

The Relationship Between the Level of Copper, Lead, Mercury and Autism Disorders: A Meta-Analysis

This article was published in the following Dove Press journal:
Pediatric Health, Medicine and Therapeutics

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Background and Objectives: There is a likelihood of a possible relationship between the concentrations of copper, lead, and mercury and autism. The present review was carried out to determine the relationship between the concentrations of these elements and autism by meta-analysis.

Methods: In this study, searching Scopus, PubMed, and Science Direct databases, 18 articles conducted in different countries from 1982 to 2019 were collected. Studies' heterogeneity was investigated using the I^2 index. The data were analyzed using R and STATA software.

Results: In these 18 studies, 1797 patients (981 cases and 816 controls) aged 2 to 16 years were examined. Concentration of the samples (blood, hair, and nails) for both case and control groups was evaluated. There was no significant relationship between copper concentration and autism (SMD (95% CI): 0.02 (-1.16,1.20); $I^2=97.7\%$; $P=0.972$); there was a significant relationship between mercury concentration and autism (SMD (95% CI): 1.96 (0.56,3.35); $I^2=98.6\%$; $P=0.006$); there was also a significant relationship between lead concentration and autism (SMD (95% CI): 2.81 (1.64,3.98); $I^2=97.8\%$; $P=0.000$).

Conclusion: There is, nevertheless, a significant relationship between mercury concentration and autism. Thus, the concentration of mercury can be listed as a pathogenic cause (disease-causing) for autism.

Keywords: autism, copper, lead, mercury, meta-analysis

Introduction

Autism is a developmental disorder of social relations which is determined through individuals' abnormal communicative and verbal behaviors. Symptoms of this disorder occur before the age of three, and its etiology is still unknown.¹⁻³ This disorder is more prevalent in boys than in girls and several studies showed a strong genetic background to the appearance of autism spectrum disorders (ASD).³ This disorder affects the normal brain development in different ways and causing some symptoms related to Difficulty in social interaction and communication skills. According to the studies carried out in this area, it is suggested that mercury and other toxic elements are involved in the pathogenesis of autism.⁴ Similar effects have also been mentioned for essential minerals and trace elements in the development of autism spectrum disorder.⁵ Compared with adults, children are more exposed to environmental toxic elements and the rate of absorption of such elements are higher in children. On the other hand, the chance of warding off

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elements' toxicity in children is less than adults.⁶ The study was done by Lonsdale et al confirms the relationship between heavy metals' toxicity and the risk of mental disorders.⁷ In a study by Priya et al, the researchers were able to prove the relationship between copper concentration and severity of autism disorders, examining the samples of hair and nails of the children with autism.⁸ Metals' biological effects are associated with their chemical properties,⁹ suggesting that excessive metal exposure can cause brain abnormalities around the world.¹⁰ Mercury is considered as a risk factor for autism⁴ since, according to previous studies, it has been recognized as a neurotoxic toxin.¹¹ Reduction in mercury content in hair¹² and teeth¹³ of the children with autism aroused the low disposal of mercury hypothesis. Blaurock-Bush et al found that heavy metals are effective in the development of autism disorder.¹⁴ The role of mercury in the pathogenesis of autism has also been proven in other studies.^{2,4,15} Copper is considered as one of the metals essential for cell metabolism, and it plays an important role in the oxidation-reduction reaction.¹⁵ Lakshmi Priya et al observed that copper level in children with autism corresponded with the severity of autism disorder in a way that a higher level of copper was found in hair and nail samples of the children with less severe symptoms of autism than those of children with moderate and severe symptoms.¹⁶ The neurotoxic effects of copper include depression, irritability, fear, unrest, as well as learning and behavioral disorders.¹⁷ Considering the previous studies on the relationship between heavy metals and autism, for validating their results, it seems necessary that a meta-analysis study be conducted to determine the authenticity or lack of relationship between the concentrations of copper, lead, and mercury and autism and to provide a reliable pattern in the field for the researchers and planners. The present study aimed to determine the relationship between the concentration of copper, lead and mercury and autism using meta-analysis and systematic review.

Methods

Data Sources and Search Strategy

This article was written according to the PRISMA guidelines. Study protocol N/A. Using a systematic review, the present study was carried out to determine the relationship between the concentration of copper, lead, and mercury and autism. To collect the data, the articles published in national and international journals as well as presentations

and theses in national and international electronic and non-electronic databases, such as SID, Magiran, Irandoc, Iranmedex, PubMed, Embase and Scopus were used. The keywords used to find the articles included autism, copper, mercury, lead, heavy elements, and toxic elements. English equivalents of these keywords were used to search the international databases to scan through all the possible combinations of keywords. Having studied all the abstracts, unrelated papers and articles were removed, and all potential papers and articles were identified to be studied in full text.

