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Normal-But-Low Serum Folate Levels and the Risks for Cognitive Impairment

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Objective This study aimed to examine the association between normal-but-low folate levels and cognitive function in the elderly population using a prospective cohort study.

Methods We analyzed 3,910 participants whose serum folate levels were within the normal reference range (1.5–16.9 ng/mL) at baseline evaluation in the population-based prospective cohort study named the "Korean Longitudinal Study on Cognitive Aging and Dementia." The association between baseline folate quartile categories and baseline cognitive disorders [mild cognitive impairment (MCI) or dementia] was examined using binary logistic regression analysis adjusting for confounding variables. The risks of incident MCI and dementia associated with the decline of serum folate level during a 4-year follow-up period were examined using multinomial logistic regression analysis.

Results The lowest quartile group of serum folate (≥1.5, ≤5.9 ng/mL) showed a higher risk of cognitive disorders than did the highest quartile group at baseline evaluation (odds ratio 1.314, p=0.012). Over the 4 years of follow-up, the risk of incident dementia was 2.364 times higher among subjects whose serum folate levels declined from the 2nd–4th quartile group to the 1st quartile than among those for whom it did not (p=0.031).

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Conclusion Normal-but-low serum folate levels were associated with the risk of cognitive disorders in the elderly population, and a decline to normal-but-low serum folate levels was associated with incident dementia. Maintaining serum folate concentration above 5.9 ng/mL may be beneficial for cognitive status.
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Key Words Folate, Elderly, Cognition, Dementia, Cohort studies, Longitudinal studies.

INTRODUCTION

Dementia is one of the most disabling and burdensome health conditions worldwide and its prevalence and economic costs are increasing rapidly along with the increasing number of older adults in the population.[1,2] Mild cognitive impairment (MCI) is a transitional phase from normal aging to dementia, and elderly individuals with MCI are at high risk of developing dementia.[3] Given that there is currently no cure for dementia, it is crucial to identify modifiable risk factors for the prevention of MCI and dementia.[4]

Nutritional factors have been widely considered to contribute to the development of dementia.[5] Folate, which is one of the B vitamins involved in the early development of the brain and the methylation process, is essential for maintaining normal brain function in later life, along with vitamin B6 and vitamin B12; folate levels in the blood are affected by dietary intake.[6] Folate acts as a donor of methyl groups for the homocysteine cycle and folate deficiency can cause an increase in blood levels of homocysteine.[7] Elevated homocysteine levels lead to cognitive impairment by increasing the risk for atherosclerosis and cerebrovascular disease[8] or through producing direct neurotoxic effects.[7] In addition to its effect in lowering homocysteine levels, folate acts as a coenzyme in the synthesis of neurotransmitters[9] and improves nitric oxide availability in the brain. Folate deficiency impairs the DNA repair mechanism in neurons and sensitizes neurons to oxidative damage and the toxicity of amyloid beta-peptide.[10]

Previous epidemiological studies have reported cross-sectional[11,12] and longitudinal[13,14] associations between low blood folate levels and the risk of cognitive impairment. In a recent meta-analysis that evaluated the associations between homocysteine, folate, vitamin B12, and Alzheimer's disease (AD), the mean folic acid and vitamin B12 levels in AD patients were significantly lower than those in healthy controls, and low folate levels were linked to an increased risk of AD occurrence.[15]

Excessive folate levels are also associated with cognitive dysfunction. Morris et al.[16] found that subjects with the highest quintile of folate intake (median, 742 μg/day) had a faster rate of cognitive decline than those in the lowest quintile of folate intake (median, 186 μg/day). Hunter et al.[17] observed mental changes and sleep disturbances in 12 out of 14 normal volunteers who ingested 15 mg of folic acid per day, over a 1 month period (mean serum folate level changed from 4.49 ng/mL to >120 ng/mL). Therefore, folate deficiency or excessive folate confirmed by laboratory testing might contribute to the risk of cognitive dysfunction.

