Original Article

Association between heavy metal mercury in body fluids and tissues and diabetes mellitus: a systematic review and meta-analysis

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Background: Recent studies have shown that the relationship between mercury exposure and diabetes is controversial. The aim of this study is to determine the relationship between mercury exposure and diabetes using a systematic review and meta-analysis approach.

Methods: We systematically searched PubMed, Web of Science, Cochrane, and Embase databases for cross-sectional, case-control, or cohort studies assessing the correlation between mercury exposure and diabetes in any population. Details of each included study were extracted using a pre-designed Excel spreadsheet. Quality assessment of cohort and case-control studies used the Newcastle-Ottawa Scale (NOS), whereas cross-sectional studies were assessed by the Agency for Healthcare Research and Quality (AHRQ) scale. Meta-analyses were performed using random-effects models to calculate the pooled odds ratio (OR), standardized mean difference (SMD), and their 95% confidence intervals (CIs). Subgroup and sensitivity analyses were employed to assess heterogeneity sources. Begg's and Egger's tests were used to evaluate publication bias.

Results: Our meta-analysis included 8 eligible articles, comprising a total of 40,891 subjects, reporting mercury OR and/or concentrations. Among the included studies, one was a case control, one was a cohort study, and the rest were cross-sectional studies. Two studies were rated as high quality and six as medium quality. The results revealed no link between mercury exposure and diabetes (OR: 1.11, 95% CI: 0.80, 1.55, n=6, I^2=73.7%; and SMD: 0.41, 95% CI: –0.32, 1.14, n=3, I^2=88.7%). In the stratified male and female subgroups, the pooled OR was 0.71 (95% CI: 0.57, 0.90, n=3, I^2=0.0%), 1.11 (95% CI: 0.69, 1.79, n=3, I^2=67.7%). The Begg's test results revealed no significant publication bias (P=0.06), but the Egger's test results did (P=0.013). The sensitivity analysis confirmed the stability of our results.

Conclusions: No significant relationship was observed between mercury and diabetes mellitus. However, more well-designed studies on mercury exposure and diabetes risk are still needed, particularly on the type of mercury (i.e., elemental, inorganic, and organic), exposure time and dose, type of biological specimen, and the population's sex and age.

Keywords: Diabetes mellitus; mercury; heavy metals; meta-analysis

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Introduction

Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia, insufficient insulin secretion, or insensitivity to insulin receptors. The International Diabetes Federation (IDF) published the 10th edition of its "IDF Diabetes Atlas" on its website on December 6, 2021, and statistics reveal that in 2021, approximately 537 million adults aged 20 to 79 years worldwide, or one in 10 people, might have diabetes (1). The total number of diabetics is expected to reach 643 million by 2023 and 783 million by 2045 (1). The exploration and intervention of diabetes risk factors is the key to reducing the incidence of diabetes. Known risk factors for diabetes include genetic predisposition, old age, obesity, lack of physical activity, environmental chemicals, etc. (2). Recently, environmental chemicals are receiving increasing attention (2-4). Humans are exposed to a variety of metal substances as a result of environmental contamination. Their multiple applications in industry, households, agriculture, medicine, and technology have led to their widespread distribution in the environment (5,6). Most countries restricted the levels of hazardous heavy metals in the environment as industrialization progressed; however, it was unavoidable that people would be exposed to them through food, drinking water, and the surrounding air (7-9).

Mercury is a toxic, non-degradable heavy metal that exists widely in the environment in three forms: elemental mercury, inorganic mercury, and organic mercury. Mercury compounds are widely used in dry batteries, arc lamps, incandescent lamps, cosmetics, pharmaceuticals, mirrors, gold and silver extracted from ores, glass thermometers, sphygmomanometers, dental amalgam fillings, and vaccine preservatives (10,11). Elemental mercury is easily converted to methylmercury by microorganisms and accumulates in foods such as seafood and rice (12,13). As a result, mercury is an inevitable environmental contaminant in our lives that poses a significant hazard to human health. Further, high levels of mercury exposure can damage a variety of cells, including islet cells, through oxidative stress, ultimately affecting the central nervous system, cardiovascular system, urinary system, endocrine system, reproductive system, and immune system (14-17).