Study Selection (Inclusion and Exclusion Criteria)

All cross-sectional that measured amount of copper, lead and mercury with autism were selected. The main inclusion criteria for the studies was referring to the relationship between the elements and autism. Study selection was carried out based on an article review in three stages: title, abstract and full text. All of the included studies investigated the relationship between the elements and autism. Studies were excluded from the analysis for any of the following reasons: studies with insufficient information, non-epidemiological studies, non-cross-sectional studies, and studies on the effects of other elements on autism. Review studies, congress summaries, studies published in languages other than Persian and English, meta-analyses and systematic studies as well as reduplicated publication of the same studies were also excluded from the analysis. The researcher first collected all papers on the relationship between the elements and autism and then prepared a list of the abstracts. At this point, 84 articles in the title of which the concentration of elements (copper, mercury, and lead) and autism had been used entered the preliminary list. Reviewing the reference lists of the articles, 11 other articles also entered the study. That is, a total of 95 articles entered the study. Then, all of the articles were independently and systematically reviewed, 38 of which were excluded from the study due to reduplication. The full text of 57 articles was evaluated, 39 of which were also excluded from the study (13 studies due to lack of reference to the type of criteria used; 18 studies due to their low quality; and 8 studies due to lack of access to the full-text of the articles). Eventually, 18 articles were selected as appropriate to be included in the meta-analysis (Figure 1).

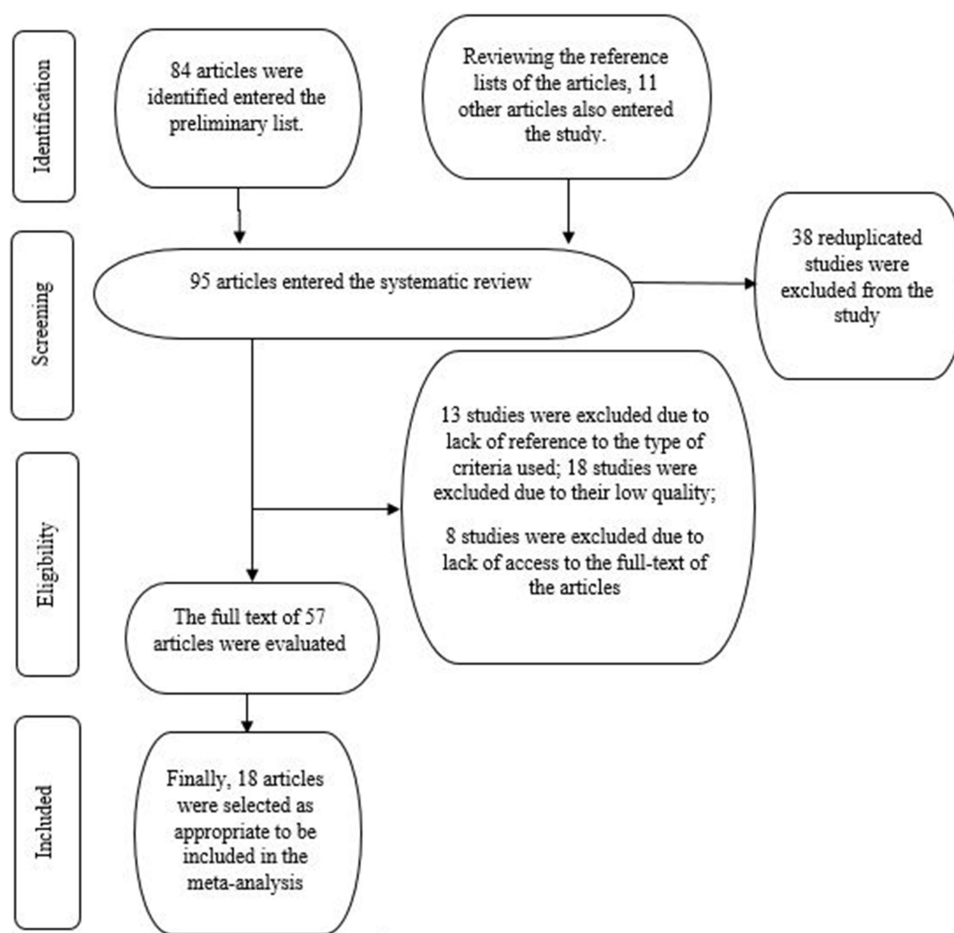


Figure 1 Flowchart for inclusion of the studies in the systematic review and meta-analysis.

