Does aluminum exposure affect cognitive function? a comparative cross-sectional study

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Abstract

Objectives
This study assessed the cognitive function of aluminum-exposed participants from an alum mining zone, compared them with unexposed subjects, and aimed to elucidate the effect of aluminum exposure on cognition.

Design
This was a comparative cross-sectional study. Univariate analyses were used to assess the differences between the aluminum-exposed and unexposed groups. Binary logistic regression models were applied to analyze the effect of aluminum exposure.

Setting
The aluminum-exposed participants were included from an alum mining zone and the unexposed subjects were residents from another district without alum-mine-related factories.

Participants
We included 539 aluminum-exposed participants (254 men, 285 women) and 1720 unexposed participants (692 men, 1028 women).

Results
The mean cognition score on Mini-Mental State Examination was 21.34 (± 6.81) for aluminum-exposed participants. The exposed group had 6.77 times (95% confidence interval, 5.09–9.00) more risk of cognitive impairment than the unexposed group, after adjusting for age, sex, and educational level. No statistically significant association was found between exposure duration and cognition.
Conclusions
This study demonstrated a significant association between aluminum exposure and lower cognitive function.

Introduction
Aluminum is the most abundant metal in the Earth’s crust. It has been widely used in cooking utensils and in recent decades, has been found in foods in China, such as deep-fried dough sticks [1, 2].

Aluminum is recognized as a catalyst for Alzheimer’s disease; in the absence of brain-burdening aluminum, Alzheimer’s disease is not an inevitable consequence of aging [3]. Since the 1960s, when Alzheimer’s-like neuronal lesions were found in rabbits that had been treated with a compound containing aluminum [4], the causal relationship between aluminum and dementia has been the subject of ongoing research [5–7].

The effect of aluminum on cognition is partially owning to its interaction with tau proteins. Aluminum may promote the development of neurofibrillary tangles (NFTs) by promoting phosphorylation of tau proteins [8]. There is also evidence that aluminum affects amyloid-β (Aβ) proteins by promoting the production of Aβ aggregates and inhibiting their degradation [9–12]. Aluminum can also upregulate the expression for amyloid-β precursor protein (APP) gene and other stress-response genes in human neural cells [13]. It has also been reported that aluminum can affect neurotransmission. Because aluminum has the ability to block the formation of calcium-permeable ion channels mediated by Aβ, it can inhibit the increase in calcium influx induced by neurotrophic factors such as the brain derived neurotrophic factor [14–17].

Few epidemiological studies have focused on the effects of occupational aluminum exposure on cognition. Cognitive decline has been found in smelting workers in aluminum factories [18–20]. Iregren et al [21] reported that aluminum welders showed reduced performance in four motor function tests and one pegboard test, however the reduction was not significant. Sim et al [22] found no significant effects in aluminum potroom workers using objective measures of neurological function. However, these studies were all limited by small sample sizes.

Alum is a natural, common, aluminum-containing compound and is a raw material used for aluminum production. A huge alum mine in southeastern China was founded about one hundred years ago, and a residential zone was developed around the mine. Before 2004, there were also many factories engaged in bauxite mining and processing, and many local residents worked in these factories. High dust concentration was a common problem in many alum mines in China before the 1990s [23], and serious health problems among miners, such as silicosis, were widely reported.

Our study enrolled workers from the alum mine, assessed their cognitive function, compared them with aluminum-unexposed participants, and aimed to demonstrate the effect of aluminum exposure on cognition. We also hypothesized that the risk of cognitive impairment increased with occupational exposure duration.

Materials and methods
Data was obtained from a public health surveillance project aimed at exploring health problems among elderly people in Zhejiang [24]. The project was conducted in all 11 cities in Zhejiang since 2014, and each city chose at least one county to recruit a minimum of 1000 permanent residents aged 60 years and older. The counties were chosen according to local...
disease patterns, exposure to certain risk factors, population stability, quality of death and disease registries, local commitment, and the capacity of staff. In Wenzhou, the surveillance population was extended to adults aged 18 years and older, and Cangnan, where the alum mine is located, was the chosen surveillance county. Face-to-face interviews were completed by well-trained interviewers with a questionnaire that included sociodemographic information, work experience, cognition data, and current medical history. The study was approved by the Ethics Committee of Zhejiang Provincial Center for Disease Control and Prevention and conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association. Written informed consent was obtained from each participant.