Some studies support a link between mercury exposure and diabetes, but reports have drawn conflicting conclusions. For example, a cross-sectional study in South Korea in 2010–2011 found a significant association between elevated blood mercury levels and increased fasting blood sugar (18). Similarly, a positive correlation between mercury and diabetes was observed in a cross-sectional study in China (19), but not in two studies in South Korea (8,20). Moreover, Roy *et al.* reported the relationship between heavy metal mercury and diabetes in a descriptive review paper, examining their possible association (21). Collectively, due to the mixed reports, little can be concluded about the relationship between mercury exposure and diabetes risk. The discrepancy is partly due to different countries of study, different sample sources, different types of studies, mercury exposure measured at only one time point, etc. Measuring mercury concentrations at only one time point is indeed problematic, and it would be better if there were multiple time points to be averaged. Unfortunately, most of the original studies did not address this issue. Furthermore, as mercury is not generally metabolized and excreted from the body, its concentration does not vary greatly from one time point to another, so the impact of this on the study has been ignored. Therefore, it is essential to explore the relationship between mercury exposure and diabetes using a systematic review and meta-analysis approach and to determine the relationship in different subgroups, which may complement new risk factors for diabetes and help delay or reduce the incidence of diabetes. We present the following article in accordance with the MOOSE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6404/rc).

Highlight box

Key findings

- No significant relationship was observed between mercury exposure and risk of diabetes mellitus.

What is known and what is new?

- Given the high incidence of diabetes and widespread exposure to mercury, as well as the inconsistent findings on the association between mercury and diabetes risk, it is essential that meta-analyses be conducted to assess this association.
- This is the first meta-analysis to focus on mercury exposure and the risk of diabetes mellitus.

What is the implication, and what should change now?

- Due to the unavoidable risk of bias, more well designed studies focusing on mercury exposure and the risk of diabetes mellitus are still needed.

Methods

Search strategy and selection criteria

The study protocol is registered on the International

Prospective Register of Systematic Reviews (PROSPERO; No. CRD42022322375), where more details can be found.

We searched the PubMed, Web of Science, Cochrane, and Embase databases to retrieve relevant literature published before March 9, 2022 using the following keywords: ("Diabetes Mellitus" OR "DM" OR "T2DM" OR "Diabetes" OR "Type 1 diabetes" OR "Type 2 diabetes") AND ("Mercury" OR "methylmercury "OR "Hg") (see Tables S1-S4). Endnote, a document management program, was used to organize all the retrieved literature information.

Two authors (Yunran Guo and Xinming Liu) independently screened the articles. After deleting the duplicate articles, the title and abstract of each article were used to determine each study's relevance, and the full text then underwent further screening as necessary. We also evaluated the retrieved articles and manually retrieved references to supplement any missing investigations. Finally, the contents and methods of the articles were evaluated, and any corresponding articles were included in the meta-analysis. Any disagreements between the authors were resolved with the assistance of the third author.

Inclusion and exclusion criteria

After discussion among all the researchers, it was agreed that the studies had to meet the following inclusion criteria for inclusion in the meta-analysis: (I) studies were included if they were cross-sectional, case-control, or cohort studies; (II) comprise adult subjects who were aged >18 years; (III) report data on the relationship between heavy metal mercury exposure and diabetes using the odds ratio (OR) and 95% confidence intervals (CIs), or report mercury concentrations in diabetic and healthy populations as the mean ± standard deviations (SDs) and sample sizes; (IV) mercury exposure in body fluids and tissues is measured by an unrestricted method; and (V) diabetes is defined as fasting serum glucose concentration ≥7.0 mmol/L and/or 2-h glucose concentration ≥11.1 mmol/L or other criterion-justified ranges. Studies were excluded from the meta-analysis if they met any of the following exclusion criteria: (I) were not of interest to us (e.g., concerned a review, report, systematic review and meta-analysis, letter, guide, conference abstract, or book); (II) had been published in a language other than English; (III) did not provide the results of interest to us; and/or (IV) the data of the study could not be accurately extracted or were missing.

Data extraction

The data, including details of the first author, study design, gender, year of publication, source of detection, study site, the main point of view, specimen, age, the exposure level of mercury, potential confounders for adjustment, OR and their associated 95% CIs, was extracted using a pre-designed Excel spreadsheet. If an article reported data on males and females separately, the OR and their 95% CIs were extracted by sex. We identified the studies with the most adjustment potential confounders from those with multiple risk estimates of adjustment reports based on distinct confounders. In addition, to make the most of the available data to enable us to conduct the most comprehensive meta-analysis possible, we also extracted heavy metal mercury concentrations from diabetic and healthy control groups to explore whether the mercury levels were higher in the biological samples of the diabetic patients than the healthy control patients. Standardized mean difference (SMD) was calculated using the available means and SDs of mercury concentrations and specimens as an effect estimate. If the articles reported standard errors (SEs) rather than SDs, the SDs were estimated based on their SEs and samples.

