Association of Circulating Magnesium Levels in Patients With Alzheimer’s Disease From 1991 to 2021: A Systematic Review and Meta-Analysis

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Alzheimer’s disease (AD) remains a medical and social challenge worldwide. Magnesium (Mg) is one of the most frequently evaluated essential minerals with diverse biological functions in human body. However, the association between circulating Mg levels and AD remains controversial. We conducted a meta-analysis of 21 studies published between 1991 and 2021 to determine whether the Mg levels in the blood and cerebrospinal fluid (CSF) are abnormal in AD. Literatures were searched in PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang Data without language limitations. A pooled subject sample including 1,112 AD patients and 1,001 healthy controls (HCs) was available to assess Mg levels in serum and plasma; 284 AD patients and 117 HCs were included for Mg levels in CSF. It was found that serum and plasma levels of Mg were significantly reduced in AD patients compared with HCs (standardized mean difference [SMD] = −0.89; 95% confidence interval [CI] [−1.36, −0.43]; P = 0.000). There was statistically non-significant for Mg level in CSF between AD and HCs, whereas a decreased tendency were detected (SMD = −0.16; 95% CI [−0.50, 0.18]; P = 0.364). In addition, when we analyzed the Mg levels of serum, plasma and CSF together, the circulating Mg levels in AD patients was significantly lower (SMD = −0.74, 95% CI [−1.13; −0.35]; P = 0.000). These results indicate that Mg deficiency may be a risk factor of AD and Mg supplementation may be a potentially valuable adjunctive treatment for AD.

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Keywords: magnesium, serum, plasma, CSF, Alzheimer’s disease, meta-analysis

INTRODUCTION

Alzheimer’s disease (AD) is the most common cause of dementia, typified by cognitive impairment and brain lesions. The typical pathological changes include plaques formed by beta-amyloid (Aβ) aggregation and intracellular neurofibrillary tangles, as well as prolonged inflammation (Akiyama et al., 2000; Lesne et al., 2006). Although there are many basic and clinical researches on AD, the etiology of AD has not been comprehensively elucidated. Currently, AD treatment largely depends on cholinesterase inhibitors, which is only a symptomatic therapy. It means that these drugs have
limited efficacy on AD progression (Sharma, 2019). Therefore, it is necessary to evaluate the risk factors for AD to provide an opportunity for delaying the AD progression.

Notably, the dyshomeostasis of nutritional minerals has been associated with AD progression (Gonzalez-Dominguez et al., 2014). Previous studies have proposed the imbalance of several minerals, such as zinc (Ventriglia et al., 2015; Kawahara et al., 2018), iron (Belaidi and Bush, 2016; Lane et al., 2018), copper (Donnelly et al., 2007; Sensi et al., 2018), and manganese (Du et al., 2017; Mezzaroba et al., 2019), as risk factors in AD. Magnesium (Mg) is an essential for the maintenance of human health. Mg plays a critical role in nerve transmission and neuromuscular conduction in nervous system and has a protective effect against excitotoxicity inducing neuronal death (Kirkland et al., 2018). It is associated with multiple neurological disorders in central nervous system, including migraine (Chiu et al., 2016; Dolati et al., 2020), epilepsy (Abdullahi et al., 2019; Yary and Kauhanen, 2019) and Parkinson’s disease (Oyanagi and Hashimoto, 2011; Shen et al., 2019). Recently, Mg investigations are paid more attention in AD researchers. However, contradictory results exist regarding abnormal Mg levels in AD patients. Several reports have described the systemic levels of Mg were significantly reduced in AD (Lemke, 1995; Kurup and Kurup, 2003; Cilliler et al., 2007; Vural et al., 2010; Babagallo et al., 2011; Singh et al., 2014; Ahmed et al., 2017; Balmus et al., 2017), but others have reported no differences or even elevated Mg levels in AD patients (Zhu et al., 1997; Cheng et al., 1999; Alimonti et al., 2007; Liu, 2008; Bostrom et al., 2009a,b; Gustaw-Rothenberg et al., 2010; Hozumi et al., 2011; Koc et al., 2015; Wang, 2015; Zheng, 2015; Xu et al., 2018; Jouini et al., 2021). However, these studies only involved single case-control investigations with small sample size. Therefore, they may lack sufficient power, leading to limitation the scope of their findings.