In our study, we selected participants from Cangnan and Yuhuan who were surveyed in 2016. Local residents of Cangnan with occupational exposure to dust (self-reported; only alum miners were occupationally exposed to dust in Cangnan) or work experience in the alummine-related factories (self-reported) were included in the aluminum-exposed group. To avoid the influence of unobserved confounders, unexposed participants were selected from Yuhuan, a county without alum-mine-related factories. Both Yuhuan and Cangnan are coastal, and the distance between the two counties is about 100 kilometers. Among the participants, there were some similarities in diets and living conditions between the two areas. We selected unexposed participants from Yuhuan instead of Cangnan because of the history of severe environmental pollution in Cangnan, which could affect cognition. In our study, the miners were local residents, meaning they were subject to both environmental and occupational exposure.

Cognitive function was measured by the Mini-Mental State Examination (MMSE), which includes 30 items. The MMSE is brief and easy to administer to elderly people and those with low education levels. It has become one of the most commonly used screening tools to evaluate cognitive function in epidemiological studies with large sample sizes [25, 26]. The maximum score on the MMSE is 30, and higher scores indicate better cognitive function. A battery of education-specific cut-off scores for cognitive impairment was used: 17/18 for illiteracy, 20/21 for people with primary education, and 24/25 for people with a higher than primary education [24]. MMSE subscores are calculated by grouping various items of the MMSE by domain: orientation to time (0–5 points possible), orientation to place (0–5), registration (0–3), recall (0–3), attention and calculation (0–5), language (0–8), and figure (0–1). More details about the MMSE scale have been described elsewhere [27].

Sociodemographic factors included age, sex, educational level, and economic status. Alummine-related work experience included the specific job type and the time when one began and left the job. Other factors included hypertension, hyperlipidemia, diabetes mellitus, stroke, acute myocardial infarction, tumor (either malignant or benign), severe head trauma, smoking status, and alcohol consumption status.

We compared sociodemographic and other characteristics between the two groups, using Welch’s t-test (for continuous variables) and Fisher’s exact test (for categorical variables). Binary logistic regression models were applied to analyze the effect of occupational exposure duration in the alum mines. Model 1 included aluminum exposure status, age, sex, and education; Model 2 included hypertension, diabetes, tumor, smoking, and alcohol consumption based on model 1. All statistical analyses in this study were performed using R version 3.5.1 and SAS version 9.2 (SAS Institute, Cary, NC, USA), and a two-tailed p-value <0.05 was considered statistically significant.

Results

The mean age of aluminum-exposed participants was 57.3 years, 13 years younger than that of unexposed group. The proportion of illiteracy among the exposed and unexposed groups was
44.9% and 68.8%, respectively. The proportions of hypertension, diabetes, and tumor in the exposed group were significantly lower than those in the unexposed group. The aluminum-exposed group performed worse than the unexposed group on the MMSE, with a lower mean score and a higher proportion of that group having cognitive impairment. More details are shown in Table 1.

