Cadmium Exposure and Risk of Any Fracture
A PRISMA-Compliant Systematic Review and Meta-Analysis

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Abstract: Several observational studies have investigated the relation between cadmium exposure and risk of any fracture. However, the results from epidemiological studies for the association are inconsistent.

We conducted a meta-analysis to evaluate the relationship between cadmium exposure and risk of any fracture. The pertinent studies were identified by a search of PubMed and Embase databases from 1966 to June 2015.

Seven articles involving 21,941 fracture cases and 504,346 participants were included. The meta-analysis showed that the pooled relative risk of any fracture for the highest versus lowest category of cadmium concentration was 1.30 (95% confidence interval = 1.13–1.49). In subgroup analyses, the significant association remained consistent when stratified by study type, geographical region, method of cadmium exposure assessment, and gender.

Our meta-analysis showed that a high cadmium exposure may be a risk factor for any fracture. However, this result should be interpreted cautiously because of the heterogeneity among studies and existence of publication bias. Additional large, high-quality prospective studies are needed to evaluate the association between cadmium exposure and the risk of development of fracture.

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Abbreviations: BMD = bone mineral density, Cd = cadmium, CI = confidence interval, D-Cd = dietary Cd, Ery-Cd = erythrocyte Cd, HR = hazard ratio, NOS = Newcastle–Ottawa scale, OR = odds ratio, RR = relative risk, U-Cd = urinary Cd.

INTRODUCTION

Cadmium (Cd) is a persistent heavy metal with high toxicity and an elimination half-life of 10 to 30 years. Cd may have a wide range of negative effects on human health.[1] In general

nonsmoking population, major sources of Cd exposure are smoking and diet because tobacco, grains, potatoes, and vegetables take up Cd from soil.[2] In a public health context, the negative effect of Cd on bone in the general population is of great concern following the outbreak of Itai-itai disease in Japan more than 50 years ago.[3] Recently, numerous observational studies were conducted to evaluate the effects of Cd exposure on any fracture risk. However, the results of those studies are inconsistent, with majority of the studies reporting positive effects,[4–8] whereas other studies found mixed results.[9–11] In addition, these studies have a modest sample size, and the magnitude of the association is variable among these studies, with relative risk (RR) varying from 0.99 (95% confidence interval [CI]: 0.93–1.05) to 4.10 (95% CI = 1.55–6.61), and thus the magnitude is limited by the low precision in risk estimates. These epidemiological studies lack comprehensive assessment of Cd exposure. Given the popularity of Cd exposure and poor prognosis of fracture, any risk factors for the development of fracture would have a substantial impact on public health. Therefore, we systematically performed a meta-analysis by combining all available data of observational studies to evaluate the association between Cd exposure and risk of fracture.

MATERIALS AND METHODS

The study was reported following the Preferred Reporting Items for Systematic Reviews.[12] No ethical issues were involved in our study given that our data were based on published studies.

Literature Search

We identified studies examining the relation between Cd exposure and any fracture risk by systematically searching the database of PubMed and Embase for papers published from 1966 to June 20, 2015. The predefined keywords were used without any limitation: ''fracture(s)'' combined with ''cadmium.'' Furthermore, we reviewed the reference lists from retrieved articles for additional relevant studies.

Eligibility Criteria and Study Selection

Studies were considered acceptable for inclusion in the meta-analysis if they met the following criteria: study design was either cohort, case–control, or cross-sectional; the exposure was Cd exposure; the outcome was fracture risk; and hazard ratio (HR) or RR and odds ratio (OR), with corresponding 95% CI (or data to calculate these) were reported. Studies were excluded if they met the following criteria: they are editorial letters, historical reviews, and descriptive studies, such as case reports and case series, or laboratory studies; they did not contain enough data for calculating RR; and when multiple publications covered the same study population, only the study

with the larger sample was included. Two authors (JKS and YXH) independently evaluated the eligibility of all retrieved studies and disagreements were resolved through discussion or consultation with a third author (HGL).