In clinical settings, we used to examine folate concentration when looking for the etiology of cognitive impairment in order to rule out folate deficiency. However, the values of "lower" folate levels in previous studies that reported an association of folate level with cognitive impairment were above the normal reference range.[11,12] If there is any possibility that even a normal folate level might be associated with the risk of cognitive impairment, it may be clinically meaningful to investigate the relationship between folate level and cognitive function when excluding the impacts of folate deficiency or excess. To our knowledge, no study has investigated the association between folate levels within the normal range and cognitive function. We investigated the association between serum folate levels and the risk of MCI and dementia in a community-dwelling population-based prospective cohort of Korean elders whose baseline folate levels were within the normal range. Furthermore, we also examined the change in folate levels over a period of 4 years in relation to incident cognitive disorders at a 4-year follow-up. Our hypothesis was that a normal-but-low level of folate is associated with a higher risk of cognitive impairment and incident cognitive disorder.

METHODS

Subjects

This study was conducted as part of the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD), which is a population-based prospective multicenter (13 centers) cohort study of Korean elders aged 60 years and older.[18] In total, 6,818 participants completed the process for cognitive function evaluation during the baseline study period, between 2010 and 2012 from the random sample (n=12,694) (response rate=53.7%). For baseline analysis, participants with no record of baseline folate levels, an abnormal value

(<1.5 or >16.9 ng/mL), or with a history of stroke or significant head trauma with a loss of consciousness of at least 10 minutes (n=2,908) were excluded (Figure 1). As a result, 3,910 subjects (mean age=69.5±6.7 years, education=8.4±5.3 years, female=55.0%) were eligible. Among the 3,910 subjects included in this study, 2,587 subjects (66.2%) completed the 4 years of follow-up evaluation (Figure 1). All participants were fully informed about the study protocol and provided written informed consent, signed by the subjects or their legal guardians. The study protocol was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (B-0912/089-010).

Folate and other biochemical measurements

At the baseline and 4-year follow-up evaluations, fasting blood was collected from each participant and transported on ice to the Seoul Clinical Laboratory (SCL, Seoul, Korea). Serum folate levels were measured using radioimmunoassay (MP Biomedicals, Solon, OH, USA). Radioactivity was measured using Gamma-10 (Shin Jin Medics Inc., Goyang, Korea). Using the normal laboratory values (1.5−16.9 ng/mL), baseline folate levels were categorized into quartiles: 1st (≥1.5, ≤5.9), 2nd (>5.9, ≤8.2), 3rd (>8.2, ≤11.0), and 4th (>11.0, ≤16.9). Folate levels at the 4-year follow-up were also divided into four groups using the same thresholds as the quartile categories at baseline.

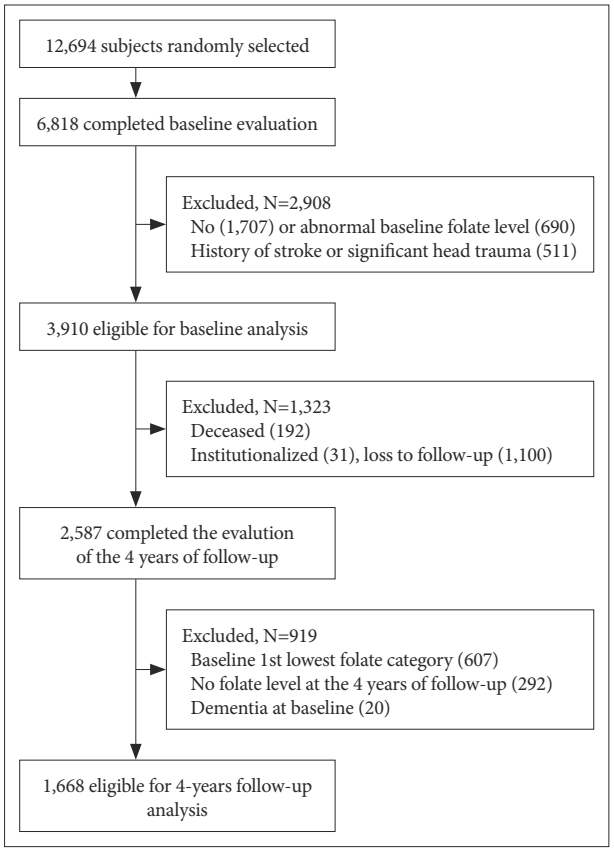

Figure 1. Enrollment and follow-up of study participants.

