

Meta-analysis of the Role of Mercury Exposure in Autoimmune Diseases: Pathogenic or Therapeutic

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Abstract: Researchers have long disagreed on whether mercury is pathogenic for autoimmune diseases such as psoriasis and rheumatoid arthritis, and it has also been used to treat autoimmune diseases. Exploring whether mercury is a risk factor for autoimmune diseases is important for disease treatment. In this paper, we searched Medline, Embase, and Cochrane Library databases, and collected the published literature on risk factors of autoimmune diseases from these databases to 2023-2, and performed Meta-analysis using RevMan 5.4 and Stata/SE 17.0 software. Meta-analysis results showed that exposure to mercury may be a risk factor for autoimmune diseases (OR=1.49, 95% CI: 0.30-7.29), but the risk factor for mercury correlated with the proportion of women included in the literature.

1. Introduction

Autoimmune diseases (AIDs) are a group of intractable diseases with multiple hazards that seriously affect the quality of life of patients, mainly including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type I diabetes, multiple sclerosis, and more than 70 other diseases. Among them, rheumatoid arthritis and psoriasis are the main clinical diseases^[1]. Rheumatoid arthritis has synovitis as the basic pathological change, and about 35% of patients lose the ability to work within 10 years, which seriously affects the quality of life of patients^[2,3]. Psoriasis is a chronic inflammatory skin disease with clinical manifestations of erythema covered with white scales and accompanied by varying degrees of pruritus, for which there is no ideal drug treatment at home and abroad so far^[4].

Mercury is a metal that exists in liquid form at room temperature and is highly volatile and highly toxic^[5]. Long-term exposure to excessive levels of mercury can be very damaging to the human body, causing severe damage to organs such as the liver and kidneys and eventually leading to death^[6]. However, it has been documented in the literature that mercury acts as a metalloids in the treatment of autoimmune diseases, such as rheumatoid arthritis and psoriasis, but the mechanism and effect of its action are still open to debate^[7,8]. At the same time, there are studies that prove the pathogenicity of mercury in the development of diseases. The investigation of the role of mercury in autoimmune diseases will provide a strong theoretical basis and direction for the treatment of the diseases.

2. Methods

2.1 Searching Strategy

Computerized search of databases, quality assessment of the literature was based on PRISMA guidelines. The literature was tested in the English databases Embase, Cochrane Library, Pubmed, and Medline using the same search terms (mercury, rheumatoid arthritis, psoriasis) since the database was created until February 2023, with the Embase search formula: ('mercury'/exp OR 'mercury') AND ('rheumatoid arthritis'/exp OR 'rheumatoid arthritis' OR 'psoriasis'/exp OR 'psoriasis').

2.2. Selection Criteria

The criteria for article inclusion were: ①Study type: case-control studies, systematic evaluations, or Meta-analyses on autoimmune diseases with mercury exposure published in English databases; ②Study population: patients with autoimmune diseases, age, gender, disease severity, and race were not restricted; ③Language: English literature; ④Intervention: Study subjects exposed to mercury; ⑤There are clear outcome indicators. Exclusion criteria: ①Duplicate detections and duplicate publications; ②Protocol design literature, abstract conference papers; ③Literature of low quality; ④Literature with incomplete and unclear data. Literature screening was conducted independently by 2 investigators to screen studies that met the inclusion criteria, and any disagreement was resolved through centralized consultation and discussion (at least 3 people), and third-party expert opinions were sought if opinions were still not unanimous.

2.3. Data Extraction and Literature Quality Evaluation

The OR values and 95% CI of risk factors for autoimmune diseases were extracted according to the purpose of the study. Uniform data extraction criteria were established before data extraction, and two investigators simultaneously performed literature reading and extracted data. For questionable literature, all authors discussed and decided. The Newcastle-Ottawa scale^[9] (NOS) was used to evaluate the quality of the included literature.

2.4. Data Analysis

Meta-analysis was performed using Stata/SE 17.0 software with Review Manager 5.4. Meta-analysis was performed using I² to test for heterogeneity of the included studies, and a fixed-effects model was used for Meta-analysis when the results of the heterogeneity test of the included studies were $I^2 < 50\%$, and a random-effects model was used for Meta-analysis when $I^2 \geq 50\%$. The combined OR and 95% CI were calculated to analyze whether mercury was a risk factor for autoimmune diseases. The OR values of the fixed-effects model and random-effects model for the included data and their 95% CIs were also calculated to perform sensitivity analysis of the included literature, and if the OR values of the two models were close to each other, they indicated better robustness. The publication bias of the included literature was analyzed and judged using funnel plots. Finally, the sources of bias and the associated factors were analyzed.