Data Extraction

Two authors (JKS and YXH) independently extracted data from the selected studies. The following data were extracted: first author, publication year, study design, country, sex, total number of cases and subjects, assessment methods for Cd exposure, and adjusted variables. The adjusted RR was extracted in preference to the nonadjusted RR; however, the unadjusted RR and CI were calculated when the RR was not provided. When more than 1 adjusted RR was reported, the ratio with the most number of adjusted variables was selected. Any disagreements were resolved through discussion and consensus.

Quality Evaluation

We evaluated the methodological quality of included studies using the Newcastle–Ottawa scale (NOS).[13] The check list contains 9 items for case–control studies and cohort studies with every item accounts for 1 point. We allocated high-quality studies with a score >5.

Statistical Analysis

We used the RR with 95% CI as a common measure across all eligible studies. The differences among risk estimates (HR, RR, and OR) were ignored and the OR and HR were directly converted to RR because fracture is a relatively rare event. A random-effects model of the DerSimonian and Laird method, which is appropriate when the heterogeneity cannot readily be explained, was used to calculate summary RR comparing the highest versus lowest level of Cd across all included studies regardless of heterogeneity.[14] If sex-specific estimates were available, then they were also regarded as 2 different studies.[7–9]

Given that patient characteristics, study design, and other confounding factors were inconsistent among studies, sensitivity analysis was performed to evaluate robustness and stability by sequentially omitting 1 study on each turn. Moreover, subgroup analyses were subsequently carried out by study type, geographical region, method of Cd exposure assessment, gender, and fracture site. We evaluated the potential publication bias using a funnel plot and Egger tests, with $P < 0.1$ indicating significant publication.[15] All statistical analyses were carried out using Stata version 13.1 (Stata Corp., College Station, TX).

RESULTS

Literature Search

A diagram showing the details of study inclusion is shown in Figure 1. The search strategy yielded 187 citations, of which 60 studies were excluded because they were duplicate publications; 127 studies were initially screened and 111 studies were excluded based on their titles and abstracts. We reviewed the 16 possible relevant articles in full-text. Three articles reporting relation between Cd exposure and bone mineral density (BMD) were excluded,[16–18] 3 articles were also excluded because the outcome was unrelated to fracture,[19–21] and 2 articles were excluded because they covered the same population.[22,23] Two articles covered the same population, but the articles employed different biomarkers to evaluate the level of Cd exposure.[4,5] Finally, 8 articles[4–11] were considered eligible in the meta-analysis.
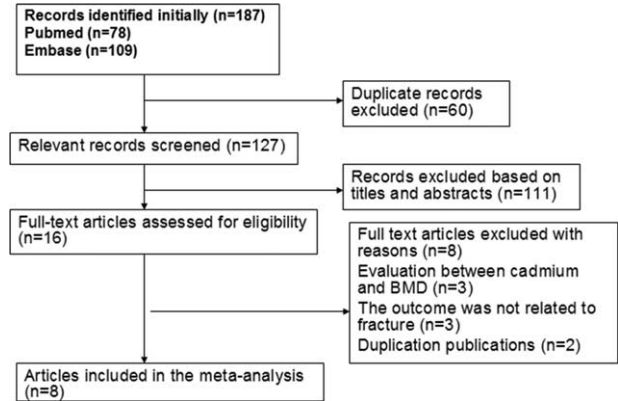

FIGURE 1. Flow diagram of systematic literature search.

