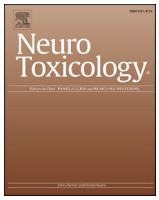
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Review



Aluminum and Alzheimer's disease in the 21st century: An umbrella review of evidence and controversies

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ABSTRACT

The potential role of aluminum (Al) in the onset and progression of Alzheimer disease (AD) remains among the most enduring and divisive controversies in environmental neurotoxicology. Although numerous narrative reviews, systematic reviews, meta-analyses, mechanistic appraisals, and toxicological assessments have been published, their conclusions remain heterogeneous and at times contradictory. The present review of reviews critically integrates the PubMed-indexed review literature published in this century (January 1, 2000, and May 2, 2026), focusing on epidemiology, exposure sources, toxicokinetics, biological plausibility, experimental models, biomarkers, preventive measures, and unresolved methodological challenges. A predefined selection strategy was applied, prioritizing reviews that directly addressed Al and AD, employed systematic or meta-analytic approaches, examined epidemiological or mechanistic evidence, evaluated exposure assessment, or offered influential conceptual frameworks. Peripheral reviews were considered only when they provided essential context. The methodological quality of the included reviews was appraised qualitatively, considering transparency of the search strategy, reproducibility of methods, consideration of bias, and relevance to the review objectives. The strength of the evidence supporting each main conclusion was graded as strong, moderate, or limited. The evidence reviewed indicates that Al can promote several AD-related biological processes in experimental settings, including oxidative stress, mitochondrial dysfunction, neuroinflammation, glial activation, disrupted calcium signaling, amyloid beta aggregation, impaired amyloid clearance, tau phosphorylation, autophagy impairment, and epigenetic alterations. Epidemiological findings are less consistent, although several meta-analyses link chronic, occupational, or drinking-water Al exposure with cognitive decline and AD risk, despite limitations from exposure misclassification, confounding, and methodological heterogeneity. Overall, the evidence neither identifies Al as the principal cause of AD nor dismisses its relevance, supporting instead a contributory role within a multifactorial disease model, especially in susceptible individuals.

1. Introduction

Alzheimer disease (AD) is the most prevalent neurodegenerative dementia and one of the major medical and social challenges associated with population aging. The main neuropathological hallmarks of AD include extracellular amyloid beta deposits, intracellular tau pathology, synaptic dysfunction, neuroinflammation, and progressive neuronal loss. However, the etiology of sporadic AD is not reducible to a single pathway. Aging, APOE genotype, vascular disease, metabolic alterations, lifestyle factors, inflammation, and environmental exposures probably interact across decades before clinical dementia becomes evident (Angelopoulou et al., 2021; Armstrong, 2019; Klotz et al., 2017; Prakash et al., 2017; Rondeau, 2002),

Among environmental factors (Chin-Chan et al., 2015; Rahman et al., 2020; Yegambaram et al., 2015), Al has generated exceptional scientific interest because of its abundance, widespread human exposure, lack of known essential biological function, capacity to interact with phosphate and oxygen donor ligands, as well as well-known neurotoxicity under certain exposure conditions (Andrade et al., 2017; Bondy, 2016; Campbell, 2002; Flaten, 2001; Gómez et al., 2005; Li et al., 2017; Makhdoomi et al., 2023; Maya et al., 2016; Miu, 2006; Morris et al., 2017). The Al hypothesis of AD has persisted for more than half

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a century, but its interpretation has evolved. Earlier formulations often asked whether Al directly caused AD. More recent reviews increasingly ask whether Al can contribute to disease-relevant pathways, accelerate pathology, or increase vulnerability in subgroups of exposed individuals (Colomina and Peris-Sampedro, 2017; Das et al., 2021; Frisardi et al., 2010; Miu, 2006; Obulesu and Rao, 2010; Perl and Moalem, 2006; Soleimani et al., 2025; Yokel, 2000; Zatta et al., 2009).

The controversy is sustained by two facts, which are both scientifically valid. Experimental studies show that Al can induce oxidative injury, neuroinflammation, mitochondrial damage, calcium dysregulation, amyloidogenic changes, and behavioral alterations in models relevant to neurodegeneration (Becaria et al., 2002; Campdelacreu, 2014; Chopra et al., 2011; Dhapola et al., 2023; Exley, 2005; Gupta et al., 2005; Martínez-Hernández et al., 2023; Obulesu and Rao, 2010; Virk and Eslick, 2015a,b,c; Walton, 2014). However, epidemiological evidence remains heterogeneous, exposure assessment is difficult, and the presence of Al in AD-affected tissue does not by itself prove etiological priority (Lidsky, 2014; McDowell, 2001; Paul and Firdous, 2026; Percy et al., 2011; Sanajou et al., 2021; Xu et al., 2018).

The present umbrella review was conducted to synthesize and critically evaluate the large body of review literature published in the current century (January 1, 2000, to May, 2026). This work adds to the existing literature in several important ways. It is the first dedicated 21st-century umbrella review focused specifically on the Al-AD relationship. It integrates epidemiological, toxicokinetic, mechanistic, and biomarker evidence, while balancing supportive and skeptical perspectives from narrative reviews, systematic reviews, and meta-analyses. Overall, the evidence supports a contributory, rather than primary causal, role for Al in AD within a multifactorial model, particularly in genetically or physiologically susceptible individuals. In addition, this review highlights key scientific advances since 2000, including stronger mechanistic insights into autophagy impairment, epigenetic regulation, and metal dyshomeostasis, as well as improved meta-analytic data on exposure sources and biomarkers. Finally, it identifies persistent methodological gaps and provides targeted recommendations for future research. A review of reviews can identify where the field has reached relative consensus, where the evidence is truly conflicting, and where future work should be concentrated.

2. Methods

This study was conducted as an umbrella review (review of reviews), following principles derived from the PRISMA 2020 statement and methodological guidance for overviews of reviews.

