Aluminum Effects in Infants and Children

Mark R. Corkins[1] and COMMITTEE ON NUTRITION: Steven A Abrams, George J Fuchs 3rd, Praveen S Goday, Tamara S Hannon, Jae H Kim, C Wesley Lindsey, Ellen S Rome.

1. Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, The University of Tennessee Health Science Center, Memphis, Tennessee mcorkins@uthsc.edu.

ABSTRACT

Aluminum has no known biological function; however, it is a contaminant present in most foods and medications. Aluminum is excreted by the renal system, and patients with renal diseases should avoid aluminum-containing medications. Studies demonstrating long-term toxicity from the aluminum content in parenteral nutrition components led the US Food and Drug Administration to implement rules for these solutions. Large-volume ingredients were required to reduce the aluminum concentration, and small-volume components were required to be labeled with the aluminum concentration. Despite these rules, the total aluminum concentration from some components continues to be above the recommended final concentration. The concerns about toxicity from the aluminum present in infant formulas and antiperspirants have not been substantiated but require more research. Aluminum is one of the most effective adjuvants used in vaccines, and a large number of studies have documented minimal adverse effects from this use. Long-term, high-concentration exposure to aluminum has been linked in meta-analyses with the development of Alzheimer disease.

ABBREVIATION:

FDA — US Food and Drug Administration

This is the author's manuscript of the article published in final edited form as:

Corkins, M. R., & Nutrition, C. O. (2019). Aluminum Effects in Infants and Children. Pediatrics, 144(6). https://doi.org/10.1542/peds.2019-3148

INTRODUCTION

Aluminum is one of the most common metals on earth.[1] Aluminum is lightweight, strong, and easily sterilizable; therefore, it is used in a variety of packaging and manufacturing processes, such as milling and blending. These uses result in the presence of aluminum in our food, water supply, and medications. The aluminum present in the body normally enters via gastrointestinal ingestion. However, the gastrointestinal mucosa is exceptionally efficient in preventing absorption, and little to none of ingested aluminum appears to be absorbed.[1] One calculated fraction of aluminum absorption in adults was only 0.14%.[1] Data from an adult human study in which an aluminum isotope was used revealed the absorption to be 0.08%.[1] The Agency for Toxic Substances and Disease Registry of the US Department of Health and Human Services has set the minimum risk level for oral aluminum intake at 1 mg/kg per day.[2]

The aluminum that does make it to the bloodstream is more than 80% bound to transferrin.[3,4] The small amounts that are absorbed are quickly excreted. Tracer studies with radioactive aluminum in human adults have revealed that only 0.5% of the total aluminum concentration is still in the bloodstream 24 hours after injection.[5,6] The great majority of aluminum that is in the bloodstream is cleared by the renal system.[1] In contrast to the wide variety of minerals that have been found to have a role in an enzymatic metalloproteins, only aluminum has not been found to have any biological role. In fact, in the presence of renal disease, when normal barriers are bypassed, aluminum has been shown to have some clearly associated toxicity.

Studies have revealed no biomarkers for aluminum levels in humans.[2] Because aluminum is poorly absorbed and rapidly excreted by the renal system, concentrations measured in blood or urine do not reflect exposures unless they are acute excessive amounts. A study in which researchers compared serum, plasma, and 24-hour urine aluminum concentrations among different reference laboratory tests revealed wide variations in the reported numbers.[7] The ranges used in these laboratory tests as normal were derived from small samples of normal individuals, often adults, and none that were age specific. The use of other tissues, such as hair, was found to be unreliable.[7]

RENAL DISEASES

The previous American Academy of Pediatrics policy statement on aluminum toxicity was focused on the aluminum effects observed in patients with renal disease.[8] At that time, the dialysates used for peritoneal dialysis had a high aluminum level and bypassed the normal protective epithelial barriers. Because the patients had decreased renal function, they could not excrete the aluminum. These patients developed symptoms of bone pain. Adults on long-term aluminum-containing dialysate had increased aluminum concentrations in the brain, with progressive dementia.[9] When the aluminum was removed from the dialysate, these issues resolved. Of ongoing concern was the use of aluminum-containing phosphate binders in pediatric patients with renal disease. Multiple case reports were published of patients who developed encephalopathy and had aluminum bone deposition.[8] The previous policy recommended discontinuing the use of aluminum-containing phosphate binders in patients with renal disease. Awareness regarding aluminum toxicity resulted in discontinued use of these agents. Patients with renal disease should also avoid aluminum-containing antacids and medications, such sucralfate.