Data Extraction

Having selected high-quality articles, a checklist of the necessary information for all the preliminarily evaluated studies was prepared for the final evaluation. Accordingly, in this study, 21 articles in which random sampling was used to determine the samples were examined. Subsequently, a form was designed consisting of multiple pieces of necessary information for the studies (investigator's name, title, year, location, the number of samples, the total prevalence of the study based on various criteria, and the patients' mean age and body mass index). Next, the basic data for this study were entered in the chart to be analyzed. The full text of the articles was examined for the analysis.

Statistical Analysis

Given that the rate of autism and concentration of elements (copper, mercury, and lead), as well as the number of samples in each article, were extracted. Variance of

each study was calculated according to the binomial distribution. Studies were combined based on their sample sizes, means and standard deviations. The difference between the average variance of normal distribution was calculated using the formula of two integrated variances. Due to the heterogeneity in the studies, random effects model was used in combining studies and Cochran Q test and I^2 statistics were used. P-value less than 0.05 were considered as a significant Heterogeneity test. The average variance was calculated using the formula of two integrated variance. The mean difference was computed using the formula $d = \frac{\bar{x}_1 - \bar{x}_2}{s}$, in which \bar{x}_1 is the case mean, \bar{x}_2 is the control mean, s is the pooled sample standard deviation defined as $s = \sqrt{s^2}$. Where it is calculated using $s^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}$ were the variances of the case group and control groups, respectively, n_1 and n_2 equals the number of participants in each group.

Statistical analyses were performed using STATA version 12.

Table 1 Overall Data of the Selected Studies in This Meta-Analysis

Author References	Year	Country	Autism				Healthy Controls				Type of Sample	Type of Measurement		
			Age (Mean)	N	Cu (m ±SD)	Hg (m ±SD)	Pb (m ±SD)	Age (Mean)	N	Cu (m ±SD)			Hg (m ±SD)	Pb (m ±SD)
Wecker.L ⁵	1985	USA	2-11	12	12.3±1.9	15.2±0.6	12.6±1.6	12.6±1.6	2-11	21	26.3±2.7	15.2±0.3	10.7±1.2	Atomic Absorption
Eisheshaway.E ¹⁸	2011	Egypt	4	32	26.5±1.9	0.55±0.06	9.75±1.8	9.75±1.8	4.1	32	19.1±4.4	3.2±0.2	6.8±0.86	Atomic Absorption
De Palma.G ²⁴	2012	Italy	9	44	10.2	0.5	1.3	1.3	8.4	61	9.4	0.25	0.8	ICP-MS
Adams.J ¹³	2006	USA	7.1	51	34.6	0.29	0.62	0.62	7.5	40	33.4	0.29	0.81	ICP-MS
Blaurockbusch.E ¹⁴	2012	KSA	3-9	44	133.8±115.4	3.35±4.8	4.56±1.4	4.56±1.4	3-9	146	0.72±0.09			ICP-MS
Adams.J ²⁵	2011	USA	5-16	55	0.76±0.08				5-16	44	9.62±1.15	2.87±0.34	16.2±1.94	ICP-MS
Lakshmi. M.D ¹⁶	2011	India	4-12	45	18.4±2.3	4.02±0.47	20.18±2.36	20.18±2.36	4-12	50	12.31±1.4	0.37±0.04	1.56±0.18	Atomic Absorption
Lakshmi. M.D ¹⁶	2011	India	4-12	45	24.04±2.88	1.61±0.19	7.72±0.92	7.72±0.92	4-12	50	19.69±9.95	0.3±0.31	0.01±0.01	Atomic Absorption
Blaurockbusch.E ²³	2011	KSA	3-9	25	21.94±21.7	0.47±0.42	0.01±0.02	0.01±0.02	3-9	25	6.6±0.7		6.3±0.8	ICP-MS
AL-Farsi. YM ²⁶	2012	Oman	1-14	27	1.2±0.1		12.2±1.1	12.2±1.1	3-14	27	10±4		4.7±3.4	ICP-MS
Shearer. TR ²⁷	1982	American	8	12	11±22		3.5±3.3	3.5±3.3	8.4	12		0.25±0.16	2.06±2.45	Atomic Absorption
El BazMohamed.F ²⁸	2015	Egypt	6.2	100		0.39±0.37	3.31±3.92	3.31±3.92	6.8	100		10.7±4.3		Atomic Absorption
Geier.D.A ²⁹	2010	USA	7.3	83		22.2±12.1			11.4	89				Cold Vapor Analysis
Torsdottir.G ³⁰	2005	Iceland	18-35	13	16.8						17.1			Atomic Absorption
Jeff Brad.M.D ³¹	2003	USA	3-15	221		4.06±8.59	18.2±43.3	18.2±43.3	3-16	18		1.29±1.54	11.8±8.6	ICP-MS
Holms.A.S ¹²	2003	USA	2-15	94		0.47±0.28			2-15	45		3.63±3.56		ICP-MS
Yassa.H.A ³²	2014	Egypt	2-10	45		4.02±0.54	55.24±10.02	55.24±10.02	2-10	45		0±0.02	9.75±0.58	Atomic Absorption
Yassa.H.A ¹⁹	2014	Egypt	2-10	45		5.21±0.08	60.04±9.75	60.04±9.75	2-10	45		0.11±0.05	12.03±0.45	Atomic Absorption
Macedoni.M ³³	2014	Slovenia	6.2	52	20.57±3.29	1.9±0.97	30.8±34.33	30.8±34.33	6.6	22	19.87±4.12	1.55±0.56	18.6±7.24	FAAS&EAAS &VAAS
Obrenwich.ME ¹⁷	2011		<6	26		0.25	0.6	0.6	<6	39		0.6	0.66	