Study Characteristics and Quality Assessment

Individual characteristics of the included 8 articles (6 cohort studies and 2 case–control articles) were summarized in Table 1. They were published from 1999 to 2014. Of the 8 articles, 7 studies were from the Europe,[4–6,8–11] and 1 study was from China.[7] Three articles were designed to evaluate the association between Cd exposure and hip fracture risk,[6,8,11] and 4 articles evaluated the relation between Cd exposure and any fracture risk,[5–7,9] 2 articles evaluated the association between Cd exposure and forearm fracture.[4,10] Four articles used urinary Cd (U-Cd) as biomarkers for long-term exposures to Cd,[4,7,9,10] whereas 2 articles evaluated the Cd exposure levels by estimating the dietary Cd (D-Cd) using food frequency questionnaire[5,6]; 1 article examined the Cd exposure levels in drinking water,[8] and 1 article investigated the Cd exposure levels in the erythrocytes (Ery-Cd).[11] One article combined the assessment of dietary and U-Cd in relation to any fracture.[5] Two studies were designed to evaluate the relationship between D-Cd exposure and fracture risk among nonsmoker populations.[4,6] Six articles adjusted for a group of conventional risk factors for fracture,[4–6,8–11] whereas 1 article did not control for other confounding factors,[7] only 3 articles adjusted for smoking status.[5,9,10] As shown in the Table 2, the quality scores ranged from 4 to 6, with mean of 5.

Quantitative Synthesis

A total of 10 studies from 7 articles[5–11] with 22,336 cases and 507,034 participants were included, because 3 results (for male and female) were reported in 3 publications.[7–9] The overall summary RR for fracture was 1.30 times (RR = 1.30; 95% CI = 1.13–1.49) for the highest category of Cd exposure compared with the lowest category, with significant heterogeneity (P of heterogeneity = 0.000, $I^2 = 80.8\%$; Figure 2; Table 3).

Sensitivity Analysis and Subgroup Analyses

To test the robustness and stability of the relation, we performed sensitivity analyses to omit 1 study at a time and to compute the combined RR for the remaining studies. The combined RR for fracture ranged from 1.22 (95% CI = 1.08–1.38) to 1.40 (95% CI = 1.16–1.68) in the sensitivity analyses after excluding 1 study at a time. In the sensitivity analysis, similar results were observed, which ranged from 1.22 (95% CI = 1.08–1.38) with low heterogeneity ($I^2 = 76.4\%$, heterogeneity $P = 0.000$) (excluding the study

TABLE 1. Characteristics of Studies Included in the Meta-Analysis

Study	Year	Country	Study Design	No. of Patients	No. of Subjects	Sex	Age, Median (Range), y	Exposure Assessment	Follow-Up	Adjustment for Covariates
Staessen	1999	Belgium	CadmiBel cohort study	44 cases of fracture	22,173	W and M	44.05 (NA)	U-Cd	6.6	Adjusted for age, BMI, calcium, physical activity, socioeconomic status, smoker, drinker, postmenopausal status, and treatment with diuretics
Alfven	2004	Sweden	Swedish OSCAR cohort	94 cases of forearm fracture	1012	W and M	NA (16–81)	U-Cd	NA	Adjusted for gender, weight (kg), calcium intake (g/d), smoker (never/current/former), and occupational exposure
Zhu	2004	China	Case–control study	50 cases of bone fracture	790	W and M	NA	U-Cd	NA	Unadjust
Engstrom	2011	Sweden	Cohort (Swedish Mammography Cohort)	395 first cases of any fracture, 248 cases of first osteoporotic fracture, and 137 cases of first fracture of the distal forearm occurred; 116 women had 2 or more fractures	2688	W	63.3 (60–69)	U-Cd	11.5	Adjusted for age (y), education (≤ 9 and >9 y; yes/no), BMI ($<$ or ≥ 20 kg/m^2), parity (0–6), use of postmenopausal hormones (yes/no), ever use of corticosteroids (yes/no), total physical activity (metabolic equivalent hours (MET) hours per day), smoking status (never/ever), alcohol intake (g ethanol/d), inflammatory joint diseases (yes/no), kidney diseases (yes/no), liver diseases (yes/no), and malabsorption (yes/no)
Thomas	2011	Sweden	A population-based prospective cohort (COSM)	2183 incident cases of any fracture and 374 hip fracture cases	22,173	W and M	59.7 (45–79)	D-Cd	10	Adjusted for attained age, height (tertiles), weight (tertiles), education (primary, secondary, tertiary), civil status (single, married/cohabiting, divorced/widowed), employment status (full-time work, part-time work/student, unemployed, disability pension/retired), alcohol intake (tertiles plus never drinker category), cortisone use (ever/never), walking/cycling (<40 min/d, >40 min/d), exercise (<1 h/wk, >1 h/wk), occupational activity (sitting down >50%, sitting down <50%), pack-years (tertiles plus never smoker category), liver disease (yes/no), kidney disease (yes/no), celiac disease (yes/no), inflammatory joint disease (yes/no), dietary intake of calcium (tertiles) and iron (tertiles), and tertiles of fruit and vegetable intake (g/d)