2.1. References and scope

PubMed/MEDLINE was used for the search, covering reviews indexed between January 1, 2000, and May 2, 2026. The list included narrative reviews, systematic reviews, meta-analyses, umbrella reviews, mechanistic reviews, toxicological assessments, and related reviews on environmental risk factors, metal dyshomeostasis, neurotoxicity, and AD. The search strategy combined controlled vocabulary and free-text terms: "aluminum" OR "aluminium" AND "Alzheimer" OR "dementia") AND (review OR systematic review OR meta-analysis). No language restriction was applied at the search stage. Reference lists of selected articles were also screened to identify additional relevant reviews. The complete search was: (“aluminum”[MeSH/Title/Abstract] OR “aluminium”) AND (“Alzheimer” OR “dementia” OR “cognitive decline” OR “cognitive impairment”) AND (“review” OR “systematic review” OR “meta-analysis”), restricted to the review, systematic review, and meta-analysis publication types, as well as to items indexed between January 1, 2000 and May 2, 2026. Dementia, cognitive decline, and cognitive impairment are clinically and epidemiologically related to AD. However, these broader neurocognitive outcomes were included only when the corresponding review explicitly linked them to AD, or to Al exposure. Reviews addressing these outcomes without any reference to Al or to AD were excluded.

2.2. Eligibility criteria

Articles were included if they met at least one of the following criteria: 1) direct focus on Al and AD, 2) systematic review or meta-analysis of Al exposure and cognitive outcomes, 3) evaluation of Al within environmental risk factors for dementia, 4) mechanistic relevance (oxidative stress, amyloid, tau, neuroinflammation, autophagy, epigenetics), 5) toxicokinetics or exposure assessment relevant to brain accumulation, and 6) analysis of exposure sources (diet, occupational, water, pharmaceuticals). In turn, exclusion criteria included: 1) primary experimental studies, 2) reviews with only marginal reference to Al, 3) publications unrelated to neurodegeneration, and 4) reviews focused exclusively on Al unrelated contexts (e.g., vaccine adjuvants or unrelated clinical applications).

2.3. Selection strategy and rationale for limiting references

Titles and abstracts were screened for eligibility, followed by full-text evaluation based on predefined criteria. Selection prioritized methodological robustness, recency, and relevance. A PRISMA-style flow diagram summarizes the literature selection process (Fig. 1).

2.4. Data abstraction and synthesis

From each included review, the following information was extracted: type of review (narrative, systematic, meta-analysis), exposure type (diet, occupational, biomarkers), study population or model, main conclusions, and reported limitations. The included reviews were categorized according to methodological rigor: a) Level I: meta-analyses and umbrella reviews, b) Level II: systematic reviews without quantitative synthesis, and c) Level III: narrative or mechanistic reviews. Interpretations in subsequent sections prioritize Level I evidence when available. The methodological quality of included reviews was evaluated qualitatively using criteria including transparency of search strategy, reproducibility, and consideration of bias. Title/abstract screening, full-text eligibility assessment, and data abstraction were independently performed by both authors. Disagreements were resolved by consensus. After removal of duplicates and application of the eligibility criteria, a total of 124 reviews were included in the qualitative synthesis (Fig. 1). The methodological quality of the reviews included was qualitatively evaluated according to predefined criteria: transparency of the search strategy, reproducibility of methods, clarity of eligibility criteria, acknowledgment of study limitations and potential sources of bias, as well as overall relevance to the objectives of the present umbrella review. Based on this appraisal and on the Level I–III hierarchy, the strength of evidence underlying each principal conclusion was categorized as strong, moderate, or limited. These judgments are summarized in Table 1. Consistent with the nature of an umbrella review, the formal synthesis is based on review-level evidence, while primary epidemiological and experimental studies are cited only as contextual examples to illustrate specific mechanisms or concepts. The principal categories of reviews included in the present synthesis, together with their specific contribution to the analysis, are also shown in Table 1.

3. Evolution of the Al hypothesis during the current century

The current review shows that the Al hypothesis has not disappeared. It has rather become more mechanistically sophisticated and more cautious in its causal language. Reviews published early in the period frequently revisited evidence from dialysis encephalopathy, animal models, drinking water studies, and postmortem tissue measurements (Dhapola et al., 2023; Flaten, 2001; Lukiw, 2012; McDowell, 2001; Percy et al., 2011; Savory et al., 2006; Singh et al., 2018; Zatta et al.,

