



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.

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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 (A β) 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 demon-

strated that Al administration increases A β 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 A β 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-adjuncted 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 $P < 0.05$.

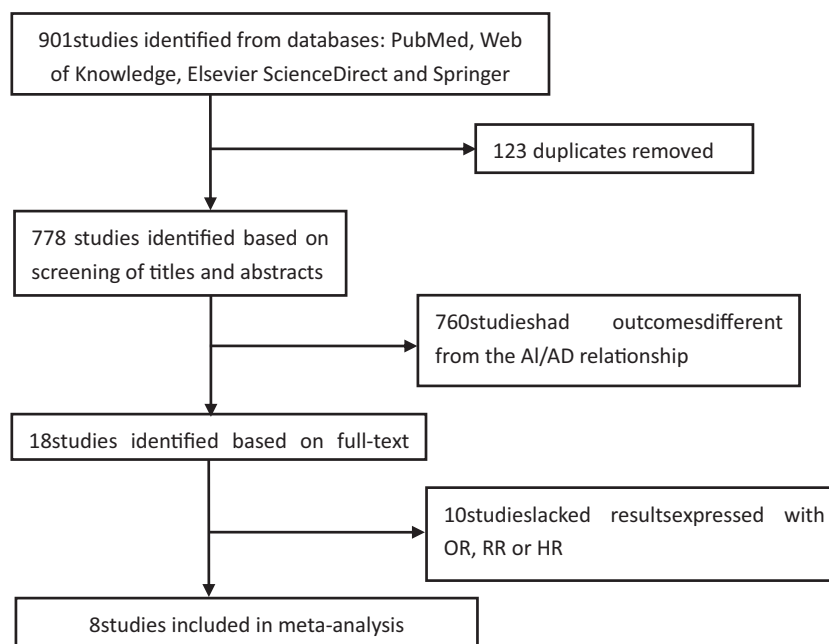


Fig. 1. Flowchart of the study search.

Table 1
Main characteristics of included studies.

First author, year	Country	Follow-up duration/type	No. of AD/sample size	Age (year)	Risk estimates (95%CI)	Definition of Al exposure	AD measurement	Adjustments	Quality score
Gauthier, 2000	Canada	NA/case control	68/1924	≥70	Altot: OR = 2.10 (0.83–5.35)	Altot ≥ 5.55 μM(150 μg/L)	Conducted with standardized questionnaires and procedures by a neurologist who identified the disease responsible for dementia according to ICD-10 and NINCDS-ADRDA criteria for probable and possible AD	Education level, presence of family cases of dementia or Alzheimer's diseases in first-degree relatives, the ApoE ε4 allele, two estimators of occupational exposure	7
Rondeau, 2000	France	8 years/prospective cohort	182/2698	≥65	RR = 2.14 (1.21–3.80)	Al levels in water supplies >0.1 mg/L	Examined by a senior neurologist, who confirmed the diagnosis and applied the NINCDS-ADRDA criteria for Alzheimer's disease	Age, gender, educational level, place of residence, wine consumption	9
Rondeau, 2009	France	15 years/prospective cohort	364/1925	≥65	RR = 2.80 (1.24–6.32)	intake of Al from drinking water ≥0.1 mg/ day	A senior neurologist subsequently confirmed and completed the diagnosis of dementia, to apply the NINCDS-ADRDA.	Age, gender, educational level, wine consumption and place of residence	8
Graves, 1998	America	NA/case control	89/418	Average: 76.8(case), 76.5 (control) ≥50	OR = 1.46 (0.62–3.42)	occupational exposure to Al	The criteria developed by the NINCDS/ADRDA were used to diagnose AD.	Age, education	7
Mclachlan, 1996	Canada	NA/case control	296/830	≥50	OR = 1.7 (1.2–2.6)	Al concentration in public drinking ≥100 μg/L	Based on a clinical history of dementia and the histopathologic findings of widespread neuritic plaques with amyloid cores and neurofibrillary tangles in neocortical and subcortical structures	None	7
Peters, 2013	Australia	48 years/prospective cohort	16/1894	Each age group	HR = 2.76 (0.88–8.82)	Gold miners working underground who inhaled Al dust	Conducted by ICD9, ICD10	Year of birth	8
Salib, 1996	England	NA/case control	198/538	Average: 77	OR = 0.98 (0.53–1.75)	occupational exposure to Al	Probable or possible Alzheimer's disease (using ADRDA-NINCDS criteria)	Age, sex, age of onset, duration of condition, duration of work, and family history of dementia	7
Gun, 1997	Australia	NA/case control	170/340	≥52	OR = 0.33 (0.01–4.16)	occupational exposure to Al	Diagnosed at one of two Sydney hospitals as being either probable AD or possible AD according to the criteria of the NINCDS-ADRDA	age and sex	8

