

Changes in folate, vitamin B₁₂ and homocysteine associated with incident dementia

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Received 1 August 2007
Revised 7 November 2007
Accepted 8 November 2007

ABSTRACT

Objectives: Prospective findings have not been consistent for folate, vitamin B₁₂ and homocysteine concentrations as predictors of dementia. This study aimed to investigate both baseline concentrations of folate, vitamin B₁₂ and homocysteine and changes in these concentrations as predictors/correlates of incident dementia.

Methods: Of 625 elderly patients without dementia at baseline, 518 (83%) were followed over a 2.4 year period and were clinically assessed for incident dementia and Alzheimer's disease (AD). Serum concentrations of folate, vitamin B₁₂ and homocysteine were measured at the baseline and follow-up assessments. Covariates included age, sex, education, disability, depression, alcohol consumption, physical activity, vascular risk factors, serum creatinine concentration, vitamin intake and weight change.

Results: Only baseline lower folate concentrations predicted incident dementia. The onset of dementia was significantly associated with an exaggerated decline in folate, a weaker increase in vitamin B₁₂ concentrations and an exaggerated increase in homocysteine concentrations over the follow-up period. These associations were reduced following adjustment for weight change over the same period.

Conclusions: Incident dementia is more strongly associated with changes in folate, vitamin B₁₂ and homocysteine than with previous concentrations. These changes may be linked to other somatic manifestations of early dementia, such as weight loss.

Folate, vitamin B₁₂ and homocysteine are involved in one carbon transfer (methylation) reactions necessary for the production of monoamine neurotransmitters, phospholipids and nucleotides.^{1,2} Homocysteine may also have a direct neurotoxic effect.³ Folate and vitamin B₁₂ deficiency, and hyperhomocysteinaemia, may therefore have a role in the pathogenesis of dementia. Several cross sectional studies have found significant associations of lower folate and hyperhomocysteinaemia with dementia or cognitive impairment,⁴⁻⁶ but the direction of cause and effect is not known. Results from prospective studies have been controversial.⁷⁻⁹ Because the emerging clinical syndrome of dementia is associated with physical changes such as weight loss and declining blood pressure,^{10,11} cross sectional associations with altered markers of one carbon metabolism may be secondary to rather than causal factors for neurodegeneration. However, there has been little research into changes in these factors in association with the incidence of dementia.

In a 2 year community based prospective survey of late life mental disorder, folate, vitamin B₁₂ and

homocysteine were assayed at both baseline and follow-up, and data were collected on the incidence of dementia during that period. We investigated associations with incident dementia, for baseline concentrations of folate, vitamin B₁₂ and homocysteine and for changes in these factors over the follow-up period.

METHODS

Study participants

A prospective community survey was carried out in Kwangju, South Korea, from 2001 to 2003. The design has been described in several previous publications.¹²⁻¹⁴ At baseline, all community residents aged 65 years or over within two geographic catchment areas (one urban, one rural) were systematically identified from national registration lists and were approached to participate in the study. Attempts were made to follow-up all participants 2 years later (mean (SD) interval 2.4 (0.3) years). The study received appropriate institute review board approval.

Ascertainment of dementia

Identical assessments for dementia were carried out at baseline and at follow-up. Examinations included the Mini-Mental State Examination,¹⁵ the Instrumental Activities of Daily Living Scale,¹⁶ the Clinical Dementia Rating scale,¹⁷ collateral information on past history and a full physical and neurological examination. A committee of senior clinical researchers assigned consensus diagnoses, using standard criteria for dementia,¹⁸ Alzheimer's disease (AD)¹⁹ and vascular dementia.²⁰ These were applied blind to all other clinical information, including the results of the blood assays which were the focus of this analysis.

Measurements

Blood samples at baseline and follow-up were collected in a fasting state and were carried out in the mornings where possible. They were placed into EDTA tubes and centrifuged, separated into plasma aliquots and stored at -70°C within 2 h of collection. Serum concentrations of folate (Advia Centaur Folate; Chiron Diagnostics, USA) and vitamin B₁₂ (Advia Centaur VB12; Chiron Diagnostics) were determined using an immunoassay, and total plasma homocysteine concentration (AxSYM Homocysteine Reagent Pack; Abbott Laboratories, USA) was measured by high performance liquid chromatography. Apolipoprotein E genotype was assayed.

