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Meta-analysis

Effect of folic acid on cognitive function in older adults: A systematic review and meta-analysis

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Abstract

Dementia is a common problem among the elderly. It is caused by a decline in cognitive abilities. Some studies have shown that folic acid supplements can improve cognitive function in older adults. However, the results are not yet conclusive. The aim of this study was to investigate whether folic acid supplementation can improve cognitive function among older adults. Relevant articles were systematically searched using PubMed, Google Scholar, ScienceDirect, and PMC databases as of June 13, 2024. Randomized controlled trials (RCT) investigating the effect of folic acid supplementation on cognitive function among older adults were included for qualitative and quantitative data syntheses. For meta-analysis, we used a random-effects model to compute the mean difference (MD) and 95% confidence interval (CI). A total of four studies with 1,855 participants were included in this meta-analysis. The meta-analysis revealed that folic acid supplementation did not improve cognitive function as measured by Mini-Mental State Examination (MMSE) score changes (1,310 participants; MD: 0.01; 95%CI: -0.14–0.17; p=0.89). However, a significant improvement by folic acid supplementation was observed based on executive function Z-score (1,610 participants; MD: 0.25; 95%CI: 0.24–0.27; p<0.001). Another improvement was observed in episodic memory Z-score (1,610 participants; MD: 1.31; 95%CI: 1.23–1.38; p<0.001). The heterogeneity was significant in episodic memory Z-score (I^2=100%) and executive function Z-score (I^2=82%), but not in MMSE (I^2=0%). Folic acid improves executive function and episodic memory among the elderly with dementia, yet the effect is suboptimal when measured through MMSE.

Keywords: Folic acid, cognitive function, elderly, MMSE

Introduction

Individuals' cognitive capacities, especially those related to memory and information processing speed, tend to decline with age.1 Variations in cognitive function, specifically in memory, have been associated with the likelihood of developing dementia in old age [1,2] Brain atrophy is a natural part of aging and is also characteristic of neurodegeneration [3]. This process becomes more prominent in people with mild cognitive impairment (MCI) and progresses more rapidly in those with Alzheimer's disease [4]. As the population grows, it is anticipated that the number of individuals with dementia will reach 150 million by 2050 [3]. This substantial increase in dementia prevalence will have significant social and economic consequences for caregivers, families, and society [5]. The substantial impact and burden, combined with the lack of effective

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treatment options, create an urgent need for strategies to prevent or slow down the progression of the disease at an early stage [6]. Certain modifiable factors have been identified as potential contributors to age-related cognitive decline, but their direct impact has not yet been confirmed. Folate deficiency is one of the suspected risk factors [1,2]

Folic acid, also known as vitamin B9, plays a vital role in managing dementia by supporting the availability of methyl groups for metabolic processes, which helps convert homocysteine to methionine. Elevated levels of serum homocysteine have been linked to cognitive decline and dementia. In light of the known effects of folate and vitamin B12 deficiencies, as well as abnormal homocysteine metabolism on the nervous system, a number of plausible mechanisms have been proposed to explain how elevated homocysteine levels may increase dementia risk. These include influences on cerebrovascular pathology, direct neurotoxic effects or impacts on methylation reactions, affecting neurofibrillary tangles and amyloid accumulation [2,3,7,8]. However, none of these mechanisms have been definitively proven, and whether the associations are causal remains unclear. Resolving the uncertainty is crucial; therefore, the aim of this study was to investigate whether folic acid supplementation can improve cognitive function in older people.

Methods

Literature search strategy

The literature search adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and recommendations [10]. Various databases, including PMC, ScienceDirect, Google Scholar, and PubMed, were used. The terms "cognitive function," "folic acid," "elderly," and "methylphenidate" were combined using the Boolean operators 'AND' and 'OR' to increase sensitivity in this study. The search was conducted on June 15, 2024. All relevant articles' reference lists were carefully reviewed to find potential studies. All relevant articles were systematically assessed based on the inclusion and exclusion criteria.