TABLE 1. (*Continued*)

Study	Year	Country	Study Design	No. of Patients	No. of Subjects	Sex	Age, Median (Range), y	Exposure Assessment	Follow-Up	Adjustment for Covariates
Engstrom	2012	Sweden	Population-based prospective cohort	394 cases of first fracture	2676	W	NA (56–69)	U-Cd D-Cd	NA	Adjusted for age (y), education (≤9 and >9 y; yes/no), BMI (kg/m²), ever use of postmenopausal hormones (yes/no), total physical activity (MET-h/d), smoking status (never/ever), alcohol intake (g ethanol/d), and in flammatory joint diseases (yes/no)
Dahl	2014	Norwegian	A NOREPOS cohort study	19,067 cases of hip fracture	455,226	W and M	64.5 (50–85)	Cd in the drinking water	6	Adjusted for age, region, urbanization, degree, water source, pH, calcium, and magnesium
Sommar	2014	Sweden	A nested case–control study from Northern Sweden Health and Disease Study (NSHDS) cohort	109 cases of hip fracture	296	W and M	60.1 (NA)	Ery-Cd	NA	Adjusted for BMI, height, and smoking status

BMI = body mass index, D-Cd = dietary cadmium, Ery-Cd = cadmium in erythrocytes, M = male, NA = not available, U-Cd = urinary cadmium, W = female.

TABLE 2. Quality Assessment of Eligible Studies Based on Newcastle–Ottawa Scale

Author	Year	Selection	Comparability	Exposure
Staessen	1999	2	1	2
Alfven	2004	2	1	1
Zhu	2004	2	0	2
Engstrom	2010	2	1	2
Thomas	2011	3	1	2
Engstrom	2012	2	1	2
Dahl	2014	3	1	1
Sommar	2014	3	1	2