Diagnostic assessments of cognitive disorders

To diagnose cognitive disorders, geriatric neuropsychiatrists in each research center with expertise in dementia research administered a face-to-face standardized diagnostic interview, as well as physical and neurological examinations using the Korean version of the Consortium to Establish a Registry for Alzheimer's disease Assessment Packet Clinical Assessment Battery (CERAD-K-C).[19] Research neuropsychologists or trained research nurses administered the Korean version of the Consortium to Establish a Registry for Alzheimer's disease Assessment Packet Neuropsychological Assessment Battery (CERAD-K-N),[19,20] Digit Span Test (DST),[21] and Frontal Assessment Battery.[22] The CERAD-K-N consists of nine neuropsychological tests: Verbal Fluency Test, 15-item Boston Naming Test, Mini Mental Status Examination for dementia screening (MMSE-DS),[23] Word List Memory Test, Constructional Praxis Test, Word List Recall Test, Word List Recognition Test, Constructional Recall Test, and Trail Making Test A/B.[19,20] A panel of four research neuropsychiatrists in the core center confirmed participants' final diagnoses after receiving the assessment data from each center. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria.[24] MCI was diagnosed according to the Consensus Criteria from the International Working Group on MCI.[25] The presence of objective cognitive impairment was ascertained when the performance of the subjects was 1.5 standard deviations (SD) or more below the age-, sex-, and education-adjusted norms in any of the neuropsychological tests.[26]

Statistical analyses

One-way analysis of variance (ANOVA) for continuous variables and a linear-by-linear test for categorical variables were used to compare the baseline sociodemographic and clinical characteristics between the four quartile categories of baseline folate levels. A post-hoc analysis using the Bonferroni method was also performed.

Binary logistic regression analysis was used to examine the association between baseline folate quartile categories and baseline cognitive disorders (MCI or dementia) adjusting for age, sex, education, presence of hypertension, diabetes mellitus, body mass index (BMI, kg/m^2), the Korean version of the Geriatric Depression Scale (GDS-K),[27] total cholesterol, serum creatinine, alcohol intake, smoking, presence of apolipoprotein (APOE) ε4 allele, and vitamin B12 levels.

To investigate the association between the decline of folate levels from baseline to 4 years of follow-up and incident cog-

nitive disorders at 4 years of follow-up, multinomial logistic regression analysis was performed. Subjects with dementia at baseline were excluded from the model, and the decline of folate levels was defined as the concentration at baseline in the 2nd to 4th categories falling to the 1st category at 4-year follow-up. The model was also adjusted for the same variables as those in the binary logistic regression model. All statistical analyses were performed using SPSS software (version 23.0; IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics according to serum folate level quartile groups

The mean baseline folate level of all participants was 8.6±3.4 ng/mL, and those of the 1st, 2nd, 3rd, and 4th folate quartile groups were 4.6±1.0, 7.1±0.7, 9.6±0.8, and 13.4±1.7 ng/mL respectively (Table 1). The mean age of the 1st lowest quartile group (70.6±7.3 years) was significantly higher than those of the other three quartile groups (F=13.873, p<0.001). Subjects within the higher quartile groups (i.e., 4th quartile vs. 3rd quartile, 3rd quartile vs. 2nd quartile, and 2nd quartile vs. 1st quartile) consisted of more women (p<0.001). Compared to the lower quartile groups (1st and 2nd groups), subjects within the 3rd (8.7±5.2) and 4th (8.8±5.4) quartiles had more years of education (F=7.209, p<0.001). At the baseline evaluation, 2,746 (70.2%) subjects were cognitively normal, 1,044 (26.7%) subjects had MCI, and 120 (3.1%) subjects had dementia. The distribution of diagnosis was significantly different between the four quartile groups (p<0.001).