Quality assessment

Guo and Liu independently performed the quality assessment. The Newcastle-Ottawa Scale (NOS) was employed to assess the quality of the cohort and case-control studies. Each cohort study was evaluated in terms of its cohort selection, comparability, and outcome measurements. Each case-control study was evaluated based on the following three aspects: selection, comparability, and exposure assessment method. The widely used score cut-off of ≥7 was used in this study as a score for high-quality studies, as formal criteria for high quality have not yet been universally established, as shown in the previously published meta-analysis (22-24). Each cross-sectional study was evaluated using the Agency for Healthcare Research and Quality (AHRQ) scale recommended by the United States. A total of 11 items were evaluated by the AHRQ scale, including sources of information, inclusion and exclusion criteria, study participants' time cycles and continuity, personnel blindness, quality assurance assessments, confusion and missing data, and patient response rates and completeness. The quality of each study was graded as follows: low quality = 0–3; moderate quality = 4–7; and high

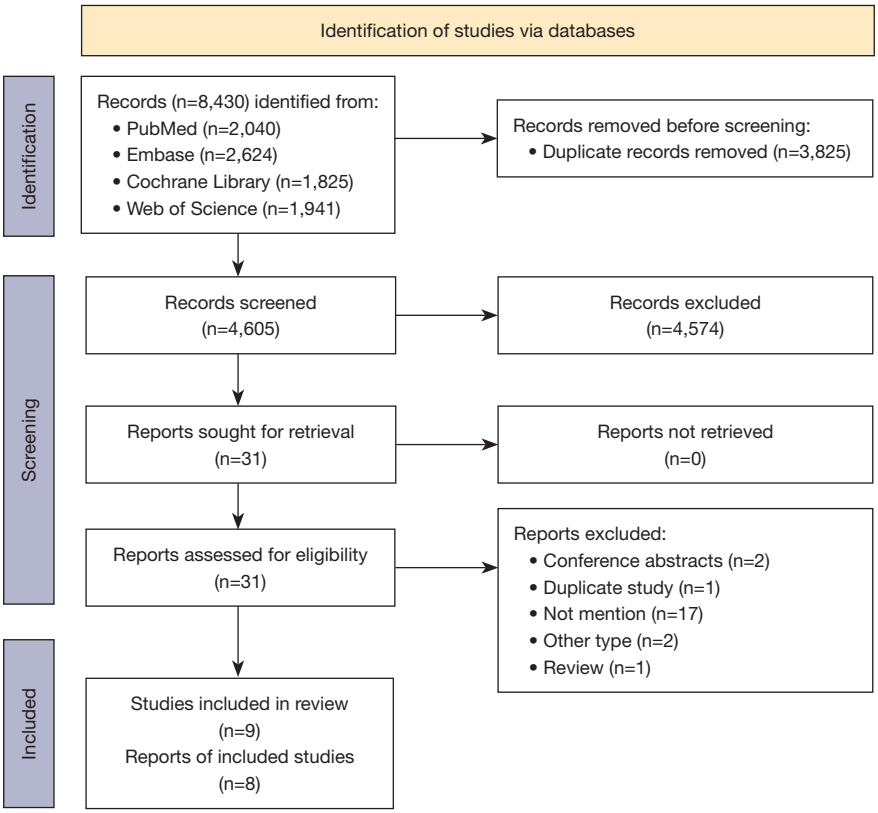

Figure 1 Flow diagram of the literature search.

quality = 8–11, as shown in the previously published meta-analysis (25-28).

Statistical analysis

We analyzed the data using Stata version 15.0 (Stata Corporation, College Station, TX, USA). The study was performed using random-effects models to calculate the pooled OR, SMD, and their 95% CIs. As the ORs extracted for each study represent how many times the risk of diabetes at the highest level of mercury exposure is the lowest level, we calculated pooled effect values (28,29). We calculated I^2 to assess the heterogeneity between the studies, with significant heterogeneity expressed at I^2>50%, P<0.1. To examine heterogeneity, we performed subgroup analyses by study type, country, sex, and specimen. A sensitivity analysis was carried out by eliminating one article at a time and re-calculating the pooled OR. Publication bias was statistically assessed by Begg's test and Egger's test. A two-tailed *P* value < 0.05 was considered statistically significant.

Results

Literature search and study characteristics

We retrieved 8,430 articles from our database searches. After removing the duplicate articles, we screened the 4,605 articles and reviewed the full text of 31 articles by reviewing the headlines and abstracts. A further 23 articles were eliminated based on the inclusion and exclusion criteria, and ultimately eight articles were included in the meta-analysis. Five articles (six studies) were used to investigate the relationship between high and low mercury exposure and diabetes, and three articles (three studies) were used to examine mercury concentration differences between diabetics and controls (*Figure 1*) (8,9,19,20,30-33). The baseline characteristics of the included studies are shown in *Table 1*.