PARENTERAL NUTRITION

Intravenous compounds containing high aluminum concentrations have a risk of resulting in aluminum toxicity because they bypass the protective gastrointestinal mucosa. As indicated previously, aluminum is normally cleared quickly by the renal system. There is greater concern with high levels of aluminum intake over longer periods of time. Parenteral nutrition solutions are the most chronic intravenous infusions used in patient care. Aluminum is present in all of the ingredients of parenteral nutrition, the highest levels being found in calcium gluconate, inorganic phosphates, and cysteine hydrochloride.[10]

DEVELOPMENTAL EFFECTS

The blood-brain barrier is efficient at blocking the passage of aluminum into the brain[3,11]; however, this barrier may not be as well developed in preterm infants. Because preterm infants are known to have immature renal function, Bishop et al[12] were concerned about aluminum toxicity in preterm infants receiving parenteral nutrition. They performed a study to compare 90 preterm infants randomly assigned to receive standard parenteral nutrition with 92 preterm infants randomly assigned to receive purposefully aluminum-depleted

parenteral nutrition.[12] At a postterm age of 18 months, a subgroup of the infants had the Bayley Scales of Infant Development Mental Developmental Index performed. The index score for 39 infants who received the standard aluminum-containing parenteral nutrition was 92, compared with a score of 102 for the 41 infants who received the aluminum-depleted parenteral nutrition (P = .02). The study revealed a loss of 1 index point for each day infants received the standard aluminum-containing parenteral nutrition solution.[12]

BONE EFFECTS

As indicated earlier, there is little accumulation of aluminum in the body. The skeleton is the only part of the body that appears to concentrate aluminum, with 54% of the body's total aluminum concentrated in bone.[13] When aluminum accumulates to a high enough level, bone formation is blocked and osteomalacia develops, increasing the risk of fracture.[1] An older study in which the authors evaluated preterm infants receiving parenteral nutrition revealed that aluminum deposited at the leading edge of bone mineralization.[14] The same infants studied by Bishop et al[12] were later examined for long-term bone effects. The researchers followed-up with these patients when they were 13 to 15 years of age with dual-energy radiograph absorptiometry scans for bone mineral content. Patients who had received the standard (higher) aluminum parenteral nutrition were found to have lower lumbar spine bone mineral content, and patients with the highest intakes had lower bone mineral content of their hips.[15]

REGULATORY RESPONSE

In response to the studies cited here, the US Food and Drug Administration (FDA) became concerned about the aluminum content of intravenous solutions. In 1990, the FDA announced an intention to regulate the aluminum in parenteral solutions. In 2000, the final rule was published but did not take effect until July 26, 2004.[16] The rule requires the reduction of aluminum content in large-volume parenteral nutrition solutions to less than 25 µg/L and requires that small-volume parenteral nutrition solutions be labeled to indicate the maximum aluminum concentration present on their expiration date. The expiration date is important because the aluminum level increases with time as it leaches out of the glass in the containers. One of the key requirements of the FDA was to add a warning onto the label stating that in patients with impaired renal function, infusion of

solutions with more than 5 μg/kg per day of aluminum may result in central nervous system and bone toxicity.[16] Because the labels on the components list the maximum aluminum concentration that could be present, when the actual final aluminum concentration of parenteral nutrition solutions has been measured, it has been less than the projected maximum value.[17] Despite the solutions having lower aluminum concentrations than the component labels project, when actually measured, none of the compounded neonatal or pediatric parenteral nutrition solutions had an aluminum concentration below the FDA-recommended 5 μg/kg per day.[17,18] When another group used the actual measured aluminum concentration in the components and formulated a parenteral nutrition solution with the lowest levels possible, the daily dose of aluminum was still greater than the recommended 5 μg/kg per day.[19] When plasma aluminum concentrations were measured in patients with intestinal failure who were receiving long-term parenteral nutrition, the average concentration was 8 times greater than that in healthy controls.[20] The aluminum concentrations present in small-volume parenteral nutrition solutions have not changed since the studies that revealed a developmental effect were published. Unfortunately, until new parenteral components with lower aluminum content are available, no matter how thoughtful the prescriber, parenteral nutrition solutions for most pediatric patients will contain aluminum concentrations above the recommended amount.