Here, we conducted a systematic review to comprehensively estimate variations in circulating Mg levels (in the plasma, serum, and cerebrospinal fluid [CSF]) in AD patients compared with healthy controls (HCs). The aim of the present study was to gain additional insights into maintaining an adequate nutritional state for AD prevention or treatment.

**METHODS**

**Search Strategies and Selection of Studies**

The review was conducted in accordance with the “Preferred Reporting Items for Systematic reviews and Meta-Analyses” (PRISMA) statement (Moher et al., 2010) and was registered in PROSPERO (CRD42021254557). We searched relevant literature from PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and WANGFANG, selecting studies from 1991 to 2021. The search terms were "magnesium," “Alzheimer’s disease,” “serum,” “plasma,” or “CSF.” Both English and Chinese languages were used. The Supplementary Materials present the PRISMA checklist (Supplementary PRISMA Checklist) and detailed search strategy (Supplementary Methods: Search strategy). The inclusion criteria were: (1) case-control study design; (2) human subjects; (3) both AD and control groups described in terms of sample size and Mg concentration in serum, blood, plasma, or CSF. The exclusion criteria were: (1) letter, review, or case reports; (2) duplicated studies with repeated data; (3) in vitro or laboratory studies; (4) animal studies; (5) studies lacking quantitative data on Mg concentrations.

**Extraction of Data and Quality Evaluation**

The studies were evaluated separately by two authors (Ke Du and Xi Zheng) and the following details were extracted: first author, publication date (year), country, sample size, sex and age of participants, sample source, and measurement method. The mean values of Mg concentration and standard deviation (SD) were recorded; otherwise, they were estimated from sample characteristics (size, median, and range) (Hozo et al., 2005). If there was a disagreement when extracting the data, it need to be discussed by all authors, and the final reasonable data was determined by the corresponding author. The nine-star Newcastle-Ottawa Scale (NOS) was used for quality assessment.

**Statistical Analysis**

Statistical analyses were performed using STATA 12.0 (Stata, College Station, TX, USA). As the heterogeneity was significant, the results from the studies were combined using a random-effects model. The standardized mean difference (SMD), which standardizes the outcome for multiple studies to the effect size found in terms of the SD, was used as the summary statistic. The Chi-square and I-square tests were used to assess heterogeneity. A subgroup analysis was then used to assess possible sources of heterogeneity, estimating the influences of different methods of Mg determination and different geographical locations of the populations. Meta-regression was also used to evaluate the moderating effect of variables on the meta-analysis outcome, including two study level characteristics (age and sex distribution) while the impact of the individual studies on the pooled SMD was assessed using sensitivity analysis. Potential publication bias was evaluated with Egger’s and Begg’s tests, as well as the “trim and fill” method. Sensitivity analysis was conducted to explore whether a significant difference in one study could markedly influence the overall outcome; this was done by eliminating successive individual studies from the repeated analysis. Finally, temporal effects were determined by a cumulative meta-analysis.

**RESULTS**

**Selection of Studies**

Twenty nine possible studies were totally found after a preliminary search in PubMed, Web of Science, CNKI, and WANGFANG. Eight articles were excluded for overlap in studies (n = 3), no AD type dementia (n = 2), no healthy control (n = 2), and unavailable serum, plasma, or CSF Mg levels (n = 1). As
a result, 21 articles were included in the current analysis (1,112 AD cases and 1,001 HCs). Figure 1 presents a flowchart of the study selection.

In the included studies, the sample sizes varied between 8 and 174. The subjects were between 44.8 and 78.8 years old, with the proportion of female subjects between 0 and 75%. The geographical locations were Asia, Europe, and Africa. Mg concentrations were measured using atomic absorption spectrometry, inductively coupled plasma-atomic emission spectrometry, inductively coupled plasma-mass spectrometry, ion-selective electrode, and spectrophotometry. The average age was omitted in two studies. In addition, criteria for AD diagnosis were missing in two studies. The analytic method of Mg level in fluid were absent in one report. The details are listed in Table 1. The NOS quality assessment scale is shown in Supplementary Table 1. Most included studies were of high quality (18 high-quality and 3 moderate-quality studies).

