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Cadmium exposure and risk of diabetes and prediabetes: A systematic review and dose-response meta-analysis

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ABSTRACT

Background: Cadmium exposure has been associated with increased diabetes risk in several studies, though there is still considerable debate about the magnitude and shape of the association.
Objective: To perform a systematic review and meta-analysis of observational studies investigating the relation between cadmium exposure and risk of type 2 diabetes and prediabetes, and to summarize data on the magnitude and shape of the association.
Data source: After conducting an online literature search through October 1, 2021, we identified 42 eligible studies investigating the association between cadmium exposure and risk of diabetes and prediabetes.
Study eligibility criteria: We included studies that assessed cadmium exposure through biomarker levels; examined type 2 diabetes or prediabetes among outcomes; and reported effect estimates for cadmium exposure for meta-analysis only.
Study appraisal and synthesis methods: Studies were evaluated using ROBINS-E risk of bias tool. We quantitively assessed the relation between exposure and study outcomes using one-stage dose-response meta-analysis with a random effects meta-analytical model.
Results: In the meta-analysis, comparing highest-versus-lowest cadmium exposure levels, summary relative risks (RRs) for type 2 diabetes were 1.24 (95% confidence interval 0.96–1.59), 1.21 (1.00–1.45), and 1.47 (1.01–2.13) for blood, urinary, and toenail matrices, respectively. Similarly, there was an increased risk of prediabetes for cadmium concentrations in both urine (RR = 1.41, 95% CI: 1.15–1.73) and blood (RR = 1.38, 95% CI: 1.16–1.63).
In the dose-response meta-analysis, we observed a consistent linear positive association between cadmium exposure and diabetes risk, with RRs of 1.25 (0.90–1.72) at 2.0 μg/g of creatinine. Conversely for blood cadmium, diabetes risk appeared to increase only above 1 μg/L. Prediabetes risk increased up to approximately 2 μg/g creatinine above which it reached a plateau with RR of 1.42 (1.12–1.76) at 2 μg/g creatinine.
Limitations and conclusions: This analysis provides moderate-certainty evidence for a positive association between cadmium exposure (measured in multiple matrices) and risk of both diabetes and prediabetes.

1. Introduction

Cadmium is a toxic metal released in the environment after both natural and anthropogenic activities, particularly in contaminated and industrial areas devoted to smelting and refining of metals, and the manufacturing of batteries, coatings, or plastics (ATSDR 2012; Cappelletti et al. 2016). Exposure to cadmium may occur through occupational activities, smoking, food, and air pollution (Chen et al. 2021; European Food Safety Authority 2012; Filippini et al. 2016; White et al. 2019). Smokers have higher concentrations of cadmium (Behera et al. 2014), whilst among non-smokers, food is the main source of exposure, especially cereals, vegetables, mollusks, and offals (Filippini et al. 2018; Kim et al. 2019). Generally, women and older individuals have a higher body burden of cadmium due to increased absorption among iron-deficient individuals, and greater accumulation with aging (Gallagher et al. 2011; Kim et al. 2019). Cadmium is absorbed through the same mechanism as other elements like zinc and manganese transporters (Himeno et al. 2019). Despite the use of these latter physiological systems to enter

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the body, cadmium has no biological role in humans. It accumulates primarily in the liver and kidney, which are considered the main targets of its toxicity (Cabral et al. 2021; Satarug 2018).

Cadmium has been classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC 2012) due to its established positive associations with lung and kidney cancers, and suggestive associations with prostate and breast cancers (Filippini et al. 2019b; Filippini et al. 2020; Nawrot et al. 2015; Vinceti et al. 2007). For breast cancer, recent findings indicate that the increase in risk occurs only at high levels of cadmium exposure (Andersson et al. 2021). In addition to cancer, elevated cadmium concentrations have been associated with an increased risk of chronic diseases, especially renal, bone, and cardiovascular diseases (Åkesson et al. 2014; Bimonte et al. 2021; Li et al. 2019; Söderholm et al. 2020; Tinkov et al. 2018). Adverse effects of cadmium were initially reported after occupational exposure and were limited to renal toxicity, due to its bioaccumulation in the kidney cortex, and bone disease, leading to osteomalacia and an increased risk of fractures (Järup and Åkesson 2009). Kidney failure and softening of bones are the main symptoms of the 'itai-itai disease' caused by cadmium poisoning through diet among individuals living in polluted mining areas in Japan (Ikeda et al. 2004).

Even low-level cadmium exposure has been associated with atherosclerosis, hypertension, and metabolic syndrome leading to both cardiovascular and cerebrovascular diseases (Åkesson et al. 2014; Bimonte et al. 2021; Li et al. 2019; Söderholm et al. 2020; Tinkov et al. 2018; Xu et al. 2021). In particular, cadmium may exert several pro-atherosclerotic effects through increased coronary artery calcification, subendothelial retention and oxidation of lipoproteins, endothelial dysfunction as well as prothrombotic and antifibrinolytic effects (Barregard et al. 2021; Fagerberg and Barregard 2021; Martins et al. 2021), even at relatively low levels of exposure. Indeed, studies suggest a positive association between elevated cadmium concentrations and type 2 diabetes (Satarug et al. 2017b; Tinkov et al. 2017). Although the mechanisms by which cadmium influences diabetes risk association are not clear, animal and laboratory evidence suggests that cadmium can injure pancreatic tissue and cause excess stimulation of gluconeogenesis, reduction of insulin incretion, and insulin resistance at target tissues, especially adipose tissue, leading to decreased glucose uptake (Attia et al. 2021; Buha et al. 2020; Edwards and Ackerman 2016; Hong et al. 2021; Moulis et al. 2021). Epidemiological studies also suggest a positive association between cadmium and both type 2 and gestational diabetes (Guo et al. 2019; Liu et al. 2018). In particular, a positive association between urinary cadmium concentrations and type 2 diabetes has been shown at concentrations above 2.4 μg/g creatinine (Guo et al. 2019). However, no previous reviews have assessed the shape of the association between blood cadmium concentrations and type 2 diabetes using a dose-response approach and there has been no investigation of prediabetes as a distinct endpoint in these reviews. In recent years, greater attention has been given to adverse effects even at exposure levels previously considered safe as well as smoking-independent effects of cadmium exposure (Fagerberg and Barregard 2021; Satarug et al. 2017a).

In this report, we provide an updated literature review of human studies on cadmium exposure and risk of both type 2 diabetes and prediabetes, and we model the shape of these associations using a dose-response approach (Orsini and Spiegelman 2020). The research question was configured according to PECOS statement (Population, Exposure, Comparator(s), Outcomes, and Study design - "In adult populations, what is the incremental effect of cadmium exposure on risk of type 2 diabetes or prediabetes from epidemiological nonexperimental studies?") (Morgan et al. 2018).

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement (Page et al. 2021) to perform this review.

2.1. Literature search and screening

We performed online literature searches in PubMed/MEDLINE, Web of Science, and EMBASE databases through October 1, 2021, by using search terms related to "cadmium" and "diabetes" or "prediabetes state". Details about the search terms are reported in Supplemental Table S1. We further applied citation chasing techniques to identify relevant studies. We performed screening of reference lists of included papers as well as backward and forward citations of included studies (Booth 2008; European Network for Health Technology Assessment (EUnetHTA) 2019). Retrieved articles were imported into Rayyan QCRI online application and duplicates were removed. Two authors (TF and MV) independently screened publication titles and abstracts and evaluated full-text publications for inclusion in the review. In case of disagreement, both authors performed a second review of the full text to determine eligibility for inclusion through a consensus-based discussion. If the two authors still disagreed, a third author (LW) was sought to resolve disagreement.

2.2. Eligibility criteria and study selection

Inclusion criteria for studies in this review were: (1) cadmium exposure assessment using any biomarker based on heavy metal concentration; (2) outcome of interest (type 2 diabetes or prediabetes); and for inclusion in the meta-analysis: (3) outcome identified using criteria defined by the World Health Organization (WHO 1999), the American Diabetes Association (American Diabetes 2021), or as follows: type 2 diabetes: glycated hemoglobin A1c (HBA_{1c}) $\geq$ 6.5%, fasting plasma glucose (FPG) $\geq$ 126 mg/dL or $\geq$ 7 mmol/L, or 2 h plasma glucose (2 h-PG) during oral glucose tolerance test (OGTT) $\geq$ 200 mg/dL or $\geq$ 11.1 mmol/L; prediabetes (i.e., impaired glucose tolerance): HBA_{1c} from 5.7% to 6.4%, FPG from 100 mg/dL to 125 mg/dL or from 5.6 to 6.9 mmol/L, or 2 h-PG during OGTT from 140 mg/dL to 199 mg/dL or from 7.8 to 11.0 mmol/L; (4) reporting of relative risk estimates using the hazard ratio (HR), rate/risk ratio (RR), or odds ratio (OR), along with the corresponding 95% confidence interval (CI), or enough data to calculate them; and for inclusion in dose-response meta-analysis: (5) reported effect estimates for all exposure categories along with dose in each category. We did not apply any language restrictions. When necessary, we also contacted authors of included studies to retrieve additional information for data analysis when not published in the report.

2.3. Risk of bias assessment

We assessed the quality of included studies using the Risk of Bias for in Non-randomized Studies of Exposures (ROBINS-E) tool (Morgan et al. 2019). Seven domains were considered including: (1) bias due to confounding; (2) bias in selecting participants in the study; (3) bias in exposure classification; (4) bias due to departures from intended exposures; (5) bias due to missing data; (6) bias in outcome measurement; (7) bias in the selection of reported results. Supplemental Table S2 reports criteria for risk of bias evaluation.

2.4. Data extraction

We extracted the following data from eligible studies: (1) first author name; (2) publication year; (3) location; (4) type of exposure assessment; (5) outcome of interest; (6) cadmium concentrations in the overall population and according diabetic/prediabetic status; (7) cut-off values for each category of exposure; (8) number of cases; (9) sample size; (10) relative risk estimates with 95% CIs and covariates from the most adjusted multivariable analysis when available.

2.5. Synthesis of evidence

We used qualitative and quantitative approaches to synthesize evidence across studies. In the quantitative approach, we applied further

inclusion criteria as reported in Section 2.2. We used Stata software (v17.0, Stata Corp., College Station, TX, 2021) for all data analyses, specifically the 'meta', 'mkspline', and 'drmeta' routines.

2.5.1. Meta-analysis

We performed a meta-analysis that involved estimating RRs from each study, comparing the highest versus lowest exposure categories. We applied a restricted maximum likelihood random effects model.