3. Results

In this study, 584 relevant articles were initially detected according to the search strategy, and 0 articles were obtained through other information supplementation. According to the inclusion and exclusion criteria, articles that did not match the study content, studies that were not case-control

studies and studies with low quality level were excluded, and 3 articles were finally included after screening^[10-12]. The flow of the included literature is shown in Figure 1, and the basic information of the included literature is shown in Table 1. Among the three included papers, there were 5933 cumulative cases and 5900 controls, including 9 cases of systemic lupus erythematosus, 16 cases of rheumatoid arthritis, 5861 cases of dry syndrome, and 47 patients with autoimmune diseases with no disease category specified. The literature has analyzed mercury exposure in patients with autoimmune diseases versus normal controls to investigate whether mercury exposure is a predisposing factor for autoimmune diseases. Two of the publications indicated that mercury is not pathogenic and one indicated that mercury is a causative factor for autoimmune diseases. We evaluated the quality of the included literature for NOS (Table 2), and according to the NOS scoring criteria, Stejskal V. et al. deducted 1 point for not describing the use of the same method to determine the exposure factors in the case and control groups, and 2 points for not describing the selection of the control group as the same population as the case group and controlling only for the most important confounding factors in the study by Rachmawati D. et al. Therefore, the literature included in this paper was of good quality and could be analyzed.

We then performed a heterogeneity analysis of the included literature, and the results showed significant heterogeneity in the findings of whether mercury exposure was a risk factor for autoimmune disease ($I^2=85.0\%$, $P=0.001$), so all of this study was subjected to Meta-analysis using a random effects model, and the findings showed that people with a history of metal mercury exposure may be at greater risk for autoimmune disease. The results showed a forest plot (Figure 2) that mercury may be a risk factor for the development of autoimmune diseases.

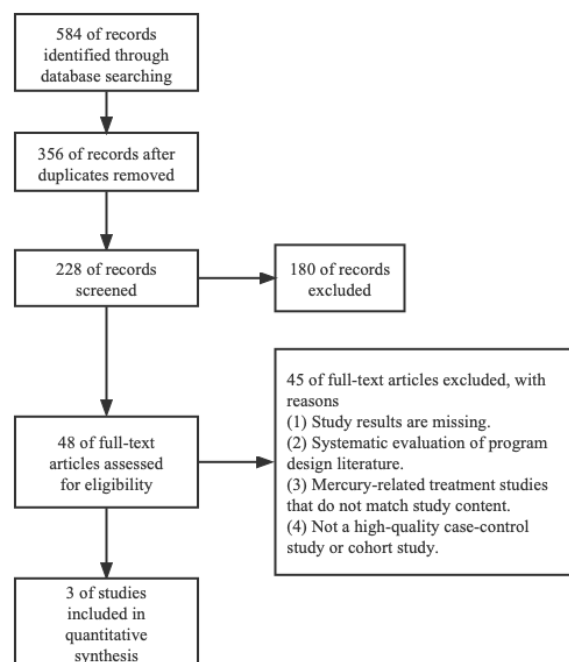


Figure 1: Flow chart of literature inclusion and exclusion.

A bias in the combined ORs and their 95% CIs was observed in the risk factor mercury studies (Figure 3, Figure 4, Table 3). Following this, funnel plots were drawn for the risk factors and the symmetry of the funnel plots was analyzed to determine the publication bias of the included literature. The results of the study showed that the funnel plot was asymmetrical and the included literature could be subject to publication bias (Figure 5), and the different doses of mercury exposure, different modes of exposure such as dental amalgam repair or ingestion of low-hygiene guaranteed seafood in

the included literature, and the difference in the gender ratio of the included studies could be factors influencing the bias in the analysis. However, due to the available data, only the gender factors that may influence the pathogenicity of mercury have been further correlated here. The results of the study showed that the proportion of females in the affected group had a significant effect on the risk factor for mercury ($r=0.997$, $p \leq 0.05$) (Table 4).

Table 1: Basic information and NOS scores of included literature.

Inclusion in the literature	Number of cases (T/C)	Age(x ±s)	Results Indicators	NOS Score
Stejskal V 2015	38/41	T: 51 years old C: 52 years old	Mercury is pathogenic	8
Chen KH 2021	5848/5848	T: 58.32 ±16.94 years C: 58.21 ±17.5 years	Mercury may be pathogenic	9
Rachmawati D 2015	47/11	T: 51 years old C: 49 years old	Mercury is not pathogenic	7

Note: T. Case group; C. Control group

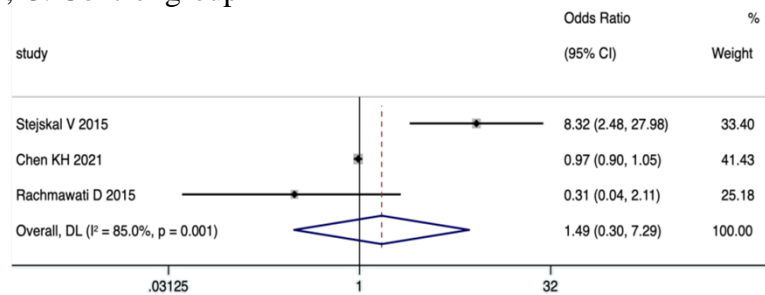


Figure 2: Forest plot of the correlation between mercury exposure and autoimmune diseases.