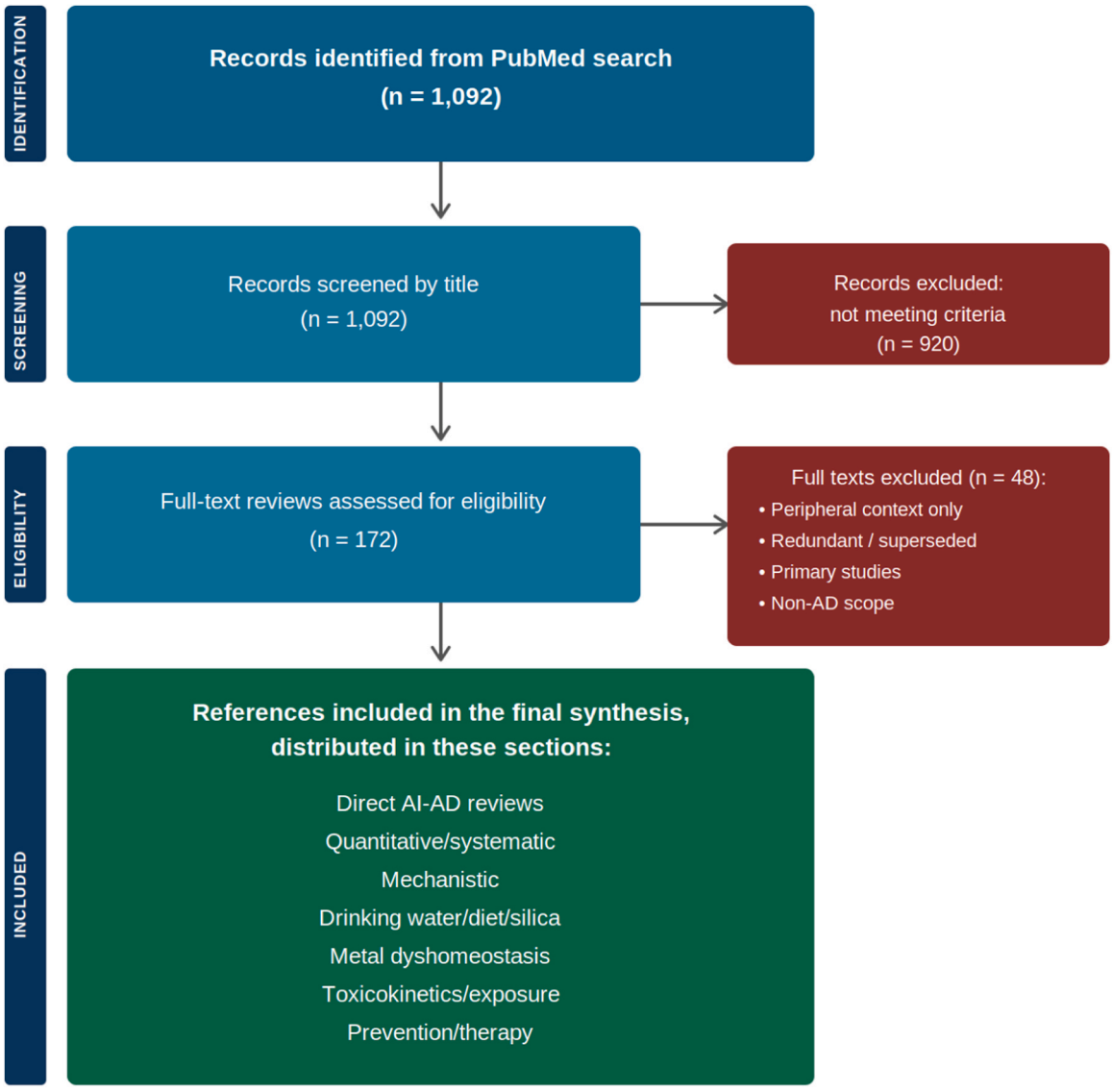


Fig. 1. Literature search and selection flow diagram.

2009). These reviews often framed the question about whether Al exposure might be a direct risk factor for AD.

By the mid-2000s, several reviews emphasized that Al could interact with certain AD pathways. Exley (2005) proposed an Al-amyloid cascade framework and discussed Al as a factor capable of promoting amyloid beta aggregation. Zhao et al. (2014) later reviewed evidence that Al might promote amyloidogenesis and impair clearance of amyloid peptides from the central nervous system. In parallel, Walton (2014) developed a strong causality-oriented interpretation, arguing that chronic Al exposure satisfies several Bradford Hill considerations and might contribute to disease progression. In contrast, other reviews were more skeptical. Lidsky (2014) asked whether the Al hypothesis was effectively dead, emphasizing the absence of definitive causal proof and the weaknesses of some occupational and epidemiological studies (Li et al., 2017). Willhite et al. (2014) provided a broad toxicological assessment of metallic, nanoscale, oxide, hydroxide, and soluble forms of Al, placing neurological hypotheses within a larger risk-assessment context. This skeptical or risk-assessment tradition is important because it prevents mechanistic plausibility from being overinterpreted as clinical causality.

More recent reviews have shifted the question again. Rather than asking whether Al alone causes AD, authors increasingly have examined how Al intersects with neuroinflammation, autophagy, epigenetics, mitochondrial dysfunction, and metal dyshomeostasis (Domingo, 2006; Huat et al., 2019; Miu and Benga, 2006; Roe, 2022; Sanajou et al., 2023; Soleimani et al., 2025; Thomas et al., 2015; Walton, 2013). This change is scientifically important. Sporadic AD is unlikely to have a single environmental cause. Therefore, the relevant question is whether Al can operate as a disease modifier within a complex exposome. The main mechanistic pathways through which Al exposure can contribute to AD-relevant neurobiology, as identified in the reviewed literature, are summarized in Table 2.

4. Epidemiological evidence

4.1. Drinking water exposure

Drinking water has been one of the most frequently reviewed exposure sources of Al because it can be assessed geographically and because Al may be present naturally, or as a residual from water treatment processes. Flaten (2001) and Rondeau (2002) reviewed epidemiological studies on Al in drinking water related to AD and/or associated disorders, with particular attention to concentration, duration of exposure, and potential modifying effects of silica. Frisardi et al. (2010) and

Table 1
Main categories of selected reviews and their contribution to the present synthesis.

Evidence domain	Representative included reviews	Principal contribution	Main limitations identified in the included reviews	Overall evidence strength
Direct Al-AD reviews	Colomina and Peris-Sampedro (2017); Dey and Singh (2022); Gupta et al. (2005); Kandimalla et al. (2016); Kawahara (2005); Miu and Benga (2006); Tomljenovic (2011)	Summarized historical, epidemiological, toxicological, and mechanistic evidence specifically linking Al exposure with AD.	Interpretative heterogeneity; uneven quality of primary studies; difficulty distinguishing causation from association.	Moderate. Consistent qualitative signal across many reviews but based largely on Level III narrative and mechanistic sources and uneven primary-study quality.
Quantitative and systematic evidence	Jones et al. (2025); Killin et al. (2016); Li et al. (2023); Virk and Eslick (2015a),b,c); Vlasak et al. (2024); Wang et al. (2016); Xu et al. (2018)	Provided meta-analytic or systematic evaluation of chronic exposure, biomarkers, occupational exposure, cognitive performance, and environmental dementia risk.	High between-study heterogeneity; exposure misclassification; limited longitudinal data; variable AD diagnostic criteria.	Moderate. Level I meta-analyses report associations, yet high heterogeneity, exposure misclassification, and few longitudinal data limit confidence.
Drinking water, diet, and silica	Flaten (2001); Frisardi et al. (2010); Gillette Guyonnet et al. (2007); Miu (2006); Rondeau (2002); Solfrizzi et al. (2006); Willhite et al. (2012)	Examined Al intake from water and diet and the possible modulating role of silica or silicon in absorption and excretion.	Ecological designs; variable water chemistry; confounding by geography, minerals, socioeconomic factors, and vascular risk.	Limited. Predominantly ecological designs with variable water chemistry and incomplete confounder control.
Mechanistic neurotoxicity	Aschner et al. (2024); Campbell and Bondy (2000); Makhdoomi et al. (2023); Sanajou et al. (2023); Savory et al. (2006); Walton (2013); Zhao et al. (2014)	Integrated oxidative stress, inflammation, calcium signaling, amyloidogenesis, tau phosphorylation, autophagy, and epigenetic mechanisms.	Dose relevance and model validity; difficulty translating high-dose experimental models to chronic human exposure.	Strong for biological plausibility; limited for human causality. Reproducible experimental effects on AD-relevant pathways, but often at doses exceeding common human exposure.
Metal dyshomeostasis and mixed exposure	Andrade et al. (2017); Das et al. (2021); Doroszkiewicz et al. (2023); Li et al. (2017); Mateo et al. (2023); Wang and Wang (2017); Zatta et al. (2003)	Placed Al within a broader framework of altered metal homeostasis and mixed-metal neurotoxicity.	Causal attribution to one metal is difficult; interactions are undermeasured in human studies.	Moderate. Conceptually well supported, but Al-specific effects are difficult to isolate within mixed-metal exposures.
Toxicokinetics, exposure, and measurement	Bryliński Ł et al. (2023); Klotz et al. (2017); Michalke et al. (2009); Niu (2018); Willhite et al. (2014); Yokel (2006)	Reviewed absorption, speciation, transport across barriers, tissue accumulation, analytical methods, and exposure routes.	Brain exposure is difficult to estimate; biological matrices differ in interpretability; standardization is incomplete.	Moderate. Absorption, speciation, and transport are reasonably characterized, whereas cumulative brain dose remains hard to quantify.
Prevention and therapy	Domingo (2006); Domingo et al. (2011); Esparza et al. (2019); Liu et al. (2005); Percy et al. (2011); Puentes-Díaz et al. (2023); Zatta et al. (2009)	Discussed chelation, metal homeostatic therapy, silicon, antioxidants, melatonin, and multifunctional ligands.	Clinical evidence remains limited; potential interference with essential metal biology; preventive relevance uncertain.	Limited. Mechanistically plausible strategies (chelation, silicon, antioxidants) lack high-quality clinical-trial evidence.