**Meta-Analysis of Mg Concentrations in Peripheral Blood**

Eighteen studies measured peripheral blood Mg levels in both AD patients and HCs. The pooled sample size contained 828 AD patients and 884 HCs (Table 1). The results indicated that AD patients had less Mg levels in peripheral blood than HCs (SMD = −0.89; 95% CI [−1.36, −0.43]; P = 0.000; Figure 2). Heterogeneity among the included studies was observed (I² = 94.4%, P = 0.000). According to sample source, subgroups analysis demonstrated significant heterogeneity in each subgroup (Table 2) and Mg levels were less in AD patients compared with HCs, in both serum subgroups (SMD = −0.54; 95% CI [−1.07, −0.01]; P = 0.045) and plasma subgroups (SMD = −1.88; 95% CI [−2.97, −0.79]; P = 0.001) (Figure 3). Additionally, according to the method of Mg measurement or geographical location, high heterogeneity still was found in subgroup analyses (Table 2). These results suggested that the sample source, Mg measurement method, and geographical location did not contribute to heterogeneity. Meta-regression analyses showed that neither the mean age nor the sex of AD patients affected Mg levels in peripheral blood (mean age: P = 0.282; sex: P = 0.103), while sensitivity analyses revealed that the individual study had no influence on the overall results (Supplementary Table 2). The cumulative analysis excluded the temporal effects affecting the results of the pooled analysis. Besides, Egger’s (P = 0.031) and Begg’s (P = 0.028) tests suggested that publication bias might be possible. Accordingly, the “trim and fill” method was used for sensitivity analysis, and it was observed that the general result was not significantly altered (SMD = −1.05; 95% CI [−1.55,
TABLE 1 | Characteristics of included studies in the meta-analysis.

| References | Year | Country | AD Patients | Health Controls |
|------------|------|---------|-------------|----------------|
|            |      |         | n | Gender | Age | Mg concentration | Criteria for AD Diagnosis | n | Gender | Age | Mg concentration |
|            |      |         |   | (% Female) | (Mean ± SD) | mean ± SD (mmol/L) |                       |   | (% Female) | (Mean ± SD) | mean ± SD (mmol/L) | Method |
| Zhu et al. (1997) | 1997 | China  | 8  | 0  | 75.0 ± 8.0 | 0.75 ± 0.04 | DSM-IIIR | 22  | 0  | 70.1 ± 7.4 | 0.83 ± 0.03 | AAS |
| Cheng et al. (1999) | 1999 | China  | 53 | 52 | 78.8 ± 7.6 | 0.87 ± 0.07 | DSM-IIIR | 49  | 61 | 77.1 ± 4.3 | 0.85 ± 0.05 | ICP-AES |
| Almonti et al. (2007) | 2007 | Italy  | 53 | 68 | 74.5 ± 6.5 | 0.72 ± 0.03 | NINCDS-ADRDA | 124 | 35 | 44.8 ± 12.7 | 0.78 ± 0.02 | ICP-AES |
| Cilliler et al. (2007) | 2007 | Turkey | 37 | 54 | - | - | DSM-IV, NINCDS-ADRDA | 34  | - | - | 1.00 ± 0.14 | ICP-AES |
| Liu (2008) | 2008 | China  | 30 | 47 | 66.2 ± 9.9 | 0.041 ± 0.01 | DSM-IV, NINCDS-ADRDA | 28  | 46 | 66.8 ± 8.3 | 0.046 ± 0.01 | ICP-AES |
| Alimonti et al. (2007) | 2007 | Italy  | 53 | 68 | 74.5 ± 6.5 | 0.72 ± 0.03 | NINCDS-ADRDA | 124 | 35 | 44.8 ± 12.7 | 0.78 ± 0.02 | ICP-AES |
| Liu (2008) | 2008 | China  | 30 | 47 | 66.2 ± 9.9 | 0.041 ± 0.01 | DSM-IV, NINCDS-ADRDA | 28  | 46 | 66.8 ± 8.3 | 0.046 ± 0.01 | ICP-AES |
| Balmus et al. (2011) | 2011 | Romania | 15 | 40 | 65.8 ± 3.9 | 0.39 ± 0.11 | NINCDS-ADRDA | 15  | 47 | 62.5 ± 3.4 | 0.54 ± 0.09 | AAS |
| Lemke (1995) | 1995 | Germany | 12 | 67 | 77.5 ± 3.5 | 0.58 ± 0.07 | DSM-IIIR | 12  | 50 | 75.2 ± 6.4 | 0.7 ± 0.06 | Spectrophotometry |
| Kurup and Kurup (2003) | 2003 | India  | 15 | 0  | 50–70 | 0.72 ± 0.05 | - | 15  | 0  | 50–70 | 0.99 ± 0.01 | AAS |
| Bostrom et al. (2009a) | 2009 | Sweden | 174 | 70 | 74 ± 5.7 | 0.89 ± 0.09 | NINCDS-ADRDA | 51  | 69 | 73 ± 6.8 | 0.88 ± 0.10 | ICP-MS |
| Vural et al. (2010) | 2010 | Turkey | 50 | 54 | 71.9 ± 6.8 | 0.784 ± 0.08 | NINCDS-ADRDA | 50  | 52 | 65.1 ± 7.1 | 0.876 ± 0.13 | Spectrophotometry |
| Ahmed et al. (2017) | 2017 | Saudi Arabia | 20 | 70 | 59.2 ± 8.3 | 0.38 ± 0.19 | NINCDS-ADRDA | 20  | 65 | 55.0 ± 5.2 | 1.02 ± 0.13 | spectrophotometry |
| Xu et al. (2018) | 2018 | UK      | 42 | 48 | 78.2 ± 1.3 | 0.70 ± 0.06 | NINCDS-ADRDA | 43  | 46 | 78.1 ± 1.1 | 0.70 ± 0.07 | ICP-MS |
| Bostrom et al. (2009a) | 2009 | Sweden | 159 | 75 | 75.4 ± 6.8 | 1.15 ± 0.08 | NINCDS-ADRDA | 49  | 69 | 73.1 ± 7.7 | 1.18 ± 0.09 | ICP-MS |
| Hozumi et al. (2011) | 2011 | Japan  | 21 | 38 | - | 1.32 ± 0.17 | DSM-IV | 15  | 60 | - | 1.23 ± 0.27 | ICP-MS |
| Jouini et al. (2021) | 2021 | Tunisia | 104 | 49 | 70.5 ± 7.5 | 1.13 ± 0.11 | DSM-IV, NINCDS-ADRDA | 53  | 53 | 68.5 ± 7.5 | 1.15 ± 0.05 | Spectrophotometry |

NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; DSM-IIIR or DSMIV, the Diagnostic and Statistical Manual for Mental Disorders; ICP-MS, inductively coupled plasma-mass spectrometry; ICP-AES, inductively coupled plasma-atomic emission spectrometry; AAS, atomic absorption spectrometry; ISE, ion-selective electrode.
Du et al. Magnesium Levels in Patients With AD

FIGURE 2 | Forest plot of the random-effects meta-analysis of difference in peripheral blood Mg concentrations in AD patients and HCs. SMD, standardized mean difference; CI, confidence interval.

TABLE 2 | The subgroup analysis of studies reporting Mg levels in peripheral blood.

| Subgroups                | n of studies | SMD (95% CI)               | I² | P-value |
|--------------------------|--------------|-----------------------------|----|---------|
| All studies              | 18           | −0.89 (−1.36, −0.43)        | 94.4% | 0.000   |
| Methods                  |              |                             |    |         |
| AAS                      | 4            | −2.62 (−4.59, −0.66)        | 95.5% | 0.000   |
| ICP-AES                  | 4            | −0.81 (−2.11, 0.49)         | 97.1% | 0.000   |
| Spectrophotometry        | 5            | −1.12 (−2.19, −0.04)        | 95.2% | 0.000   |
| ICP-MS                   | 3            | 0.09 (−0.13, 0.31)          | 0.0%  | 0.881   |
| ISE                      | 1            | −0.30 (−0.71, −0.11)        | -    | -       |
| -                        | 1            | 0.14 (−0.20, 0.48)          | -    | -       |
| Geographic locations     |              |                             |    |         |
| Asia                     | 11           | −1.01 (−1.54, −0.47)        | 93.1% | 0.000   |
| Europe                   | 7            | −0.65 (−1.58, 0.28)         | 96.2% | 0.000   |

ICP-MS, inductively coupled plasma-mass spectrometry; ICP-AES, inductively coupled plasma-atomic emission spectrometry; AAS, atomic absorption spectrometry; ISE, ion-selective electrode.

−0.55]; P = 0.000), indicating a lack of impact by unpublished negative data.

Meta-Analysis of Mg Levels in CSF Between AD and HCs

Three studies reported different CSF Mg levels in AD patients and HCs (Table 1). The pooled sample included 401 subjects, including 284 AD patients and 117 HCs. Patients with AD showed a tendency toward lower CSF Mg levels compared with HCs, although this difference was non-significant (SMD = −0.16; 95% CI [−0.50, 0.18]; P = 0.364; Figure 4). Due to the small number of studies, further analysis was not conducted.

