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Cadmium exposure and risk of breast cancer: a dose-response meta-analysis of cohort studies

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Background

Cadmium is a toxic heavy metal that has been implicated in breast cancer etiology, albeit with inconsistent results. The general population is exposed to cadmium through dietary intake, cigarette smoking, emissions of motorized traffic and industrial facilities. We carried out a systematic review and dose-response meta-analysis of the cohort studies investigating the association between cadmium exposure and breast cancer risk.

Methods

Following a literature search through September 10, 2019, we carried out a systematic review and a dose-response meta-analysis using the 'one-stage' approach. We used a restricted cubic spline model with 3 knots at fixed percentiles (10, 50, 90%) and we pooled study specific estimates using restricted maximum likelihood methods in a random effects meta-analysis. We carried out stratified analyses by exposure assessment method and menopausal status.
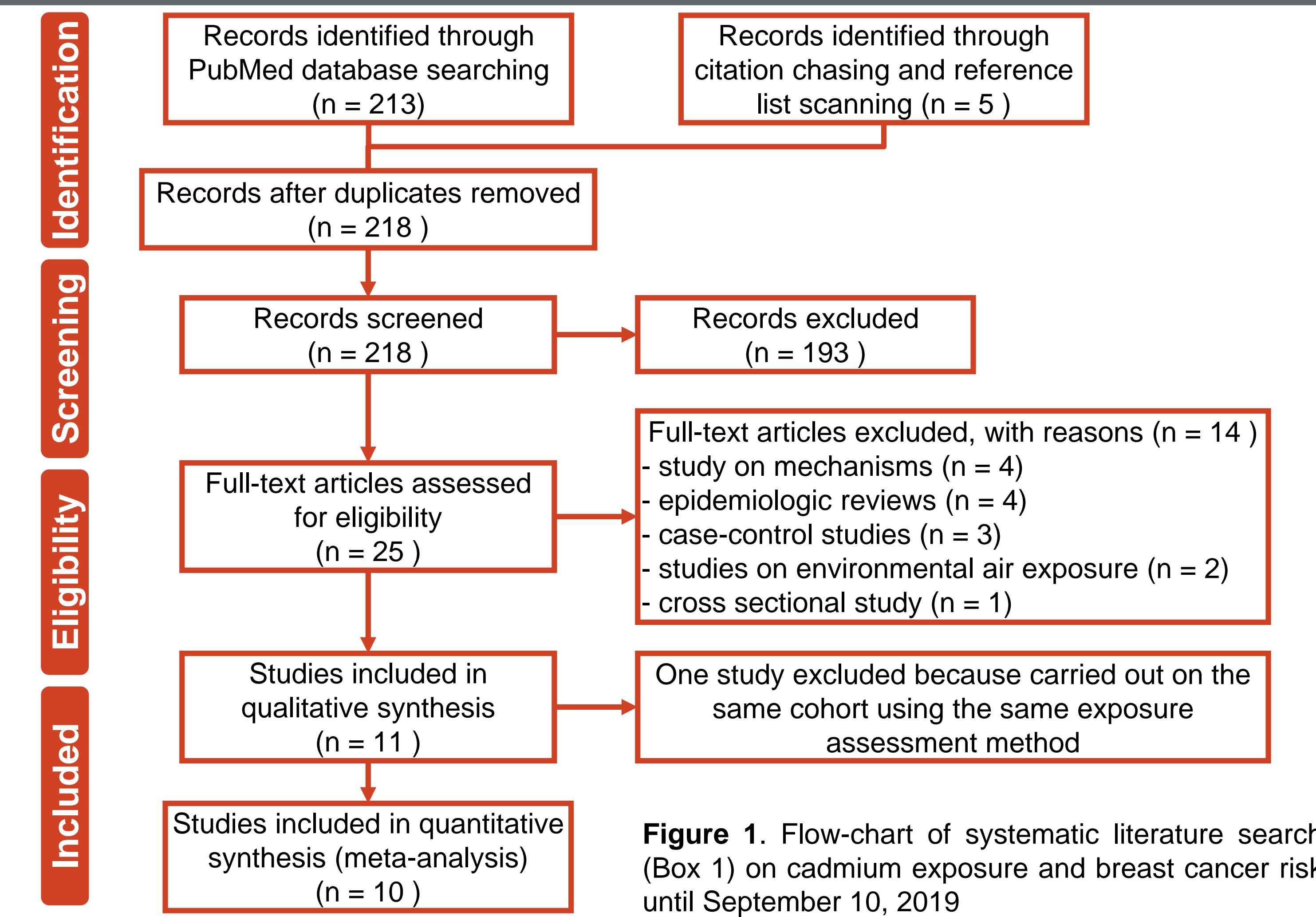