Table 2 The Relationship Between the Concentrations of Copper, Lead, and Mercury and Autism in Terms of Number and Type of Studies Included in the Meta-Analysis

Element	Subgroup	NO. of Date from Studies	I ²	SMD(95% CI)	P value for Significant	Z
Sample CU	Serum and plasma	1	0.000%	0.47(0.07,0.87)	0.021	2.31
	Blood	1	0.000%	0.20(-0.30,0.70)	0.439	0.77
	Hair	8	97.8%	-0.75(-2.29,0.80)	0.344	0.95
	Nail	1	0.000%	4.91(4.10,5.72)	0.000	11.84
Sample Hg	Serum and Plasma	2	90.2%	0.83(-0.10,1.76)	0.082	1.74
	Blood	2	99.3%	5.43(-4.48,15.35)	0.283	1.07
	Hair	7	98.9%	1.74(-0.64,4.12)	0.152	1.43
	Nail	1	0.000%	2.83(2.26,3.40)	0.000	9.69
Sample Pb	Serum and Plasma	1	0.00%	0.15(-0.33,0.63)	0.532	0.62
	Blood	2	99.0%	3.40(-2.47,9.27)	1.13	0.257
	Hair	8	98.1%	3.18(1.47,4.89)	3.65	0.000
	Nail	1	0.000%	1.85(1.37,2.33)	7.52	0.000

For sensitivity analysis we did analysis with outlier and without outlier studies. Sensitivity analysis shows that there was not any influential study to change the results essentially (referred to part B each fig). Depending on the analyzed data, usually need to determine publication bias and drawing the Beggs funnel plot.

Results

The present study systematically reviewed 18 articles conducted from 1982 to 2019, in which 1797 patients (981 cases and 816 controls) aged 2 to 16 years were examined. Average concentrations of copper, mercury and lead in samples of hair, nails, and plasma of the children with autism and a control group in studies included in the meta-analysis are presented in [Table 1](#).

Of the 18 articles included in the study, 13 articles were on hair samples, 1 article was on nail samples, 3 articles were on plasma samples, and 2 articles were on blood samples. [Table 2](#) shows that there was no significant relationship found in hair and blood samples; however, a significant relationship was found in studies with plasma and nail samples ([Table 2](#)).

The highest concentrations of copper, lead and mercury in children with autism were respectively reported in studies by Blaurock-Bush et al in the US (133.8±1154 in the hair sample), Geier et al in the US (22.2±12.1 in the plasma sample), and Yassa (2014) in Egypt (60.04±9.75 in the hair sample). The lowest levels of concentrations of copper, lead and mercury in children with autism were, respectively, reported in studies by Adams (2011) in the US (0.76±0.08 in the nail sample), Obrenovich (2012) (0.25

in the hair sample), and Blaurock-Bush et al in the US (0.01±0.02 in the hair sample).

Copper

The results of the study indicate that there was no significant relationship between copper concentration and autism (SMD (95% CI): 0.02 (-1.16, 1.20); I²=97.7%; P=0.972) ([Figure 2A.Cu](#)).

CU concentrations were measured in serum and plasma, blood, hair and toenails. There are differences between sample source concentrations in the studies.

Subgroups analysis showed that there are significant relationship between serum and plasma concentration 0.47 (95% CI: 0.07–0.87) and nail 4.91 (95% CI: 4.10–5.72) with autism, which means concentration in children with autism was higher than the concentration of CU in the control group. In blood 0.20 (95% CI: -0.30–0.70) and hair -0.75 (95% CI: -2.29–0.80) no significant relationship ([Table 2](#)).