Quality assessment of the included studies

Two studies were rated as high quality and six as medium

Table 1 Characteristics of the included studies

Study	Country	Design	Specimen	Population	Age (years)	Gender	Exposure level (values or mean ± standard deviation)	Adjustment	OR (95% CI)
Flores *et al.* (30), 2011	Mexico	Cross-sectional	Blood	88	42–67	M/F	(1.12±0.97) *vs.* (0.18±0.35)	NA	NA
Moon (20), 2013	South Korea	Cross-sectional	Blood	3,184	≥30	M/F	Q1: 2.10±1.01; Q2: 3.53±1.00; Q3: 5.16±1.01; Q4: 9.62±1.01	Age, sex, region, smoking, alcohol consumption and regular exercise	1.076 (0.758, 1.526)
Pal *et al.* (32), 2013	Canada	Cross-sectional	Hair	72	>18	M/F	(1763.8±2218.9) *vs.* (982.6±918.46)	NA	NA
Hansen *et al.* (31), 2017	Norway	Case-control	Blood	883	≥20	M/F	3.47 *vs.* 3.18	Age, sex, body mass index, waist-to-hip ratio, education, income, smoking and family history of diabetes	1.66 (0.79, 3.47)
Tsai *et al.* (19), 2019	China	Cross-sectional	RBC	646	≥19	M/F	T1: <10.66; T2: 10.66–18.80; T3: >18.80	Age, sex, BMI, educational status, hypertension, total cholesterol, fasting glucose, cigarette smoking, alcohol consumption, saltwater fish consumption, total calorie intake, protein and fat intake, geographical strata, seasonality, C-reactive protein and hemoglobin	4.71 (1.86, 11.93)
Wang *et al.* (9), 2020	America	Cohort	Urine	1,237	45–56	M/F	(1.22±1.11) *vs.* (1.46±1.32)	NA	NA
Zhang *et al.* (33), 2021	China	Cross-sectional	Blood	30,994	>20	F	Q1: ≤0.44; Q2: 0.45–0.84; Q3: 0.85–1.69; Q4: >1.69	Data release cycle, age, sex, race/ethnicity, body mass index, hypertension, poverty-income ratio, education, marital status, and daily intakes of protein, total fat, sugar, fiber	0.76 (0.63, 0.92)
Moon *et al.* (8), 2022	South Korea	Cross-sectional	Blood	3,787	≥19	M/F	NA	Age, sex, cigarette smoking, alcohol drinking, exercise, and education levels	0.87 (0.59, 1.29)
Moon *et al.* (8), 2022	South Korea	Cross-sectional	Urine	3,787	≥19	M/F	NA	Age, sex, cigarette smoking, alcohol drinking, exercise, and education levels	0.97 (0.62, 1.51)

M, male; F, female; NA, not available; OR, odds ratio; CI, confidence interval; Q1/Q2/Q3/Q4, quartile 1/2/3/4; T1/T2/T3, tertile1/2/3; BMI, body mass index.

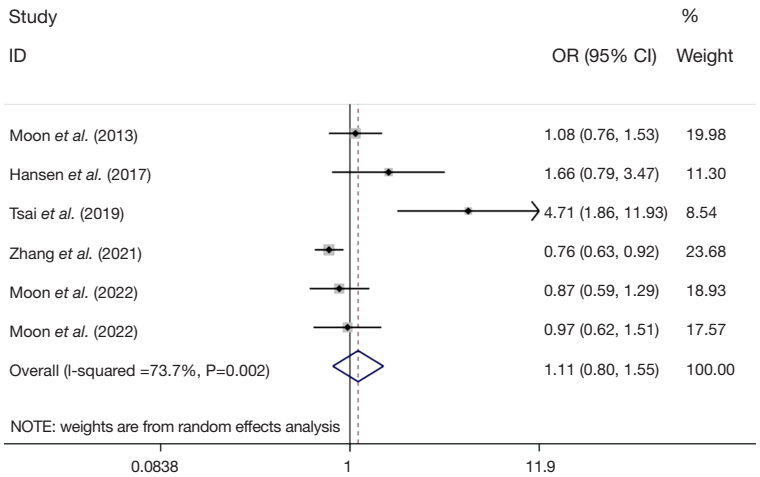

Figure 2 Forest plot of the association between the heavy metal mercury and diabetes mellitus. OR, odds ratio; CI, confidence interval.

quality according to the NOS Quality Evaluation and AHRQ Checklist (Tables S5-S7 of the Supplementary material)

Meta-analyses and subgroup analyses

The meta-analyses using random-effects models revealed no statistically significant association between high mercury exposure and diabetes as compared to lower mercury exposure (OR: 1.11, 95% CI: 0.80, 1.55, n=6, I^2=73.7%) (*Figure 2*).

