Clinical Nutrition 40 (2021) 4579–4584

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Hypohomocysteinemia may increases the risk of dementia and Alzheimer's disease: A nationwide population-based prospective cohort study

Jong Bin Bae [a, b], Ji Won Han [a, b], Junghan Song [c], Kyunghoon Lee [c], Tae Hui Kim [d], Kyung Phil Kwak [e], Bong Jo Kim [f], Shin Gyeom Kim [g], Jeong Lan Kim [h], Seok Woo Moon [i], Joon Hyuk Park [j], Seung-Ho Ryu [k], Jong Chul Youn [l], Dong Young Lee [b, m], Dong Woo Lee [n], Seok Bum Lee [o], Jung Jae Lee [o], Jin Hyeong Jhoo [p], Ki Woong Kim [a, b, q, *]

[a] Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, South Korea
[b] Department of Psychiatry, Seoul National University, College of Medicine, Seoul, South Korea
[c] Department of Laboratory Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea
[d] Department of Psychiatry, Yonsei University Wonju Severance Christian Hospital, Wonju, South Korea
[e] Department of Psychiatry, Dongguk University Gyeongju Hospital, Gyeongju, South Korea
[f] Department of Psychiatry, Gyeongsang National University, School of Medicine, Jinju, South Korea
[g] Department of Neuropsychiatry, Soonchunhyang University Bucheon Hospital, Bucheon, South Korea
[h] Department of Psychiatry, School of Medicine, Chungnam National University, Daejeon, South Korea
[i] Department of Psychiatry, School of Medicine, Konkuk University and Konkuk University Chungju Hospital, Chungju, South Korea
[j] Department of Neuropsychiatry, Jeju National University Hospital, Jeju, South Korea
[k] Department of Psychiatry, School of Medicine, Konkuk University and Konkuk University Medical Center, Seoul, South Korea
[l] Department of Neuropsychiatry, Kyunggi Provincial Hospital for the Elderly, Yongin, South Korea
[m] Department of Neuropsychiatry, Seoul National University Hospital, Seoul, South Korea
[n] Department of Neuropsychiatry, Inje University Sanggye Paik Hospital, Seoul, South Korea
[o] Department of Psychiatry, Dankook University Hospital, Cheonan, South Korea
[p] Department of Psychiatry, Kangwon National University, School of Medicine, Chuncheon, South Korea
[q] Department of Brain and Cognitive Science, Seoul National University College of Natural Sciences, Seoul, South Korea

ARTICLE INFO

Article history:
Received 22 January 2021
Accepted 31 May 2021

Keywords:
Homocysteine
Dementia
Alzheimer disease
Vitamin
Folic acid

SUMMARY

Background: Hyperhomocysteinemia has been repeatedly found to increase the risk of dementia. However, the effects of hypohomocysteinemia on the risk of dementia have been barely investigated. If hypohomocysteinemia, like hyperhomocysteinemia, increases the risk of dementia, misuse or overuse of homocysteine-lowing agents such as vitamin supplements may increase the risk of dementia.
Aims: To investigate whether hypohomocysteinemia, like hyperhomocysteinemia, could increase the risk of dementia and Alzheimer's disease (AD) in a large population-based cohort of older adults.
Methods: This prospective cohort study followed 2655 randomly sampled, community-dwelling, non-demented individuals aged 60 years or older from 2010 to 2018. We measured baseline serum total homocysteine (tHcy) levels and examined the effect of serum tHcy on the risks of dementia and AD using Cox proportional hazards models.
Results: During the follow-up period (mean = 5.4 years, SD = 0.9), dementia and AD developed in 85 and 64 participants, respectively. Not only the participants with high serum tHcy (≥10.6 μmol/L) but also those with low serum tHcy (≤8.9 μmol/L) were 4–5 times more likely to develop dementia and AD compared to those with serum tHcy levels between 9.0 and 10.5 μmol/L. With the increase in serum tHcy concentration, the use of vitamin supplements decreased, and 41.2% of the participants with low serum tHcy (≤8.9 μmol/L) were taking vitamin supplements.

