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Malnutrition and Risk of Structural Brain Changes Seen on Magnetic Resonance Imaging in Older Adults

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ABSTRACT

Objectives: To study the associations between protein energy malnutrition, micronutrient malnutrition, brain atrophy, and cerebrovascular lesions

Design: Cross-sectional.

Setting: Geriatric outpatient clinic.

Participants: Older adults (N=475; mean age 80±7).

Measurements: Nutritional status was assessed using the Mini Nutritional Assessment (MNA) and according to serum micronutrient levels (vitamins B1, B6, B12, D; folic acid). White matter hyperintensities (WMHs), global cortical brain atrophy, and medial temporal lobe atrophy on

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magnetic resonance imaging (MRI) were rated using visual rating scales. Logistic regression analyses were performed to assess associations between the three MNA categories (<17 , $17-23.5$, ≥ 23.5) and micronutrients (per SD decrease) and WMHs and measures of brain atrophy. Results: Forty-eight participants (13%) were malnourished ($MNA < 17$), and 197 (55%) were at risk of malnutrition ($MNA = 17-23.5$). Participants at risk of malnutrition (odds ratio (OR)=1.93, 95% confidence interval (CI)=1.01–3.71) or who were malnourished (OR=2.80, 95% CI=1.19–6.60) had a greater probability of having severe WMHs independent of age and sex than those with adequate nutritional status. Results remained significant after further adjustments for cognitive function, depressive symptoms, cardiovascular risk factors, history of cardiovascular disease, smoking and alcohol use, and micronutrient levels. Lower vitamin B1 (OR=1.51, 95% CI=1.11–2.08) and B12 (OR=1.45, 95% CI=1.02–2.04) levels were also related to greater risk of severe WMHs, independent of age and sex. Results remained significant after additional adjustments. MNA and vitamin levels were not associated with measures of brain atrophy. Conclusion: Malnutrition and lower vitamin B1 and B12 levels were independently associated with greater risk of WMHs. Underlying mechanisms need to be further clarified, and whether nutritional interventions can modify these findings also needs to be studied.

Keywords: older adults; nutritional status; brain atrophy; white matter hyperintensities; Mini Nutritional Assessment; malnutrition

Protein energy malnutrition, a term used for deficiency of macronutrients (energy, protein), is a frequently reported condition in older adults, with prevalence rates ranging from 10% in community-dwelling older adults to 50% in institutionalized individuals, depending on setting and method used to identify individuals at risk (1–3). Older adults with cognitive impairment or dementia are at even greater risk of protein energy malnutrition because of, for example, changes in eating and inadequate food intake (4–6).

It could also be hypothesized that malnutrition could cause neurodegeneration or microvascular lesions. Although evidence supporting this hypothesis is scarce, previous studies in individuals with anorexia nervosa and individuals undergoing dialysis have shown that severe weight loss is related to greater risk of brain atrophy (7) and that lower body fat is related to white matter hyperintensities (WMHs) (8). It has been found that malnutrition at the micronutrient level may aggravate brain pathology in old age (9). Studies have shown that deficiencies in B-vitamins are

associated with risk of brain atrophy and WMHs(10–13), possibly through high homocysteine levels (14).

Nevertheless, to the knowledge of the authors of the current study, there are no data on the relationship between protein energy malnutrition and brain damage, including brain atrophy and WMHs, in older adults at risk of malnutrition and dementia.

The current study was therefore designed to investigate the association between (risk of) protein energy malnutrition and micronutrient status and the presence of brain atrophy or WMHs on magnetic resonance imaging (MRI) in a large population of older adults. Whether these associations were (in)dependent of cognitive status was also investigated.

METHODS

Study population, design, and preparation

For this cross-sectional study, data were collected from an inception cohort of 475 individuals who consecutively visited the geriatric outpatient department of Haga Hospital (the Hague, the Netherlands) between October 2005 and March 2010. The main reason for referral to the outpatient clinic was memory complaints, but the majority of individuals presented with multiple problems in the somatic, psychological, social, or functional domain (Table 1). Data were collected prospectively as part of standard care during each person's first visit. In addition to neurocognitive functioning, individuals were assessed for nutritional status, lifestyle factors, functional status, anthropometric parameters, depression, demographic characteristics, medication use, and medical history. MRI was performed as indicated by the geriatrician (SL) in individuals who presented with memory complaints or mood problems; 359 members of the cohort (76%) were referred for MRI of the brain and were eligible to be included in this study. Participants were more often female, were younger, and were more often referred because of cognitive complaints but had higher MMSE scores than those who were excluded (n=116) (Table 1). Participants also had higher MNA scores and were less often dependent in activities of daily living (ADLs) and instrumental activities of daily living (IADLs) (Table 1). Because this research was based on data obtained for regular care, the requirement for individual informed consent was waived. Ethical guidelines were followed in accordance with the Declaration of Helsinki.