Sensitivity analysis showed that by carrying out the sensitivity analysis and removing the studies demonstrating significantly different results, this result is significant ([Figure 2B.Cu](#)). The result of the publication bias figure also indicated that there was no error (P=0.413) ([Figure 2C.Cu](#)).

Mercury

There was a significant relationship between mercury concentration and autism (SMD (95% CI): 1.96 (0.56–3.35); I²=98.6%; P=0.006) ([Figure 3A.Hg](#)).

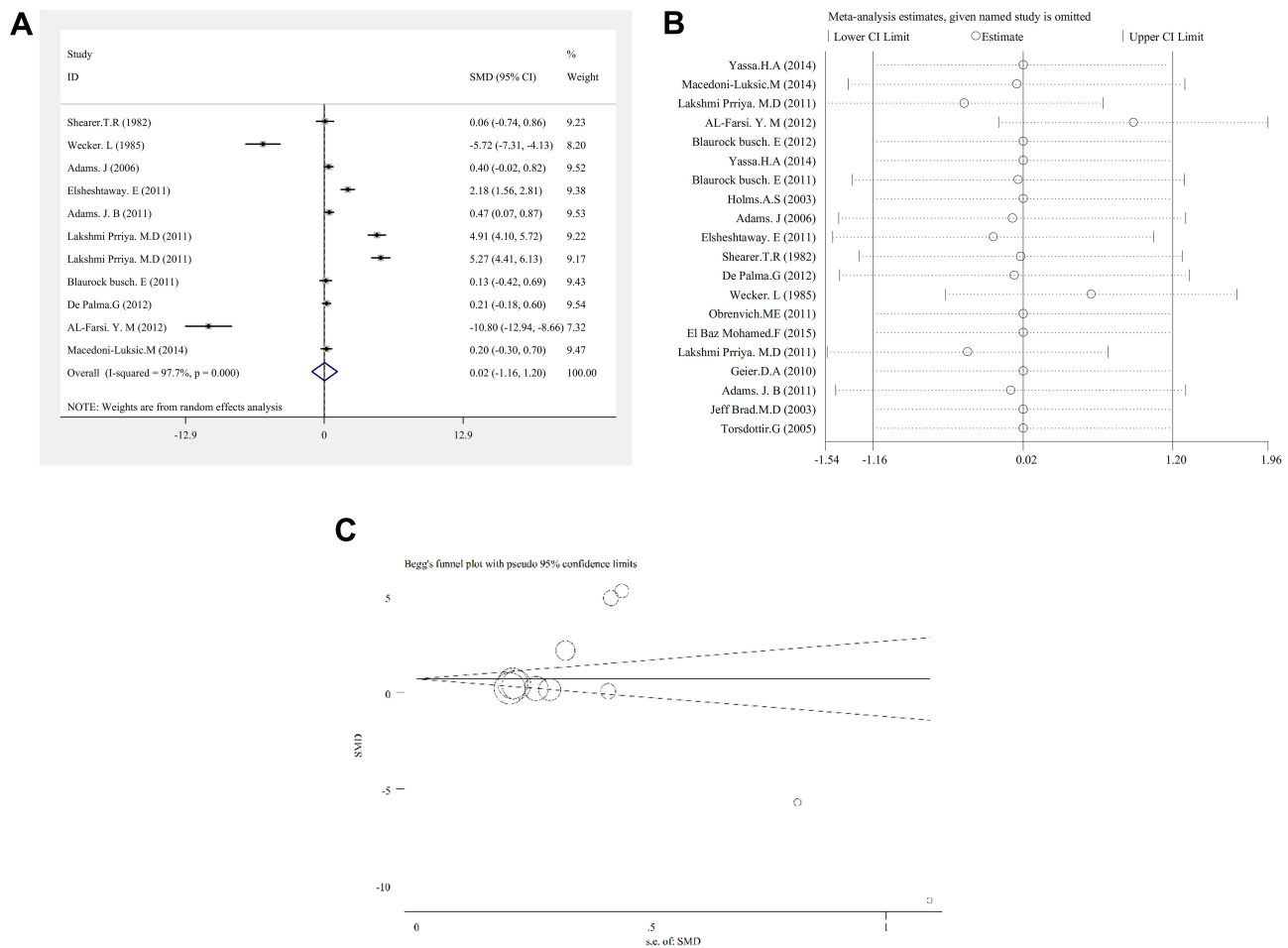


Figure 2 (A) Forest plots for the studies Cu concentration statuses combination difference between autistic patients and healthy individuals. The area of each square is proportional to the percentage weight of each individual study in the meta-analysis (CI 95%). In this chart, studies are stored in order of year publication and author's names, based on a random effects model. (B) Sensitivity analysis for studies in overall study copper for autism patients versus healthy controls. (C) Begg's funnel plot for publication bias in the risk difference (RD) analysis. The diameter of each circle represents the weight in the meta-analysis.