Abbreviations: AD, Alzheimer's disease; IRB, Institutional Review Board; CIRS, Cumulative Illness Rating Scale; GDS, Geriatric Depression Scale; DM, Diabetes mellitus; APOE, apolipoprotein E; tHcy, total homocysteine; DMSO, Dimethyl sulfoxide; HR, Hazards ratios; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine.

* Corresponding author. Department of Neuropsychiatry, Seoul National University College of Medicine and Seoul National University Bundang Hospital, 166 Gumiro, Bundanggu, Seongnamsi, Gyeonggido, 13620, South Korea. Fax: +82 31 787 4058.
E-mail address: kwkimmd@snu.ac.kr (K.W. Kim).

https://doi.org/10.1016/j.clnu.2021.05.034
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Conclusions: Not only hyperhomocysteinemia but also hypohomocysteinemia considerably increased the risk of dementia and AD in older adults. The risk of dementia that results from overuse or misuse of vitamin supplements should be acknowledged and homocysteine-lowering health policies should be tailored to consider dementia risks that are associated with hypohomocysteinemia.

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1. Introduction

Homocysteine is an amino acid that is formed by the demethylation of nutritional methionine, and it is involved in several metabolic processes, including methylation and sulphuration pathways [1]. Hyperhomocysteinemia increases the production of beta-amyloid [2] and inhibits the growth of vascular endothelial cells in cell lines [3]. Most prospective cohort studies demonstrate that hyperhomocysteinemia increases the risk of dementia in humans [4–10], and a recent meta-analysis reported that vitamin B supplementation, a homocysteine-lowering therapy, was beneficial for cognition [11]. Countries like the United States and Australia mandate folic acid fortification in some foods, such as enriched grain products or wheat flour for bread-making [12,13]. However, there is little research on the degree to which blood homocysteine levels can be lowered. In humans, hypohomocysteinemia may reduce DNA methylation [14] and increase its susceptibility to oxidative stress [15]. Several prospective cohort studies suggested that hypohomocysteinemia may also increase the risk of dementia and Alzheimer's disease (AD), however, the increased risks of dementia and AD were not statistically significant, possibly due to small sample sizes (N = 228–624) [6,8,16]. If hypohomocysteinemia can increase the risk of dementia, over- or misuse of homocysteine-lowering therapies may increase the risk of dementia in individuals whose blood homocysteine levels are not high, and the implementation of homocysteine-lowering policies for the general population may need to be reconsidered. In this prospective study, we investigated whether hypohomocysteinemia, like hyperhomocysteinemia, could increase the risk of dementia and AD in a large population-based cohort of older adults.

2. Materials and methods

2.1. Study population

This study was part of the Korean Longitudinal Study on Cognitive Aging and Dementia [17]. In the Korean Longitudinal Study on Cognitive Aging and Dementia, 6818 community-dwelling Koreans aged 60 years or older were randomly sampled from 30 villages and towns across South Korea. They participated in baseline assessments from November 2010 through October 2012 and were subsequently followed every two years, with the first follow-up assessment conducted between November 2012 and October 2014, the second between November 2014 and October 2016 and the third between November 2016 and October 2018.

We included 2655 participants in the current study after excluding those that (a) did not provide blood samples (N = 1729), (b) refused apolipoprotein E (APOE) genotyping (N = 53), (c) had dementia (N = 186) or major psychiatric disorders (N = 480), (d) received three points or higher on the CIRS (N = 79), (e) did not provide a history of smoking, alcohol intake, or physical activity (N = 25) at the baseline assessment, or (f) did not participate in the second follow-up assessment (N = 1611).

2.2. Assessments

At the baseline and follow-up assessments, geriatric neuropsychiatrists with expertise in dementia research conducted face-to-face, standardised, diagnostic interviews, as well as physical and neurological examinations. These were performed using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Clinical Assessment Battery and the Korean version of the Mini International Neuropsychiatric Inventory. Research neuropsychologists or trained research nurses administered the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Neuropsychological Assessment Battery, Digit Span Test, and Frontal Assessment Battery. The Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Neuropsychological Assessment Battery consists of nine neuropsychological tests: the Verbal Fluency Test, 15-item Boston Naming Test, Mini Mental Status Examination, Word List Memory Test, Constructional Praxis Test, Word List Recall Test, Word List Recognition Test, Constructional Recall Test, and Trail Making Test. We established that there was objective cognitive impairment if a participant performed below a 1.5 standard deviation of the age-, gender-, and education-adjusted norms in any of these 11 neuropsychological tests. A panel of geriatric neuropsychiatrists determined the final diagnosis of each participant. Dementia and depressive disorders were diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and AD was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. We evaluated comorbid medical illnesses using the Cumulative Illness Rating Scale (CIRS) and the severity of depressive symptoms using the Korean version of the Geriatric Depression Scale (GDS). We also obtained information on the use of vitamin supplements and antacids, because these could affect the patients' levels of tHcy. Hypertension and diabetes mellitus (DM) were classified from a self-report of a clinical diagnosis and medication use. The information on alcohol use, smoking and vitamin supplementations were obtained from a self-report.