Baseline measures also included sociodemographic data, disability (World Health Organization Disability Assessment Schedule II),²¹

Table 1 Baseline characteristics by incident dementia status

Demographic characteristic	No incident dementia (n = 473)	Incident dementia (n = 45)	p Value*
Age (y) (mean (SD))	71.6 (4.9)	74.3 (5.7)	0.001
Female sex (n (%))	267 (54.9)	30 (63.8)	0.273
Education (y) (median (IQR))	3 (0–6)	0 (0–2)	<0.001
Assessment scales			
MMSE (mean (SD))	23.7 (4.4)	20.5 (4.2)	<0.001
WHODAS II (median (IQR))	2.1 (0–6)	5.4 (1–12)	0.001
GMS depression (n (%))	50 (10.6)	7 (15.6)	0.307
Lifestyle characteristics			
Current smoker (n (%))	199 (42.1)	16 (35.6)	0.397
High alcohol intake (n (%))	141 (29.8)	14 (31.1)	0.855
Low physical activity (n (%))	118 (24.9)	24 (53.3)	<0.001
Vascular risk score (median (IQR))	1 (0–2)	1 (1–2)	0.121
Serum creatinine (mg/dl) (mean (SD))	0.8 (0.2)	0.8 (0.2)	0.941
Body mass index (kg/m ²) (mean (SD))	22.9 (3.4)	22.2 (3.5)	0.245
APOE e4 allele (n (%))	74 (15.6)	14 (31.1)	0.008

*t test, χ^2 test or Mann–Whitney U test as appropriate.

APOE, apolipoprotein E; GMS, Geriatric Mental State Schedule; MMSE, Mini-Mental State Examination; WHODAS II, World Health Organization Disability Assessment Scale II.

depression (Geriatric Mental State schedule),^{22, 23} smoking and alcohol history (high alcohol consumption over the previous 3 months defined as >14 drinks/week for men and >7 drinks/week for women), and daily physical activity (low activity defined on the basis of a predominantly sedentary lifestyle). For vascular risk factors and disorders, a summary risk score was calculated by summing self-reported disorders (stroke, heart disease, hypertension, diabetes), measured obesity (body mass index >25 kg/m²) and hypercholesterolaemia (fasting cholesterol >200 mg/dl). Serum creatinine concentration was assayed. Body weight was measured at baseline and at follow-up. Vitamin supplementation was ascertained at follow-up.

Statistical analysis

SPSS 12.0 software was used. For the analysis presented here, participants with dementia at baseline were excluded. Incident dementia was the dependent variable for all analyses. Because baseline values for folate, vitamin B₁₂ and homocysteine were positively skewed, they were log transformed for the mean comparison analyses between those with and without incident dementia. Baseline concentrations of folate, vitamin B₁₂ and homocysteine, and individual changes in these factors from baseline to follow-up were categorised into quintiles and analysed as ordinal independent variables. Associations with incident dementia were assessed initially by χ^2 tests for linear trend (1 df). Logistic regression models were used to adjust for

other covariates. Final analyses were carried out to investigate associations with standard categories of folate/vitamin B₁₂ deficiency and hyperhomocysteinaemia.²⁴ Folate deficiency was defined as <11.4 nmol/l and homocysteine >13.9 μ mol/l; vitamin B₁₂ deficiency was defined as <258 pmol/l; and hyperhomocysteinaemia as plasma levels >15.0 μ mol/l.

RESULTS

At baseline, 732 of 1204 identified residents completed all assessments and measurements for the study (participation rate 61%). Of 732 participants at baseline, 625 did not have dementia. Of these, 518 (83%) completed all evaluations at follow-up and comprised the sample for this analysis. Participants lost to follow-up (n = 107) did not differ significantly from the analysed sample for any baseline variable (data not shown).