Study	Odds Ratio	[95% Conf. Interval]	% Weight
Stejskal V 2015	8.325	2.480 - 27.980	33.40
Chen KH 2021	0.974	0.900 - 1.050	41.43
Rachmawati D 2015	0.307	0.040 - 2.110	25.18
Overall, DL	1.491	0.305 - 7.292	100.00

Table 2: NOS quality evaluation of included literature.

Inclusion of articles Evaluation items	Appropriateness of cases	Representativeness of cases	Selection of controls	Identification of controls	Comparability of cases and controls	Certainty of exposure factors	Uniformity of approach	Non-response rate	Total score
Stejskal V 2015	1	1	1	1	2	1	0	1	8
Chen KH 2021	1	1	1	1	2	1	1	1	9
Rachmawati D 2015	1	1	0	1	1	1	1	1	7

Table 3: Comparison of calculated results of fixed-effects and random-effects models for autoimmune diseases.

Study omitted	Estimate [95% Conf.]	
	Fixed effects model	Random effects model
Stejskal V 2015	-0.03 [-0.11, 0.05]	-0.16 [-0.89, 0.57]
Chen KH 2021	1.22 [0.19, 2.26]	0.57 [-2.66, 3.79]
Rachmawati D 2015	-0.02 [-0.09, 0.06]	0.96 [-1.14, 3.05]
Overall, DL	-0.02 [-0.10, 0.06]	0.40 [-1.19, 1.99]

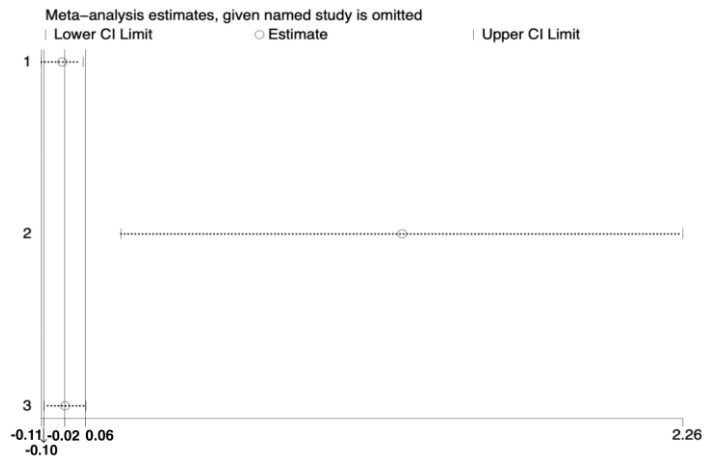


Figure 3: Fixed-effects model for correlation analysis of mercury exposure and autoimmune diseases.

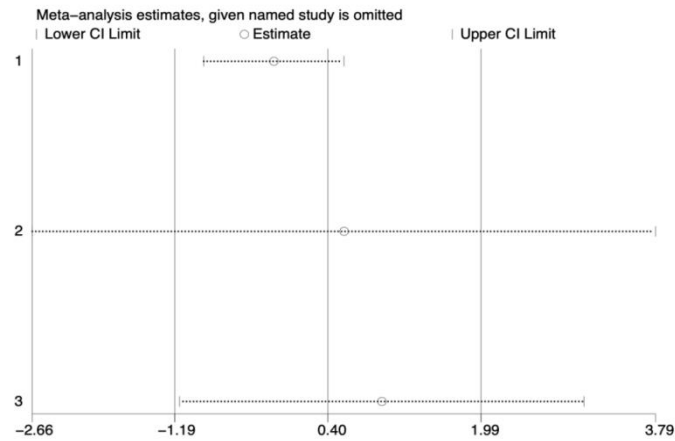


Figure 4: Random effects model for correlation analysis of mercury exposure and autoimmune diseases.