2.3. Laboratory tests

During the baseline assessments, we collected venous blood samples in a serum separation tube and immediately centrifuged the samples to separate the serum from the cells. Then, 0.3 mL of serum was pipetted into several vials and stored at −80 °C before analysis.

We measured the serum's total homocysteine (tHcy) levels using ARCHTECT i2000SR (Abbott Laboratories, Abbott Park, IL, USA). The coefficients of variation of the total precision were within the range of 1.6–3.4%. We measured serum folate and vitamin B12 levels were using radioimmunoassay (MP Biomedicals, Solon, OH, USA) and radioactivity using Gamma-10 (Shin Jin Medics Inc., Goyang, Korea). Inter-assay coefficients of variation was between 4.2% and 11.7%. We analyzed serum creatinine levels using

ADVIA1800 Auto Analyzer (Siemens medical Sol., Deerfield, IL, USA). The coefficient of variation was 3.8% at 1.8. We determined APOE genotype from genomic DNA using QIAamp DNA Blood Mini Kit (Qiagen Inc., Valencia, CA, USA). We amplified a 462-bp product from the APOE gene using LightCycler 2.0 (Roche, Indianapolis, IN, USA). We used a mixture containing 10 mL of the QIAGEN-Multiplex-NoRox kit (Qiagen Inc.) as a master mixture and 2 mL of 10% dimethyl sulfoxide (DMSO). We adjusted the concentrations of all primers and probes to 0.2 mM, and used 3 mL of the isolated genomic DNA (80 ng) for amplification.

We also measured the serum's complete blood cell counts and chemistry profiles including alanine aminotransferase, aspartate aminotransferase, free T4 and thyroid-stimulating hormone.

2.4. Statistics

We categorised serum tHcy into five levels. We first classified the serum tHcy into four levels as proposed by Hooshmand et al. [9] ($\leq$10.5 μmol/L, 10.6–12.8 μmol/L, 12.9–16 μmol/L, and $\geq$16.1 μmol/L), and then further divided the serum with $\leq$10.5 μmol/L of tHcy into two other levels ($\leq$8.9 μmol/L and 9.0–10.5 μmol/L) because a median level of serum tHcy was 8.9 μmol/L in the participants with $\leq$10.5 μmol/L of tHcy. Continuous variables were compared using a Student's *t*-test or analysis of variance and categorical variables were compared using Chi-Squared tests between the groups. We investigated the associations between folate, vitamin B12, and tHcy using Pearson's correlation coefficient. We used Cox proportional hazards models to estimate the hazards ratios (HR) and 95% CI of incident dementia and AD in association with tHcy levels. We adjusted for age (<65, 65–74, 75–84, or $\geq$85 years old), sex, education ($\leq$6, 7–12 or >12 years), hypertension, diabetes mellitus, GDS score (<16 or not), alcohol use, smoking, level of exercise ($\geq$450 metabolic equivalent of task per week or not), APOE ε4 allele (present or absent), serum creatinine (<1.0 mg/dL or not), folate (classified into quartiles), vitamin B12 (classified into quartiles) and vitamin supplementations in the Cox proportional hazards models. We used the Kolmogorov–Smirnov test to determine the normal distribution within the groups. We performed the same analyses in the participants who did not take vitamin supplements and in those who did not take antacids. We performed the analyses using the Statistical Package for Social Sciences, version 20 (SPSS Inc., Chicago, IL).