In the sample analysed (n = 518), incident cases of dementia were identified in 45 participants (8.7%): 34 (6.6%) AD, seven (1.4%) vascular dementia and four "other" dementia (0.8%). Baseline characteristics are compared by incident dementia status in table 1. Incident dementia was significantly predicted by older age, lower education, more severe cognitive impairment and disability, lower physical activity and presence of the apolipoprotein e4 allele. Mean (SD) change in body weight was –0.3 (3.8) kg in the total sample, –1.4 (3.9) kg in those who did develop dementia and –0.1 (3.7) kg in the remainder (t = 1.98, p = 0.048).

Baseline and the change in values for folate, vitamin B₁₂ and homocysteine are compared by incident dementia status in table 2. Incident dementia was significantly associated with lower baseline folate, and decreasing follow-up folate and vitamin B₁₂ values. Baseline folate concentration was correlated positively with vitamin B₁₂ concentration (r = 0.138, p = 0.001) and negatively with homocysteine concentration (r = –0.367, p < 0.001). Vitamin B₁₂ concentration was negatively correlated with homocysteine concentration (r = –0.312, p < 0.001). Mean (SD) changes in concentrations from baseline to follow-up were as follows: folate –5.1 (12.2) nmol/l; vitamin B₁₂ +50.8 (135.8) pmol/l; and homocysteine +1.7 (4.6) μ mol/l. Over the follow-up period, folate and vitamin B₁₂ concentrations were positively correlated (r = 0.192, p = <0.001), indicating that participants with declining folate had a smaller increase (or a decrease) in B₁₂. Decreasing folate concentration was associated with an increase in homocysteine concentration (r = –0.222, p < 0.001). Increasing vitamin B₁₂ concentration was correlated with decreasing homocysteine concentration (r = –0.232, p < 0.001).

The incidence of dementia increased significantly across descending quintiles of baseline folate concentrations (χ^2 = 5.005; p = 0.025) but was not associated with baseline

Table 2 Baseline and changed values for folate, vitamin B₁₂ and homocysteine by incident dementia status

	No incident dementia (n = 473)	Incident dementia (n = 45)	p Value*
Baseline values			
Folate (nmol/l)	25.2 (12.8; 7.8–88.4)	21.3 (11.1; 8.5–54.5)	0.018
Vitamin B ₁₂ (pmol/l)	381.5 (147.7; 104–1334)	372.6 (164.7; 141–983)	0.483
Homocysteine (μ mol/l)	12.3 (5.2; 1.0–50.0)	14.3 (8.1; 5.4–44.0)	0.146
Changed values			
Folate (nmol/l)	–4.5 (12.1; –45.8~+43.9)	–10.8 (11.2; –37.4~+11.5)	0.001
Vitamin B ₁₂ (pmol/l)	+55.5 (136.7; –485~+675)	+0.3 (115.5; –240~+282)	0.010
Homocysteine (μ mol/l)	+1.6 (4.6; –20.1~+24.7)	+2.6 (4.4; –17.1~+9.0)	0.194

Data are mean (SD; range).

*t test (baseline values were log transformed as they were positively skewed).

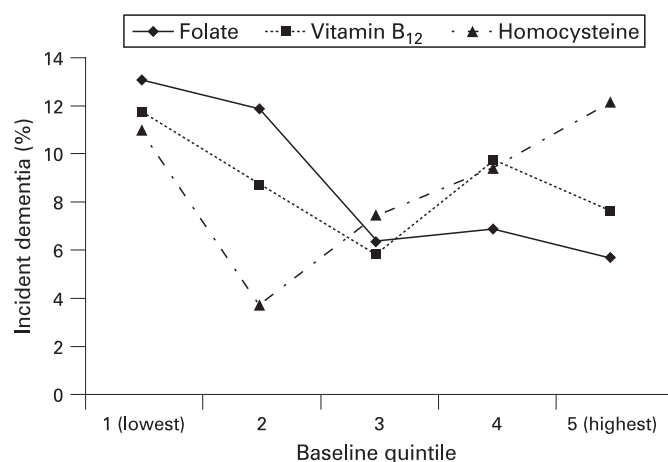


Figure 1 Two year incidence of dementia by baseline folate, vitamin B₁₂ and homocysteine.

vitamin B₁₂ concentrations ($\chi^2 = 0.654$; $p = 0.419$) or homocysteine ($\chi^2 = 0.908$; $p = 0.341$) (fig 1). In regression analysis (table 3), the association between incident dementia and lower baseline folate remained significant after adjustment for other covariates (model 7) and was little changed when adjusted for homocysteine concentration as a potential mediator (model 10). With respect to associations with AD, adjusted odds ratios (model 7) for lower folate and vitamin B₁₂, and for higher homocysteine, were 1.32 (1.00 to 1.75), 0.93 (0.71 to 1.21) and 1.03 (0.77 to 1.38), respectively.