Sensitivity analysis showed that by carrying out the sensitivity analysis and removing the studies demonstrating significantly different results, this result is also significant (Figure 3B.Hg). The result of the publication bias figure also revealed that there was no error here.

Lead

There is a significant relationship between lead concentration and autism (SMD (95% CI): 2.81 (1.64–3.98); I²=97.8%; P=0.000) (Figure 4A.Pb). Sensitivity analysis showed that by carrying out the sensitivity analysis and removing the studies demonstrating significantly different results, this result is also significant (Figure 4B.Pb). The result of the publication bias figure showed that there was an error.

Discussion

The present study was performed using meta-analysis to investigate the concentration of copper, mercury, and lead in samples of hair, nails and plasma in 2–16-year-old samples, showing that there was no significant difference between the concentration of copper in children with autism and those of a control group (95% CI:0.02 (-1.16, 1.20)).

These results are consistent with the findings of Luksic et al and Elsheshtaway.^{18,19} On the other hand, Lakshmi Priya and Geetha (2011) found that levels of copper concentration in hair and nail samples of the children with different degrees of autism severity showed a high statistical difference compared to those of the control group.¹⁸ Weker et al found that the mean copper concentration (ppm) in the hair of children with autism was lower than that of the control group (12, 3 vs. 26, 3).⁵

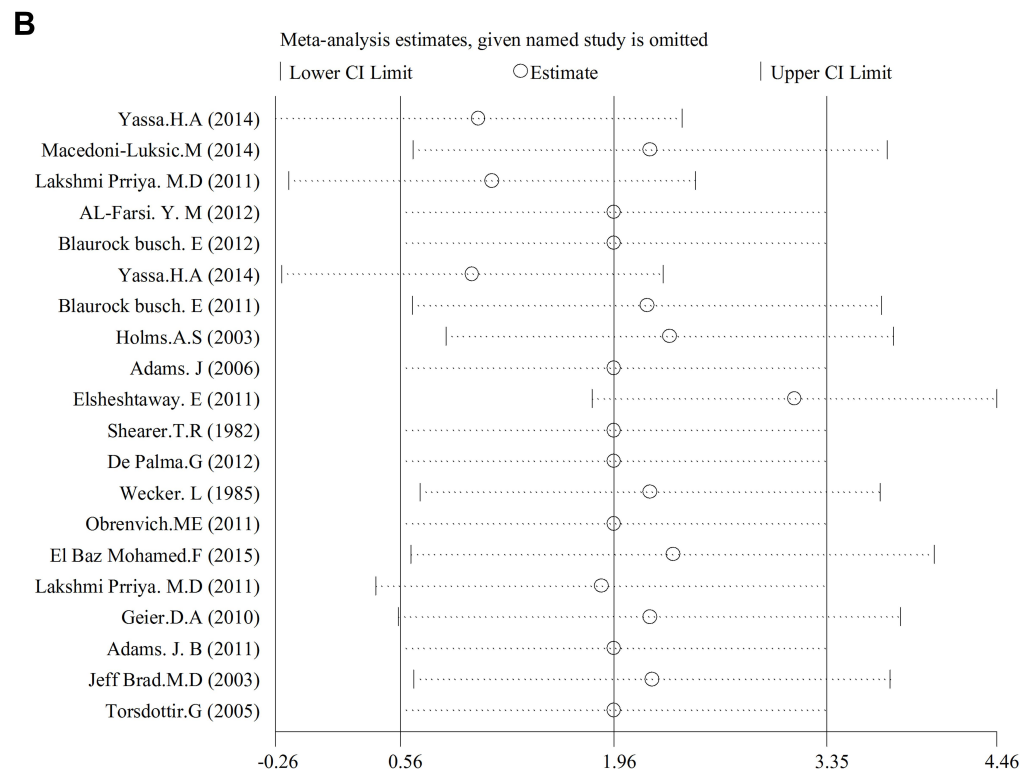
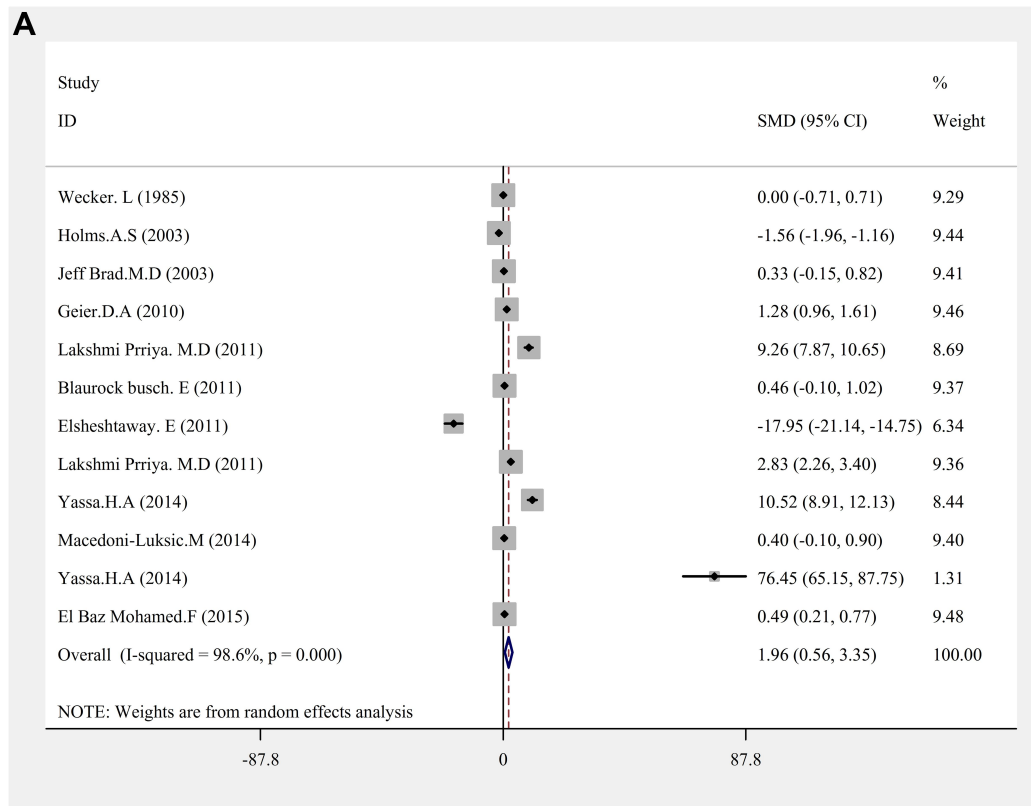