3. Results

The participants were followed for 5.4 ± 0.9 years on average. Mean concentration of serum tHcy at baseline assessment was 12.0 ± 4.8 μmol/L. The participants with higher serum tHcy levels were more likely to be older, male, and less educated. They were also more likely to have hypertension and DM as well as smoke and drink alcohol; however, they were less likely to use vitamin supplements (Table 1).

During the follow-up period, dementia and AD developed in 85 and 64 participants, respectively. In the Cox proportional hazards models that were adjusted for age, sex, education, hypertension, DM, GDS score, alcohol use, smoking, exercise, serum creatinine, folate, vitamin B12 and the use of vitamin supplements (Table 2), serum tHcy levels $\leq$8.9 μmol/L and $\geq$10.6 μmol/L were associated with about a four-fold higher risk of dementia and AD than serum tHcy levels that were around 9.0–10.5 μmol/L. The risks of dementia and AD were comparable between the three levels of serum tHcy (10.6–12.8 μmol/L, 12.9–16 μmol/L, and $\geq$16.1 μmol/L). In the same model, the risks of dementia and AD were not significantly associated with serum folate levels ($P = 0.064$) vitamin B12 levels ($P = 0.530$) and the use of vitamin supplements ($P = 0.092$).

With the increase in serum tHcy concentration, the use of vitamin supplements decreased ($\chi^2 = 76.797$, $P < 0.001$), and 41.2% of the participants with serum tHcy levels $\leq$8.9 μmol/L were taking vitamin supplements. The proportion of vitamin supplements use was 32.3% in those with serum tHcy levels that were around 9.0–10.5 μmol/L and 22.3% in those with serum tHcy levels $\geq$10.6 μmol/L. The participants who took vitamin supplements had higher folate (16.5 ± 11.9 versus 9.6 ± 7.2 ng/mL, $P < 0.001$) and vitamin B12 (731.1 ± 912.4 versus 602.3 ± 458.1 pg/mL, $P < 0.001$) levels but lower serum tHcy (11.0 ± 4.2 versus 12.4 ± 5.0, $P < 0.001$) than those who did not. Serum tHcy levels were inversely correlated with serum folate ($r = -0.181$, $P < 0.001$) and vitamin B12 ($r = -0.107$, $P < 0.001$). The use of antacids was not different between the serum tHcy levels. When we analysed the participants who did not take vitamin supplements or antacids separately, the effects of high and low serum tHcy on the risks of dementia and AD did not change (Table 3).

4. Discussion

This study found that both low serum tHcy levels ($\leq$8.9 μmol/L) as well as high serum tHcy levels ($\geq$10.6 μmol/L) increased the risks of dementia and AD by about four times.

In line with our observations, the association of hyperhomocysteinemia with the risks of dementia or AD has been repeatedly reported in many prospective population- or hospital-based cohort studies. In those studies, high plasma tHcy levels $\geq$10.8 μmol/L [8], >14.0 μmol/L [4,6], and >15.0 μmol/L [5,7] as well as high serum tHcy levels $\geq$11.5 μmol/L [10] or >16.0 μmol/L [9] increased the risk of dementia or AD. Homocysteine is a sulphur-containing amino acid that is biosynthesised from methionine as an intermediate in the one-carbon pathway, which occurs via S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) [1]. SAM is an important co-substrate for DNA methylation, and SAH is formed by the demethylation of SAM. As SAH is reversibly synthesised to homocysteine, elevated tHcy leads to elevated SAH, which inhibits DNA methylation. Hyperhomocysteinemia causes demethylation of CpG residues in the promoter region of the presenilin gene in mice [18], and increases beta-amyloid production in neuroblastoma cell lines [2]. In a population-based autopsy study, hyperhomocysteinemia was associated with increased neurofibrillary tangles count at the time of death [19]. In addition, elevated tHcy directly induces apoptosis of neurons and astrocytes of the brain, and increases the risk of stroke and small vessel disease by inhibiting vascular endothelial cell growth, decreasing endothelium-dependent vasorelaxation, and promoting atherothrombogenesis.

