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Cadmium Exposure and Risk of Pancreatic Cancer: A Systematic Review and Meta-Analysis

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SUPPLEMENTARY MATERIALS

Supplementary Table S1-a. PRISMA Checklist
Supplementary Table S1-b. PRISMA Abstract Checklist
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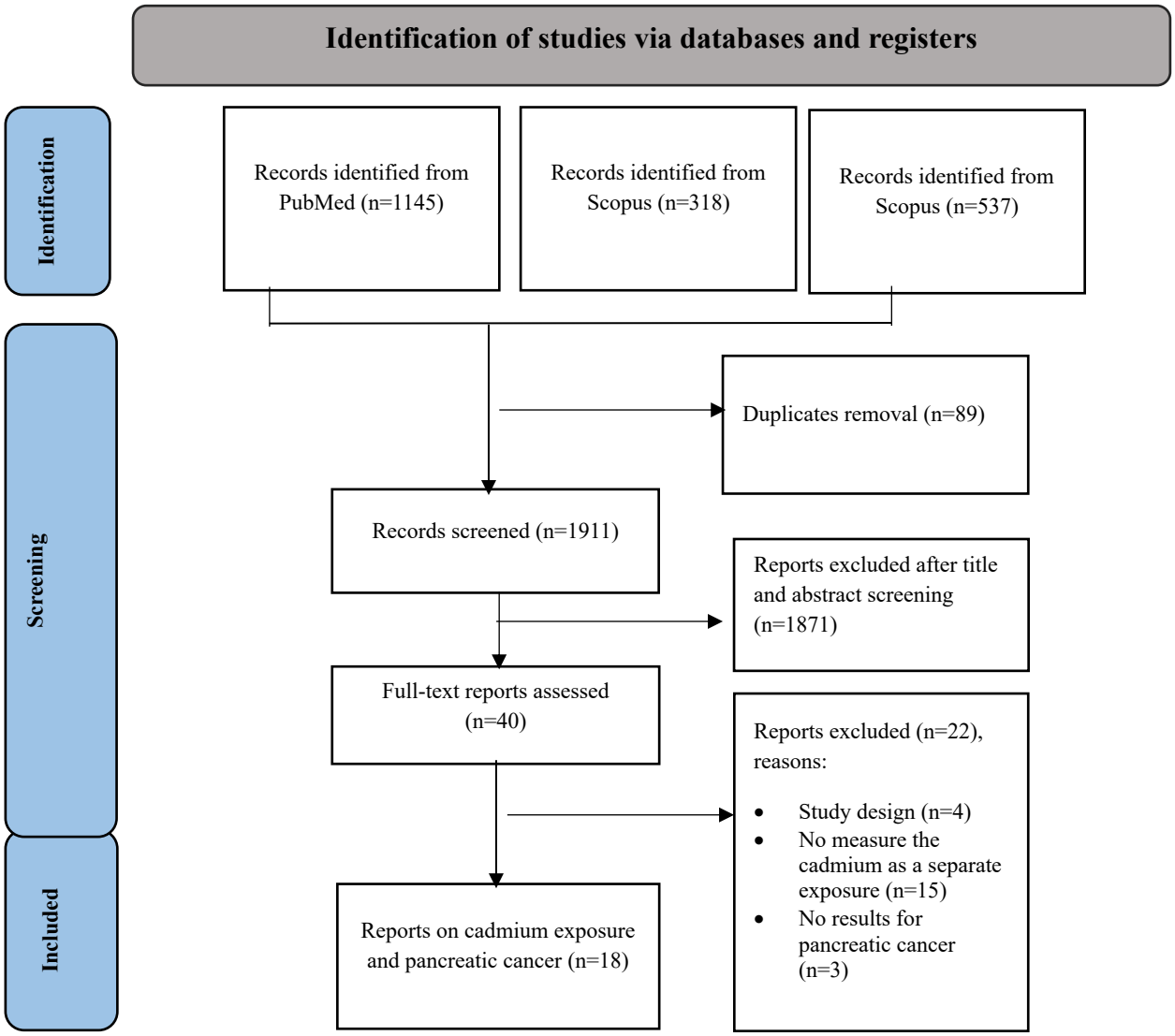
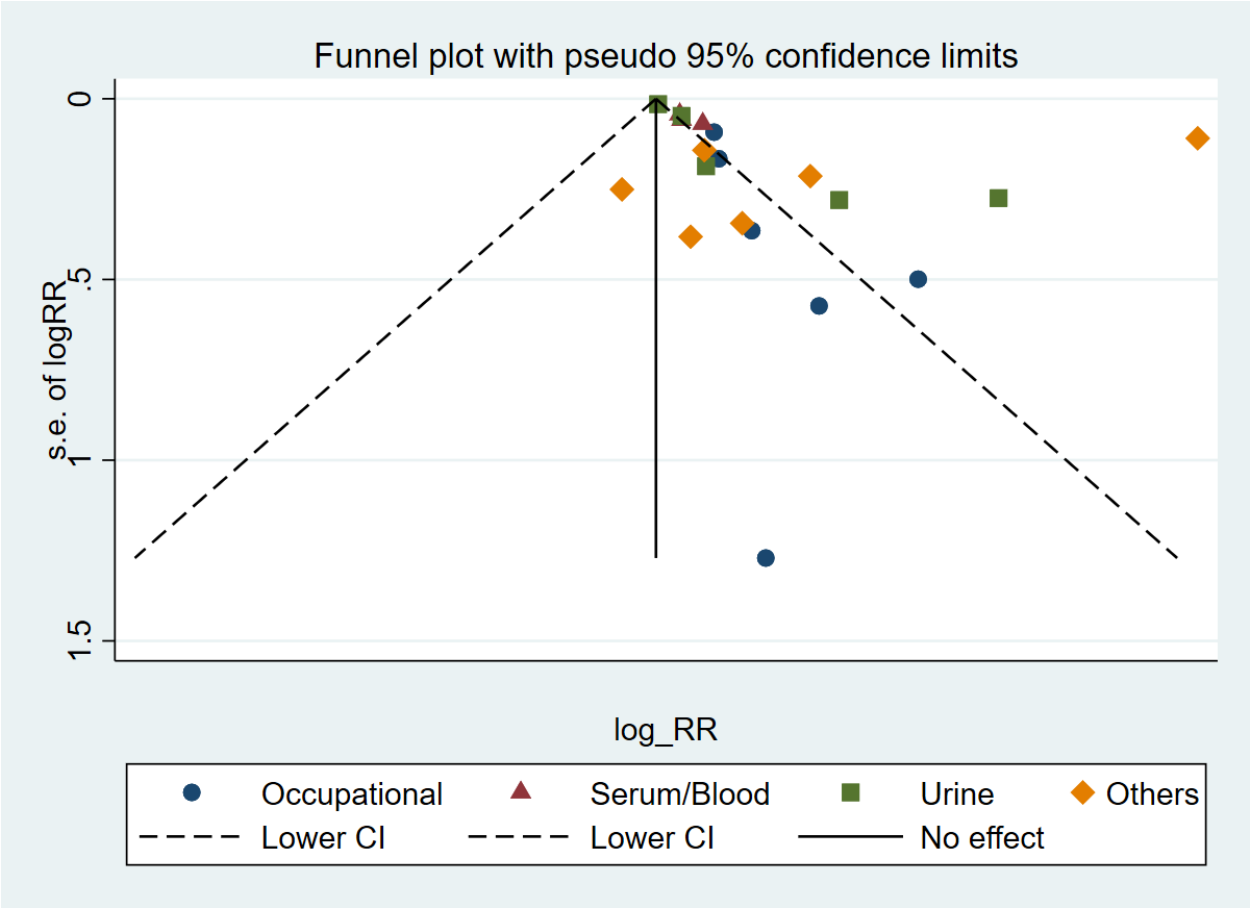
Supplementary Table S3. Modified version of the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies adopted for quality assessment.
Supplementary Table S4: Quality Assessment of Included Studies Using the Newcastle–Ottawa Scale (NOS) mentioned in supplementary table 4
Supplementary Figure 1. Flowchart describing the study selection process.
Supplementary Figure 2. Funnel plot results in the association between cadmium exposure and pancreatic cancer by different exposure sources.