Inclusion and exclusion criteria

This study included studies examining the effects of folic acid on cognitive function and clinical outcomes. Studies comparing a population that received additional folic acid treatment to a control group were included. Cohort and cross-sectional studies were eligible. A review article, editorial, case report, and conference abstract were excluded.

Screening and selection

A screening process was divided into two phases after duplicate entries in EndNote 19 (Clarivate, Philadelphia, USA) were automatically deleted. The abstract, title, and full text were reviewed in the first phase, and the full text was reviewed in the second phase. The review process was conducted separately by two reviewers (SA and KIA), with any differences resolved by consensus. A third reviewer (MI) was consulted in case a consensus was not reached.

Data extraction

The data were extracted from eligible studies, including author, publication year, study location, and study design. From the included studies, we also obtained data on the treatment and subjects' characteristics (age, sex, weight, and BMI). All outcomes reported in the included studies were extracted. No additional conversion was carried out on the outcome data. A statistical significance determination was based on the analysis performed by each study, where the cut-off point for statistical significance was $p<0.05$.

Critical appraisal

Studies were independently assessed by two review authors (SA and KIA). For observational studies, the Newcastle-Ottawa Scale (NOS) was used, an appraisal instrument comprised of three domains: selection, comparability, and outcome. Disagreements were settled either through consensus or by consulting the third author (MI).

Qualitative synthesis

In view of the non-uniform data reported by the included studies, a quantitative meta-analysis could not be conducted. Instead, the findings were summarized through a qualitative synthesis. A detailed examination of each study was performed to identify common themes, patterns, and significant findings. Each study's results were compared and contrasted, providing a narrative overview of the evidence on the efficacy of folic acid across different contexts and populations. The key outcomes, methodological differences, and limitations of the study were also discussed to provide input for future research.

Results

Search results

The initial screening of four databases resulted in the identification of 17,902 records. PubMed showed 5,098 articles, Google Scholar showed 12,400 articles, ScienceDirect showed 200 articles, and PMC showed 202 articles. Through title and abstract screening, 4,366 articles were removed, and 616 articles were screened for sought retrieval. A total of 469 articles were further assessed for eligibility, and 147 articles were removed due to different control and irrelevant outcomes. The final step resulted in four studies included in the qualitative synthesis. The PRISMA flow diagram depicting the overall process of the screening and selection is presented in **Figure 1**.

