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ORIGINAL ARTICLE

The Risk of Exposure To Pesticides on Autism Disorder: a Systematic Review and Meta-analysis

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KEYWORDS

Autism;
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ABSTRACT: There are always concerns about the environmental and human consequences of the widespread use of pesticides. This study aimed to determine the role of pesticides in the development of autism spectrum disorders in children through meta-analysis .All studies (11 articles) that had the potential to be used in our study were exported in EndNote X8 software and reviewed by authors. We extracted the required data, and we used Stata software (version 12) to analyze the pooled effect. Random and fixed-effect models were used to determine the combined estimation using the "metan" command.The results showed exposure to organochlorine pesticides could increase the risk of autism by 32% (OR=1.32; 95% CI: 1.14-1.53). The first trimester of pregnancy had the highest risk for autism (OR=1.23; 95% CI: 1.15-1.31). The cumulative meta-analysis showed a decreasing trend for crude and adjusted odds ratio over time. This study showed that exposure to pesticides can increase the risk of autism, and the time of exposure to pesticides is associated with the risk of autism. These results came as the cumulative meta-analysis results for crude and adjusted odds ratios showed a decreasing trend over time.

INTRODUCTION

Pesticides are known as a large and heterogeneous group of chemicals [1] and one of the few toxic substances deliberately used in the environment to kill organisms such as weeds, insects, fungi, and rodents. Pesticide is often mistakenly used to only refer to insecticides, although it includes herbicides, fungicides, and various other materials that are used to control pests [2]. Generally, over the last century, pesticides and chemical substances have played a crucial role in global agricultural systems leading to a significant increase in crop and food production.[3].

Nevertheless, there have always been concerns about the impact of the widespread use of pesticides on the environment and human health. In *The Silent Spring*, Carson specifically addresses this issue and discusses the related problems. [4]. Human occupational exposure to pesticides during the production and application process is predictable. This is while, general population exposure through contaminated water and food is unexpected [5]. On the other hand, the use of pesticides to control and eliminate annoying pests is one of the main sources of both local and world population exposure to hazardous substances. [6].

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Autism spectrum disorder (ASD) is a chronic disease in childhood that has harmful effects on adaptive functioning throughout the human life span [7-9]. ASD is a developmental disorder defined by diagnostic criteria, including impairments in communication and social interactions, limited presence, repetitive behavior, interests, or activities that can be maintained over a lifetime [10]. This usually occurs in early childhood before the age of three. Boys are four-five times more likely to be diagnosed with autism than girls [11]. An evidence suggests that genetic and environmental factors contribute to the development of ASD [12-14]. But so far, there has been no reported scientific evidence supporting the effect of these environmental factors on autism [15-18].

Organochlorine pesticides are classified as a group of toxins that have the potential to cross the placenta, [19], and affect the pathways of ASD and neurodevelopment, including endocrine disruption and its effects on the immune, reproductive and nervous systems. . In a study, Roberts et al. report that maternal exposure to pyrethroid and bifenthrin during the critical period of pregnancy, is associated with an increased risk of ASD [25]. Exposure to low organophosphorus pesticides doses may also impair the development of the nervous system, especially if it occurs after childbirth, when the child's brain is developing rapidly and lacks the ability to detoxify [26].

As noted above, there is still insufficient information on the impacts of the environmental factors, including pesticides, on neurodevelopmental disorders such as autism. Therefore, this study aims to provide a systematic and meta-analysis of the role of pesticides in the development of autism spectrum disorders in children.

MATERIALS AND METHODS

Search Strategy

In this study, we used the guideline of PRISMA 2009 [27] (Preferred Reporting Items for System reviews and Meta-Analyses) that is a statement for a systematic review report and meta-analysis. We examined five electronic databases, including Web of Science, Scopus, Google Scholar, PubMed, and ProQuest, to access titles and abstracts by the end of 2018. We also searched manually for references of previous articles and review articles to find eligible studies. Only studies in English were included. The keywords to search were included *Autism OR autism spectrum disorder AND Pesticides*. These words were adjusted for each database. All the studies export to EndNote X8, and we eliminated duplicate articles.