Meta-Analysis of Circulating Mg Levels in AD and HCs

Furthermore, we conducted a joint analysis of 21 studies investigating circulating Mg levels, including serum, plasma and CSF. The pooled sample size contained 2,113 subjects, including 1,112 AD patients and 1,001 HCs (Table 1). The results revealed that circulating Mg levels in AD patients were significantly decreased compared with that in HCs (SMD = −0.74; 95% CI [−1.13, −0.35]; P = 0.000; Figure 5), in addition to high heterogeneity among these studies (I² = 93.6%, P=0.006). Analysis of subgroups according to Mg measurement method and geographical location also showed significant heterogeneity (Table 3), suggesting that neither Mg measurement methods nor geographical location were the primary sources of heterogeneity. Neither the mean age nor sex of AD patients had obvious effects on circulating Mg levels by meta-regression analysis (mean age: P = 0.251; sex: P = 0.111), nor did individual studies influence the pooled SMD by sensitivity analysis (Supplementary Table 3). The cumulative meta-analysis did not show any significant
temporal biases. Egger’s ($P = 0.046$) and Begg’s ($P = 0.037$) tests indicated the potential publication bias. However, sensitivity analysis using the “trim and fill” method showed that the conclusion was not substantially altered ($\text{SMD} = -0.933; 95\% \text{ CI} [-1.35, -0.52]; P = 0.000$), indicating that the results were statistically robust.
FIGURE 5 | Forest plot of random-effects meta-analysis of differences in circulating Mg between AD and HCs. SMD, standardized mean difference; CI, confidence interval.

TABLE 3 | The subgroup analysis of studies reporting circulating Mg levels.

| Subgroups              | n of studies | SMD (95% CI) | I²   | P-value |
|------------------------|--------------|--------------|------|---------|
| All studies            | 21           | −0.74 (−1.13, −0.35) | 93.6% | 0.000   |
| Methods                |              |              |      |         |
| AAS                    | 4            | −2.62 (−4.59, −0.66) | 95.5% | 0.000   |
| ICP-AES                | 4            | −0.81 (−2.11, 0.49)  | 97.1% | 0.000   |
| Spectrophotometry      | 6            | −0.93 (−1.74, −0.11) | 94.4% | 0.000   |
| ICP-MS                 | 5            | 0.01 (−0.24, 0.25)   | 44.4% | 0.128   |
| ISE                    | 1            | −0.30 (−0.71, −0.11) | -    | -       |
|                        | 1            | 0.14 (−0.20, 0.48)   | -    | -       |
| Geographic locations   |              |              |      |         |
| Asia                   | 12           | −0.88 (−1.39, −0.37) | 92.6% | 0.000   |
| Europe                 | 8            | −0.61 (−1.36, 0.15)  | 95.6% | 0.000   |
| Africa                 | 1            | −0.21 (−0.54, 0.12)  | -    | -       |

ICP-MS, inductively coupled plasma-mass spectrometry; ICP-AES, inductively coupled plasma-atomic emission spectrometry; AAS, atomic absorption spectrometry; ISE, ion-selective electrode.

DISCUSSION

The challenges associated with various nutritional deficiencies and the role of nutritional supplementation have received more attentions owing to the high incidence of AD in aging population throughout the world (Chiu et al., 2014; Shlisky et al., 2017; Tan et al., 2019). Mg is an essential mineral involved in many AD-associated biological processes (Toffa et al., 2019). However, previous reports about the circulating Mg status in AD still remain controversial. The major findings of this study revealed that Mg concentrations in peripheral blood were significantly lower in AD patients. Furthermore, it was also consistent with the joint meta-analysis performed on serum, plasma, and CSF levels, increasing the statistical power of our meta-analysis. In addition, although AD patients showed a tendency toward decreasing Mg concentrations in the CSF compared with HCs, the difference was not statistically significant. Because the sample size were limited for the studies on CSF Mg levels (three studies, including 284 AD patients and 117 HCs), further studies with large sample sizes are necessary to evaluate the CSF Mg levels in AD.