2.5.2. Dose-response meta-analysis

We explored the shape of the association between cadmium exposure and risk of diabetes and prediabetes using a one-stage approach (Adani et al. 2020; Filippini et al. 2019a; Filippini et al. 2021). In this approach, we used the mean/median concentration or the midpoint of each exposure category depending on data availability. If the highest and lowest exposure categories were 'open,' we used as boundary a value that was 20% higher or lower, respectively, than the closest cutpoint (Vinceti et al. 2016). In the analysis on blood cadmium concentrations, all but one study provided data suitable for the dose-response meta-analysis assessing cadmium in whole blood. We also estimated blood cadmium from plasma cadmium concentrations in the only study using this biomarker, considering that 90% is bound to erythrocytes and the remaining is bound to metallothionein proteins in plasma (Deutsche Forschungsgemeinschaft 2006; Kjellström and Nordberg 1978; Nordberg et al. 1971). We used a restricted cubic spline model with 3 knots at fixed cutpoints (10, 50, and 90 percentiles). We also used a generalized least-squares regression model that accounted for the correlation within each set of published effect estimates through the restricted maximum likelihood method in a random-effects meta-analysis (Crippa et al. 2019; Orsini et al. 2012; Vinceti et al. 2020).

2.5.3. Subgroup and sensitivity analyses

We stratified all analyses by exposure matrix (i.e., blood or urine). Whenever possible, we also stratified the data by sex, geographic region (namely Asia, Europe, North America, Africa and Oceania to account for differences in ethnic origin or dietary habits), and study design (cross-sectional, case-control, and cohort). We ran sensitivity analyses using an alternative estimate (i.e., ±15% and ±10% instead of ±20%) for the highest and lowest exposure boundaries when median/mean values were not reported. We excluded studies that did not account for smoking in multivariate models, and studies judged to be at high risk of bias. Finally, in the dose-response analysis only, we assessed the presence of a linear trend in spline analyses (Orsini et al. 2012).

2.5.4. Heterogeneity and small study bias assessment

We assessed heterogeneity of studies using the τ^2, I^2 and H^2 statistics (Higgins et al. 2003). For the dose-response analysis, we provided a graphical overlay of study-specific trends using predicted curves of analysis showing the influence of variation across studies (Crippa et al. 2019). We also performed meta-regression analysis to further explore heterogeneity, in particular using as moderator cadmium concentrations in blood and urine. Finally, we evaluated the presence and influence of small-study bias using funnel plots with Egger's test (Egger et al. 1997), and the trim-and-fill analysis (Duval and Tweedie 2000).

2.6. Certainty of the evidence

We assessed the overall certainty of the evidence using the GRADE approach (Atkins et al. 2004). Taking into account the PECO question, we assessed the certainty assessment for diabetes and prediabetes risk due to incremental cadmium exposure (assessed through blood or urinary levels) yielded by the dose-response analysis in all studies and after excluding studies at high risk of bias. We used GRADEPro GDT (https://gradepro.org) to present the certainty assessment and summarize findings in tabular form.

3. Results

3.1. Study selection

The PRISMA checklist is reported in Supplemental Table S3. The PRISMA flow-chart of the literature search is presented in Fig. 1. We retrieved 1311 unique studies, from which 1241 were excluded after title and abstract screening. After full-text assessment of the remaining 70 studies, 29 were further excluded because the outcome was not type 2 diabetes or prediabetes (N = 13); the exposure assessment did not include cadmium (N = 6); or the publication was a duplicate (N = 5), a preliminary report of a subsequently included study (N = 4), or a commentary (N = 1). One study was added through backward citation searching of included studies (Tadayon et al. 2013).

3.2. Characteristics of included studies in the review

Summary characteristics of the 42 included studies are reported in Table 1. Overall, studies were published between 1992 and 2022, with most from Asia (N = 22), followed by North America (N = 8) and South America (N = 1), Europe (N = 6), Africa (N = 2) Oceania (N = 1), and multiple geographic regions (N = 2). Cadmium concentrations were measured in urine (N = 21), blood (N = 18), hair (N = 4), nails (N = 2), tears (N = 1) or adipose tissue (N = 1), with two studies assessing exposure in both hair and nails (Sukumar and Subramanian 1992; 2007), two studies in both urine and blood (Afridi et al. 2008; Barregard et al. 2013), and one study in blood, urine, and hair (Flores et al. 2011). Diabetes was investigated as an outcome in thirty-one studies, prediabetes in four studies, and both diabetes and prediabetes in seven studies. Thirteen studies (all assessing diabetes only) did not report enough data to assess risk estimates, thus the meta-analysis could not be performed (Adams et al. 2016; Afridi et al. 2008; Akinloye et al. 2010; Anetor et al. 2016; Flores et al. 2011; Hotta et al. 2019; Joda and Ward 2021; Serdar et al. 2009; Skalnaya et al. 2017; Sukumar and Subramanian 1992; 2007; Tadayon et al. 2013; Zhu and Hua 2020).

3.3. Risk of bias assessment

Results of study quality assessment by risk of bias are reported in Table 2. Overall, seven of the included studies were deemed to be at high risk of bias (Adams et al. 2016; Haswell-Elkins et al. 2007; Joda and Ward 2021; Lei et al. 2019; Moon et al. 2022; Saba et al. 2020; Swaddiwudhipong et al. 2010). Thirteen studies (Adams et al. 2016; Afridi et al. 2008; Akinloye et al. 2010; Anetor et al. 2016; Flores et al. 2011; Hotta et al. 2019; Joda and Ward 2021; Serdar et al. 2009; Skalnaya et al. 2017; Sukumar and Subramanian 1992; 2007; Tadayon et al. 2013; Zhu and Hua 2020) did not report relative risk estimates for diabetes or prediabetes, and did not provide row data to calculate them. One study was considered at moderate risk of bias due to lack of control for smoking (Schwartz et al. 2003) and additional four studies were considered at high risk of bias due to confounding, since one study did not adjust for age (Saba et al. 2020), and three did not use multivariable model (Haswell-Elkins et al. 2007; Lei et al. 2019; Swaddiwudhipong et al. 2010). Nonetheless, for the latter three studies, we used crude data in the analysis. We cannot exclude selection bias as a source of bias in six studies conducted among individuals living in cadmium-contaminated areas; these studies were considered at moderate risk of bias. Regarding information bias, risk of exposure misclassification is unlikely because all studies assessed cadmium exposure though analysis of biological specimens at the beginning of the study. With respect to bias in departure from intended exposure, none of the study was at high risk of bias because it did not report mean values of cadmium exposure. None of the studies excluded participants due to missing data ≥20%. Outcome identification was based on self-report in two studies (Adams et al. 2016; Moon et al. 2022), and another three studies reported no information about method of outcome ascertainment (Joda

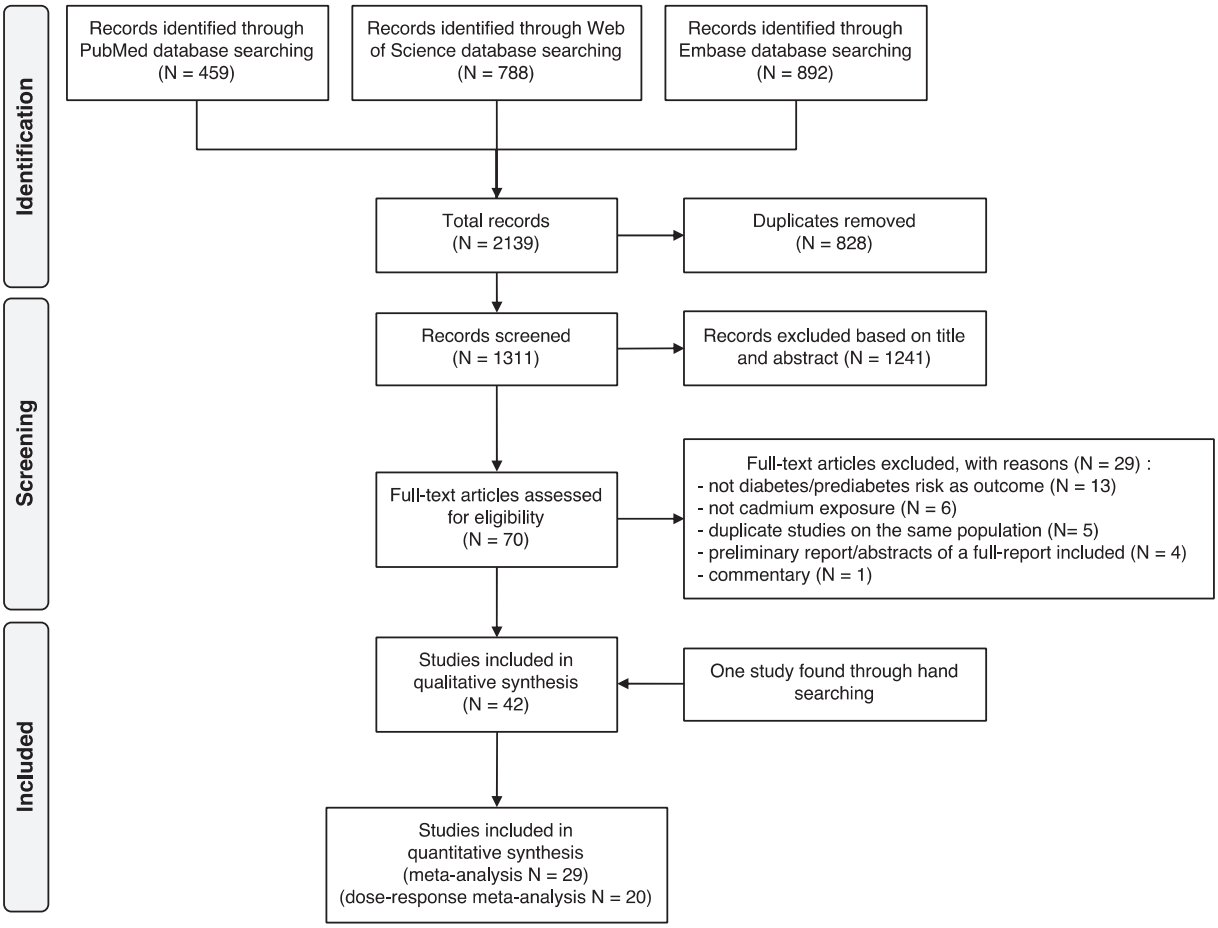

Fig. 1. Flow-chart of systematic literature search through October 1, 2021.

and Ward 2021; Lei et al. 2019; Tadayon et al. 2013) thus they were considered at high risk of bias.