Study Selection

In the present study, we reviewed and selected the researches that examine the association of maternal exposure to pesticides with autism. The studies that examine exposure to a combination of environmental pollutants and pesticides were excluded. The current study considered those researches that link between pesticides and autism. In addition, the studies that do not report odds ratio (OR), relative risk (RR), confidence interval (CI), or standard error (SE), and use inadequate data to calculate the parameters were excluded. Also, the present study does not contain previous systematic reviews, letters to the editor, and case reports. The authors' names or the titles of the journals had no effect on the selection of articles. Finally, 11 articles were reviewed in the meta-analysis (Figure 1).

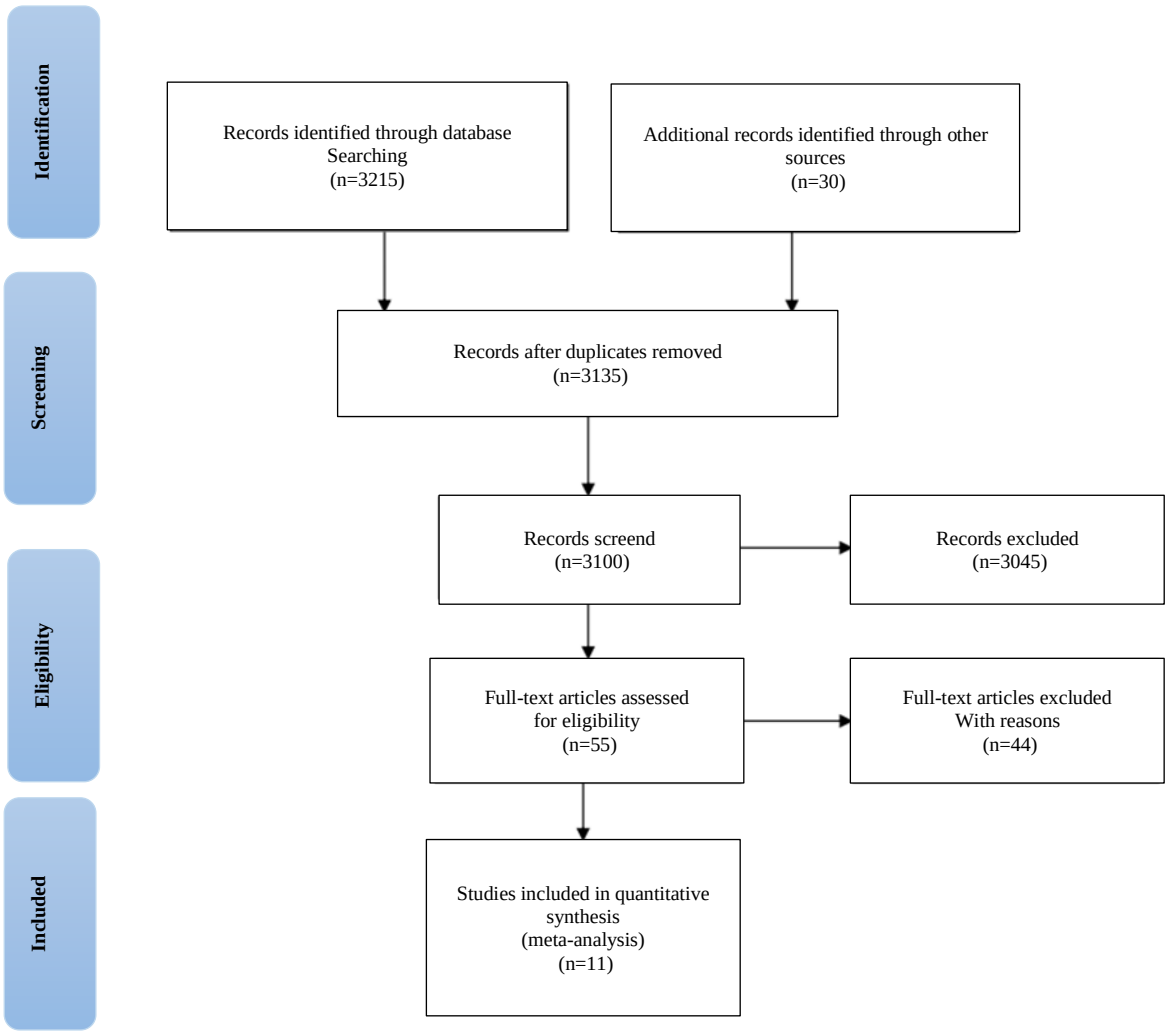

Figure 1. Flow diagram of publication inclusion in the meta-analysis

Data extraction

All the selected studies were entered in EndNote X8 software and reviewed by three independent authors. The disagreement between the investigators was resolved by two experts through discussion. Then, we obtained the full text of the eligible studies. In cases where there was no original information in the articles, we communicated with the authors via email. In all cases, the authors responded after three attempts, and the problem was resolved. We extracted the required data and imported it into a form designed by the authors. Data extraction includes: First author's name, country, year of publication, sample size, type of pesticide, the amount of pesticide exposure, number of patients with ASD and autism, 95% confidence interval, crude and adjusted RR and OR.

Quality assessment

The risk of bias [28] in all included studies was low. In one of the studies, the risk of allocation concealment bias was high and also the risk of attrition bias in two studies was high [29].

Table 1. Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Rebecca J. chmidt	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Alan S. Brown	Low Risk	Low Risk	Low Risk	Low Risk	Unclear	Low Risk	Low Risk
MacKinsey A.Christian	Low Risk	High Risk*	Unclear	Unclear	High Risk*	Low Risk	Low Risk
Chenxiao	Unclear	Low Risk	Unclear	Unclear	Low Risk	Low Risk	Low Risk
Steven D. Hicks	Unclear	Unclear	Unclear	Unclear	Unclear	Low Risk	Low Risk
Claire Philippat	Low Risk	Unclear	Unclear	Unclear	Unclear	Low Risk	Low Risk
Janie F. Shelton	Low Risk	Low Risk	Unclear	Unclear	High Risk*	Low Risk	Low Risk
Keely Cheslack Postava	Low Risk	Low Risk	Unclear	Unclear	Low Risk	Low Risk	Low Risk