As the I^2 analysis revealed significant heterogeneity, we conducted a subgroup analysis based on sex, country of study, type of study, and specimen, and found the following: (I) Gender: a significant association was only found in the male subgroup (pooled OR: 0.71, 95% CI: 0.57, 0.90, n=3, I^2=0.0%), but no such correlation was found in the female subgroup (pooled OR: 1.11, 95% CI: 0.69, 1.79, n=3, I^2=67.7%) (*Table 2*). (II) Study countries: no statistical associations were found in South Korea (pooled OR: 0.98, 95% CI: 0.78, 1.22, n=3, I^2=0.0%), China (pooled OR: 1.78, 95% CI: 0.30, 10.62, n=2, I^2=93.0%), or Norway (pooled OR: 1.66, 95% CI: 0.79, 3.48, n=1) (*Table 2*). (III) Study design: no statistical associations were detected in the cross-sectional studies (pooled OR: 1.05, 95% CI: 0.75, 1.49, n=5, I^2=75.4%), or case-control studies (pooled OR: 1.66, 95% CI: 0.79, 3.48, n=1) (*Table 2*). (IV) Specimen: no statistical associations were detected in the blood (pooled OR: 0.93, 95% CI: 0.72, 1.21, n=4, I^2=51.9%), urine (OR: 0.97, 95% CI: 0.62, 1.51, n=1), or red blood cell (RBC) (OR: 4.71, 95% CI: 1.86, 11.93, n=1) (*Table 2*).

In three studies, comprising 1,798 participants, no statistically significant difference was observed in the heavy metal levels between the diabetic and control groups (SMD: 0.41, 95% CI: –0.32, 1.14) (*Figure 3*).

Sensitivity analysis

The sensitivity analysis showed no significant change in the overall effects when each study was sequentially removed, and the pooled OR was recalculated, demonstrating the robustness of the results (*Figure 4*).

Publication bias

Begg's test was used to examine publication bias, and none of the studies included in this study demonstrated potential publication bias (P=0.060) (*Figure 5*). However, the Egger's test results showed publication bias (P=0.013) (*Figure 6*). After a trim-and-fill correction for publication bias, no missing studies were found, and the results did not change (*Figure 7*).

Discussion

Diabetes mellitus is a chronic metabolic disorder caused by a variety of factors. Some metals in the environment are regarded as risk factors for diabetes (34). Mercury is a redox passivating metal, and current research suggests that it may induce oxidative stress by decreasing the enzymatic activity of superoxide dismutase, lowering antioxidants, or binding to protein-Sulfhydryl (-SH) groups (35,36). Some of the

Table 2 Subgroup analysis of meta-analysis between mercury and diabetes mellitus

Subgroups	No. of studies	OR (95% CI)	Heterogeneity test	
			I^2	P value
Gender				
Male	3	0.71 (0.57, 0.90)	0.0%	0.912
Female	3	1.11 (0.69, 1.79)	67.7%	0.045
Study countries				
South Korea	3	0.98 (0.78, 1.22)	0.0%	0.729
China	2	1.78 (0.30, 10.62)	93.0%	0.002
Norway	1	1.66 (0.79, 3.48)	–	–
Study types				
Cross-sectional study	5	1.05 (0.75, 1.49)	75.4%	0.003
Case-control	1	1.66 (0.79, 3.48)	–	–
Specimen				
Blood	4	0.93 (0.72, 1.21)	51.9%	0.100
RBC	1	4.71 (1.86, 11.93)	–	–
Urine	1	0.97 (0.62, 1.51)	–	–

OR, odds ratio; CI, confidence interval; RBC, red blood cell.

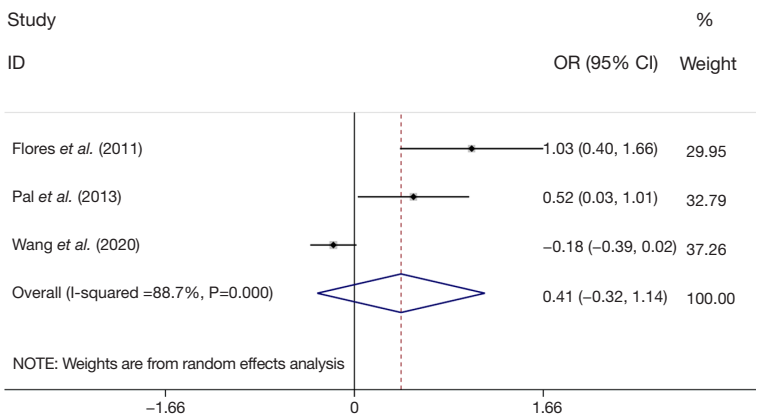

Figure 3 Pooled SMD in mercury concentration from random-effects meta-analysis. SMD, standardized mean difference; CI, confidence interval.

toxic effects of mercury have also been found to be related to mitochondrial dysfunction, which has been found to be related to oxidative damage and the inflammation of the β-cell apoptotic signaling pathway, lowering β-cell function, and increasing susceptibility to diabetes (34). In summary, oxidative stress, apoptosis, and inflammation play roles in mercury-induced diabetes (16,17,35,37,38). However, their exact roles and mechanisms in islet beta-cell function and glucose regulation are unclear.

