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Review Article

Association between dental amalgam fillings and multiple sclerosis: A systematic review and meta-analysis

Ali Taghavi Zonouz[1], Fatemeh Pournaghi Azar[2], Solmaz Pourzare[1], Hossien Hosinifard[3], Zahra Molaei[4*]

[1]Department of Oral Medicine, Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Operative dentistry, Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Tabriz University of Medical Sciences, Tabriz, Iran
[4]Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran

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Abstract

Introduction: Mercury is a neurotoxic element that is released from dental amalgam restorations. Since circumstantial evidence exists that the pathology of multiple sclerosis (MS) disease might be in part caused or exacerbated by inorganic mercury, we conducted a systematic review and meta-analysis using a comprehensive search strategy.

Methods: Data bases (PubMed, Google scholar, Cochrane, Embase, Scopus, Ovid, Proquest, and Web of Science) were searched systematically to find the relationship between dental amalgam and MS. Studies were screened according to a pre-defined protocol. The quality of the articles was evaluated by two individuals. The titles and abstracts of the articles were organized and duplicate articles were discovered with the help of Endnote X5 resource management software. Finally, 6 articles were included in the meta-analysis. Random effect model was chosen to conduct the meta-analysis.

Results: Pooled mean difference of restoration numbers between two groups was 0.58 (95% CI: 0.33-0.83, *P* value < 0.001) with greater numbers in MS patients. The pooled OR was 1.02 (95% CI, 0.86-1021, *P* = 0.81), which was slightly higher for those with amalgam so they were more likely to develop MS. This slight increase in risk was not statistically significant.

Conclusion: Although those who underwent a large number of amalgam fillings were at higher risk for MS, the difference between the two groups of patients and controls was statistically insignificant. It seems that the number of amalgam fillings can be an influential factor in the possibility of developing MS.

Introduction

Dental amalgam has been used since the early nineteenth century.[1] This restorative material consists of approximately fifty percent of metallic alloys (silver, copper, tin) and 50% of elemental mercury.[2] Mercury used in dental restorations accounts for about 10% of world consumption of mercury and is its biggest global consumer.[3]

Amalgam restorations constantly release a small amount of mercury vapor. The amount of vapor release depends on the amount of amalgam used, tooth type and the number of repaired surfaces, chewing, food structure, its composition and age, brushing and dental abrasion. The absorption rate of inorganic mercury through gastrointestinal is less than 10%.[4]

Neurodegenerative diseases are increasingly affecting populations around the world, and are characterized by the loss of neural structures and its function.[5] The cause of these diseases is unknown, but there are several accepted theories, such as genetics,[6] and the accumulation of abnormal proteins in nerve tissues and environmental factors, including heavy metals, can play a more prominent role.[7]

Multiple sclerosis (MS) is the most common cause of non-traumatic disability in young people The global prevalence of MS is increasing along with its socioeconomic effects. The cause of its increasing prevalence is unknown, however, the main reason is the complex interaction of genes and the environment. Some of the most influential factors in this disease are: childhood overweightness, smoking, the Epstein–Barr virus infection and low vitamin D levels in plasma.[8] Both developed and developing countries have an increasing rate of MS.[9]

This autoimmune disease, which affects the central nervous system, causes progressive demyelination due to chronic inflammation.[10] Prevalence of MS disease have been reported as low as 2 per 100 000 in East Asia and in South Africa to as high as 100 per 100 000 in Europe and North America.[11] The symptoms of this disease include difficulty walking, fatigue, vision loss, sexual function

***Corresponding Author:** Zahra Molaei, Email: Zahra.molayi@gmail.com

disorder, intestinal problems, and etc.[12]

About 75% to 80% of the breathing mercury vapor enters the bloodstream quickly through respiration and is circulated throughout the body by the bloodstream.[13,14] Elemental mercury can pass through the blood brain barrier easily before being ionized.[15] It was found that mercury levels in the brains of patients with MS are 7.5 fold increased.[16] Despite low levels of mercury in the brain, people with genetic predisposition are more at risk for these diseases.[17-19]Acute contact to mercury vapor or lead had caused several MS epidemics occurrence.[20] Destruction of Schwann cells was found in animal models due to inorganic mercury exposure. These cells are responsible for making myelin sheaths and facilitating nerve conduction. Low concentrations of mercury ($HgCl_2$) are toxic to oligodendroglial cells and contact with low concentrations of $HgCl_2$, in MO3.13 cell line leads to apoptosis.[21] Heavy metals like mercury can destroy myelin basic protein by producing antibodies (autoimmune pathogenesis).[22] Decreased nerve conduction due to myelin sheaths destruction and blood-brain barrier derangement are seen in both mercury exposure and MS. [23,24]