by Zhu et al[7]) to 1.40 (95% CI = 1.16–1.68) with significant heterogeneity ($I^2 = 82.9\%$, heterogeneity $P = 0.000$) (excluding the study by Dahl et al[8]). Furthermore, subgroup analysis was also performed (Figure 3; Table 3). In subgroup analyses for study design, the summary RR values of any fracture for the highest category of Cd exposure versus lowest category were 2.47 (95% CI = 1.51–4.03) and 1.15 (95% CI = 1.04–1.28) for the 2 case–control studies and 5 cohort studies, respectively. When stratified by method of Cd assessment, we found an increase of any fracture risk in both U-Cd (RR = 1.60, 95% CI = 1.19–2.14) and D-Cd exposure (RR = 1.21, 95% CI = 1.09–1.35). The combined RR for any fracture was 1.16 (95% CI = 1.05–1.28) for studies conducted in Europe and 2.95 (95% CI = 1.87–4.65) for that in Asia. When stratified by fracture site, Cd exposure significantly increased the risk of forearm fracture (RR = 1.19, 95% CI = 1.03–1.37) and any fracture risk (RR = 1.59, 95% CI = 1.19–2.12), but not the risk of hip fracture (RR = 1.08, 95% CI = 0.97–1.20). Compared with the low NOS score (OR = 2.16, 95% CI = 1.03–4.53), the association remained significant among studies with high NOS score (OR = 1.16, 95% CI = 1.03–1.30). When stratified by gender, we found an increase of any fracture risk in both male (OR = 1.26, 95% CI = 1.02–1.55) and female (OR = 1.60, 95% CI = 1.07–2.39). Only 2 studies evaluated the effect of D-Cd exposure and risk of any fracture among nonsmoker populations; the overall RR was 1.30 (95% CI = 1.05–1.61), with low heterogeneity ($I^2 = 17.1\%$, heterogeneity $P = 0.272$). For the
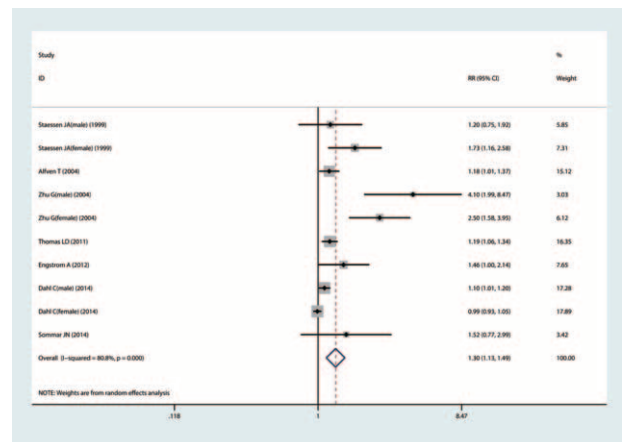

FIGURE 2. Forest plot for the association between cadmium exposure and any fracture risk.

TABLE 3. Results of Overall Subgroup Analysis

	Studies, N	RR (95% CI)	*P* Value	*P* of Heterogeneity	I^2, %
Total	10	1.30 (1.13−1.49)	0.000	0.000	80.8
Geographic location					
European	8	1.16 (1.05−1.28)	0.005	0.004	66.4
Asian	2	2.95 (1.87−4.65)	0.000	0.258	21.9
Fracture sites					
Any fracture	6	1.59 (1.19−2.12)	0.002	0.000	77.7
Hip fracture	4	1.08 (0.97−1.20)	0.187	0.058	59.9
Forearm fracture	2	1.19 (1.03−1.37)	0.020	0.854	0.0
NOS score					
High	7	1.16 (1.03−1.30)	0.013	0.004	68.7
Low	3	2.16 (1.03−4.53)	0.042	0.000	89.5
Study design					
Cohort	7	1.15 (1.04−1.28)	0.003	0.007	69.7
Case−control study	3	2.47 (1.51−4.03)	0.145	0.000	48.3
Exposure type					
U-Cd	6	1.60 (1.19−2.14)	0.002	0.001	77.1
D-Cd	2	1.21 (1.09−1.35)	0.000	0.499	0.0
Gender					
Female	5	1.60 (1.07−2.39)	0.023	0.000	87.5
Male	4	1.26 (1.02−1.55)	0.031	0.004	77.2

CI = confidence interval, High = NOS score of ≥5, Low = NOS score of <5, NOS = Newcastle−Ottawa scale, RR = relative risk.

4 studies adjusted for smoking status, the pooled RR was 1.30 (95% CI = 1.10−1.54), with low heterogeneity ($I^2 = 20.3\%$, heterogeneity $P = 0.288$).

