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Research paper

Chronic exposure to aluminum and risk of Alzheimer's disease: A meta-analysis

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HIGHLIGHTS

- This meta-analysis included 8 cohort and case control studies, with a total of 10567 individuals.
- Two main types of chronic Al exposure are reported: Al in drinking water and occupational exposure.
- This meta-analysis shows that chronic Al exposure is associated with 71% increased risk of AD.

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ABSTRACT

A meta-analysis was performed to investigate whether chronic exposure to aluminum (Al) is associated with increased risk of Alzheimer's disease (AD). Eight cohort and case-control studies (with a total of 10567 individuals) that met inclusion criteria for the meta-analysis were selected after a thorough literature review of PubMed, Web of Knowledge, Elsevier ScienceDirect and Springer databases up to June, 2015. The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies. Q test and I^2 statistic were used to examine heterogeneity between selected studies. The overall odds ratio (OR) was calculated using a fixed-effect model because no significant heterogeneity between studies was found. No publication bias was observed based on a funnel plot and Egger's test. Results showed that individuals chronically exposed to Al were 71% more likely to develop AD (OR: 1.71, 95% confidence interval (CI), 1.35–2.18). The finding suggests that chronic Al exposure is associated with increased risk of AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative cerebral disorder. AD is the major cause of dementia and accounts for 60–70% of cases of progressive cognitive deterioration in the elderly [1,2]. Histopathologically, AD is characterized by deposition of amyloid β-peptide (Aβ) and neurofibrillary degeneration of neurons in the brain. Although the pathogenesis of AD is still unclear, concordance studies on identical versus non-identical twin pairs indicate that the etiology of AD is multi-factorial with both environmental and genetic susceptibility factors [3]. Aluminum (Al) is a known neurotoxin and Al exposure is considered to be a risk factor for the pathogenesis of AD. *In vivo* laboratory evidence has demonstrated that Al administration increases Aβ production, promotes its aggregation and inhibits its degradation in the brains of experimental animals, consistent with the process of AD [4,5]. Al-induced accumulation of Aβ has also been confirmed by *in vitro* studies with cultured neurons of rat cerebral cortex [6,7]. Recently, the association between Al and AD has been reinforced by the postmortem examination of the Al content in AD-affected brains that revealed an excessive load of Al in patient's brain after chronic exposure to Al [8,9].

Al and its compounds have long been extensively used in industry, water purification, medications, food additives, Al-adjuvanted vaccines and many other products [1,10,11]. Al pollution of water and soil is also increasing due to acid rain that solubilizes Al and enhances Al uptake into plants, animals, and humans. Thus, human body is readily exposed to a significant amount of Al and may be at risk of AD due to chronic Al exposure. However, the associations between chronic exposure to Al and AD in previous epidemiological studies are not consistent, possibly due to differences in study

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populations, levels of Al exposure and study designs. Some studies found a significant association between chronic Al exposure and an increased risk of AD [12,13], while other studies failed to demonstrate the association [14,15]. We performed a systematic review and meta-analysis of relevant epidemiological studies, with the calculation of pooled odds ratio (OR) and further subgroup analyses for heterogeneity between studies, to comprehensively examine whether, and to what extent, chronic Al exposure is associated with increased risk of AD.

2. Methods

2.1. Data search

A systematic and extensive literature search of PubMed, Web of Knowledge, Elsevier ScienceDirect and Springer databases was conducted for relevant epidemiological studies up to June, 2015. Subject words and random words were used for the literature search, including aluminum OR aluminium OR Al OR metal AND Alzheimer's disease OR Alzheimer OR dementia AND epidemiology. The studies were limited to humans.