Supplementary Figure 1. Flowchart describing the study selection process.





Supplementary Figure 2. Funnel plot results in the association between cadmium exposure and pancreatic cancer by different exposure sources. [Occupational [P = 0.087], Serum/blood [P = 0.371], Urine [P = 0.045], Others [P = 0.169]].

Supplementary Table S1. PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P4, Supplementary Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of	P5

Section and Topic	Item #	Checklist item	Location where item is reported
		evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P6, supplementary figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	supplementary figure 1
Study characteristics	17	Cite each included study and present its characteristics.	P6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P6, Supplementary Table 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P6, Supplementary Table 3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P6, Figures 1
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P6, Figure 2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P6
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P8
	23b	Discuss any limitations of the evidence included in the review.	P8
	23c	Discuss any limitations of the review processes used.	P8
	23d	Discuss implications of the results for practice, policy, and future research.	P8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P1, 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P1
Competing interests	26	Declare any competing interests of review authors.	P1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P1

Supplementary Table S1-b. PRISMA Abstract Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	P2-line4
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Page3-line5
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	-
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	p3-line7
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Page3-line12
Synthesis of results	6	Specify the methods used to present and synthesise results.	page3-line10
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	page3-line9, line
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Page3-line 14 to 20

Supplementary Table S2. Detailed search strategy used on the different databases.

Database	Search string
PubMed	((Cadmium[MeSH Terms] OR cadmium[Text Word] OR cadmium exposure[Text Word] OR environmental cadmium[Text Word] OR cadmium toxicity[Text Word] OR Cd[Text Word]) AND ("Neoplasms"[MeSH Terms] OR cancer[Text Word] OR neoplasm[Text Word] OR malignant[Text Word] OR tumor[Text Word] OR tumour[Text Word] OR malignan[Text Word] OR carcinoma[Text Word])) AND ("pancreas"[MeSH Terms] OR pancreatic [Text Word] OR pancreas [Text Word]))
Scopus	(TITLE-ABS-KEY ("Cadmium")) AND (ALL("Neoplasms") OR ALL("cancer") OR ALL("neoplasm") OR ALL("malignant") OR ALL("tumor") OR ALL("tumour") OR ALL("malignan") OR ALL("carcinoma ")) AND (ALL ("pancreas") OR ALL ("pancreatic")) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (LANGUAGE,"English")) AND (LIMIT-TO (EXACTKEYWORD,"Human") OR LIMIT-TO (EXACTKEYWORD,"Humans") OR LIMIT-TO (EXACTKEYWORD,"Male") OR LIMIT-TO (EXACTKEYWORD,"Female")) AND (EXCLUDE (SUBJAREA,"ARTS") OR EXCLUDE (SUBJAREA,"EART") OR EXCLUDE (SUBJAREA,"SOCI") OR EXCLUDE (SUBJAREA,"VETE") OR EXCLUDE (SUBJAREA,"MATE") OR EXCLUDE (SUBJAREA,"ENGI") OR EXCLUDE (SUBJAREA,"COMP") OR EXCLUDE (SUBJAREA,"CENG") OR EXCLUDE (SUBJAREA,"MULT") OR EXCLUDE (SUBJAREA,"BIOC") OR EXCLUDE (SUBJAREA,"PHAR") OR EXCLUDE (SUBJAREA,"NURS") OR EXCLUDE (SUBJAREA,"AGRI") OR EXCLUDE (SUBJAREA,"IMMU") OR EXCLUDE (SUBJAREA,"CHEM") OR EXCLUDE (SUBJAREA,"NEUR") OR EXCLUDE (SUBJAREA,"PSYC") OR EXCLUDE (SUBJAREA,"DENT") OR EXCLUDE (SUBJAREA,"PHYS"))
Embase	(Cadmium).tx. and (Neoplasms or cancer or neoplasm or malignant or tumor or tumour or malignan or carcinoma). tx. and (pancreas or pancreatic). tx. limit to original articles

	limit to (alternative & complementary medicine or clinical medicine or health professions or life & biomedical sciences or life sciences or medical humanities or nursing or patient education or pharmacology or public health or science or traditional Chinese medicine)

Supplementary Table S3: Newcastle - Ottawa quality assessment scale

CASE CONTROL STUDIES (maximum score: 9)

Selection

1) Is the case definition adequate?