Abbreviation: NA, not available; HR, hazard ratio; OR, odds ratio; RR, relative risk; Al, aluminum; Altot, total aluminum; ICD, International Classification of Diseases; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

3. Results

3.1. Literature search and characteristics of studies

A total of 901 studies were identified through literature search, however, only 8 studies [14,16–22] met the inclusion criteria and were included in the meta-analysis. Fig. 1 shows the study selection process.

Table 1 presents characteristics of selected studies, including 3 cohort and 5 case-control studies. Sample sizes ranged from 340 to 2698, and a combined total of 10,567 individuals from all 8 studies were included for the meta-analysis. Follow-up duration of the cohort studies varied from 8 to 48 years. The case-control studies varied in number of study cases between 68 and 296. Two main types of Al exposure were reported: drinking water and occupational exposure. Al exposure was defined by a concentration equal to or greater than 100 µg Al/L in the drinking water. Important confounding factors were adjusted when the OR (RR or HR) was calculated. According to the NOS scoring system, one study was scored 9 [17], 3 studies scored 8 [18,21,22] and 4 studies scored 7 [14,16,19,20]. All of the 8 studies met the criteria of high quality.

3.2. Meta-analysis

Q test ($P=0.382$) and I^2 statistic (6.2%) demonstrated that there was no significant heterogeneity between studies. The pooled OR was 1.71 (95% CI: 1.35–2.18) using a fixed-effects model. A forest plot of the risk between Al exposure and AD is shown in Fig. 2.

Table 2

The subgroup analyses.

Subgroups	No. of studies	OR(95% CI)	I^2 , %	P_Q
Location				
North America	3	1.71(1.23–2.37)	0.0	0.853
Europe	3	1.68(1.16–2.43)	62.5	0.070
Australia	2	2.11(0.72–6.18)	39.9	0.197
Year				
After 2000	4	2.34(1.58–3.47)	0.0	0.938
Before 2000	4	1.43(1.05–1.93)	6.7	0.359
Type of study				
Case control	5	1.48(1.11–1.97)	0.0	0.431
Cohort control	3	2.39(1.55–3.69)	0.0	0.840
The way of Al exposure				
Drinking water	4	1.95(1.47–2.59)	0.0	0.713
Occupational exposure	4	1.25(0.80–1.94)	9.9	0.344

P_Q , P value of Q test.

3.3. Subgroup analysis

Subgroup analyses showed no significant heterogeneity in each subgroup, including study location, publication year, type of study and the type of Al exposure (Table 2).