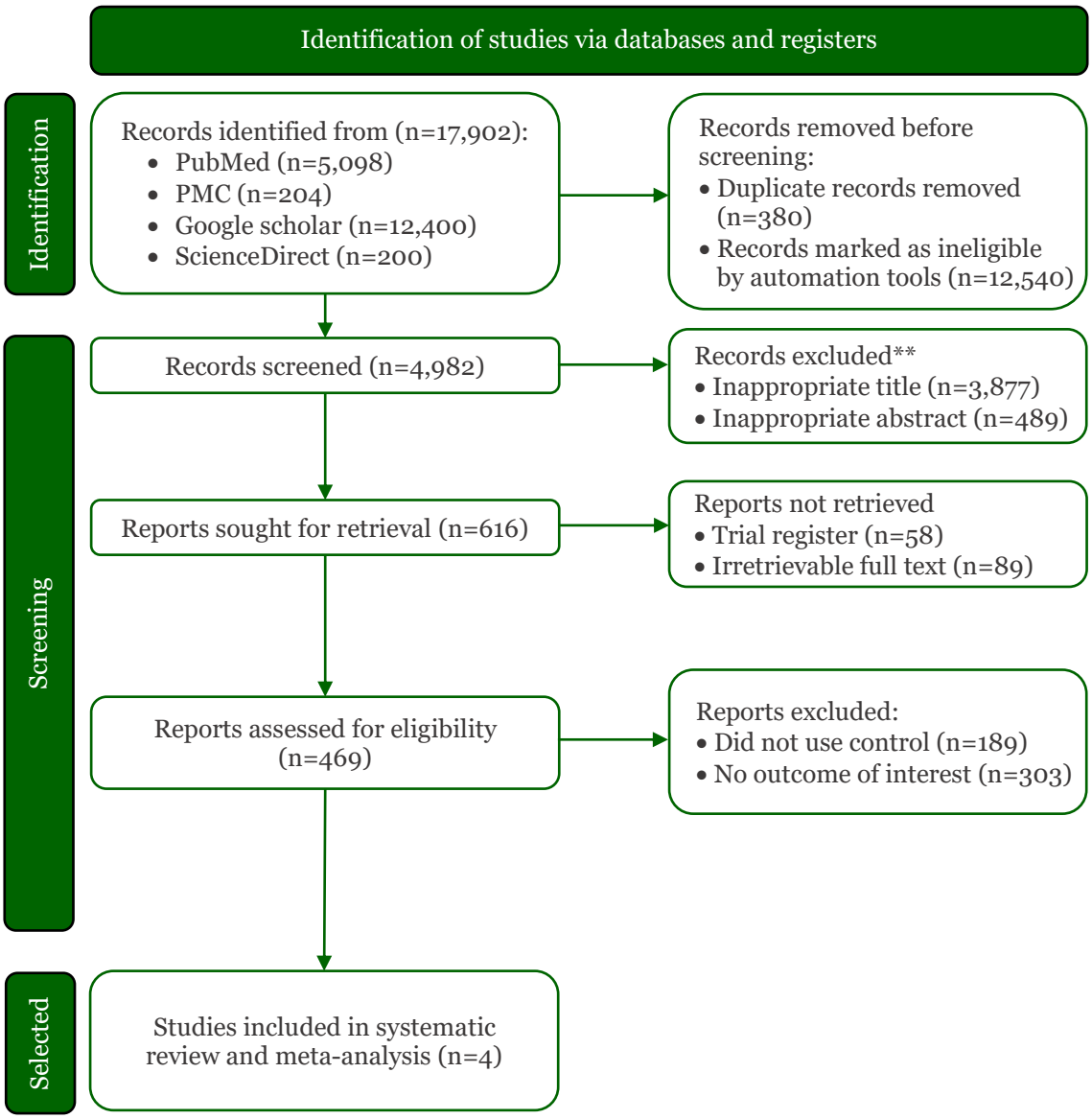

Figure 1. PRISMA flow diagram.

Characteristics of the included studies

The four included studies that investigate the characteristics and outcomes of folic acid supplementation in preventing dementia among elderly individuals in various countries is presented in **Table 1**. Annick *et al.* [3] in the Netherlands treated 391 participants with 800 µg of folic acid daily for three years, while 400 participants received a placebo. Ma *et al.* [1] in China gave 60 participants two 400 µg tablets of folic acid daily for six months, with no treatment for the control group. Kwok *et al.* [6] in China treated 138 participants with 500 µg of methylcobalamin and 400 µg of folic acid daily for 24 months, with 141 participants in the control group receiving a placebo. Lastly, Wu *et al.* [8] conducted a study in Hong Kong and the UK, treating 271 participants with a combination of cyanocobalamin, folic acid, and vitamin B6, while 274 participants received a placebo. Across the studies, the age range was around 60 to 77 years, with sex and BMI distributions similar between intervention and control groups.