### Table 1. Characteristics of the aluminum-exposed and unexposed participants.

| Characteristics                        | Overall | Unexposed group | Exposed group | P     |
|----------------------------------------|---------|-----------------|---------------|-------|
| Age (years, mean (SD))                 | 67.0 (11.0) | 70.0 (7.8) | 57.3 (13.7) | <0.001 |
| Sex                                    | Male    | 946 (41.9)     | 692 (40.2)    | 254 (47.1) | 0.005  |
|                                        | Female  | 1313 (58.1)    | 1028 (59.8)   | 285 (52.9) |
| Education (%)                          | Illiteracy | 1426 (63.1) | 1184 (68.8)  | 242 (44.9) | <0.001 |
|                                        | Primary school | 660 (29.2) | 460 (26.7)   | 200 (37.1) |
|                                        | Middle school and higher | 173 (7.7) | 76 (4.4)     | 97 (18.0)  |
| Hypertension (%)                       | No      | 1193 (52.8)    | 810 (47.1)    | 383 (71.1) | <0.001 |
|                                        | Yes     | 1066 (47.2)    | 910 (52.9)    | 156 (28.9) |
| Hyperlipidemia (%)                     | No      | 2136 (94.6)    | 1625 (94.5)   | 511 (94.8) | 0.828  |
|                                        | Yes     | 123 (5.4)      | 95 (5.5)      | 28 (5.2)  |
| Diabetes (%)                           | No      | 1987 (88.0)    | 1477 (85.9)   | 510 (94.6) | <0.001 |
|                                        | Yes     | 272 (12.0)     | 243 (14.1)    | 29 (5.4)  |
| Tumor (%)                              | No      | 2208 (97.7)    | 1670 (97.1)   | 538 (99.8) | <0.001 |
|                                        | Yes     | 51 (2.3)       | 50 (2.9)      | 1 (0.2)   |
| Smoking (%)                            | Never smokers | 1835 (81.2) | 1395 (81.1)  | 440 (81.6) | 0.075  |
|                                        | Current smokers | 305 (13.5) | 225 (13.1)   | 80 (14.8) |
|                                        | Ex-smokers       | 119 (5.3)   | 100 (5.8)    | 19 (3.5)  |
| Alcohol consumption (%)                | Never drinkers    | 1380 (61.1) | 1322 (76.9)  | 58 (10.8)  | <0.001 |
|                                        | Current drinkers | 65 (2.9)    | 56 (3.3)     | 9 (1.7)   |
|                                        | Ex-drinkers       | 814 (36.0)  | 342 (19.9)   | 472 (87.6) |
| MMSE score (mean (sd))                 | 22.56 (5.85) | 22.95 (5.46) | 21.34 (6.81) | <0.001 |
| Cognitive impairment                   | No      | 1779 (78.8)    | 1414 (82.2)   | 365 (67.7) | <0.001 |
|                                        | Yes     | 480 (21.2)     | 306 (17.8)    | 174 (32.3) |

#### Aluminum exposure and cognition

We used two logistic regression models to detect the effect of aluminum exposure on cognitive impairment. The aluminum-exposed group had 6.77 times more risk of cognitive impairment than the unexposed group, adjusted for age, sex, and educational level (Model 1). The prevalence odds ratio (POR) remained high when adjusted for more covariates (Model 2). More details are shown in Table 2.

#### Occupational exposure duration and cognition

The mean exposure duration was 13.2 (± 11.3) years in the exposed group. We found no statistically significant association between occupational exposure duration and cognition after analysis by logistic regression (covariates included age, sex, and education; \( p = 0.232 \)).

### Discussion

This study demonstrated a correlation between aluminum exposure and lower cognition test scores and increased risk of cognitive impairment. Aluminum-exposed subjects had over six times more risk of cognitive impairment than unexposed subjects.
Most aluminum-exposed subjects in our study reported a history of dust inhalation when working in the alum mine, and had been living in the area surrounding the alum mine for decades. The working environment of alum mine workers before 2000 was problematic. According to He et al [28], the incidence of silicosis in alum mine workers increased from 1970 to 1988, and in newly diagnosed patients, the average exposure duration from working in the mine was 17.87 years. Also, the air pollution resulting from aluminum production in the area cannot be ignored. In this study, the association between the risk of cognitive impairment and exposure duration was not statistically significant. A possible reason for this was that the effect of occupational exposure duration was masked by the effect of environmental exposure. Our study had a larger sample size than did previous studies. In contrast to the studies by Iregren et al [21] and Sim et al [22], our study showed a statistically significant association between aluminum exposure and cognitive impairment.

Aluminum is neurotoxic and among the most studied metals, with many studies investigating its relationship with dementia [29–31]. Experimental studies in rats and mice have shown that aluminum can accumulate in the cerebral cortex, hippocampus, and cerebellum [32]. The PAQUID cohort study of almost 4000 older adults in southwest France found that levels of aluminum consumption in drinking water in excess of 0.1 mg per day were associated with a doubling of dementia risk and a three-fold increase in the risk of Alzheimer’s disease [33]. Several studies have shown that an elevated aluminum content could be detected in the brains of Alzheimer’s patients [29, 34, 35] and is often associated with NFTs, lipofuscin, and senile plaques [34]. There is considerable evidence that aluminum plays an important role in the dephosphorylation of tau proteins, development of NFTs, accumulation of amyloid beta protein, and formation of amyloid plaques [36–38]. Studies on occupational aluminum exposure have found similar results [18, 19, 39], and Yang et al. [19] observed that workers with occupational aluminum exposure showed significant decreases in global DNA methylation with an increase in serum aluminum concentration. Although the epidemiological evidence is inconsistent, it
cannot be denied that the weight of evidence implicating aluminum in the causation of Alzheimer’s in at least some patients is increasing.