The right-hand column indicates the overall strength of the review-level evidence (strong, moderate, or limited) for each evidence domain, based on qualitative methodological appraisal and the Level I–III hierarchy described in the Methods section.

Table 2
Mechanistic pathways linking Al exposure with AD-relevant biology.

Pathway	Evidence summarized in reviews	AD relevance	Key interpretative caution
Oxidative stress	Al exposure associated with lipid peroxidation, reactive oxygen species (ROS), antioxidant depletion, and redox imbalance.	Oxidative injury is a recurrent feature of AD and may precede overt neuronal loss.	Al may act indirectly; experimental doses often exceed common environmental exposure.
Mitochondrial dysfunction	Reviews describe impaired energy metabolism, mitochondrial injury, and oxidative amplification.	Mitochondrial decline contributes to synaptic failure and neuronal vulnerability in AD.	Human dose-response evidence is limited.
Neuroinflammation	Al can activate microglia, inflammatory cytokine signaling, and NF-κB-related pathways.	Chronic neuroinflammation is involved in AD progression and synaptic injury.	Inflammation is non-specific and may be consequence as well as driver.
Amyloid beta aggregation and clearance	Al has been reviewed as promoting aggregation and impairing amyloid clearance.	Amyloid beta pathology is one defining feature of AD.	In vitro aggregation does not by itself prove in vivo causality.
Tau and kinase signaling	Reviews discuss GSK-related tau phosphorylation and altered signal transduction.	Tau burden correlates strongly with neurodegeneration and clinical severity.	Tau mechanisms require more human validation.
Autophagy and lysosomal dysfunction	Recent reviews propose Al-related impairment of autophagy and proteostasis.	Protein clearance failure is central to AD pathobiology.	Evidence is emerging and largely preclinical.
Epigenetic regulation	Non-coding RNAs and epigenetic changes have been proposed as mediators of Al neurotoxicity.	Epigenetic mechanisms may explain long-latency exposure effects.	Human longitudinal exposome-epigenome studies are scarce.
Metal dyshomeostasis	Al interacts conceptually with iron, copper, zinc, manganese, and other metals in neurodegeneration.	Metal imbalance can modulate aggregation, oxidative stress, and inflammation.	Difficult to isolate Al-specific effects in mixed exposures.

Solfrizzi et al. (2003) expanded this discussion by linking dietary Al, water Al, other metals, and cognitive decline. A recurring interpretation is that elevated Al in drinking water can be associated with increased dementia or AD risk in some populations, but the evidence is not uniform. Several methodological problems recur across the reviews by Flaten (2001), Rondeau (2002), Frisardi et al. (2010), Klotz et al. (2017), and related syntheses. They include ecological exposure classification, insufficient individual exposure histories, incomplete adjustment for vascular and socioeconomic confounders, and regional differences in water chemistry. Importantly, the bioavailable fraction of Al depends on chemical speciation, pH, complexation with organic ligands, and the presence of silica. Thus, total Al concentration in water could not reliably represent internal dose (Exley, 2006; Klotz et al., 2017; Sharma et al., 2020). The possible protective role of silica or silicon has received specific attention. Reviews proposed that soluble silica can reduce Al absorption or facilitate urinary Al excretion, thereby decreasing Al

bioavailability (Domingo et al., 2011; Dragomir et al., 2026; Singh et al., 2018). This hypothesis is biologically plausible and potentially relevant for prevention, but the clinical evidence remains insufficient for establishing firm recommendations. A systematic review by Wasick and Kim (2024) specifically evaluated the association between the mineral composition of drinking water and cognitive function in elderly populations. Of the 10 studies included, Al was the most frequently evaluated trace element. Four studies reported that Al exposure was associated with an increased risk of cognitive decline, while the remainder found no significant association. Higher silica concentrations and elevated water pH were identified as protective factors against cognitive decline, whereas calcium also showed a beneficial effect in two studies. This updated Level II synthesis confirms that both Al and co-occurring water minerals modulate cognitive aging risk, reinforcing the need for studies that simultaneously measure multiple trace elements rather than Al in isolation (Wasick and Kim, 2024).

4.2. Occupational exposure and cognitive impairment

Occupational exposure is theoretically more informative than low-level environmental exposure considering that industrial settings can involve higher airborne Al exposure. Santibáñez et al. (2007) reviewed occupational risk factors in AD and emphasized the methodological quality of the available epidemiological studies. In turn, Virk and Eslick (2015a,b,c) conducted a series of meta-analysis specifically addressing occupational Al exposure and AD, while Lu (2018) later reviewed occupational exposure to Al and cognitive impairment.