3.4. Sensitivity analysis and publication bias

Sensitivity analysis showed that no studies substantially influenced the overall OR (Fig. 3A). The overall ORs range from 1.63 (95% CI 1.26–2.13) to 1.91 (95% CI 1.47–2.48) after removing one study at a time. The roughly symmetrical funnel plot (Fig. 3B) shows absence

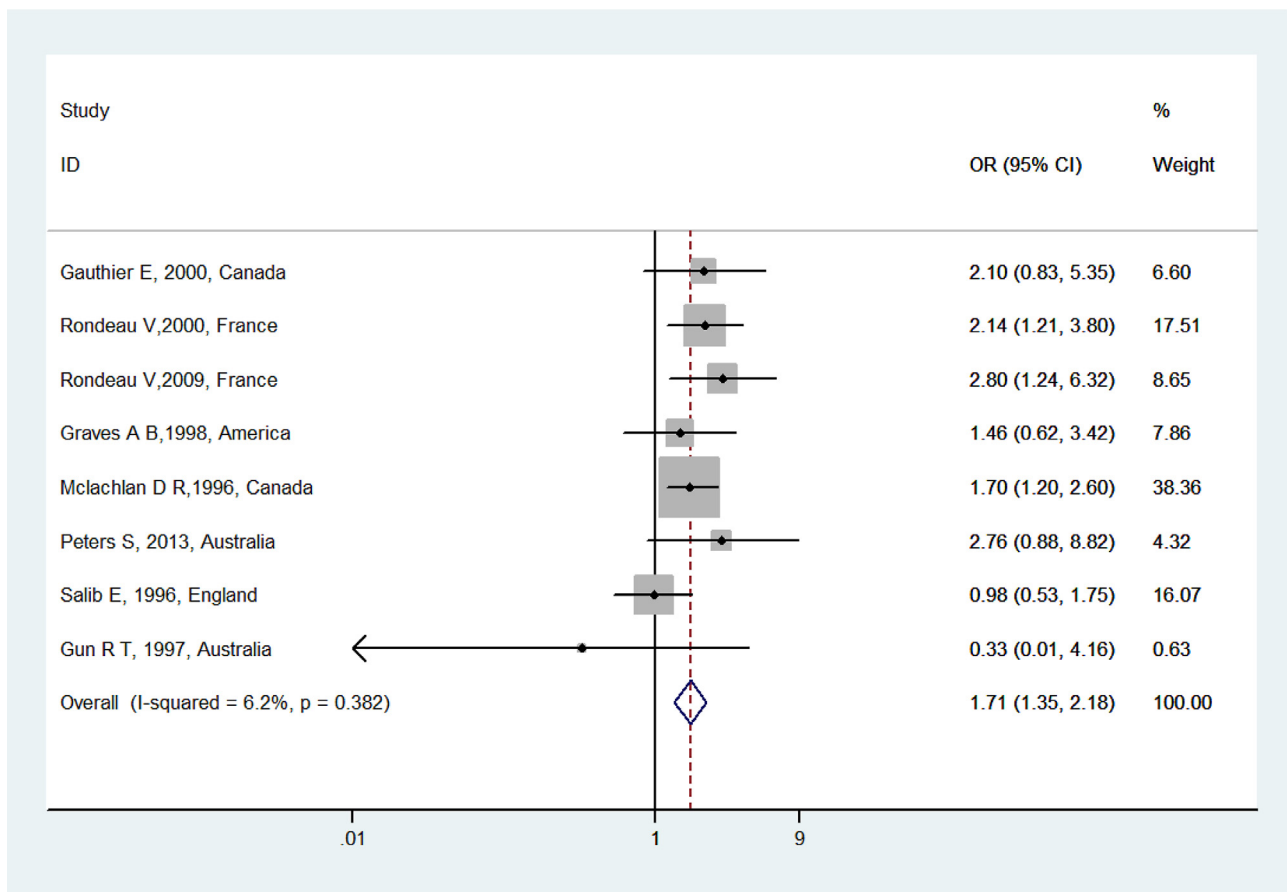


Fig. 2. A forest plot of the risk between exposure to aluminum and AD.