Some epidemiological studies support a link between mercury and diabetes. A cross-sectional study in Greenland found that high whole-blood mercury is a risk factor for impaired fasting blood sugar (OR: 1.03, 95% CI: 1.02, 1.05) and type 2 diabetes (OR: 1.02, 95% CI: 1.01, 1.04) (39). In a prospective observational study, He *et al.* found that individuals exposed to high levels of mercury during their

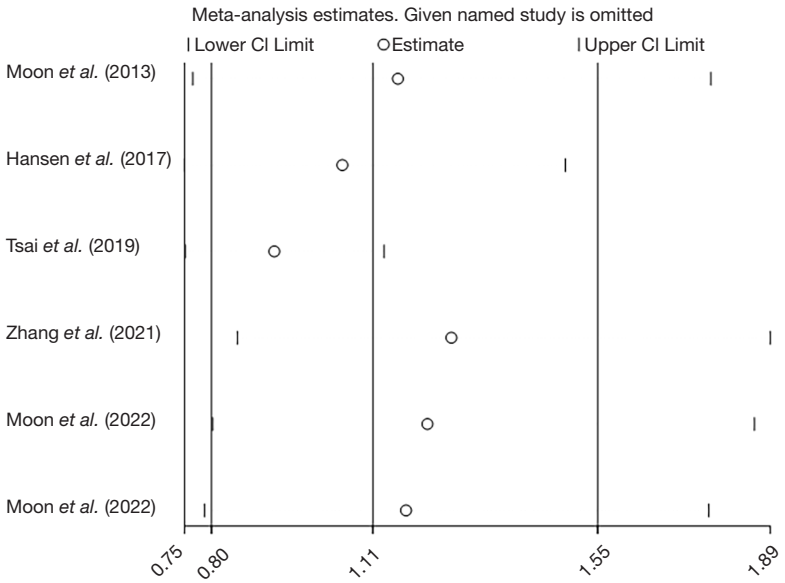

Figure 4 Plot of sensitivity analysis. CI, confidence interval.

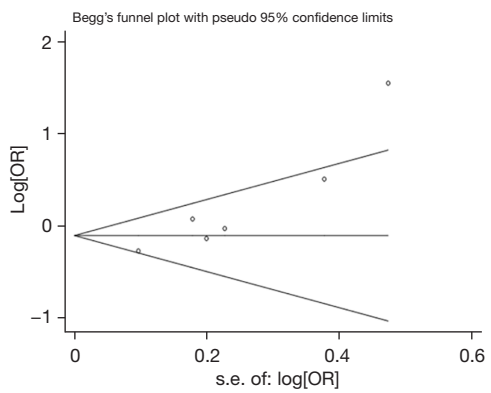

Figure 5 Begg's publication bias plot. OR, odds ratio.

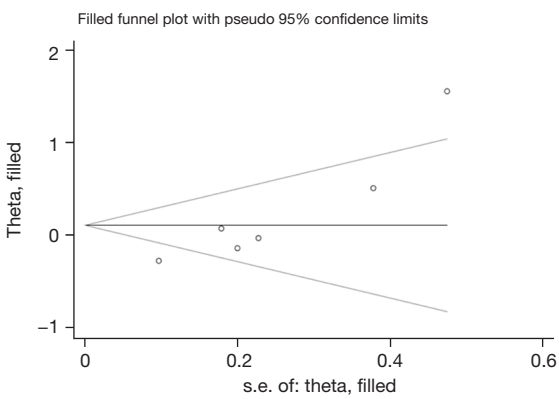

Figure 7 Plot of trim-and-fill.

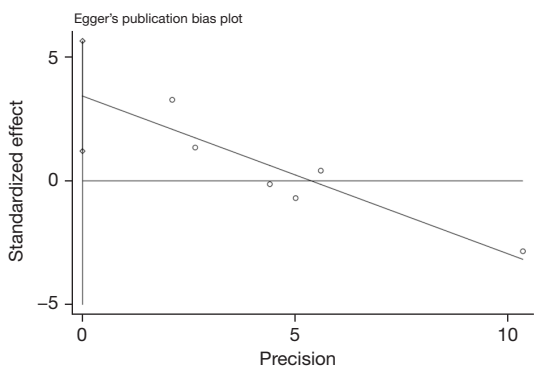

Figure 6 Egger's publication bias plot.

youth may have an increased risk of diabetes later in life (OR: 1.65, 95% CI: 1.07, 2.56) (40). Tsai *et al.* discovered that increased levels of mercury in red blood cells were substantially related to the risk of type 2 diabetes in the studies included in their meta-analysis (19). Studies by Flores *et al.* and Pal *et al.* also showed that the mercury levels in biological samples were higher in diabetics than in healthy people (30,32). All this evidence suggests that mercury may be a risk factor for diabetes, but our meta-analysis results did not support this conclusion.