Association of the baseline serum folate levels with the baseline cognitive disorders

The first lowest quartile group of serum folate levels showed a 1.314-fold higher risk of cognitive disorders (MCI or dementia) compared to subjects in the highest quartile group [odds ratio (OR) 1.314, 95% CI 1.062−1.626, p=0.012] adjusting for age, sex, education, presence of hypertension, diabetes mellitus, BMI, GDS-K, total cholesterol, serum creatinine, alcohol intake, smoking, presence of APOE ε4 allele, and vitamin B12 levels (Table 2).

Table 1. Baseline sociodemographic and clinical characteristics among baseline serum folate quartile groups

	Total (N=3,910)	Baseline serum folate levels				p value*	post-hoc†
		1st quartile (N=991)	2nd quartile (N=991)	3rd quartile (N=973)	4th quartile (N=955)		
Folate (ng/mL) (range)	8.6±3.4 (≥1.5, ≤16.9)	4.6±1.0 (≥1.5, ≤5.9)	7.10±0.7 (>5.9, ≤8.2)	9.6±0.8 (>8.2, ≤11.0)	13.4±1.7 (>11.0, ≤16.9)	<0.001	1<2<3<4
Age (years)	69.5±6.7	70.6±7.3	69.5±6.4	68.8±6.5	69.0±6.3	<0.001	1>2,3,4
Female (N, %)	2,151 (55.0)	391 (39.5)	540 (54.5)	584 (60.0)	636 (66.6)	<0.001	
Education (years)	8.4±5.3	8.0±5.2	8.0±5.3	8.7±5.2	8.8±5.4	<0.001	1,2<3,4
GDS-K (points)	9.7±6.6	10.1±6.8	9.7±6.4	9.6±6.6	9.5±6.5	0.202	
Baseline diagnosis (N, %)							
Normal cognition	2,746 (70.2)	639 (64.5)	700 (70.6)	708 (72.8)	699 (73.2)	<0.001	
MCI	1,044 (26.7)	306 (30.9)	267 (26.9)	241 (24.8)	230 (24.1)		
Dementia	120 (3.1)	46 (4.6)	24 (2.4)	24 (2.5)	26 (2.7)		

Data are shown as mean±standard deviation (SD) for continuous variables. *derived from one-way analysis of variance for continuous variables, from a linear-by-linear association test for categorical variables, †post-hoc analysis using Bonferroni; 1, 2, 3, and 4 denote baseline 1st quartile, 2nd quartile, 3rd quartile, and 4th quartile respectively. GDS-K: Korean version of the Geriatric Depression Scale, MCI: mild cognitive impairment

Table 2. Association of the baseline serum folate levels with the baseline cognitive disorders*

Variables	B	S.E.	Wald	Sig.†	OR (95% CI)
1st quartile (≤ 5.9 ng/mL)	0.273	0.109	6.299	0.012	1.314 (1.062−1.626)
2nd quartile (≤ 8.2 ng/mL)	0.066	0.108	0.375	0.541	1.068 (0.865−1.319)
3rd quartile (≤11.0 ng/mL)	0.032	0.108	0.087	0.768	1.032 (0.835−1.277)
4th quartile (>11.0 ng/mL)	Ref.				

*mild cognitive impairment or dementia, †binary logistic regression that computed age, sex, education, presence of apolipoprotein ε4 allele, Geriatric Depression Scale, presence of hypertension, diabetes mellitus, body mass index, total cholesterol, serum creatinine, alcohol intake, smoking, and serum vitamin B12 levels as covariates. CI: confidence interval, OR: odds ratio

Risks of cognitive disorders at the 4-year follow-up evaluation associated with the decline of serum folate levels

Among the 2,587 subjects who completed the evaluation over the 4 years of follow-up, the 607 subjects included in the 1st lowest folate category at baseline and 292 subjects who did not have their folate levels examined at the 4-year follow-up were excluded in order to investigate the relationship between the decline of folate levels and longitudinal cognitive impairment. After the additional 20 subjects with dementia at baseline were excluded, 1,668 subjects (1,306 with normal cognition, 362 with MCI at baseline) were eligible for analysis (Figure 1). Among them, 293 (17.6%) were diagnosed with MCI and 31 (1.9%) were diagnosed with dementia at the 4-year follow-up (mean follow-up period of 3.9±0.3 years).