Nutritional status

Nutritional status was assessed using the full Mini Nutritional Assessment (MNA), a validated nutritional assessment questionnaire that assesses protein energy malnutrition in older individuals (15). The questionnaire consists of 18 questions covering four domains: anthropometric, general, dietary, and subjective. Scores range from 0 to 30. A score of 23.5 or greater indicates adequate nutritional status, a score of 17 and 23.5 indicates risk of malnutrition, and a score less than 17 indicates malnutrition. The geriatrician assessed MNA with the caregiver of the participant, and trained nurses measured body weight, height, blood pressure, cognitive function, and depression.

All participants underwent routine laboratory assessment, including micronutrients (vitamins B1, B6, B12, D, and folic acid), using standard assays. The cut-off values for deficiencies (B vitamins) or insufficiency (vitamin D) were defined as less than 90 nmol/L for vitamin B1, less than 35 nmol/L for vitamin B6, less than 150 pmol/L for vitamin B12, less than 5 nmol/L for folic acid, and less than 50 nmol/L for vitamin D.

Brain atrophy and WMHs

MRI (1.5 T, Philips, Eindhoven, The Netherlands) of the brain was used to identify the presence and severity of brain atrophy (global and hippocampal atrophy) and WMHs. A radiologist assessed MRI. Global cortical brain atrophy (GCA) was assessed using the Global Cortical Atrophy Scale (range 0–3) (16), medial temporal lobe atrophy (MTA) was assessed using the Medial Temporal Lobe Scale (range 0–4) (17), and WMHs were rated using the Fazekas Scale (range from 0–3) (18). Scores were dichotomized for analysis ($GCA \geq 2$ vs <2 , $MTA \geq 2$ vs <2 , $WMHs \geq 2$ vs <2).

Other variables

During the first outpatient visit, systolic and diastolic blood pressure were measured in a lying position, and body weight was measured to the nearest kilogram, with clothes and shoes on, on a nondigital scale. Measured body weight was corrected for clothing by deducting 2 kg. Height was measured using a stadiometer to the nearest centimeter. Body mass index (BMI) was calculated by dividing weight by the square of height (kg/m^2). The geriatrician measured upper arm circumference, calf circumference, and waist circumference to the nearest centimeter using a flexible tape with the individual standing. For the measurement of waist circumference, the tape was placed approximately 3 cm below the navel. Information on comorbidities (e.g. cardiovascular disease, stroke, hypertension, diabetes mellitus, malignancies, lung and kidney

disease) and medication use was retrieved from the medical records, and medication use was verified with the caregiver or participant during the first outpatient visit with the geriatrician. Comorbidities were calculated, and multimorbidity was defined as having four or more chronic diseases (the median of the study group). Polypharmacy was defined as use of six or more medications (the median of the study group), including over-the-counter medication. Trained nurses administered the Geriatric Depression Scale (GDS-15) (19) and the Mini-Mental State Examination (MMSE) (20). A GDS score of 5 or greater indicate clinically important depressive symptoms, and a MMSE less than 24 indicated cognitive impairment. Activities of daily living (ADLs) were assessed based on questions about whether the individual was able to dress or wash himself or herself. Instrumental activities of daily living (IADL) were assessed based on questions about whether the individual was able to run errands, maintain their finances, and keep house. The questions were dichotomized as independent (and partly independent) versus dependent (with help only). Smoking habits and alcohol use were classified as current, former, or never user.