Sharon K.Sagiv	Unclear	Low Risk	Unclear	Unclear	Unclear	Low Risk	Low Risk
Kristen Lyall	Low Risk	Low Risk	Unclear	Unclear	Unclear	Low Risk	Low Risk
Eric M. Roberts	Low Risk	Low Risk	Low Risk	Unclear	Low Risk	Low Risk	Low Risk

Statistical analysis

We used Stata software to analyze the pooled effect. Random and fixed-effect models were used to determine the combined estimation using the "metan" command. Overall crude odds ratios for exposure to pesticides were calculated using a fixed-effect model by pesticide type. Pooled crude odds ratios for different regions were determined using the fixed effect model. The risk of autism in exposure to pesticides at different gestational ages (three trimesters) was also assessed using the fixed effect model. Finally, cumulative meta-analysis was performed for both crude and adjusted odds ratios. Cochran's Q test was used to detect heterogeneity among studies. Higgins and Thompson I^2 were also used to determine the degree of heterogeneity between studies.

RESULTS

11 articles were found on the topic, and meta-analysis was conducted up to 2018 (Table 2).

Three articles were not included in the meta-analysis. Since article 4 reports β, article 5 does not consider unexposed patients in the baseline for calculating the odds ratio, and article 7 is not categorized into four pesticide groups, i.e. organochlorine, organophosphate, carbamate and pyrethroid, these three articles were not included in the meta-analysis.

Results by crude odds ratio

Exposure to all pesticides

Exposure to pesticides increases the risk of autism. The overall adjusted odds ratio shows that the risk of autism in the exposure to pesticides increases by 23% (OR=1.23; 95% CI: 1.15-1.31) (Figure 2).

Table 2. Details of Studies in the Meta-Analysis

	Ref.	year	Country	Study Design	Type of Pesticide	Outcome
1	[30]	2017	California	Case-control	Any agricultural pesticides	ASD
2	[31]	2018	Finland	Case-control	organochlorines	Autism
3	[32]	2017	United States	Retrospective cohort	aerial pyrethroid pesticide	ASD
4	[33]	2018	United States	-	organophosphorus	Restricted& Repetitive Behaviors
5	[34]	2017	United States	Case-control	organochlorines	ASD
6	[35]	2013	Finland	pilot study	organochlorines	ASD
7	[36]	2018	United States	Case-control	Fungicide, Herbicide, Insecticide	Autism
8	[37]	2018	United States	cohort	organophosphorus	ASD
9	[38]	2014	United States	Case-control	Organophosphorus, Pyrethroids, Carbamates	ASD
10	[39]	2019	Jamaica	Case-control	organochlorines	ASD
11	[25]	2007	California	Case-control	organochlorine	ASD