Among the 1,668 subjects in the 2nd, 3rd, 4th baseline folate categories with a diagnosis of cognitive normal or MCI at baseline, 375 (22.5%) dropped to the 1st lowest folate category at the 4-year follow-up. They had a 2.364-fold risk of dementia at the 4-year follow-up compared to the subjects who did not drop to this group (OR 2.364, 95% CI 1.080−5.177, p=0.031) after adjusting for age, sex, education, presence of hypertension, diabetes mellitus, BMI, GDS-K, total cholesterol, serum creatinine, alcohol intake, smoking, presence of APOE ε4 allele, and vitamin B12 levels (Table 3). They also showed a 1.318-fold risk of MCI at the 4-year follow-up compared to the subjects who did not, but statistical significance was not achieved.

DISCUSSION

In this study, serum folate in the normal-but-low range (≥1.5, ≤5.9 ng/mL) was significantly associated with cognitive disorders (MCI or dementia). Among the participants with normal baseline folate, the lowest quartile group of serum folate showed a higher risk of MCI or dementia than the other quartiles after controlling for various confounding factors that could affect cognitive function. Furthermore, during the 4-year follow-up period, the risk of incident dementia was significantly higher in subjects whose folate levels dropped to the lowest quartile after adjustment for potential confounders.

Previous studies suggest that lower folate levels are associated with a higher risk of cognitive impairment,[11-15] which is consistent with our results. Clark et al.[11] revealed that the OR of confirmed AD associated with a folate level in the lower third (≤7.5 ng/mL) compared with the upper third (>10.7 ng/mL) of the control distribution was 3.3 (95% CI 1.8−6.3). Quadri et al.[12] found that the lowest folate tertile (<6.0 ng/mL) had significantly higher odds ratios for MCI (OR=3.1, 95% CI 1.2−8.1) and dementia (OR=3.8, 95% CI 1.3−11.2) than that of the highest tertile (>8.6 ng/mL). In a Korean prospective cohort study, over a 2.4-year follow-up period, the incidence of dementia increased significantly across descending quintiles of baseline folate concentration (OR=1.41, 95% CI 1.08−1.83).[13] In another 4-year longitudinal study conducted in Italy, compared with the top folate quartile (>6.7 ng/mL), hazard ratios (HR) for dementia were 2.22 (95% CI 1.21−4.05) for the bottom quartile (<3.9 ng/mL) and 1.83 (95% CI 1.00−3.34) for the second lowest quartile (3.9−5.2 ng/mL); the HR for the third quartile (5.3−6.7 ng/mL) was not statistically significant.[14]

The prevalence of folate deficiency (<3.0 ng/mL) was reported to be low at 0.056% to 1.73%[28,29] in Western countries since folic acid fortification began in 1998. In a population of individuals aged 50 years or more, 2.2−2.3% had a deficiency in folic acid (<3.0 ng/mL).[28] In healthy Korean adults, about 13.3% of men and 3.2% of women showed a folate deficiency (<3.0 ng/mL)[30] but there has been a lack of research in elderly populations. Folate deficiency was observed in 0.02% (<1.5 ng/mL) and 1.8% (<3.0 ng/mL) of individuals in the KLOSCAD sample. When we focus on folate deficiency alone, we can treat a relatively small proportion of people at-risk of dementia. However, when we may give clinical attention to people with normal folate levels but below 5.9 ng/mL or people who have folate levels that have fallen below 5.9 ng/mL, it may be helpful to the larger population at risk of dementia. A study from Italy, which has demonstrated that low folate concentrations (≤5.2 ng/mL) were related to incident dementia, reported a similar threshold to that observed in our study.[14]

In this study, a decline in the folate level from the 2nd−4th quartile groups to the 1st lowest quartile group during the 4-year follow-up period increased the risk of incident demen-

Table 3. The risks of cognitive disorders at the 4-year follow-up evaluation associated with the decline of serum folate level* during the 4-year follow-up period

	B	SE	Wald	Sig.†	OR (95% CI)
MCI	0.276	0.157	3.086	0.079	1.318 (0.969−1.793)
Dementia	0.860	0.400	4.630	0.031	2.364 (1.080−5.177)