Table 1. Characteristics of the included study

Author, Year	Country	Treatment			Characteristics		
		Intervention	Control	Duration	Variable	Intervention	Control
Annick *et al.* 2021 [3]	Netherland	FA 800 µg qd	Placebo qd	3 years	n	391	400
					Age (years)	60.0±5.5	60.4±5.7
					Sex (M/F)	282/109	283/117
					BMI	26.6±3.6	26.5±3.6
Ma *et al.* 2019 [1]	China	FA 400 µg qd	No treatment	6 months	n	60	60
					Age (years)	68.42±3.62	68.54±3.90
					Sex (M/F)	22/38	22/38
Kwok *et al.* 2020 [6]	China	FA 400 µg qd	Placebo qd	24 months	n	138	141
					Age (years)	76.9±5.4	78.0±5.3
					Sex (M/F)	87/51	79/62
					BMI (kg/m²)	24.6±3.4	24.8±3.2
Wu *et al.* 2021 [8]	United Kingdom	FA 800 µg qd	Placebo qd	24 months	n	271	274
					Age (years)	76.9±5.1	77.4±5.1
	Hongkong	FA 400 µg qd			Sex (M/F)	135/136	127/147
					BMI (kg/m²)	25.2±3.6	25.5±3.8

FA: folic acid; BMI: body mass index; M/F: male/female; qd: *quaque die* (once daily)

Quality of included studies

Quality assessment of four cohort studies—by Annick *et al.* 2021 [3], Ma *et al.* 2019 [1], Kwok *et al.* 2022 [6], Wu *et al.* 2021 [8] using the Newcastle-Ottawa Scale [9] is presented in **Table 3**. The four studies were rated as "Good quality".

Table 2. Critical appraisal using NOS

Author, year (ref)	Study design	Selection	Comparability	Outcome	Total score	Remark
Annick *et al.* 2021 [3]	Cohort	★★★	★	★★★	7	Good quality
Ma *et al.* 2019 [1]	Cohort	★★★	★	★★	6	Good quality
Kwok *et al.* 2020 [6]	Cohort	★★★	★	★★	6	Good quality
Wu *et al.* 2021 [8]	Cohort	★★★	★	★★	6	Good quality

Meta-analysis results

For general cognitive function, the studies largely utilized the Mini-Mental State Examination (MMSE) to measure outcomes. In a study by Annick *et al.* [3], both the folic acid group and the control group had the same MMSE score of 28.6 after three years of treatment, indicating no

noticeable difference. Similarly, Kwok *et al.* [6] found only a minor, statistically insignificant improvement in the MMSE score for the intervention group (26) compared to the control group (25.7) after 24 months. Ma *et al.* [6] also found no improvement in MMSE scores with 800 µg of folic acid daily for six months, as both groups scored around 21.6. When these results were combined, the overall impact of folic acid on cognitive function was negligible, with a mean difference of 0.01 (**Figure 2A**).

In the case of executive function, which reflects higher-level cognitive processes, the studies presented mixed findings. Annick *et al.* [3] reported no significant difference between the folic acid group and the control group, with both having similar z-scores (0.04 and -0.04, respectively). On the other hand, Kwok *et al.* [6], who administered a combination of 500 µg of methylcobalamin and 400 µg of folic acid daily, saw a meaningful improvement in executive function, with the experimental group scoring 0.13 compared to -0.13 in the control group. Wu *et al.* [8] also found a slight improvement in executive function, with the folic acid group scoring 0.09 compared to -0.09 in the control group. The effect of folic acid in improving executive function was significant ($p<0.001$) (**Figure 2B**). The heterogeneity between the studies was high, with an I^2 value of 84% (**Figure 2B**).