FORMULAS

Studies have documented significantly higher aluminum concentrations in infant formulas compared with human milk.[21,22] Despite this, there are no studies reporting any evidence of clinical aluminum toxicity related to formula feeding. Nonetheless, the disparity in the measured concentrations has resulted in some calls for an effort to reduce the aluminum content in infant formulas.[22] As indicated earlier, there is minimal absorption of aluminum via the gastrointestinal tract, so regulatory agencies have not responded to these calls. One study measured the plasma aluminum concentrations of infants fed human milk versus a variety of infant formulas and found no significant differences, except with hydrolysate formulas.[23] In this study, the hydrolysate formulas were all used in infants with a gastrointestinal illness; however, data on aluminum content

in hydrolysate infant formulas are insufficient to make recommendations at this time. Studies are greatly needed on the potential health risks attributable to the aluminum in infant formulas, especially in populations such as preterm infants and those with gastrointestinal or renal diseases.

ANTIPERSPIRANTS

Skin is an excellent barrier against aluminum; however, claims have been made that the high levels of aluminum in antiperspirants lead to dermal absorption. This concern has been used to market antiperspirants low in aluminum. There are no published medical studies in which authors report large numbers of patients with toxicity attributable to transdermal aluminum absorption. The concern is that increased absorption may occur in skin that has been abraded by shaving. There is a single case report of an adult female patient who used a daily aluminum-containing antiperspirant, regularly shaved the skin under her arms, and had elevated aluminum concentrations.[24] In vitro studies in which researchers used skin biopsies in a diffusion cell revealed little absorption of an aluminum antiperspirant preparation.[25] However, when the skin was stripped by using adhesive tape, the uptake was significantly greater. The clinical relevance of this model to skin that has been shaved is difficult to extrapolate. A study in adults in which researchers used radiolabeled aluminum in an antiperspirant revealed absorption of only 0.012% of the tracer.[26] This study involved using tape to strip the previously shaved underarm area for skin samples. This would indicate that the absorption of aluminum from antiperspirants, even with skin that has been shaved, is apparently minimal. Mixed epidemiological data from population studies reveal no association[27] or a possible association[28] of aluminum-containing antiperspirants with breast cancer. Although there is no solid clinical evidence of toxicity, there are calls in the literature for reduction of the aluminum in antiperspirants.[29]

VACCINE ADJUVANTS

Aluminum is the predominant adjuvant used in human vaccines, although not all vaccines. The aluminum content of vaccines is limited by the Code of Federal Regulations to 1.25

mg per dose.[30] The regulations also stipulate that data are required to reveal that the amount of aluminum is safe and necessary to produce the intended effect. The Centers for Disease Control and Prevention has stated that the amount of aluminum exposure from following the recommended vaccine schedule is low and that the aluminum is not readily absorbed by the body.[31] The Centers for Disease Control and Prevention cited a study in which researchers calculated the aluminum exposure from vaccines during infancy and found the total to be far below the minimal risk levels established by the Agency for Toxic Substances and Disease Registry.[32] The aluminum-containing adjuvants are reported to have minimal adverse effects but are effective at improving the antibody response.[33] There are reports of a chronic local granulomatous inflammation known as macrophagic myofasciitis in a small number of patients after receiving intramuscular vaccines containing aluminum.[33,34] This condition allegedly results from a chronic inflammatory response to the residual adjuvant aluminum at the vaccination site that leads to a constellation of neurologic symptoms, including myalgia, arthralgia, chronic fatigue, weakness, and cognitive issues.[34] The number of patients reported to have the neurologic symptoms is low compared with the number of vaccinated individuals. The World Health Organization Global Advisory Committee of Vaccine Safety has not found that the data support an association between aluminum adjuvants and chronic neurologic diseases.[35] The aluminum content of vaccines has been blamed for autism spectrum disorders, but a large meta-analysis of cohort studies evaluating vaccination and the risk of autism revealed that in pooled data of 1 256 407 children, the odds ratio of developing autism after vaccination was 0.99, with a 95% confidence interval of 0.92 to 1.06.[36]