*the participants whose serum folate level was within the 2nd–4th quartile at baseline but declined to the lowest quartile at the 4-year follow-up evaluation, †multinomial logistic regression that computed age, sex, education, presence of apolipoprotein ε4 allele, Geriatric Depression Scale, presence of hypertension, diabetes mellitus, body mass index, total cholesterol, serum creatinine, alcohol intake, smoking, and serum vitamin B12 level as covariates. CI: confidence interval, OR: odds ratio, MCI: mild cognitive impairment

tia. A decrease in serum folate status was reported to be associated with cognitive decline[31] or incident dementia[13] in previous studies. Folate directly plays a biological role in cognition by possessing an antioxidant potential to counteract oxidative stress, which is involved in the pathogenesis of AD, and by being involved in the synthesis or repair mechanism of DNA, which could stimulate adult neurogenesis in the hippocampus, a critical area of the brain for memory function.[10,32] Moreover, folate is an important mediator of homocysteine levels and is thus indirectly related to cognitive function through multiple mechanisms, such as increasing the risk of cerebrovascular disease[8] or influencing amyloid beta-peptide metabolism.[10] Therefore, low folate levels or a decrease in folate levels may be associated with incident cognitive disorders. However, it is not conclusive whether a decline in folate level may lead to incident dementia or the neurodegenerative process leads to a decline of folate level. Evidence from an animal study indicated that low folate levels might contribute to neurodegeneration and also that low folate levels might be triggered by the neurodegeneration process itself because folate requirements are increased due to oxidative stress.[33] Thus, low folate levels could result from early neurodegeneration, and in fact, cognitively impaired people often had insufficient dietary intake, leading them to have a poor folate status.[13]

There are several limitations of this study. First, we did not consider the homocysteine levels, which play a role in the relationship between folate and cognitive function, as data on this were unavailable.[7] Second, the conversion rate to dementia was relatively small (1.1% over 4 years compared with 1−2% in the general population per year[34]) because those subjects with conversion to dementia were likely to be lost to follow-up.

The strengths of this study include the large sample size and the fact that the diagnosis of dementia or MCI was made by geropsychiatrists with dementia expertise. Additionally, most previous studies only demonstrated that the change in folate level from baseline to follow-up may affect cognitive decline.[13,31] However, we suggested the optimal maintenance concentration of folate to prevent cognitive decline. To our knowledge, this study is the first to report that a normal-but-low folate level is associated with worse cognitive status and outcomes. These results suggest that, in terms of cognitive function, higher cut-offs for serum folate deficiency (e.g., 5.9 ng/mL) and regular screening of folate concentration to ensure that it is maintained above a certain level would be beneficial; earlier intervention in older adults might also be helpful to prevent cognitive decline. In the future, long-term randomized controlled clinical trials with a large sample size should be conducted to investigate whether supplementation of folic acid may improve cognitive function in the elderly, even in the absence of clinically manifested folate deficiency.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptulization: Ji Won Han, Ki Woong Kim. Data curation: Ji Won Han. Formal Analysis & Software & Visualization: Soomin Jang, Jiyoon Shin, Ji Won Han, Ki Woong Kim. Funding acquisition: Ki Woong Kim. Investigation & Methodology & Resources & Writing—review & editing: Ji Won Han, Tae Hui Kim, Kyung Phil Kwak, Kayoung Kim, Bong Jo Kim, Shin Gyeom Kim, Jeong Lan Kim, Tae Hyun Kim, Seok Woo Moon, Jae Young Park, Joon Hyuk Park, Seonjeong Byun, Seung Wan Suh, Jiyeong Seo, Yoonseop So, Seung-Ho Ryu, Jong Chul Youn, Kyoung Hwan Lee, Dong Young Lee, Dong Woo Lee, Seok Bum Lee, Jung Jae Lee, Ju Ri Lee, Hyeon Jeong, Hyun-Ghang Jeong, Jin Hyeong Jhoo, Kyuhee Han, Jong Woo Hong, Ki Woong Kim. Project administration & Supervision & Validation: Ji Won Han, Ki Woong Kim. Writing—original draft: Soomin Jang, Ji Won Han, Ki Woong Kim.

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