3.4. Quantitative synthesis

3.4.1. Diabetes

Analyses comparing highest versus lowest concentrations of cadmium showed a positive association with diabetes independent from exposure assessment method, with RR of 1.24 (95% CI 0.96–1.59, 9 studies), 1.21 (95% CI 1.00–1.45, 15 studies), and 1.47 (95% CI 1.01–2.13, one study) for blood, urine, and toenail matrices, respectively (Fig. 2). Analyses stratified by region suggested somewhat higher risk estimates in North American populations (based on one study only), followed by Asian populations in studies using blood cadmium concentrations. Conversely, a stronger association was observed in Oceania populations (based on one study only), followed by Asian populations using urinary cadmium concentrations for exposure assessment (Supplemental Figure S1-S2). Conversely, analyses stratified by sex showed comparable risk estimates for both men and women (Supplemental Figure S3), though these results were based on fewer studies compared with the main analysis. Similarly, we found comparable results among men and women when we considered studies reporting RRs estimated for both sexes (Supplemental Figure S4). Analyses stratified by study design showed generally stronger RRs when considering case-control and cross-sectional studies compared with cohort studies (Supplemental Figures S5-S6).

In the dose-response meta-analysis, we detected a substantial linear positive association with diabetes risk for increasing levels of urinary cadmium. Compared with no exposure, RRs were 1.07 (95% CI 0.95–1.20), 1.13 (95% CI 0.91–1.41), 1.25 (95% CI 0.90–1.72), and 1.42 (95% CI 0.93–2.17) at concentrations of 0.5, 1.0, 2.0, and 4.0 μg/g creatinine, respectively (Fig. 3). Conversely for blood concentrations, the RR increased at values above 1 μg/L compared with no exposure, with RRs of 0.92 (95% CI 0.61–1.40), 1.47 (95% CI 0.79–2.76), 2.43 (05% CI 0.91–6.51), and 4.00 (95% CI 1.00–16.01) at 1.0, 1.5, 2.0 and 2.5 μg/L, respectively (Fig. 3).

3.4.2. Prediabetes

With regard to prediabetes, we found a positive association for cadmium concentrations in both urine (RR 1.41, 95% CI 1.15–1.73, 8 studies) and blood (RR 1.38, 95% CI 1.16–1.63, 3 studies) when comparing the highest versus lowest exposure categories (Fig. 4). Similarly, a positive association can be noted in the dose-response meta-analysis: compared to no exposure, RRs increased up to approximately 2 μg/g creatinine, above which a plateau was reached, with RRs of 1.12 (95% CI 1.03–1.21), 1.23 (95% CI 1.06–1.43), 1.40 (95% CI 1.12–1.76), and 1.55 (95% CI 1.21–1.99) at 0.5, 1.0, 2.0, and 4.0 μg/g creatinine, respectively (Fig. 5). In the region-stratified analyses, we found similar RRs among different regions on blood studies, whilst we found a somewhat stronger RR among North Americans than Asians in studies that assessed urinary cadmium concentrations (Supplemental Figures S7-S8). The three studies that assessed blood cadmium concentrations all had cross-sectional designs, as did the majority of studies using urinary excretion (one cohort and seven cross-sectional studies). In urinary excretion studies, substantially stronger associations were observed for cross-sectional studies (Supplemental Figure S9).

3.4.3. Sensitivity analyses

In sensitivity analyses using a value ±15% or ±10% instead of 20% to the closest (lower and upper) available boundary in open categories, we found comparable results (Supplemental Figures S10-S13). After

Table 1
Characteristics of the included studies divided by type of cadmium (Cd) exposure assessment and ordered by first author's name and publication year.

Reference	Country	Population characteristics	Study design and period	Overall cadmium levels[a]	Cd levels across categories	DM/preDM risk estimate (95% CI)	Outcome assessment	Adjustment factors
Blood Cd				µg/L	µg/L			
(Afridi et al. 2008)	Pakistan	434 men from Hyderabad aged 31–60 years: 238 non-DM (115 non-smokers, 123 smokers) and 196 DM (110 non-smokers, 86 smokers)	Cross-sectional	non-smokers: non-DM: 4.2 (1.25) DM: 5.7 (1.3) smokers: non-DM: 5.3 (1.4) DM: 8.9 (1.2)	NR	NR	FPG, HbA_{1c}	NR
(Akinloye et al. 2010)	Nigeria	90 subjects(40 non-DM, 50 DM) from LAUTECH Teaching Hospital, Osogbo	Case-control	non-DM: 0.64 (0.18) DM: 0.80 (0.16)	NR	NR	FPG	NR
(Anetor et al. 2016)	Nigeria	65 subjects, 20 non-DM, 45 DM mean age 57 and 62 years, respectively from Ibadan	Case-control	Plasma non-DM: 0.95 (0.311) DM: 0.50 (0.201)	NR	NR	FPG, HbA_{1c}	NR
(Barregard et al. 2013)	Sweden	616 women from Gothenburg aged 64-year (183 NGT, 207 IGT, 215 DM)	Cross-sectional 2001–2003	Median (IQR) NGT: 0.34 (0.17–1.61) IGT: 0.34 (0.14–1.58) DM: 0.34 (0.13–1.92)	0.174 0.274 0.431 1.265	IGT Ref. 0.56 (0.30–1.04) 0.63 (0.34–1.19) 1.27 (0.58–2.81) DM Ref. 0.36 (0.18–0.71) 0.34 (0.17–0.70) 1.11 (0.48–2.60)	FPG, OGTT, HbA_{1c}	pack-years of smoking, waist circumference, and serum adiponectin
(Borne et al. 2014)	Sweden	Malmo Diet and Cancer Study: 4585 subjects (M/F: 1831/2754) aged 46–67 years, 622 DM (M/F: 299/323) IFG 390	Cohort 1991–1994	non-DM: 0.46 IFG: 0.52 DM: NR	men 0.01–0.15 0.15–0.24 0.24.0.51 0.51–5.07 women 0.02–0.18 0.18–0.27 0.27–0.50 0.50–4.83	DM men: Ref. 0.82 (0.59–1.14) 0.94 (0.67–1.32) 0.90 (0.59–1.38) women: Ref. 0.93 (0.68–1.27) 0.96 (0.70–1.31) 1.21 (0.81–1.82) IFG Ref. Q4: 0.80 (0.51–1.24)	FPG, HbA_{1c} (registry-based)	age, waist circumference, and smoking status
(Ettinger et al. 2014)	Ghana, South Africa, Seychelles, Jamaica and US	METS study: 150 African descent young adults aged 25–45 years (99 non-DM, 51 pre-DM)	Cross-sectional	GM (95% CI) all: 0.03 (0.02–0.04) non-DM: 0.02 (0.01–0.03) pre-DM: 0.06 (0.03–0.14)	pre-DM >0.008	1.69 (0.77–3.68)	FPG	age, sex, site location, marital status, education, paid employment, smoking, alcohol use, and fish intake
(Flores et al. 2011)	Mexico	88 subjects from Department of Medical Research, University of Guanajuato (12 non-DM, 76 DM)	Cross-sectional	Plasma non-DM: 0.04 (0.01) DM: 0.13 (0.48)	NR	NR	FPG, HbA_{1c}	NR
(Hansen et al. 2017)	Norway	HUNT3 study: 883 subjects ≥ 20 years (755 non-DM, 128 DM)		Median non-DM: 0.35	0.168 0.281			age, sex, BMI, waist-to-hip ratio, education, income, smoking and family history of diabetes

(*continued on next page*)

Table 1 (*continued*)

Reference	Country	Population characteristics	Study design and period	Overall cadmium levels[a]	Cd levels across categories	DM/preDM risk estimate (95% CI)	Outcome assessment	Adjustment factors
			Case-control cohort nested 2006–2008	DM: 0.40	0.461 1.40	Ref. 1.99 (0.92–4.28)	FPG, OGTT (+HbA_{1c} in cases only)	
(Ji et al. 2021)	South Korea	Changwon industrial city: 34,814 subjects mean age 35 years (1033 DM)	Cohort 2002–2018	Blood DM: 2 μg/L	NR	1.48 (0.61–3.55)	FPG, HbA_{1c}, history of DM	age, hemoglobin A1c, fasting blood sugar, BMI, current smoking, and ferritin
(Li et al. 2017)	China	551 subjects from Suzhou City, Jiangsu Province, mean age 66 years (429 non-DM, 122 DM)	Cross-sectional 2014–2016	Plasma (Median) all: 0.071 non-DM: 0.065 DM: 0.096	<0.051 0.051–0.096 >0.096	Ref. 1.086 (0.617–1.912) 2.511 (1.486–4.245)	FPG, OGTT, HbA_{1c}	age, sex, BMI, family history, smoking and drinking status
(Little et al. 2020)	US	Superfund Cleanup in Dallas, TX: 875 subjects aged 19–88 years (766 non-DM, 109 DM)	Cross-sectional 2002	non-DM: 0.07 DM: 0.18	NR	1.85 (1.14–2.99)	HbA_{1c}	age, sex, smoking tobacco, duration of residence, smelter workers, lead blood level, arsenic blood level, mercury blood level, abnormal GGT, hypertension
(Moon 2013)	South Korea	KNHANES 2007–2012 study: 3284 subjects ≥ 30 years (2851 non-DM, 333 DM)	Cross-sectional 2009–2010	non-DM: 1.10 DM: 1.16	0.55 0.96 1.34 2.11	Ref. 0.774 (0.544–1.101) 0.787 (0.553–1.120) 0.778 (0.540–1.119)	FPG, DM treatment, history of DM (physician-based)	age, sex, region, smoking, alcohol consumption and regular exercise
(Nie et al. 2016)	China	SPECT-China study: 5544 subjects ≥ 18 years (3410 non-DM, 565 DM)	Cross-sectional 2014	Median (IQR) all: 1.70 (0.58–3.62) non-DM: 1.61 (0.57–3.29) IFG: 1.80 (0.51–3.61) DM: 1.70 (0.59–3.62)	≤0.80 0.81–2.94 ≥2.95	DM Ref. 0.89 (0.69–1.15) 1.13 (0.88–1.46) IFG Ref. 1.19 (1.01–1.40) 1.37 (1.14–2.63)	FPG, history of DM (physician-based)	age, sex, residence area, economic status, current smoker, hypertension, dyslipidemia, estimate glomerular filtration rate, blood lead, and BMI
(Serdar et al. 2009)	Turkey	87 subjects aged 30–70 years (22 non-DM, 20 IGT, 14 IFG, 31 DM)	Case-control	non-DM: 0.01 (0.01–0.02) IFG: 0.01 (0.01–0.10) IGT: 0.01 (0.01–0.06) DM: 0.01 (0.01–0.08)	NR	NR	FPG, OGTT, HbA_{1c}	NR
(Simić et al. 2017)	Norway	HUNT3 study: 868 subjects ≥ 20 years (609 non-DM, 267 DM)	Case-control 2006–2008	Median non-DM: 0.35 DM: 0.32	0.163 0.282 0.472 1.56	Ref 0.64 (0.38–1.10) 0.67 (0.39–1.16) 0.61 (0.30–1.23)	FPG, OGTT	matched by sex and age, and adjusted for BMI, waist-to-hip ratio, first-degree family history of diabetes, smoking habits, area, education and economic status
(Skalnaya et al. 2017)	Russia	128 postmenopausal women living in Moscow men age 56 years (64 non-DM, 64 DM)	Case-control	Serum non-DM: 0.0001 (0.0000) DM: 0.0001 (0.0001)	NR	NR	HbA_{1c}	NR
(Son et al. 2015)	South Korea	HESRAM study: 719 (M/F: 489/230) residents of abandoned metal mines aged 40–70 years (561 non-DM, 158 DM)	Cross-sectional 2008–2011	all: 1.70 (0.97) men 1.73 (0.97) women: 1.64 (0.95) non-DM: 1.70	NR	NR	FPG	NR