Figure 1. Flow-chart of systematic literature search (Box 1) on cadmium exposure and breast cancer risk until September 10, 2019

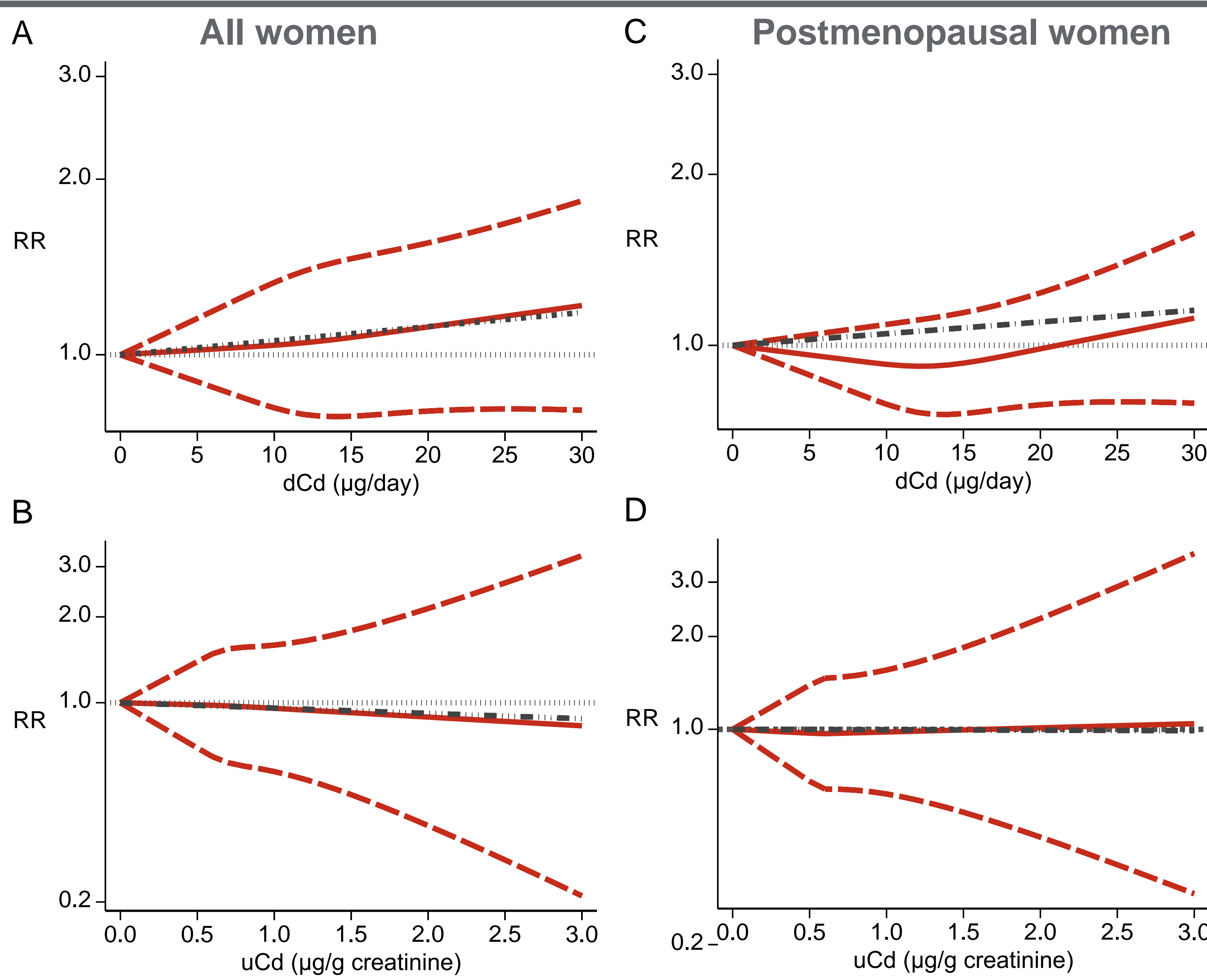| Box 1	Search strategy
PubMed	("cadmium"[MeSH Terms] OR ("cadmium"[MeSH Terms] OR "cadmium"[All Fields]) AND tiab[All Fields] OR ("cadmium"[MeSH Terms] OR "cadmium"[All Fields])) AND ("breast neoplasms"[MeSH Terms] OR breast cancer[TIAB]) AND "humans"[MeSH Terms]