2.2. Study selection and extraction

Redundant papers pertaining to the same study were excluded. For inclusion in the meta-analysis the studies had to meet the following criteria: (1) being a cohort study or a case control study; (2) involving chronic Al exposure by any route, such as drinking water or occupational exposure; (3) having an outcome of AD; (4) performing an analysis adjusted for main confounding factors; (5) reporting an odds ratio (OR), relative risk (RR) or hazard ratio (HR) and its 95% confidence interval (CI) or supplying enough data to calculate OR and its 95% CI. AD was defined by the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) or other high quality clinical criteria. A total of 8 cohort or case-control studies that met the inclusion criteria were finally included in the meta-analysis.

Two authors of the paper independently extracted following information about each study: first author of the study, publication year, study country/location, follow-up duration, type of study, number of AD cases, sample size, mean age, OR (RR or HR) and its 95% CI, diagnostic criteria of AD, and adjustment for potential confounders. Any disagreement was settled by discussion.

2.3. Study quality assessment

The Newcastle–Ottawa Scale (NOS) was applied to assess the quality of included studies. Each study was rated on the selection of study groups, comparability of study groups, the adequacy of follow-up period and outcome measures for cohort studies or exposure measures and response rates for case control studies. The 8 studies were scored from 7 to 9 points. The study quality was considered high if the score was equal to or greater than 7, and moderate if the score was between 4 and 6.

2.4. Statistical analysis

Q test and I^2 statistic were used to examine heterogeneity between selected studies. If heterogeneity was not significant ($P \geq 0.05$, $I^2 \leq 50\%$), a fixed-effects model was used to calculate pooled OR. If heterogeneity was significant ($P < 0.05$, $I^2 > 50\%$), a random-effect model was used. Subgroup analyses were conducted to examine the effect of study location, publication year, type of study and the type of Al exposure. Sensitivity analyses were performed to examine if any study had significant effect on the pooled OR. One study was found to have significant effect when its outlier removal analysis lay beyond the 95% CI of the overall analysis. Publication bias was finally estimated based on a funnel plot and Egger's test. $P \geq 0.05$ indicated lack of publication bias, $P < 0.05$ indicated potential publication bias. If publication bias was identified, the "fill and trim" method was used to calculate unbiased estimates. STATA version 13.0 was used to perform all data analysis. All tests in this analysis were 2-sided with statistical significance set at $P < 0.05$.

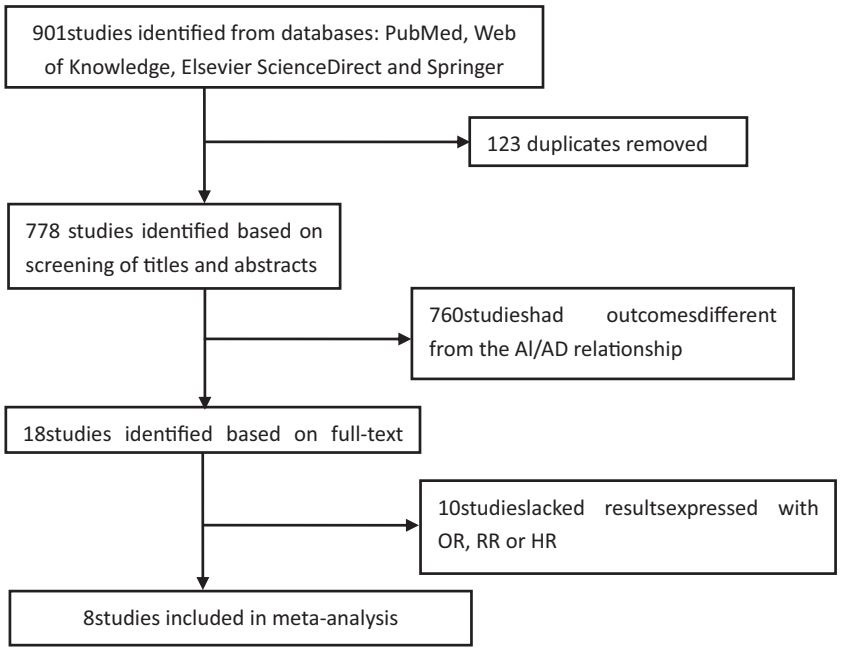

Fig. 1. Flowchart of the study search.