diet, Cancer and Health cohort. Environ. Int. 150, 106428 https://doi.org/10.1016/j.envint.2021.106428.

Shen, J., Wang, X., Zhou, D., Li, T., Tang, L., Gong, T., Su, J., Liang, P., 2018. Modelling cadmium-induced cardiotoxicity using human pluripotent stem cell-derived cardiomyocytes. J. Cell Mol. Med. 22, 4221–4235. https://doi.org/10.1111/jcmm.13702.

Snoj Tratnik, J., Kocman, D., Horvat, M., Andersson, A.M., Juul, A., Jacobsen, E., Olafsdottir, K., Klanova, J., Andryskova, L., Janasik, B., Wasowicz, W., Janev Holcer, N., Namorado, S., Coelho, I., Rambaud, L., Riou, M., Van Nieuwenhuyse, A., Appenzeller, B., Kolossa-Gehring, M., Weber, T., Esteban-Lopez, M., Castano, A., Gilles, L., Rodriguez Marti, L., Schoeters, G., Sepai, O., Govarts, E., 2022. Cadmium exposure in adults across Europe: results from the HBM4EU Aligned Studies survey 2014-2020. Int. J. Hyg Environ. Health 246, 114050. https://doi.org/10.1016/j.ijheh.2022.114050.

Suwazono, Y., Nogawa, K., Sakurai, M., Watanabe, Y., Nishijo, M., Ishizaki, M., Morikawa, Y., Kido, T., Nakagawa, H., 2021. Environmental cadmium exposure and noncancer mortality in a general Japanese population in cadmium nonpolluted regions. J. Appl. Toxicol. 41, 587–594. https://doi.org/10.1002/jat.4067.

Tagt, J., Helte, E., Donat-Vargas, C., Larsson, S.C., Michaelsson, K., Wolk, A., Vahter, M., Kippler, M., Akesson, A., 2022. Long-term cadmium exposure and fractures, cardiovascular disease, and mortality in a prospective cohort of women. Environ. Int. 161, 107114 https://doi.org/10.1016/j.envint.2022.107114.

Tellez-Plaza, M., Guallar, E., Howard, B.V., Umans, J.G., Francesconi, K.A., Goessler, W., Silbergeld, E.K., Devereux, R.B., Navas-Acien, A., 2013. Cadmium exposure and incident cardiovascular disease. Epidemiology 24, 421–429. https://doi.org/10.1097/EDE.0b013e31828b0631.

Tellez-Plaza, M., Navas-Acien, A., Menke, A., Crainiceanu, C.M., Pastor-Barriuso, R., Guallar, E., 2012. Cadmium exposure and all-cause and cardiovascular mortality in the U.S. general population. Environ. Health Perspect. 120, 1017–1022. https://doi.org/10.1289/ehp.1104352.

Timmis, A., Townsend, N., Gale, C.P., Torbica, A., Lettino, M., Petersen, S.E., Mossialos, E.A., Maggioni, A.P., Kazakiewicz, D., May, H.T., De Smedt, D., Flather, M., Zuhlke, L., Beltrame, J.F., Huculeci, R., Tavazzi, L., Hindricks, G., Bax, J., Casadei, B., Achenbach, S., Wright, L., Vardas, P., European Society of, C., 2020. European society of cardiology: cardiovascular disease statistics 2019. Eur. Heart J. 41, 12–85. https://doi.org/10.1093/eurheartj/ehz859.

Tinkov, A.A., Filippini, T., Ajsuvakova, O.P., Aaseth, J., Gluhcheva, Y.G., Ivanova, J.M., Bjorklund, G., Skalnaya, M.G., Gatiatulina, E.R., Popova, E.V., Nemereshina, O.N., Vinceti, M., Skalny, A.V., 2017. The role of cadmium in obesity and diabetes. Sci. Total Environ. 601–602, 741–755. https://doi.org/10.1016/j.scitotenv.2017.05.224.

Tinkov, A.A., Filippini, T., Ajsuvakova, O.P., Skalnaya, M.G., Aaseth, J., Bjorklund, G., Gatiatulina, E.R., Popova, E.V., Nemereshina, O.N., Huang, P.T., Vinceti, M., Skalny, A.V., 2018. Cadmium and atherosclerosis: a review of toxicological

mechanisms and a meta-analysis of epidemiologic studies. Environ. Res. 162, 240–260. https://doi.org/10.1016/j.envres.2018.01.008.

Tsai, C.Y., Su, C.L., Wang, Y.H., Wu, S.M., Liu, W.T., Hsu, W.H., Majumdar, A., Stettler, M., Chen, K.Y., Lee, Y.T., Hu, C.J., Lee, K.Y., Tsuang, B.J., Tseng, C.H., 2023. Impact of lifetime air pollution exposure patterns on the risk of chronic disease. Environ. Res. 229, 115957 https://doi.org/10.1016/j.envres.2023.115957.