Consistent with our findings that AD patients present reduced circulating Mg levels, previous studies have suggested that Mg concentrations in the hair of AD patients were considerably less than controls (Kobayashi et al., 1989; Veronese et al., 2016). Additionally, Mg levels were lower in AD-affected brain areas such as Ammon’s horn, entorhinal cortex, and frontal cortex (Andrasi et al., 2000, 2005). However, the mechanisms underlying the reduced brain levels of Mg remain unclear. The barrier function of the blood-brain barrier (BBB) is possibly damaged during aging and AD (Yamazaki and Kanekiyo, 2017). Therefore, the reduced Mg levels in
AD-affected brains may be primarily attributed to disrupted BBB permeability. Nevertheless, the possibility of dietary deficiency cannot be ruled out, which requires further research to testify.

The normal range of circulating Mg levels may be also influenced by age, sex, sample type, and geographical location. Therefore, we have reviewed those factors in each study included in this meta-analysis, and found that in most studies these factors were matched between the AD and control groups. Therefore, these factors should not influence our results. As studies included in this meta-analysis focused on the AD patients, it is difficult to confirm the causal association between Mg deficiency and AD. The dietary intake of AD patients is often poor in comparison with that of age-matched controls with normal cognitive function (Shatenstein et al., 2007). Therefore, Mg decrease may be a consequence of AD, possibly induced by malnutrition and poor nutrient intake. In addition to Mg, iron (Fe) and copper (Cu) are required for human health. Wang et al. did not observed the altered serum Fe levels in AD patients (Wang et al., 2015), whereas Ventriglia et al. described higher serum Cu concentrations in AD patients (Ventriglia et al., 2012). Therefore, these differences in circulating minerals could not be explained solely based on differences in dietary intake of AD patients. However, several studies have supported this causal relationship. For example, Cherbuin et al. reported that higher dietary Mg intake was associated with a lower risk of mild cognitive impairment (MCI) (Cherbuin et al., 2014). Glick and McMillan found that the cognitive decline associated with AD might be improved by increasing Mg dietary intake (Glick and McMillan, 2016). In addition, animal experiments have revealed the benefits of Mg supplementation on the performance of learning and memory. A study on rats pointed out that a formulated Mg compound administration increased the brain Mg levels and enhanced learning and working memory, as well as short-term synaptic facilitation and long-term potentiation (Slutsky et al., 2010). Increased Mg levels in the brain and plasma of elderly rats seemed to improve the maze performance and potentiation in the hippocampus after diet intake (Landfield and Morgan, 1984). Additionally, Yu et al. reported that high Mg concentration modulated Aβ protein precursor processing.
and reduced Aβ secretion in a mouse neuroblastoma cells (Yu et al., 2010). Mg is postulated to target multiple steps and various stages of AD pathogenesis (Figure 6). It has been shown to promote Aβ protein precursor α-cleavage (Yu et al., 2010), increase Aβ fibril clearance by regulating BBB permeability (Zhu et al., 2018), decrease tau hyperphosphorylation (Xu et al., 2014), inhibit Aβ-induced neuroinflammation (Wang et al., 2017; Yu et al., 2018), disrupt RBC (red blood cell)-fibrin aggregates which promotes oxygen delivery to the brain (Lipinski and Pretorius, 2013), and prevent the downregulation of N-methyl-D-aspartate receptors in AD models (Li et al., 2014; Huang et al., 2018) (Table 4). The present study increased statistical power by combining the results of different studies, and showed that AD patients have a poor circulating Mg status, further supporting the hypothesis that Mg deficiency is an AD risk factor. Based on these findings, clinical trials are demanded to explore the potential effects of Mg for AD prevention or treatment.

This meta-analysis has a few limitations. First, there are still few reports on CSF Mg levels although we have performed possibly comprehensive searches. Additional investigations with larger samples are required to confirm our findings. Second, circulating Mg levels varied among included studies. Typically, variations occur due to different techniques used for sampling or the analytic methods. Third, we just searched studies written in English or Chinese, studies in other languages were not included. Fourth, the high degree of heterogeneity among the studies necessitates cautious interpretation.

CONCLUSIONS

In summary, our analysis concluded that circulating Mg levels in AD patients were significantly lower than those in HCs, providing more evidence that Mg supplementation or Mg rich diets possibly exerted a promising preventive or
therapeutic strategies for treating AD patients with a poorer Mg status.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

KD and M-YL contributed to the conception and design of the study. KD and XZ searched the databases, analyzed the data, and drafted the manuscript. KD, XZ, Z-TM, J-YL, and W-JJ screened the publications, conducted the quality assessment of the included studies, and extracted the data. M-YL had primary responsibility for the final content. All authors contributed to the writing, reviewing, and revising of the manuscript and read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.799824/full#supplementary-material
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