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Table 1 (*continued*)

Reference	Country	Population characteristics	Study design and period	Overall cadmium levels[a]	Cd levels across categories	DM/preDM risk estimate (95% CI)	Outcome assessment	Adjustment factors
				(0.95) DM: 1.70 (1.02)				
(Zhu and Hua 2020)	China	92 subjects aged 42–94 years (33 non-DM, 58 DM)	Case-control	Serum non-DM: 0.0072 DM: 0.0101	NR	NR	HbA_{1c}	NR
Urinary Cd				μg/g creatinine				
(Adams et al. 2016)	US	188 adults (M/F: 26/160) aged 40–85 years from New Mexico, Doña Ana County (120 non-DM, 68 DM)	Cross-sectional 2011–2012	non-DM: 0.35 (0.27) DM: 0.41 (0.37)	NR	NR	History of DM (self-reported)	NR
(Afridi et al. 2008)	Pakistan	434 men from Hyderabad aged 31–60 years: 238 non-DM (115 non-smokers, 123 smokers) and 196 DM (110 non-smokers, 86 smokers)	Cross-sectional	non-smokers: non-DM: 3.2 (0.9) DM: 4.65 (0.79) smokers: non-DM: 3.98 (1.3) DM: 5.88 (1.0)	NR	NR	FPG, HbA_{1c}	NR
(Barregard et al. 2013)	Sweden	616 women from Gothenburg aged 64-year (183 NGT, 207 IGT, 215 DM)	Cross-sectional 2001–2003	Median (IQ R) non-DM: 0.36 (0.16–0.92) IGT: 0.35 (0.14–1.03) DM: 0.36 (0.14–1.14)	0.178 0.297 0.438 0.892	DM risk Ref. 0.72 (0.37–1.40) 0.57 (0.28–1.10) 1.17 (0.52–2.60) IGT risk Ref. 0.79 (0.42–1.48) 0.79 (0.42–1.48) 0.95 (0.46–1.96)	FPG, OGTT, HbA_{1c}	pack-years of smoking, waist circumference, and serum adiponectin
(Feng et al. 2015)	China	2242 subjects aged 18–80 years from Wuhan city (1765 non-DM, 259 IFG, 218 DM)	Cross-sectional 2011	Median (IQR): 0.885 (0.529–1.420)	DM risk <0.52 0.52–0.88 0.89–1.43 >1.43	DM risk Ref. 1.473 (0.947–2.292) 1.275 (0.796–2.042) 1.383 (0.817–2.341)	FPG, DM treatment, history of DM (physician-based)	age, sex, BMI, smoking status, pack year, alcohol status, family history of diabetes, diabetic drug use, hypertension, hyperlipidemia, and urinary creatinine
					IFG risk <0.53 0.53–0.89 0.90–1.44 >1.44	IFG risk Ref. 0.892 (0.599–1.326) 0.902 (0.592–1.374) 0.816 (0.509–1.308)		age, sex, BMI, smoking status, pack year, alcohol status, family history of diabetes, hypertension, hyperlipidemia, and urinary creatinine
(Flores et al. 2011)	Mexico	88 subjects from Department of Medical Research, University of Guanajuato (12 non-DM, 76 DM)	Cross-sectional	non-DM: 0.32 (0.21) DM: 0.13 (0.12)	NR	NR	FPG and HbA_{1c}	NR
(Haswell-Elkins et al. 2007)	Australia	Torres Strat Islanders: 182 (M/F: 58/124) subjetcs aged 37 years (139 non-DM, 43 DM)	Cross-sectional 1996 and 2003	GM: all: 0.93 non-DM: 0.86 DM: 1.20	<1.00 1.00–1.99 ≥2.00	Ref. 7.88 (2.49–27.20) 7.22 (1.52–33.04)	FPG, OGTT	crude
(Jiang et al. 2018)	US	NHANES 2007–2012: 3552 subjects (M/F:	Cross-sectional 2007–2012	all: 3.49 (3.72) non-DM: 3.05	NR	men Ref. 1.61 (1.21–2.23)	FPG, OGTT, and HbA_{1c}	age, sex, race/ethnicity, poverty income ratio, smoking status, alcohol consumption, physical activity and BMI

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Reference	Country	Population characteristics	Study design and period	Overall cadmium levels[a]	Cd levels across categories	DM/preDM risk estimate (95% CI)	Outcome assessment	Adjustment factors
		1783/1769) aged 20–60+ (2132 non DM, 1420 pre-DM)		(3.65) pre-DM: 4.14 (3.72)		1.77 (1.27–2.46) 1.95 (1.34–2.84) women Ref. 1.08 (0.77–1.51) 1.43 (1.01–2.03) 1.34 (0.92–2.18)		
(Lei et al. 2019)	China	593 (M/F: 215/378) subjects mean age 63 years, 427 (M/F: 62/104) non-DM, 166 (M/F: 153/274) DM	Case-control	Median (25th-75th) non-DM: 0.87 (0.46–1.64) DM: 0.95 (0.57–1.94)	NR	1.61 (1.08–2.41)	FPG, OGTT, and DM treatment	crude
(Liu et al. 2016)	China	1595 coke oven workers in Wuhan (1111 non-DM, 382 pre-DM, 102 DM)	Cross-sectional	Median (25th-75th) non-DM: 0.92 (0.51–1.47) pre-DM: 0.96 (0.51–1.47) DM: 1.08 (0.59–1.81)	≤0.64 0.64–1.22 ≥1.22	DM risk Ref. 0.72 (0.40–1.31) 0.98 (0.53–1.81) pre-DM risk Ref. 1.08 (0.78–1.49) 1.15 (0.80–1.63)	FPG, DM treatment, history of DM (physician-based)	sex, age, BMI, smoking status, drinking status, physical activity, education levels, urinary creatinine, hypertension, hyperlipidemia, and urinary polycyclic aromatic hydrocarbons levels
(Menke et al. 2016)	US	NHANES 1999–2010 study: 9447 subjects aged ≥ 20 years (8083 non-DM, 1364 DM)	Cross-sectional 1999–2010	Median (25th-75th) 0.26 (0.13–0.51)	μg/L <0.13 0.13–0.26 0.26–0.51 >0.51	1.00 1.16 (0.79–1.50) 0.74 (0.49–1.13) 0.82 (0.56–1.22)	HbA_{1c}	age, race-ethnicity, sex, menopausal status, education, income, alcohol consumption, smoking status, pack years smoked, waist circumference, high alanine aminotransferase, high gamma glutamyl transferase, daily calories consumed, percent of calories from saturated fat, and C-reactive protein
(Moon et al. 2022)	South Korea	KoNEHS 2015–2017 study: 3787 (M/F: 1648/2139) participants aged > 18 years	Cross-sectional 2015–2017	Median (25th-75th) 0.42 (0.18–0.81)	μg/L <0.18 0.18–0.42 0.42–0.81 >0.81	1.00 1.00 (0.61–1.63) 1.49 (0.93–2.38) 0.83 (0.54–1.26)	DM medication history (self-reported)	age, sex, cigarette smoking, alcohol drinking, exercise, and education levels
(Saba et al. 2020)	Pakistan	724 participants aged > 40 years (273 non-DM, 451)	Cross-sectional 2019	NR	ppm <50.46 50.46–57.47 57.47–63.88 ≥63.88	1.00 1.23 (0.77–1.94) 1.05 (0.66–1.66) 1.62 (1.00–2.61)	FPG, HbA_{1c}	education, sex, job, smoking and urinary heavy metal concentration
(Schwartz et al. 2003)	US	NHANES III: 8112 subjects (6905 non-DM, 610 pre-DM, 1207 DM)	Cross-sectional 1988–1994	NR	0–0.99 1.00–1.99 ≥2.00	DM risk Ref. 1.24 (1.06–1.45) 1.45 (1.07–1.97) IFG Ref. 1.48 (1.21–1.82) 2.05 (1.42–2.95)	FPG	age, sex, ethnicity, and BMI
(Son et al. 2015)	South Korea	HESRAM study: 719 (M/F: 489/230) residents of abandoned metal mines aged 40–70 years (561 non-DM, 158 DM)	Cross-sectional 2008–2011	all: 2.29 (2.20) men 2.13 (2.18) women: 2.63 (2.21) non-DM: 2.16 (1.70) DM: 2.72 (3.41)	≤1 1–2 ≥2	men: Ref. 1.42 (0.83–2.45) 1.81 (1.05–3.12) women: Ref. 0.66 (0.25–1.73) 1.39 (0.52–3.72)	FPG	age, BMI, smoking, alcohol consumption, region, family income (and menopausal status in women)