This study had some limitations. First, the association between aluminum exposure and cognitive impairment was not proof of the cause of one by the other. Second, our study was limited by the lack of measurements of aluminum concentration in blood and urine samples. Thus, biochemical investigation is called for in future studies. Third, the survey lacked information about neurological disease.

Aluminum production is an important industry in China. In 2017, China’s bauxite production ranked second worldwide. Thus, more attention needs to be paid to the risk of aluminum exposure among workers in factories and residents of the surrounding areas, including the possible risk of consequent cognitive impairment. Further research is warranted to establish a causal link between aluminum exposure and cognitive impairment.

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References
1. Hua H, Jiang X, Wu S. Validation and comparable analysis of aluminum in the popular Chinese fried bread youltiao by wavelength dispersive XRF. Food chemistry. 2016; 207(undefined):1–5. https://doi.org/10.1016/j.foodchem.2016.03.067 PMID: 27080872
2. Weidenhamer J, Fitzpatrick M, Biro A, Kobunski P, Hudson M, Corbin R, et al. Metal exposures from aluminum cookware: An unrecognized public health risk in developing countries. The Science of the total environment. 2017; 579(undefined):805–13. https://doi.org/10.1016/j.scitotenv.2016.11.023 PMID: 27866735
3. Exley C. Aluminum Should Now Be Considered a Primary Etiological Factor in Alzheimer’s Disease. J Alzheimers Dis Rep. 2017; 1(1):23–5. https://doi.org/10.3233/ADR-170010 PMID: 30480226; PubMed Central PMCID: PMC6159653.
4. TERRY R, Peña C. Experimental production of neurofibrillary degeneration. Journal of neuropathology and experimental neurology. 1965; 24(2):200–10. https://doi.org/10.1097/00005072-19650400-00003 PMID: 14280497

5. Bansal VK, Bansal S. Nervous system disorders in dialysis patients. Handbook of clinical neurology. 2014; 119:395–404. Epub 2013/12/25. https://doi.org/10.1016/B978-0-7020-4086-3.00025-4 PMID: 24365308.

6. Krewski D, Yokel RA, Nieboer E, Borchelt D, Cohen J, Harry J, et al. Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. Journal of toxicology and environmental health Part B, Critical reviews. 2007; 10 Suppl 1(Suppl 1):1–269. Epub 2007/12/22. https://doi.org/10.1080/1093740700197766 PMID: 18085842; PubMed Central PMCID: PMC2782734.

7. Davenport A, Goodall R. Aluminium and dementia. Lancet (London, England). 1992; 339(8803):1236. Epub 1992/05/16. PMID: 1349972.

8. Shin RW, Lee VM, Trojanowski JQ. Aluminium modifies the properties of Alzheimer’s disease PHF tau proteins in vivo and in vitro. The Journal of neuroscience: the official journal of the Society for Neuroscience. 1994; 14(11 Pt 2):7221–33. Epub 1994/11/01. https://doi.org/10.1523/JNEUROSCI.14-11-07221.1994 PMID: 7525898; PubMed Central PMCID: PMC2967229.

9. Exley C, Price NC, Kelly SM, Birchall JD. An interaction of beta-amyloid with aluminium in vitro. FEBS letters. 1993; 324(3):293–5. Epub 1993/06/21. https://doi.org/10.1016/0014-5793(93)80137-j PMID: 8405368.

10. Luo Y, Niu F, Sun Z, Cao W, Zhang X, Guan D, et al. Altered expression of Abeta metabolism-associated molecules from D-galactose/AlCl(3) induced mouse brain. Mechanisms of ageing and development. 2009; 130(4):248–52. Epub 2009/01/20. https://doi.org/10.1016/j.mad.2008.12.005 PMID: 19150622.

11. Mantyh PW, Ghilardi JR, Rogers S, DeMaster E, Allen CJ, Stimson ER, et al. Aluminium, iron, and zinc ions promote aggregation of physiological concentrations of beta-amyloid peptide. Journal of neurochemistry. 1993; 61(3):1171–4. Epub 1993/09/01. https://doi.org/10.1111/j.1471-4159.1993.tb03639.x PMID: 8360682.