In mercury-intoxicated animals, a decrease in neuronal RNA and protein production was observed, which caused the death of these neurons. Other disorders reported in animals exposed to mercury include enzymatic disorders in the glycolytic pathway of the brain, unusual excitation spikes in the neurons, and degenerative changes in nerves. The most sensitive cells to mercury are the granule cells of cerebellum and sensory neurons of spinal ganglia.

Systematic reviews and meta-analyses have shown increasingly important in medical studies.[25]

The relationship between inorganic mercury with neurons vacuolar degradation and organic mercury with coagulation neuron degradation has been proven by studies.[26-28]

Several studies have evaluated the association of mercury in amalgam restorations and MS occurrences. Due to the widespread use of amalgam in dental restorations especially in posterior teeth, the safety of mercury in it, including its neurological side effects, should be further studied. The high prevalence of MS, the unknown etiological factors associated with it, and the conflicting results of previous studies have led us to study the relationship between dental amalgam and pathogenesis of MS. For this reason, we arranged a systematic review and meta-analysis of resources.

Methods

We searched resources systematically to investigate the association between dental amalgam and the possibility of MS based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[25]

Search strategy

The PubMed, Google scholar, Embase, Scopus, Cochrane, Proquest, Web of science and Ovid databases were used to search articles from January 1995 up to May 2020. The following keywords were selected based on Medical Subject Heading (MeSH) terms and their combinations were used to search for articles:

(‘’ silver restoration(s) ‘’ OR ‘’ amalgam ‘’ OR ‘’ dental amalgam ‘’) AND (‘’ multiple sclerosis ‘’ OR ‘’ ms ‘’ OR ‘’ multiple sclerosis, chronic progressive ‘’ OR ‘’ multiple sclerosis, relapsing-remitting ‘’ OR ‘’ sclerosis, multiple]).

In addition, the reference lists in related articles and reviews are also considered as eligible studies. Data were extracted by two reviewers using data extraction form and according to the inclusion and exclusion criteria. In cases of disagreement between the two evaluators, a third person intervened.

Study selection and eligibility criteria were as follows: Observational studies which investigated the relationship between amalgam restorations and MS diseases, published from January 1995 to May 2020. The articles in which effect size was reported as mean ± SD of amalgam filling numbers or odds ratio (OR) with 95% confidence interval (CI). Articles published in English language with available full texts.

The following studies were excluded: animal studies, laboratory studies, systematic reviews, case reports, invalid theories, letters to the editor or suggestions, as well as duplicate articles that used the same sample information, articles of poor quality, and studies published in languages other than English.

Quality assessment

Using JBI (Joanna Briggs Institute) appraisal checklist for systematic review of observational studies the included articles were assessed by two specialists in oral medicine (AT, SP). Independent and low quality studies were excluded. The studies selected by the two reviewers were evaluated for risk of bias. In the cases of disagreement between the two reviewers, a third person intervened.

Data extraction

After the information was obtained, they were entered into the extraction table. The data extracted included the name of first author, publication year of the articles, the study type, the race of the subjects, the sample and control group size, and the number of restorations and OR with 95% CI in the subjects studied. The titles and abstracts of the articles were organized and also duplicate articles were discovered with the help of Endnote X5 resource management software.

Statistical analysis

The comprehensive Meta-Analysis v.20 (CMA Englewood, NJ, USA) was used for data analysis of data extracted from the selected articles. A significant level of *P* value was considered as less than 0.05. Mean ± SD of amalgam restorations and OR with 95% CI were used for data

interpretation.

The heterogeneity between studies was assessed by the Cochrane scores (Q) and I2, which shows the percentage of changes between studies. If the I^2 statistical values were less than 50%, the fixed effects model was used. If it was more than 50% or *P* value < 0.05, random effects model was chosen for calculating the overall effect size.