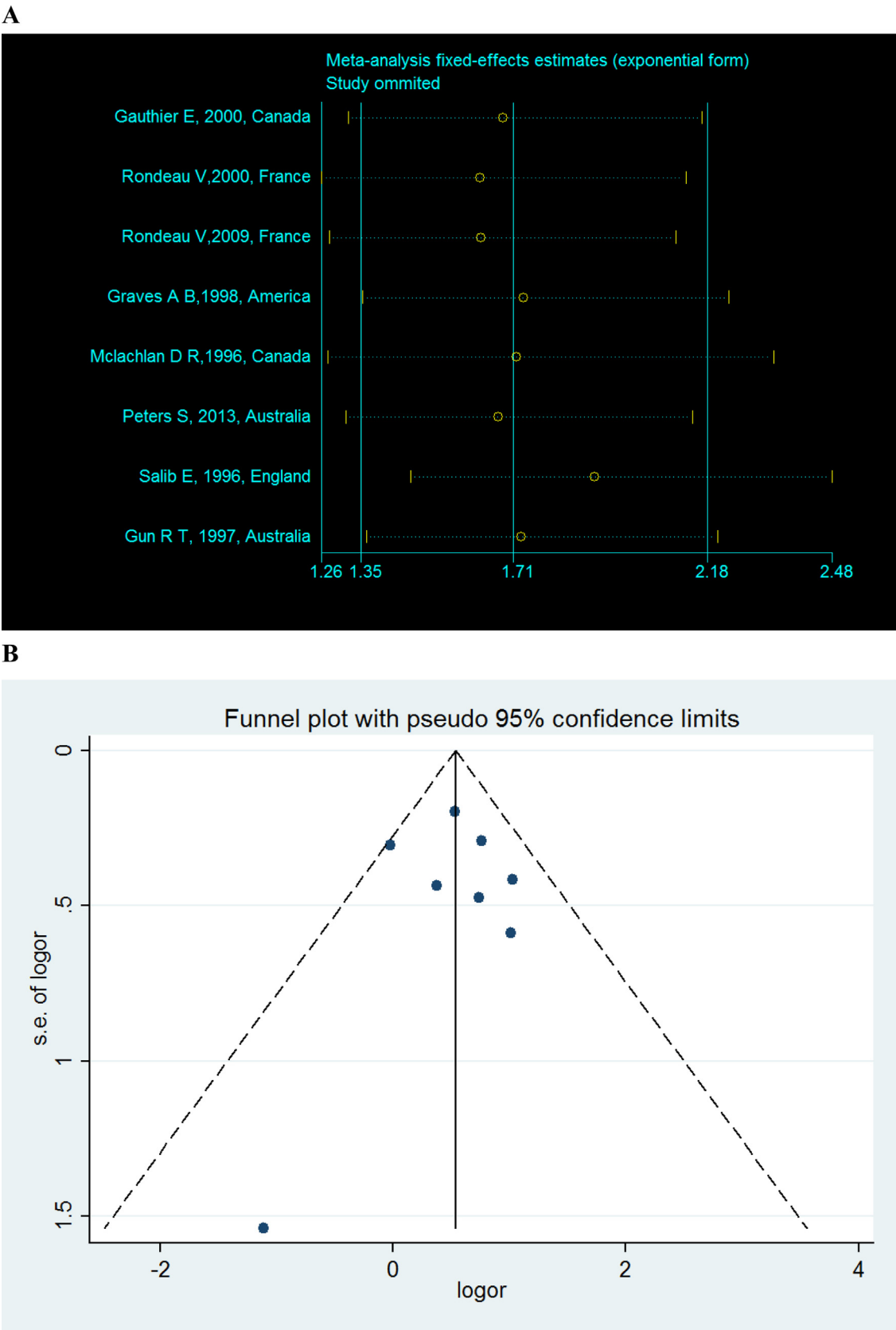


Fig. 3. Sensitivity analysis (A) and the funnel plot (B) for this meta-analysis.

of publication bias in this meta-analysis. This result was confirmed by Egger's test ($P > 0.05$) and Begg's test ($P > 0.05$).