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Reference	Country	Population characteristics	Study design and period	Overall cadmium levels[a]	Cd levels across categories	DM/preDM risk estimate (95% CI)	Outcome assessment	Adjustment factors
(Swaddiwudhipong et al. 2010)	Thailand	5273 (M/F: 2370/2903) subjects aged ≥ 35 years (4926 non-DM, 347 DM)	Cross-sectional 2009	all: 2.2 (2.3) men: 2.0 (2.2) women: 2.4 (2.3)	<1.54 1.54–3.32 >3.32	Ref. 1.23 (0.92–1.63) 1.38 (1.04–1.82)	FPG, DM treatment	crude
(Tangvarasittichai et al. 2015)	Thailand	535 rural population in Cd exposed (258) and non-exposed (277) areas ≥ 30 years (315 non-DM, 20 DM)	Cross-sectional 2010–2011	Median (25th-75th) Cd non-exposed: 0.7 (0.4.1.3) Cd-exposed: 8.3 (6.4–10.7)	0.7 8.3	Ref. 3.02 (1.23–7.38)	FPG, DM treatment, history of DM (physician-based)	sex, age, chronic kidney disease, protein excretion, calcium excretion, BMI, drinking, and smoking
(Velmurugan et al. 2018)	India	865 subjects from typical farming village in Tamil Nadu aged > 20 years (252 non-DM, 271 pre-DM, 142 DM)	Cross-sectional 2015	non-DM: 2.22 pre-DM: 1.90 DM: 3.35	0.03–0.04 0.04–1.68 1.6–4.53 >13.89	DM Ref. 0.99 (0.54–1.84) 0.92 (0.49–1.72) 1.46 (0.79–2.75) pre-DM Ref. 1.09 (0.69–1.71) 1.02 (0.65–1.60) 1.67 (1.06–2.64)	HbA_{1c}, DM treatment, history of DM (physician-based)	age, sex, education, occupation, waist circumference, BMI, diastolic and systolic blood pressure, low-density lipoprotein- cholesterol, familial diabetic history, smoking, and alcohol and tobacco usage.
(Wallia et al. 2014)	US	NHANES 2005–2010: 2398 (M/F: 1194/1204) subjects aged ≥ 40 years (1191 non-DM, 1207 pre-DM)	Cross-sectional 2005–2010	all: 0.4	0.014–0.183 0.183–0.285 0.285–0.420 0.420–0.656 0.656–3.74	men Ref. 1.22 (0.83–2.11) 1.55 (0.95–2.52) 1.75 (1.09–2.81) 2.29 (1.27–4.11) women Ref. 0.80 (0.51–1.26) 1.16 (0.71–1.91) 0.95 (0.53–1.71) 1.45 (0.88–2.39)	FPG, OGTT, HbA_{1c}	age, race/ethnicity, sex, education, BMI, hypertension, smoking status, pack-years, and survey year
(Wang et al. 2020)	US	SWAN study: women aged 42–52 years at enrollment: 1237 at 15th follow-up (1135 non-DM, 102 DM)	Cohort 1995–2016	Median (25th-75th) non-DM: 0.47 (0.23–0.82) DM: 0.50 (0.22–0.85)	risk for twofold cadmium increase	0.96 (0.86–1.07)	HbA_{1c}, DM treatment, history of DM (physician-based)	age, race/ethnicity, study site, and specific gravity, education, household income, body mass index (baseline level), waist circumference (baseline level), smoking status, alcohol consumption, physical activity score, total energy intake, menopausal status, and use of hormone, seafood and rice intake
(Xiao et al. 2021)	China	Wuhan-Zhuhai cohort: 3521 urban adults, 82 DM	Cohort 2011–2012	GM all: 1.13 at baseline	<0.53 0.53–0.84 0.84–1.43 ≥1.43	Ref. 0.97 (0.48–1.94) 1.00 (0.49–2.08) 1.45 (0.74–2.93)	FPG, HbA_{1c}, DM treatment, history of DM (physician-based)	sex, age, BMI, education, smoking status, drinking status, physical activity, and family history of diabetes
(Yang et al. 2017)	China	Jinchang Cohort: 464 (M/F: 236/238) metal-exposed workers aged 20-50 years, 334 (M/F: 155/179) non-DM, 130 (M/F: 81/49) pre-DM)	Cohort 2011–2013	Median (25th-75th) 0.50 (0.34–0.79)	<0.43 0.43–0.68 0.68–1.17 ≥1.17	Ref. 1.12 (0.55–2.27) 1.09 (0.51–2.35) 1.04 (0.46–2.38)	FPG, DM treatment	sex, age, education, occupation, BMI, pack-years, current drinker, family history of diabetes, abnormal lipid, C-reactive protein, hypertension, urinary creatinine level, and arsenic, cobalt, copper, nickel and zinc fitted simultaneously
Hair Cd				μg/g	μg/g			
(Afridi et al. 2008)	Pakistan	434 men from Hyderabad aged 31–60 years: 238 non-DM (115 non-smokers, 123 smokers) and 196 DM (110 non-smokers, 86 smokers)	Cross-sectional	non-smokers: non-DM: 1.42 (0.3) DM: 2.5 (0.26) smokers: non-DM: 1.98	NR	NR	FPG, HbA_{1c}	NR

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Table 1 (*continued*)

Reference	Country	Population characteristics	Study design and period	Overall cadmium levels[a]	Cd levels across categories	DM/preDM risk estimate (95% CI)	Outcome assessment	Adjustment factors
				(0.58) DM: 3.18 (0.83)				
(Hotta et al. 2019)	Japan	96 residents in Hokkaido, Aomori, Miyagi and Iwate Prefectures and the Tokyo Metropolitan area, 54 (M/F: 23/31) nonDM and 42 (M/F: 27/15) DM.	Case-control 2009–2016	non-DM: 0.016 (0.015) DM: 0.019 (0.027)	NR	NR	HbA_{1c}	NR
(Sukumar and Subramanian 1992)	India	Urban residents of New Delhi: 129 (M/F: 29/100) subjects, 100 (M/F: 25/85) non-DM, 19 (M/F: 4/15) DM	Cross-sectional 1987	Mean (SE) men non-DM: 0.8 (0.2) DM: 0.7 (0.3) women non-DM: 0.9 (0.09) DM: 0.8 (0.2)	NR	NR	History of DM	NR
(Sukumar and Subramanian 2007)	India	154 /M/F: 72/82) subjects from urban areas of New Delhi (2 with DM)	Cross-sectional	Mean (SE) men 0.5 (0.1) women 0.5 (0.8)	NR	NR	History of DM	NR
(Tadayon et al. 2013)	Iran	100 women aged 35–70 years from Tehran	Cross-sectional	Levels higher in DM than non-DM (figure only)	NR	NR	NR	NR
Nail Cd				μg/g	μg/g			
(Sukumar and Subramanian 1992)	India	67 (M/F: 30/37) urban residents of New Delhi (M/F: 24/34 non-DM, 6/3 DM)	Cross-sectional 1987	Mean (SE) men non-DM: 1.1 (0.2) DM: 1.0 (0.4) women non-DM: 1.2 (0.2) DM: 0.9 (0.5)	NR	NR	History of DM	NR
(Sukumar and Subramanian 2007)	India	154 (M/F: 72/82) subjects from urban areas of New Delhi (2 with DM)	Cross-sectional	Mean (SE) men 1.0 (0.5) women 1.2 (1.3)	NR	NR	History of DM	NR
(Xun et al. 2013)	US	CARDIA study: prospective cohort of 3,898 American young adults, aged 20–32 years, free of diabetes in 1987 (433 DM)	Cohort 1987–2010	NR	0.003 0.005 0.008 0.015 0.047	Ref. 1.43 (1.02–2.02) 1.37 (0.97–1.94) 1.43 (1.004–2.03) 1.47 (1.01–2.12)	FPG, OGTT, HbA_{1c}	age, sex, ethnicity, study center, education, serum cotinine, alcohol consumption, physical activity, family history of diabetes, BMI, the ratio of low to high density lipoprotein cholesterol, and baseline homeostatic model assessment
Teardrop Cd				μg/L	μg/L			
(Joda and Ward 2021)	Iraq and UK	111 (M/F: 42/69) healthy controls and 44 (M/F: 18/26) DM from Karbala (Iraq) plus 18 (M/F: 12/6) healthy controls from UK aged 3–75 years	Case-control	non-DM Iraq: 1.9 (1.7) non-DM UK: 3.8 (2.7) DM: 2.2 (2.21)	NR	NR	NR	NR
Adipose tissue Cd				ng/g	ng/g			

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Table 1 (*continued*)

Reference	Country	Population characteristics	Study design and period	Overall cadmium levels[a]	Cd levels across categories	DM/preDM risk estimate (95% CI)	Outcome assessment	Adjustment factors
(Salcedo-Bellido et al. 2021)	Span	GraMO cohort with 214 participants mean age 52 years (175 non-DM and 39 DM)	Cohort 2003–2019	non-DM DM	≤5 5.1–8 8.1–15 >15	1.19 (0.74, 1.89) 1.00 1.13 (NR) 1.23 (NR) 1.97 (NR)	History of DM (registry based), DM treatment	age, BMI, smoking habit, educational level, self-perceived exposure to paints, and meat consumption

Footnotes: [a]Values are mean and standard deviation if not differently reported. Abbreviations: BMI: body mass index; CI: confidence interval; DM: diabetic subjects; F: females; FPG: fasting plasma glucose; GM_geometric mean; HbA1c: glycosylated hemoglobin; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; IQR: interquartile range; M: males; NGT: normal glucose tolerance; non-DM: non diabetic subjects; NR: not reported; OGTT: oral glucose tolerance test; pre-DM: prediabetic subjects; SD: standard deviation.

excluding studies that did not adjust for smoking, results were largely unchanged for both diabetes and prediabetes in both the highest versus lowest exposure category comparison (Supplemental Figures S14-S15) and in the dose-response meta-analysis (Supplemental Figures S16-S17). Exclusion of studies at high risk of bias (all assessing diabetes) showed almost identical results (Supplemental Figures S18-S19). Analyses stratified by whole blood and plasma showed stronger RRs for the latter, though based on only one study (Supplemental Figure S20), while the analysis restricted to whole blood showed substantial similar results to the overall analysis, in both the forest plot and in the dose-response meta-analysis (Supplemental Figures S20-S21).