Publication Bias

Some asymmetry was observed in the funnel plot (Figure 4), with *P* values of 0.074 for Begg test and 0.001 for Egger test, suggesting the existence of publication bias.
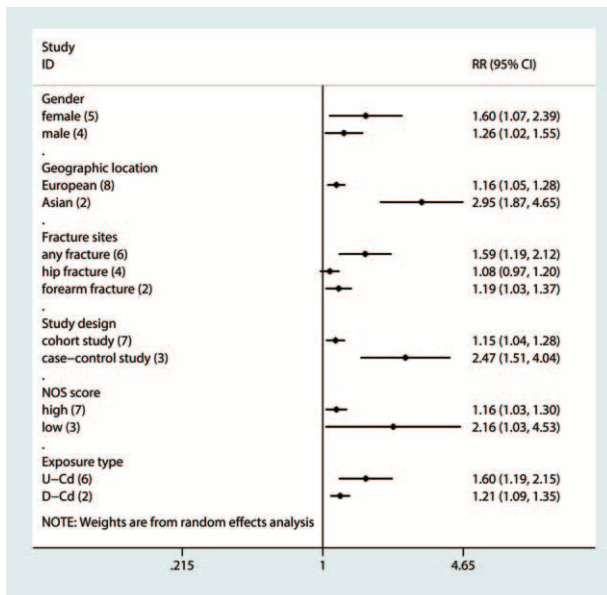

FIGURE 3. Subgroup analyses for the association between cadmium exposure and any fracture risk.

DISCUSSION

To the best of our knowledge, this article presents the first meta-analysis to explore the role of exposure to Cd in patients with any form of fracture. The overall results of the present meta-analysis using a random-effects model provide evidence that a high Cd exposure may be a risk factor for increased risk of any fracture. The pooled estimates were robust according to sensitivity and subgroup analyses.

Cadmium is widely distributed in the environment through industrial and agricultural activities. A prospective cohort of CadmiBel study in Belgium found a higher risk of any fractures in women (RR = 1.73, 95% CI = 1.16−2.57) and a nonsignificant increase in risk of any fractures in men (RR = 1.20, 95% CI = 0.75−1.93) with a doubling of U-Cd.[9] Similarly, a cohort study conducted in Sweden found an 18% (95% CI = 1.01−1.37) increase in risk of forearm fracture per unit increment in U-Cd (nmol Cd/mmol creatinine) in those over 50 years of age, but nonsignificant in those below 50 years old.[10] A significant association between U-Cd exposure and any fracture risk was found among women and men in a case−control study conducted in China[7] and in a population-based prospective cohort.[6] In a same cohort in Sweden, the combination of the 2 biomarkers, U-Cd and D-Cd, showed Cd exposure increased the risk of any fracture in the general population.[4,5] In a Norwegian cohort study, a considerably low level of Cd in drinking water was positively associated with increased risk of any fracture.[8] In another cohort study in Sweden, Sommar et al[11] examined the effect of Cd in erythrocytes on risk of any fracture and found positive association among women, but not among men. In the present meta-analysis, we found a positive association between Cd exposure and risk of any fracture.

Results from subgroup analyses indicated that geographic region, study design, NOS scale, gender, fracture type, and method of Cd assessment are potential sources of heterogeneity. Despite intrinsic limitations of observational study, some results from subgroup analyses remain notable. When stratified by
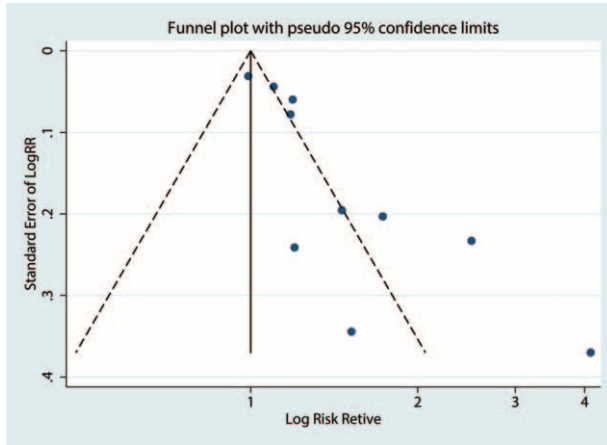
FIGURE 4. Funnel plot of Cd exposure and any fracture risk.