a) yes, with independent validation **(1)**

b) yes, eg record linkage **(1)** or based on self-reports **(0.5)**

c) no description **(0)**

2) Representativeness of the cases

a) consecutive or obviously representative series of cases **(1)**

b) potential for selection biases or not stated **(0)**

3) Selection of Controls

a) community controls **(1)**

b) hospital controls **(0.5)**

c) no description **(0)**

4) Definition of Controls

a) no history of disease (endpoint) **(1)**

b) no description of source **(0)**

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

a) study controls for age, gender, province **(0)**

b) study controls for age, gender, province +smoking **(1)**

c) study controls for age, gender, province +smoking + other additional factors **(2)**

Exposure

1) Ascertainment of exposure

a) secure record (eg surgical records) **(1)**

b) structured interview where blind to case/control status **(1)**

c) interview not blinded to case/control status **(0.5)**

d) written self-report or medical record only **(0.5)**

e) no description **(0)**

2) Same method of ascertainment for cases and controls

a) yes **(1)**

b) no **(0)**

3) Non-Response rate

a) one or both groups over 90% **(1)**

b) one or both groups between 60- 90% **(0.5)**

c) one or both groups under 60% **(0)**

d) no statemen **(0)**

COHORT STUDIES (maximum score: 10)

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community **(2)**

b) somewhat representative of the average _____ in the community **(1)**

c) selected group of users eg nurses, volunteers **(0.5)**

d) no description of the derivation of the cohort **(0)**

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort **(1)**

b) drawn from a different source **(0.5)**

c) no description of the derivation of the non-exposed cohort **(0)**

3) Ascertainment of exposure

a) secure record (eg surgical records) **(1)**

b) structured interview **(1)**

c) written self-report **(0.5)**

d) no description **(0)**

4) Demonstration that outcome of interest was not present at start of study

a) yes **(1)**

b) no **(0)**

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for age, gender, province **(0)**

b) study controls for age, gender, province +smoking **(1)**

c) study controls for age, gender, province +smoking + other additional factors **(2)**

Outcome

1) Assessment of outcome

a) independent blind assessment **(1)**

b) record linkage **(1)**

c) self-report **(0.5)**

d) no description **(0)**

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) **(1) (average 15 years)**

b) no **(0)**

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for over 90% **(1)**

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ___ % (select an adequate %) follow up, or description provided of those lost) between 60- 90% **(0.5)**

c) follow up rate < ___% (select an adequate %) and no description of those lost under 60% **(0)**

d) no statemen **(0)**

Supplementary Table S4: Quality Assessment of Included Studies Using the Newcastle–Ottawa Scale (NOS) mentioned in supplementary table 3										
Ref.	Study design	Selection				Comparability	Exposure			
		Item1	Item2	Item3	Item4	Item1	Item1	Item2	Item3	Total
Kriegel,2006	Case control	1	1	0.5	1	1	1	1	0	6.5/9
Luckett,2012	Case control	1	0.5	1	1	1	1	1	0	6.5/9
Sawada,2012	Cohort	2	1	1	1	2	1	1	1	10/10
Amaral,2012	Case control	1	0	0.5	0.5	2	1	1	0.5	6.5/9
Adams,2012	Cohort	2	1	1	1	2	1	1	1	10/10
Garca-Esquinas,2014	Cohort	2	1	1	1	2	1	1	1	10/10
Watanabe,2020	Cohort	2	1	1	1	2	1	1	1	10/10
Stolzenberg-Solomon,2025	Nested case control	1	1	1	1	2	1	1	1	9/9
Weiderpass,2003	Cohort	1	1	1	1	1	1	1	1	8/10
Djordjevic,2019	Case control	1	1	0.5	1	0	1	1	0	5.5/9
Zhang,2005	Case control	1	1	1	1	2	0.5	1	0.5	8/9
Duell,2018	Nested case control	1	1	1	1	2	1	1	1	9/9
Järup,1998	Cohort	2	0.5	1	1	1	1	1	1	8.5/10
Nishijo,2018	Cohort	2	1	1	1	1	1	1	1	9/10
Nyqvist,2017	Cohort	2	1	1	1	0	1	1	1	8/10
Sakurai,2021	Cohort	2	0	1	1	1	1	1	1	8/10
Sorahan ,1995	Cohort	1	1	1	1	0	1	1	1	7/10
Carrigan,2007	Case control	1	1	0.5	1	1	1	1	1	7.5/9