Figure 3 (A) Hg. Forest plots for the studies Hg statuses combination difference between autistic patients and healthy individuals. The area of each square is proportional to the percentage weight of each individual study in the meta-analysis (CI 95%). In this chart, studies are stored in order of year publication and author's names, based on a random effects model. **(B)** Hg. Sensitivity analysis for studies in overall study for autism patients versus healthy controls.

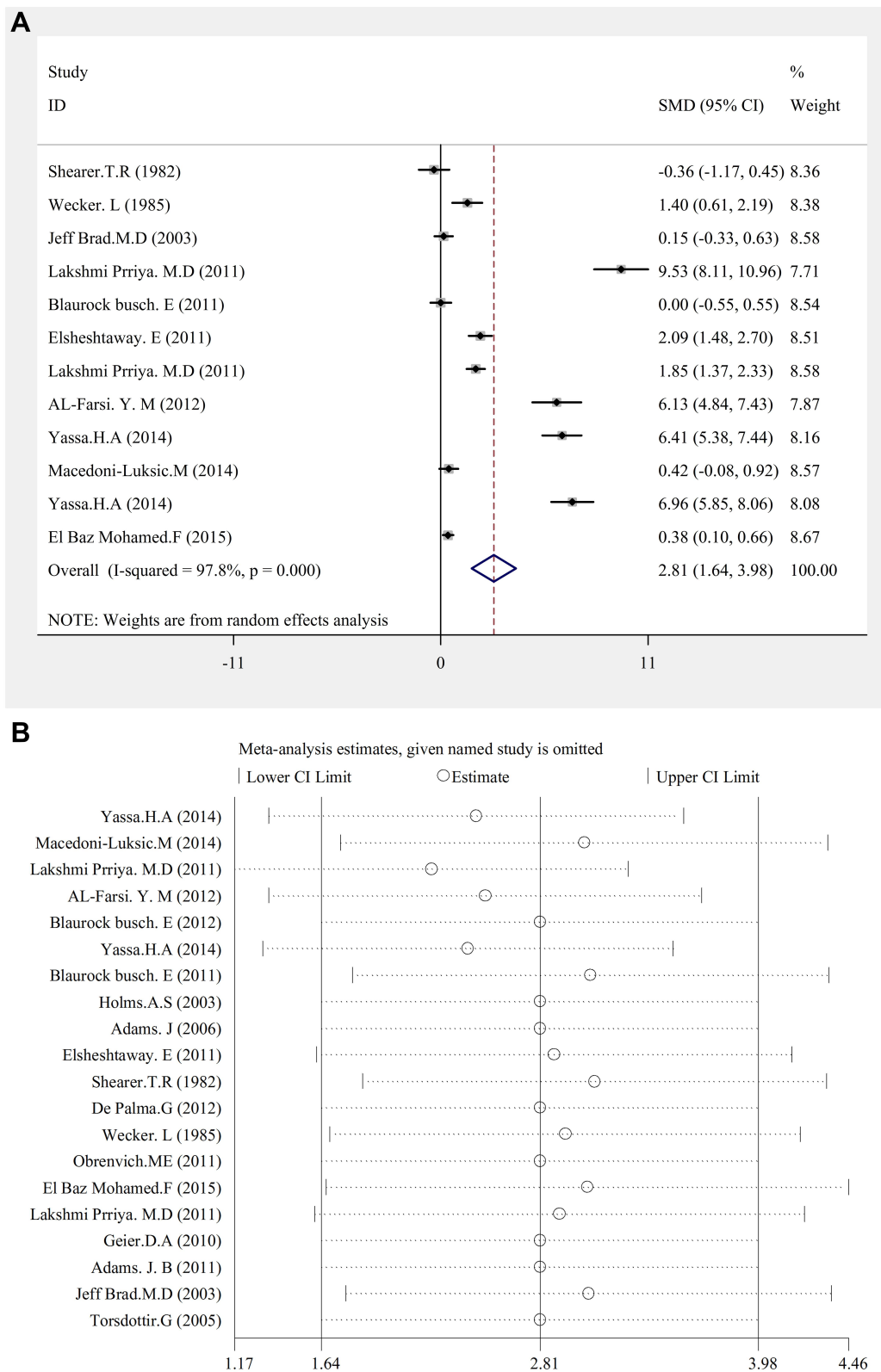


Figure 4 (A) Pb. Forest plots for the studies Pb statuses combination difference between autistic patients and healthy individuals. The area of each square is proportional to the percentage weight of each individual study in the meta-analysis (CI 95%). In this chart, studies are stored in order of year publication and author's names, based on a random effects model. **(B)** Pb. Sensitivity analysis for studies in overall study for autism patients versus healthy controls.

The difference in results could be due to differences in methods of measuring the concentration of copper, mercury, and lead and the amount of children's exposure to the elements before and after their birth. In this study, there was a significant relationship between the concentration of mercury in plasma samples and nails and autism (95% CI: 1.96 (0.56, 3.35)). This result shows that heavy elements are directly related to the incidence of diseases, such as autism. This finding is in agreement with the results of other studies.^{3,4,7,14,17,18,20-22}

The results of the present study revealed that there is a significant relationship between lead concentration and autism (95% CI: 2.81 (1.64, 3.98)). This finding is also line with the results of other studies.^{4,5,7,18,20-23}

Human hair accurately evaluated for trace element value regarding observing either the environmental-occupational exposure to toxic metals level of body upon long exposure duration. In a study by Elsheshtaway, lead concentration in the hair of children with autism ($9.75 \pm 1.8 \mu\text{g}/\text{mg}$) was higher than the concentration of lead in the control group ($6.8 \pm 0.86 \mu\text{g}/\text{mg}$).^{18,24}