Study-specific lines in dose-response relations, in addition to the overall dose-response meta-analyses, demonstrated substantial homogeneity (Supplemental Figures S22-S23), with partial exceptions for estimates from studies using blood (N = 2) and urinary (N = 1) cadmium concentrations, respectively (Supplemental Figure S22). Comparisons of spline and linear regression analyses of the relation between cadmium and diabetes showed slightly different patterns for blood exposure, with a RR of 1.29 (95% CI 0.95–1.74) for every 1 μg/L increase in blood concentrations for all studies, none at high risk of bias (Supplemental Figure S24). Conversely, a similar trend was noted for urinary cadmium, with RRs of 1.10 (95% CI 0.99–1.21) for every 1 μg/g creatinine increase of urinary levels considering all studies (Supplemental Figure S24) and 1.14 (95% CI 1.04–1.25) after exclusion of studies at high risk of bias (Supplemental Figure S25). For prediabetes, the linear trend showed a monotonic increase with no indication of the plateau suggested by dose-response analysis, with a RR of 1.15 (95% CI 1.04–1.27) for every 1 μg/g creatinine increase in urinary cadmium concentrations for all studies, none at high risk of bias (Supplemental Figure S26).

The meta-regression analysis showed little association between blood cadmium concentrations and diabetes risk, but a positive though very imprecise association was observed with increasing urinary cadmium concentrations (Supplemental Figure S27). Similarly, though based on a limited number of studies, we found no appreciable association between blood cadmium concentrations and risk of prediabetes, while we found a positive relation with urinary cadmium concentrations (Supplemental Figure S28).

3.4.4. *Small-study bias assessment*

Funnel plots based on the different exposure assessment methods indicated moderate small-study effects for studies investigating diabetes using urinary cadmium (Supplemental Figure S29), but almost negligible effects for diabetes and blood cadmium (Supplemental Figure S29) and prediabetes (Supplemental Figure S30). After exclusion of the studies at high risk of bias in diabetes analysis, the magnitude of Egger's test decreased, though still suggesting some possible small-study effect for urinary cadmium (Supplemental Figure S31). Trim-and-fill analyses showed identical results for blood cadmium and diabetes, while results were weaker for urinary cadmium with the addition of two inputted studies (RR 1.15, 95% CI 0.95–1.41). Conversely, trim-and-fill analysis for either blood or urinary cadmium with prediabetes showed no difference with the original estimates.

3.5. *Certainty of the evidence*

There were no major issues due to inconsistency, indirectness, or imprecision for either outcome in the GRADE assessment (Table 3). Risk of bias was of concern in analyses of all studies for diabetes risk due to increased urinary cadmium levels, since two studies have been rated at high risk of bias. In all scenarios, we upgraded the evidence due to presence of dose-response gradient. Overall, when all studies were considered, there was moderate-certainty of the evidence for increased risk of type 2 diabetes due to increase of blood cadmium levels, but low-certainty for increasing urinary cadmium concentrations. For prediabetes, there was moderate-certainty due to increasing urinary cadmium concentrations. After excluding studies at high risk of bias, we found moderate-certainty for both outcomes.

Table 2
Risk of bias assessment using Risk of Bias for in Non-randomized Studies of Exposures (ROBINS-E) tool.

Studies	Type of exposure assessment	Bias due to confounding	Bias in selecting participants in the study	Bias in exposure classification	Bias in departure from intended exposure	Bias due to missing data	Bias in outcome measurement	Bias in selection of reported results	Study-level RoB Judgment
(Adams et al. 2016)	U	NA	Low	Low	Moderate	Low	High	Low	High
(Afridi et al. 2008)	B, U, H,	NA	Low	Low	Moderate	Low	Low	Moderate	Low
(Akinloye et al. 2010)	B	NA	Low	Low	Moderate	Low	Low	Moderate	Low
(Anetor et al. 2016)	B	NA	Low	Low	Moderate	Low	Low	Moderate	Moderate
(Barregard et al. 2013)	B, U	Low	Low	Low	Low	Low	Low	Low	Low
(Borne et al. 2014)	B	Low	Low	Low	Low	Low	Low	Low	Low
(Ettinger et al. 2014)	B	Low	Low	Low	Low	Low	Low	Low	Low
(Feng et al. 2015)	U	Low	Low	Low	Low	Moderate	Low	Low	Moderate
(Flores et al. 2011)	B, U	NA	Low	Low	Moderate	Low	Low	Moderate	Moderate
(Hansen et al. 2017)	B	Low	Low	Low	Moderate	Low	Low	Low	Moderate
(Haswell-Elkins et al. 2007)	U	High	Low	Low	Low	Low	Low	Low	High
(Hotta et al. 2019)	H	NA	Low	Low	Moderate	Low	Low	Moderate	Moderate
(Ji et al. 2021)	B	Low	Moderate	Low	Moderate	Low	Low	Low	Moderate
(Jiang et al. 2018)	U	Low	Low	Low	Moderate	Moderate	Low	Low	Moderate
(Joda and Ward 2021)	T	NA	Moderate	Low	Moderate	Low	High	Moderate	High
(Lei et al. 2019)	U	High	Low	Low	Moderate	Low	High	Moderate	High
(Li et al. 2017)	B	Low	Low	Low	Low	Moderate	Low	Moderate	Moderate
(Little et al. 2020)	B	Low	Moderate	Low	Moderate	Low	Low	Moderate	Moderate
(Liu et al. 2016)	U	Low	Moderate	Low	Low	Low	Low	Moderate	Moderate
(Menke et al. 2016)	U	Low	Low	Low	Low	Low	Low	Low	Low
(Moon 2013)	B	Low	Low	Low	Low	Low	Low	Low	Low
(Moon et al. 2022)	U	Moderate	Low	Low	Low	Low	High	Low	High
(Nie et al. 2016)	B	Low	Low	Low	Low	Moderate	Low	Low	Moderate
(Saba et al. 2020)	U	High	Low	Moderate	Low	Low	Low	Moderate	High
(Salcedo-Bellido et al. 2021)	AT	Low	Low	Low	Low	Low	Low	Low	Low
(Schwartz et al. 2003)	U	Moderate	Low	Low	Low	Low	Low	Low	Moderate
(Serdar et al. 2009)	B	NA	Low	Low	Moderate	Low	Low	Moderate	Moderate
(Simić et al. 2017)	B	Low	Low	Low	Moderate	Low	Low	Low	Moderate
(Skalnaya et al. 2017)	B	NA	Low	Low	Moderate	Low	Low	Moderate	Moderate
(Son et al. 2015)	U	Low	Moderate	Low	Low	Low	Low	Low	Moderate
(Sukumar and Subramanian 1992)	H, N	NA	Low	Low	Moderate	Low	High	Moderate	High
(Sukumar and Subramanian 2007)	H, N	NA	Low	Low	Moderate	Low	Low	Moderate	Moderate
(Swaddiwudhipong et al. 2010)	U	High	Low	Low	Low	Low	Low	Moderate	High
(Tadayon et al. 2013)	H	NA	Low	Low	Moderate	Low	High	Moderate	High
(Tangvarasittichai et al. 2015)	U	Low	Moderate	Low	Moderate	Low	Low	Moderate	Moderate
(Velmurugan et al. 2018)	U	Low	Low	Low	Low	Low	Low	Low	Low
(Wallia et al. 2014)	U	Low	Low	Low	Low	Low	Low	Low	Low
(Wang et al. 2020)	U	Low	Low	Low	Moderate	Moderate	Low	Low	Moderate
(Xiao et al. 2021)	U	Low	Low	Low	Low	Low	Low	Low	Low
(Xun et al. 2013)	N	Low	Low	Low	Low	Low	Low	Low	Low
(Yang et al. 2017)	U	Low	Moderate	Low	Low	Low	Low	Low	Moderate
(Zhu and Hua 2020)	B	NA	Moderate	Low	Low	Low	Low	Moderate	Moderate

AT: adipose tissue; B: blood; H: hair; N: nails; T: tears; U: urine. NA: not assessed, no risk estimates reported in the study.

4. Discussion

Overall, we found consistent epidemiological evidence that higher cadmium exposure was associated with increased risks of both diabetes and prediabetes. However, the positive associations were found mainly in cross-sectional and case-control studies; cohort studies indicated weaker evidence for an association. In the dose-response meta-analysis, we found evidence of a positive association for the highest cadmium blood concentrations (above 2 μg/L) and monotonic linear increase in risk in studies that measured urinary cadmium concentrations.

Possible explanations for the different patterns of association between blood and urinary cadmium concentrations with respect to risk of diabetes might be due to the properties of each biomarker, with urinary cadmium generally reflecting longer-term accumulation, while blood levels tend to reflect more recent exposure (Järup and Åkesson 2009). Additionally, for blood cadmium concentrations, we considered studies