Statistical analyses

Participant characteristics were assessed according to the three categories of nutritional status (MNA score <17 , $17-23.5$, ≥ 23.5). Between-group differences in characteristics were analyzed using one-way analysis of variance for normally distributed continuous variables and chi-square tests for categorical variables. Logistic regression analyses were used to assess the relationship between protein energy malnutrition, assessed using the MNA, and GCA, MTA, or WMHs. Logistic regression analyses were performed to assess the relationship between serum micronutrient levels (vitamins B1, B6, B12, D, and folic acid) and GCA, MTA, or WMHs. Micronutrient levels were analyzed as a continuous variable (per standard deviation decrease). All analyses were adjusted for age, sex, and education (Model 1) and additionally adjusted for possible confounders of the relationship between nutritional status and brain structures: depressive symptoms (GDS) and cognitive status (MMSE) (Model 2) and blood pressure, history of hypertension, diabetes mellitus, presence of cardiovascular disease and stroke, smoking, and alcohol use (Model 3). Finally, to assess whether micronutrients explained the association between protein energy malnutrition (MNA) and GCA, MTA, and WMHs, vitamin levels were added to Model 3. Results from the logistic regression analyses are presented as odds ratios (ORs) with 95%

confidence intervals (95% CIs). Significance was set at $p < .05$. All statistical analyses were performed using SPSS version 21.0 for Windows (IBM Corp., Armonk, NY).

RESULTS

The mean age of the study population was 80 ± 7 , and 34% were male. Thirteen percent were malnourished (MNA < 17.0), 55% were at risk of malnutrition (MNA 17.0–23.5), and 32% had adequate nutritional status (MNA > 23.5).

Participants with malnutrition had lower BMI and smaller waist circumference, were more often smokers, used alcohol less often, and took more medications than those with better nutritional status (Table 2). They also had worse cognitive performance (lower MMSE score) and had more depressive symptoms (higher GDS score) than those with adequate nutritional status. Prevalence of cardiovascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia) and comorbidities (cardiovascular disease, stroke and malignancy) was not significantly different according to MNA category. Lifestyle factors were different according to MNA category, with malnourished participants being less likely to drink alcohol and more likely to smoke.

Nutritional status and brain structures

Of the total population ($N=359$), 225 (63%) were classified as having, 204 (57%) as having MTA, and 83 (23%) as having severe WMHs. Table 3 shows that, participants at risk of malnutrition ($OR=1.93$, 95% $CI=1.01-3.71$) and those who were malnourished ($OR=2.80$, 95% $CI=1.19-6.60$) had greater risk of severe WMHs than those with adequate nutritional status, independent of age and sex. Further adjustments slightly attenuated the effect estimates, but a significant relation remained (Table 3, Models 2 and 3). The most-important confounders in the relationship between nutritional status and severe WMHs were alcohol use and history of stroke (data not shown). Finally, regression analyses performed with additional adjustments for vitamin B1 or B12 to investigate whether low levels could explain the relationship between nutritional status and WMHs indicated an association between (risk of) malnutrition and severe WMHs, independent of low vitamin B1 or B12 levels (risk of malnutrition: $OR=2.79$, 95% $CI=1.25-6.20$; malnutrition: $OR=3.90$, 95% $CI=1.41-10.79$). Nutritional status was not associated with risk of GCA or MTA (Table 3).

Micronutrients and brain structures

Low vitamin B1 level was significantly associated with greater probability of having severe WMHs ($OR=1.51$, 95% $CI=1.11-2.08$) (Table 4). In addition lower vitamin B12 levels were

associated with greater risk of severe WMHs (Table 4). These associations were independent of age, sex, cognitive status, depressive symptoms, and cardiovascular risk factors (Models 1–3). To investigate whether malnutrition could explain the associations between vitamin B1 and B12 and WMHs, regression analyses performed with additional adjustments for MNA category indicated an association between vitamin B1 or B12 levels and severe WMHs, independent of (risk of) malnutrition (low vitamin B1, per SD: OR=1.52, 95% CI=1.08–2.12; low vitamin B12, per SD: OR=1.38, 95% CI=0.97–1.96). Vitamin B1 and B12 levels were not associated with presence of atrophy (GCA, MTA), and there was no association between other micronutrient deficiencies and risk of severe brain atrophy or severe WMHs (Table 4).

DISCUSSION

This study of 359 older adults showed an association between protein energy malnutrition and presence of severe WMHs. Low vitamin B1 and B12 levels were also associated with presence of severe WMHs. These results were independent of cognitive status, depressive symptoms, and well-known confounders and were independent of each other. Protein energy malnutrition and lower micronutrient levels were not associated with measures of brain atrophy.