It is well known that the heterogeneity and suboptimal quality of a study may affect the final outcome. Since our

study had a high degree of heterogeneity, we performed subgroup analyses to understand the origin of the heterogeneity. In subgroups with both genders (the data from the original study were not grouped by sex), there was no association between mercury and diabetes. Despite the limited number of studies, the results demonstrated a negative correlation between mercury and diabetes in the male subgroup but no association in the female subgroup. There is no (published) plausible mechanism to explain this phenomenon. Thus, further research should be conducted to collect gender-specific data to better understand the role of gender in the relationship between mercury exposure and diabetes. The different study designs of the studies we included may result in clinical heterogeneity. In subgroups with both case-control and cross-sectional studies, there was no association between mercury and diabetes. However, more well-designed studies are needed to verify the results in the future. Low-quality studies might reduce the credibility of results, whereas this meta-analysis did not include low-quality studies.

In some of the studies analyzed in this article, the dominance ratio was calculated based on the total mercury concentration's quartile or tertile, and the highest concentration's dominance ratio was extracted. Moon *et al.* found no correlation between mercury exposure and diabetes in the fourth quartile, but found that mercury exposure was negatively correlated to diabetes in the third quartile (8). This suggests a possible link between mercury exposure and diabetes at specific concentrations. As a non-biodegradable, non-essential heavy metal, mercury can accumulate to toxic levels in organisms by various means and can be highly toxic even at low concentrations (35). In addition, a study has linked elevated mercury levels in the brains of mice to increased neurobehavioral effects (41). This suggests that future studies should focus on the effect of various concentrations of mercury exposure on the risk of diabetes.

Mercury exists in three forms in the environment, each with its own source of exposure and hazardous effects (42). Notably, methylmercury is the most toxic and dangerous mercury in the environment (43). The long-term consumption of methylmercury in fish and marine mammals is unavoidable due to its accumulation in the food chain (44). Methylmercury toxicity to the liver has been reported to affect the activity of key enzymes involved in glucose metabolism (45). A previous study has found that methylmercury can impair the development and function of pancreatic beta cells, resulting in insulin resistance and elevated blood sugar levels (46). However, this study measured the total mercury concentration in biological samples, making it impossible to analyze data on various types of mercury further.

Our study had some limitations. First, there was publication bias in the included studies. As no literature search in non-English language databases and no non-English articles were included in this meta-analysis, there may be language bias. We await the subsequent publication of high-quality articles to address this deficiency. Second, in addition to the insufficient number of articles included in the study, other factors, including the type of mercury (i.e., elemental, inorganic, and organic), exposure time and dose, type of biological specimen, and the population's sex and age, may have affected our judgment of the genuine relationship between mercury and diabetes, which needs to be addressed in future studies. Third, adjusting for confounding factors has an important influence on the results of our study. Adjusted OR and their 95% CI were directly extracted from most of the included original studies in this meta-analysis. However, three original studies only provided mean and SDs, but more specific data were not provided (9,30,32). Therefore, we could not adjust these results.

Conclusions

Based on the data of 40,891 patients collected from eight articles, our results revealed no association between heavy metal mercury exposure and diabetes. More research needs to be conducted to adjust for potential confounding factors and re-assess the relationship between mercury exposure and diabetes.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6404/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.

amegroups.com/article/view/10.21037/atm-22-6404/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Search strategy in PubMed

Search	Query
#1	(((((Diabetes Mellitus[Title]) OR (DM[Title])) OR (T2DM[Title])) OR (Diabetes[Title])) OR (Type 1 diabetes[Title])) OR (Type 2 diabetes[Title])
#2	((("Mercury"[Mesh]) OR (Mercury)) OR (methylmercury)) OR (Hg)
#3	#1 AND #2

Table S2 Search strategy in Embase

Search	Query
#1	“diabetes mellitus”:ti OR dm:ti OR t2dm:ti OR diabetes:ti OR “type 1 diabetes”:ti OR “type 2 diabetes”:ti
#2	“mercury”/exp
#3	mercury OR methylmercury OR hg
#4	#2 OR #3
#5	#4 AND #1