Results

Characteristics of included studies

A complete search of all the databases obtained 1920 articles, and then 282 duplicate articles were deleted by EndNote software. After manually deleting duplicate items, 1575 articles remained in the search results. Finally, only 6 articles that were relevant to the topic were selected. OR data were reported in 5 articles and the mean ± SD data were reported in 3 of the articles. The articles based on their data were included in the meta-analysis. Two of the articles that had both types of data were meta-analyzed twice. The flow chart for the identified and read articles is shown in Figure 1. We demonstrated the attributes of the included articles and patients in Table 1.

Publication bias

An estimation of potential publication bias was carried out using the funnel plot. Egger's linear regression test showed no statistically significant publication bias (*P* value = 0.71, 0.47 for mean ± SD and OR studies, respectively) (Figures 2 and 3).

Meta-analysis results

Three included studies reported the mean number of amalgam restorations. The results revealed that the pooled mean difference of restoration numbers between two groups was 0.58, (95% CI: 0.33-0.83, *P* value < 0.001) with greater numbers in MS patients (Figure 4a).

Considering the significant heterogeneity ($I^2 = 92.91$, Q-value = 28.22, *P* value < 0.001), Random effect model was used.

The pooled OR for developing MS risk in people

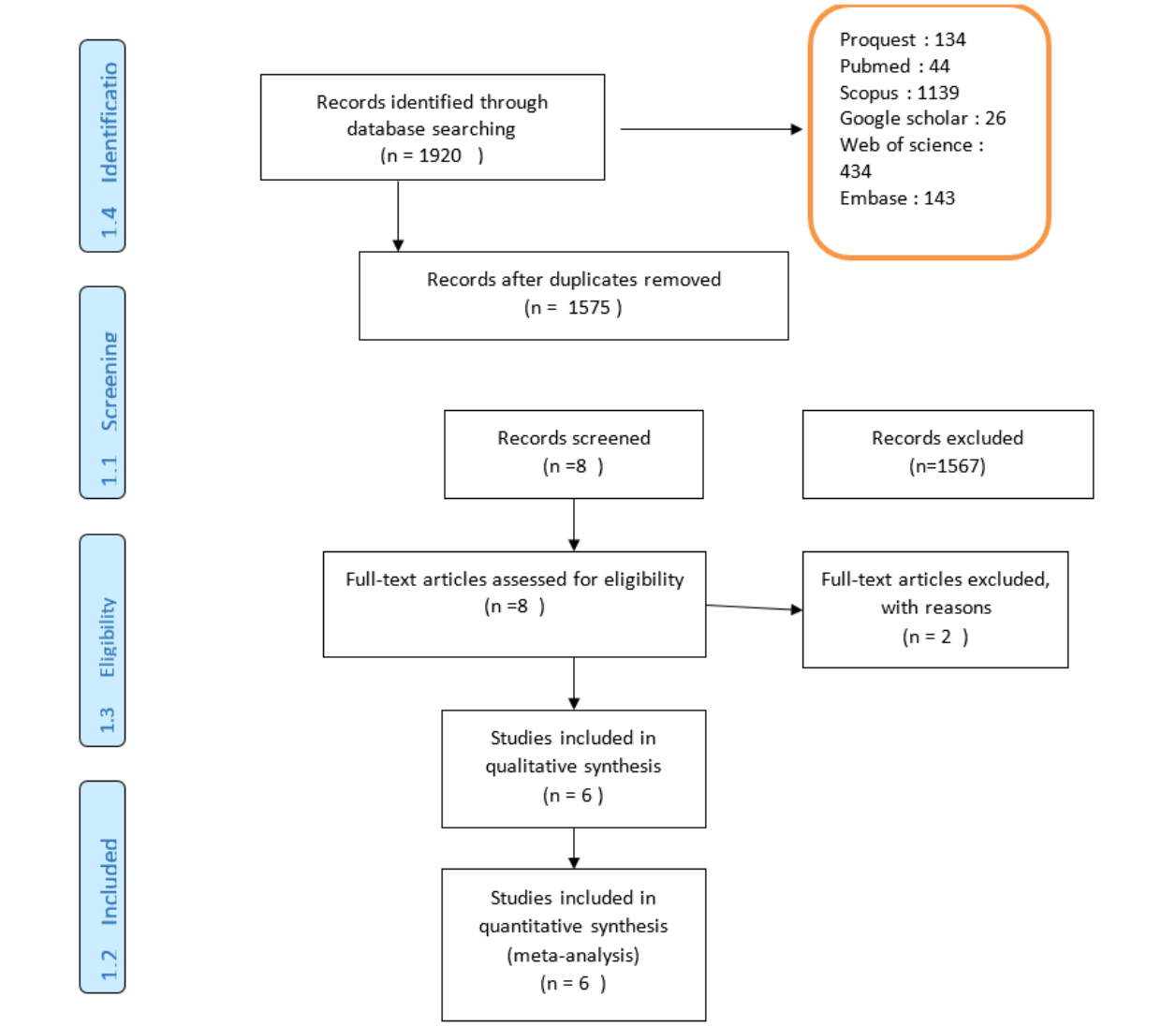

Figure 1. The flowchart of searching strategy based on PRISMA guidelines .

Table 1. Characteristics of studies included in the meta-analysis

Author Name	Polished year	Sample size		Mean age		People with amalgam		Number of amalgam fillings		OR (95% CI)
		Control	Case	Control	Case	Case	Control	Case	Control	
Bangsi et al [27]	1998	128	143	37.9±0.84	36.9±0.76	135	115	9.36±0.53	8.78±0.51	1.90 (0.76-4.76)
Tavangar et al [29]	2018	174	174	38.1±14.1	36.4±9.7			4.2±3.54	3.4±3.43	
McGrother et al[30]	1999	62	39	25-65	25-65			8.87±5.20	9.69±4.86	0.96 (0.87–1.06)
Casetta et al[31]	2001	423	132	36.7±10.7	38.4±10.7	117	373			1.04 (0.56-1.93)
Tseng et al[32]	2020	612	612	50.69±17.20	50.61±16.46	366	391			0.84 (0.66-1.05)
Bates et al[33]	2004	20000	7	16-75	16-75					1.24 (0.99–1.53)

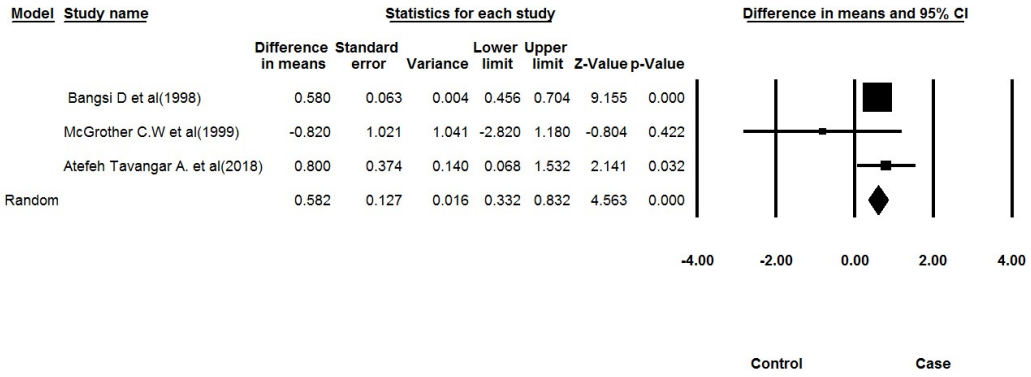

Figure 2. Forest plot diagram of difference in mean numbers of restorations in MS and normal people.

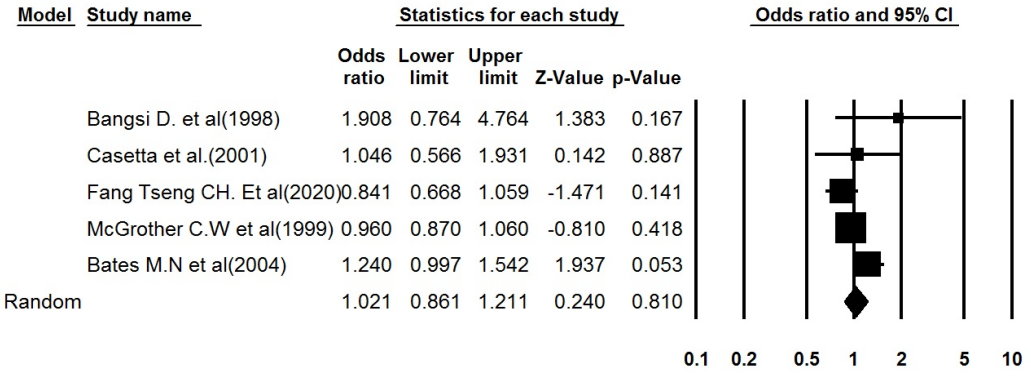

Figure 3. Forest plot diagram of OR in MS and normal people.