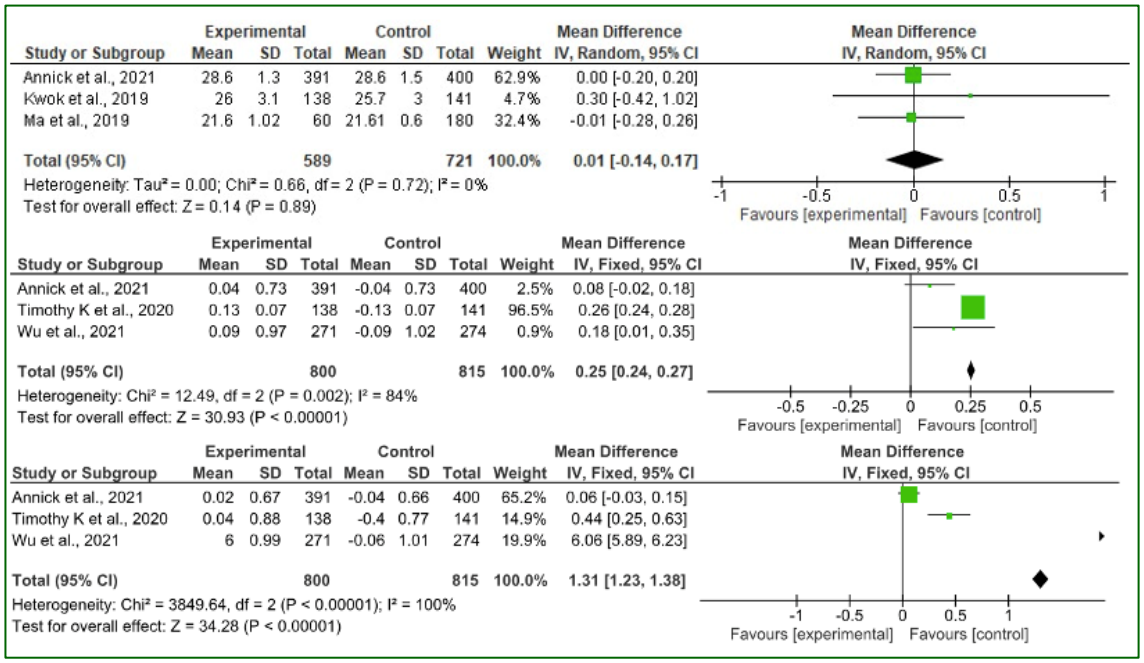

Figure 2. Forest plots for the pooled effects of folic acid supplementation on cognitive functions among older adults based on MMSE (A), executive function z-score (B), and episodic memory z-score (C).

The results related to episodic memory, which involves the ability to recall specific events, were more promising. Annick *et al.* [3] reported a small difference in memory z-scores between the folic acid group (0.02) and the control group (-0.04), resulting in a minor improvement of 0.06. Kwok *et al.* [6] found a larger difference, with the folic acid group scoring 0.04 and the control group -0.4, yielding a mean difference of 0.44. Wu *et al.* [1] saw the most significant improvement, with the folic acid group scoring 6.00 compared to -0.06 in the control group, giving a mean difference of 6.06. When these results were pooled in the meta-analysis, the overall mean difference for episodic memory was 1.31, indicating a strong positive effect of folic acid on memory function in elderly populations (**Figure 2C**). Despite this, the analysis revealed significant variability between the studies, with an I^2 value of 100%, suggesting that the strength of the effect varied greatly depending on the study (**Figure 2C**).

Discussion

This study undertook an analysis of four published studies on the effects of folate-based vitamin B supplementation and cognitive function in older adults. The efficacy of folic acid intervention

was evaluated in two cohorts: the intervention group, which received folic acid supplementation, and the control group, which received placebo supplementation. A subsequent meta-analysis revealed that folate-based vitamin B supplementation did not significantly enhance cognitive function in older adults. Nevertheless, an examination of the data according to subgroup characteristics revealed noteworthy findings with regard to the advancement of z-score executive function and z-score episodic memory. This finding is at odds with the results of a prior meta-analysis, which indicated that folic acid administration did not result in a notable benefit concerning memory performance in the adult population [10-12]. Zanin *et al*. [13] found that folic acid supplementation or dietary folic acid intake was not associated with cognitive decline, in contrast to the effects observed with vitamin B12 supplementation. However, a study of 466,224 participants in the UK Biobank cohort found that folic acid supplementation was associated with an increased risk of Alzheimer's disease [14]. A meta-analysis showed that vitamin B supplementation was associated with a slowing of cognitive decline, particularly in the early and long-term intervention groups. In addition, a diet rich in folic acid was associated with a reduced risk of incident dementia in the non-demented group [15]. Moreover, the findings of the meta-analysis have been inconsistent.