4. Discussion

The relationship between Al and AD has been the subject of scientific debate because precise mechanism of AD pathogenesis remains unknown [4,23,24]. In the present meta-analysis of epidemiological studies, we found that chronic Al exposure was significantly associated with increased risk of AD, (OR = 1.71, 95% CI: 1.35–2.18). The finding of the Al exposure-AD association in the meta-analysis is supported by the followings. First, there is no significant heterogeneity between selected studies. Second, subgroup analysis excluded the effect of potential confounding factors. Third, sensitivity analysis demonstrates that the overall OR is resistant to influence by any individual study. Fourth, publication bias analysis excluded the association due to publication bias. Furthermore, the pooled OR among those who drank water containing an Al level at or higher than 100 $\mu\text{g/L}$ is 1.95 (95% CI, 1.47–2.59) compared to those who drank water containing less than 100 $\mu\text{g/L}$. This finding is consistent with conclusions from previous studies [25,26].

Studies have demonstrated that the brain is sensitive to Al, owing to the non-dividing nature of most neurons and their vulnerability to oxidative stress [27,28]. Al can cross through the blood–brain barrier and accumulate in the brain, and Al clearance from the brain is more slow than in other organs [29,30]. Al is characterized by a strong positive charge and a relatively small ionic radius, which facilitates its binding with the metal-binding amino acids of various proteins [4]. Indeed, Al can form a complex with A β and cause A β oligomerization, inducing the conformational changes that can inhibit their degradation, thus enhancing the production and aggregation of A β [7]. Studies have shown that Al increases the deposition of A β in animal brains [31,32]. The extracellular accumulation of A β in the brain is regarded as an early event in the development of AD [33]. Furthermore, A β coupled with Al has been found to be more toxic than normal A β causing membrane disruption, loss of calcium homeostasis, perturbation of mitochondrial respiration and finally death of neurons [4,34,35]. Additionally, the AD brain is characterized by markers of oxidative stress and dysregulated inflammatory signaling [36]. Substantial studies suggest that Al can elicit a neuroinflammatory response and exacerbate the formation of reactive oxygen species (ROS) in the brain *in vivo* and *in vitro* [37–39]. Also, the Al-induced upregulation of NF- κ B-sensitive pro-inflammatory miRNAs has been found in primary human cells in culture and in the brain of murine AD models [36,40]. It is clear that oxidative and inflammatory events contribute to the AD process [41–44].

However, almost all of the Al studies in animals are based on abnormally high Al concentrations with acute or sub-acute (1–3 month) Al exposure periods [45–47]. Recently, an Al-based rat model for AD, that chronically ingested Al (throughout their middle age and old age) at levels equivalent to the high end of the dietary Al range routinely ingested by humans [10], has exhibited profound memory loss in old age and features of Al neurotoxicity in AD-relevant brain regions that also occur in AD-affected neurons [48]. Furthermore, the implication of excessive Al exposure in the development and/or progression of AD is supported by the analysis of brain autopsy samples from AD patients, as mentioned above [8,9]. Moreover, chelation therapy to reduce the Al burden in AD patients has been reported as beneficial [49].

Although the present study demonstrates a positive link between Al exposure and AD, our meta-analysis has several limitations. Above all, we were unable to consider every report of Al exposure (including drinking water, occupational exposure, drugs, processed foods, vaccinations, sun protection lotions, deodorants

and other sources), particularly where there were insufficient studies for some Al exposure categories. There may be practical difficulties in obtaining compliance from large numbers of humans to reliably record data for some types of Al exposure; in particular, to accurately record human data for long-term (decades) of food consumption, which is especially important for AD patients. Next, dose-dependent response relationships were not considered. In addition, only 8 studies were included in the meta-analysis.

Despite these limitations, our findings of the meta-analysis of epidemiological studies suggest that chronic Al exposure is associated with increased risk of AD.

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