The study is the first to investigate the relationship between protein energy malnutrition and brain structures in older adults. Underlying mechanisms explaining the association between malnutrition and WMHs but not CGA or MTA can only be hypothesized about. Explanations may be found in the presence of chronic inflammation, as has been described in malnourished individuals and in people with Alzheimer's disease (21,22). Alternatively, the fact that malnutrition was associated with WMHs but not with atrophy suggests that the mechanism may be found through a vascular rather than a neurodegenerative route. A previous study in the same cohort showed that smoking was associated with greater risk of being malnourished (23), and smoking is also a well-known risk factor for cardiovascular disease. In addition, protein malnutrition impairs cardiovascular homeostasis, increasing mean arterial pressure, which is an important cardiovascular risk factor (24), but adjusting for cardiovascular risk factors, including smoking behavior, hypertension, and history of cardiovascular disease, did not materially change the effect estimates.

Another hypothesis is that micronutrients mediate the association between protein energy malnutrition and WMHs. Lower vitamin B1 levels and vitamin B12 deficiency were independently associated with presence of severe WMHs. Previous studies have found an

association between B vitamin levels and cognitive impairment and dementia in older adults as well (25,26). The same has been shown for low folic acid levels in previous studies (27), but this was not confirmed in the present study. Still, there is some evidence that micronutrient deficiencies are associated with brain atrophy and WMHs. B vitamins play an important role as cofactors in methionine metabolism, which is important for synthesis and activation of neurotransmitters in the brain (28), and lower B vitamin levels are associated with higher homocysteine levels, which have been identified as risk factors for cardio- and cerebrovascular disease (29,30). In a few earlier studies, high homocysteine levels were also associated with presence and severity of WMHs (31,32). The current study specifically investigated whether vitamin B levels could have explained the association between protein energy malnutrition and WMHs, but this was not the case. Unfortunately, homocysteine levels were not measured in this study.

Finally, individuals with cognitive impairment may become nutritionally deficient by not eating well. To determine whether cognitive impairment explains the relationship between poor nutritional status and WMHs, all analyses were adjusted for cognitive status.

This study has several strengths and limitations. The main strength was the availability of extensive data on nutritional status and serum micronutrient levels in a large cohort of individuals at a geriatric clinic. One geriatrician consistently performed data collection with assistance of trained nurses. Also, validated measures, such as MNA (15,33) and MMSE (20), were used.

A limitation is the cross-sectional design, which limits conclusions regarding causal effect or intraindividual changes. Second, it was a practice-based study that was not specifically designed with to investigate the association between brain structures, nutritional status, and dementia, which means, for example, that a team of radiologists judged MRI scans—albeit based on a strict protocol—which may have influenced the reliability of the scores. Interrater reliability was not assessed, because this study was not initiated as a research project. Furthermore, not all patients had brain MRI, which resulted in a selected healthy study sample. The excluded group was older and had more functional, cognitive, and physical impairments and poorer nutritional status, which may have led to underestimation of the effect.

Finally, the MNA questionnaire comprises one question on dementia and depression and classifies respondents with dementia or depression as being at higher nutritional risk. Therefore,

to exclude incorporation bias, analyses were adjusted for cognitive status and presence of depressive symptoms.

In summary, in a large cohort of older adults, (risk of) malnutrition and lower vitamin B1 levels and B12 deficiency were independently associated with greater risk of having severe WMHs. These associations were independent of depression or cognitive status. Further in-depth studies to investigate the relationship between protein energy malnutrition, micronutrient malnutrition, and structural brain MRI changes are planned for the next few years. These future studies will be designed to identify nutrition risk factors for changes in brain structure, formulating dietary guidelines, and developing recommendations for trial design in stratified participant groups.

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Author Contributions: de van der Schueren, Muller: study design, drafting the manuscript. Lonterman-Monasch: data collection. All authors: approval of final version.

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Table 1. Characteristics of Included (with Magnetic Resonance Imaging (MRI)) and Excluded (without MRI) Individuals

Characteristic	Study Sample, n=359	Excluded Sample, n=116	P-Value ^a
General			
Male, n (%)	123 (34)	54 (47)	.01
Age, mean±SD	80±7	82±7	<.001
Body mass index, kg/m ²	25.4±4.4	24.7±4.6	.14
Current alcohol use, n (%)	144 (42)	49 (46)	.78
Current smoker, n (%)	41 (12)	14 (13)	.82
Referral reason, n (%)			.004
Cognitive complaints	194 (54)	41 (35)	
Mobility complaints	16 (5)	9 (8)	
Multiple complaints	58 (16)	25 (22)	
Other	91 (25)	41 (36)	
Cardiovascular disease and risk, n (%)			
Diabetes mellitus	100 (28)	38 (33)	.19
Hypercholesterolemia	140 (39)	44 (38)	.46