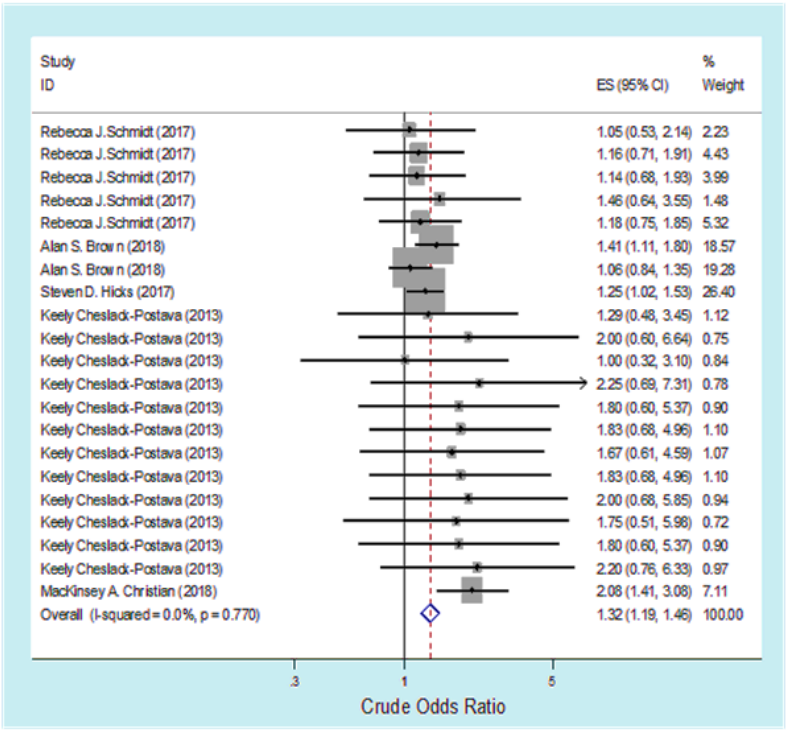

Figure 2. Total analysis using the Fixed Effect Model for Crude Odds Ratio.

Exposure by type of pesticide

The crude odds ratios for exposure to each type of pesticides showed that organochlorine pesticides could increase the risk of autism by 32% (Figure 3).

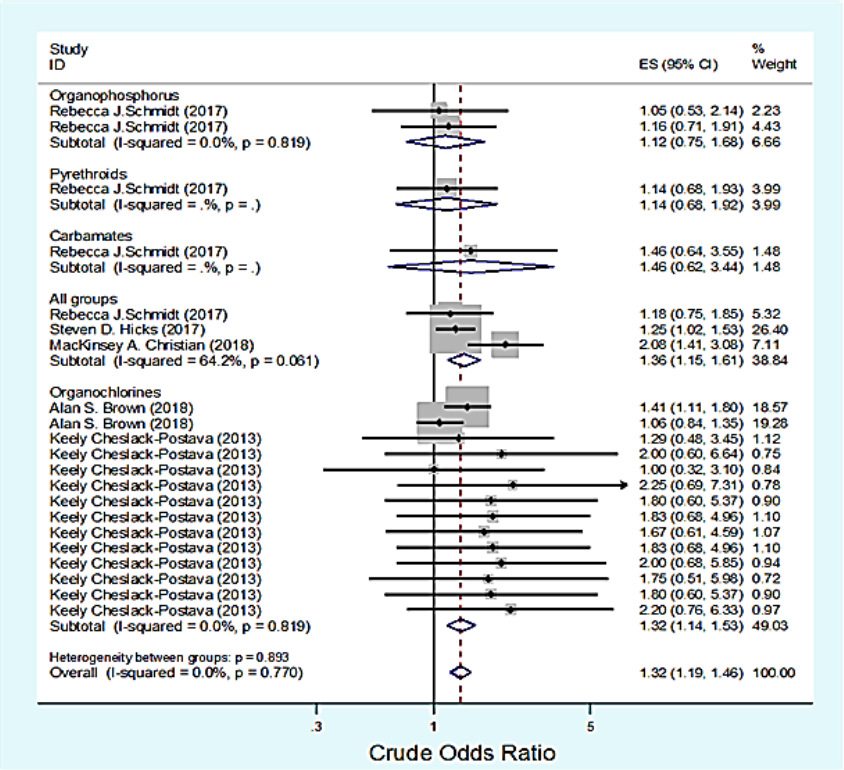

Figure 3. Analysis by pesticide type using the Fixed Effect Model for Crude Odds Ratio.