Overall, the occupational literature suggests that high or prolonged exposure to Al may be associated with cognitive impairment or AD in some settings, but conclusions remain limited by exposure reconstruction, co-exposures, healthy-worker effects, diagnostic variability, and insufficient prospective follow-up. The occupational literature also raises a broader point: Al exposure rarely occurs in isolation. Workers may be also exposed to other metals, particulates, solvents, combustion products, or physical stressors, making attribution to Al alone difficult.

4.3. Biological matrices and biomarkers

Several reviews and meta-analyses addressed Al concentrations in biological matrices. In a series of meta-analyses, Virk and Eslick (2015a, b,c) reported higher Al levels in brain, serum, and cerebrospinal fluid among AD cases than those found in controls. Xu et al. (2018) performed a quantitative meta-analysis and systematic review of circulatory levels of toxic metals, including Al, in patients with AD, while Mohseni and Chettle (2016) reviewed the history of in vivo neutron activation analysis for measuring Al in human subjects. Although these findings are relevant, they are not decisive. Elevated Al in tissue or fluids can indicate exposure, altered distribution, impaired elimination, disease-related barrier disruption, or contamination during sampling and analysis. Reviews on speciation and analytical chemistry emphasize that the biological form of Al is critical and that total concentrations may be difficult to interpret without speciation, matrix validation, and standardized protocols (Exley, 2006; Sharma et al., 2020).

4.4. Meta-analytic synthesis

The strongest epidemiological evidence derives from Level I studies (meta-analyses), whereas Level II and III reviews provide contextual and interpretative synthesis. Meta-analyses have generally moved the debate forward but have not resolved it. Wang et al. (2016) reported an association between chronic Al exposure and AD risk. Virk and Eslick (2015a,b,c) reported associations in occupational exposure and biological matrices. Recently, Vlasak et al. (2024) examined Al exposure and cognitive performance, while Li et al. (2023a) evaluated trace elements and Alzheimer dementia in population-based studies. More recent umbrella and environmental risk factor reviews have situated Al within the broader field of dementia risk determinants.

The strength of meta-analytic work is its transparency and reproducibility. Its limitation is dependence on heterogeneous primary studies. The most common problems include inconsistent exposure metrics, diverse outcome definitions, small study numbers in subgroup analyses, possible publication bias, and uncertainty over whether measured Al represents past exposure, current exposure, or disease-related redistribution. Across Level I and II reviews, common methodological limitations include exposure misclassification, heterogeneous outcome definitions, insufficient longitudinal data, and incomplete adjustment for confounders. Few reviews explicitly evaluated risk of bias using standardized tools, limiting confidence in pooled estimates.

5. Exposure sources and toxicokinetic considerations

Although human exposure to Al is unavoidable, the internal dose is not determined simply by its environmental abundance. Reviews of dietary Al, drinking water, pharmaceuticals, cosmetics, occupational settings, and consumer products, indicate that absorbed dose depends strongly on chemical form, route, solubility, complexing agents, renal function, and gastrointestinal physiology (Andrade et al., 2017; Campbell and Bondy, 2000; Dey and Singh, 2022; Klotz et al., 2017; Sanajou et al., 2021; Tyczyńska et al., 2024).

For the general population, diet is generally considered a major source of Al exposure. Food additives, processed foods, tea, and cookware have been considered as potential contributors, although the relative importance of each source varies by region and dietary habits (Andrade et al., 2017; Drago et al., 2008; Tyczyńska et al., 2024). Drinking water contributes less total Al than food in many settings, but its relevance may be greater when Al is present in more bioavailable forms, or in combination with low silica (Klotz et al., 2017; McDowell, 2001; Percy et al., 2011).

The broader context of diet and dementia risk is relevant here. Cao et al. (2016) conducted a systematic review and meta-analysis of 43 cohort studies examining the association between dietary patterns and dementia risk. Higher intake of unsaturated fatty acids, antioxidants, and vitamin B, as well as adherence to the Mediterranean diet, were each associated with reduced dementia risk. Although that review was not specific to Al, it contextualized Al dietary exposure within a wider nutritional framework in which overall dietary quality modifies the risk of neurodegeneration. Díaz et al. (2022) specifically reviewed the relationships between nutrients and brain amyloid beta (Aβ) status in humans, synthesizing evidence from observational studies and clinical trials. High intake of fruits, vegetables, and low-glycemic-index foods was associated with favorable Aβ status, while disturbances in calcium, iron, zinc, and other trace elements altered Aβ levels. It was noted that Al itself could perturb metal homeostasis in ways that affect Aβ aggregation and clearance. Moreover, the finding that nutritional factors shape brain Aβ burden adds a preventive dietary dimension to the Al-AD mechanistic discussion (Díaz et al., 2022).

Pharmaceutical and medical sources, including antacids, buffered aspirin, parenteral nutrition, dialysis-related exposure, and some adjuvant contexts, have been also included and reviewed in the broader Al toxicology literature (Andrade et al., 2017; Sanajou et al., 2021; Savory et al., 2006). For AD etiology, chronic oral is more relevant than short-term exposure, but susceptible groups such as individuals with impaired renal function may have altered elimination.

Transport to the brain remains a central toxicokinetic question. Yokel (2006) reviewed blood-brain barrier flux of Al and other metals implicated in neurodegeneration, and Bryliński Ł et al. (2023) later, discussed routes of penetration and accumulation in the human brain. Potential mechanisms include transferrin-mediated transport, altered barrier permeability, olfactory pathways, and uptake of Al complexes. However, quantifying cumulative brain Al exposure in humans remains technically difficult.

6. Mechanistic plausibility

6.1. Oxidative stress and mitochondrial dysfunction

Oxidative stress is among the most consistently cited mechanisms linking Al exposure to AD-relevant pathology. Campbell and Bondy, (2000) discussed Al-induced oxidative events and their relationship to inflammation, while Kumar and Gill (2014) reviewed oxidative stress and mitochondrial dysfunction in Al neurotoxicity. In turn, Bondy (2014) emphasized that prolonged exposure to low levels of Al could produce behavioral and morphological changes associated with brain aging and neurodegeneration. Although Al is not a classic redox-active transition metal like iron or copper, it can promote oxidative injury indirectly. Proposed mechanisms include disruption of mitochondrial function, promotion of lipid peroxidation, alteration of antioxidant defenses, interference with iron homeostasis, and amplification of inflammatory signaling. This is important because oxidative damage is a well-established component of AD pathology (Khattab et al., 2026).