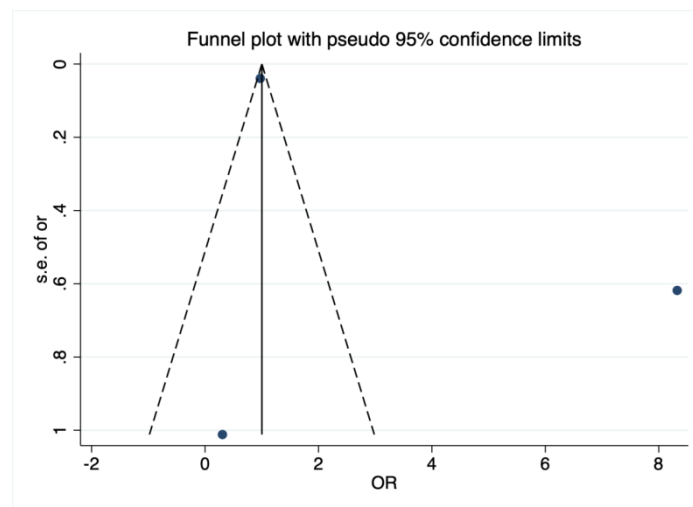


Figure 5: Funnel plot of correlation analysis between mercury exposure and autoimmune diseases.

Table 4: Correlation between the percentage of females in the diseased and control groups and the mercury risk factor.

	OR	nvT	nvC
OR	1.000		
nvT	0.997	1.000	
	0.050		
nvC	0.303	0.378	1.000
	0.804	0.754	

Note: OR. correlation coefficient between mercury pathogenicity and autoimmune diseases. nvT. proportion of females in the disease group; nvC. Proportion of females in the control group

4. Discussion

The main role of the immune system is to recognize and eliminate foreign antigens, and if the immune system mistakenly attacks its own normal components, it may lead to the development of autoimmune diseases^[13]. Autoimmune diseases are difficult to cure, and most patients require long-term or even lifelong medication. And some of them are dangerous, affecting the quality of life of patients in mild cases or endangering their lives in severe cases. However, the etiology of most autoimmune diseases is still unclear, and environmental factors play an important role in the pathogenesis of autoimmune diseases. Among them, the role of mercury, a metallic substance, is controversial.

A total of 5933 patients were included in the three papers included here. In the included studies, there were both views of the pathogenicity of mercury for autoimmune diseases and the absence of pathogenicity; The results of the Meta-analysis suggest that mercury may be a risk factor for autoimmune diseases. The data available for analysis in this study are limited and do not provide a complete picture of the causes of the bias in the pathogenicity of mercury, but there is a correlation between the proportion of women in the affected group and the occurrence of autoimmune diseases caused by mercury. In addition, the influence of the amount of mercury exposure of patients, as well as their lifestyle habits (presence of smoking, alcoholism, dietary ratio, etc.) and physical condition (Body mass index, presence of other diseases) on the pathogenicity of mercury should be taken into account. Waciewicz Muczyńska M^[14] made detailed statistics on the amount of mercury exposure of patients and measured their blood mercury levels. The results showed that the autoimmune occurrence was not significantly correlated with blood mercury levels.

Previous studies have suggested that mercury induces autoimmune diseases and that mercury-induced autoimmune responses are characterized by T-cell-dependent polyclonal B-cell proliferation, increased serum immunoglobulin (IgG1 and IgE) concentrations, increased production of specific antibodies, and formation of renal IgG deposits^[15]. It has also been shown that mercury aggravates the pathological state of autoimmune diseases such as lupus in susceptible strains of rats and mice, suggesting that mercury-induced autoimmune diseases are closely related to individual susceptibility and genetic factors^[16]; Hultman et al^[17] showed that the pathogenicity of mercury is related to the dose of mercury, with high doses of mercury being highly toxic and low doses having immunomodulatory effects. The pathological state of autoimmune diseases in mice was observed to show an aggravating trend after 10 weeks of intervention with different doses of mercury, indicating that the development of autoimmune diseases was positively correlated with the dose of mercury intake. And in an environment with fewer inflammatory factors, low doses of mercury lead to a skewed immune response toward a Th2 response^[18]. In a study by Guan T^[19] similarly indicated that blood mercury concentrations were negatively correlated with arthritis in autoimmune diseases when patients had blood mercury concentrations less than 5 ug/L. In a study by Roether^[15] it was shown that prolonged exposure to mercury leads to suppression of mercury-induced autoimmune responses

and loss of corresponding pathological features, and that control of the major histocompatibility complex (MHC) gene may be a major cause of immunosuppression [20-23].

The relationship between mercury and autoimmune diseases is still a question that is being explored, and it has been documented that mercury has been used for a long time as a treatment for autoimmune diseases such as psoriasis. Due to the limitations of the literature, the conclusions reached in this study need to be further confirmed by more high quality, multicenter, and real studies with large samples.

Limitations of this study: First, the literature documents that the observed population is ethnically different from the country, and it is not yet possible to determine whether population ethnicity leads to publication bias. Second, the literature does not cover all autoimmune diseases, which may make the conclusions uncertain for those diseases not covered. Again, different studies have different definitions and descriptions of symptoms and comorbidities, and different time points for laboratory index testing, leading to greater heterogeneity in the initial analysis. In conclusion, the conclusions drawn from this study need to be further confirmed by more high-quality, multicenter, real studies with large samples.

Declarations

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Disclosures: None.

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