The incidence of dementia increased across descending quintiles of follow-up folate concentrations ($\chi^2 = 11.80$; $p = 0.001$) and vitamin B₁₂ concentrations ($\chi^2 = 7.929$; $p = 0.005$), and across ascending quintiles of follow-up homocysteine concentrations ($\chi^2 = 6.793$; $p = 0.009$) (fig 2). In regression analyses (table 4), these associations generally became stronger after adjustment for other covariates. However, all were weakened when weight change was included in the models. When entered in combination, the associations between folate/vitamin B₁₂ concentrations and incident dementia were little changed after adjustment for homocysteine change. In contrast, the association between homocysteine change and incident dementia was moderately reduced after adjustment for either folate or vitamin B₁₂ change. With respect to incident AD, the adjusted associations (model 7) with decline

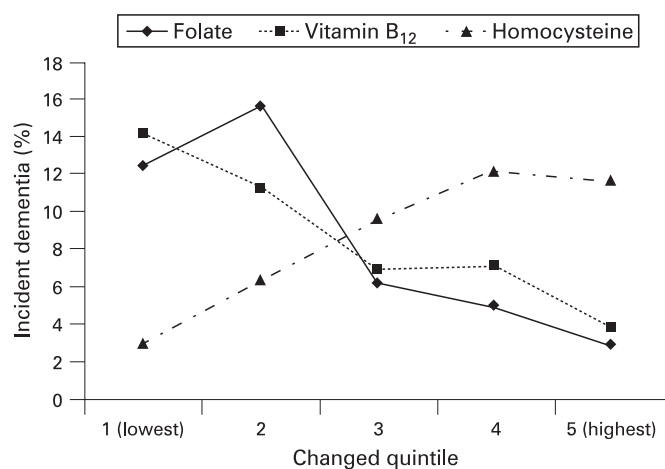


Figure 2 Incidence of dementia by change in folate, vitamin B₁₂ and homocysteine over a 2 year follow-up period.

in folate and vitamin B₁₂, and increase in homocysteine, were 1.49 (1.10 to 2.03), 1.55 (1.08 to 2.23) and 1.21 (0.91 to 1.62).

The prevalence of baseline folate deficiency was 3.5%, vitamin B₁₂ deficiency 17.4% and hyperhomocysteinaemia 19.7%. Odds ratios (ORs, and 95% CIs) for associations with incident dementia were 3.20 (1.01 to 10.17) for folate deficiency, 1.61 (0.78 to 3.32) for vitamin B₁₂ deficiency and 1.75 (0.88 to 3.48) for hyperhomocysteinaemia. After adjustment for the other factors listed in table 3 (model 7), respective ORs (95% CIs) were 3.43 (0.83 to 14.15), 1.53 (0.69 to 3.38) and 1.57 (0.69 to 3.54).

DISCUSSION

Principal findings of the study

In this prospective study of a community population, lower folate concentrations predicted incident dementia and AD over a 2.4 year follow-up period, but no associations were found with baseline vitamin B₁₂ or homocysteine concentrations. Over the follow-up period, dementia occurred more commonly in those with a relative decline in folate and vitamin B₁₂ concentrations or a relative increase in homocysteine concentrations. The association between change in homocysteine and incident dementia was reduced in strength following adjustment for contemporaneous folate and vitamin B₁₂ changes. All

Table 3 Logistic regression models for the association between baseline folate/vitamin B₁₂/homocysteine and incident dementia over the 2.4 year follow-up period (n = 518)