The aluminum adjuvants in the human papillomavirus vaccine have also been suggested as causing primary ovary insufficiency. However, the relationship suggested is based on a total of 6 case reports, most occurring years after vaccination, with only 1 patient having ovarian failure within several months of vaccination.[37] These cases reports come after more than 170 million doses of the human papillomavirus vaccine have been administered. The aluminum adjuvants in vaccines are also accused of potentially triggering an autoimmune process. The autoimmune syndrome induced by adjuvants was proposed in 2011.[38] The proposed criteria for this syndrome are extremely vague and general. Two of the major criteria are exposure to an external stimulus (infection, vaccine,

silicone, or adjuvant) before symptoms occur and appearance of a long list of general somatic complaints. A review of the available literature for the purported autoimmune syndrome induced by adjuvants revealed that the human cases were so dissimilar in proposed triggers and clinical conditions that there was no evidence for a relationship between adjuvants and autoimmune conditions.[39]

ALUMINUM AND ALZHEIMER DISEASE

A long-standing hypothesis has been that aluminum is involved in the etiology of Alzheimer disease. This theory is based on the assumption that a long-term accumulation of aluminum in the brain could produce symptoms like dialysis-associated encephalopathy. The aluminum-induced neurofibrillary degeneration in animal studies also was similar to the pathology observed in human patients with Alzheimer disease.[40] A meta-analysis used to evaluate chronic aluminum-containing antacid use and the risk of Alzheimer disease revealed no association.[41] In another meta-analysis, researchers examined dietary patterns of food consumption high in aluminum and the risk of dementia (70% of dementia is attributable to Alzheimer disease).[42] This meta-analysis also included 1 study of aluminum in drinking water and 1 study of aluminum-containing dust inhalation. The meta-analysis revealed an increased relative risk of dementia of 2.24 with increased aluminum exposure ($P < .001$).[42] The largest meta-analysis of the association between aluminum and Alzheimer disease included a total of 8 studies and a total of 10 567 individuals.[43] The follow-up time from the cited studies ranged from 8 to 48 years, and the studies included drinking water (>100 µg/L aluminum concentration) and occupational exposures. Regarding the increased risk of Alzheimer disease, the authors of this meta-analysis reported a pooled odds ratio of 1.71, with a 95% confidence interval of 1.35 to 2.18.[43]

SUMMARY OF KEY POINTS

The 1996 American Academy of Pediatrics publication regarding aluminum toxicity was a policy statement. The primary concern in 1996 was renal dialysates, which has resolved. Currently, there are a variety of new issues concerning aluminum, the primary

one being the aluminum concentration in parenteral nutrition components. However, there are no clinic alternatives for some of these components, and some of the other issues are still lacking the depth of data to support more definitive policy statements. Therefore, this updated document on aluminum toxicity was prepared as a technical review. A summary of the primary issues concerning aluminum is provided in the following points:

1. The greatest risk of aluminum exposure occurs in intravenous preparations for micronutrient delivery in parenteral nutrition. Aluminum exposure via parenteral nutrition has been shown to have long-term effects in preterm infants. Every effort should be made to minimize the aluminum content, although with the currently available products, the concentration will still be above the recommended amount.
2. Patients with renal disease should reduce aluminum exposure by avoiding aluminum-containing phosphate binders and other medications containing high amounts of aluminum to reduce aluminum exposure.
3. Despite having aluminum concentrations higher than those in human milk, infant formulas have not been documented to result in any long-term health concerns. Studies are needed to assess the potential health risks attributable to the aluminum content in infant formulas, especially in potentially vulnerable populations.
4. Antiperspirants have a high aluminum content, but there is not enough evidence to suggest long-term health concerns.
5. Aluminum adjuvants are extremely safe and effective at producing an immune response with rare adverse effects.
6. Meta-analyses have suggested an association between aluminum and Alzheimer disease with long-term high-concentration exposures.