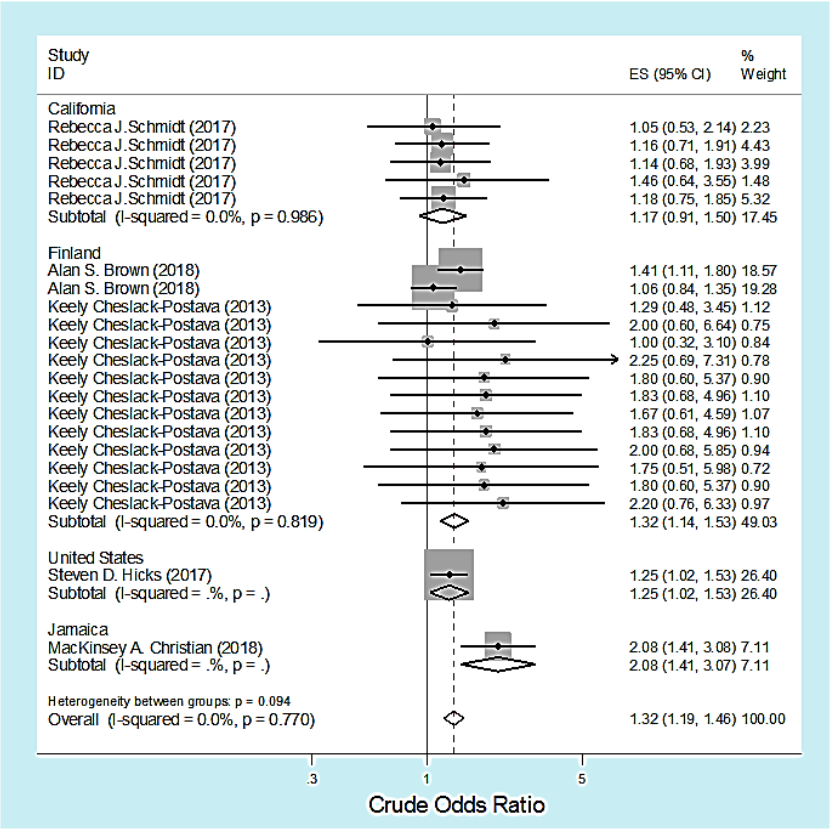

Figure 4. Country-based analysis for Crude Odds Ratio using the Fixed Effect Model.

Exposure by different regions

The crude odds ratios for different regions were also analyzed according to the region mentioned in the articles. This was done using a fixed effects model. The results show that exposure to pesticides increases the risk

of autism by 32 and 25 percent in Finland and the United States, respectively. . And in the case of Jamaica, the risk was doubled (OR=2.08; 95% CI: 1.41-3.07) (Figure 4).

Results by adjusted odds ratio

Exposure by different gestation periods

In three studies, different pregnancy periods are also investigated. The results show that exposure to pesticides in the first trimester of pregnancy has the highest risk of autism (OR=1.23; 95% CI: 1.15-1.31) (Table 3).

Exposure by type of pesticides & regions

As shown in Table 3 Exposure to pesticides increase the risk of autism by 67 percent. According to the results of the fixed effects model, Jamaica has the highest risk of autism due to exposure to pesticides. More information is given in Table 3.

Cumulative meta-analysis for crude and adjusted OR

Finally, cumulative meta-analysis was performed for crude and adjusted odds ratios. The cumulative meta-analysis shows decreasing trend in crude and adjusted odds ratio over time (Figure 5).

Table 3. Analysis using Fixed Effect Model for Adjusted Odds Ratio by different variables.