Folic acid is a heterocyclic compound comprising 4-(pterin-6-methylamino) benzoic acid with one or more L-glutamic acids. Moreover, folic acid is a key participant in the process of one-carbon metabolism (OCM), which is instrumental in regulating the flexibility of nerve cells and maintaining neuronal integrity [16,17]. Aging is associated with a notable decline in the levels of folic acid and its metabolite S-adenosylmethionine in the cerebrospinal fluid, which ultimately contributes to hyperhomocysteinemia [18]. Hyperhomocysteinemia has been demonstrated to manifest in a number of neurological pathologies, including dementia and Alzheimer's disease [19,20]. Furthermore, folic acid deficiency and elevated homocysteine levels have been demonstrated to impair neuronal function, leading to DNA damage and apoptosis in the hippocampus, which plays a pivotal role in memory formation [21]. Consequently, the potential benefits of folic acid supplementation on memory have been subjected to investigation.

Folic acid is a vitamin that plays a significant role in the stabilization of short-term and long-term memory, as well as the reduction of memory impairment [22,23]. Nevertheless, the precise biochemical mechanisms remain uncertain. The current evidence indicates that folic acid-mediated OCM and DNA methylation events play a significant role [24]. It is now established that folic acid increases the methylation potential and activity of DNA methyl transferase (DNMT), remodels DNA methylation, and ultimately reduces β-amyloid precursor protein (APP) and Aβ protein levels. This has been demonstrated to improve individual memory and cognition [25,26]. Furthermore, folic acid possesses antioxidant properties that can mitigate the effects of Alzheimer's disease and other cognitive disorders [27]. Additionally, it may inhibit tau phosphorylation and neurofibrillary tangle formation by indirectly regulating cyclin-dependent protein phosphatase and glycogen synthase kinase activity [28,29].

It is frequently observed that older Europeans are deficient in folic acid, with the prevalence of this deficiency increasing with age [30]. The etiology of folic acid deficiency encompasses decreased dietary intake and malabsorption, age-related disturbances in folate transport and metabolism, the use of anti-folate drugs, genetic factors, and excessive alcohol intake [31]. Furthermore, other studies have demonstrated that a low folate status is associated with an elevated risk of cognitive impairment and dementia [32-40]. In a study involving participants aged 60 years and over, patients with mild cognitive impairment or dementia exhibited significantly lower serum folate levels compared to healthy controls. The adjusted odds ratio (aOR) for dementia in subjects in the lowest tertile (≤13.5 nmol/L) was 3.8 (95%CI: 1.3–11.2; p=0.018) [32]. Moreover, a meta-analysis comprising 13 studies involving individuals aged 60 years and above revealed that general and specific cognitive impairments, including attention, episodic memory, and visuospatial or abstract reasoning, were associated with folic acid levels (OR:1.66; 95%CI: 1.40–1.96) [38]. In this study, the results for episodic memory were also lower in patients with dementia or the elderly. Administration of folic acid also demonstrated improvement in episodic memory. Therefore, folic acid administration in elderly patients is recommended. This may be due to folic acid's role in hippocampal neurogenesis, as demonstrated in animal models [41,42].

This study has several limitations that must be acknowledged. Firstly, the differences in study designs, participant demographics, and outcome measures across the included studies restricted the possibility of conducting a pooled analysis. Secondly, the quality of the studies included was inconsistent, with some lacking robust methodologies or adequate sample sizes, which may have led to potential bias in the results. Furthermore, excluding non-English language studies might have omitted pertinent research, potentially affecting the review's comprehensiveness.

Conclusion

Folic acid supplementation may enhance executive function and episodic memory in the elderly, thereby reducing the risk of mild cognitive impairment and dementia. Despite the lack of evidence supporting the efficacy of folic acid supplementation in improving cognitive function in the elderly, we still recommend its use due to the fact that old age is associated with folic acid deficiency, which in turn affects homocysteine.

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Competing interests

The authors have no competing interest to declare.

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Underlying data

All underlying data have been presented in this article.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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