FOOTNOTES

Address correspondence to Mark R. Corkins, MD, FAAP. E-mail: mcorkins@uthsc.edu

Technical reports from the American Academy of Pediatrics benefit from expertise and resources of liaisons and internal (AAP) and external reviewers. However, technical

reports from the American Academy of Pediatrics may not reflect the views of the liaisons or the organizations or government agencies that they represent.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All technical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

FINANCIAL DISCLOSURE: The author has indicated he has no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The author has indicated he has no potential conflicts of interest to disclose.

REFERENCES

1. Priest ND. The biological behaviour and bioavailability of aluminium in man, with special reference to studies employing aluminium-26 as a tracer: review and study update. J Environ Monit. 2004;6(5):375–403
2. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Aluminum. Atlanta, GA: Agency for Toxic Substances and Disease Registry; 2008
3. Yokel RA, McNamara PJ. Aluminium toxicokinetics: an updated minireview. Pharmacol Toxicol. 2001;88(4):159–167
4. Harris WR. Equilibrium model for speciation of aluminum in serum. Clin Chem. 1992;38(9):1809–1818

5. Priest ND, Newton D, Day JP, Talbot RJ, Warner AJ. Human metabolism of aluminium-26 and gallium-67 injected as citrates. Hum Exp Toxicol. 1995;14(3):287–293
6. Priest ND, Newton D, Talbot RJ. Metabolism of Aluminum-26 and Gallium-67 in a Volunteer Following Their Injection as Citrates. Abingdon, United Kingdom: United Kingdom Atomic Energy Authority; 1991
7. Zeager M, Woolf AD, Goldman RH. Wide variation in reference values for aluminum levels in children. Pediatrics. 2012;129(1). Available at: www.pediatrics.org/cgi/content/full/129/1/e142
8. American Academy of Pediatrics, Committee on Nutrition. Aluminum toxicity in infants and children. Pediatrics. 1996;97(3):413–416
9. O'Hare JA, Callaghan NM, Murnaghan DJ. Dialysis encephalopathy. Clinical, electroencephalographic and interventional aspects. Medicine (Baltimore). 1983;62(3):129–141
10. Hernández-Sánchez A, Tejada-González P, Arteta-Jiménez M. Aluminium in parenteral nutrition: a systematic review. Eur J Clin Nutr. 2013;67(3):230–238
11. Yokel RA, Allen DD, Ackley DC. The distribution of aluminum into and out of the brain. J Inorg Biochem. 1999;76(2):127–132
12. Bishop NJ, Morley R, Day JP, Lucas A. Aluminum neurotoxicity in preterm infants receiving intravenous-feeding solutions. N Engl J Med. 1997;336(22):1557–1561
13. International Commission on Radiological Protection. Report of Task Force on Reference Man. Oxford, United Kingdom: Pergamon Press; 1975
14. Koo WW, Kaplan LA, Bendon R, et al. Response to aluminum in parenteral nutrition during infancy. J Pediatr. 1986;109(5):877–883
15. Fewtrell MS, Bishop NJ, Edmonds CJ, Isaacs EB, Lucas A. Aluminum exposure from parenteral nutrition in preterm infants: bone health at 15-year follow-up. Pediatrics. 2009;124(5):1372–1379
16. US Food and Drug Administration. Aluminum in large and small volume parenterals used in total parenteral solutions. Fed Regist. 2000;65(17):4103–4111
17. Speerhas RA, Seidner DL. Measured versus estimated aluminum content of parenteral nutrient solutions. Am J Health Syst Pharm. 2007;64(7):740–746