Variables		OR (95% CI)	P for Heterogeneity	I^2 (%)
Pesticide Type	Organophosphorus	1.06 (1-1.12)	<0.001	51.4
	Pyrethroids	1.47 (1.31-1.65)	-	-
	Carbamates	1.52 (1.04-2.23)	0.83	-
	Organochlorines	1.16 (0.99-1.36)	0.5	43.3
	All groups	1.67 (1.07-2.58)	-	-
Regions	California	1.25 (0.87-1.79)	0.44	-
	Finland	1.14 (0.95-1.36)	0.35	10
	United States	1.13 (1.07-1.18)	<0.001	42.2
	Jamaica	1.67 (1.07-2.58)	-	-
Pregnancy	Gestational	1.12 (1.04-1.2)	0.04	32.1
	1st Trimester	1.37 (1.15-1.62)	0.96	-
	2nd Trimester	1.18 (1.06-1.31)	0.01	46.3
	3rd Trimester	1.09 (1-1.18)	0.001	59.5

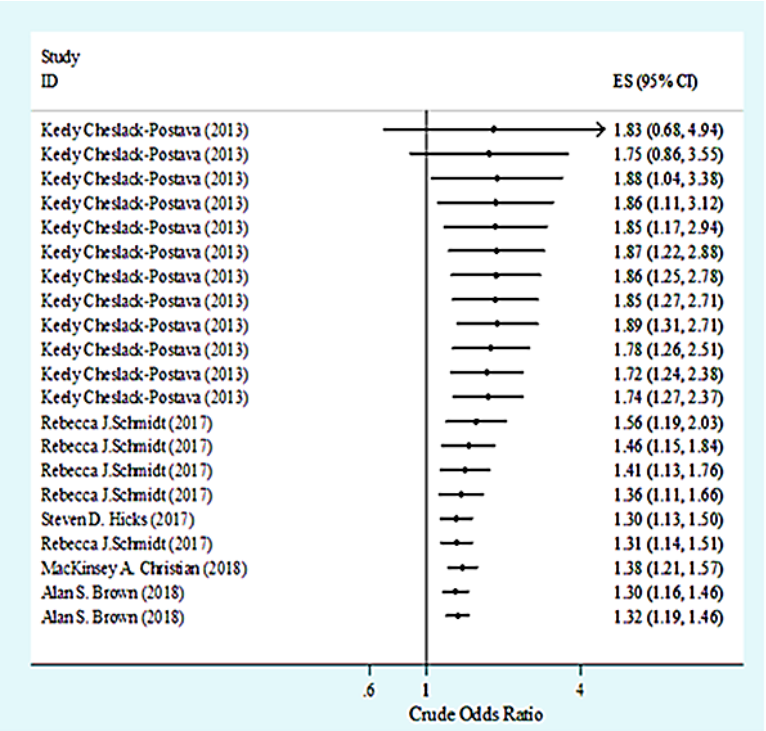

Figure 5. Cumulative meta-analysis for the Crude Odds Ratio

DISCUSSION

Exposure to pesticides during pregnancy and childhood is an environmental risk factor for autism spectrum disorder [25, 40]. Although autism was previously considered rare, recent prevalence estimated show that 1.7 to 2.6 percent of children in developed countries are affected by autism [40]. Autism Spectrum Disorder (ASD) is a complex neurological disorder with poor cognitive etiology [31]. The present study was conducted to investigate the effect of pesticides on autism spectrum disorders.

In the meta-analysis, the odds ratio of autism in the fixed effects model increased by 32%. In this study, the autism spectrum disorders in offspring of pregnant mothers were investigated. An increase in the odds ratio may be due to disorders that occur in the normal development of the child's brain because the development of the nervous system occurs in very structured stages [32, 41]. Exposure to pesticides during embryonic and early stages of life alters activities such as synaptogenesis, glycogenesis, myelination, and apoptosis. Exposure to pesticides in pregnancy is predicted to lead to functional and behavioral changes. These changes are likely to be permanent. The function of neurotransmitters can be altered if these exposures are prolonged. However, the possibility of this is low [42, 43].