However, we confirmed the association between hypohomocysteinemia and the risks of incident dementia and AD. Serum tHcy levels $\leq$8.9 μmol/L quadrupled the risks of dementia and AD. Because age, sex, medical disease, use of vitamin supplements and kidney function were shown to be associated with the levels of serum tHcy in the current and previous studies, we controlled these factors to estimate risks of dementia and AD accurately. Using the model adjusting confounding factors associated with serum tHcy levels, we found that both hypohomocysteniemia and hyperhomocysteinemia were associated with the risk of dementia and AD. Although no studies have proven an association between hypohomocysteinemia and the risk of dementia or AD, three population- and hospital-based cohort studies suggested a possible link between them. Among the 634 elderly Japanese subjects who were followed for 7.3 years, those with plasma tHcy between 8.3 and 10.7 μmol/L showed a lower risk of

Table 1
Baseline characteristics of the participants stratified by their total serum homocysteine levels.

	All	Serum total homocysteine level (μmol/L)					
		≤8.9 (N = 554)	9–10.5 (N = 591)	10.6–12.8 (N = 752)	12.9–16 (N = 482)	≥16.1 (N = 276)	P[a]
Age, mean (SD), years	68.6 (5.9)	66.6 (5.1)	67.8 (5.5)	68.6 (5.7)	70.4 (6.3)	71.1 (6.5)	<0.001
Women, N (%)	1525 (57.4)	481 (86.8)	368 (62.3)	378 (50.3)	193 (40.0)	105 (38.0)	<0.001
Education, mean (SD), years	9.12 (5.2)	9.2 (4.9)	9.5 (5.3)	9.5 (5.2)	8.8 (5.3)	7.8 (5.2)	<0.001
Hypertension, N (%)	1332 (49.8)	221 (39.9)	275 (46.5)	590 (51.9)	269 (55.8)	167 (60.5)	<0.001
Diabetes mellitus, N (%)	425 (16.0)	62 (11.2)	83 (14.0)	119 (15.8)	107 (22.2)	54 (19.6)	<0.001
Vitamins use, N (%)	755 (28.4)	228 (41.2)	191 (32.3)	192 (25.5)	97 (20.1)	47 (17.1)	<0.001
Antacids use, N (%)	105 (4.0)	17 (3.1)	25 (4.1)	31 (4.4)	21 (4.0)	11 (4.2)	0.822
Smoking, N (%)[b]	917 (34.5)	7 (1.3)	44 (7.4)	69 (9.2)	70 (14.5)	42 (15.2)	<0.001
Alcohol, N (%)[b]	232 (8.7)	128 (23.1)	213 (36.0)	282 (37.5)	188 (39.0)	106 (38.4)	<0.001
Exercise, N (%)[c]	1626 (61.2)	364 (65.7)	366 (61.9)	456 (60.6)	279 (57.9)	161 (58.3)	0.086
GDS, mean (SD), point	9.11 (6.0)	9.5 (6.0)	8.9 (5.8)	9.2 (6.3)	8.7 (5.8)	9.4 (6.2)	0.173
Vitamin B12, mean (SD), pg/mL	638.9 (624.5)	754.3 (638.3)	665.5 (841.0)	625.6 (655.8)	569.3 (284.9)	508.0 (237.3)	<0.001
Folate, mean (SD), ng/mL	11.6 (9.3)	15.6 (10.2)	13.0 (10.2)	10.5 (7.8)	8.8 (7.6)	8.5 (8.3)	<0.001
Creatinine, mean (SD), mg/dL	1.0 (0.2)	0.9 (0.1)	1.0 (0.1)	1.0 (0.1)	1.1 (0.2)	1.2 (0.3)	<0.001
APOE ε4 allele, N (%)	616 (23.2)	144 (26.0)	143 (24.2)	174 (23.1)	97 (20.1)	58 (21.0)	0.195

SD: standard deviation; GDS: Geriatric Depression Scale; APOE: apolipoprotein E.
[a] Variance analysis for continuous variables and $\chi 2$ test for categorical variables.
[b] In the past year.
[c] 450 metabolic equivalent of task or more per week recommended by the American Heart Association and the American College of Sports Medicine.

Table 2
Effects of serum total homocysteine levels on the future risk of dementia.