Table S3 Search strategy in Cochrane Library

Search	Query
#1	MeSH descriptor: [Mercury] explode all trees
#2	(mercury) OR (Hg) OR (methylmercury)
#3	#1 OR #2
#4	(diabetes mellitus):ti OR (dm):ti OR (t2dm):ti OR (diabetes):ti OR (type 1 diabetes):ti OR (type 2 diabetes):ti
#5	#3 AND #4

Table S4 Search strategy in Web of Science

Search	Query
#1	TI=(''Diabetes Mellitus'' OR ''DM'' OR ''T2DM'' OR ''Diabetes'' OR ''Type 1 diabetes'' OR ''Type 2 diabetes'')
#2	TS=(''Mercury'' OR '' methylmercury'' OR ''Hg'')
#3	#1 AND #2

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Table S5 Agency for healthcare research and quality (AHRQ) checklist (cross-sectional) (28) for six studies included in this meta-analysis

Item	I	II	III	IV	V	VI
1) Define the source of information (survey, record review)	1	1	1	1	1	1
2) List the inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications.	1	1	1	1	1	1
3) Indicate the period used for identifying the patients.	0	1	1	1	1	1
4) Indicate whether or not the subjects were consecutive if not population-based.	1	1	1	1	1	1
5) Indicate if the evaluators of the subjective components of study were masked to other aspects of the status of the participants.	1	1	1	1	1	1
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements).	1	1	1	1	1	1
7) Explain any patient exclusions from the analysis.	1	0	0	0	0	0
8) Describe how confounding was assessed and/or controlled	0	1	1	1	1	1
9) If applicable, explain how missing data were handled in the analysis.	0	0	0	0	0	0
10) Summarize patient response rates and completeness of data collection.	0	0	0	0	0	0
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.	0	0	0	0	0	0
Total score	6	7	7	7	7	7

Studies: I=6; II=7; III=7; IV=7; V=7; VI=7.

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Table S6 Newcastle-Ottawa Scale (NOS) (case-control) (28) for one study included in this meta-analysis

Item	Options	I
Was the case definition adequate	a. Yes, with independent validation*;	1
	b. Yes, for example, record linkage or based on self-reports;	
	c. No description.	
Representativeness of the cases	a. Consecutive or obviously representative series of cases*;	1
	b. Potential for selection biases or not stated.	
Selection of controls	a. Community controls*;	1
	b. Hospital controls;	
	c. No description.	
Definition of controls	a. No history of disease (endpoint)*;	1
	b. No description of source.	
Comparability	a. Study controls for_ _ _ (selecting the most important factor) *; b. Study controls for any additional factor* (these criteria could be modified to indicate specific control for a second important factor.)	1
Ascertainment of exposure	a. Secure records (e.g., surgical records) *;	1
	b. Structured interview blinded to case/control status*;	
	c. Interview not blinded to case/control status;	
	d. Written self-report or medical record only;	
	e. No description.	
Same method of ascertainment for cases and controls	a. Yes*; b. No.	1
Non-response rate	a. Same rate for both groups*;	0
	b. Non-respondents described;	
	c. Rate different and no designation.	
Total score		7

Study: I=7; *One point.

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Table S7 Newcastle-Ottawa Scale (NOS) (cohort) (28) for one study included in this meta-analysis

Item	Options	I
Representativeness of the exposed cohort	a) Truly representative of the average __(describe) in the community#;	1
	b) Somewhat representative of the average __in the community#;	
	c) Selected group of users e.g., nurses and volunteers);	
	d) No description of the derivation of the cohort.	
Selection of the non-exposed cohort	a) Drawn from the same community as the exposed cohort#;	1
	b) Drawn from a different source;	
	c) No description of the derivation of the non-exposed cohort.	
Ascertainment of exposure	a) Secure record (e.g., surgical records)#;	1
	b) Structured interview#;	
	c) Written self-report;	
	d) No description.	
Demonstration that the outcome of interest was not present at start of study	a) Yes# b) No.	1
Comparability of cohorts on the basis of the design or analysis	a) Study controls for __ (select the most important factor)#; b) Study controls for any additional factor# (These criteria could be modified to indicate specific control for a second important factor.)	1
Assessment of outcome	a) Independent blind assessment#;	1
	b) Record linkage#	
	c) Self-report;	
	d) No description.	
Was follow-up long enough for outcomes to occur	a) Yes (select an adequate follow-up period for outcome of interest)#; b) No.	1
Adequacy of follow-up of cohorts	a) Complete follow-up - all subjects accounted for#;	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)#;	
	c) Follow-up rate <___% (select an adequate%) and no description of those lost;	
	d) No statement.	
Score		8

Study: I=8; #One point.

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