undergoing amalgam restorations was 1.02 (95% CI, 0.86-1021, $P=0.81$) with a slight non-statistically significant increase in amalgam fillings related MS risk. Considering substantial heterogeneity ($I^2=52.3$, $P=0.07$), random effect model was used (Figure 4b).

Discussion

The farther we go from the equator, the greater the prevalence of dental caries and MS, so they may have a common cause. It was later hypothesized that there was a link between MS and dental amalgam fillings.[26] Despite a history of using amalgam fillings for more than 150 years, unlike other medical implants, they have not been evaluated qualitatively for safety and risk.[3]

According to the research conducted in this study, 6 studies have directly examined the relationship between this disease and dental amalgam. One study was a retrospective cohort, and the rest were case-controls.

In a study by Bangsi et al, the count of amalgam fillings and the length of their stay in 143 patients with MS and 128 healthy individuals were measured. Information on social and demographic attributes, the count of dental amalgam fillings and the duration of their presence in the mouths of individuals based on dental records were obtained through interviews. Both patient and controls were matched for sex, age, education and smoking. The odds ratio for those who had more than 15 restorations was OR=2.57 (95% CI: 0.78- 8.54). They concluded that the large number of amalgam restorations and the long duration of their presence in the mouth can increase the risk of MS, but the difference between the control group and the patients was not statistically significant.[27]

In Bangsi's study, the number of restored surfaces with amalgam and the amount of amalgam used were not