Serum homocysteine (μmol/L)	Duration, person-year	Incident cases	Hazard ratio with 95% confidence interval[a]	
			Model 1[b]	Model 2[c]
Dementia				
5-group comparisons				
≤8.9	3091	10	3.68 (1.14–11.94)	3.70 (1.14–11.99)
9–10.5	3288	4	1.00	1.00
10.6–12.8	4087	24	4.20 (1.44–12.26)	4.19 (1.44–12.23)
12.9–16	2550	28	5.12 (1.72–15.24)	5.23 (1.76–15.56)
≥16.1	1450	19	4.75 (1.52–14.81)	4.62 (1.49–14.37)
3-group comparisons				
≤8.9	3091	10	3.74 (1.15–12.10)	3.76 (1.16–12.16)
9–10.5	3288	4	1.00	1.00
≥10.6	8087	71	4.57 (1.62–12.86)	4.57 (1.63–12.85)
Alzheimer's disease				
5-group comparisons				
≤8.9	3091	9	4.22 (1.12–15.85)	4.19 (1.12–15.75)
9–10.5	3288	3	1.00	1.00
10.6–12.8	4087	15	3.76 (1.07–13.18)	3.70 (1.05–12.96)
12.9–16	2550	25	7.50 (2.15–26.20)	7.64 (2.20–26.65)
≥16.1	1450	12	4.80 (1.27–18.19)	4.64 (1.23–17.53)
3-group comparisons				
≤8.9	3091	9	4.34 (1.16–16.29)	4.33 (1.15–16.24)
9–10.5	3288	3	1.00	1.00
≥10.6	8087	52	4.95 (1.50–16.36)	4.90 (1.48–16.19)

[a] Cox proportional hazard models.
[b] Adjusted for age, sex, education, hypertension, diabetes mellitus, Geriatric Depression Scale score, alcohol use, smoking, level of exercise, apolipoprotein E ε4 allele, and serum creatinine, folate, and vitamin B12 levels.
[c] Adjusted for vitamin supplementations in addition to Model 1.

dementia than those with plasma tHcy levels below 8.3 μmol/L, although the risk was not statistically significant (HR = 0.69, 95% CI = 0.25–1.94) [8]. Among the 228 elderly Swedish subjects who were followed for 6.7 years, those with second quartile plasma tHcy showed lower risks of dementia and AD than those with the lowest quartile plasma tHcy, although the risks were not statistically significant (HR = 0.88, 95% CI = 0.42–1.83 for dementia; HR = 0.65, 95% CI = 0.24–1.71 for AD) [6]. Among the 518 elderly Koreans who were followed for 2.4 years, those with the lowest quintile showed a higher incidence of dementia than those with the second quartile plasma tHcy, although the difference was not statistically tested (10% versus 4%) [16]. Hypohomocysteinemia may also reduce DNA methylation. Phenylketonuria patients who adhere to dietary treatments (restriction of natural proteins in addition to a high intake of vitamin B12 and folic acid supplementation in dietary products) showed lower plasma homocysteine levels and decreased methylation capacity than their age- and gender-matched healthy controls [14]. In addition, hypohomocysteinemia may increase susceptibility to oxidative stress by reducing *de novo* production of glutathione [15]. In a large retrospective cohort study using claim data, hypohomocysteinemia was associated with the risk of idiopathic peripheral neuropathy [20].

Supplementation of vitamin B12 or folic acid reduced blood homocysteine levels in humans. In the current study, the

Table 3
Sensitivity analyses on the effects of total serum homocysteine levels on the future risk of dementia.

tHcy (μmol/L)	tHcy level[a](μmol/L)	Duration (person-year)	Dementia		Alzheimer's disease	
			IC	HR (95% CI)[b]	IC	HR (95% CI)[b]
Non-users of vitamin supplements						
≤8.9	8.0 ± 0.8[c]	1841	7	3.74 (0.95–14.67)	6	3.10 (0.76–12.65)
9–10.5	9.8 ± 0.5	2236	3	1.00	3	1.00
≥10.6	14.5 ± 5.3[c]	6275	61	4.53 (1.39–14.77)	43	3.43 (1.04–11.39)
Non-users of antacids						
≤8.9	7.9 ± 0.8	2994	10	3.69 (1.14–12.00)	9	4.06 (1.08–15.29)
9–10.5	9.8 ± 0.5	3155	4	1.00	3	1.00
≥10.6	14.4 ± 5.2	7744	66	4.28 (1.51–12.08)	48	4.57 (1.38–15.19)

tHcy, serum total homocysteine; HR, hazard ratio; CI, confidence interval; IC, number of incident cases.
[a] Comparison between non-users and users using Student's *t*-tests.
[b] Hazard ratios with 95% confidence intervals estimated by Cox proportional hazards models adjusted for age, sex, education, hypertension, diabetes mellitus, Geriatric Depression Scale score, alcohol use, smoking, level of exercise, apolipoprotein E ε4 allele, and serum creatinine, folate, and vitamin B12 levels.
[c] <0.05.