Hypertension	199 (55)	64 (55)	.52
Cardiovascular disease	161 (45)	62 (53)	.07
Stroke	47 (13)	19 (16)	.23
Medical history, n (%)			
≥6 medications	187 (52)	67 (58)	.17
≥4 comorbidities	179 (50)	64 (55)	.19
Malignancy	84 (23)	35 (30)	.09
Physical and cognitive function			
Dependent in activities of daily living, n (%)	39 (11)	26 (23)	.002
Dependent in instrumental activities of daily living, n (%)	92 (26)	51 (46)	<.001
Mini Mental State Examination score, mean±SD	23.7±4.7	22.4±5.0	.02
Geriatric Depression Scale score, mean±SD	4.2±3.4	4.7±3.7	.20
Nutritional status, mean±SD			
Mini Nutritional Assessment score	21.4±4.2	20.0±4.7	.003
Vitamin B1, nmol/L ^b	132±34	137±37	.18
Vitamin B6, nmol/L ^b	120±212	150±466	.36
Vitamin B12, pmol/L ^b	279±129	274±126	.69
Folic acid, nmol/L ^b	19±16	20±15	.57
Vitamin D, nmol/L ^b	41±23	40±25	.66

^aP-value derived from analysis of variance or chi-square test.

^bMissing values between 22 and 42 cases. All other variables had 0–20 missing values.

SD=standard deviation.

Table 2. Characteristics of Study Population (N=359) According to Nutritional Status Category

Characteristic	Adequate Nutritional Status (MNA ≥ 23.5), n=114 (32%)	Risk of Malnutrition (MNA 17–23.5), n=197 (55%)	Malnutrition (MNA < 17), n=48 (13%)	P-Value
General				
Male, n (%)	49 (43)	61 (31)	13 (27)	.05

Age, mean±SD	79±7	80±7	82±6	.04
Height, cm, mean±SD				
Male	173±7	175±8	173±7	.53
Female	163±6	161±7	161±7	.04
Weight, kg, mean±SD				
Male	78±12	75±12	71±17	.19
Female	71±11	67±15	56±12	<.001
Body mass index, kg/m ² , mean±SD	26.5±3.3	25.5±4.5	22.2±4.7	<.001
Waist circumference, cm, mean±SD				
Male	102±10	101±10	99±16	.77
Female	102±9	101±12	93±13	<.001
Current alcohol use, n (%)	58 (55)	72 (39)	14 (30)	.03
Cardiovascular risk factors				
Current smoker, n (%)	7 (6)	24 (13)	10 (21)	.03
Diabetes mellitus, n (%)	30 (26)	56 (28)	14 (29)	.90
Hypercholesterolemia, n (%)	44 (39)	81 (41)	15 (31)	.45
Systolic blood pressure, mmHg, mean±SD	144 (22)	141 (22)	141 (17)	.49
Diastolic blood pressure, mmHg, mean±SD	75 (12)	74 (12)	74 (12)	.56
Hypertension, n (%)	62 (54)	109 (55)	28 (58)	.90
Medical history, n (%)				
≥6 medications	48 (42)	109 (55)	30 (63)	.02
≥4 comorbidities	52 (45)	101 (51)	26 (54)	.51
Cardiovascular disease	42 (37)	95 (48)	24 (50)	.11
Stroke	12 (11)	29 (15)	6 (13)	.57
Malignancy	26 (23)	48 (24)	10 (21)	.86
Physical and cognitive function				
Dependent in activities of daily	5 (5)	18 (10)	16 (34)	<.001

living, n (%)				
Dependent in instrumental activities of daily living, n (%)	14 (13)	54 (28)	24 (52)	<.001
Mini Mental State Examination score, mean±SD	24.8±3.9	23.3 ±4 .8	22.6±5.3	.007
Geriatric Depression Scale score, mean±SD	3.2±2.7	4.5±3.4	5.8±3.9	<.001
Micronutrients, mean±SD ^a				
Vitamin B1, nmol/L	138±38	130±31	127±31	.08
Vitamin B6, nmol/L	132±183	122±250	86±46	.46
Vitamin B12, pmol/L	287±117	274±126	279±171	.69
Folic acid, nmol/L	21±23	17±11	17±11	.12
Vitamin D, nmol/L	41±20	40±24	44±24	.49

^aMissing values between 22 and 42 cases. All other variables had 0–20 missing values.