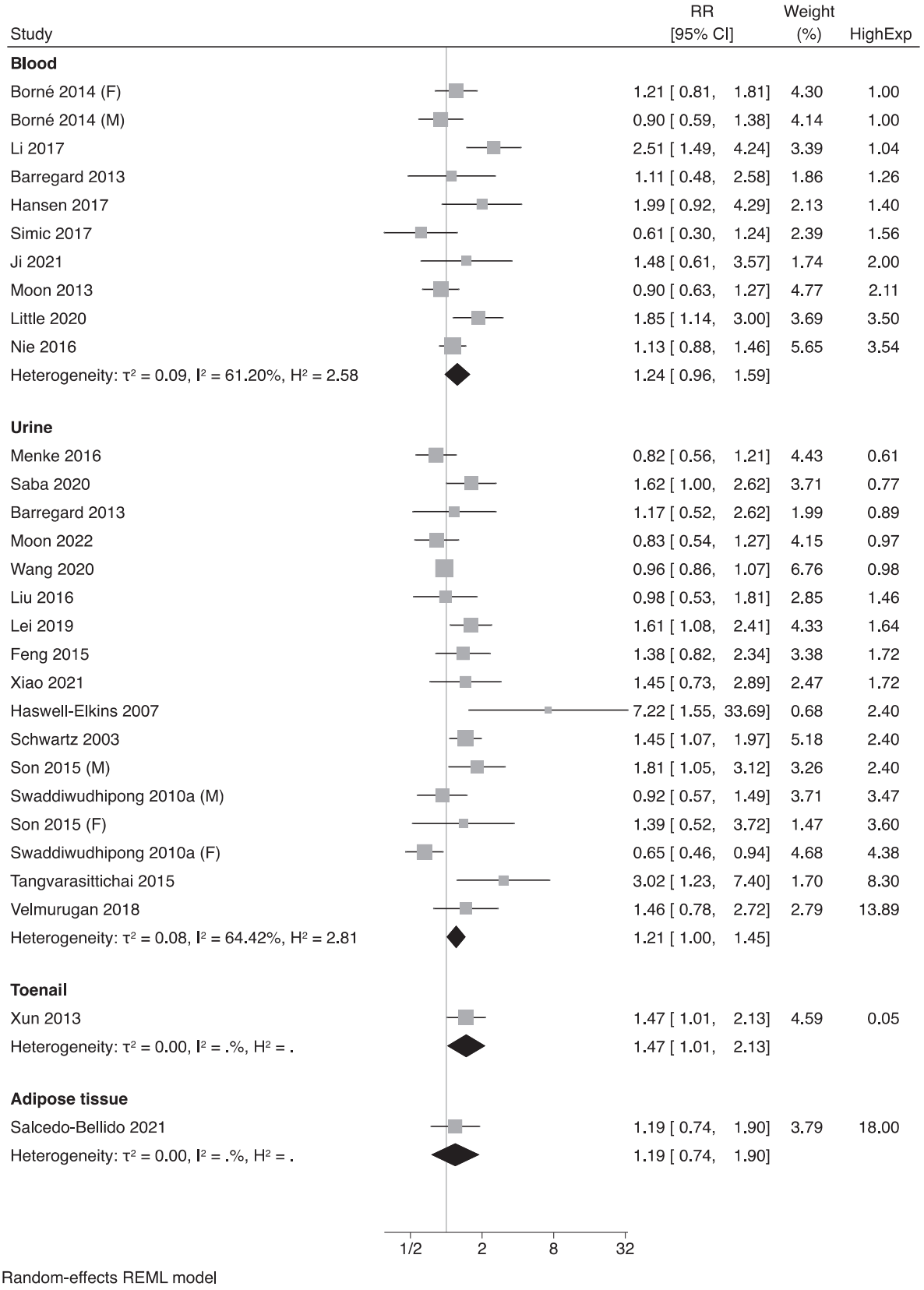

Fig. 2. Forest plot for diabetes risk by type of exposure assessment. RR: risk ratio; CI: confidence interval; HighExp: cadmium concentrations in the highest category. Values in μg/L, μg/g creatinine, and μg/g for blood, urinary and toenail cadmium concentrations, respectively.

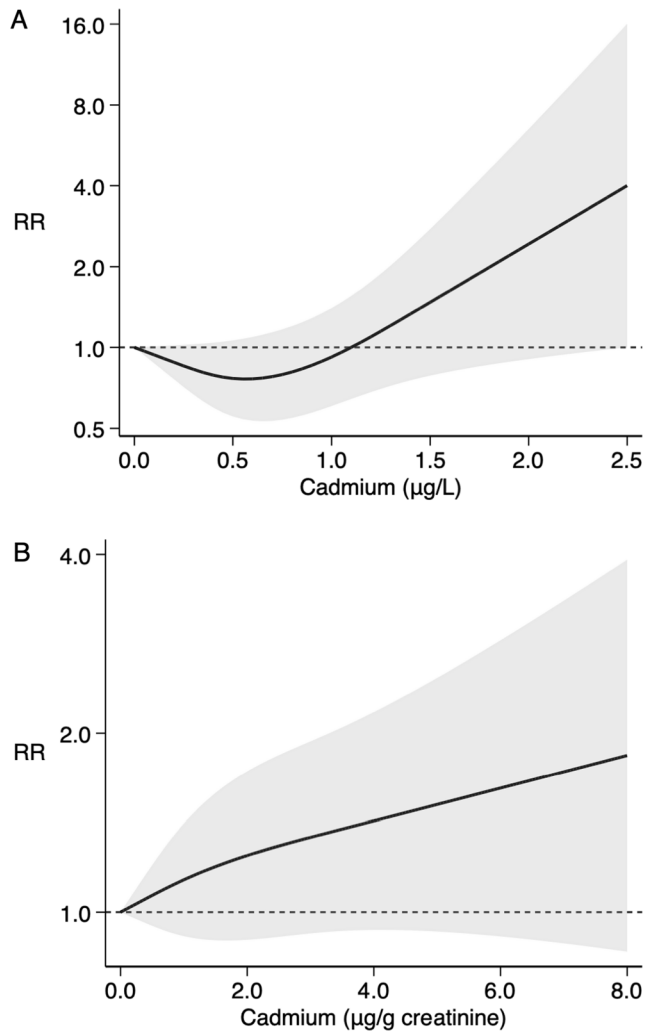

Fig. 3. Dose-response meta-analysis between cadmium exposure and diabetes using blood (A) (Barregard et al. 2013; Borne et al. 2014; Hansen et al. 2017; Li et al. 2017; Moon 2013; Nie et al. 2016; Simić et al. 2017) or urinary concentrations (B) (Barregard et al. 2013; Feng et al. 2015; Haswell-Elkins et al. 2007; Liu et al. 2016; Menke et al. 2016; Moon et al. 2022; Saba et al. 2020; Schwartz et al. 2003; Son et al. 2015; Swaddiwudhipong et al. 2010; Tangvarasittichai et al. 2015; Velmurugan et al. 2018). Spline curve (solid line) with 95% confidence limits (grey area). RR: risk ratio.

assessing exposure through either whole blood or plasma levels. Despite some heterogeneity of these two methodologies, we found comparable results across both exposure matrices.

Studies comparing blood and urinary concentrations report that they are generally positively-correlated (Adams and Newcomb 2014; Akerstrom et al. 2013; Julin et al. 2011; Shimbo et al. 2000). However, blood levels may only partially explain the variation in urinary concentrations (Adams and Newcomb 2014), especially among non-occupational and low-exposed individuals, in whom there was a weaker to null correlation (Olsson et al. 2002; Shimbo et al. 2000). Conversely, at higher cadmium exposure, above 1.3–1.8 µg/L of blood levels, corresponding to approximately to 2.2–2.6 µg/g creatinine (Higashikawa et al. 2000), the correlation is generally stronger. This may due to accumulation of cadmium in the kidney, accounting for approximately half of the total cadmium body burden. After absorption from gastrointestinal tract to the bloodstream, cadmium binds plasma proteins like albumin and transferrin, it is transported to the liver where it is bound to metallothionein (Li et al. 2020). The cadmium-metallothionein complex is filtered in the renal glomerulus, is reabsorbed by tubular cells, and accumulates in the kidney cortex with a biological half-life of 10–30 years (Järup and Åkesson 2009; Nawrot et al. 2010). Therefore, for chronic diseases with long latency periods, use of blood concentrations for exposure assessment would likely attenuate the risk estimates (Adams and Newcomb 2014), while urinary cadmium concentrations are considered a more reliable biomarker of exposure (Åkesson et al. 2014; Satarug et al. 2017a), characterized by temporal stability and high correlation with total body burden (Akerstrom et al. 2013; Meliker et al. 2019).

Our study assessed for the first time evidence of a dose-response relation between urinary cadmium concentrations and prediabetes status. This finding is not entirely unexpected since most previous studies suggest a dose-response association (Jiang et al. 2018; Nie et al. 2016; Velmurugan et al. 2018; Wallia et al. 2014). However, we demonstrated that risk appears to increase in a linear manner up to approximately 2 µg/g creatinine, while further elevation of cadmium concentrations was associated with little increase in risk.

There is a biological plausibility for exposure to environmental factors like cadmium and the pathogenesis of type 2 diabetes. Cadmium may exert a toxic effect through damage of pancreatic beta cells, causing islet dysfunction and impaired insulin release (Edwards and Ackerman 2016; Fitzgerald et al. 2020). Although most cadmium is found in the kidney, chronic exposure is associated with cadmium accumulation in the pancreas, and specifically in beta islets. Damage to the pancreas may be responsible for an increase of blood glucose along with a decrease in insulin levels (Kurata et al. 2003; Tinkov et al. 2017). Several underlying mechanisms have been proposed, including impairment of energy metabolism and antioxidant system, inflammation, and mitochondrial damage of pancreatic beta cells (Buha et al. 2020; Edwards and Ackerman 2016). Some studies also suggest that cadmium may stimulate gluconeogenesis though increased activity of the gluconeogenic enzymes, and may decrease insulin sensitivity by altering expression of glucose transporter leading to decrease uptake of glucose (Edwards and Ackerman 2016).

The dose-response modeling of cadmium exposure allowed us to investigate the dose-response relation with diabetes and prediabetes. A similar dose-response assessment was performed in a previous study, but it was based on urinary concentrations only and on a smaller number of reports (Guo et al. 2019). Conversely, our analysis took advantage of availability of additional data and, to our knowledge, was the first to investigate the shape of the association with prediabetes status. Persistence of a positive association after exclusion of studies at high risk of bias lends credibility to our findings.

Due to limited data (i.e., only three published studies), we could not assess the dose-response relation between blood levels and prediabetes risk. Also, the limited number of studies reporting sex-stratified results hampered the investigation of possible interaction between sex and the diabetogenic effects of cadmium. Another limitation was the different control variables included in the multivariate models, though most studies appropriately accounted for cigarette smoking, which represents a relevant source of cadmium exposure. Cigarette smoking may also increase risk of diabetes via inflammation, oxidative stress and free radical levels, and possibly direct injury of beta cells (Śliwińska-Mossoń and Milnerowicz 2017). However, contrasting findings have been reported in the only studies of cadmium and diabetes risk that carried out analyses stratified by smoking status. In particular, cadmium exposure was associated with higher diabetes risk among never and former smokers in some studies (Borne et al. 2014; Xiao et al. 2021), and current smokers in another study (Nie et al. 2016). Also, no difference by smoking history has been reported (Wang et al. 2020). Nonetheless, a recent paper investigating the relation between blood cadmium concentrations and glycated haemoglobin levels showed a positive association, especially among never smokers, thus supporting the hypothesis of an independent relation of cadmium with diabetes, independent of tobacco use (Trouiller-Gerfaux et al. 2019). Conversely for prediabetes, a higher risk among smokers as compared with non-smokers has been reported (Wallia et al. 2014). Nonetheless, almost all studies included