Another meta-analysis result was the odds ratio analysis based on the type of pesticide exposure. The results showed that The results show that exposure to organochlorine pesticides would increase the risk of autism by 32%. Part of these results is related to the study of Brown et al (2018). They investigate prenatal exposure to organochlorine pesticides and the risk of autism using maternal exposure markers. To this end, they scrutinize the effects of persistent organic pollutants, such as fatty acid-containing halogenated organic compounds, including diphenyl trichloroethane and its metabolites including p, p: - dichloro diphenyl dichloroethane (p, p: -DDE) and Polychlorinated biphenyls (PCBs). Their study show that the risk of autism significantly increases among children with increasing levels of p, p: -DDE. The highest rate is for the 75th percentile, which significantly increases with advanced maternal age and history of psychiatric disorders (odds ratio=1.32, 95% CI=1.02, 1.71) [31]. Another part of the results in the present meta-analysis is related to the study of Postava et al. (2013). They investigate the relationship between prenatal exposure to

persistent organic pollutants (POPs) and autism. The results of their study show that POPs were detected at various levels in the serum samples of the subjects before birth. In addition, they indicate that a higher quality level of the whole PCB might be associated with the risk of childhood autism. [35]. In all of these studies, the effect of PCBs is noticeable. Another research highlights that polychlorinated biphenyls are closely related to neurological cognitive effects [44].

In Finland and the United States, the odds ratio of autism due to exposure to pesticides increases by 32 and 25 percent, respectively and in Jamaica, the risk is doubled. In addition, adjusted odds ratios due to exposure to pesticides are also evaluated. The results show that Jamaica has the highest risk of autism due to exposure to pesticides. Perhaps one of the reasons is the rate of pesticide use, and genetic variation among different nations. In the present meta-analysis, it was not possible to investigate this variable as a moderating variable in meta-analysis and explain the percentage of variance difference between studies. Various studies have shown that a number of genes have been identified that are strongly linked to autism in different societies. Therefore, it can vary from 60 to 90 percent depending on biological inheritance [45]. A study compares genetic susceptibility to organophosphorus pesticides in American and Italian families. This study reveals that American children have specific protein-coding genes causing less enzyme activity due to diazinon pesticide [46]. In their study, Roberts et al. (2007) investigateprenatal exposure to nearby pesticide during critical pregnancy periods. Therefore, residential proximity to agricultural fields during pregnancy may also be associated with autism spectrum disorder in children. This factor can justify the odds ratio in the United States [25]. According to Schmidt et al., folic acid is another factor which makes difference in the odds ratio of autism.This study declares that pregnant women with folate deficiency in exposure to pesticides are 2.5 times more likely to have children diagnosed with autism compared to those with higher intake of folic acid [30]. In order to conduct a regression analysis to prove this effect, other studies were also considered to examine this change. A study asserts that prenatal exposure to oil colors may be one of the reasons for the high rate of autism in Jamaica. These environmental factors may alter the relationship between maternal exposure to pesticides and ASD. Therefore, they apply their effects on odds ratios. . In the present study, exposure to pesticides in the first trimester of pregnancy shows the highest risk of autism (OR=1.23; 95% CI: 1.15-1.31). Some other studies have shown that exposure to pesticides can affect the early stages of growth in the uterus. (cell proliferation, migration, and cell differentiation) [41]. This issue is investigated more closely by Roberts et al. (2007). They investigate the risk of autism spectrum disorders immediately before and concurrently with the formation and development of the fetal central nervous system (First to eighth fetal weeks). For children whose mothers had the highest quartile of organochlorine exposure within 500 m of the fields, risk of autism at the CNS growth stage were significantly increased compared to the other group, also in stage A posteriori (26 to 81 days after pregnancy). [25]. In some studies, the effect of pesticides on autism spectrum disorders has also been observed at the other stages.[47]. This evidence strongly supports the effect of pesticides on the autism spectrum disorders.

Cumulative meta-analysis results for crude and adjusted odds ratios show a decreasing trend over time. However, the prevalence of autism has dramatically increased over the past two decades [48]. This decreasing trend could be due to the ban on the use of some pesticides, especially in developed countries [49]. Due to the heterogeneity of the studies included in the present meta-analysis, we did not examine other aspects such as household income and the comparison of autism in different genders. It requires a systematic literature review. It is hoped that the present research could help to shed light on the matter of autism in connection with exposure to pesticides.

CONCLUSIONS

The results of this study showed that exposure to pesticides could increase the risk of autism. The time of exposure to pesticides is associated with the risk of autism, so exposure to pesticides in the first trimester of pregnancy had the highest risk of autism. These results came as the cumulative meta-analysis results for crude and adjusted odds ratios showed a decreasing trend over time. The epidemiological data presented in these studies

indicate the human results in the early stages of development. Therefore, genetic studies in the future are needed to confirm the causal factors mentioned in this study.

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Conflict of interest

The authors declare that there is no conflict of interest.

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