Recently, Cassera et al. (2025) reviewed how metal ions, including Al, promote oxidative stress and DNA damage via interactions with catecholamines like dopamine and norepinephrine. These metal ions catalyze catecholamine auto-oxidation, generating reactive quinones and oxygen radicals that injure neuronal DNA and membrane lipids. Because catecholaminergic neurotransmission is impaired in AD, this mechanism offers an additional pathway linking Al exposure to AD-related neurochemical and neuropathological changes. The authors emphasize that pro-oxidant effects of Al involve not only lipid peroxidation but also specific neurotransmitter-mediated damage pathways.

6.2. Neuroinflammation, microglia, and astrocytes

Neuroinflammation provides another biologically plausible link between Al exposure and AD. Campbell (2006) reviewed the role of Al and copper in neuroinflammation and AD, while Huat et al. (2019) linked metal toxicity to AD and neuroinflammation more broadly, and Lukiw (2012) identified NF-κB-regulated proinflammatory microRNAs in AD. More recent reviews on microglial activation (Martínez-Hernández et al., 2023; Roe, 2022) support the view that metals can modulate innate immune pathways in neurodegeneration.

Astrocytes may also be relevant targets. Thus, Aremu and Meshitsuka (2006) reviewed astroglial functions and Al implications for neurodegeneration, while Li et al. (2021) reviewed astrocytes in heavy metal neurotoxicity. Astrocytes regulate glutamate homeostasis, antioxidant responses, blood-brain barrier function, and neurovascular coupling. Consequently, Al-mediated astrocytic dysfunction could therefore contribute indirectly to neuronal vulnerability. On the other hand, Canales et al. (2001) showed that chronic Al exposure disrupts the glutamate–nitric oxide–cyclic GMP (Glu–NO–cGMP) signaling pathway in cerebellar neurons and rat brain. Long-term and prenatal Al exposure reduced nitric oxide synthase activity, decreased guanylate cyclase responsiveness, and markedly lowered glutamate-stimulated cGMP. Since this pathway supports synaptic plasticity, memory consolidation, and neuronal survival, its disruption by Al offers an additional mechanism linking the metal to cognitive impairment and AD–related neuropathology.

6.3. Amyloid beta aggregation and clearance

Various reviews have connected Al to Aβ metabolism. Exley (2005) proposed an Al-amyloid cascade hypothesis. The same author later discussed the role of Al and iron in precipitation of beta-sheet structures in plaque cores (Exley, 2006), while Zhao et al. (2014) reviewed evidence that Al might promote amyloidogenesis and impair clearance of amyloid peptides from the central nervous system. The mechanistic relevance of these observations lies in the ability of metals to affect protein conformation, aggregation kinetics, and clearance pathways. However, the field must distinguish between in vitro aggregation phenomena and in vivo disease causation. Metal-induced aggregation is plausible but does not prove that environmental exposure initiates AD in humans.

6.4. Tau phosphorylation, GSK pathways, and calcium signaling

Tau pathology is central to AD severity and clinical progression. Reviews have discussed Al-induced changes in kinase signaling and tau phosphorylation, including the glycogen synthase kinase pathway (Sanajou et al., 2023). Walton (2012) emphasized disruption of calcium homeostasis and signal transduction as a mechanism resembling changes observed in aging and AD. Calcium dysregulation may be particularly important because it links membrane excitability, mitochondrial stress, synaptic dysfunction, protease activation, and cell death. Aluminum can interact with phosphate groups and signaling molecules, potentially influencing intracellular signaling even at relatively low concentrations. Nevertheless, dose-response relationships relevant to human exposure require further clarification.

Croom and Taylor (2001) reviewed how neuropeptide Y (NPY) and peptide YY (PYY), which are members of the pancreatic polypeptide family acting as neurotransmitters and humoral agents in the brain and gut, interact with Al and AD. It was noted that NPY/PYY receptor numbers and circulating levels are altered in AD, and animal studies suggest these peptides participate in Al metabolism. It was proposed that Al-induced disruption of NPY/PYY signaling might underlie some cognitive and metabolic features of AD, adding a neuroendocrine mechanism to potential roles of Al in the AD.

6.5. Autophagy, proteostasis, and lysosomal pathways

Autophagy dysfunction has recently become a prominent theme. Makhdoomi et al. (2023) reviewed Al neurotoxicity from an autophagy perspective, and Li et al. (2023b) reviewed recent insights into autophagy and metals and/or nanoparticles exposure. Because AD involves failure of proteostasis and impaired clearance of misfolded proteins, Al-related disturbance of autophagy and lysosomal function may be mechanistically important. This area is especially promising because it connects Al exposure to both amyloid and tau pathobiology without requiring Al to be the initiating event. A modest impairment of clearance mechanisms over decades could plausibly amplify age-related accumulation of pathogenic proteins.

6.6. Epigenetic and non-coding RNA mechanisms

Recent reviews have introduced epigenetic regulation into the Al-AD debate. Aschner et al. (2024) reviewed epigenetic mechanisms of Al-induced neurotoxicity with a focus on non-coding RNAs. It represents a notable evolution of the field. Earlier reviews largely emphasized metal accumulation and oxidative stress, while newer reviews consider gene regulation, microRNAs, long non-coding RNAs, and inflammatory transcriptional networks. Epigenetic mechanisms are relevant because they provide a plausible explanation for how chronic low-level exposures might produce durable changes in neuronal or glial function. However, the current evidence is still mainly mechanistic and preclinical. Human longitudinal studies integrating exposure biomarkers with epigenetic signatures and AD biomarkers are needed.