Figure 2. Dose-response meta-analysis of breast cancer risk from cadmium exposure using dietary intake – dCd (A-C) or urine levels – uCd (B-D) in all women (A-B) and in post-menopausal women only (C-D). Spline curve (solid line) with 95% confidence limits (long dashed lines) with a background gray line assuming a linear increase. RR risk ratio.
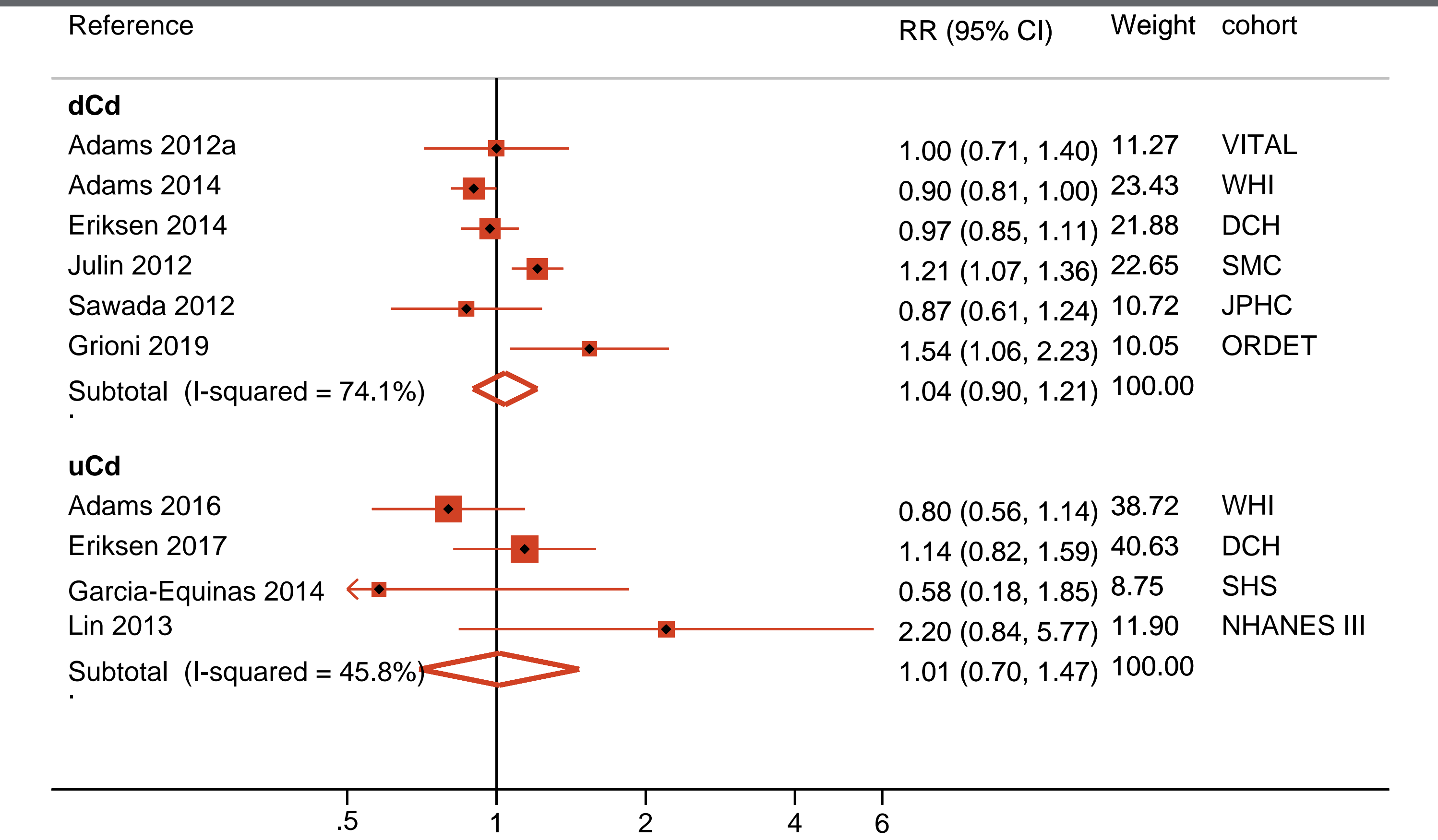
Results

We identified eleven studies on breast cancer risk (**Figure 1**), six based on cadmium dietary intake, and five on urinary excretion levels. None of the included studies was at high risk of bias and main confounders in risk of bias: age, smoking habits, body mass index, hormone replacement therapy (+ energy intake or creatinine adjustment).
In dose-response analysis, we observed a positive, statistically imprecise linear relation between dietary cadmium intake and disease risk (**Figure 2A**). Risk ratio (RR) at 20 µg/day compared with no intake was 1.12 (95% confidence interval-CI 0.80-1.56). Conversely, we detected a very imprecise negative association between urinary cadmium excretion and disease risk (RR=0.89, 95% CI 0.37-2.14 at 2 µg/g creatinine of cadmium excretion, **Figure 2B**). Analysis restricted to post-menopausal women showed substantially no association (**Figure 2C** and **2D**), as was true for all meta-analyses carried out by comparing the highest versus the lowest exposure category (**Figure 3**). Funnel plots for publication bias showed substantial symmetric distribution (**Figure 4**).