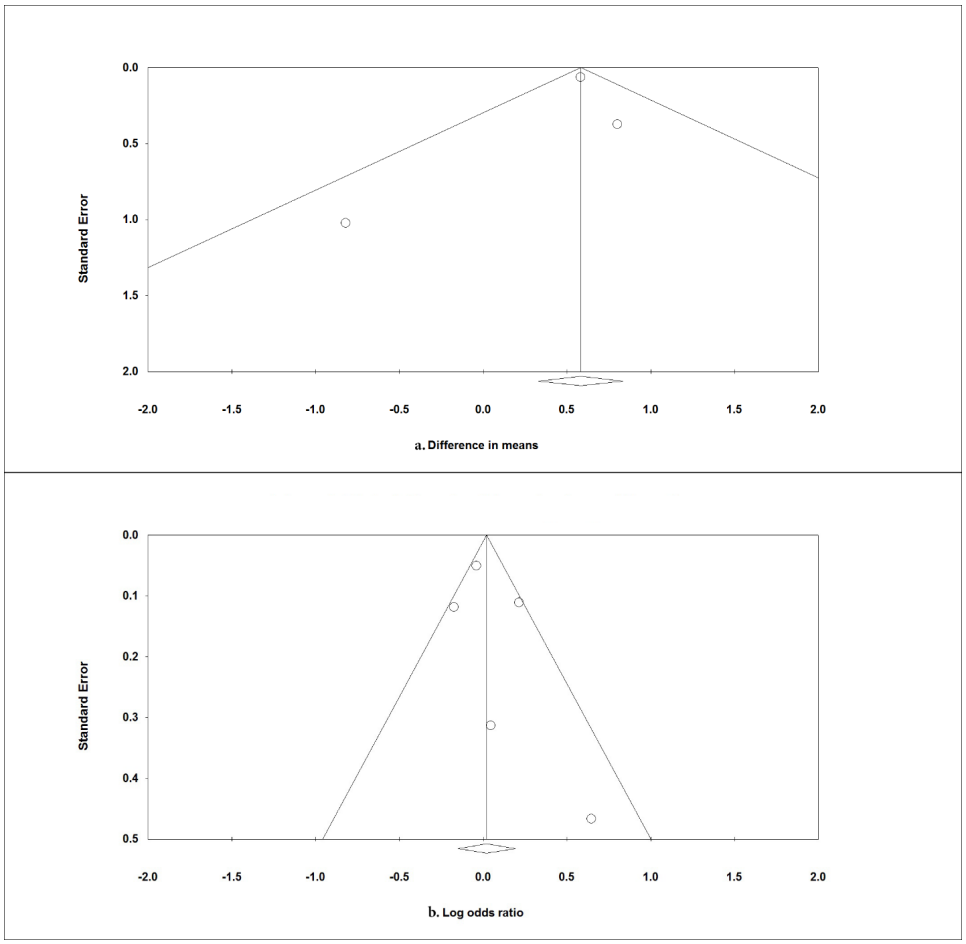

Figure 4. (a) Funnel plot of standard error by difference in Means. (b) Funnel plot of standard error by log odds ratio.

considered.[27] Also, in this study, both case and control groups were not matched in terms of other etiological factors of MS. So, the results can be influenced by these factors.[29]

In 1999, McGregor et al examined the number of caries and amalgam fillings in 39 women with MS (who were 25 to 65 years old at the time of the diagnosis) and 62 healthy people who, in other respects, matched the patient's group. Information was obtained through interviews. They concluded that dental caries was higher in MS patients compared to the control group, but there was no difference in the number and size of amalgam restorationsl.[30] As in the previous study, the number of surfaces filled with amalgam and the time faced with amalgam were not examined. Patients who received amalgam fillings after diagnosis of MS were also included in OR calculations. It seems that this study may not have enough power to prove the relationship between amalgam and MS.[29]

Another case-control study was conducted in 2001 in Italy on this subject. In this study, the relationship between the number of amalgam repairs and the duration of amalgam exposure with the risk of MS was not observed. In this study, 132 patients with MS and 423 individuals were selected as controls from acquaintances of patients with other neurological diseases, and were matched in terms of gender, age, and place of residence. The odds ratio was not statistically significant for individuals with different exposure times or different counts of amalgam restorations.[31] In this study, as in the previous two studies, the count of amalgam surfaces and the amount of mercury were not investigated. Also, instead of a clinical examination, the patients' medical records were used and the exact number of these fillings and the amount of them were not obtained, all of which could affect the results.[29]

In 2018, Tavangar et al conducted a study on two groups of patients with MS (n = 174) and healthy individuals (n = 174) in Al-Zahra MS Clinic and MS Association of Isfahan. The information was obtained through a questionnaire that included job, level of education and other risk factors like genetic history, low levels of vitamin D in the serum, anxiety and smoking. The checklist of dental examinations included the count of amalgam restorations and the other factors like the tooth type, the amount of surfaces filled with amalgam, the date that tooth filled with amalgam and the caries size. They found that considering other variables, amalgam-restored dental surfaces were higher in MS patients than the control group, but the difference between the two groups was not significant in terms of the count of amalgam restorations. They concluded that amalgam restoration, the number of surfaces involved with amalgam, and having a long-lasting repair in the mouth are factors influencing MS. This study

is more comprehensive than previous studies because it accurately examined the surfaces of amalgam and the exposure duration of amalgam and the teeth type involved with amalgam. Both of the groups (case and control) were matched with other etiological factors of MS, but since MS is a multifactorial disease, it is not possible to pinpoint the exact relationship between amalgam and MS. Also, in this study, a large number of patients who were not in a good mental state did not want to attend the study, which could affect the results.[29]

Another case-control study was conducted in 2020 in Taiwan, in which case groups (612 people) and control (612 people) in terms of age, gender, level of urbanization, monthly salary and Charleson correlation index with a trend score of 1: 1 were adapted from 2000 to 2013. In this study, individuals were evaluated for the presence of amalgam fillings and the relevant data were obtained from the Longitudinal Health Insurance Database of the National Health Institute of Taiwan. The difference between the two groups was statistically insignificant. In this study, the association of amalgam fillings with MS was not established. The limitations of this study are as follows:

Patients with minor symptoms of MS did not enter the study and some of confounding factors, such as disability, smoking, daily food intake, amalgam brands, and amalgam formulation, were not recorded. Other metal restorations, such as crowns and inlays that can have a synergistic toxicity of mercury, were not considered. Also, amalgam restorations before 2000 were not achieved.[32]