	OR (95% CI) for dementia per quintile difference		
	Folate (lower)	Vitamin B ₁₂ (lower)	Homocysteine (higher)
Unadjusted	1.29 (1.03 to 1.62)	1.09 (0.88 to 1.36)	1.11 (0.89 to 1.39)
(1) Adjusted for age, sex and education	1.35 (1.06 to 1.73)	1.08 (0.86 to 1.35)	1.10 (0.86 to 1.40)
(2) Model 1 plus disability and depression	1.39 (1.08 to 1.78)	1.07 (0.85 to 1.34)	1.10 (0.86 to 1.40)
(3) Model 2 plus smoking, alcohol and activity	1.35 (1.05 to 1.74)	1.04 (0.82 to 1.32)	1.07 (0.83 to 1.38)
(4) Model 3 plus vascular risk score	1.35 (1.05 to 1.74)	1.05 (0.83 to 1.32)	1.06 (0.82 to 1.37)
(5) Model 4 plus serum creatinine	1.35 (1.05 to 1.74)	1.05 (0.83 to 1.32)	1.08 (0.83 to 1.40)
(6) Model 5 plus vitamin intake	1.35 (1.05 to 1.74)	1.07 (0.84 to 1.36)	1.05 (0.81 to 1.37)
(7) Model 6 plus baseline body weight	1.41 (1.08 to 1.82)	1.06 (0.83 to 1.34)	1.08 (0.83 to 1.41)
(8) Model 7 plus folate concentration		1.03 (0.82 to 1.31)	0.99 (0.76 to 1.31)
(9) Model 7 plus vitamin B ₁₂ concentration	1.40 (1.08 to 1.82)		1.07 (0.82 to 1.41)
(10) Model 7 plus homocysteine concentration	1.41 (1.08 to 1.83)	1.04 (0.82 to 1.33)	

Table 4 Logistic regression models for the association between change in folate/vitamin B₁₂/homocysteine concentrations and co-occurring dementia incidence over the 2.4 year follow-up period (n = 518)

	OR (95% CI) for dementia per quintile change		
	Folate (decline)	Vitamin B ₁₂ (decline)	Homocysteine (increase)
Unadjusted	1.50 (1.18 to 1.91)	1.38 (1.10 to 1.74)	1.35 (1.07 to 1.70)
(1) Adjusted for age, sex and education	1.53 (1.19 to 1.97)	1.38 (1.09 to 1.74)	1.38 (1.08 to 1.75)
(2) Model 1 plus disability and depression	1.58 (1.22 to 2.04)	1.40 (1.10 to 1.77)	1.41 (1.10 to 1.80)
(3) Model 2 plus smoking, alcohol and activity	1.60 (1.23 to 2.09)	1.42 (1.11 to 1.81)	1.38 (1.08 to 1.77)
(4) Model 3 plus vascular risk score	1.59 (1.22 to 2.08)	1.41 (1.11 to 1.80)	1.38 (1.08 to 1.76)
(5) Model 4 plus serum creatinine	1.59 (1.22 to 2.07)	1.41 (1.11 to 1.80)	1.38 (1.08 to 1.76)
(6) Model 5 plus vitamin intake	1.59 (1.22 to 2.08)	1.72 (1.24 to 2.37)	1.41 (1.10 to 1.81)
(7) Model 6 plus weight change	1.47 (1.11 to 1.94)	1.67 (1.16 to 2.30)	1.30 (0.99 to 1.69)
(8) Model 7 plus folate change		1.50 (1.03 to 2.19)	1.17 (0.89 to 1.55)
(9) Model 7 plus vitamin B ₁₂ change	1.37 (1.03 to 1.82)		1.23 (0.93 to 1.61)
(10) Model 7 plus homocysteine change	1.41 (1.06 to 1.88)	1.59 (1.10 to 2.29)	

associations were reduced in strength following adjustment for weight change over the same period.

Strength and limitations of the study

A strength of this study was that prospective data were obtained not only for dementia and cognitive status but also for the independent variables of interest. Diagnoses of dementia were made blind to these assay results and followed standard criteria. Furthermore, a large number of potential confounding factors were considered in the analyses, including change in body weight. The follow-up rate was reasonable and not differential with respect to the exposures of interest. The principal limitations of the study were that incident dementia was evaluated over a relatively short period and accurate timing of the onset was not possible. Furthermore, data on vitamin supplementation were only available at the follow-up assessment and detailed constituents of vitamin preparations were not collected. Vitamin B₆, also important in homocysteine metabolism, was not assayed. The annual incidence of dementia in this sample was approximately 3.6%. This finding is comparable with a 3–4% range reported by some studies^{9, 25} but higher than the 1–2% range suggested by others.⁷ The relatively high prevalence of dementia observed at baseline^{12, 13} does not suggest that the observed high incidence was accounted for by previously missed cases.