participants who supplemented their diet with vitamins showed lower serum tHcy levels than those who did not. Previous clinical trials showed that supplementation of vitamin B12 and/or folic acid reduced serum or plasma tHcy levels [21–23]. The use of dietary supplements is very common in older adults (40–63%), with multivitamins being the most commonly used [24].

In the current study, four out of 10 subjects were taking vitamin supplements; this was even observed among the participants with low serum tHcy. Therefore, dementia risks associated with hypohomocysteinemia may need to be conveyed to people who are taking or going to take vitamin supplements. Overuse or misuse of vitamin supplements may lead to adverse health outcomes. In addition, health policies such as the fortification of food materials with folic acid need to be carefully implemented with considerations for the risks of dementia associated with hypohomocysteinemia. In countries like Korea where people consume more vegetables and have lower average blood tHcy, overuse of vitamin supplements and folic acid fortification may more likely induce hypohomocysteinemia than other countries. It was observed that the implementation of mandatory fortification of enriched grain products with folic acid resulted in considerable changes in blood homocysteine levels of the general population. In the United States, fortification of enriched grain products with folic acid reduced plasma tHcy in older adults from 10.1 μmol/L (95% CI = 9.8–10.5) to 9.4 μmol/L (95% CI = 9.1–9.7) [12], and in Australia, folic acid fortification of wheat flour reduced plasma tHcy in older adults from 14.5 μmol/L (95% CI = 13.3–15.7) to 10.6 μmol/L (95% CI = 10.0–11.1) [13].

This study has some limitations. First, we measured serum tHcy levels only once, and individual levels of serum tHcy could have changed during the follow-up period. Second, although we obtained data on the use of vitamin supplements, details on their constituents were not collected. If the participants took vitamin supplements that did not include vitamin B6, B12, and folic acid, the association between vitamin supplements and serum tHcy could be underestimated. Third, we could not investigate the association between serum tHcy and non-AD dementia because the number of incident non-AD dementia cases was small (N = 21). Fourth, we could not examine how and why hypohomocysteinemia increase the risk of dementia and AD in this study. Therefore, further study investigating the mechanisms on detrimental effect of hypohomocysteinemia on brain is needed. Fifth, we did not collected data of all medications that could affect the results of this study. For example, metformin is one of the medications that is associated with the risk of dementia and also increase tHcy concentration [25]. However, we could not control the effect of metformin because we did not obtain the exact information on DM medication.

5. Conclusions

Both hypohomocysteinemia and hyperhomocysteinemia increased the risk of dementia and AD in older adults. The risk of dementia associated with overuse or misuse of vitamin supplements should be considered at the individual level, and homocysteine-lowering health policies should be tailored while considering dementia risks associated with hypohomocysteinemia.

Ethics approval and consent to participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB No. B-0912-089-010). All participants were fully informed of the study protocol, and/or their legal guardians provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Authors' contributions

KWK had full access to all the data in the study and was responsible for the decision to submit for publication.

Study concept and design: JBB, JWH, and KWK.

Acquisition of data: JWH, JS, KL, THK, KPK, BJK, SGK, JLK, SWM, JHP, S-HR, JCY, DYL, DWL, SBL, JJL, JHJ, and KWK.

Analysis and interpretation of data: JBB and KWK.

Drafting of the manuscript: JBB and KWK.

Critical revision of the manuscript for important intellectual content: All authors.

Funding

This study was supported by a grant of the Korean Health Technology R&D Project, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (grant number I09C1379) (A092077).

Conflict of interest

The authors have no conflicts of interest to report.

Acknowledgements

The authors thank the patients and their families for their participation in the study and the research clinicians, nurses, and neuropsychologists for their contributions in gathering the data.

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