18. Hall AR, Arnold CJ, Miller GG, Zello GA. Infant parenteral nutrition remains a significant source for aluminum toxicity. JPEN J Parenter Enteral Nutr. 2017;41(7):1228–1233
19. Poole RL, Pieroni KP, Gaskari S, Dixon T, Kerner JA. Aluminum exposure in neonatal patients using the least contaminated parenteral nutrition solution products. Nutrients. 2012;4(11):1566–1574
20. Courtney-Martin G, Kosar C, Campbell A, et al. Plasma aluminum concentrations in pediatric patients receiving long-term parenteral nutrition. JPEN J Parenter Enteral Nutr. 2015;39(5):578–585
21. Fernandez-Lorenzo JR, Cocho JA, Rey-Goldar ML, Couce M, Fraga JM. Aluminum contents of human milk, cow's milk, and infant formulas. J Pediatr Gastroenterol Nutr. 1999;28(3):270–275
22. Chuchu N, Patel B, Sebastian B, Exley C. The aluminium content of infant formulas remains too high. BMC Pediatr. 2013;13:162
23. Hawkins NM, Coffey S, Lawson MS, Delves HT. Potential aluminium toxicity in infants fed special infant formula. J Pediatr Gastroenterol Nutr. 1994;19(4):377–381
24. Guillard O, Fauconneau B, Olichon D, Dedieu G, Deloncle R. Hyperaluminemia in a woman using an aluminum-containing antiperspirant for 4 years. Am J Med. 2004;117(12):956–959
25. Pineau A, Guillard O, Favreau F, Marrauld A, Fauconneau B. In vitro study of percutaneous absorption of aluminum from antiperspirants through human skin in the FranzTM diffusion cell [published correction appears in J Inorg Biochem. 2012;116:228]. J Inorg Biochem. 2012;110:21–26
26. Flarend R, Bin T, Elmore D, Hem SL. A preliminary study of the dermal absorption of aluminium from antiperspirants using aluminium-26. Food Chem Toxicol. 2001;39(2):163–168
27. Mirick DK, Davis S, Thomas DB. Antiperspirant use and the risk of breast cancer. J Natl Cancer Inst. 2002;94(20):1578–1580
28. McGrath KG. An earlier age of breast cancer diagnosis related to more frequent use of antiperspirants/deodorants and underarm shaving. Eur J Cancer Prev. 2003;12(6):479–485

29. Pineau A, Fauconneau B, Sappino AP, Deloncle R, Guillard O. If exposure to aluminium in antiperspirants presents health risks, its content should be reduced. J Trace Elem Med Biol. 2014;28(2):147–150
30. Code of Federal Regulations Title 21 – Food and Drugs, 21 CFR §610.15 (2016)
31. Centers for Disease Control and Prevention. Adjuvants help vaccines work better. 2018. Available at: www.cdc.gov/vaccinesafety/concerns/adjuvants.html#alum. Accessed July 8, 2019
32. Mitkus RJ, King DB, Hess MA, Forshee RA, Walderhaug MO. Updated aluminum pharmacokinetics following infant exposures through diet and vaccination. Vaccine. 2011;29(51):9538–9543
33. Petrovsky N. Comparative safety of vaccine adjuvants: a summary of current evidence and future needs. Drug Saf. 2015;38(11):1059–1074
34. Shaw CA, Li D, Tomljenovic L. Are there negative CNS impacts of aluminum adjuvants used in vaccines and immunotherapy? Immunotherapy. 2014;6(10):1055–1071
35. World Health Organization, Global Advisory Committee on Vaccine Safety. Statement from the Global Advisory Committee on Vaccine Safety on Aluminum-Containing Vaccines. Geneva, Switzerland: World Health Organization; 2008
36. Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. Vaccine. 2014;32(29):3623–3629
37. Hawkes D, Buttery JP. Human papillomavirus vaccination and primary ovarian insufficiency: an association based on ideology rather than evidence. Curr Opin Obstet Gynecol. 2016
38. Shoenfeld Y, Agmon-Levin N. ‘ASIA’ - autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun. 2011;36(1):4–8
39. Hawkes D, Benhamu J, Sidwell T, Miles R, Dunlop RA. Revisiting adverse reactions to vaccines: a critical appraisal of Autoimmune Syndrome Induced by Adjuvants (ASIA). J Autoimmun. 2015;59:77–84
40. Miu AC, Benga O. Aluminum and Alzheimer’s disease: a new look. J Alzheimers Dis. 2006;10(2–3):179–201

41. Virk SA, Eslick GD. Brief Report: meta-analysis of antacid use and Alzheimer's disease: implications for the Aluminum Hypothesis. Epidemiology. 2015;26(5):769–773
42. Cao L, Tan L, Wang HF, et al. Dietary patterns and risk of dementia: a systematic review and meta-analysis of cohort studies. Mol Neurobiol. 2016;53(9):6144–6154
43. Wang Z, Wei X, Yang J, et al. Chronic exposure to aluminum and risk of Alzheimer's disease: a meta-analysis. Neurosci Lett. 2016;610:200–206