MNA=Mini Nutritional Assessment; SD=standard deviation.

Table 3. Nutritional Status (Mini Nutritional Assessment (MNA)) and Risk of Severe Global Cortical Atrophy (GCA), Medial Temporal Lobe Atrophy (MTA), or White Matter Hyperintensities (WMHs)

Model	GCA ≥ 2, n=225	MTA ≥ 2, n=204	WMHs ≥ 2, n=83
	Odds Ratio (95% Confidence Interval)		
Risk of malnutrition (MNA 17–23.5)			
1	0.95 (0.55–1.63)	1.04 (0.62–1.76)	1.93 (1.01–3.71)
2	0.98 (0.56–1.71)	1.07 (0.63–1.84)	1.97 (1.19–7.42)
3	0.78 (0.42–1.43)	0.95 (0.54–1.69)	1.88 (0.99–3.76)
Malnutrition (MNA <17)			
1	0.71 (0.32–1.58)	0.97 (0.44–2.14)	2.80 (1.19–6.60)
2	0.75 (0.32–1.76)	1.07 (0.47–2.46)	2.98 (1.19–7.42)
3	0.60 (0.24–1.49)	0.93 (0.39–2.24)	2.72 (1.04–7.09)

Reference adequate nutritional status (MNA >23.5)

Model 1: Adjusted for age and sex.

Model 2: Additionally adjusted for Mini-Mental State Examination and Geriatric Depression Scale scores.

Model 3: Additionally adjusted for blood pressure, history of hypertension, diabetes mellitus, cardiovascular disease, stroke, smoking, and alcohol use.

Table 4. Micronutrient Levels (per Standard Deviation (SD) decrease) and Risk of Severe Global Cortical Atrophy (GCA), Medial Temporal Lobe Atrophy (MTA), or White Matter Hyperintensities (WMHs)

Model	GCA ≥ 2 , n=225	MTA ≥ 2 , n=204	WMHs ≥ 2 , n=83
	Odds Ratio (95% Confidence Interval)		
Vitamin B1 (SD 34 nmol/L)			
1	1.08 (0.85–1.39)	0.97 (0.75–1.25)	1.51 (1.11–2.08)
2	1.06 (0.80–1.35)	0.99 (0.76–1.30)	1.51 (1.10–2.08)
3	1.05 (0.65–1.37)	1.10 (0.64–1.45)	1.57 (1.12–2.19)
Vitamin B6 (SD 212 nmol/L)			
1	1.00 (0.79–1.25)	0.88 (0.62–1.25)	1.61 (0.74–3.50)
2	1.00 (0.78–1.26)	0.88 (0.61–1.25)	1.56 (0.73–3.32)
3	1.01 (0.78–1.35)	1.10 (0.84–1.45)	1.46 (0.68–3.13)
Vitamin B12 (SD 130 pmol/L)			
1	1.14 (0.90–1.45)	0.98 (0.75–1.28)	1.45 (1.02–2.04)
2	1.12 (0.88–1.45)	0.97 (0.74–1.37)	1.41 (1.00–2.00)
3	1.08 (0.83–1.39)	1.10 (0.84–1.45)	1.37 (0.96–1.96)
Folic acid (SD 16 nmol/L)			
1	1.28 (0.88–1.85)	0.90 (0.61–1.33)	1.18 (0.75–1.81)
2	1.28 (0.88–1.89)	0.90 (0.61–1.35)	1.15 (0.74–1.78)
3	1.33 (0.89–2.00)	1.10 (0.89–1.45)	1.12 (0.73–1.77)
Vitamin D (SD 23 nmol/L)			
1	1.03 (0.80–1.32)	1.08 (0.83–1.39)	0.86 (0.66–1.12)
2	1.00 (0.75–1.28)	1.10 (0.84–1.43)	0.85 (0.65–1.12)
3	0.94 (0.72–1.23)	1.10 (0.84–1.45)	0.83 (0.62–1.10)

Model 1: Adjusted for age and sex.

Model 2: Additionally adjusted for Mini-Mental State Examination and Geriatric Depression Scale scores.

Model 3: Additionally adjusted for blood pressure, history of hypertension, diabetes mellitus, cardiovascular disease, stroke, smoking, and alcohol use.

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