7. Experimental models and translational limitations

Animal and cellular models provide much of the mechanistic evidence supporting Al neurotoxicity. Reviews of Al-induced neurodegeneration in animals, experimental approaches to metallotoxicity, Al-maltolate-treated aged rabbits, and Al chloride models describe cognitive impairment, oxidative stress, glial activation, neurotransmitter alterations, amyloidogenic changes, and tau-related effects

(Alasfar and Isaifan, 2021; Dhapola et al., 2023; Inan-Eroglu and Ayaz, 2018; Platt, 2006; Suay Llopis and Ballester Díez, 2002). These models are valuable because they permit controlled exposure and mechanistic interrogation. Nevertheless, they are also a major source of controversy. Exposure levels, chemical forms, routes of administration, age of animals, duration of exposure, and behavioral paradigms vary widely. Some models may produce general neurotoxicity rather than AD-specific pathology. Therefore, findings should be interpreted as evidence that Al can affect AD-relevant pathways, not as proof that ordinary human exposure causes AD.

Platt (2006) critically evaluated experimental strategies used to identify Alzheimer- and dementia-related targets for exogenous toxins, focusing on Al as a model neurotoxin. The review compared chemical, cellular, physiological, histochemical, and epidemiological methods, outlining their respective strengths and limitations for linking metal exposure to AD-like pathology. It was highlighted that neuronal function should be probed with multiple complementary approaches (from electrophysiology and synaptic plasticity to behavior) and that consistent findings across these methods support mechanistic plausibility, but they do not by themselves prove clinical causality. The best future models will need to use environmentally relevant exposures, aging animals, genetic susceptibility factors, mixed-metal exposure, and clinically relevant biomarker endpoints. Such models would better reflect the multifactorial nature of sporadic AD.

Recently, Hu et al. (2026) reviewed neural mechanisms and MRI biomarkers linked to Al-induced cognitive impairment, focusing on how Al alters apoptosis, necroptosis, and neurotransmitter systems. The authors highlighted MRI findings such as hippocampal gray matter atrophy, default-mode network dysfunction, and iron deposition revealed by quantitative susceptibility mapping. It was concluded that multimodal MRI offers a promising, non-invasive approach for early detection of Al-related neurodegeneration and for translating mechanistic insights into clinically useful biomarkers.

8. Metal dyshomeostasis and mixed exposures

A major development in the review literature is the shift from single-metal causation to metal dyshomeostasis. AD brains show altered handling of several metals, including iron, copper, zinc, manganese, and of course, also Al (Domingo, 2006; Doroszkiewicz et al., 2023; Kandimalla et al., 2016; Kawahara, 2005; Shah et al., 2025; Shcherbatykh and Carpenter, 2007; Virk and Eslick, 2015a,b,c; Walton, 2013; Wang and Wang, 2017). These metals can influence amyloid aggregation, tau biology, oxidative stress, inflammatory responses, and synaptic function. This broader perspective is both scientifically stronger and methodologically more demanding. It avoids treating Al in isolation, but it also complicates causal inference. Aluminum may interact with iron-mediated oxidative stress, copper or zinc effects on Aβ, manganese neurotoxicity, and other environmental contaminants (Campbell, 2006; Hsu et al., 2018; Jomova et al., 2025; Shah et al., 2025; Wang and Wang, 2017). Reviews on metal mixtures emphasize that combined exposures can produce additive, synergistic, or antagonistic effects that cannot be inferred from single-metal studies (Andrade et al., 2017; Campbell, 2006; Jomova et al., 2025).

Several key reviews collectively position Al as a major neurotoxic metal whose effects must be interpreted within a broader landscape of mixed metal exposures in AD and related neurodegenerative disorders. Shcherbatykh and Carpenter (2007) reviewed epidemiological and experimental evidence implicating Al alongside other metals such as copper, zinc, iron, and fluoride. It was argued that environmental and nutritional metal exposures interacted with genetic susceptibilities rather than acting as isolated causes and thereby helping to situate Al within a multi-metal etiological framework. More recently, Kawahara et al. (2023) deepen this perspective by examining how four essential trace elements (iron, zinc, copper, manganese) and the non-essential Al were absorbed, transported to the brain, and integrated into neurobiology. It was shown that amyloidogenic proteins both regulate synaptic metal homeostasis and undergo metal-induced conformational changes that can initiate neurodegeneration, while also emphasizing metal–metal crosstalk between Al and essential elements as a key modulator of neurotoxicity.

On the other hand, Carpenter (2001) added an occupational and environmental health lens, noting that although Al is poorly absorbed from the gastrointestinal tract, sustained exposure allows gradual accumulation in the brain, while daily exposures, such as ingesting soil residues on unwashed vegetables, contribute to its ubiquity. By comparing Al with other neurotoxic metals such as lead, mercury, and manganese, Carpenter (2001) highlighted shared mechanistic themes such as disruption of signal transduction pathways, alterations in neurotransmitter function, and impairment of cellular energy metabolism, thereby clarifying how Al fits within the broader spectrum of metal-induced neurodegeneration. Hester et al. (2022) formalized this multi-metal, multi-disease view by developing a systematic evidence map to catalog epidemiological and experimental data on 18 metals, including Al, across tauopathies, synucleinopathies, and TDP−43 proteinopathies. Rather than drawing immediate causal conclusions, their framework identified areas of evidence density and scarcity, highlighting that Al should be assessed alongside other metals and across several neurodegenerative phenotypes. Recently, Zaitseva et al. (2025) conducted a comparative review of the neurotoxic effects of Al and manganese, from molecular mechanisms to clinical manifestations, showing that overexposure to both metals leads to brain accumulation, disruption of redox homeostasis, neuroinflammation, and impairment of neurotransmitter systems. This comparative lens reinforces the idea that the neurotoxic profile of Al overlaps with (but is not identical to) that of other metals, while real-world risk likely arises from combined exposures rather than single metals considered in isolation.

Together, the above contributions converge on a coherent picture in which Al is a significant, yet not solitary, contributor to metal-related neurodegeneration, and in which its role in AD and related conditions is best understood within complex mixtures and metal–metal interactions rather than as an individual exposure. The implication for AD research is clear: studies limited to one metal may miss relevant biological interactions. Future studies should incorporate metallomic profiles and exposome-based models rather than isolated Al measurements alone.

9. Prevention, therapeutic implications, and public health relevance

The therapeutic literature has considered whether decreasing Al burden or modifying metal-mediated toxicity might prevent or slow AD. Chelating agents have been discussed as potential interventions, but their application in AD is uncertain because metals also serve essential biological functions (Cirovic et al., 2023; Doroszkiewicz et al., 2023). Domingo (2006) reviewed Al and other metals in AD with attention to chelating agents, while later reviews discussed nanoparticle and metal chelation therapeutics (Liu et al., 2005), multifunctional ligands targeting metal-protein interactions (Puentes-Díaz et al., 2023), as well as the protection of EDTA in neurodegenerative diseases (Ferrero, 2022).