Figure 3. Risk ratio (RR) with 95% confidence interval (CI) of breast cancer risk for highest versus lowest cadmium exposure assessed through diet (dCd) or urinary excretion (uCd). The area of red squares is proportional to the inverse of the variance of the estimated log RR. Open diamonds represent the combined RR for each subgroup.
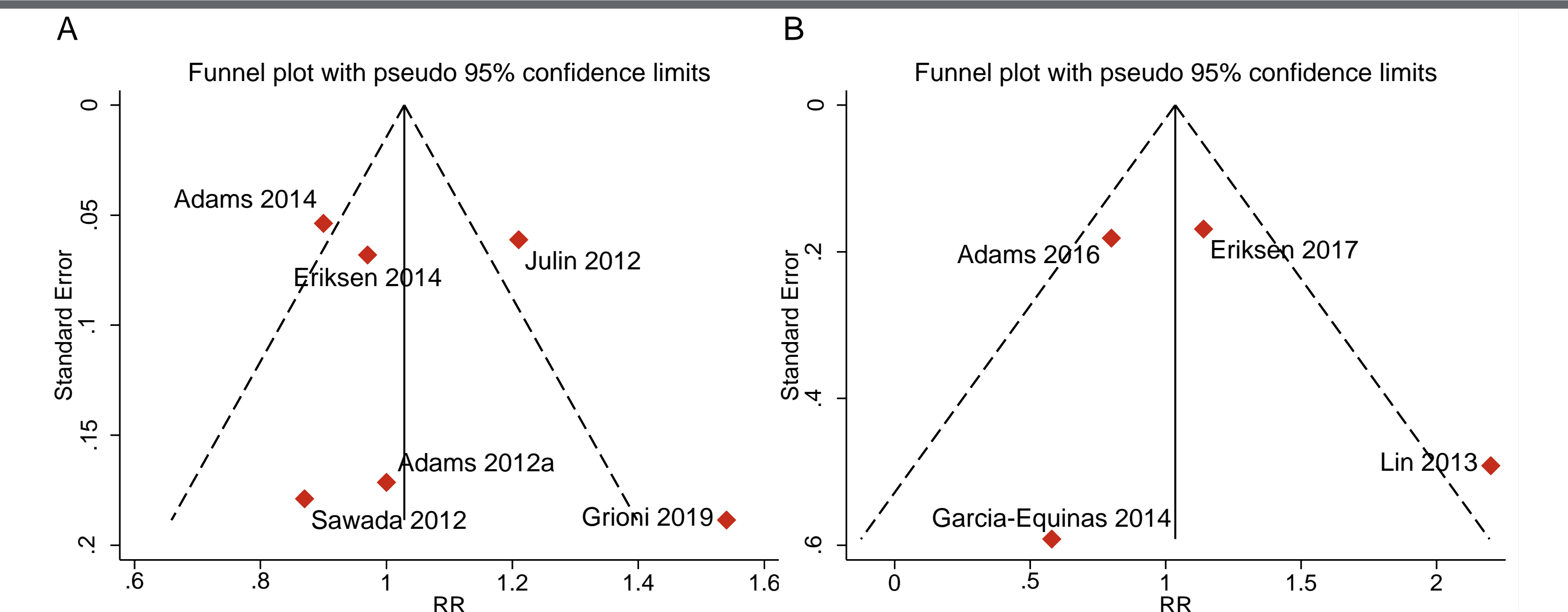

Figure 4. Funnel plots for publication bias for dietary (A) and urine level (B). The outer dash lines indicate the triangular region within which 95% of studies are expected to lie in the absence of both bias and heterogeneity.

Outcome	Relative effect (95% CI)	No. participants (No. of cases)	Quality of the evidence	Comments
Breast cancer (dietary Cd)	RR 1.04 (0.90 to 1.21)	314,767 (11,942)	++ low	Small but imprecise effect. Not serious inconsistency nor risk of bias. No publication bias detected.
Breast cancer (urinary Cd)	RR 1.01 (0.70 to 1.47)	6,932 (1,459)	++ low	Not large and imprecise effect. Not serious Not serious inconsistency nor risk of bias. No publication bias detected.

Table 1. Summary of findings table. Research question: Does high cadmium exposure compared to low exposure increase risk of breast cancer?

Conclusions

Overall, we found scant evidence of positive association between cadmium and breast cancer also based on the summary of findings evaluation using GRADE approach (**Table 1**). Available data were too limited to carry out stratified analyses according to age, smoking and hormone receptor status. Therefore, possible associations between cadmium exposure and breast cancer risk in selected subgroups cannot be entirely ruled out.

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