gender, the association remained significant for both male and female. Given that Cd concentrations in urine and whole blood are the most common biomarkers for Cd exposure, U-Cd mainly reflects Cd accumulation in the kidney, which is determined by lifelong exposure, whereas D-Cd and whole-blood Cd demonstrate a combination of both current and historical exposure. Results from subgroup analyses stratified by assessment of Cd exposure showed that both U-Cd and D-Cd were associated with increased risk of any fracture. Smoking is a primary source of exposure in the general population. In addition, smoking is known to cause reduced BMD and may act on bone both directly and indirectly. Thus, we also performed subgroup analyses among nonsmokers to minimize any possible non-Cd-mediated negative effects of tobacco smoking on bone. Cadmium exposure was related to increased risk of any fracture among nonsmoker population (RR = 1.30, 95% CI = 1.05–1.61). Only 3 publications adjusted for smoking status, and the results showed that Cd exposure is associated with increased risk of any fracture (OR = 1.30, 95% CI = 1.10–1.54), with low heterogeneity (I^2 = 20.3%, *P* for heterogeneity = 0.288).

The mechanisms for Cd-induced bone effects remain unclear. Several studies using in vivo animal studies demonstrated that Cd exposure can negatively impact the bone health.[24–27] The negative effects on bone health are considered to be mediated by indirect renal damage and/or a result of a direct effect on the skeleton.[28] Experimental data show a direct effect of Cd on bone with decreased bone formation and increased bone resorption at Cd concentrations related to human exposures.[17,28] Cadmium may interfere with the metabolism of calcium, vitamin D, and collagen, and bone disorders such as osteomalacia or osteoporosis are late manifestations of severe Cd poisoning.[29] Nevertheless, the associations between Cd exposure and kidney tubular damage and osteoporosis support a kidney-mediated indirect effect.[16,30]

The present meta-analysis has several strengths. First, to the best of our best knowledge, no meta-analysis of the relation between Cd exposure and any risk of fracture has been published. Second, the large number of total cases provided high statistical power for quantitative assessment of the association between Cd exposure and risk of any fracture. Third, the meta-analysis used U-Cd and D-Cd as biomarkers of Cd, which indirectly reflected Cd concentrations; both U-Cd and D-Cd exposures were positively associated with increased risk of any

fracture. Fourth, the association of Cd exposure with risk of any fracture remains statistically significant according to sensitivity and subgroup analyses, which indicated that our main findings are robust and Cd exposure may be independent of conventional risk factors of any form of fracture.

Nevertheless, some limitations should be considered in the present meta-analysis. First, observational studies have inherent limitations, such as selective bias and recall or memory bias. Therefore, the findings should be interpreted with caution. Second, the evidence of publication bias was observed; the results could be biased by the publication bias because studies with small sample size and null results may have been rejected for publication. Third, the small number of studies included in the meta-analysis limits the ability to draw a reliable conclusion, especially in the subgroup analyses. Fourth, between-study heterogeneity is common in the meta-analysis, and exploring the potential sources of between-study heterogeneity is essential. Our sensitivity and subgroup analyses indicated the existence of heterogeneity. Fifth, given that the included studies used different methods to assess and categorize Cd exposure, our findings are likely influenced by the misclassification of exposure. Moreover, the potential for misclassification of exposure to Cd may contribute to the heterogeneity among all studies in the summary analysis. Therefore, this result should be considered with caution because of exposure misclassification. In general, the aforementioned limitations may affect our final conclusions.

In summary, the current meta-analysis demonstrates that a high Cd exposure may be a risk factor for any fracture. However, this result should be interpreted cautiously because of the heterogeneity among studies and existence of publication bias. Additional large, high-quality prospective studies are needed to evaluate the association between Cd exposure and the risk of development of fracture.

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