Baseline folate/vitamin B₁₂/homocysteine levels and incident dementia

Associations have been reported previously between dementia and lower folate, lower vitamin B₁₂ and higher homocysteine concentrations.^{4–6} Cross sectional findings for our sample were similar (data not shown). However, cross sectional studies are limited in the extent to which causal relationships can be inferred as cognitive decline may be associated with dietary changes influencing observed blood concentrations. Findings from more recent prospective studies have been inconsistent. Low folate predicted incident dementia in one study,²⁵ but prospective associations between vitamin B₁₂ concentrations were not found.²⁵ Three prospective studies have found associations between homocysteine and incident dementia,^{7, 9, 25} but others have not.⁸ With respect to vitamin B₁₂, holotranscobalamin concentrations may be a more accurate marker of risk²⁶ but were not assayed in this study. It should also be borne in mind that this study had a relatively short follow-up period so that low folate at baseline may have been a consequence of earlier neurodegeneration.

Change in folate/vitamin B₁₂/homocysteine levels and incident dementia

Longitudinal changes in concentrations of folate, vitamin B₁₂ or homocysteine around the onset of dementia have received little attention. In a recent prospective study, a decrease in folate and an increase in homocysteine were associated with cognitive decline over a 6 year period.²⁷ In our study, incident dementia was more strongly associated with changes in these factors than baseline concentrations. Although these changes may have an effect on neurodegenerative processes (eg, during stages of mild cognitive impairment), the opposite direction of causation is also possible. There is growing evidence that somatic changes associated with dementia are already occurring prior to the onset of the clinical syndrome. These include weight loss¹¹ and blood pressure decline,¹⁰ and may also include changes in micronutrient concentrations. Of interest, adjustment for weight change reduced the strength of our observed associations with incident dementia and may be an important confounding factor. However, little is known about the cause of weight loss in early neurodegeneration and further research is required (eg, to establish whether this may be explained by changes in quantity of food consumed, changes in type of food consumed or changes in physiological systems dealing with nutrient uptake and metabolism). Because neurodegenerative processes begin a long time before the onset of dementia, it is difficult to establish causal processes with certainty during the prodromal period. The relationship might be complex and bidirectional with weight loss, and other physical changes, both causes and consequences of neurodegenerative processes. However, research, to date at least, suggests that the associations are evident before the clinical onset of dementia and less likely to be explained by overt behavioural symptoms present in more advanced disease. The relationship between weight loss and micronutrient concentrations is also potentially complex. Weight loss is unlikely to cause changes in micronutrient concentrations directly; however, it might be a manifestation of changes in dietary intake (whether in quantity or quality) which include changes in intake of specific nutrients. Change in weight and change in micronutrient concentrations may therefore be “markers” of a common underlying process. In this respect, it is noteworthy that adjustment for folate or vitamin B₁₂ had a similar impact on the association of each with dementia as did adjustment for weight change. Changes in folate and vitamin B₁₂ concentration also accounted substantially for associations between dementia and a rise in homocysteine. This suggests that a rise in homocysteine associated

with dementia may have a nutritional basis. Over the course of the study, folate levels declined for the whole sample while vitamin B₁₂ levels increased. This might possibly reflect vitamin supplementation habits as most supplements in Korea contain vitamin B₁₂ but not folate. It is possible therefore that the differences associated with dementia might reflect use of supplements, although we believe this is unlikely to be the sole explanation. Further research is required to clarify these complex longitudinal inter-relationships. In the meantime, attention needs to be paid to the nutritional status of people with dementia from the time of diagnosis onwards, regardless of whether this is a cause or effect of their condition. In addition, there may be good arguments for focusing interventions for the prevention of dementia on nutritionally deficient frail populations.²⁸

Funding: The research was supported by a grant from the Korea Health 21 R&D, Ministry of Health and Welfare, Republic of Korea (A050174).

Competing interests: None.

Ethics approval: Yes.

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