12. Sakamoto T, Saito H, Ishii K, Takahashi H, Tanabe S, Ogasawara Y. Aluminium inhibits proteolytic degradation of amyloid beta peptide by cathepsin D: a potential link between aluminium accumulation and neuritic plaque deposition. FEBS letters. 2006; 580(28–29):6543–9. Epub 2006/11/23. https://doi.org/10.1016/j.febslet.2006.10.075 PMID: 17112520.

13. Lukiw WJ, Percy ME, Kruck TP. Nanomolar aluminium induces pro-inflammatory and pro-apoptotic gene expression in human brain cells in primary culture. J Inorg Biochem. 2005; 99(9):1895–8. Epub 2005/06/18. https://doi.org/10.1016/j.jinorgbio.2005.04.021 PMID: 15961160.

14. Ghribi O, Herman MM, Forbes MS, DeWitt DA, Savory J. GDNF protects against aluminium-induced apoptosis in rabbits by upregulating Bcl-2 and Bcl-XL and inhibiting mitochondrial Bax translocation. Neurobiology of disease. 2001; 8(5):764–73. Epub 2001/10/11. https://doi.org/10.1006/nbdi.2001.0429 PMID: 11592846.

15. Johnson VJ, Sharma RP. Aluminium disrupts the pro-inflammatory cytokine/neurotrophin balance in primary brain rotation-mediated aggregate cultures: possible role in neurodegeneration. Neurotoxicology. 2003; 24(2):261–8. Epub 2003/02/28. https://doi.org/10.1016/S0161-813X(02)00194-8 PMID: 12606298.

16. Kawahara M. Neurotoxicity of β-amyloid protein: oligomerization, channel formation, and calcium dyshomeostasis. Current pharmaceutical design. 2010; 16(25):2779–89. Epub 2010/08/12. https://doi.org/10.2174/138161210793176545 PMID: 20698821.

17. Huat TJ, Camats-Perna J, Newcombe EA, Valmas N, Kitazawa M, Medeiros R. Metal Toxicity Links to Alzheimer’s Disease and Neuroinflammation. Journal of molecular biology. 2019; 431(9):1843–68. Epub 2019/01/03. https://doi.org/10.1016/j.jmb.2019.01.018 PMID: 30664867; PubMed Central PMCID: PMC6475603.

18. Lu X, Liang R, Jia Z, Wang H, Pan B, Zhang Q, et al. Cognitive disorders and tau-protein expression among retired aluminum smelting workers. J Occup Environ Med. 2014; 56(2):155–60. https://doi.org/10.1097/JOM.0000000000000100 PMID: 24451610.

19. Yang X, Yuan Y, Lu X, Yang J, Wang L, Song J, et al. The Relationship Between Cognitive Impairment and Global DNA Methylation Decrease Among Aluminum Potroom Workers. J Occup Environ Med. 2015; 57(7):713–7. https://doi.org/10.1097/JOM.0000000000000474 PMID: 26147539.

20. Longstreth WT Jr., Rosenstock L, Heyer NJ. Potroom palsy? Neurologic disorder in three aluminum smelter workers. Arch Intern Med. 1985; 145(11):1972–5. Epub 1985/11/01. https://doi.org/10.1001/archinte.145.11.1972 PMID: 4062445.

21. Iregren A, Sjogren B, Gustafsson K, Hagman M, Nylen L, Frech W, et al. Effects on the nervous system in different groups of workers exposed to aluminium. Occupational and environmental medicine. 2001;
22. Sim M, Dick R, Russo J, Bernard B, Grubb P, Krieg E, et al. Are aluminium potroom workers at increased risk of neurological disorders? Occupational and environmental medicine. 1997; 54(4):229–35. https://doi.org/10.1136/oem.54.4.229 PMID: 9166127

23. Lou JZ, Zhou C. The prevention of silicosis and prediction of its future prevalence in China. American journal of public health. 1989; 79(12):1613–6. Epub 1989/12/01. https://doi.org/10.2105/ajph.79.12.1613 PMID: 2817188; PubMed Central PMCID: PMC1349763.

24. Zhang T, Yan R, Chen Q, Ying X, Zhai Y, Li F, et al. Body mass index, waist-to-hip ratio and cognitive function among Chinese elderly: a cross-sectional study. BMJ open. 2018; 8(10):e022055. https://doi.org/10.1136/bmjopen-2018-022055 PMID: 30341119; PubMed Central PMCID: PMC6196809.