Adams et al study discuss about the role of age and autistic children are exposed to toxic metals. In this study, the amount of mercury level was $0.21 \mu\text{g}/\text{g}$ (age 3–6 years), also in NHANES study (1999–2000) of 838 children (1–6 years) $0.12 \mu\text{g}/\text{g}$ reported.

According to points raised in the present study about the relationship between copper, mercury, and lead (risk factors) and the development of autism, it would be quite reasonable to advise prevention of exposure to mercury and lead in children and provision of suitable conditions during the sensitive period of mothers' pregnancy as vital measures to prevent the disease from infecting the children. The main limitation of this meta-analysis study was the high heterogeneity among the studies. Random effects model was a way to reduce this heterogeneity. Some other limitations and weaknesses of the study include:

1. The absence of an identical method to measure the variance.
2. Lack of information about the participants' nutrition and lifestyle
3. Diversity of screening methods and lack of a standard unit to measure the concentration of elements in various articles.
4. Lack of access to some relevant studies

Conclusion

According to the results of this study, there is no significant relationship between copper and lead concentration and the development of autism. There is, nevertheless, a significant relationship between mercury concentration and autism. Thus, the concentration of mercury can be listed as a pathogenic cause (disease-causing) for autism.

Acknowledgments

The authors extend their gratitude to the Arak University of Medical Science.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this article. The authors report no conflicts of interest for this work.

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