A retrospective cohort study was performed in 2004 to investigate the long-term effects of amalgam. The dental data of the individuals from 1977 up to 1999 and the incidence of systemic diseases like MS were examined. Although the incidence of MS was low, the HR for one unit of amalgam exposure was relatively high. Finally, an association between exposure to amalgam and MS was suggested.[33]

The following should be considered to overcome the shortcomings of the studies:

Careful clinical examination is necessary to ensure the accuracy of the dental history, and all fillings must be performed before MS diagnosis.[29]

The first shortcoming of the studies, based on information about the dental history of individuals through interviews, is the possibility of forgetting the exact time of filling teeth with amalgam, as well as the possibility of replacing them in the past.[30]

Studies examining the count of amalgam fillings should consider its size, including the number of amalgam-restored surfaces and the mass of amalgam used in the restorations, because these factors determine mercury volume evaporated from the restorations. These studies should also take into account the duration of amalgam fillings due to the cumulative effect of mercury release over time. Since MS is a multifactorial disease; in the studies, both control groups and cases should be well matched in terms of other possible etiological aspects and demographic characteristics, and the sample sizes should be sufficient.[29]

In 2007, Aminzadeh et al conducted a systematic review and meta-analysis to explore and quantify the relationship between MS and amalgam restorations. They used the random effects model for pooling relative risks and ORs. The obtained OR showed that people who used amalgam to restore their teeth had a higher risk of developing MS, however this association was slight and not statistically significant.[28] They did not consider variables such as the count of amalgam fillings and its relationship to mercury release rate was not considered. In this study, we first tried to review all the studies on this topic and point out some of their shortcomings. In order to perform meta-analysis, studies that examined a common variable (number of amalgam restorations) were combined. Then articles with ORs were meta-analyzed to update the previous meta-analysis conducted in 2007. The ORs calculated in this meta-analysis was lower than in the 2007 meta-analysis. One possibility is that this difference is because of one of the studies included in this meta-analysis was a new study conducted in Taiwan. With the introduction of new amalgam brands such as high cupper ones, the amount of mercury release in them has decreased and the possibility of neurotoxicity may be lesser.

Conclusion

Although in this systematic review the pooled OR was consistent for the risk of developing MS in people undergoing amalgam fillings, but this slight increase in risk was not statistically significant. Based on the results we suggest that the number of amalgam fillings can be one of the factors affecting the risk of developing MS. These results could be a new insight into the principle of disease prevention in individuals at higher risk, especially dentists and those who have dental visits.[29] Finally, we recommend that the use of amalgam be limited to amalgams with lesser mercury release. However, newer studies are needed to prove the safety of these amalgams in terms of mercury and neurotoxicity release.

Authors' Contribution

Conceptualization: Ali Taghavi Zonouz, Fatemeh Pournaghi Azar.
Data curation: Ali Taghavi Zonouz, Fatemeh Pournaghi Azar, Solmaz Pourzare, Hossien Hosinifard, Zahra Molaei.
Formal analysis: Solmaz Pourzare, Hossien Hosinifard.
Funding acquisition: Zahra Molaei.
Methodology: Ali Taghavi Zonouz, Fatemeh Pournaghi Azar.
Investigation: Ali Taghavi Zonouz, Fatemeh Pournaghi Azar.
Project administration: Ali Taghavi Zonouz, Fatemeh Pournaghi Azar.
Resources: Ali Taghavi Zonouz, Fatemeh Pournaghi Azar.
Supervision: Ali Taghavi Zonouz, Fatemeh Pournaghi Azar,
Validation: Zahra Molaei, Fatemeh Pournaghi Azar.
Visualization: Zahra Molaei
Writing–original draft: Ali Taghavi Zonouz, Fatemeh Pournaghi Azar, Solmaz Pourzare, Hossien Hosinifard, Zahra Molaei.
Writing–review & editing: Ali Taghavi Zonouz, Fatemeh Pournaghi

Azar, Solmaz Pourzare, Hossien Hosinifard, Zahra Molaei.

Competing Interests

The Authors declare no conflict of interest related to the publication of this work.

Ethical Approval

Ethical approval and informed consent were not required for this study, as these studies were based on previously published articles.

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