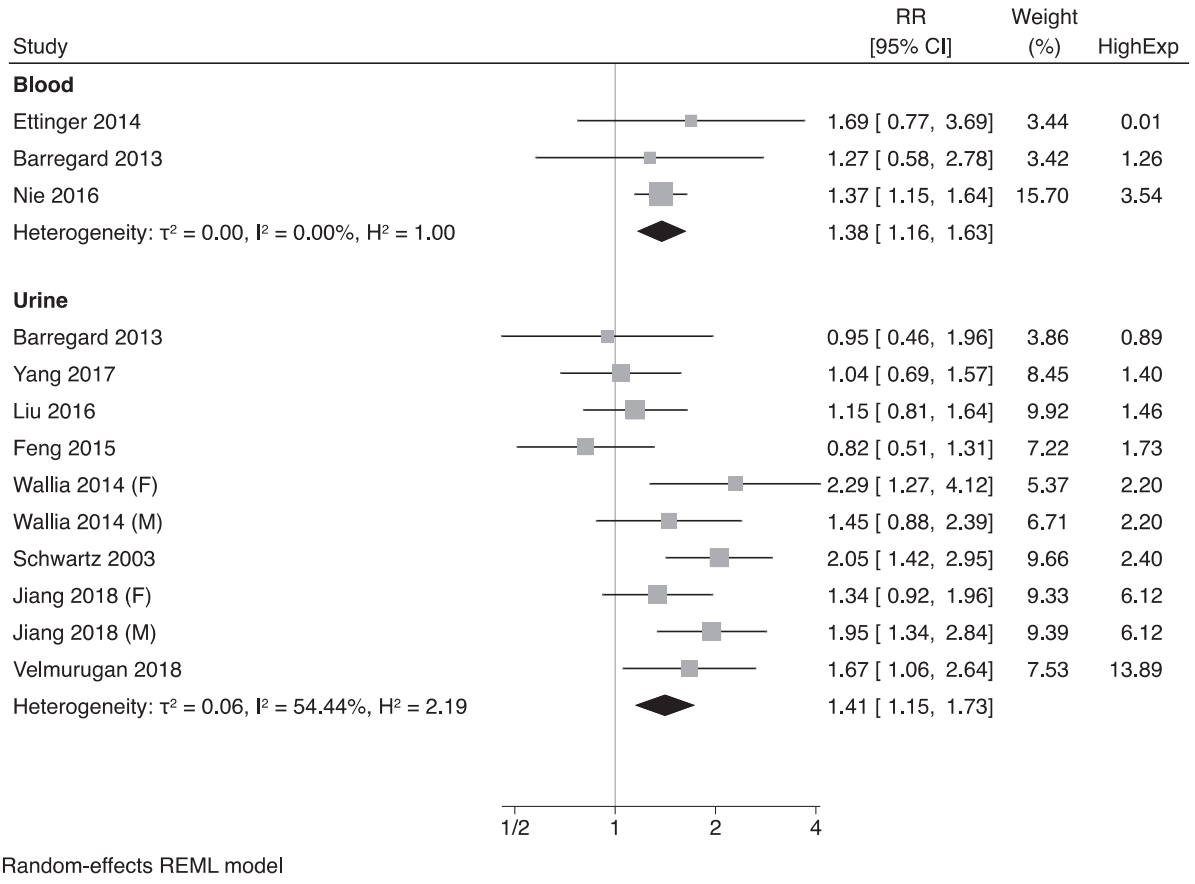

Fig. 4. Forest plot for prediabetes risk by type of exposure assessment. RR: risk ratio; CI: confidence interval; HighExp: cadmium concentrations in the highest category. Values in μg/L and μg/g creatinine for blood and urinary cadmium concentrations, respectively.

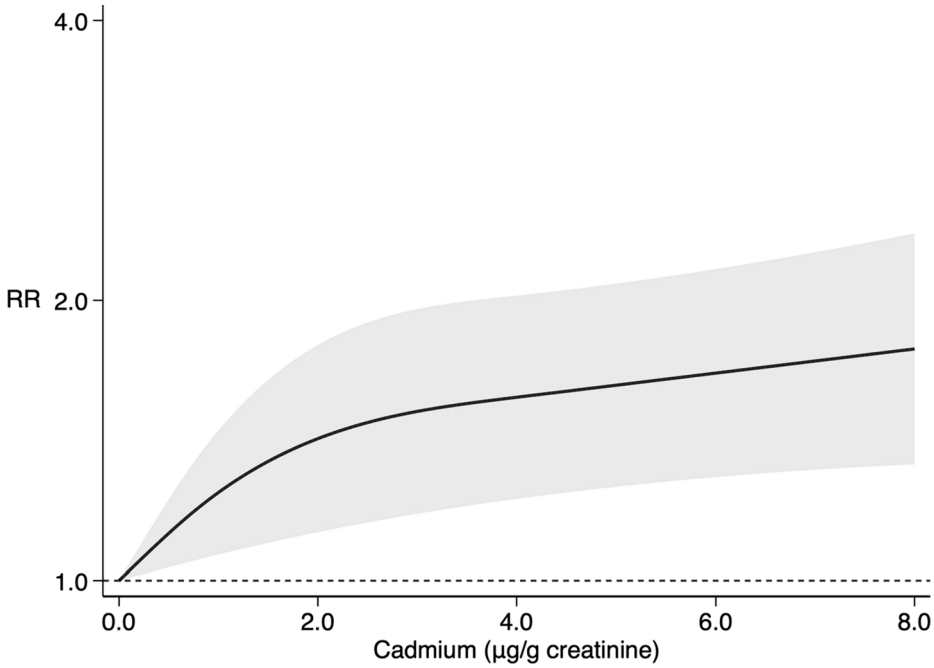

Fig. 5. Dose-response meta-analysis between cadmium exposure and pre-diabetes using urinary concentrations (Barregard et al. 2013; Feng et al. 2015; Jiang et al. 2018; Liu et al. 2016; Schwartz et al. 2003; Velmurugan et al. 2018; Wallia et al. 2014; Yang et al. 2017). Spline curve (solid line) with 95% confidence limits (grey area). RR: risk ratio.

Table 3
Summary of findings table. Research question: "In adult population, what is the incremental effect of cadmium exposure on risk of type 2 diabetes or prediabetes from epidemiological nonexperimental studies?". Assessment in all subjects, divided by exposure assessment methods: blood cadmium (BCd) and urinary excretion (uCd), and by outcome: type 2 diabetes (DM) and prediabetes (pre-DM) excluding studies at high risk of bias.

Certainty assessment							Summary of findings				Certainty	Importance
Exposure	Outcome (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of participants		Effect			
							With event	Total	Relative (95% CI)	Absolute (95% CI)		
All studies												
BCd	Diabetes (7 studies)	Not serious	Not serious	Not serious	Not serious	Dose-response gradient	2255	13,690	**RR 1.29** (0.95 to 1.74)	**48 more per 1000** (from 8 fewer to 122 more)	⊕⊕⊕⊖ MODERATE	CRITICAL[b]
UCd	Diabetes (12 studies)	Serious[a]	Not serious	Not serious	Not serious	Dose-response gradient	4164	36,359	**RR 1.10** (0.99 to 1.21)	**11 more per 1.000** (from 1 fewer to 24 more)	⊕⊕⊖⊖ LOW	CRITICAL[b]
UCd	prediabetes (8 studies)	Not serious	Not serious	Not serious	Not serious	Dose-response gradient	5060	11,535	**RR 1.15** (1.04 to 1.27)	**66more per 1000** (from 18 more to 118 more)	⊕⊕⊕⊖ MODERATE	CRITICAL[b]
Excluding studies at high risk of bias												
BCd	Diabetes (7 studies)	Not serious	Not serious	Not serious	Not serious	Dose-response gradient	2255	13,690	**RR 1.29** (0.95 to 1.74)	**48 more per 1000** (from 8 fewer to 122 more)	⊕⊕⊕⊖ MODERATE	CRITICAL[b]
UCd	Diabetes (9 studies)	Not serious	Not serious	Not serious	Not serious	Dose-response gradient	3789	27,175	**RR 1.14** (1.04 to 1.25)	**20 more per 1000** (from 6 more to 35 more)	⊕⊕⊕⊖ MODERATE	CRITICAL[b]
UCd	prediabetes (8 studies)	Not serious	Not serious	Not serious	Not serious	Dose-response gradient	5060	11,535	**RR 1.15** (1.04 to 1.27)	**66 more per 1000** (from 18 more to 118 more)	⊕⊕⊕⊖ MODERATE	CRITICAL[b]

[a] Serious since two studies are at high risk of bias;
[b] Critical since type 2 diabetes (and prediabetes as its precondition) is a chronic disease leading to high disability and increased risk of cardiovascular diseases, and prevention strategies may be effective in decrease disease risk as well as improve prognosis.

smoking among adjustment factors, and the exclusion of studies that did not adjust for smoking gave comparable results. Furthermore, this review included all types of observational study designs, namely case-control, cross-sectional, and cohort studies. We performed stratified analyses by study design when comparing highest versus lowest categories of cadmium exposure in both diabetes and prediabetes, but we had insufficient data for the dose-response meta-analysis. Indeed, cohort studies were too limited to perform dose-response meta-analysis stratified by type of exposure matrix, i.e. urinary or blood concentrations. Thus, we urge some caution when interpreting results from the dose-response analysis. In addition, findings differed by study design, as summary estimates from cohort studies yielded smaller RRs for diabetes/prediabetes compared with case-control and cross-sectional studies, thus we cannot entirely rule out reverse causation as an explanation of the positive findings. Moreover, other pollutants that are correlated with cadmium may have confounded our results. In particular, other trace elements and heavy metals that are correlated with cadmium have been suggested to increase type 2 diabetes risk, including arsenic and selenium (Kuo et al. 2017; Roy et al. 2017; Vinceti et al. 2018; Vinceti et al. 2021), and other endocrine-disrupting chemicals like phthalates and polychlorinated biphenyls (Sargis and Simmons 2019). Finally, we cannot entirely rule out publication bias, especially for studies using urinary cadmium concentrations and diabetes due to the magnitude of Egger's test. However, estimates from trim-and-fill analysis showed identical or comparable estimates, although in some cases, they were less precise.

5. Conclusions

Overall, our review and meta-analysis found a positive association between cadmium exposure and risk of both type 2 diabetes and prediabetes with a dose-response relation and moderate-certainty evidence. Diabetes risk increased linearly in studies using urinary cadmium concentrations, while disease risk increased only at the highest exposure levels when assessed using blood concentrations. The analysis for prediabetes also showed a linear increase in risk from low exposure, with a flattening effect at higher urinary cadmium concentrations. Although our results are limited by the inability to perform stratified analysis in specific subgroups, such as non-smokers, or restricted to prospective cohort studies, these findings add to the available evidence on potential adverse health effects of environmental exposure to cadmium. Future research focusing on the assessment of the health effects of cadmium among non-smokers, especially at low levels of exposure, and using prospective cohort study designs would be worthwhile.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Lauren Wise receives in-kind donations for primary data collection in Pregnancy Study Online (PRESTO) from Sandstone Diagnostics, Swiss Precision Diagnostics, Kindara.com, and FertilityFriend.com. She also serves as a fibroid consultant for AbbVie, Inc. All of these relationships are for work unrelated to this manuscript. All other authors have nothing to disclosure.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106920.

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