25. Lv X, Li W, Ma Y, Chen H, Zeng Y, Yu X, et al. Cognitive decline and mortality among community-dwelling Chinese older people. BMC Med. 2019; 17(1):63. https://doi.org/10.1186/s12916-019-1295-8 PMID: 30871536; PubMed Central PMCID: PMC6419492.

26. Xiang Y, Zare H, Guan C, Gaskin D. The impact of rural-urban community settings on cognitive decline: results from a nationally-representative sample of seniors in China. BMC geriatrics. 2018; 18(1):323. https://doi.org/10.1186/s12877-018-1003-0 PMID: 30594142

27. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res. 2009; 43(4):411–31. https://doi.org/10.1016/j.jpsychires.2008.04.014 PMID: 18579155.

28. He X, Yuan W. Analysis of the incidence of silicosis in Pingyang alum mine during 23 years. Zhejiang Journal of Preventive Medicine. 1996;(1):3.

29. Klotz K, Weistenhofer W, Neff F, Hartwig A, van Thriel C, Drexler H. The Health Effects of Aluminum Exposure. Dtsch Arztebl Int. 2017; 114(39):653–9. https://doi.org/10.3238/arztebl.2017.0653 PMID: 29034866; PubMed Central PMCID: PMC5651828.

30. McLachlan D, Bergeron C, Alexandrov P, Walsh W, Pogue A, Percy M, et al. Aluminum in Neurological and Neurodegenerative Disease. Molecular neurobiology. 2019; 56(2):1531–8. https://doi.org/10.1007/s12035-018-1441-x PMID: 30706368.

31. Kandimalla R, Vallamkonda J, Corgiat E, Gill K. Understanding Aspects of Aluminum Exposure in Alzheimer’s Disease Development. Brain pathology (Zurich, Switzerland). 2016; 26(2):139–54. https://doi.org/10.1111/bpa.12333 PMID: 26494454.

32. Colomina MT, Peris-Sampero F. Aluminum and Alzheimer’s Disease. Adv Neurobiol. 2017; 18:183–97. https://doi.org/10.1007/978-3-319-60189-2_9 PMID: 2889268.

33. Kilin LOJ, Starr JM, Shuei IU, Russ TC. Environmental risk factors for dementia: a systematic review. BMC Geriatrics. 2016; 16(1):175–. https://doi.org/10.1186/s12877-016-0342-y PMID: 27729011.

34. Mirza A, King A, Troakes C, Exley C. Aluminum in brain tissue in familial Alzheimer’s disease. Journal of trace elements in medicine and biology: organ of the Society for Minerals and Trace Elements (GMS). 2017; 40(undefined):30–6. https://doi.org/10.1016/j.jtemb.2016.12.001 PMID: 28159219.

35. Candy J, Oakley A, Klinowski J, Carpenter T, Perry R, Atack J, et al. Aluminosilicates and senile plaque formation in Alzheimer’s disease. Lancet (London, England). 1986; 1(8477):354–7. https://doi.org/10.1016/s0140-6736(86)92333-6 PMID: 2868298.

36. Morris G, Puri BK, Frye RE. The putative role of environmental aluminium in the development of chronic neuropathology in adults and children. How strong is the evidence and what could be the mechanisms involved? Metab Brain Dis. 2017; 32(5):1335–55. https://doi.org/10.1007/s11011-017-0777-2 PMID: 28752219; PubMed Central PMCID: PMC5596046.

37. Kawahara M. Effects of aluminium on the nervous system and its possible link with neurodegenerative diseases. Journal of Alzheimer’s disease: JAD. 2005; 8(2):171–82; discussion 209–15. https://doi.org/10.3233/jad-2005-8210 PMID: 16308486.

38. Shah S, Yoon G, Ahmad A, Ullah F, Amin F, Kim M. Nanoscale-alumina induces oxidative stress and accelerates amyloid beta (Aβ) production in ICR female mice. Nanoscale. 2015; 7(37):15225–37. https://doi.org/10.1039/c5nr03598h PMID: 26315713.

39. Zawilla NH, Taha FM, Kishk NA, Farahat SA, Farghaly M, Hussein M. Occupational exposure to aluminium and its amylodigenic link with cognitive functions. J Inorg Biochem. 2014; 139:57–64. https://doi.org/10.1016/j.jinorgbio.2014.06.003 PMID: 24973993.