Tsao, C.W., Aday, A.W., Almarzooq, Z.I., Alonso, A., Beaton, A.Z., Bittencourt, M.S., Boehme, A.K., Buxton, A.E., Carson, A.P., Commodore-Mensah, Y., Elkind, M.S.V., Evenson, K.R., Eze-Nliam, C., Ferguson, J.F., Generoso, G., Ho, J.E., Kalani, R., Khan, S.S., Kissela, B.M., Knutson, K.L., Levine, D.A., Lewis, T.T., Liu, J., Loop, M.S., Ma, J., Mussolino, M.E., Navaneethan, S.D., Perak, A.M., Poudel, R., Rezk-Hanna, M., Roth, G.A., Schroeder, E.B., Shah, S.H., Thacker, E.L., VanWagner, L.B., Virani, S.S., Voecks, J.H., Wang, N.Y., Yaffe, K., Martin, S.S., 2022. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. Circulation 145, e153–e639. https://doi.org/10.1161/CIR.0000000000001052.

Urbano, T., Filippini, T., Wise, L.A., Lasagni, D., De Luca, T., Sucato, S., Polledri, E., Malavolti, M., Rigon, C., Santachiara, A., Pertinhez, T.A., Baricchi, R., Fustinoni, S., Vinceti, M., 2022. Associations of urinary and dietary cadmium with urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine and blood biochemical parameters. Environ. Res. 210, 112912 https://doi.org/10.1016/j.envres.2022.112912.

Urbano, T., Verzelloni, P., Malavolti, M., Sucato, S., Polledri, E., Agnoli, C., Sieri, S., Natalini, N., Marchesi, C., Fustinoni, S., Vinceti, M., Filippini, T., 2023. Influence of dietary patterns on urinary excretion of cadmium in an Italian population: a cross-sectional study. J. Trace Elem. Med. Biol. 80, 127298 https://doi.org/10.1016/j.jtemb.2023.127298.

Vacchi-Suzzi, C., Kruse, D., Harrington, J., Levine, K., Meliker, J.R., 2016. Is urinary cadmium a biomarker of long-term exposure in humans? A review. Curr Environ Health Rep 3, 450–458. https://doi.org/10.1007/s40572-016-0107-y.

Veneri, F., Iamandii, I., Vinceti, M., Birnbaum, L.S., Generali, L., Consolo, U., Filippini, T., 2023a. Fluoride exposure and skeletal fluorosis: a systematic review and dose-response meta-analysis. Curr Environ Health Rep. 10, 417–441. https://doi.org/10.1007/s40572-023-00412-9.

Veneri, F., Vinceti, M., Generali, L., Giannone, M.E., Mazzoleni, E., Birnbaum, L.S., Consolo, U., Filippini, T., 2023b. Fluoride exposure and cognitive neurodevelopment: systematic review and dose-response meta-analysis. Environ. Res. 221, 115239 https://doi.org/10.1016/j.envres.2023.115239.

Vinceti, M., Filippini, T., Wise, L.A., Rothman, K.J., 2021. A systematic review and dose-response meta-analysis of exposure to environmental selenium and the risk of type 2 diabetes in nonexperimental studies. Environ. Res. 197, 111210 https://doi.org/10.1016/j.envres.2021.111210.

Wen, Y., Huang, S., Zhang, Y., Zhang, H., Zhou, L., Li, D., Xie, C., Lv, Z., Guo, Y., Ke, Y., Wu, T., Cheng, J., 2019. Associations of multiple plasma metals with the risk of ischemic stroke: a case-control study. Environ. Int. 125, 125–134. https://doi.org/10.1016/j.envint.2018.12.037.

WHO, 2020. The Top 10 Causes of Death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

WHO, 2021. Cardiovascular Diseases (CVDs). https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds.

Wu, X., Cobbina, S.J., Mao, G., Xu, H., Zhang, Z., Yang, L., 2016. A review of toxicity and mechanisms of individual and mixtures of heavy metals in the environment. Environ. Sci. Pollut. Res. Int. 23, 8244–8259. https://doi.org/10.1007/s11356-016-6333-x.

Xing, X., Xu, M., Yang, L., Shao, C., Wang, Y., Qi, M., Niu, X., Gao, D., 2023. Association of selenium and cadmium with heart failure and mortality based on the National Health and Nutrition Examination Survey. J. Hum. Nutr. Diet. 36, 1496–1506. https://doi.org/10.1111/jhn.13107.

Xu, C., Weng, Z., Zhang, L., Xu, J., Dahal, M., Basnet, T.B., Gu, A., 2021. HDL cholesterol: a potential mediator of the association between urinary cadmium concentration and cardiovascular disease risk. Ecotoxicol. Environ. Saf. 208, 111433 https://doi.org/10.1016/j.ecoenv.2020.111433.

Yang, A.M., Lo, K., Zheng, T.Z., Yang, J.L., Bai, Y.N., Feng, Y.Q., Cheng, N., Liu, S.M., 2020. Environmental heavy metals and cardiovascular diseases: status and future direction. Chronic Dis Transl Med 6, 251–259. https://doi.org/10.1016/j.cdtm.2020.02.005.