Silicon or silica represents another preventive concept. Reviews proposed that silicon may reduce Al absorption and enhance excretion (Dragomir et al., 2026; Singh et al., 2018). This is mechanistically plausible and potentially safer than systemic chelation, but high-quality clinical trials are lacking. Therefore, the evidence is insufficient to recommend silicon supplementation as an AD-preventive therapy, although the hypothesis remains worthy of controlled investigation. Antioxidants and anti-inflammatory approaches have also been discussed in Al-related neurodegeneration. Melatonin has been reviewed as a potential protective agent in Al-related neurodegenerative disorders (Esparza et al., 2019). Other reviews discussed phytochemicals, resveratrol, and dietary patterns, although these are not Al-specific

interventions (Bakrim et al., 2022; Drago et al., 2008).

Sánchez-Muniz et al. (2019) reviewed how beer-related nutrients, especially silicon, polyphenols, and hop-derived compounds within a Mediterranean dietary pattern, might influence neurodegeneration and AD. These authors highlighted experimental evidence that non-alcoholic beer can mitigate Al-induced behavioral and neurochemical alterations via anti-inflammatory, antioxidant, and cholinesterase-inhibiting effects. Silicon was singled out for its capacity to lower Al absorption and brain accumulation, suggesting that Si-rich dietary sources offer a practical strategy to modulate Al bioavailability and support nutritional neuroprotection. From a public health perspective, the most notable conclusion would be precautionary rather than therapeutic. Avoiding unnecessary high Al exposure is reasonable, particularly in occupational settings and in vulnerable populations. However, current evidence does not support claims that Al reduction alone can prevent AD.

10. Areas of consensus and disagreement

The review literature reveals several areas of reasonable consensus. First, Al is neurotoxic under some exposure conditions. Second, Al can influence biological pathways relevant to AD in experimental systems. Third, some epidemiological and biomarker studies report positive associations. Fourth, exposure assessment and analytical standardization remain major obstacles. Fifth, the evidence does not establish Al as the sole or primary cause of AD. The main disagreement concerns interpretation. Supportive reviews argue that mechanistic plausibility, tissue accumulation, positive epidemiological trends, and coherence with AD pathways justify considering Al a causal or contributory factor (Bondy, 2016; Christen, 2000; Frisardi et al., 2010; Perl and Moalem, 2006; Virk and Eslick, 2015a,b,c). In contrast, skeptical reviews emphasize inconsistent epidemiology, uncertain exposure relevance, and insufficient proof of temporality (Li et al., 2017; Sanajou et al., 2021). Finally, balanced reviews tend to position Al as one potential component of a broader environmental and biological risk network (Colomina and Peris-Sampedro, 2017; Domingo, 2006, 2026; Exley, 2014; Obulesu and Rao, 2010; Walton, 2013; Wang and Wang, 2017).

This manuscript adopts the third position. It is scientifically unwarranted to dismiss Al because definitive proof is lacking, especially when mechanistic plausibility is substantial. It is equally unwarranted to present Al as an established primary cause of AD. The most accurate conclusion is that Al remains a plausible contributory factor requiring better human evidence.

11. Recommendations for future research

Future epidemiological studies should be prospective, longitudinal, and designed around individual-level exposure assessment. Drinking water studies should measure Al speciation, silica, pH, and co-occurring metals. Occupational studies should include quantitative exposure reconstruction, co-exposure control, and standardized neuropsychological outcomes. Biomarker studies should distinguish serum, plasma, urine, cerebrospinal fluid, and brain tissue measurements, and should apply rigorous contamination control. On the other hand, mechanistic studies should prioritize environmentally relevant doses, aging models, genetic susceptibility, mixed exposures, and clinically interpretable endpoints. Integration with amyloid, tau, neurofilament, glial, inflammatory, and imaging biomarkers could improve translation. The field would also benefit from standardized reporting guidelines for Al exposure studies in neurodegeneration. Finally, future reviews should avoid polarized language. The Al hypothesis should neither be accepted as proven nor rejected as obsolete. It should be evaluated within modern multifactorial models of AD, where environmental toxicants may contribute modestly but meaningfully to population risk.

12. Critical appraisal of the review literature

The methodological quality of the included reviews varies substantially. Few systematic reviews applied standardized risk-of-bias tools, and many narrative reviews lacked transparent methodology. Common limitations identified across the literature include: exposure misclassification, lack of temporal evidence linking exposure and disease onset, inadequate control of confounding variables, and reliance on cross-sectional or ecological designs. Mechanistic studies frequently rely on high-dose experimental models with uncertain relevance to human exposure scenarios. These limitations constrain causal inference and highlight the need for more standardized, longitudinal, and biomarker-integrated research.

13. Conclusions

The current review of the scientific literature published since 2000 supports a biologically plausible relationship between Al exposure and AD-relevant neurodegenerative mechanisms. The most consistent evidence concerns oxidative stress, neuroinflammation, mitochondrial dysfunction, amyloid beta aggregation or clearance impairment, tau-related signaling, calcium dyshomeostasis, autophagy impairment, astrocyte and microglial dysfunction, and epigenetic regulation. Human evidence is suggestive but not definitive. Meta-analyses and systematic reviews report associations in some exposure and biomarker domains, but causality remains unresolved because of methodological heterogeneity, exposure misclassification, confounding, and uncertainty over temporality. The strongest conclusion is that Al should be regarded as a plausible contributory environmental neurotoxicant, not as an established sole cause of AD.

A review of reviews is useful because it shows that the field has moved from a simple causal controversy toward a more nuanced model of cumulative environmental risk, metal dyshomeostasis, and biological susceptibility. Continued research is warranted, especially using longitudinal exposome-based designs and standardized Al measurement methods. Future progress will depend on integrating high-quality epidemiological evidence with mechanistic insights under standardized methodological frameworks.

CRediT authorship contribution statement

Maria Teresa Colomina: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Conceptualization. **Domingo Jose L:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Conceptualization.

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Data availability

This is a Review of Reviews. No specific data were obtained to prepare it.

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